

Genetics, Mammographic Density and Breast Cancer Risk

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Abstract

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Mammographic, or breast density, describing breast tissue composition, is one of the strongest risk factors for breast cancer, the most common cancer type among women in the US. In general, women in the highest breast density quartile are estimated to have a three to five-fold higher risk of developing breast cancer, compared to those in the lowest. Despite this strong association, the underlying biological mechanism remains unexplained. The association between mammographic density and breast cancer risk is not homogeneous in the general population. Previous studies suggest that menopausal status and postmenopausal hormone use may interact with high breast density to modify breast cancer risk. To our knowledge, only one previous study in postmenopausal women has focused on the interaction between breast density and other risk factors in relation to breast cancer risk. Further, it is not known whether established risk factors affect breast cancer risk differently by breast density among premenopausal women, or if certain risk factors interplay with breast density to alter the risk of specific breast cancer subtypes with worse prognosis.

In addition to being associated with non-genetic factors such as age, parity, body mass index (BMI) and menopausal status, mammographic density is highly heritable, with approximately 60% of the variation attributable to genetics. However, genetic variants identified by previous genome-wide association studies (GWAS) only explain up to 1% of the variation in density. The limited number of identified mammographic density loci is likely a consequence of limited sample sizes. Meanwhile, previous GWAS have focused on genome-wide significant signals, failing to further investigate the potential importance of genetic variants with comparatively weak effects. Estimating the heritability explained by common variants throughout the genome regardless of their marginal association statistics can provide a better understanding of the genetic basis of the traits.

In this dissertation, we attempted to extend our knowledge of mammographic density as an intermediate phenotype of breast cancer, from both environmental (Chapter 1) and genetic (Chapter 2) perspectives. The mammographic density traits studied in this work are the area of dense (epithelial, stromal and muscle) tissue, non-dense (adipose) tissue, and percentage of dense tissue, which have all been demonstrated to be significantly associated with breast cancer risk independently.

Specifically, we assessed multiplicative interactions between mammographic density and thirteen established breast cancer risk factors, in relation to risk of breast cancer overall and by molecular subtypes, using a case-control population nested under Nurses' Health Studies I&II (Chapter 1). Although no interaction remained statistically significant after adjusting for number of comparisons, we did observe some noteworthy interactions with nominal significance at $p < 0.05$ level.

Next, we performed a meta-analysis of GWAS for mammographic density measures, using genotype and phenotype data collected by the Marker of Density (MODE) consortium and the Breast Cancer Association Consortium (BCAC). We also conducted exploratory bioinformatics analyses, including genetic correlation analyses and a transcriptome-wide association study (TWAS) (Chapter 2). Using data on up to 27,900 women of European ancestry, we identified twenty-eight distinct genome-wide significant loci for mammographic density measures, including nine novel signals (*5q11.2*, *5q14.1*, *5q31.1*, *5q33.3*, *5q35.1*, *7p11.2*, *8q24.13*, *12p11.2*, *16q12.2*) that have not been reported before. Fourteen loci identified were also

observed with significant association with the risk of overall, ER-positive and/or ER-negative breast cancer. Subsequent exploratory analyses improved our understanding of a shared genetic basis between mammographic density and breast cancer.

In summary, this work can help understand the underlying mechanisms driving the mammographic density-breast cancer association as well as the genetic architecture of mammographic density. Findings discovered through this dissertation will help to better understand the determinants of breast density, which in turn can help identify strategies that reduce the risk of breast cancer, and ultimately mitigate the burden brought by the disease.

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Chapter 1.

Interactions between mammographic density phenotypes and established risk factors on breast cancer risk, by tumor subtype and menopausal status

ABSTRACT

Previous studies suggest that the association between mammographic density (MD) and breast cancer risk may be modified by other breast cancer risk factors. In this study, we assessed multiplicative interactions between MD measures and established risk factors on the risk of invasive breast cancer overall and by menopausal and estrogen receptor (ER) status. We used data on 2,137 cases and 4,346 controls from a nested case-control study within the Nurses' Health Studies I and II, for whose data on percent mammographic density (PMD), absolute area of dense tissue (DA) and non-dense tissue (NDA) were available. No interaction remained statistically significant after adjusting for number of comparisons. For breast cancer overall, we observed nominally significant interactions ($P < 0.05$) between nulliparity and PMD/NDA, age at menarche and DA, and body mass index (BMI) and NDA. Individual nominally significant interactions across MD measures and risk factors were also observed in analyses stratified by either menopausal or ER status. Our findings help provide further insights into potential mechanisms underlying the association between MD and breast cancer.

INTRODUCTION

Breast tissue composition can be determined via radiographic imaging through mammography. Radiologically dense area (DA) on mammogram is a quantitative measure of the epithelial, stroma and connective tissue in the breast; while the non-dense area (NDA) reflects the adiposity in the breast¹. Mammographic density (MD) has been widely accepted as one of the strongest risk factors for breast cancer²⁻⁴. Women with 75% or greater percent mammographic density (PMD) are estimated to have a four to six-fold higher risk of developing breast cancer, compared to those with 25% or less PMD⁵⁻⁹. In addition, DA and NDA are both independent risk factors for breast cancer⁹⁻¹³. DA is positively associated with breast cancer risk, while NDA is inversely associated with the risk. DA, NDA and PMD are all strongly related to all molecular subtypes of breast cancer, although the magnitude of association has been observed to be slightly different across subtypes^{2; 14}.

Although the association between MD and breast cancer risk is well-established, this association is heterogeneous. Several breast cancer risk factors, including parity, oral contraceptive use, body mass index (BMI) and menopausal hormone therapy (MHT), have been found to interact with PMD in relation to breast cancer risk^{6; 7; 15-20}. In contrast, there is limited data on the interactions of DA and NDA with breast cancer risk factors. We have previously studied the interactions between MD measures and breast cancer risk factors in postmenopausal women, and found the association between PMD/NDA and breast cancer risk differ significantly by MHT use and parity, respectively²⁰. To our knowledge, there are no studies have comprehensively assessed the interactions between MD measures and breast cancer risk factors, in both pre- and postmenopausal women or by tumor subtype. Therefore, we set out to study interactions between MD measures and established breast cancer risk factors in relation to the risk of invasive breast cancer overall, as well as by menopausal and ER status. Specifically, we evaluated potential interactions of MD measures (PMD, DA and NDA) with alcohol consumption, history of benign breast disease, first-degree family history of breast cancer, smoking status, parity, breast feeding history, BMI, physical activity, age

at menarche, MHT use, and age at menopause, using breast cancer cases and controls nested within the Nurses' Health Studies I and II (NHS and NHSII).

METHODS

Study population

Our study population comprises of breast cancer cases and controls nested within NHS and NHSII, two large population-based prospective cohorts²¹. NHS was established in 1976, with 121,700 women included in the initial study population²²; and NHSII was established in 1989, with an initial cohort size of 116,430 women²³. Eligible cases in our study were women diagnosed with breast cancer after blood collection but before June 1, 2004 for NHS or before June 1, 2007 for NHSII. Breast cancer diagnoses were identified through biennial questionnaires or regular searches of the National Death Index, and further confirmed through medical record review. One (NHS) or two (NHSII) controls were matched to each case. The matching criteria included age, menopausal status, month/year of blood collection, time of day of blood draw, and fasting status for both cohorts. Additional matching on race/ethnicity and luteal day (premenopausal women with timed samples) were conducted in NHSII. The exact matching scheme has been described previously²⁴. Reference date was defined as the date of breast cancer diagnosis for cases and their matched controls.

To study the interaction between MD measures and breast cancer risk factors, we further restricted the study population to women with mammograms taken at least 6-month prior to the reference date. The final study population consisted of 2,137 invasive breast cancer cases (1,379 from NHS; 758 from NHS II) and 4,346 controls (2,514 from NHS; 1,832 from NHS II). In analysis stratified by menopausal status, we only included women whose menopausal status remained unchanged between time of mammogram and reference date to eliminate any potential effect of menopause transition on breast density change^{25; 26}. Analyses among premenopausal women included 558 cases and 1,260 controls. Analyses among postmenopausal women included 1,245 cases and 2,343 controls. 1,412 ER-positive and 315 ER-negative

breast cancer cases were classified by immunohistochemistry on tumor microarray or pathology report if tissue was unavailable. All study participants gave informed consent which was implied by return of the questionnaires. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Measurement of mammographic density

To quantify MD, craniocaudal views of both breasts for all film mammograms in the NHS and for the first two batches of mammograms in the NHSII were digitized at 261 μm per pixel with a Lumisys 85 laser film scanner (Lumisys, Sunnyvale, CA) with bit depth of 12. The third batch of NHSII mammograms was digitized using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) and comparable resolution of 150 dots/in. and 12-bit depth. Correlation between PMD measures from the two scanners is 0.88²⁷. Trained observers were blinded to case-control status and used a computer-assisted thresholding software Cumulus to measure MD²⁸. Although within-batch reproducibility was high (intraclass correlation coefficient ≥ 0.90)¹², MD measures varied across the NHSII batches. We included a small subset of identical mammograms in all batches to account for batch drift in MD readings. MD measures from the second and third batches of NHSII mammograms were then adjusted to account for the batch effect, as previously described²⁹. The average MD measures of left and right breasts were used in this analysis.

Covariate collection

Demographic information of the participants was collected at baseline. Information on breast cancer risk factors was collected throughout the follow-up via a biennial self-reported questionnaire. Data used in this study was based on the last questionnaire prior to the reference date.

Statistical analysis

We tested the distribution of breast cancer risk factors between cases and controls using a two-sample T-test (for continuous risk factors) or a X^2 test (categorical risk factors). Given that there were unmatched pairs of women with available mammograms, we conducted unconditional analyses and included matching factors in our analyses to maximize sample size. We utilized multivariable logistic regression models to evaluate associations between MD measures and invasive breast cancer risk. PMD was categorized as <10%, 10-24% (reference), 25-49% and $\geq 50\%$; while DA and NDA were categorized into quartiles based on the distribution in controls, with the lowest quartile as the reference. In stratified analysis by menopausal status, subpopulation-specific quartiles were used for DA and NDA. We included covariates reported to be associated with both MD measures and breast cancer risk as potential confounders in our regression models. These included race (white/non-white), age at breast cancer diagnosis (continuous, year), age at menarche (continuous, year), BMI (continuous, kg/m^2), history of benign breast disease (yes/no), first degree family history of breast cancer (yes/no), parity and age at first birth (nulliparity, parous with first child at birth <25 years, parous with first child at birth ≥ 25 years), menopausal status (yes/no), MHT use (never, past, current), alcohol consumption (0, 0-5, $\geq 5\text{g}/\text{day}$), smoking status (never, past, current), and physical activity (continuous, METs/week). Investigations of reproductive factors were limited to parous women, which were further adjusted for number of children (1, 2, 3+) and history of breast feeding (yes/no). Analyses among postmenopausal women were further adjusted for age at menopause (continuous, years). Finally, we conducted analysis stratified by ER status. We report odds ratios (ORs) and corresponding 95% confidence intervals (CIs) as estimates of risk.

To quantify the multiplicative interactions between MD measures and breast cancer risk factors in relation to breast cancer risk, we added a two-way interaction term into the logistic regression models. We used a Wald test to test for potential interactions. An ordinal variable was created for each MD measure for the interaction test. For continuous risk factors (alcohol consumption, BMI and physical activity), the interaction with MD measures was first tested by modelling these variables as continuous. We then

categorized these variables by either pre-determined cutoffs (alcohol consumption: 0, 0-5 and ≥ 5 g/day; BMI: <25 , 25-30 and ≥ 30 kg/m²) or distribution among controls (physical activity: <4.5 , 4.5-12, 12-25.5 and ≥ 25.5 METs/week), and reassessed their interaction with MD measures. For categorical risk factors (smoking status, MHT use), an ordinal variable was created and combined with MD measures as the interaction term. In addition to modeling MD measures ordinally, we also modeled MD continuously as sensitivity analysis and observed no qualitative difference in the results (data not shown). Considering the number of tests we conducted in this study (thirteen risk factors, three MD measures and five breast cancer outcomes), we adjusted our results for multiple comparisons, which resulted in p-value $<0.05/(13*5*3)=2.5 \times 10^{-4}$ to be considered statistically significant. Nominally significant results with p-value <0.05 are still reported and discussed. The analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Compared to controls, breast cancer cases had significantly higher PMD (32.9% vs. 27.2%) and DA (45.7 cm² vs. 37.0 cm²) but lower NDA (109.6 cm² vs. 120.8 cm²). Cases were also more likely to be postmenopausal, be current user of MHT, be older at time of first birth, and have higher prevalence of first-degree breast cancer family history and benign breast disease history. Cases and controls did not differ significantly in the distributions of other covariates (**Supplementary Table 1.1**).

Higher PMD was significantly associated with elevated breast cancer risk. Women with more than 50% PMD had a 2.21-fold odds (95% CI: 1.83-2.66, $p < 0.001$, **Supplementary Table 1.2**) of developing breast cancer, relative to those with 10-24% PMD. Greater DA was associated with increased breast cancer risk (4th vs. 1st quartile: OR=2.53, 95% CI: 2.12-3.01, $p < 0.001$), while NDA was inversely associated with risk (4th vs. 1st quartile: OR=0.52, 95% CI: 0.43-0.64, $p < 0.001$). Similar significant associations were observed when we stratified analyses by menopausal status (**Supplementary Table 1.2**).

We assessed the association between MD measures and breast cancer risk stratified by established breast cancer risk factors. Relative to parous women, PMD was more strongly associated with breast cancer risk among nulliparous women (p-interaction=0.048, **Table 1.1, Supplementary Table 1.3**), and DA was more strongly associated with breast cancer among women with early age at menarche (p-interaction=0.02). NDA was more strongly associated with an inverse risk of breast cancer risk among women with high BMI (continuous p-interaction=0.02), and among nulliparous women (p-interaction=0.04), compared to parous women.

Among premenopausal women, the associations of PMD and NDA with breast cancer risk were more prominent in non-drinkers (continuous p-interaction: PMD=0.047; NDA=0.04, **Table 1.2, Supplementary Table 1.4**). The association between PMD and breast cancer was more pronounced in nulliparous women (p-interaction=0.02) and women with high BMI (categorical p-interaction=0.045, continuous p-interaction=0.02). Furthermore, among premenopausal women, BMI showed a positive interaction with DA and a negative interaction with NDA (categorical p-interaction: DA=0.04; NDA=0.01; continuous p-interaction: DA=0.01; NDA=0.01). The association between DA and breast cancer risk was stronger with earlier age at menarche (p-interaction=0.048) among premenopausal women.

Among postmenopausal women, both PMD and DA were more strongly associated with breast cancer risk among current users of MHT (p-interaction: PMD=0.047; DA=0.03, **Table 1.3, Supplementary Table 1.5**). The association between DA and breast cancer risk was weaker among women who had multiple children, relative to those who had only given birth once (p-interaction=0.01). NDA was more strongly inversely associated with breast cancer risk than expected in nulliparous women than women who had given birth to at least one child (p-interaction=0.02).

Finally, we studied interactions between MD measures and breast cancer risk factors stratified by ER status (**Tables 1.4&1.5, Supplementary Tables 1.6&1.7**). BMI showed positive interaction with PMD (continuous p-interaction=0.01) and negative interaction with NDA (continuous p-interaction=0.01) for ER-positive breast cancer. PMD (p-interaction=0.02) and DA (p-interaction=0.002) both interacted with

current use of MHT to increase risk of ER-positive disease. We further observed that the association between DA and ER-positive breast cancer differed by age at menarche (p-interaction=0.02). For ER-negative breast cancer, alcohol consumption (continuous p-interaction=0.04) and physical activity (categorical p-interaction =0.03, continuous p-interaction=0.045) showed interactions with PMD. Moreover, the risk of ER-negative breast cancer associated with high DA was attenuated among women with high levels of physical activity (continuous p-interaction=0.01), whereas the protective effect against ER-negative breast cancer associated with high NDA showed negative interaction with alcohol consumption (continuous p-interaction=0.02).

DISCUSSION

In this breast cancer nested case-control study of 2,137 cases and 4,346 controls, we comprehensively investigated the interaction between MD measures and established breast cancer risk factors in relation to invasive breast cancer risk overall and stratified by menopausal and ER status. After adjusting for multiple testing, no interaction remained statistically significant. However, we did observe some noteworthy interactions with unadjusted $p < 0.05$. For example, the breast cancer risk associated with PMD was more prominent in nulliparous women. Furthermore, we found that MD measures interacted with various distinct risk factors in changing the risk of pre- and postmenopausal disease risk as well as across subtypes defined by ER status.

Our results provide suggestive evidence that the association between PMD and breast cancer risk is modified by parity, which was observed in overall analysis as well as in premenopausal women. In addition, parity interacted with DA to change postmenopausal breast cancer risk, and with NDA to change both overall and postmenopausal breast cancer risk. In agreement with our study, previous studies have suggested that nulliparous women have up to 50% breast cancer risk increase associated with DA compared to women who had at least one full-term pregnancy³⁰⁻³³. Only a few other studies focused on the combined effect of parity and breast density. A multi-ethnic case-control study found that the association between

dense-breast pattern (defined by the Tabar classification) and breast cancer risk was stronger among women with 1-2 children (OR=4.35), relative to women with 3 or more children (OR=1.08)¹⁶. Similarly, a case-control study in UK reported that nulliparous women with more than 5% density had a 7.1-fold breast cancer risk compared to parous women with 5% or less density, which was higher than expected given the individual risk increases associated with nulliparity (OR=1.1) and high breast density (OR=2.7), respectively¹⁷. Parity has been proposed to protect against breast cancer via multiple potential biological mechanisms, including decreasing circulating estrogen levels, reduction in estrogen responsiveness of parous gland, stimulation of cell differentiation, and decreased number of mammary stem cells³⁴⁻³⁷. These mechanisms may provide possible explanations to our observation that the association between PMD and postmenopausal disease risk becomes weaker with more full-time pregnancies. Our finding that NDA, rather than DA, shows significant interaction with nulliparity in changing overall and postmenopausal disease risk suggests potential biological mechanisms beyond those mentioned here and further research is needed to understand the relationship between parity, breast density, and breast cancer risk.

We found that the associations between both PMD and DA and postmenopausal breast cancer were modified by MHT use. This is consistent with several previous studies, including previous analyses in NHS, that reported significant interactions between MHT and PMD^{19; 20; 38; 39}. Our findings suggest that this interaction is driven by the amount of dense tissue in the breast. Our results are highly consistent with the theory of hormone stimulation⁴⁰⁻⁴², which states that women with a larger area of dense tissue have a higher number of epithelial and stromal cells in the breast^{43; 44} that can mutate due to stimulation by circulating hormones, and may subsequently increase the population size of susceptible cells and ultimately elevate the risk of breast cancer⁴⁵.

We observed a negative interaction between BMI and NDA for overall breast cancer. Furthermore, interactions between BMI and all three MD measures were nominally significant among premenopausal women. Several studies have shown that the association between PMD and breast cancer risk is stronger with increasing BMI. In a case-control study in Asian population, leaner women (BMI<26.5) with > 75%

PMD had an OR of 3.95 compared to women with 0-10% PMD, while corresponding association in women with BMI >26.5 was substantially stronger (OR=9.53)¹⁸. Similar results were observed in another case-control study nested under the Multiethnic Cohort Study, which observed a stronger association between PMD and breast cancer in overweight women (BMI≥25, OR=1.29 per 10% PMD increase) compared to normal-weight women (BMI<25, OR=1.16)⁶. In another multi-ethnic case-control study, association of PMD with breast cancer risk was strongest in obese women (per 10%-increase in PMD: OR=1.20 for BMI≤21; OR=1.09 for 21<BMI<30; OR=1.34 for BMI≥30)⁷. Of note, these studies all included both pre- and postmenopausal women. Here, we show that this interaction is apparent in premenopausal women only. This is highly consistent with the results of a recent case-control study, which indicated that the odds of premenopausal breast cancer were elevated by 39%, 119% and 188% per 10% increase in volumetric percent density for women with BMI<25, 25-30 and >30 kg/m²⁴⁶. The role of BMI in the development of premenopausal breast cancer remains unclear, as premenopausal BMI has been inversely associated with breast cancer⁴⁷⁻⁵⁰. It has been hypothesized that women with higher BMI have an imbalanced secretion of leptin and adiponectin⁵¹. The ratio of leptin to adiponectin is abnormally high in obese or overweight individuals relative to people with normal BMI^{52; 53}. Leptin has been observed to promote the growth of breast cancer cells, whereas adiponectin may stimulate cell proliferation and apoptosis⁵⁴. Alternatively, excessive adiposity may increase breast cancer risk via chronic low-level inflammation and insulin resistance^{55; 56}. Our findings suggest that these mechanisms, if valid, would have a heterogeneous impact on breast cancer risk at different stages throughout life.

This is the first study to assess interactions between MD measures and breast cancer risk factors by ER status. We found that the joint effect of breast density and risk factors differ by ER status. For ER-positive breast cancer, we observed interactions of PMD and DA with age at menarche, BMI, and MHT use. Earlier onset of age at menarche is thought to increase the risk of breast cancer via excessive life-time cumulative estrogen exposure and earlier timing of the first exposure of the mammary gland to cyclic hormones⁵⁷. Excessive adiposity in postmenopausal women has been associated with elevated exposure to circulating

estrogens via upregulated aromatase activity⁵⁸. Along with MHT use, these factors are all related to increased exposure of circulating hormones at various stages throughout life, which reaffirms that hormone stimulation is important in explaining the relationship between breast density and breast cancer, especially for ER-positive subtype⁴⁰⁻⁴². Meanwhile, we observed significant interactions between MD measures and alcohol consumption as well as physical activity in relation to ER-negative breast cancer. Previous studies have attributed the association between MD measures and ER-negative breast cancer to their shared genetic basis^{59; 60}. Alternatively, our study suggests that this association is not homogeneous in the population and may be modified through life-style changes. Population-based studies with larger sample sizes are needed to confirm this.

Our study has several strengths. To date, this is the only study that comprehensively investigates the interactions between quantified MD measures and breast cancer risk factors in both pre- and postmenopausal women. Furthermore, we also considered breast cancer as a molecularly heterogeneous disease and tested interaction effects separately for ER-positive and ER-negative breast cancer. We collected a comprehensive set of covariates and adjusted for them in our logistic regression models, which made our results less likely to be affected by confounding. Our MD data was generated by trained mammogram readers using a semi-automated computer thresholding software. It is important to recognize the limitations in our study. Our study has a limited power to detect statistical significance after Bonferroni correction, as we have less than 80% power to detect interaction with an odds ratio less than 1.18 in overall population and 1.45 in premenopausal women, under a type I error rate of 0.05. We have relatively small number of cases, especially ER-negative cases, in some of the analyses, which may result in imprecise effect estimates and thus should be interpreted with caution. Some breast cancer risk factors, including BMI, parity, and age at first birth, can also influence MD measures, which suggests MD might act as mediators rather than effect modifiers on their causal pathway to breast cancer⁶¹. Valid tumor markers other than ER were only available in a subset of participants, thus not allowing us to assess more detailed subtypes, including HER-2 positive and triple-negative breast cancer. Furthermore, majority of our study population

is of European ancestry, limiting our ability to generalize our findings to women in other race or ethnicity groups.

In conclusion, we comprehensively assessed the interactions of MD measures with established breast cancer risk factors on overall breast cancer as well as by menopausal and ER status. Although no interactions were significant after adjusting for number of tests, we identified several suggestive interactions. Our results, if confirmed, may help better understand the association between breast composition and breast cancer risk, and provide novel insights into the possibility of identifying women with especially high risk of developing breast cancer.

TABLES AND FIGURES

Table 1.1. Nominally significant (P-value < 0.05) Interactions between Mammographic Density Measures and Breast Cancer Risk Factors, in Relation to the Overall Risk of Invasive Breast Cancer, among 2,137 cases and 4,346 controls¹

Breast Cancer Risk Factors	Category 1		Category 2		Category 3		Category 4		P for Trend	Interaction Odds Ratio	P for Interaction
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)			
Percent Density²											
Nulliparity										0.813	0.048
Nulliparous	15/76	0.33 (0.15-0.71)	53/125	1.00 (Ref)	119/188	1.60 (1.00-2.56)	64/76	2.69 (1.54-4.70)	< 0.0001	(0.660-0.999)	
Parous	200/706	0.72 (0.58-0.89)	507/1309	1.00 (Ref)	802/1337	1.77 (1.51-2.07)	344/491	2.10 (1.71-2.57)	< 0.0001		
Dense Area²											
Age at Menarche, yrs										0.907	0.02
< 12	80/285	1.00 (ref.)	116/262	1.51 (1.03-2.21)	126/228	2.26 (1.55-3.30)	201/248	3.27 (2.29-4.65)	< 0.0001	(0.836-0.984)	
12-13	176/595	1.00 (ref.)	286/631	1.75 (1.36-2.25)	330/660	2.00 (1.56-2.56)	448/617	2.72 (2.13-3.46)	< 0.0001		
> 13	70/202	1.00 (ref.)	71/190	1.24 (0.79-1.94)	92/196	1.41 (0.91-2.19)	129/217	1.72 (1.13-2.62)	0.009		
Non-dense Area²											
Body Mass Index, kg/m²										0.986	0.02
< 25	498/866	1.00 (ref.)	298/662	0.76 (0.63-0.92)	151/410	0.65 (0.51-0.83)	55/140	0.78 (0.53-1.13)	0.0007	(0.976-0.998)	(Continuous)
25-30	137/181	1.00 (ref.)	194/330	0.78 (0.57-1.08)	226/417	0.72 (0.52-0.98)	136/377	0.46 (0.32-0.64)	< 0.0001		
>= 30	22/25	1.00 (ref.)	50/79	0.74 (0.35-1.59)	95/242	0.43 (0.21-0.88)	236/551	0.47 (0.24-0.91)	0.02		
Nulliparity										1.181	0.04
Nulliparous	86/132	1.00 (ref.)	73/119	0.91 (0.58-1.43)	52/87	0.68 (0.40-1.16)	40/127	0.25 (0.12-0.50)	0.0004	(1.003-1.391)	
Parous	576/946	1.00 (ref.)	466/952	0.76 (0.64-0.90)	425/993	0.65 (0.54-0.79)	386/952	0.57 (0.46-0.71)	< 0.0001		

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, \geq 5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Percent density was categorized by <10%, 10-24% (reference), 24-49% and \geq 50%; Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls, as the lowest quantile group was regarded as the reference.

Table 1.2. Nominally significant (P-value < 0.05) Interactions between Mammographic Density Measures and Breast Cancer Risk Factors, in Relation to the Risk of Premenopausal Breast Cancer, among 558 cases and 1,260 controls¹

Breast Cancer Risk Factors	Category 1		Category 2		Category 3		Category 4		P for Trend	Interaction Odds Ratio	P for Interaction	
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)				
<i>Percent Density²</i>												
Alcohol Consumption											0.982	0.047
0	8/59	0.48 (0.20-1.14)	43/147	1.00 (Ref)	85/143	2.33 (1.42-3.83)	49/83	2.23 (1.25-3.98)	0.0001	(0.965-0.999)	(Continuous)	
0-5	13/51	0.57 (0.26-1.26)	34/101	1.00 (Ref)	99/174	1.80 (1.07-3.02)	48/84	2.14 (1.16-3.95)	0.0004			
>= 5	9/35	0.67 (0.25-1.81)	23/90	1.00 (Ref)	70/150	1.83 (1.01-3.32)	35/66	2.15 (1.07-4.32)	0.007			
Body Mass Index, kg/m²											1.191	0.045
< 25	2/72	0.14 (0.02-1.07)	41/141	1.00 (Ref)	149/300	1.72 (1.09-2.69)	103/203	1.68 (1.05-2.70)	0.003	(1.003-1.414)	(Categorical)	
25-30	10/50	0.50 (0.22-1.13)	41/106	1.00 (Ref)	69/127	1.18 (0.71-1.99)	23/27	2.26 (1.06-4.85)	0.003	1.027	0.02	
>= 30	19/79	1.17 (0.53-2.56)	26/103	1.00 (Ref)	42/47	4.08 (2.01-8.29)	9/10	3.50 (1.02-12.02)	0.0003	(1.004-1.055)	(Continuous)	
Nulliparity											0.652	
Nulliparous	2/26	0.27 (0.05-1.39)	12/49	1.00 (Ref)	51/80	3.98 (1.61-9.82)	31/40	6.56 (2.33-18.46)	< 0.0001	(0.454-0.937)	0.02	
Parous	30/133	0.65 (0.38-1.11)	100/308	1.00 (Ref)	220/410	1.76 (1.27-2.43)	106/206	1.81 (1.23-2.67)	< 0.0001			
<i>Dense Area²</i>												
Age at Menarche, yrs											0.852	0.048
< 12	22/97	1.00 (ref.)	27/63	2.60 (1.17-5.80)	30/61	3.50 (1.59-7.71)	54/76	4.20 (2.04-8.64)	0.0001	(0.727-0.999)		
12-13	38/172	1.00 (ref.)	70/208	1.56 (0.95-2.58)	98/191	2.33 (1.43-3.81)	126/174	3.30 (2.05-5.33)	< 0.0001			
> 13	17/46	1.00 (ref.)	19/44	1.33 (0.52-3.38)	25/62	1.49 (0.62-3.60)	28/65	1.38 (0.59-3.23)	0.47			
Body Mass Index, kg/m²											1.148	0.04
< 25	37/123	1.00 (ref.)	68/192	1.35 (0.80-2.27)	88/190	1.87 (1.13-3.11)	102/166	2.15 (1.29-3.58)	0.0008	(1.007-1.309)	(Categorical)	

25-30	20/95	1.00 (ref.)	30/59	1.85 (0.90-3.81)	36/83	1.87 (0.96-3.63)	57/73	3.24 (1.71-6.16)	0.0005	1.025	0.01
>= 30	14/88	1.00 (ref.)	15/56	1.80 (0.69-4.69)	22/32	4.54 (1.77-11.61)	45/63	5.13 (2.31-11.40)	< 0.0001	(1.006-1.044)	(Continuous)
Non-dense Area²											
Alcohol Consumption										1.014	0.04
0	54/96	1.00 (ref.)	51/97	1.11 (0.66-1.87)	40/116	0.64 (0.36-1.13)	40/123	0.57 (0.29-1.14)	0.06	(1.000-1.028)	(Continuous)
0-5	61/111	1.00 (ref.)	56/103	0.94 (0.57-1.53)	36/101	0.55 (0.31-0.97)	41/95	0.63 (0.34-1.19)	0.05		
>= 5	43/93	1.00 (ref.)	37/96	0.75 (0.42-1.33)	36/83	0.99 (0.54-1.82)	21/69	0.59 (0.26-1.31)	0.38		
Body Mass Index, kg/m²										0.810	0.01
< 25	131/272	1.00 (ref.)	88/206	0.98 (0.69-1.38)	58/156	0.77 (0.50-1.17)	18/37	1.18 (0.62-2.25)	0.60	(0.697-0.942)	(Categorical)
25-30	24/31	1.00 (ref.)	41/85	0.67 (0.32-1.39)	42/91	0.69 (0.33-1.44)	36/103	0.53 (0.25-1.12)	0.14	0.970	0.01
>= 30	8/4	1.00 (ref.)	14/12	0.84 (0.15-4.88)	15/56	0.15 (0.03-0.78)	59/167	0.19 (0.04-0.89)	0.004	(0.950-0.992)	(Continuous)
¹ Multivariate adjusted logistic regression model were adjusted for the following covariates, with exception of the covariate used for stratification: <i>Race</i> (White/Non-white); <i>Age at diagnosis</i> (Continuous); <i>Body mass index at diagnosis</i> (Continuous); <i>Age at menarche</i> (Continuous); <i>Parity and age at 1st birth</i> (Nulliparous, Any number of children and 1 st birth no later than 25 yrs-old, Any number of children and 1 st birth after 25 yrs-old); <i>First-degree family history of breast cancer</i> (Binary); <i>History of benign breast disease</i> (Binary); <i>Alcohol consumption</i> (0, 0-5, >=5 g/day); <i>Smoking status</i> (Never, Past, Current); <i>Physical activity</i> (Continuous, METs/week).											
² Percent density was categorized by <10%, 10-24% (reference), 24-49% and ≥50%; Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls, as the lowest quantile group was regarded as the reference.											

Table 1.3. Nominally significant (P-value < 0.05) Interactions between Mammographic Density Measures and Breast Cancer Risk Factors, in Relation to the Risk of Postmenopausal Breast Cancer, among 1,245 cases and 2,343 controls¹

Breast Cancer Risk Factors	Category 1		Category 2		Category 3		Category 4		P for Trend	Interaction Odds Ratio	P for Interaction
	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)			
Percent Density²											
Menopausal Hormone Therapy Use										1.117	0.047
Never	62/172	0.98 (0.62-1.56)	78/231	1.00 (Ref)	84/152	1.84 (1.17-2.89)	25/30	2.46 (1.07-5.66)	0.004	(1.002-1.246)	
Past	44/132	0.80 (0.48-1.31)	88/203	1.00 (Ref)	77/163	1.27 (0.83-1.96)	34/39	2.17 (1.15-4.10)	0.006		
Current	56/231	0.55 (0.37-0.80)	175/387	1.00 (Ref)	340/403	1.87 (1.44-2.43)	130/117	2.41 (1.69-3.45)	< 0.0001		
Dense Area²											
Parity³										0.844	0.01
1	9/37	1.00 (ref.)	9/52	0.87 (0.24-3.11)	27/47	4.03 (1.31-12.42)	52/46	5.53 (1.97-15.54)	< 0.0001	(0.747-0.955)	
2	42/141	1.00 (ref.)	55/155	1.15 (0.67-1.98)	82/169	1.81 (1.09-3.02)	138/168	2.78 (1.71-4.51)	< 0.0001		
3+	122/366	1.00 (ref.)	155/333	1.33 (0.97-1.83)	177/314	1.55 (1.13-2.12)	231/296	2.13 (1.56-2.91)	< 0.0001		
Menopausal Hormone Therapy Use										1.105	0.03
Never	61/174	1.00 (ref.)	49/151	1.00 (0.61-1.64)	60/132	1.25 (0.76-2.06)	79/128	1.55 (0.94-2.54)	0.06	(1.012-1.206)	
Past	44/140	1.00 (ref.)	60/138	1.20 (0.72-2.02)	54/139	1.30 (0.76-2.22)	85/120	2.11 (1.28-3.49)	0.003		
Current	69/253	1.00 (ref.)	129/278	1.70 (1.16-2.48)	204/294	2.42 (1.70-3.47)	299/313	3.31 (2.34-4.69)	< 0.0001		
Non-dense Area²											
Nulliparity										1.329	0.02
Nulliparous	52/56	1.00 (ref.)	24/47	0.50 (0.23-1.09)	28/42	0.46 (0.20-1.04)	20/57	0.19 (0.06-0.58)	0.004	(1.037-1.704)	
Parous	367/527	1.00 (ref.)	269/534	0.76 (0.60-0.95)	234/541	0.67 (0.52-0.86)	229/522	0.63 (0.47-0.84)	0.0006		

¹Multivariate adjusted logistic regression model were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *Body mass index at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children

and 1st birth after 25 yrs-old); *First-degree family history of breast cancer* (Binary); *Age at Menopause* (Continuous); *Menopausal hormone therapy use* (Never, Past, Current); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, \geq 5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Percent density was categorized by <10%, 10-24% (reference), 24-49% and \geq 50%; Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls, as the lowest quantile group was regarded as the reference.

³Analysis conducted among parous women only. *Parity and age at 1st birth* were removed from the set of adjusting factors in the regression model. *Age at 1st Child* (before/after 25 yrs-old) and *History of breast feeding* (Binary) were further adjusted for.

Table 1.4. Nominally significant (P-value < 0.05) Interactions between Mammographic Density Measures and Breast Cancer Risk Factors, in Relation to the Risk of ER-positive Breast Cancer, among 1,412 cases and 4,346 controls¹

Breast Cancer Risk Factors	Category 1		Category 2		Category 3		Category 4		P for Trend	Interaction Odds Ratio	P for Interaction
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)			
Percent Density²											
Body Mass Index, kg/m²										1.018	0.01
< 25	19/153	0.59 (0.33-1.07)	124/577	1.00 (ref.)	315/918	1.75 (1.34-2.30)	170/430	1.92 (1.41-2.62)	< 0.0001	(1.003-1.033)	(Continuous)
25-30	55/275	0.62 (0.43-0.92)	160/492	1.00 (ref.)	208/437	1.41 (1.07-1.86)	53/101	1.58 (1.03-2.42)	< 0.0001		
>= 30	77/350	0.76 (0.51-1.14)	101/359	1.00 (ref.)	81/158	2.09 (1.39-3.14)	18/30	2.18 (1.05-4.53)	< 0.0001		
Menopausal Hormone Therapy Use³										1.175	0.02
Never	48/172	1.38 (0.80-2.36)	45/231	1.00 (ref.)	54/152	2.06 (1.19-3.57)	12/30	2.23 (0.76-6.50)	0.14	(1.026-1.345)	
Past	33/132	0.78 (0.44-1.38)	62/203	1.00 (ref.)	53/163	1.17 (0.71-1.93)	18/39	1.97 (0.93-4.19)	0.04		
Current	33/231	0.42 (0.26-0.68)	126/387	1.00 (ref.)	206/403	1.57 (1.16-2.12)	71/117	1.78 (1.17-2.70)	< 0.0001		
Dense Area²											
Age at Menarche										0.890	0.02
< 12	52/285	1.00 (ref.)	82/262	1.90 (1.20-3.01)	88/228	2.92 (1.85-4.61)	126/248	3.73 (2.42-5.74)	< 0.0001	(0.810-0.980)	
12-13	136/595	1.00 (ref.)	192/631	1.45 (1.09-1.92)	211/660	1.55 (1.17-2.06)	273/617	2.01 (1.53-2.64)	< 0.0001		
> 13	46/202	1.00 (ref.)	46/190	1.13 (0.66-1.93)	68/196	1.54 (0.93-2.54)	86/217	1.67 (1.02-2.73)	0.02		
Menopausal Hormone Therapy Use³										1.186	0.002
Never	46/174	1.00 (ref.)	33/151	0.75 (0.42-1.33)	37/132	0.96 (0.53-1.71)	43/128	1.06 (0.58-1.91)	0.78	(1.065-1.321)	
Past	33/140	1.00 (ref.)	41/138	1.10 (0.60-2.02)	39/139	1.27 (0.69-2.35)	53/120	1.94 (1.10-3.43)	0.02		
Current	46/253	1.00 (ref.)	72/278	1.53 (0.97-2.41)	137/294	2.51 (1.65-3.83)	181/313	3.16 (2.09-4.77)	< 0.0001		
Non-dense Area²											

Body Mass Index, kg/m²										0.982	0.01
< 25	305/866	1.00 (ref.)	189/662	0.77 (0.61-0.98)	99/410	0.71 (0.53-0.95)	35/140	0.82 (0.52-1.29)	0.02	(0.970-0.995)	(Continuous)
25-30	85/181	1.00 (ref.)	132/330	0.81 (0.56-1.17)	164/417	0.83 (0.58-1.19)	95/377	0.49 (0.33-0.72)	0.0006		
>= 30	16/25	1.00 (ref.)	29/79	0.57 (0.24-1.32)	69/242	0.39 (0.18-0.82)	163/551	0.38 (0.18-0.79)	0.01		

¹Multivariate adjusted logistic regression model were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Percent density was categorized by <10%, 10-24% (reference), 24-49% and ≥50%; Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls, as the lowest quantile group was regarded as the reference.

³Conducted among menopausal women only. *Menopausal status* was removed from the covariate set for adjustment. *Age at menopause* (Continuous) was further adjusted for.

Table 1.5. Nominally significant (P-value < 0.05) Interactions between Mammographic Density Measures and Breast Cancer Risk Factors, in Relation to the Risk of ER-negative Breast Cancer, among 315 cases and 4,346 controls¹

Breast Cancer Risk Factors	Category 1		Category 2		Category 3		Category 4		P for Trend	Interaction Odds Ratio	P for Interaction
	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)	Cases/ Controls	OR (95% CI)			
Percent Density²											
Alcohol Consumption, g/day										0.984	0.04
0	12/305	0.72 (0.33-1.55)	35/530	1.00 (ref.)	45/459	1.76 (1.01-3.05)	18/180	2.21 (1.10-4.43)	0.003	(0.968-0.999)	(Continuous)
0 - 5	12/257	0.98 (0.46-2.12)	24/429	1.00 (ref.)	45/517	1.81 (1.03-3.20)	22/171	2.93 (1.48-5.77)	0.002		
>= 5	5/166	0.42 (0.14-1.30)	22/370	1.00 (ref.)	39/452	1.66 (0.91-3.02)	21/186	1.79 (0.87-3.67)	0.007		
Physical Activity, METs/week										0.869	0.03
< 4.5	7/234	0.83 (0.30-2.33)	17/357	1.00 (ref.)	44/321	4.07 (2.02-8.24)	11/106	2.46 (0.97-6.27)	0.0009	(0.766-0.985)	(Categorical)
4.5 - 12	8/184	0.74 (0.29-1.90)	21/343	1.00 (ref.)	33/385	1.57 (0.79-3.11)	21/119	4.43 (2.02-9.72)	0.0002	0.993	0.045
12 - 25.5	6/190	0.74 (0.27-2.01)	18/314	1.00 (ref.)	23/384	1.20 (0.59-2.47)	15/167	1.82 (0.80-4.11)	0.08	(0.985-1.000)	(Continuous)
>= 25.5	8/153	0.71 (0.29-1.77)	25/372	1.00 (ref.)	32/394	1.30 (0.71-2.38)	15/160	1.42 (0.65-3.09)	0.15		
Dense Area²											
Physical Activity, METs/week										0.992	0.01
< 4.5	11/277	1.00 (ref.)	13/266	0.77 (0.29-2.05)	22/221	2.45 (1.08-5.56)	33/254	2.87 (1.31-6.26)	0.0005	(0.987-0.998)	(Continuous)
4.5 - 12	13/249	1.00 (ref.)	11/255	1.00 (0.40-2.52)	22/273	1.54 (0.66-3.57)	37/254	2.99 (1.39-6.43)	0.0008		
12 - 25.5	5/279	1.00 (ref.)	12/234	2.56 (0.86-7.64)	19/261	3.05 (1.06-8.72)	26/281	4.77 (1.75-12.98)	0.001		
>= 25.5	15/243	1.00 (ref.)	20/276	1.43 (0.66-3.09)	19/291	1.44 (0.66-3.12)	26/269	1.70 (0.80-3.62)	0.20		
Non-dense Area²											
Alcohol Consumption, g/day										1.016	0.02

0	33/326	1.00 (ref.)	26/330	0.76 (0.42-1.39)	24/371	0.51 (0.26-1.00)	27/447	0.48 (0.22-1.04)	0.03	(1.002-1.030)	<i>(Continuous)</i>
0-5	35/341	1.00 (ref.)	22/337	0.66 (0.37-1.18)	21/355	0.49 (0.26-0.94)	25/341	0.72 (0.35-1.46)	0.16		
>= 5	31/347	1.00 (ref.)	27/347	0.82 (0.45-1.49)	16/272	0.65 (0.32-1.32)	13/208	0.48 (0.19-1.19)	0.09		

¹Multivariate adjusted logistic regression model were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Percent density was categorized by <10%, 10-24% (reference), 24-49% and ≥50%; Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls, as the lowest quantile group was regarded as the reference.

Chapter 2.

Genome-wide Association Study Reveals Novel Loci Associated with Mammographic Density and Further Establishes Its Shared Genetic Basis with Breast Cancer

ABSTRACT

Mammographic density (MD) phenotypes, including percent mammographic density (PMD), area of dense tissue (DA) and non-dense tissue (NDA), adjusted for age and body mass index (BMI), are independently associated with breast cancer risk. Twin studies suggest that these MD phenotypes are highly heritable with estimates exceeding 60%. However, only a small proportion of their variance (0.4-1%) is explained by genetic variants known to be associated at genome-wide significance, leaving most of their heritability unexplained. In this study, we conducted a meta-analysis of genome-wide association studies (GWAS) of age- and BMI-adjusted DA, NDA, and PMD, in up to 27,900 European Ancestry women from the MODE and BCAC consortia. We identified 28 distinct genome-wide significant loci for MD phenotypes, including 9 novel signals (*5q11.2*, *5q14.1*, *5q31.1*, *5q33.3*, *5q35.1*, *7p11.2*, *8q24.13*, *12p11.2*, *16q12.2*) that have not been reported before. Phenotypic variance explained by the lead SNPs of genome-wide significant loci for DA, NDA and PMD was 2.6%, 0.8%, 1.6%, respectively. Fourteen of the 28 MD lead SNPs were also associated with breast cancer risk in a study of 122,977 cases and 105,974 controls. A transcriptome-wide association study (TWAS) identified three of the GWAS loci and further discovered four novel genes whose genetically predicted expression level was significantly associated with MD phenotypes. Finally, we conducted a fine-mapping analysis and enumerated a 95% credible set of potential causal variants for each GWAS locus. This study, which is the largest GWAS of MD phenotypes to date, found multiple novel loci associated with MD phenotypes, and improved the understanding of the shared genetic basis between MD and breast cancer.

Introduction

Heterogeneity of tissue composition in the breast can be reflected via radiographic imaging using mammography. Epithelial and connective tissues are radiologically dense with white appearance, while adipose tissue shows lucent with dark appearance on a mammogram¹. Mammographic density (MD) has been widely established as one of the strongest risk factors for breast cancer^{9; 62}, the most common cancer type among women in the US⁶³. Specifically, quantitative MD measures, including mammographic dense area (DA), non-dense area (NDA) as well as the percentage of dense area in the whole breast (PMD), have all been independently associated with breast cancer^{6; 7; 9; 12}. In analyses adjusting for body mass index (BMI), women with extensive DA and PMD have an elevated risk of breast cancer, while NDA is associated with a decreased risk.

Genetic factors have been suggested to explain a large proportion of the variation in MD phenotypes. Twin studies have reported that DA, NDA and PMD are all highly heritable with heritability estimates exceeding 60%, after adjusting for age and individual-specific shared environmental factors⁶⁴⁻⁶⁶. Previous genome-wide association studies (GWAS) have identified several genetic variants that are significantly ($p < 5 \times 10^{-8}$) associated with DA, NDA or PMD⁶⁷⁻⁷². However, only a small fraction of the total variance of MD phenotypes can be explained by the significant variants^{69; 72}, and the vast majority of MD heritability remains unexplained. To further enhance our understanding of the genetic basis of mammographic density, additional GWAS with larger sample sizes are needed.

In the present study, we conducted a GWAS meta-analysis of MD phenotypes, leveraging data from 30 studies with a total sample size of up to 27,900 women of European ancestry. We identified 28 distinct genome-wide significant loci associated with at least one MD phenotype, including nine novel signals. Exploratory bioinformatic analyses further enhanced our understanding of the genetic architecture of mammographic density, and expanded the evidence of its shared genetic basis with breast cancer.

Methods

Study Design

In this study, we conducted a GWAS meta-analysis for three MD phenotypes (DA, NDA, PMD) based on 30 individual studies, including 21 studies with individual-level genotype and phenotype data (**Supplementary Table 1**) and nine studies which provided GWAS summary statistics (**Supplementary Table 2**). Among the studies with individual-level data, we had data on PMD for all 21 studies (N=17,216), DA for 19 studies (N=13,805), and NDA for 19 studies (N=13,915). Nine of these studies generated genotype data using the OncoArray SNP array; six studies used the iCOGs SNP array; and six studies had samples genotyped with either OncoArray or iCOGs. Association analysis was performed by study for each MD measure, and study-specific results were then meta-analyzed. We also added summary statistics of nine previously conducted GWAS (N=10,774 for all three MD phenotypes) to the meta-analysis. Meta-analysis was performed using a sample-size weighted approach. Final sample sizes of the GWAS meta-analyses were 24,579 (DA), 24,689 (NDA), and 27,900 (PMD). The included studies had various study designs, including family-based studies, population-based case-control studies, and prospective cohort studies. The overall study population comprised of 6,666 breast cancer cases and 21,234 controls.

Genotyping, Imputation and Quality Control

Genotype data were generated with either the iCOGs⁷³ or OncoArray⁷⁴ SNP arrays. Both SNP arrays are customized and manufactured by Illumina. The iCOGS array consists of 211,155 SNPs, and the OncoArray array consists of 533,000 SNPs. For individuals genotyped by both SNP arrays, OncoArray data was used. Standard quality control filters of call rate, Hardy-Weinberg equilibrium and heterozygosity were applied to eliminate SNPs and samples with low quality as described elsewhere⁷⁵. Genotype data was imputed to 1000 Genomes phase 3 version 5 using *IMPUTE2*⁷⁶ to generate a shared set of SNPs between platforms for the subsequent analyses. Continuously coded genotype dosage, ranging between 0 and 2, was generated for imputed variants. SNPs with low imputation quality (INFO<0.3) or with a minor allele frequency (MAF)

less than 1% were excluded. Approximately 9.8 million variants passed the quality control process and were included in the association analysis. Genomic positions of the SNPs were based on Genome Reference Consortium GRCh37 (hg19).

Phenotype and Covariate Data

Quantitative MD data (DA, NDA and PMD) used in this study were measured using *CUMULUS*, a computer-assisted thresholding software⁷⁷. For each digitalized mammogram, a trained analyst first set the approximate gray-scale threshold level to define the edge of the breast. The software then calculates the number of pixels within the whole breast as well as within the dense breast region, which are utilized to calculate DA, NDA and PMD. Average MD measures of left and right breast were calculated as the outcome for controls when they were both available. Since tumor tissue is radiologically dense and appears light on the mammogram, only measures from tumor-free breast was used for breast cancer cases, in order to eliminate potential overestimation of DA and PMD. Breast cancer cases with MD measures collected only from tumor breast were removed from the study. Age and BMI at the time of mammogram collection were included as covariates in the GWAS. For the participants with missing BMI at mammogram (N=1,767), self-reported BMI within five years of mammogram collection was used as an approximate.

GWAS analysis

We conducted study-specific GWAS. For studies having samples genotyped with both iCOGS and OncoArray, we conducted one GWAS for each genotype array. We adopted a multivariate adjusted linear regression model to investigate the association between single nucleotide polymorphisms (SNPs) and each MD phenotype. Additive inheritance model was used throughout the analyses, with the estimated number of alleles coded continuously from 0 to 2. All MD phenotypes were square-root transformed before analysis. Age and BMI at mammogram, as well as the first ten principal components (PCs) representing population structure were included in each regression model as covariates. The association analyses were performed using R 3.6.1 (R Foundation).

Collected MD GWAS summary statistics

Most of the MD GWAS summary statistics collected for our meta-analysis came from a previous GWAS of MD phenotypes published in 2014⁶⁹. Detailed quality control and statistical analysis protocol have been described in the original publication. Genotype data were generated using various SNP arrays and imputed to 1000 Genomes Phase 1 v.3 or 1000 Genomes Phase 3.v.5 as reference panel, and then filtered to eliminate SNPs with low imputation quality ($INFO < 0.8$) and allele frequency ($MAF < 1\%$). Quality control, phenotype data collection and association analysis approach was otherwise identical to our GWAS as described above. Statistical analysis was conducted by study and further stratified by case/control status and genotype platform if the samples were genotyped by various SNP arrays. Beyond these, we further collected the GWAS results from 2,485 cancer-free populations from the Australian Mammographic Density Twins and Sisters Study (AMDTSS)⁷⁸. Quality control and imputation of genotype data, MD measurement, and association analysis protocol in AMDTSS study was identical to the other GWAS. In total, we collected study-specific summary statistics of MD GWAS from nine studies, based on a total number of 10,774 women of European ancestry.

Meta-Analysis

Sample-size weighted meta-analysis was then conducted using the marginal Z-statistics generated from the GWAS of each individual study, based on the ‘SAMPLESIZE’ scheme provided by the *METAL* software⁷⁹. To be included in the meta-analysis, a SNP needed to have a valid Z-statistic from at least three individual studies and a minimum sample size of 3,000. For each SNP, we used the Cochran’s Q statistic to test for the heterogeneity across studies. Regional association plot for each genome-wide significant locus in the meta-analysis was generated using the *LocusZoom* software⁸⁰.

Sensitivity Analysis

The majority of our study population were part of population-based or nested breast cancer case-control studies. To assess if any identified SNP-MD associations was an artifact resulting from oversampling of

breast cancer cases in our population, we replicated the association analysis for all genome-wide significant SNPs in controls only (N=21,234), as a sensitivity analysis. As mammographic NDA is strongly associated with BMI, we also assessed the association between significant NDA SNPs and BMI among 13,915 individuals with NDA, BMI, and genotype data available. The model was adjusted for the first 10 PCs.

Conditional Analysis

To quantify the number of independent signals in each significant GWAS locus, we performed a conditional analysis using the COndition and JOint analysis tool implemented in the Genome-wide Complex Trait Analysis software (*COJO-GCTA*)⁸¹. Since *COJO-GCTA* requires beta and standard error estimates, which were not available in our sample-size weighted meta-analysis data, we alternatively performed a standard error weighted meta-analysis with the normalized square-rooted MD phenotypes (per study, $[\text{sqrt-MD} - \text{mean}(\text{sqrt-MD})]/\text{stderr}(\text{sqrt-MD})$) as the outcomes. For each locus, we defined the lead SNP as the first independent signal, and performed the conditional analysis for SNPs located within +/- 500kb. The top-ranked SNP with conditional P-value $< 10^{-5}$ was added to the independent signal list, and the conditional analysis was run again for rest of the SNPs. The conditional analysis was halted when no SNP reached the threshold of conditional P-value $< 10^{-5}$. For the loci with multiple independent signals identified in the conditional analysis, all signals were annotated on the regional association plot.

Breast Cancer Association Analysis

We looked up the association between significant MD SNPs and breast cancer overall and by estrogen receptor (ER) status, using publicly available GWAS summary statistics⁷⁵ based on 122,977 cases and 105,974 controls of European ancestry. ER status was available for 90,969 cases, with 69,501 ER-positive and 21,468 ER-negative cases. We considered a SNP significantly associated with breast cancer if $p < 5.98 \times 10^{-4}$, conservatively adjusting for the multiple comparison of 117 tests (39 SNPs*3 breast cancer subtypes). We also assessed if known breast cancer SNPs (defined by 205 independent breast cancer loci⁸²) were associated with MD phenotypes.

SNP Heritability and Genetic Correlation Analysis

We used LD score regression to estimate the SNP-heritability (h^2_{SNP}) of MD phenotypes, which was defined as the proportion of phenotypic variance explained by additive effects of common SNPs⁸³. We further partitioned the h^2_{SNP} by 74 functional genomic categories⁸⁴, and estimated the heritability enrichment as the proportion of h^2_{SNP} in the category divided by the proportion of SNPs it occupied on the genome. We also quantified the genetic correlation between each MD phenotype and breast cancer subtype based on LD score regression⁸⁵, using the MD and breast cancer GWAS results⁷⁵.

Local Genetic Correlation Analysis

We estimated the local genetic correlation between MD phenotypes and overall breast cancer using ρHES ^{86; 87}, a Python-based bioinformatic package measuring the local heritability shared between traits across 1,703 independent genomic blocks. The blocks were defined based on linkage disequilibrium (LD) in European ancestry populations as previously described⁸⁸. We defined statistically significant local genetic correlation as $p < 0.05/1,703 = 2.94 \times 10^{-5}$.

Transcriptome-wide Association Analysis

We conducted a transcriptome-wide association analysis (TWAS) to estimate the association between imputed gene expression and MD phenotypes. We used genotype and gene expression data in mammary tissue from 396 individuals collected by the GTEx consortium (Release V8) to build gene-specific SNP prediction models of gene expression⁸⁹. Predictive models were built based on SNPs located +/- 500 kb of each gene, using four different approaches (BLUP⁹⁰, Elastic Net⁹¹, LASSO, and SuSiE⁹²). Gene-specific expression levels was then imputed with the model showing the highest predictive R-square based on cross-validation, as previously described. A total of 7,882 genes with nominally significant ($p\text{-value} < 0.01$) heritability were included in the association analysis with each MD phenotype. Since the genotype data released by the GTEx consortium was based on a different genomic build (GRCh38/hg38), we lifted over the MD GWAS summary statistics from hg19 to hg38 using the R-package ‘*liftOver*’ before running the

association analysis. Construction of predictive models and association analysis were performed using the R-based pipeline *FUSION*⁹³. A significance threshold of $p < 0.05/7,882 = 6.34 \times 10^{-6}$ was utilized to identify statistically significant associations between imputed gene expression level and MD phenotypes.

Fine-mapping

For each MD locus identified in the GWAS meta-analysis, we selected the SNPs located within +/- 500kb around the lead SNP and estimated the SNP-specific posterior probabilities (PP) of causality using ‘*PAINTOR*’ V3.0⁹⁴. *PAINTOR* is a Bayesian-based tool that prioritizes plausible causal variants through integrating association test statistics, LD structure and functional annotation data. Since there is very limited prior knowledge about MD heritability enrichment across functional annotations, we did not include any functional annotation as prior to avoid potential bias. The analyses were conducted under the assumption that there was only one causal variant per locus of interest. We used the European ancestry population in the 1000 Genomes phase 3 version 5 to generate the LD reference panel. For each MD locus, we ranked the variants by PP and reported a credible set covering 95% PP of being causal.

Results

GWAS identifies novel MD phenotypes loci

The sample size of individual-level GWAS data for DA, NDA and PMD was 13,805, 13,915, and 17,126, respectively. The study population was on average 56.6 years old and had an average BMI of 26.5 kg/m² at mammogram collection. Average measure of DA, NDA and PMD in the study population was 28.5 cm², 120.4 cm² and 23.4%, respectively (**Supplementary Table 1**). Age and BMI at mammogram, as well as the square-root transformed MD measures all approximately followed a normal distribution (**Supplementary Figure 1**).

We performed a sample-size weighted meta-analysis, using study-specific GWAS summary statistics. The sample sizes of the meta-analyses were 24,579 for DA, 24,689 for NDA, and 27,900 for PMD. Genomic

inflation factors (λ_{GC}) of the GWAS meta-analysis of MD phenotypes were between 1.11 and 1.13 (**Supplementary Figure 2**). LD score regression intercepts of three MD phenotypes were between 1.05 and 1.06, indicated that polygenicity partly accounted for the increase of test statistics.

We observed 28 distinct loci associated with at least one MD phenotype at p -value $< 5 \times 10^{-8}$ (**Table 1**, **Supplementary Figures 3-8**). Specifically, we identified 18 SNPs associated with DA, 6 SNPs associated with NDA, and 15 SNPs associated with PMD (**Figure 1**). Seven regions (1q21.2, 5q23.2, 5p35.1, 6q25.1, 11p15.5, 12q23.2, 19q13.33) were significantly associated with both DA and PMD. The 8q11.23 locus was associated with both NDA and PMD, while the 22q13.2 locus was associated with both DA and NDA. The 10q21.2 locus was associated with all three MD phenotypes. Lead SNPs of all genome-wide significant loci can combinedly explain 2.6%, 0.8% and 1.6% of the phenotypic variance for DA, NDA and PMD, suggesting that all three MD phenotypes are highly polygenic. Nine of the significant loci (5q11.2, 5q14.1, 5q31.1, 5q33.3, 5q35.1, 7p11.2, 8q24.13, 12p11.2, 16q12.2) have never been associated with MD phenotypes before.

We evaluated the association between significant loci and MD phenotypes among 21,234 controls as a sensitivity analysis (**Supplementary Table 3**). All SNPs remained statistically significant after Bonferroni correction at $p < 0.05/39 = 1.28 \times 10^{-3}$. None of the NDA SNPs showed a statistically significant association with BMI at $p < 0.05$ level using data on 13,915 women (**Supplementary Table 4**), suggesting that the SNP-NDA association was not due to residual confounding of BMI.

We performed conditional analyses for each genome-wide significant locus to identify any additional independent signals within each locus (**Supplementary Table 5**). Four DA loci (5q35.1, 10q21.2, 20q13.13, 22q13.2) and one NDA locus (8p11.23) showed evidence of two independent signals at a conditional p -value $< 10^{-5}$ level. None of the 15 PMD loci showed evidence of multiple independent signals.

Associations between MD SNPs and breast cancer risk

We assessed if identified MD SNPs were also associated with breast cancer. Out of the 28 loci, 14 were associated with at least one subtype of breast cancer (overall, ER-positive, and/or ER-negative) at genome-wide significance level (**Table 2**). An additional four other lead SNPs were significantly associated with at least one type of breast cancer, after Bonferroni correction, and three additional had a breast cancer association $p\text{-value} < 0.05$. For most SNPs, we observed consistent directions of effect for MD phenotypes and breast cancer associations (i.e., same direction for DA, PMD and breast cancer risk, and opposite direction for NDA and breast cancer risk). However, the lead SNPs for *1q21.2* and *2q14.2*, which were associated with both DA and PMD, showed opposite direction of effect between DA/PMD and breast cancer risk. Two other SNPs (*8q24.13*, *22q13.2*) with genome-wide significant associations for both DA and breast cancer had opposite directions as well. The *8q11.23* SNP had the same direction of effect on NDA and breast cancer, and opposite direction of effect between PMD and breast cancer risk. Some of these conflicting results have been observed previously⁶⁹.

We then selected all genome-wide significant SNPs for breast cancer (overall, ER-positive, and ER-negative)⁷⁵, and assessed their association with MD phenotypes (**Supplementary Figure 9**). Meanwhile, we also collected 205 independent breast cancer SNPs from previous publications⁸². We observed multiple associations between breast cancer SNPs and MD phenotypes, including the newly identified MD loci 12q22 and 16q12.2. At $p < 0.05$ level, 63 (30.7%) breast cancer SNPs were associated with DA, 36 (17.5%) with NDA, and 62 (30.2%) with PMD, respectively (**Supplementary Table 6**).

Genome-wide heritability analyses

We estimated the phenotypic variance attributable to common variants included in the HapMap 3 project based on our GWAS summary statistics as previously described⁸³. SNP-heritability (h^2_{SNP}) was estimated to 0.32 (se=0.036) for DA, 0.24 (se=0.030) for NDA, and 0.27 (se=0.029) for PMD. We then partitioned the h^2_{SNP} of MD phenotypes by functional annotations and tested their enrichment across 74 functional

genomic categories⁸⁴. Active enhancers marked by histone modification H3K27ac showed the most significant enrichment for all phenotypes (2.25-fold for DA, $p=7.10 \times 10^{-11}$; 2.11-fold for NDA, $p=9.71 \times 10^{-7}$ and 2.22-fold for PMD $p=7.71 \times 10^{-10}$, **Supplementary Table 7**)

We further quantified the genetic correlation between MD phenotypes and breast cancer risk (**Figure 2**). DA and PMD showed positive genetic correlations with overall breast cancer (DA: $r_g=0.24$, $p=1.11 \times 10^{-4}$; PMD: $r_g=0.29$, $p=1.90 \times 10^{-9}$), ER-positive subtype (DA: $r_g=0.21$, $p=2.59 \times 10^{-4}$; PMD: $r_g=0.26$, $p=4.71 \times 10^{-8}$), and ER-negative subtype (DA: $r_g=0.26$, $p=1.04 \times 10^{-3}$; PMD: $r_g=0.27$, $p=5.95 \times 10^{-5}$). In contrast, NDA showed a negative genetic correlation with breast cancer (overall: $r_g=-0.17$, $p=9.50 \times 10^{-4}$; ER-positive subtype: $r_g=-0.12$, $p=0.021$; ER-negative subtype: $r_g=-0.17$, $p=0.018$).

Local Genetic Correlation

We estimated the local genetic correlation between MD and overall breast cancer using ρ HESST, which partitioned the genome into 1,703 independent blocks based on the LD pattern in European populations. In total, we identified nine pairwise significant local genetic correlations between MD phenotypes and overall breast cancer (DA: 6q25.1, 10q21.2, 11p15.5, 12p11.2, 22q13.2; NDA: 8p11.23; PMD: 5q33.3, 6q25.1, 10q21.2) (**Supplementary Figure 10**). All regions with disproportionately high shared heritability harbored at least one MD genome-wide significant locus, and was highly consistent with our results for breast cancer associations with MD SNPs.

TWAS of MD phenotypes

We performed a TWAS investigating the association between imputed gene expression and MD phenotypes (**Supplementary Figure 11, Supplementary Tables 7-9**). Using the genotype and gene expression data in mammary tissue collected in the GTEx consortium ($N = 396$), we constructed predictive models for the expression of 7,882 genes with nominally significant heritability ($P < 0.01$). Association analysis suggested that genetically predicted expression of the MTMR11 gene was negatively associated with DA ($p=4.45 \times 10^{-11}$) and PMD ($p=3.05 \times 10^{-8}$), after adjusting for multiple comparisons. Additionally, imputed expression of

SMIM25 was positively associated with DA ($p=7.02 \times 10^{-8}$), while the NTN4 gene were negatively associated with NDA ($p=1.04 \times 10^{-10}$). Since these regions were also identified in our GWAS, the observed significant phenotype-genotype associations may partially be mediated through altered gene expression. Our TWAS further discovered four novel genes to be associated with MD phenotypes, including EP300 (negatively associated with DA: $p=6.89 \times 10^{-7}$), SHOX2 (negatively associated with NDA: $p=1.68 \times 10^{-6}$), RP11-419C23.1 (negatively associated with NDA: $p=4.15 \times 10^{-6}$), and CRISPLD2 (positively associated with PMD: $p=3.14 \times 10^{-6}$).

Fine-mapping

For each identified MD GWAS signal, we performed a fine-mapping analysis using *PAINTOR* V3.0 and generated a credible set covering 95% PP of causality per locus (**Supplementary Tables 10-12**). The 95% PP credible set of eight, two, and three loci for DA, NDA and PMD included five or less SNPs, respectively. In contrast, the largest size of 95% PP credible sets for DA, NDA and PMD was 168 (*22q13.2*), 99 (*22q13.1*) and 75 (*15q26.1*) SNPs, respectively.

Discussion

In this study, we conducted a meta-analysis of GWAS for three MD phenotypes among 27,900 European ancestry women. To date, it is the biggest GWAS of MD phenotypes. We identified 28 distinct loci that were associated with at least one MD phenotype at genome-wide significant level. Nine of these have not been previously reported to be associated with mammographic density. In addition, 14 of the 28 loci were also associated with the risk of overall, ER-positive and/or ER-negative breast cancer at genome-wide significant level. We also quantified the genetic correlation between MD phenotypes and breast cancer, which further confirmed the shared genetic basis between MD phenotypes and breast cancer risk. Using TWAS, we validated three GWAS loci and discovered four novel genes, whose imputed expression level was significantly associated with MD phenotypes. Finally, we conducted a fine-mapping analysis and enumerated a 95% credible set of potential causal variants for each GWAS locus.

Previous GWASs based on the BCAC population have identified 12 MD loci including *MTMR11* (1q21.2), *AREG* (4q13.3), *PRDM6* (5q23.2), *TAB2* (6q25.1), *ESR1* (6q25.1), *8p11.23*, *ZNF365* (10q21.2), *LSP1* (11p15.5), *IGF1* (12q23.2), *12q24*, *TMEM184B* (22q13.1), and *MKLI* (22q13.2)⁶⁷⁻⁷¹. A recent GWAS of MD based on 24,192 women further discovered 31 novel loci⁷². In addition, a recent GWAS investigating volumetric mammographic density revealed one novel locus for percent dense volume (*HABP2* at 10q25.3) and two loci for absolute dense volume (*INHBB* at 2q14.2, *LINC01483* at 17q24.3)⁹⁵. Our results were consistent with these previous findings, as 18 of the 28 significant loci identified in our analysis were confirmation of previous reported loci. Furthermore, the local genetic correlation analysis in our study highlighted specific loci (DA: *ESR1*, *ZNF365*, *LSP1* and *MKLI*; NDA: *8p11.23*; PMD: *ESR1* and *ZNF365*) which showed significant local genetic correlation between MD phenotypes and breast cancer. These regions are of particular interest when studying the shared genetic basis and identifying causal mechanisms between mammographic density and breast cancer.

Our study identified nine novel loci associated with at least one MD phenotype. The nearest gene of some of these identified signals have been previously associated with breast cancer. SNP rs11745230 is an intronic variant in the *EBF1* gene at chromosome 5q33.3, a highly conservative DNA-binding transcription factors which act as a crucial regulator during B-cell development⁹⁶. Genomic loss of the *EBF1* gene has been demonstrated to contribute to the pathogenesis, drug resistance and relapse of B-progenitor acute lymphoblastic leukemia⁹⁷, but the biological evidence supporting its tumor suppressive role in solid tumors is still preliminary. Previous fine-mapping analysis has identified rs7297051 as one of the four independent association signals of breast cancer at chromosome 12p11⁹⁸, which is approximately 50 kb upstream of the *PTHLH* gene. *PTHLH* encodes parathyroid hormone-related protein (PTHrP), which aids in normal mammary gland development⁹⁹. PTHrP has also been related to the prognosis of breast cancer, as its occasional secretion by tumor cells may promote osteoclastic activity and contribute to osteolytic bone metastases¹⁰⁰. SNP rs11646715 is located in the *FTO* gene at chromosome 16q12.2. The *FTO* gene encodes an mRNA demethylase and is well-known for its association with fat mass and obesity. Research has

indicated that *FTO* gene may play a role in cellular sensing of macronutrients and involved in the regulation of cell growth, which can at least partially explain its relationship with both obesity and breast cancer¹⁰¹. As we have appropriately adjusted for BMI in our GWAS model, the *FTO* gene may affect mammographic density and breast cancer using causal pathways other than its effect on adiposity. Future studies are essential to elucidate potential biological mechanisms that link these genes with mammographic density and breast cancer susceptibility.

The novel DA locus at chromosome *8q24* has previously been associated with multiple types of cancer, including breast¹⁰². Our sensitivity analysis results suggested its association with DA was unlikely an artifact incurred by the oversampling of breast cancer cases. Interestingly, the lead SNP at this locus (rs58847541) has an opposite direction of effect on DA and breast cancer, and it remains unclear how this region acts on mammographic dense area and breast cancer risk.

Previous studies have provided some evidence to support the association between other novel MD loci and breast density. Lead SNP rs150249911 at DA locus 5q11.2 is an intronic variant of the *ITGAI* gene. *ITGAI*-coded integrin $\alpha 1$ protein is upregulated following the expression of estrogen receptor β , a widely-found marker of breast cancer¹⁰³. SNP rs413472 (5q14.1) located in the *SSBP2* gene, which has previously been associated with breast cancer at suggestive level ($p=4.00 \times 10^{-5}$) based on a pilot GWAS in Indonesian women¹⁰⁴. SNP rs10155920 locates in a long non-coding RNA located downstream of the *EGFR* gene at chromosome 7p11.2. *EGFR* is one of the most well-studied signaling pathways that contribute to the invasion, dissemination, and metastasis of breast tumors¹⁰⁵.

Our TWAS identified seven genes whose imputed expression levels were significantly associated with MD phenotypes. Three of these (MTMR11, NTN4, and SMIM25) were also significant loci in the GWAS meta-analysis, which suggests that the observed genotype-phenotype association may be mediated through gene expression. Four additional genes, including SHOX2, RP11-419C23.1, CRISPLD2 and EP300, were also

associated with at least one MD phenotype, although no previous research supports this association. Future studies are thus needed to validate these findings.

Our study has several strengths. It is the largest GWAS of mammographic density to date. The expanded sample size enabled us to discover nine novel MD loci and generate robust GWAS summary statistics, which allowed us to conduct follow-up genome-wide analyses. The measurement error of the mammographic density phenotypes was minimized in our study, as quantitative measures were assessed by trained technicians using a computer-assisted thresholding software. Considering our study population included a considerable proportion of breast cancer cases, we performed a sensitivity analysis among controls, which reaffirmed that all significant genotype-phenotype associations discovered were not spurious artifacts due to oversampling of cases. Our study also has limitations. We lack statistical power to investigate the associations for rare variants ($MAF < 1\%$). A major weakness with our study is the lack of diversity in our study population as it only included European ancestry women. Considering that the risk of breast cancer attributable to mammographic density is heterogeneously distributed by race/ethnicity¹⁰⁶, future efforts should collect mammograms and genotype data in racially diverse populations.

In summary, we conducted a GWAS of MD phenotypes in up to 27,900 European ancestry women. We identified 28 loci showing genome-wide significant associations with at least one MD phenotype, including nine novel loci. Four novel MD loci have previously been reported as susceptibility loci for breast cancer. Genetic correlation analyses fortified the shared genetic basis between MD phenotypes and breast cancer risk, and also highlighted specific shared loci.

TABLES AND FIGURES

Table 2.1. Lead SNPs of the genome-wide significant loci identified in the GWAS meta-analysis of mammographic dense area (DA), non-dense area (NDA) and percent mammographic density (PMD)

Region	rs ID	Chromosome	Position ¹	Gene	Allele ²	MAF ³	Z-score ⁴	P-value	Novel Locus ⁵
<i>DA Allele (N = 18)</i>									
1q21.2	rs11205303	1	149906413	MTMR11	T/C	0.369	-6.772	1.25E-11	No
2q14.2	rs17625845	2	121089731	INHBB	T/C	0.221	7.949	1.87E-15	No
4q13.3	rs6851733	4	75518708	AREG	T/C	0.226	6.874	6.23E-12	No
5q11.2	rs150249911	5	52119132	ITGA1	A/G	0.018	-5.928	3.06E-09	Yes
5q23.2	rs335189	5	122446856	PRDM6	C/G	0.265	6.655	2.84E-11	No
5q35.1	rs2042239	5	169566329	DOCK2	A/G	0.354	6.485	8.87E-09	Yes
6q25.1	rs9397436	6	151952002	ESR1	A/G	0.073	7.951	1.86E-15	No
7p11.2	rs10155920	7	55308930	ELDR	T/C	0.145	5.755	8.66E-09	Yes
8q24.13	rs58847541	8	124610166	-	A/G	0.153	5.994	2.05E-09	Yes
10q21.2	rs10995187	10	64273026	ZNF365	A/G	0.148	8.933	4.14E-19	No
11p15.5	rs4980383	11	1902097	LSP1	T/C	0.451	-7.228	4.90E-13	No
12p12.1	rs11836164	12	26446625	SSPN/ITPR2	T/C	0.248	6.028	1.66E-09	No
12p11.2	rs7297051	12	28174817	PTHLH	T/C	0.233	6.166	7.01E-10	Yes
12q23.2	rs833472	12	103005100	IGF1	T/C	0.032	7.134	9.76E-13	No
19q13.33	rs1231281	19	49239200	FUT2/MAMSTR	A/G	0.458	6.860	6.87E-12	No
20q13.13	rs17789629	20	48892374	SMIM25	A/C	0.137	-5.478	4.30E-08	No
22q13.1	rs34066050	22	38612604	TMEM184B	A/G	0.467	-5.534	3.14E-08	No
22q13.2	rs6001939	22	40892794	MKL1	T/C	0.102	8.791	1.48E-18	No
<i>NDA Allele (N = 6)</i>									
1p12	rs78395856	1	119495096	TBX15	A/C	0.046	5.525	3.29E-08	No
5q14.1	rs413472	5	80930992	SSBP2	T/C	0.445	5.551	2.84E-08	Yes
8p11.23	rs16885613	8	36848357	-	T/C	0.148	-12.788	1.92E-37	No
10q21.2	rs2138555	10	64220494	ZNF365	A/G	0.419	5.900	3.63E-09	No
12q22	rs61938093	12	96026737	NTN4	T/C	0.290	-6.266	3.72E-10	No
22q13.2	rs73169097	22	41027870	MKL1	T/C	0.100	6.012	1.83E-09	No
<i>PMD Allele (N = 15)</i>									
1q21.2	rs1868992	1	149908108	MTMR11	A/G	0.259	5.517	3.44E-08	No
5q23.2	rs335189	5	122446856	PRDM6	C/G	0.265	6.196	5.78E-10	No
5q31.1	rs76876329	5	131237759	MEIKIN	T/C	0.151	5.530	3.21E-08	Yes
5q33.3	rs11745230	5	158171008	EBF1	T/G	0.166	-5.793	6.90E-09	Yes
5q35.1	rs2112670	5	169557594	FOXI1	A/G	0.345	-5.598	2.17E-08	Yes
6p22.3	rs3819405	6	16399557	ATXN1	T/C	0.340	5.806	6.42E-09	No
6q25.1	rs4897107	6	149601591	TAB2	T/C	0.162	6.842	7.81E-12	No
6q25.1	rs9397436	6	151952002	ESR1	A/G	0.073	7.303	2.81E-13	No
8p11.23	rs10087804	8	36858140	-	C/G	0.142	6.282	3.35E-10	No
10q21.2	rs10995187	10	64273026	ZNF365	A/G	0.148	10.424	1.92E-25	No
11p15.5	rs4980383	11	1902097	LSP1	T/C	0.451	-5.860	4.62E-09	No
12q23.2	rs61941038	12	102989316	IGF1	A/T	0.033	-6.477	9.37E-11	No

15q26.1	rs4499190	15	94275057	-	G/C	0.341	-5.654	1.57E-08	No
16q12.2	rs11646715	16	53824007	FTO	A/G	0.456	7.183	6.84E-13	Yes
19q13.33	rs12462111	19	49171306	FUT2/MAMSTR	T/C	0.427	5.847	5.02E-09	No

¹Genomic positions based on build GRCh37/hg19

²Coded as reference allele/effect allele

³Minor Allele Frequencies, based on the European Ancestry population in the 1000 Genome project

⁴Zscores were obtained using the sample size weighted meta-analysis of GWASs. The multivariate adjusted linear regression model used in GWAS analysis adjusted for age and BMI at mammogram, as well as the first ten principle components representing population structure. Additive inheritance model was used. Square-root transformed mammographic density phenotype was used as the outcome variable in the corresponding GWAS model

⁵Whether the locus has never been reported to be associated with MD phenotypes in previous publications

Table 2.2. Association between MD significant loci and breast cancer risk (overall, ER-positive, and ER-negative)

Region	rs ID	CHR	Position ¹	Allele ²	MD Phenotype		Overall Breast Cancer ⁴			ER-positive Breast Cancer ⁴			ER-negative Breast Cancer ⁴		
					Z-score	P-value	Beta	SE ³	P-value ⁵	Beta	SE	P-value	Beta	SE	P-value
<i>DA Allele</i>															
1q21.2	rs11205303	1	149906413	T/C	-6.772	1.25E-11	0.050	0.006	1.05E-14	0.057	0.008	8.25E-14	0.040	0.012	6.67E-04
2q14.2	rs17625845	2	121089731	T/C	7.949	1.87E-15	-0.046	0.008	1.73E-08	-0.032	0.010	8.94E-04	-0.114	0.015	1.13E-13
4q13.3	rs6851733	4	75518708	T/C	6.874	6.23E-12	0.009	0.008	2.20E-01	0.001	0.009	9.58E-01	0.018	0.014	1.97E-01
5q11.2	rs150249911	5	52119132	A/G	-5.928	3.06E-09	0.038	0.027	1.49E-01	0.048	0.032	1.33E-01	0.053	0.050	2.87E-01
5q23.2	rs335189	5	122446856	C/G	6.655	2.84E-11	0.027	0.007	8.38E-05	0.026	0.008	1.46E-03	0.012	0.012	3.32E-01
5q35.1	rs2042239	5	169566329	A/G	6.485	8.87E-09	0.028	0.006	9.80E-06	0.037	0.008	1.02E-06	0.003	0.012	7.72E-01
6q25.1	rs9397436	6	151952002	A/G	7.951	1.86E-15	0.184	0.012	2.00E-54	0.138	0.014	1.71E-22	0.272	0.021	4.01E-40
7p11.2	rs10155920	7	55308930	T/C	5.755	8.66E-09	0.011	0.008	2.01E-01	0.012	0.010	2.50E-01	-0.001	0.015	9.35E-01
8q24.13	rs58847541	8	124610166	A/G	5.994	2.05E-09	-0.063	0.009	4.33E-13	-0.055	0.010	1.17E-07	-0.077	0.016	1.00E-06
10q21.2	rs10995187	10	64273026	A/G	8.933	4.14E-19	0.129	0.009	2.85E-49	0.134	0.011	1.74E-37	0.092	0.016	8.18E-09
11p15.5	rs4980383	11	1902097	T/C	-7.228	4.90E-13	-0.076	0.006	4.36E-34	-0.083	0.007	6.20E-29	-0.051	0.011	8.31E-06
12p12.1	rs11836164	12	26446625	T/C	6.028	1.66E-09	-0.013	0.007	6.81E-02	-0.003	0.009	7.32E-01	-0.025	0.013	5.78E-02
12p11.2	rs7297051	12	28174817	T/C	6.166	7.01E-10	0.120	0.007	1.73E-60	0.110	0.009	3.49E-36	0.140	0.014	6.45E-25
12q23.2	rs833472	12	103005100	T/C	7.134	9.76E-13	0.078	0.020	7.59E-05	0.085	0.024	3.04E-04	0.049	0.037	1.80E-01
19q13.33	rs1231281	19	49239200	A/G	6.860	6.87E-12	-0.008	0.006	2.30E-01	-0.010	0.008	2.07E-01	-0.002	0.012	8.72E-01
20q13.13	rs17789629	20	48892374	A/C	-5.478	4.30E-08	-0.011	0.008	1.32E-01	-0.001	0.009	9.48E-01	-0.034	0.014	1.44E-02
22q13.1	rs34066050	22	38612604	A/G	-5.534	3.14E-08	-0.034	0.006	5.58E-08	-0.042	0.008	2.35E-08	-0.010	0.011	3.78E-01
22q13.2	rs6001939	22	40892794	T/C	8.791	1.48E-18	-0.117	0.010	1.31E-32	-0.106	0.012	1.20E-19	-0.115	0.018	8.77E-11
<i>NDA Allele</i>															
1p12	rs78395856	1	119495096	A/C	5.525	3.29E-08	-0.037	0.018	3.46E-02	-0.044	0.021	3.31E-02	-0.037	0.031	2.35E-01
5q14.1	rs413472	5	80930992	T/C	5.551	2.84E-08	0.004	0.006	5.49E-01	0.010	0.008	2.11E-01	-0.012	0.012	3.18E-01
8p11.23	rs16885613	8	36848357	T/C	-12.788	1.92E-37	-0.076	0.008	1.58E-20	-0.070	0.010	5.06E-13	-0.099	0.015	2.38E-11
10q21.2	rs2138555	10	64220494	A/G	5.900	3.63E-09	-0.044	0.006	1.48E-12	-0.047	0.008	3.89E-10	-0.030	0.011	8.58E-03
12q22	rs61938093	12	96026737	T/C	-6.266	3.72E-10	0.089	0.007	1.34E-38	0.091	0.008	5.53E-28	0.069	0.013	3.39E-08
22q13.2	rs73169097	22	41027870	T/C	6.012	1.83E-09	-0.120	0.010	1.98E-34	-0.110	0.012	5.34E-21	-0.117	0.018	4.33E-11
<i>PMD Allele</i>															
1q21.2	rs1868992	1	149908108	A/G	5.517	3.44E-08	-0.027	0.007	1.64E-04	-0.029	0.008	7.09E-04	-0.030	0.013	1.98E-02
5q23.2	rs335189	5	122446856	C/G	6.196	5.78E-10	0.027	0.007	8.38E-05	0.026	0.008	1.46E-03	0.012	0.012	3.32E-01
5q31.1	rs76876329	5	131237759	T/C	5.530	3.21E-08	0.012	0.009	1.87E-01	0.007	0.011	5.11E-01	0.014	0.017	3.99E-01
5q33.3	rs11745230	5	158171008	T/G	-5.793	6.90E-09	-0.064	0.008	1.30E-14	-0.065	0.010	3.47E-11	-0.068	0.015	6.72E-06
5q35.1	rs2112670	5	169557594	A/G	-5.598	2.17E-08	-0.013	0.006	4.71E-02	-0.023	0.008	2.83E-03	0.012	0.012	3.03E-01
6p22.3	rs3819405	6	16399557	T/C	5.806	6.42E-09	0.040	0.007	1.25E-08	0.045	0.008	5.38E-08	0.027	0.013	3.45E-02
6q25.1	rs4897107	6	149601591	T/C	6.842	7.81E-12	0.036	0.008	5.98E-06	0.049	0.010	3.55E-07	0.018	0.015	2.15E-01
6q25.1	rs9397436	6	151952002	A/G	7.303	2.81E-13	0.184	0.012	2.00E-54	0.138	0.014	1.71E-22	0.272	0.021	4.01E-40
8p11.23	rs10087804	8	36858140	C/G	6.282	3.35E-10	-0.077	0.008	8.34E-21	-0.071	0.010	3.64E-13	-0.098	0.015	6.55E-11
10q21.2	rs10995187	10	64273026	A/G	10.424	1.92E-25	0.129	0.009	2.85E-49	0.134	0.011	1.74E-37	0.092	0.016	8.18E-09
11p15.5	rs4980383	11	1902097	T/C	-5.860	4.62E-09	-0.076	0.006	4.36E-34	-0.083	0.007	6.20E-29	-0.051	0.011	8.31E-06
12q23.2	rs61941038	12	102989316	A/T	-6.477	9.37E-11	-0.075	0.020	1.47E-04	-0.085	0.024	3.07E-04	-0.032	0.037	3.86E-01
15q26.1	rs4499190	15	94275057	G/C	-5.654	1.57E-08	-0.001	0.007	8.90E-01	0.001	0.009	8.71E-01	-0.008	0.013	5.69E-01
16q12.2	rs11646715	16	53824007	A/G	7.183	6.84E-13	0.046	0.006	6.89E-13	0.042	0.008	4.14E-08	0.055	0.012	1.60E-06

19q13.33	rs12462111	19	49171306	T/C	5.847	5.02E-09	-0.017	0.007	1.03E-02	-0.015	0.008	5.32E-02	-0.011	0.012	3.51E-01
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¹Genomic positions based on build GRCh37/hg19

²Coded as reference allele/effect allele

³Standard Error

⁴Beta estimates, SEs, and P-values of overall, ER-positive, and ER-negative breast cancer were based on the GWAS results published by the Breast Cancer Association Consortium (BCAC)

⁵***Bold-italics*** font denotes the statistically significant association of p-value less than 5.98E-04, which adjust for the multiple comparison of 117 tests (39 SNPs*3 breast cancer types).

Figure 2.1. Manhattan plots of the GWAS meta-analysis results of mammographic (a) dense area (DA, N = 19,416), (b) non-dense area (NDA, N=19,512), and (c) percent mammographic density (PMD, N=21,663). P-value thresholds for genome-wide significance ($p < 5 \times 10^{-8}$, red line) and suggestive significance ($p < 10^{-5}$, blue line) are shown as horizontal lines.

Figure 2.1a. Manhattan plot of the GWAS meta-analysis results of DA

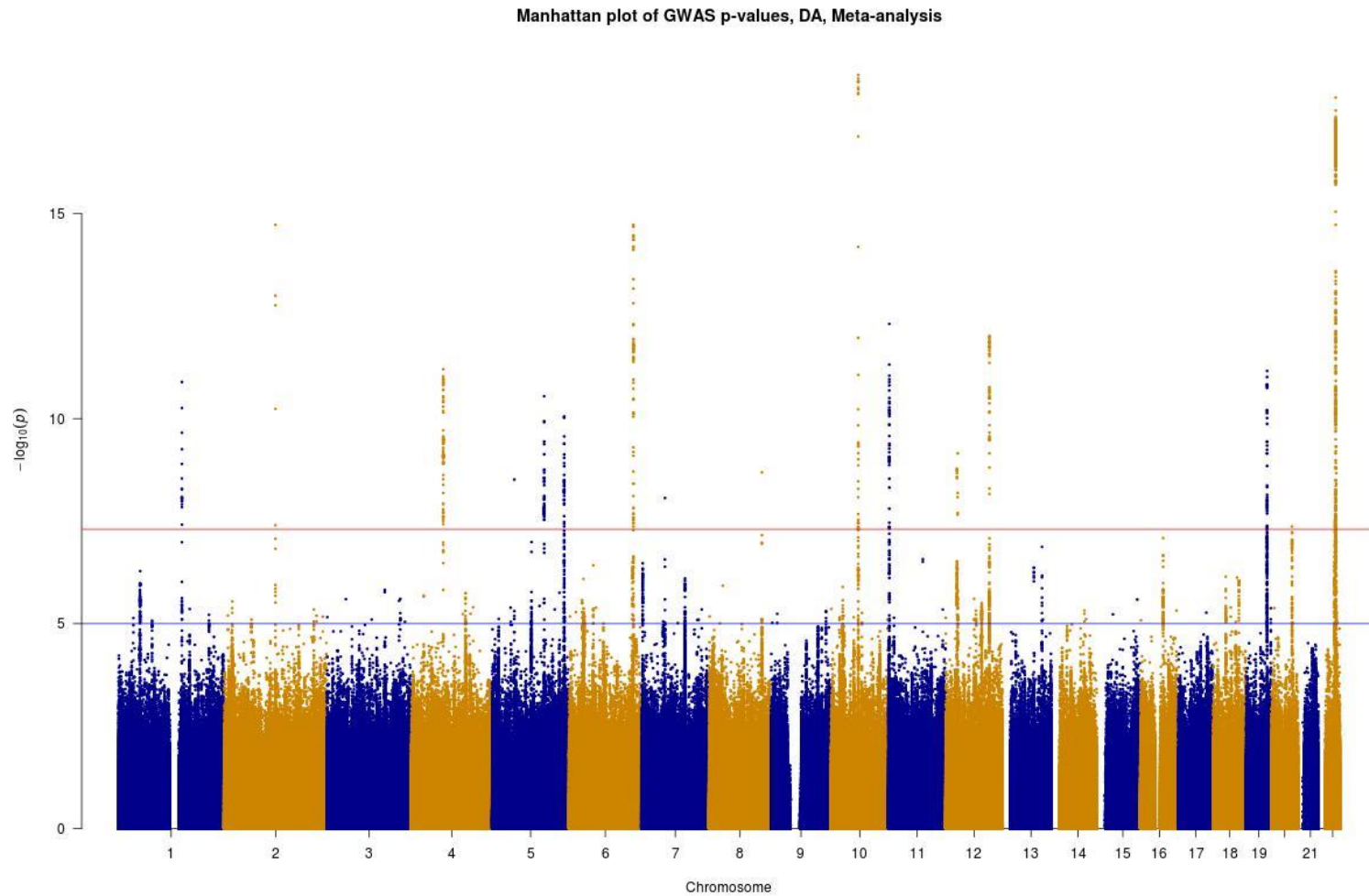


Figure 2.1b. Manhattan plot of the GWAS meta-analysis results of NDA

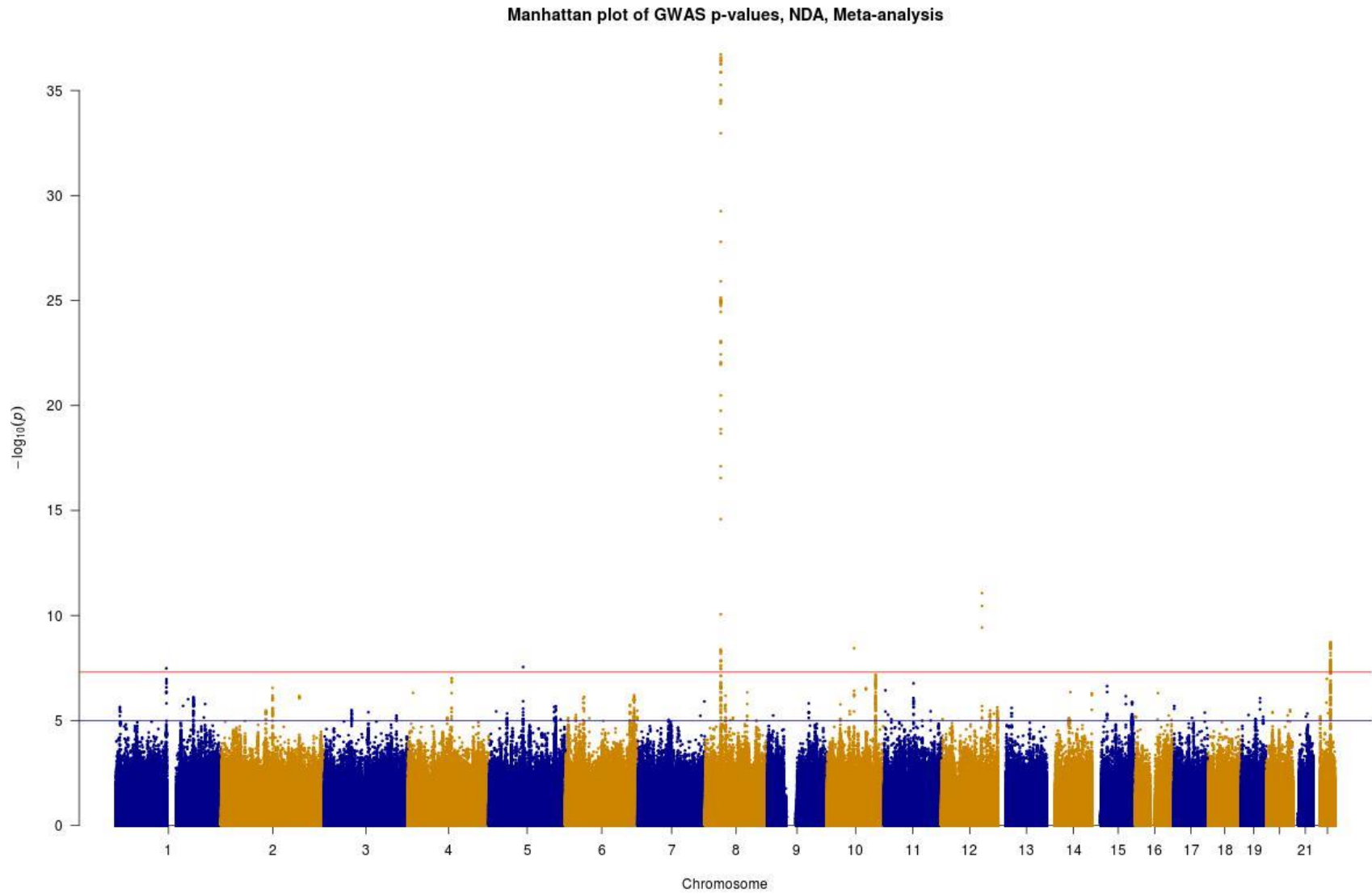


Figure 2.1c. Manhattan plot of the GWAS meta-analysis results of PMD

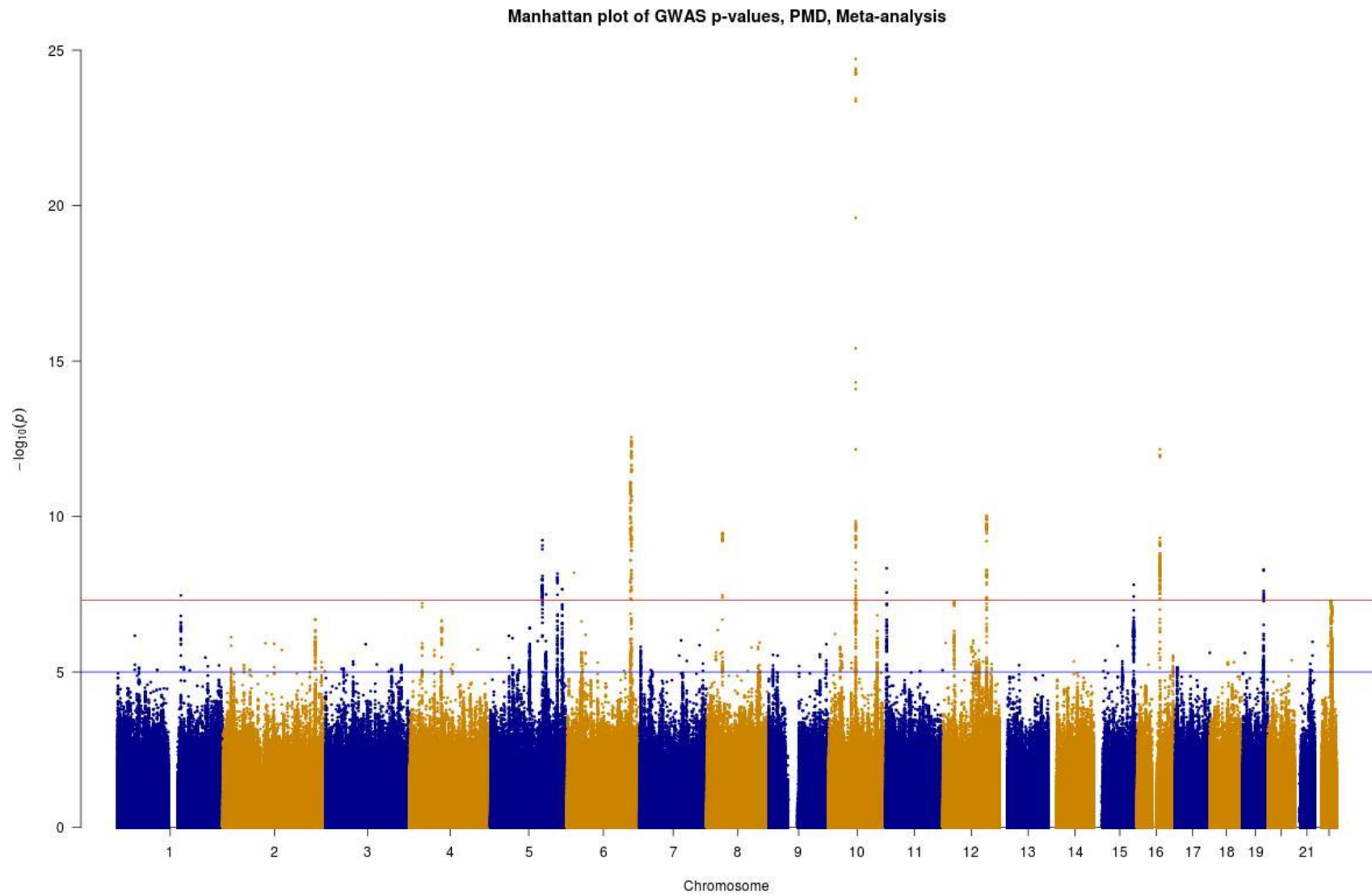


Figure 2.2. Genetic correlation between mammographic phenotypes (DA, NDA, PMD) and breast cancer (overall, ER-positive, and ER-negative), estimated by LD score regression.

	Overall BrCa	ER-positive BrCa	ER-negative BrCa
Dense Area	0.239 (P = 1.11E-04)	0.211 (P = 2.59E-04)	0.255 (P = 1.04E-03)
Nondense Area	-0.166 (P = 9.50E-04)	-0.122 (P = 2.09E-02)	-0.166 (P = 1.76E-02)
Percent Density	0.292 (P = 1.90E-09)	0.257 (P = 4.71E-08)	0.269 (P = 5.95E-05)

Genetic Correlation -0.5 0 0.5

CONCLUSION

In this dissertation, we aimed to investigate mammographic density (MD) as an intermediate phenotype of breast cancer, from both environmental and genetic perspectives. To achieve this aim, we conducted two in-depth analyses: one focused on the heterogeneous association between MD and breast cancer risk in the population, the other tried to identify genetic loci associated with MD measures.

Specifically, we first comprehensively investigated interactions between MD measures (DA, NDA, PMD) and established breast cancer risk factors in relation to invasive breast cancer risk overall and stratified by menopausal and ER status. After adjusting for multiple testing, no interaction remained statistically significant. However, we did observe some noteworthy interactions with unadjusted $p < 0.05$. For the risk of overall breast cancer, we observed interactions between nulliparity and PMD/NDA, age at menarche and DA, and BMI and NDA. Individual nominally significant interactions across MD measures and risk factors were also observed in analyses stratified by either menopausal or ER status. Our study covered thirteen established risk factors of breast cancer, and was the first investigation of its kind that stratified the analysis by menopausal status and cancer molecular subtype. The results of our study, if confirmed, shed lights for a better understanding the association between breast composition and breast cancer risk, and provide novel insights into the possibility of identifying women with especially high risk of developing breast cancer.

In the second chapter, we reported a meta-analysis of GWAS for the three MD measures in up to 27,900 women of European ancestry. We identified twenty-eight distinct genome-wide significant loci for MD measures, including nine novel signals (*5q11.2*, *5q14.1*, *5q31.1*, *5q33.3*, *5q35.1*, *7p11.2*, *8q24.13*, *12p11.2*, *16q12.2*) that have never been reported before. Lead SNPs of genome-wide significant signals together explain 2.6%, 0.8% and 1.6% of the phenotypic variance for DA, NDA and PMD, respectively. Fourteen identified MD loci were also significantly associated with the risk of overall, ER-positive and/or ER-negative breast cancer. By conducting secondary exploratory bioinformatic analyses, including genetic correlation quantification, heritability partitioning, fine-mapping and transcriptome-wide association study,

we enhanced the understanding of genetic architecture of this complex trait, and expanded the evidence of its shared genetic basis with breast cancer.

A limitation with current research on MD is the lack of diversity in population studied, as studies to date have almost exclusively focused on European ancestry population. We would like to collect mammograms and genotype data in racially diverse populations to see if we can replicate our findings and discover additional MD loci.

Breast cancer is the most common cancer type among the women in the US, and mammographic density is one of the strongest risk factors of the disease. We hope our findings add to the knowledge of the biological and genetic background of mammographic density, help identify a subset of the population with elevated risk of breast cancer, and ultimately help mitigate the disease burden.

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Supplementary Tables and Figures

Supplementary Table 1.1 Distribution of established breast cancer risk factors, by breast cancer case status, among 2,137 cases and 4,346 controls.

Risk Factors	Cases (N = 2,137)	Controls (N = 4,346)	P-value ¹
<u>Continuous Variables, Mean (SD)</u>			
PMD, %	32.9 (19.1)	27.2 (18.3)	< 0.001
DA, cm ²	45.7 (31.0)	37.0 (28.5)	< 0.001
NDA, cm ²	109.6 (70.4)	120.8 (76.8)	< 0.001
BMI, kg/m ²	26.3 (5.2)	26.4 (5.5)	0.66
Alcohol Consumption, g/day	5.4 (9.1)	5.1 (8.4)	0.12
Physical Activity, MET/week	18.3 (20.5)	19.4 (23.0)	0.06
Age at menarche, yrs	12.4 (1.5)	12.4 (1.5)	0.07
Age at first birth ² , yrs	25.7 (4.0)	25.5 (3.8)	0.02
Age at menopause ³ , yrs	49.7 (4.2)	49.2 (4.6)	0.001
<u>Categorical Variables, Frequency (%)</u>			
Smoking Status			0.07
Never	1139 (53.4)	2425 (55.9)	
Past	844 (39.6)	1587 (36.6)	
Current	150 (7.0)	324 (7.5)	
Menopausal Status			0.001
Premenopausal	564 (26.9)	1315 (30.8)	
Postmenopausal	1530 (73.1)	2951 (69.2)	
Race			0.17
White	2047 (95.8)	4193 (96.5)	
non-White	90 (4.2)	153 (3.5)	
Family History			< 0.001
Yes	376 (18.8)	552 (13.1)	
No	1623 (81.2)	3645 (86.9)	
Benign Breast Disease			< 0.001
Yes	696 (32.6)	1052 (24.2)	
No	1441 (67.4)	3294 (75.8)	
Nulliparous			0.18
Yes	251 (11.9)	465 (10.8)	
No	1853 (88.1)	3843 (89.2)	
Parity ²			0.65
1	208 (11.2)	412 (10.7)	
2	652 (35.2)	1397 (36.4)	
3+	993 (53.6)	2034 (52.9)	
Breast Feeding History ²			0.59
Yes	1349 (73.7)	2811 (74.4)	
No	482 (26.3)	970 (25.7)	
Postmenopausal Hormone Use ³			< 0.001
Never	326 (21.5)	771 (26.3)	
Past	313 (20.7)	700 (23.9)	
Current	875 (57.8)	1459 (49.8)	

¹P-values were calculated using two-sample T test for continuous variables, and χ^2 test for categorical variables. All tests were two-sided.

²Analysis conducted among parous women only.

³Analysis conducted among postmenopausal women only.

Supplementary Table 1.2 Effect of categorized and continuous mammographic density measures (PMD, DA and NDA) on risk of invasive breast cancer and by menopausal status.

	Crude OR	95% CI	P-value	Adjusted OR¹	95% CI	P-value
<i>Overall Breast Cancer</i>						
PMD						
< 10	0.72	0.60-0.86	<0.001	0.68	0.55-0.83	0.002
10-24	1.00	reference		1.00	reference	
25-49	1.55	1.37-1.76	< 0.001	1.75	1.52-2.03	< 0.001
>= 50	1.85	1.57-2.16	< 0.001	2.21	1.83-2.66	< 0.001
Continuous	1.016	1.013-1.019	< 0.001	1.020	1.017-1.024	< 0.001
DA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	1.45	1.23-1.71	< 0.001	1.52	1.26-1.83	< 0.001
3 rd Quartile	1.69	1.44-1.98	< 0.001	1.87	1.56-2.24	< 0.001
4 th Quartile	2.40	2.06-2.80	< 0.001	2.53	2.12-3.01	< 0.001
Continuous	1.010	1.008-1.012	< 0.001	1.010	1.008-1.012	< 0.001
NDA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	0.83	0.72-0.95	< 0.001	0.77	0.66-0.89	< 0.001
3 rd Quartile	0.73	0.63-0.84	< 0.001	0.64	0.54-0.75	< 0.001
4 th Quartile	0.65	0.56-0.76	< 0.001	0.52	0.43-0.64	< 0.001
Continuous	0.998	0.997-0.999	< 0.001	0.997	0.996-0.998	< 0.001
<i>Premenopausal Breast Cancer</i>						
PMD						
< 10	0.66	0.43-1.01	0.05	0.56	0.34-0.91	0.02
10-24	1.00	reference		1.00	reference	
25-49	1.75	1.35-2.27	< 0.001	1.94	1.44-2.63	< 0.001
>= 50	1.75	1.30-2.36	< 0.001	2.14	1.50-3.06	< 0.001
Continuous	1.015	1.010-1.020	< 0.001	1.018	1.011-1.024	< 0.001
DA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	1.51	1.09-2.09	0.01	1.67	1.15-2.43	0.007
3 rd Quartile	1.99	1.45-2.72	< 0.001	2.34	1.62-3.36	< 0.001
4 th Quartile	2.75	2.03-3.73	< 0.001	3.01	2.13-4.26	< 0.001
Continuous	1.012	1.009-1.016	< 0.001	1.011	1.007-1.016	< 0.001
NDA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	0.87	0.66-1.14	0.31	0.92	0.69-1.24	0.59
3 rd Quartile	0.75	0.56-0.99	0.04	0.69	0.50-0.96	0.03
4 th Quartile	0.69	0.52-0.91	0.01	0.60	0.41-0.90	0.01
Continuous	0.998	0.997-1.000	0.009	0.997	0.994-0.999	0.002
<i>Postmenopausal Breast Cancer</i>						
PMD						
< 10	0.75	0.61-0.93	0.007	0.73	0.57-0.93	0.01
10-24	1.00	reference		1.00	reference	
25-49	1.66	1.41-1.97	< 0.001	1.76	1.45-2.13	< 0.001
>= 50	2.40	1.90-3.03	< 0.001	2.50	1.90-3.29	< 0.001
Continuous	1.021	1.017-1.025	< 0.001	1.023	1.018-1.028	< 0.001
DA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	1.34	1.07-1.67	0.01	1.32	1.03-1.70	0.03
3 rd Quartile	1.75	1.42-2.17	< 0.001	1.74	1.36-2.22	< 0.001
4 th Quartile	2.57	2.10-3.15	< 0.001	2.48	1.96-3.13	< 0.001
Continuous	1.012	1.010-1.014	< 0.001	1.011	1.008-1.014	< 0.001

NDA						
1 st Quartile	1.00	reference		1.00	reference	
2 nd Quartile	0.71	0.59-0.86	<0.001	0.69	0.56-0.86	0.001
3 rd Quartile	0.63	0.52-0.76	< 0.001	0.61	0.49-0.77	< 0.001
4 th Quartile	0.60	0.50-0.73	< 0.001	0.55	0.42-0.72	< 0.001
Continuous	0.997	0.996-0.998	< 0.001	0.997	0.995-0.998	< 0.001

¹Multivariate adjusted logistic regression models were adjusted for the following covariates: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

Supplementary Table 1.3. Associations of percent mammographic density, absolute dense and non-dense area with invasive breast cancer risk by breast cancer risk factors, among 2,137 cases and 4,346 controls¹.

<i>Percent Density</i>		< 10%		10 - 25% (Ref.)		25 - 49%		≥50%		P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)			
Age at Menarche, yrs											
< 12	69/221	0.84 (0.57-1.24)	137/377	1.00 (Ref)	234/328	2.59 (1.91-3.53)	83/97	3.55 (2.34-5.37)	< 0.0001	0.07	
12-13	118/425	0.66 (0.50-0.87)	332/840	1.00 (Ref)	541/888	1.68 (1.39-2.04)	249/350	1.96 (1.53-2.50)	< 0.0001		
> 13	34/139	0.48 (0.28-0.81)	94/225	1.00 (Ref)	159/319	1.17 (0.81-1.70)	75/122	1.57 (0.99-2.48)	0.0002		
Alcohol Consumption, g/day											
0	98/305	0.73 (0.54-1.00)	217/530	1.00 (Ref)	301/459	1.76 (1.38-2.25)	114/180	1.93 (1.39-2.68)	< 0.0001	0.60 <i>Categorical</i>	
0-5	62/257	0.60 (0.42-0.87)	165/429	1.00 (Ref)	269/517	1.44 (1.11-1.87)	153/171	2.62 (1.89-3.61)	< 0.0001		
≥ 5	52/166	0.66 (0.42-1.02)	131/370	1.00 (Ref)	300/452	2.08 (1.58-2.74)	125/186	2.04 (1.44-2.89)	< 0.0001		
History of Benign Breast Disease											
No	178/642	0.69 (0.54-0.87)	406/1140	1.00 (Ref)	626/1125	1.84 (1.54-2.20)	231/387	2.01 (1.59-2.54)	< 0.0001	0.39	
Yes	43/146	0.61 (0.39-0.95)	161/308	1.00 (Ref)	312/416	1.53 (1.15-2.03)	180/182	2.37 (1.69-3.32)	< 0.0001		
Body Mass Index, kg/m²											
< 25	28/153	0.54 (0.33-0.88)	184/577	1.00 (Ref)	498/918	1.80 (1.43-2.25)	292/430	2.21 (1.71-2.85)	< 0.0001	0.86 <i>Categorical</i>	
25-30	84/275	0.69 (0.50-0.97)	219/492	1.00 (Ref)	301/437	1.55 (1.21-1.99)	89/101	2.00 (1.39-2.88)	< 0.0001		
≥ 30	105/350	0.74 (0.53-1.03)	150/359	1.00 (Ref)	120/158	2.00 (1.41-2.84)	28/30	2.06 (1.09-3.87)	< 0.0001		
First-Degree of Family History of Breast Cancer											
No	164/658	0.64 (0.51-0.80)	421/1212	1.00 (Ref)	731/1289	1.77 (1.50-2.08)	307/486	2.11 (1.72-2.60)	< 0.0001	0.41	
Yes	40/83	0.85 (0.52-1.41)	106/186	1.00 (Ref)	160/212	1.61 (1.11-2.33)	70/71	2.41 (1.48-3.91)	< 0.0001		
Nulliparity											
Nulliparous	15/76	0.33 (0.15-0.71)	53/125	1.00 (Ref)	119/188	1.60 (1.00-2.56)	64/76	2.69 (1.54-4.70)	< 0.0001	0.048*	
Parous	200/706	0.72 (0.58-0.89)	507/1309	1.00 (Ref)	802/1337	1.77 (1.51-2.07)	344/491	2.10 (1.71-2.57)	< 0.0001		
Parity²											
1	15/69	0.73 (0.33-1.59)	38/126	1.00 (Ref)	108/155	2.70 (1.58-4.60)	47/62	2.93 (1.53-5.62)	< 0.0001	0.52	
2	62/221	0.70 (0.48-1.02)	170/464	1.00 (Ref)	275/497	1.57 (1.20-2.06)	145/215	1.82 (1.32-2.51)	< 0.0001		
3+	123/416	0.71 (0.53-0.94)	299/719	1.00 (Ref)	419/685	1.75 (1.41-2.17)	152/214	2.14 (1.60-2.88)	< 0.0001		
Age at 1st Child, yrs²											
≤ 25.5	124/435	0.78 (0.59-1.04)	293/802	1.00 (Ref)	465/752	1.95 (1.58-2.39)	188/265	2.36 (1.79-3.10)	< 0.0001	0.69	
> 25.5	76/272	0.62 (0.44-0.88)	216/511	1.00 (Ref)	343/584	1.55 (1.21-1.97)	156/227	1.81 (1.33-2.46)	< 0.0001		
Breast Feeding History²											
No	50/200	0.50 (0.33-0.77)	144/318	1.00 (Ref)	202/323	1.64 (1.19-2.26)	86/129	1.77 (1.17-2.66)	< 0.0001	0.91	
Yes	145/492	0.79 (0.61-1.02)	357/967	1.00 (Ref)	591/988	1.85 (1.54-2.23)	256/359	2.18 (1.72-2.77)	< 0.0001		
Physical Activity, METs/week											
< 4.5	60/234	0.74 (0.50-1.10)	142/357	1.00 (Ref)	241/321	2.34 (1.72-3.18)	78/106	1.90 (1.25-2.89)	< 0.0001	0.12 <i>Categorical</i>	
4.5 - 12	57/184	0.72 (0.48-1.07)	134/343	1.00 (Ref)	237/385	1.73 (1.29-2.33)	115/119	3.00 (2.05-4.39)	< 0.0001		
12 - 25.5	43/190	0.47 (0.30-0.73)	127/314	1.00 (Ref)	210/384	1.41 (1.05-1.90)	94/167	1.59 (1.09-2.31)	< 0.0001		
≥ 25.5	56/153	0.83 (0.54-1.28)	121/372	1.00 (Ref)	208/394	1.67 (1.23-2.26)	114/160	2.37 (1.64-3.44)	< 0.0001		
Smoking Status											
Never	106/403	0.61 (0.46-0.82)	312/795	1.00 (Ref)	498/888	1.68 (1.37-2.06)	223/339	2.19 (1.70-2.83)	< 0.0001	0.99	
Past	99/310	0.77 (0.56-1.06)	218/547	1.00 (Ref)	366/540	1.78 (1.41-2.27)	161/190	2.17 (1.59-2.95)	< 0.0001		
Current	16/72	0.60 (0.25-1.43)	36/102	1.00 (Ref)	72/110	2.13 (1.14-3.98)	26/40	2.18 (0.96-4.95)	0.002		
Dense Area²											
		< 18.85 cm ²		18.85-31.32 cm ²		31.32-48.09 cm ²		≥ 48.09 cm ²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction	
Age at Menarche, yrs											
< 12	80/285	1.00 (ref.)	116/262	1.51 (1.03-2.21)	126/228	2.26 (1.55-3.30)	201/248	3.27 (2.29-4.65)	< 0.0001	0.02*	
12-13	176/595	1.00 (ref.)	286/631	1.75 (1.36-2.25)	330/660	2.00 (1.56-2.56)	448/617	2.72 (2.13-3.46)	< 0.0001		
> 13	70/202	1.00 (ref.)	71/190	1.24 (0.79-1.94)	92/196	1.41 (0.91-2.19)	129/217	1.72 (1.13-2.62)	0.009		

Alcohol Consumption, g/day										0.96
0	122/399	1.00 (ref.)	166/356	1.55 (1.14-2.11)	187/344	2.03 (1.51-2.74)	255/375	2.40 (1.80-3.22)	< 0.0001	<i>Categorical</i>
0-5	86/342	1.00 (ref.)	133/345	1.65 (1.18-2.31)	168/339	2.17 (1.56-3.03)	262/348	2.98 (2.17-4.10)	< 0.0001	0.25
>= 5	95/275	1.00 (ref.)	136/294	1.49 (1.06-2.12)	148/307	1.51 (1.07-2.13)	229/298	2.41 (1.73-3.36)	< 0.0001	<i>Continuous</i>
History of Benign Breast Disease										
No	245/859	1.00 (ref.)	325/862	1.49 (1.20-1.85)	383/803	1.98 (1.59-2.46)	488/770	2.52 (2.04-3.11)	< 0.0001	0.85
Yes	82/229	1.00 (ref.)	149/223	1.81 (1.25-2.63)	169/284	1.77 (1.23-2.53)	296/316	2.77 (1.96-3.90)	< 0.0001	
Body Mass Index, kg/m²										0.70
< 25	105/416	1.00 (ref.)	250/565	1.83 (1.36-2.45)	287/566	2.18 (1.63-2.91)	360/531	2.94 (2.20-3.92)	< 0.0001	<i>Categorical</i>
25-30	129/339	1.00 (ref.)	142/300	1.33 (0.96-1.84)	165/332	1.39 (1.01-1.91)	257/334	2.03 (1.50-2.74)	< 0.0001	0.10
>= 30	87/322	1.00 (ref.)	74/200	1.52 (1.00-2.32)	86/173	2.49 (1.65-3.77)	156/202	3.25 (2.23-4.72)	< 0.0001	<i>Continuous</i>
First-Degree of Family History of Breast Cancer										
No	243/905	1.00 (ref.)	362/936	1.57 (1.28-1.94)	442/914	2.04 (1.66-2.50)	576/890	2.68 (2.20-3.26)	< 0.0001	0.30
Yes	66/132	1.00 (ref.)	84/118	1.53 (0.97-2.41)	84/143	1.29 (0.82-2.05)	142/159	2.13 (1.38-3.26)	0.002	
Nulliparity										
Nulliparous	24/95	1.00 (ref.)	50/100	2.89 (1.50-5.59)	77/129	3.52 (1.87-6.63)	100/141	3.57 (1.95-6.56)	0.0002	0.74
Parous	297/983	1.00 (ref.)	418/975	1.49 (1.23-1.82)	465/945	1.79 (1.47-2.17)	673/940	2.53 (2.10-3.06)	< 0.0001	
Parity³										
1	19/76	1.00 (ref.)	40/120	1.98 (0.95-4.14)	54/111	2.44 (1.18-5.05)	95/105	4.77 (2.38-9.54)	< 0.0001	0.09
2	92/314	1.00 (ref.)	125/346	1.20 (0.85-1.71)	178/355	1.76 (1.26-2.46)	257/382	2.25 (1.63-3.09)	< 0.0001	
3+	186/593	1.00 (ref.)	253/509	1.70 (1.31-2.20)	233/479	1.74 (1.34-2.27)	321/453	2.46 (1.91-3.18)	< 0.0001	
Age at 1st Child, yrs³										
<= 25.5	174/618	1.00 (ref.)	242/564	1.63 (1.26-2.12)	257/521	1.90 (1.47-2.46)	397/551	2.75 (2.15-3.53)	< 0.0001	0.74
> 25.5	123/368	1.00 (ref.)	178/412	1.30 (0.95-1.76)	211/425	1.62 (1.20-2.19)	279/389	2.28 (1.70-3.05)	< 0.0001	
Breast Feeding History³										
No	68/264	1.00 (ref.)	118/229	2.25 (1.50-3.36)	121/245	2.28 (1.53-3.39)	175/232	3.57 (2.42-5.28)	< 0.0001	0.21
Yes	223/704	1.00 (ref.)	294/728	1.35 (1.07-1.69)	343/683	1.72 (1.37-2.16)	489/691	2.31 (1.86-2.87)	< 0.0001	
Physical Activity, METs/week										
< 4.5	87/277	1.00 (ref.)	113/266	1.24 (0.85-1.81)	122/221	1.96 (1.35-2.86)	199/254	2.22 (1.55-3.17)	< 0.0001	0.35
4.5 - 12	84/249	1.00 (ref.)	93/255	1.22 (0.83-1.78)	155/273	1.84 (1.28-2.64)	211/254	2.71 (1.92-3.84)	< 0.0001	<i>Categorical</i>
12 - 25.5	60/279	1.00 (ref.)	116/234	2.56 (1.72-3.80)	122/261	2.37 (1.60-3.52)	176/281	3.42 (2.34-5.00)	< 0.0001	0.17
>= 25.5	79/243	1.00 (ref.)	119/276	1.56 (1.07-2.27)	126/291	1.62 (1.11-2.35)	175/269	2.25 (1.57-3.24)	< 0.0001	<i>Continuous</i>
Smoking Status										
Never	161/560	1.00 (ref.)	263/622	1.66 (1.28-2.16)	305/605	2.07 (1.60-2.68)	410/638	2.49 (1.95-3.20)	< 0.0001	0.42
Past	147/429	1.00 (ref.)	168/390	1.24 (0.92-1.67)	213/399	1.59 (1.19-2.12)	316/369	2.51 (1.90-3.31)	< 0.0001	
Current	19/95	1.00 (ref.)	41/71	4.05 (1.79-9.16)	33/79	3.57 (1.54-8.31)	57/79	5.17 (2.30-11.62)	0.0004	
Non-dense Area²										
< 67.12 cm²		67.12-104.59 cm²			104.59-155.67 cm²			>= 155.67 cm²		
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	127/190	1.00 (ref.)	130/262	0.69 (0.49-0.98)	132/255	0.59 (0.41-0.85)	134/316	0.43 (0.28-0.66)	0.0001	0.85
12-13	410/661	1.00 (ref.)	321/604	0.85 (0.69-1.04)	263/633	0.69 (0.55-0.86)	246/605	0.62 (0.48-0.81)	0.0001	
> 13	125/233	1.00 (ref.)	99/217	0.71 (0.49-1.04)	86/193	0.64 (0.42-0.97)	52/162	0.39 (0.23-0.68)	0.0009	
Alcohol Consumption, g/day										0.97
0	200/326	1.00 (ref.)	170/330	0.83 (0.63-1.10)	168/371	0.67 (0.50-0.91)	192/447	0.55 (0.40-0.78)	0.0003	<i>Categorical</i>
0-5	208/341	1.00 (ref.)	171/337	0.77 (0.58-1.01)	141/355	0.59 (0.43-0.79)	129/341	0.55 (0.39-0.78)	0.0002	0.31
>= 5	215/347	1.00 (ref.)	175/347	0.70 (0.53-0.92)	135/272	0.73 (0.53-1.00)	83/208	0.49 (0.32-0.73)	0.0009	<i>Continuous</i>
History of Benign Breast Disease										
No	409/774	1.00 (ref.)	361/811	0.78 (0.64-0.95)	347/847	0.68 (0.56-0.84)	324/862	0.53 (0.42-0.68)	< 0.0001	0.65
Yes	258/312	1.00 (ref.)	190/276	0.76 (0.58-1.01)	137/239	0.61 (0.44-0.84)	111/225	0.55 (0.37-0.81)	0.0006	
Body Mass Index, kg/m²										0.26
< 25	498/866	1.00 (ref.)	298/662	0.76 (0.63-0.92)	151/410	0.65 (0.51-0.83)	55/140	0.78 (0.53-1.13)	0.0007	<i>Categorical</i>
25-30	137/181	1.00 (ref.)	194/330	0.78 (0.57-1.08)	226/417	0.72 (0.52-0.98)	136/377	0.46 (0.32-0.64)	< 0.0001	0.02*
>= 30	22/25	1.00 (ref.)	50/79	0.74 (0.35-1.59)	95/242	0.43 (0.21-0.88)	236/551	0.47 (0.24-0.91)	0.02	<i>Continuous</i>

First-Degree of Family History of Breast Cancer										
No	526/938	1.00 (ref.)	415/922	0.77 (0.65-0.92)	368/899	0.68 (0.56-0.82)	314/886	0.53 (0.42-0.67)	< 0.0001	0.46
Yes	107/128	1.00 (ref.)	101/140	0.81 (0.54-1.22)	91/152	0.56 (0.36-0.87)	77/132	0.54 (0.32-0.90)	0.007	
Nulliparity										
Nulliparous	86/132	1.00 (ref.)	73/119	0.91 (0.58-1.43)	52/87	0.68 (0.40-1.16)	40/127	0.25 (0.12-0.50)	0.0004	0.04*
Parous	576/946	1.00 (ref.)	466/952	0.76 (0.64-0.90)	425/993	0.65 (0.54-0.79)	386/952	0.57 (0.46-0.71)	< 0.0001	
Parity³										
1	67/115	1.00 (ref.)	63/98	1.11 (0.67-1.84)	44/92	0.71 (0.40-1.28)	34/107	0.43 (0.21-0.87)	0.02	0.70
2	217/387	1.00 (ref.)	161/330	0.82 (0.62-1.09)	146/357	0.73 (0.54-0.98)	128/323	0.66 (0.46-0.95)	0.01	
3+	292/444	1.00 (ref.)	242/524	0.67 (0.53-0.85)	235/544	0.60 (0.46-0.77)	224/522	0.54 (0.40-0.73)	< 0.0001	
Age at 1st Child, yrs³										
<= 25.5	320/502	1.00 (ref.)	271/573	0.68 (0.54-0.85)	245/612	0.57 (0.45-0.73)	234/567	0.53 (0.40-0.71)	< 0.0001	0.51
> 25.5	257/446	1.00 (ref.)	199/381	0.86 (0.67-1.12)	181/381	0.77 (0.59-1.02)	154/386	0.63 (0.45-0.89)	0.007	
Breast Feeding History³										
No	135/239	1.00 (ref.)	127/216	0.93 (0.66-1.31)	113/221	0.80 (0.55-1.16)	107/294	0.51 (0.33-0.78)	0.003	0.87
Yes	439/700	1.00 (ref.)	331/720	0.71 (0.59-0.87)	304/746	0.61 (0.49-0.75)	275/640	0.60 (0.47-0.78)	< 0.0001	
Physical Activity, METs/week										
< 4.5	142/191	1.00 (ref.)	127/222	0.75 (0.53-1.06)	120/283	0.50 (0.35-0.72)	132/322	0.52 (0.34-0.79)	0.0004	Categorical
4.5 - 12	168/257	1.00 (ref.)	134/252	0.78 (0.56-1.07)	132/239	0.77 (0.55-1.09)	109/283	0.51 (0.34-0.77)	0.003	0.74
12 - 25.5	155/290	1.00 (ref.)	129/270	0.80 (0.58-1.10)	104/260	0.80 (0.57-1.13)	86/235	0.60 (0.39-0.90)	0.02	Continuous
>= 25.5	179/309	1.00 (ref.)	133/294	0.77 (0.57-1.04)	98/264	0.58 (0.41-0.82)	89/212	0.52 (0.34-0.80)	0.0006	
Smoking Status										
Never	363/637	1.00 (ref.)	286/621	0.77 (0.62-0.96)	264/590	0.66 (0.52-0.83)	226/577	0.51 (0.38-0.68)	< 0.0001	0.79
Past	251/369	1.00 (ref.)	220/387	0.77 (0.59-1.00)	196/410	0.68 (0.51-0.89)	177/421	0.58 (0.42-0.80)	0.0006	
Current	52/79	1.00 (ref.)	45/78	0.86 (0.46-1.60)	22/83	0.50 (0.24-1.06)	31/84	0.47 (0.20-1.09)	0.04	

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls.

³Analysis conducted among parous women only. *Parity and age at 1st birth* were removed from the set of adjusting factors in the regression model. *Number of Children* (1, 2, 3+), *Age at 1st Child* (before/after 25 yrs-old) and *History of breast feeding* (Binary) were further adjusted for, with exception of the covariate used for stratification.

*Statistically significant with p-value < 0.05

Supplementary Table 1.4 Associations of percent mammographic density, absolute dense and non-dense area with invasive breast cancer risk by breast cancer risk factors, among premenopausal cases (N=558) and controls (N=1,260)¹

<i>Percent Density</i>		< 10%		10 - 25% (Ref.)		25 - 49%		≥ 50%		P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)			
Age at Menarche, yrs											
< 12	10/52	0.47 (0.18-1.26)	29/96	1.00 (Ref)	71/103	2.95 (1.54-5.62)	23/46	2.33 (1.01-5.35)	0.0002	0.31	
12-13	20/88	0.73 (0.39-1.38)	68/218	1.00 (Ref)	155/289	1.79 (1.21-2.65)	89/150	2.24 (1.42-3.52)	< 0.0001		
> 13	3/19	0.17 (0.03-0.94)	17/46	1.00 (Ref)	46/101	1.26 (0.57-2.76)	23/51	1.18 (0.48-2.89)	0.08		
Alcohol Consumption, g/day											
0	8/59	0.48 (0.20-1.14)	43/147	1.00 (Ref)	85/143	2.33 (1.42-3.83)	49/83	2.23 (1.25-3.98)	0.0001	0.24 <i>Categorical</i> 0.047*	
0-5	13/51	0.57 (0.26-1.26)	34/101	1.00 (Ref)	99/174	1.80 (1.07-3.02)	48/84	2.14 (1.16-3.95)	0.0004		
≥ 5	9/35	0.67 (0.25-1.81)	23/90	1.00 (Ref)	70/150	1.83 (1.01-3.32)	35/66	2.15 (1.07-4.32)	0.007		
History of Benign Breast Disease											
No	25/135	0.53 (0.30-0.94)	89/301	1.00 (Ref)	197/385	1.88 (1.33-2.66)	83/178	1.82 (1.19-2.77)	< 0.0001	0.96	
Yes	8/24	0.75 (0.26-2.21)	25/59	1.00 (Ref)	77/109	2.07 (1.10-3.89)	54/69	3.22 (1.59-6.53)	0.0005		
Body Mass Index, kg/m²											
< 25	2/27	0.14 (0.02-1.07)	41/141	1.00 (Ref)	149/300	1.72 (1.09-2.69)	103/203	1.68 (1.05-2.70)	0.003	0.045* <i>Categorical</i> 0.02*	
25-30	10/50	0.50 (0.22-1.13)	41/106	1.00 (Ref)	69/127	1.18 (0.71-1.99)	23/27	2.26 (1.06-4.85)	0.003		
≥ 30	19/79	1.17 (0.53-2.56)	26/103	1.00 (Ref)	42/47	4.08 (2.01-8.29)	9/10	3.50 (1.02-12.02)	0.0003		
First-Degree of Family History of Breast Cancer											
No	26/144	0.55 (0.32-0.96)	94/323	1.00 (Ref)	234/427	2.11 (1.52-2.94)	109/223	2.07 (1.40-3.06)	< 0.0001	0.69	
Yes	6/14	0.52 (0.14-1.91)	20/36	1.00 (Ref)	38/65	0.98 (0.43-2.21)	23/24	2.28 (0.87-5.93)	0.04		
Nulliparity											
Nulliparous	2/26	0.27 (0.05-1.39)	12/49	1.00 (Ref)	51/80	3.98 (1.61-9.82)	31/40	6.56 (2.33-18.46)	< 0.0001	0.02*	
Parous	30/133	0.65 (0.38-1.11)	100/308	1.00 (Ref)	220/410	1.76 (1.27-2.43)	106/206	1.81 (1.23-2.67)	< 0.0001		
Parity²											
1	4/23	0.45 (0.10-1.99)	14/45	1.00 (Ref)	45/55	3.68 (1.47-9.19)	15/34	2.46 (0.80-7.56)	0.01	0.46	
2	18/58	0.84 (0.41-1.72)	49/143	1.00 (Ref)	102/190	1.66 (1.03-2.67)	49/98	1.65 (0.95-2.89)	0.02		
3+	8/52	0.47 (0.17-1.29)	37/120	1.00 (Ref)	73/165	1.42 (0.82-2.45)	42/74	1.78 (0.94-3.38)	0.01		
Age at 1st Child, yrs²											
≤ 25.5	18/70	0.83 (0.41-1.70)	44/153	1.00 (Ref)	96/181	1.82 (1.12-2.98)	44/104	1.50 (0.84-2.67)	0.04	0.14	
> 25.5	12/63	0.43 (0.19-0.99)	58/157	1.00 (Ref)	126/228	1.78 (1.14-2.78)	62/103	2.11 (1.24-3.59)	< 0.0001		
Breast Feeding History²											
No	8/32	0.57 (0.19-1.70)	24/50	1.00 (Ref)	42/69	1.83 (0.83-4.03)	17/43	1.32 (0.52-3.34)	0.14	0.49	
Yes	22/98	0.69 (0.37-1.28)	74/249	1.00 (Ref)	173/330	1.84 (1.28-2.65)	88/162	1.93 (1.25-2.98)	< 0.0001		
Physical Activity, METs/week											
< 4.5	12/55	0.50 (0.20-1.27)	31/77	1.00 (Ref)	72/104	2.55 (1.36-4.77)	30/39	2.42 (1.12-5.23)	0.0002	0.15 <i>Categorical</i> 0.26 <i>Continuous</i>	
4.5 - 12	8/33	0.85 (0.31-2.32)	21/99	1.00 (Ref)	72/129	2.84 (1.50-5.38)	35/60	3.44 (1.58-7.46)	0.0005		
12 - 25.5	5/38	0.29 (0.10-0.89)	25/76	1.00 (Ref)	59/126	1.22 (0.65-2.27)	33/76	1.43 (0.70-2.92)	0.01		
≥ 25.5	7/27	0.75 (0.27-2.14)	27/98	1.00 (Ref)	57/129	1.59 (0.88-2.89)	36/66	1.90 (0.97-3.72)	0.03		
Smoking Status											
Never	20/103	0.54 (0.29-1.01)	72/238	1.00 (Ref)	184/338	1.97 (1.35-2.86)	87/165	2.18 (1.41-3.39)	< 0.0001	0.97	
Past	10/38	0.74 (0.29-1.86)	36/103	1.00 (Ref)	75/124	1.89 (1.08-3.31)	38/69	1.81 (0.93-3.53)	0.02		
Current	3/18	0.32 (0.04-2.37)	6/19	1.00 (Ref)	14/32	1.48 (0.32-6.91)	12/13	2.65 (0.44-16.18)	0.05		
Dense Area²											
		< 23.80 cm ²		23.80- 35.05 cm ²		35.05- 51.52 cm ²		≥ 51.52 cm ²		P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)			
Age at Menarche, yrs											
< 12	22/97	1.00 (ref.)	27/63	2.60 (1.17-5.80)	30/61	3.50 (1.59-7.71)	54/76	4.20 (2.04-8.64)	0.0001	0.048*	
12-13	38/172	1.00 (ref.)	70/208	1.56 (0.95-2.58)	98/191	2.33 (1.43-3.81)	126/174	3.30 (2.05-5.33)	< 0.0001		
> 13	17/46	1.00 (ref.)	19/44	1.33 (0.52-3.38)	25/62	1.49 (0.62-3.60)	28/65	1.38 (0.59-3.23)	0.47		

Alcohol Consumption, g/day										0.35
0	22/121	1.00 (ref.)	37/113	1.95 (1.01-3.77)	53/85	4.21 (2.19-8.10)	73/113	3.51 (1.90-6.49)	< 0.0001	<i>Categorical</i>
0-5	24/92	1.00 (ref.)	38/100	1.70 (0.90-3.21)	66/121	2.72 (1.50-4.94)	66/97	2.72 (1.50-4.94)	0.0004	0.11
>= 5	21/84	1.00 (ref.)	31/83	1.44 (0.72-2.88)	23/91	0.86 (0.41-1.79)	62/83	2.81 (1.48-5.33)	0.003	<i>Continuous</i>
History of Benign Breast Disease										
No	60/271	1.00 (ref.)	82/245	1.69 (1.10-2.61)	113/248	2.46 (1.62-3.74)	139/235	2.87 (1.92-4.29)	< 0.0001	0.92
Yes	17/44	1.00 (ref.)	34/70	1.50 (0.68-3.33)	40/67	1.93 (0.88-4.21)	73/80	3.02 (1.43-6.39)	0.0009	
Body Mass Index, kg/m²										0.04*
< 25	37/123	1.00 (ref.)	68/192	1.35 (0.80-2.27)	88/190	1.87 (1.13-3.11)	102/166	2.15 (1.29-3.58)	0.0008	<i>Categorical</i>
25-30	20/95	1.00 (ref.)	30/59	1.85 (0.90-3.81)	36/83	1.87 (0.96-3.63)	57/73	3.24 (1.71-6.16)	0.0005	0.01*
>= 30	14/88	1.00 (ref.)	15/56	1.80 (0.69-4.69)	22/32	4.54 (1.77-11.61)	45/63	5.13 (2.31-11.40)	< 0.0001	<i>Continuous</i>
First-Degree of Family History of Breast Cancer										
No	62/283	1.00 (ref.)	97/278	1.72 (1.14-2.61)	130/285	2.46 (1.65-3.67)	174/271	3.20 (2.18-4.70)	< 0.0001	0.17
Yes	14/30	1.00 (ref.)	19/37	1.38 (0.53-3.62)	23/29	1.62 (0.61-4.30)	31/43	1.96 (0.76-5.02)	0.15	
Nulliparity										
Nulliparous	5/47	1.00 (ref.)	23/46	5.87 (1.80-19.19)	25/53	5.10 (1.55-16.75)	43/49	10.21 (3.25-32.03)	< 0.0001	0.11
Parous	71/266	1.00 (ref.)	92/267	1.37 (0.91-2.06)	126/259	2.06 (1.39-3.04)	167/265	2.42 (1.66-3.53)	< 0.0001	
Parity³										
1	8/40	1.00 (ref.)	19/43	2.88 (0.93-8.93)	20/44	2.86 (0.92-8.82)	31/30	7.14 (2.36-21.65)	0.0006	0.22
2	40/127	1.00 (ref.)	38/124	1.00 (0.55-1.80)	63/110	2.10 (1.22-3.64)	77/128	1.99 (1.17-3.37)	0.001	
3+	23/99	1.00 (ref.)	35/100	1.45 (0.73-2.91)	43/105	1.72 (0.87-3.39)	59/107	2.11 (1.11-4.03)	0.02	
Age at 1st Child, yrs³										
<= 25.5	28/128	1.00 (ref.)	38/124	1.43 (0.76-2.69)	52/117	2.11 (1.14-3.90)	84/139	2.53 (1.43-4.47)	0.0005	0.88
> 25.5	44/140	1.00 (ref.)	55/142	1.31 (0.76-2.24)	74/143	2.09 (1.25-3.49)	85/126	2.39 (1.44-3.99)	0.0001	
Breast Feeding History³										
No	14/53	1.00 (ref.)	26/41	3.38 (1.32-8.66)	15/44	1.99 (0.74-5.37)	36/56	3.97 (1.63-9.62)	0.01	0.80
Yes	54/208	1.00 (ref.)	65/217	1.17 (0.74-1.85)	109/211	2.22 (1.44-3.42)	129/203	2.34 (1.53-3.58)	<.0001	
Physical Activity, METs/week										
< 4.5	25/81	1.00 (ref.)	21/65	1.32 (0.61-2.84)	42/55	3.32 (1.59-6.93)	57/74	2.79 (1.41-5.53)	0.0005	0.56
4.5 - 12	17/70	1.00 (ref.)	26/83	1.24 (0.58-2.68)	41/90	1.73 (0.82-3.63)	52/78	2.51 (1.24-5.09)	0.004	<i>Categorical</i>
12 - 25.5	14/73	1.00 (ref.)	28/79	2.29 (1.01-5.17)	27/80	2.54 (1.12-5.75)	53/84	4.17 (1.96-8.87)	0.0002	0.25
>= 25.5	18/80	1.00 (ref.)	31/83	2.20 (1.04-4.62)	36/84	2.34 (1.12-4.89)	42/73	2.82 (1.35-5.86)	0.01	<i>Continuous</i>
Smoking Status										
Never	53/212	1.00 (ref.)	73/215	1.43 (0.91-2.27)	108/212	2.34 (1.50-3.64)	129/205	2.60 (1.70-3.97)	< 0.0001	0.56
Past	20/75	1.00 (ref.)	33/84	1.60 (0.76-3.38)	38/86	1.79 (0.86-3.71)	68/89	3.03 (1.52-6.07)	0.0009	
Current	4/28	1.00 (ref.)	10/16	8.67 (1.38-54.52)	6/17	6.17 (0.94-40.47)	15/21	7.48 (1.28-43.78)	0.05	
Non-dense Area²										
	< 56.66 cm²		56.66-94.97 cm²		94.97-138.17 cm²		>= 138.17 cm²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	31/60	1.00 (ref.)	32/65	0.88 (0.44-1.75)	32/76	0.64 (0.30-1.36)	38/96	0.44 (0.19-1.02)	0.05	0.96
12-13	100/191	1.00 (ref.)	89/178	1.03 (0.70-1.52)	74/191	0.75 (0.49-1.14)	69/185	0.79 (0.48-1.31)	0.20	
> 13	36/64	1.00 (ref.)	25/72	0.75 (0.37-1.52)	19/47	0.69 (0.30-1.60)	9/34	0.29 (0.09-0.95)	0.07	
Alcohol Consumption, g/day										0.16
0	54/96	1.00 (ref.)	51/97	1.11 (0.66-1.87)	40/116	0.64 (0.36-1.13)	40/123	0.57 (0.29-1.14)	0.06	<i>Categorical</i>
0-5	61/111	1.00 (ref.)	56/103	0.94 (0.57-1.53)	36/101	0.55 (0.31-0.97)	41/95	0.63 (0.34-1.19)	0.05	0.04*
>= 5	43/93	1.00 (ref.)	37/96	0.75 (0.42-1.33)	36/83	0.99 (0.54-1.82)	21/69	0.59 (0.26-1.31)	0.38	<i>Continuous</i>
History of Benign Breast Disease										
No	110/228	1.00 (ref.)	104/241	1.03 (0.72-1.47)	96/259	0.69 (0.46-1.02)	84/271	0.59 (0.37-0.94)	0.009	0.23
Yes	59/87	1.00 (ref.)	43/74	0.71 (0.41-1.24)	30/56	0.78 (0.41-1.49)	32/44	0.74 (0.33-1.67)	0.41	
Body Mass Index, kg/m²										0.01*
< 25	131/272	1.00 (ref.)	88/206	0.98 (0.69-1.38)	58/156	0.77 (0.50-1.17)	18/37	1.18 (0.62-2.25)	0.60	<i>Categorical</i>
25-30	24/31	1.00 (ref.)	41/85	0.67 (0.32-1.39)	42/91	0.69 (0.33-1.44)	36/103	0.53 (0.25-1.12)	0.14	0.01*
>= 30	8/4	1.00 (ref.)	14/12	0.84 (0.15-4.88)	15/56	0.15 (0.03-0.78)	59/167	0.19 (0.04-0.89)	0.004	<i>Continuous</i>

First-Degree of Family History of Breast Cancer										
No	142/281	1.00 (ref.)	121/280	0.93 (0.68-1.29)	106/274	0.74 (0.52-1.06)	94/282	0.59 (0.39-0.91)	0.01	0.69
Yes	23/34	1.00 (ref.)	23/35	0.98 (0.43-2.27)	19/38	0.50 (0.20-1.29)	22/32	0.63 (0.21-1.90)	0.26	
Nulliparity										
Nulliparous	29/59	1.00 (ref.)	32/47	1.31 (0.65-2.64)	18/35	0.81 (0.35-1.86)	17/54	0.35 (0.12-1.02)	0.08	0.67
Parous	140/254	1.00 (ref.)	112/266	0.84 (0.61-1.18)	108/278	0.68 (0.47-0.98)	96/259	0.64 (0.41-0.98)	0.02	
Parity³										
1	20/42	1.00 (ref.)	20/38	0.93 (0.37-2.32)	23/35	1.56 (0.58-4.18)	15/42	0.39 (0.12-1.31)	0.35	0.08
2	63/122	1.00 (ref.)	54/124	1.00 (0.61-1.62)	50/132	0.65 (0.38-1.11)	51/111	0.81 (0.43-1.51)	0.25	
3+	57/90	1.00 (ref.)	38/104	0.68 (0.39-1.18)	35/111	0.53 (0.28-0.99)	30/106	0.56 (0.26-1.17)	0.06	
Age at 1st Child, yrs³										
<= 25.5	53/108	1.00 (ref.)	49/125	0.93 (0.55-1.56)	49/136	0.66 (0.37-1.18)	51/139	0.79 (0.41-1.50)	0.30	0.50
> 25.5	87/148	1.00 (ref.)	65/139	0.79 (0.51-1.22)	59/143	0.70 (0.44-1.14)	47/121	0.52 (0.28-0.94)	0.03	
Breast Feeding History³										
No	22/50	1.00 (ref.)	23/39	1.30 (0.58-2.88)	22/46	0.69 (0.28-1.69)	24/59	0.65 (0.23-1.81)	0.32	0.66
Yes	117/202	1.00 (ref.)	86/222	0.77 (0.53-1.11)	83/220	0.67 (0.45-1.01)	71/195	0.60 (0.37-0.97)	0.02	
Physical Activity, METs/week										
< 4.5	33/46	1.00 (ref.)	42/55	1.27 (0.65-2.49)	28/81	0.51 (0.24-1.08)	42/93	0.55 (0.24-1.28)	0.04	0.14
4.5 - 12	48/78	1.00 (ref.)	38/78	0.92 (0.51-1.65)	27/82	0.40 (0.20-0.83)	23/83	0.28 (0.12-0.65)	0.001	Categorical
12 - 25.5	36/95	1.00 (ref.)	30/85	1.04 (0.56-1.93)	37/68	1.56 (0.82-2.99)	19/68	0.98 (0.43-2.25)	0.58	0.38
>= 25.5	48/91	1.00 (ref.)	30/92	0.63 (0.35-1.14)	27/75	0.65 (0.34-1.24)	22/62	0.82 (0.38-1.77)	0.40	Continuous
Smoking Status										
Never	113/212	1.00 (ref.)	96/226	0.85 (0.59-1.22)	83/209	0.67 (0.44-1.01)	71/197	0.61 (0.37-1.00)	0.03	0.84
Past	42/85	1.00 (ref.)	41/72	1.10 (0.61-1.98)	38/83	0.86 (0.47-1.58)	38/94	0.65 (0.31-1.38)	0.24	
Current	14/18	1.00 (ref.)	10/17	0.87 (0.22-3.41)	4/23	0.44 (0.09-2.18)	7/24	0.46 (0.08-2.56)	0.30	

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *Body mass index at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Categorization of absolute area of dense and non-dense tissue was based on their distribution among premenopausal controls.

³Analysis conducted among parous women only. *Parity and age at 1st birth* were removed from the set of adjusting factors in the regression model. *Number of Children* (1, 2, 3+), *Age at 1st Child* (before/after 25 yrs-old) and *History of breast feeding* (Binary) were further adjusted for, with exception of the covariate used for stratification.

*Statistically significant with p-value < 0.05

Supplementary Table 1.5 Associations of percent mammographic density, absolute dense and non-dense area with postmenopausal breast cancer risk by breast cancer risk factors, among postmenopausal cases (N=1,245) and controls (N=2,343)¹.

<i>Percent Density</i>		< 10%	10 - 25% (Ref.)	25 - 49%	≥ 50%			P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	
Age at Menarche, yrs									
< 12	52/144	1.10 (0.67-1.81)	74/213	1.00 (Ref)	128/151	3.21 (2.09-4.94)	43/29	6.40 (3.34-12.26)	< 0.0001
12-13	90/296	0.63 (0.45-0.88)	218/485	1.00 (Ref)	293/432	1.52 (1.18-1.97)	113/116	1.80 (1.24-2.61)	< 0.0001
> 13	31/108	0.65 (0.36-1.17)	62/151	1.00 (Ref)	96/158	1.33 (0.82-2.16)	39/49	1.95 (1.00-3.78)	0.003
Age at Menopause, yrs									
< 50	51/202	0.50 (0.32-0.77)	140/317	1.00 (Ref)	188/294	1.42 (1.04-1.94)	55/70	1.55 (0.97-2.46)	< 0.0001
50 - 55	110/304	0.87 (0.63-1.20)	188/447	1.00 (Ref)	280/375	2.04 (1.55-2.69)	112/96	3.36 (2.28-4.95)	< 0.0001
≥ 55	9/25	0.78 (0.22-2.77)	19/44	1.00 (Ref)	32/33	1.95 (0.80-4.72)	11/9	1.38 (0.37-5.22)	0.19
Alcohol Consumption, g/day									
0	84/225	0.78 (0.54-1.12)	150/315	1.00 (Ref)	177/239	1.67 (1.21-2.30)	52/61	2.20 (1.31-3.70)	< 0.0001
0-5	46/182	0.77 (0.48-1.21)	104/275	1.00 (Ref)	132/262	1.43 (0.99-2.05)	77/50	4.04 (2.45-6.64)	< 0.0001
≥ 5	37/116	0.62 (0.36-1.08)	87/221	1.00 (Ref)	184/205	2.28 (1.59-3.28)	62/76	1.74 (1.05-2.87)	< 0.0001
History of Benign Breast Disease									
No	139/440	0.73 (0.55-0.98)	251/654	1.00 (Ref)	329/514	1.84 (1.45-2.34)	99/125	2.17 (1.50-3.12)	< 0.0001
Yes	34/111	0.69 (0.41-1.16)	107/200	1.00 (Ref)	190/230	1.62 (1.13-2.34)	96/69	2.70 (1.67-4.36)	< 0.0001
Body Mass Index, kg/m²									
< 25	26/110	0.76 (0.44-1.29)	120/363	1.00 (Ref)	284/446	2.03 (1.51-2.72)	130/143	2.48 (1.70-3.63)	< 0.0001
25-30	68/200	0.68 (0.46-1.02)	144/308	1.00 (Ref)	172/211	1.64 (1.18-2.28)	52/38	2.49 (1.46-4.22)	< 0.0001
≥ 30	78/235	0.71 (0.46-1.11)	89/176	1.00 (Ref)	60/80	1.46 (0.87-2.45)	13/13	2.14 (0.76-5.98)	0.002
First-Degree of Family History of Breast Cancer									
No	127/448	0.71 (0.54-0.93)	253/685	1.00 (Ref)	390/601	1.75 (1.40-2.17)	130/151	2.34 (1.70-3.21)	< 0.0001
Yes	30/59	0.87 (0.48-1.60)	65/120	1.00 (Ref)	85/105	1.85 (1.14-3.01)	37/33	2.66 (1.34-5.28)	0.0009
Nulliparity									
Nulliparous	10/39	0.34 (0.13-0.95)	35/58	1.00 (Ref)	51/77	1.05 (0.53-2.11)	28/28	1.49 (0.62-3.55)	0.03
Parous	159/507	0.77 (0.59-1.00)	319/790	1.00 (Ref)	457/662	1.85 (1.50-2.28)	164/165	2.50 (1.84-3.39)	< 0.0001
Parity²									
1	10/42	0.61 (0.20-1.86)	20/56	1.00 (Ref)	45/69	2.15 (0.95-4.87)	22/15	3.87 (1.26-11.91)	0.001
2	38/135	0.63 (0.37-1.05)	92/233	1.00 (Ref)	122/201	1.59 (1.08-2.36)	65/64	2.47 (1.46-4.17)	< 0.0001
3+	111/330	0.84 (0.62-1.16)	207/501	1.00 (Ref)	290/392	1.94 (1.49-2.53)	77/86	2.37 (1.56-3.60)	< 0.0001
Menopausal Hormone Therapy Use									
Never	62/172	0.98 (0.62-1.56)	78/231	1.00 (Ref)	84/152	1.84 (1.17-2.89)	25/30	2.46 (1.07-5.66)	0.004
Past	44/132	0.80 (0.48-1.31)	88/203	1.00 (Ref)	77/163	1.27 (0.83-1.96)	34/39	2.17 (1.15-4.10)	0.006
Current	56/231	0.55 (0.37-0.80)	175/387	1.00 (Ref)	340/403	1.87 (1.44-2.43)	130/117	2.41 (1.69-3.45)	< 0.0001
Age at 1st Child, yrs²									
≤ 25.5	100/325	0.87 (0.62-1.20)	189/518	1.00 (Ref)	294/412	2.14 (1.64-2.79)	100/94	3.15 (2.11-4.70)	< 0.0001
> 25.5	59/183	0.62 (0.41-0.95)	130/272	1.00 (Ref)	165/249	1.45 (1.03-2.04)	64/71	1.77 (1.09-2.87)	< 0.0001
Breast Feeding History²									
No	42/153	0.51 (0.31-0.83)	96/219	1.00 (Ref)	128/191	1.58 (1.06-2.34)	47/55	2.00 (1.13-3.55)	< 0.0001
Yes	112/344	0.85 (0.62-1.16)	219/557	1.00 (Ref)	325/461	2.01 (1.57-2.57)	116/109	2.71 (1.88-3.91)	< 0.0001
Physical Activity, METs/week									
< 4.5	47/162	0.95 (0.59-1.53)	91/238	1.00 (Ref)	133/160	2.42 (1.59-3.68)	38/45	2.20 (1.16-4.17)	< 0.0001
4.5 - 12	43/134	0.60 (0.37-1.00)	98/193	1.00 (Ref)	128/187	1.39 (0.94-2.06)	57/37	2.87 (1.63-5.05)	< 0.0001
12 - 25.5	34/129	0.53 (0.31-0.92)	84/183	1.00 (Ref)	125/190	1.57 (1.06-2.34)	50/51	2.59 (1.48-4.55)	< 0.0001
≥ 25.5	45/115	0.97 (0.57-1.62)	76/227	1.00 (Ref)	123/190	1.89 (1.25-2.85)	48/58	2.19 (1.23-3.92)	0.001

Smoking Status										
Never	76/265	0.67 (0.47-0.97)	179/431	1.00 (Ref)	238/394	1.57 (1.18-2.09)	94/102	2.37 (1.58-3.57)	< 0.0001	0.96
Past	84/239	0.75 (0.52-1.09)	153/349	1.00 (Ref)	232/298	1.74 (1.29-2.34)	88/72	2.51 (1.62-3.88)	< 0.0001	
Current	13/45	0.91 (0.31-2.66)	25/70	1.00 (Ref)	48/50	3.56 (1.59-7.97)	12/20	2.20 (0.71-6.85)	0.01	
Dense Area										
Breast Cancer Risk Factors										
	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	43/141	1.00 (ref.)	54/135	1.17 (0.67-2.02)	76/133	1.80 (1.07-3.01)	124/128	3.51 (2.15-5.73)	< 0.0001	0.08
12-13	95/319	1.00 (ref.)	163/326	1.63 (1.16-2.30)	191/351	1.97 (1.41-2.76)	265/333	2.39 (1.72-3.31)	< 0.0001	
> 13	48/121	1.00 (ref.)	33/124	0.82 (0.46-1.49)	56/100	1.26 (0.71-2.24)	91/121	1.83 (1.06-3.16)	0.01	
Alcohol Consumption, g/day										
0	88/233	1.00 (ref.)	95/188	1.29 (0.86-1.92)	115/216	1.39 (0.95-2.02)	165/203	2.16 (1.49-3.14)	< 0.0001	0.23 <i>Categorical</i>
0-5	47/185	1.00 (ref.)	65/203	1.15 (0.71-1.86)	96/188	1.95 (1.22-3.13)	151/193	2.62 (1.68-4.08)	< 0.0001	
>= 5	44/145	1.00 (ref.)	79/162	1.59 (0.97-2.61)	98/149	2.11 (1.29-3.44)	149/162	2.66 (1.66-4.27)	< 0.0001	
History of Benign Breast Disease										
No	145/457	1.00 (ref.)	176/459	1.25 (0.93-1.67)	204/410	1.68 (1.25-2.25)	293/407	2.28 (1.72-3.03)	< 0.0001	0.23
Yes	42/129	1.00 (ref.)	74/127	1.57 (0.93-2.64)	123/175	2.14 (1.32-3.46)	188/179	3.04 (1.90-4.86)	< 0.0001	
Body Mass Index, kg/m²										
< 25	56/211	1.00 (ref.)	115/283	1.61 (1.06-2.44)	177/283	2.31 (1.55-3.44)	212/285	2.78 (1.87-4.15)	< 0.0001	0.59 <i>Categorical</i>
25-30	73/185	1.00 (ref.)	84/185	1.24 (0.80-1.91)	103/194	1.28 (0.83-1.96)	176/193	2.19 (1.46-3.29)	0.0001	
>= 30	58/186	1.00 (ref.)	47/110	0.98 (0.56-1.72)	45/102	1.73 (0.99-3.01)	90/106	2.48 (1.52-4.06)	< 0.0001	
First-Degree of Family History of Breast Cancer										
No	139/473	1.00 (ref.)	179/484	1.17 (0.88-1.56)	254/480	1.76 (1.34-2.31)	328/448	2.45 (1.88-3.18)	< 0.0001	0.37
Yes	33/72	1.00 (ref.)	49/71	2.06 (1.11-3.83)	46/73	1.58 (0.84-2.98)	89/101	2.35 (1.31-4.22)	0.02	
Nulliparity										
Nulliparous	10/36	1.00 (ref.)	28/42	4.98 (1.61-15.41)	34/50	3.87 (1.30-11.49)	52/74	3.50 (1.23-9.97)	0.18	0.47
Parous	173/544	1.00 (ref.)	219/540	1.21 (0.93-1.58)	286/530	1.68 (1.30-2.17)	421/510	2.45 (1.91-3.14)	< 0.0001	
Parity³										
1	9/37	1.00 (ref.)	9/52	0.87 (0.24-3.11)	27/47	4.03 (1.31-12.42)	52/46	5.53 (1.97-15.54)	< 0.0001	0.01*
2	42/141	1.00 (ref.)	55/155	1.15 (0.67-1.98)	82/169	1.81 (1.09-3.02)	138/168	2.78 (1.71-4.51)	< 0.0001	
3+	122/366	1.00 (ref.)	155/333	1.33 (0.97-1.83)	177/314	1.55 (1.13-2.12)	231/296	2.13 (1.56-2.91)	< 0.0001	
Age at 1st Child, yrs³										
<= 25.5	108/357	1.00 (ref.)	144/345	1.72 (1.03-2.87)	171/333	2.08 (1.26-3.43)	260/314	3.06 (1.86-5.05)	< 0.0001	0.71
> 25.5	65/188	1.00 (ref.)	75/196	1.02 (0.65-1.60)	117/196	1.67 (1.10-2.54)	161/195	2.40 (1.60-3.59)	< 0.0001	
Breast Feeding History³										
No	43/154	1.00 (ref.)	68/152	1.72 (1.03-2.87)	85/168	2.08 (1.26-3.43)	117/144	3.06 (1.86-5.05)	< 0.0001	0.83
Yes	126/381	1.00 (ref.)	148/379	1.10 (0.80-1.51)	200/352	1.64 (1.21-2.23)	298/359	2.34 (1.75-3.14)	< 0.0001	
Physical Activity, METs/week										
< 4.5	54/150	1.00 (ref.)	60/158	0.86 (0.52-1.44)	77/146	1.44 (0.88-2.35)	118/151	1.70 (1.05-2.74)	0.005	0.78 <i>Categorical</i>
4.5 - 12	46/143	1.00 (ref.)	58/127	1.37 (0.81-2.32)	88/150	1.60 (0.97-2.64)	134/131	3.05 (1.89-4.92)	< 0.0001	
12 - 25.5	37/147	1.00 (ref.)	57/136	1.91 (1.10-3.31)	85/126	2.83 (1.69-4.75)	114/144	3.55 (2.13-5.91)	< 0.0001	
>= 25.5	45/136	1.00 (ref.)	66/154	1.34 (0.81-2.24)	73/148	1.64 (0.99-2.73)	108/152	2.07 (1.26-3.38)	0.003	
Smoking Status										
Never	86/269	1.00 (ref.)	120/299	1.32 (0.90-1.92)	148/317	1.62 (1.13-2.33)	233/307	2.37 (1.67-3.35)	< 0.0001	0.94
Past	89/267	1.00 (ref.)	106/241	1.26 (0.86-1.84)	152/223	1.81 (1.26-2.60)	210/227	2.47 (1.74-3.53)	< 0.0001	
Current	12/48	1.00 (ref.)	23/43	2.28 (0.81-6.45)	26/42	4.35 (1.44-13.15)	37/52	3.29 (1.15-9.42)	0.02	
Menopausal Hormone Therapy Use										
Never	61/174	1.00 (ref.)	49/151	1.00 (0.61-1.64)	60/132	1.25 (0.76-2.06)	79/128	1.55 (0.94-2.54)	0.06	0.03*
Past	44/140	1.00 (ref.)	60/138	1.20 (0.72-2.02)	54/139	1.30 (0.76-2.22)	85/120	2.11 (1.28-3.49)	0.003	
Current	69/253	1.00 (ref.)	129/278	1.70 (1.16-2.48)	204/294	2.42 (1.70-3.47)	299/313	3.31 (2.34-4.69)	< 0.0001	

Age at Menopause										
< 50	57/199	1.00 (ref.)	99/226	1.55 (1.00-2.41)	121/238	2.00 (1.30-3.08)	157/220	2.53 (1.66-3.86)	< 0.0001	0.79
50 - 55	116/342	1.00 (ref.)	131/303	1.25 (0.90-1.75)	180/280	1.82 (1.32-2.52)	263/297	2.49 (1.82-3.39)	< 0.0001	
>= 55	12/26	1.00 (ref.)	12/26	0.94 (0.28-3.18)	16/37	0.53 (0.16-1.73)	31/22	2.80 (0.92-8.56)	0.09	
Non-dense Area²										
< 76.60 cm ²			76.60-114.52 cm ²		114.52-167.68 cm ²		≥ 167.68 cm ²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	83/98	1.00 (ref.)	65/139	0.51 (0.32-0.83)	77/132	0.67 (0.41-1.09)	72/168	0.44 (0.25-0.79)	0.02	0.88
12-13	256/357	1.00 (ref.)	178/322	0.88 (0.66-1.17)	140/327	0.68 (0.50-0.94)	140/323	0.63 (0.44-0.91)	0.005	
> 13	85/128	1.00 (ref.)	57/122	0.60 (0.36-1.00)	46/126	0.51 (0.29-0.89)	40/90	0.62 (0.31-1.22)	0.06	
Alcohol Consumption, g/day										
0	139/196	1.00 (ref.)	100/174	0.81 (0.55-1.17)	96/220	0.57 (0.39-0.85)	128/250	0.60 (0.39-0.93)	0.007	0.29
0-5	119/171	1.00 (ref.)	93/198	0.64 (0.43-0.95)	81/204	0.62 (0.41-0.95)	66/196	0.56 (0.34-0.91)	0.02	Categorical
>= 5	149/197	1.00 (ref.)	96/182	0.68 (0.47-0.98)	77/135	0.82 (0.53-1.26)	48/104	0.48 (0.28-0.84)	0.03	Continuous
History of Benign Breast Disease										
No	241/408	1.00 (ref.)	201/432	0.77 (0.59-1.01)	185/436	0.71 (0.53-0.94)	191/457	0.57 (0.41-0.79)	0.0008	0.25
Yes	183/178	1.00 (ref.)	100/153	0.65 (0.45-0.96)	81/151	0.55 (0.36-0.84)	63/128	0.63 (0.38-1.07)	0.02	
Body Mass Index, kg/m²										
< 25	310/450	1.00 (ref.)	148/333	0.70 (0.53-0.93)	70/201	0.61 (0.43-0.87)	32/78	0.74 (0.44-1.26)	0.006	0.72
25-30	100/111	1.00 (ref.)	120/190	0.75 (0.50-1.13)	131/251	0.67 (0.45-0.99)	85/205	0.48 (0.31-0.74)	0.001	Categorical
>= 30	14/22	1.00 (ref.)	29/56	0.85 (0.33-2.18)	64/128	0.74 (0.31-1.77)	133/298	0.77 (0.33-1.77)	0.58	Continuous
First-Degree of Family History of Breast Cancer										
No	309/479	1.00 (ref.)	231/480	0.78 (0.62-1.00)	186/464	0.66 (0.51-0.85)	174/462	0.59 (0.43-0.80)	0.0002	0.33
Yes	78/84	1.00 (ref.)	41/79	0.50 (0.29-0.87)	56/88	0.67 (0.38-1.16)	42/66	0.52 (0.26-1.04)	0.09	
Nulliparity										
Nulliparous	52/56	1.00 (ref.)	24/47	0.50 (0.23-1.09)	28/42	0.46 (0.20-1.04)	20/57	0.19 (0.06-0.58)	0.004	0.02 [†]
Parous	367/527	1.00 (ref.)	269/534	0.76 (0.60-0.95)	234/541	0.67 (0.52-0.86)	229/522	0.63 (0.47-0.84)	0.0006	
Parity³										
1	39/52	1.00 (ref.)	21/42	0.95 (0.41-2.19)	20/42	0.44 (0.17-1.13)	17/46	0.59 (0.21-1.63)	0.16	0.28
2	112/159	1.00 (ref.)	80/168	0.65 (0.42-1.00)	59/152	0.61 (0.38-0.97)	66/154	0.56 (0.32-0.96)	0.03	
3+	216/316	1.00 (ref.)	168/324	0.79 (0.59-1.06)	155/347	0.72 (0.52-0.98)	146/322	0.66 (0.45-0.95)	0.02	
Age at 1st Child, yrs³										
<= 25.5	230/322	1.00 (ref.)	171/357	0.69 (0.52-0.92)	142/344	0.61 (0.44-0.83)	140/326	0.59 (0.41-0.85)	0.002	0.58
> 25.5	138/205	1.00 (ref.)	99/176	0.88 (0.60-1.29)	92/197	0.80 (0.53-1.19)	89/197	0.69 (0.43-1.10)	0.11	
Breast Feeding History³										
No	101/153	1.00 (ref.)	80/143	0.84 (0.55-1.30)	69/140	0.79 (0.49-1.26)	63/182	0.46 (0.26-0.79)	0.009	0.67
Yes	265/370	1.00 (ref.)	186/381	0.73 (0.56-0.96)	159/390	0.61 (0.46-0.83)	162/330	0.68 (0.48-0.97)	0.007	
Physical Activity, METs/week										
< 4.5	95/121	1.00 (ref.)	65/135	0.59 (0.36-0.95)	77/169	0.50 (0.30-0.82)	72/180	0.54 (0.30-0.95)	0.02	0.47
4.5 - 12	108/141	1.00 (ref.)	77/133	0.81 (0.51-1.26)	74/133	0.86 (0.54-1.37)	67/144	0.65 (0.38-1.12)	0.17	Categorical
12 - 25.5	110/144	1.00 (ref.)	77/156	0.55 (0.36-0.83)	48/129	0.50 (0.31-0.82)	58/124	0.46 (0.26-0.81)	0.003	0.40
>= 25.5	104/173	1.00 (ref.)	76/146	1.07 (0.69-1.64)	59/142	0.79 (0.49-1.28)	53/129	0.64 (0.36-1.15)	0.11	Continuous
Smoking Status										
Never	198/299	1.00 (ref.)	139/294	0.78 (0.57-1.07)	119/301	0.59 (0.42-0.84)	131/298	0.61 (0.41-0.92)	0.005	0.74
Past	188/241	1.00 (ref.)	135/246	0.69 (0.50-0.96)	132/231	0.82 (0.58-1.16)	102/240	0.55 (0.37-0.83)	0.02	
Current	37/45	1.00 (ref.)	27/44	0.85 (0.37-1.91)	14/53	0.31 (0.12-0.82)	20/43	0.57 (0.18-1.79)	0.07	
Menopausal Hormone Therapy Use										
Never	58/97	1.00 (ref.)	47/142	0.54 (0.31-0.94)	64/160	0.65 (0.37-1.12)	80/186	0.52 (0.28-0.96)	0.10	0.09
Past	62/134	1.00 (ref.)	56/121	1.03 (0.62-1.70)	64/136	1.08 (0.65-1.81)	61/146	0.84 (0.46-1.52)	0.67	
Current	292/337	1.00 (ref.)	186/303	0.74 (0.56-0.97)	122/269	0.54 (0.39-0.74)	101/229	0.54 (0.37-0.79)	< 0.0001	
Age at Menopause										
< 50	137/223	1.00 (ref.)	119/218	0.84 (0.60-1.19)	97/234	0.68 (0.46-0.99)	81/208	0.58 (0.37-0.93)	0.01	0.19
50 - 55	239/303	1.00 (ref.)	157/299	0.67 (0.50-0.91)	148/304	0.62 (0.45-0.85)	146/316	0.53 (0.37-0.77)	0.0005	
>= 55	21/23	1.00 (ref.)	20/35	0.60 (0.21-1.70)	13/24	1.16 (0.33-4.02)	17/29	0.74 (0.20-2.74)	0.98	

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: Race (White/Non-white); Age at diagnosis (Continuous); Body mass index at diagnosis (Continuous); Age at menarche (Continuous); Parity and age at 1st birth (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); First-degree family history of breast cancer (Binary); Age at Menopause (Continuous); Menopausal hormone therapy use (Never, Past, Current); History of benign breast disease (Binary); Alcohol consumption (0, 0-5, >=5 g/day); Smoking status (Never, Past, Current); Physical activity (Continuous, METs/week).

²Categorization of absolute area of dense and non-dense tissue was based on their distribution among postmenopausal controls.

³Analysis conducted among parous women only. Parity and age at 1st birth were removed from the set of adjusting factors in the regression model. Number of Children (1, 2, 3+), Age at 1st Child (before/after 25 yrs-old) and History of breast feeding (Binary) were further adjusted for, with exception of the covariate used for stratification.

*Statistically significant with p-value < 0.05

Supplementary Table 1.6 Associations of percent mammographic density, absolute dense and non-dense area with ER-positive breast cancer risk by breast cancer risk factors¹.

<i>Percent Density</i>		< 10%	10 - 25% (Ref.)		25 - 49%		>= 50%		P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)		
Age at Menarche, yrs										
< 12	45/221	0.66 (0.41-1.07)	96/377	1.00 (ref.)	156/328	2.53 (1.77-3.59)	51/97	3.15 (1.95-5.11)	< 0.0001	0.07
12 - 13	87/425	0.73 (0.53-1.00)	235/840	1.00 (ref.)	348/888	1.54 (1.23-1.92)	142/350	1.56 (1.17-2.09)	< 0.0001	
> 13	22/139	0.45 (0.24-0.84)	63/225	1.00 (ref.)	113/319	1.25 (0.81-1.93)	48/122	1.53 (0.89-2.62)	0.001	
Alcohol Consumption, g/day										
0	69/305	0.73 (0.51-1.04)	149/530	1.00 (ref.)	200/459	1.74 (1.31-2.30)	61/180	1.56 (1.05-2.31)	< 0.0001	Categorical
0 - 5	40/257	0.53 (0.34-0.82)	118/429	1.00 (ref.)	179/517	1.30 (0.96-1.75)	93/171	2.11 (1.45-3.07)	< 0.0001	
>= 5	38/166	0.74 (0.44-1.23)	85/370	1.00 (ref.)	195/452	2.09 (1.50-2.90)	74/186	1.93 (1.28-2.92)	< 0.0001	Continuous
History of Benign Breast Disease										
No	126/642	0.70 (0.53-0.92)	278/1140	1.00 (ref.)	408/1125	1.79 (1.46-2.19)	134/387	1.72 (1.30-2.28)	< 0.0001	0.33
Yes	28/146	0.52 (0.30-0.89)	117/308	1.00 (ref.)	212/416	1.41 (1.02-1.94)	109/182	1.94 (1.32-2.86)	< 0.0001	
Body Mass Index, kg/m²										
< 25	19/153	0.59 (0.33-1.07)	124/577	1.00 (ref.)	315/918	1.75 (1.34-2.30)	170/430	1.92 (1.41-2.62)	< 0.0001	Categorical
25-30	55/275	0.62 (0.43-0.92)	160/492	1.00 (ref.)	208/437	1.41 (1.07-1.86)	53/101	1.58 (1.03-2.42)	< 0.0001	
>= 30	77/350	0.76 (0.51-1.14)	101/359	1.00 (ref.)	81/158	2.09 (1.39-3.14)	18/30	2.18 (1.05-4.53)	< 0.0001	Continuous
First-Degree of Family History of Breast Cancer										
No	112/658	0.61 (0.47-0.80)	294/1212	1.00 (ref.)	471/1289	1.69 (1.39-2.04)	179/486	1.84 (1.44-2.35)	< 0.0001	0.33
Yes	31/83	0.94 (0.54-1.65)	77/186	1.00 (ref.)	115/212	1.53 (1.01-2.33)	41/71	1.83 (1.05-3.19)	0.01	
Nulliparity										
Nulliparous	12/76	0.38 (0.16-0.88)	37/125	1.00 (ref.)	86/188	1.65 (0.96-2.82)	39/76	2.31 (1.21-4.40)	< 0.0001	0.12
Parous	137/706	0.70 (0.54-0.90)	351/1309	1.00 (ref.)	522/1337	1.68 (1.40-2.01)	202/491	1.78 (1.40-2.26)	< 0.0001	
Parity										
1	7/69	0.43 (0.16-1.22)	29/126	1.00 (ref.)	80/155	2.90 (1.58-5.31)	28/62	2.35 (1.09-5.07)	< 0.0001	0.41
2	45/221	0.75 (0.49-1.17)	116/464	1.00 (ref.)	177/497	1.45 (1.06-1.99)	81/215	1.44 (0.97-2.12)	0.002	
3+	85/416	0.68 (0.49-0.95)	206/719	1.00 (ref.)	265/685	1.66 (1.30-2.13)	93/214	1.97 (1.39-2.79)	< 0.0001	
Age at 1st Child, yrs²										
<= 25.5	85/435	0.75 (0.54-1.03)	205/802	1.00 (ref.)	289/752	1.71 (1.35-2.18)	105/265	1.86 (1.34-2.59)	< 0.0001	0.54
> 25.5	52/272	0.62 (0.41-0.93)	148/511	1.00 (ref.)	238/584	1.64 (1.23-2.17)	97/227	1.70 (1.18-2.44)	< 0.0001	
Breast Feeding History²										
No	36/200	0.54 (0.33-0.87)	103/318	1.00 (ref.)	126/323	1.44 (0.99-2.09)	45/129	1.29 (0.78-2.14)	0.001	0.36
Yes	97/492	0.74 (0.55-1.01)	245/967	1.00 (ref.)	389/988	1.81 (1.47-2.24)	156/359	1.97 (1.49-2.60)	< 0.0001	
Physical Activity, METs/week										
< 4.5	40/234	0.70 (0.43-1.13)	94/357	1.00 (ref.)	157/321	2.28 (1.59-3.26)	45/106	1.48 (0.90-2.46)	< 0.0001	0.39
4.5 - 12	39/184	0.63 (0.39-1.00)	100/343	1.00 (ref.)	158/385	1.52 (1.09-2.12)	61/119	2.10 (1.34-3.28)	< 0.0001	
12 - 25.5	33/190	0.52 (0.32-0.86)	86/314	1.00 (ref.)	140/384	1.39 (0.98-1.96)	58/167	1.53 (0.98-2.36)	< 0.0001	0.35
>= 25.5	38/153	0.85 (0.51-1.42)	79/372	1.00 (ref.)	137/394	1.71 (1.19-2.46)	71/160	2.39 (1.53-3.71)	< 0.0001	Continuous
Smoking Status										
Never	72/403	0.58 (0.41-0.82)	214/795	1.00 (ref.)	332/888	1.64 (1.30-2.08)	134/339	1.94 (1.44-2.62)	< 0.0001	0.75
Past	71/310	0.76 (0.53-1.09)	157/547	1.00 (ref.)	241/540	1.60 (1.22-2.11)	92/190	1.65 (1.14-2.38)	< 0.0001	
Current	11/72	0.74 (0.26-2.11)	23/102	1.00 (ref.)	46/110	2.24 (1.03-4.84)	17/40	2.52 (0.95-6.73)	0.01	
Menopausal Hormone Therapy Use³										
Never	48/172	1.38 (0.80-2.36)	45/231	1.00 (ref.)	54/152	2.06 (1.19-3.57)	12/30	2.23 (0.76-6.50)	0.14	0.02*
Past	33/132	0.78 (0.44-1.38)	62/203	1.00 (ref.)	53/163	1.17 (0.71-1.93)	18/39	1.97 (0.93-4.19)	0.04	
Current	33/231	0.42 (0.26-0.68)	126/387	1.00 (ref.)	206/403	1.57 (1.16-2.12)	71/117	1.78 (1.17-2.70)	< 0.0001	

Age at Menopause³										
< 50	37/202	0.49 (0.30-0.82)	95/317	1.00 (ref.)	121/294	1.21 (0.84-1.74)	33/70	1.34 (0.77-2.31)	0.001	0.99
50 - 55	75/304	0.85 (0.59-1.24)	130/447	1.00 (ref.)	177/375	1.97 (1.43-2.71)	56/96	2.56 (1.61-4.06)	<0.0001	
>= 55	7/25	0.56 (0.12-2.55)	12/44	1.00 (ref.)	18/33	2.08 (0.70-6.24)	8/9	1.32 (0.25-6.99)	0.16	
<i>Dense Area⁴</i>	< 18.85 cm²		18.85-31.32 cm²		31.32-48.09 cm²		>= 48.09 cm²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	52/285	1.00 (ref.)	82/262	1.90 (1.20-3.01)	88/228	2.92 (1.85-4.61)	126/248	3.73 (2.42-5.74)	< 0.0001	0.02*
12-13	136/595	1.00 (ref.)	192/631	1.45 (1.09-1.92)	211/660	1.55 (1.17-2.06)	273/617	2.01 (1.53-2.64)	< 0.0001	
> 13	46/202	1.00 (ref.)	46/190	1.13 (0.66-1.93)	68/196	1.54 (0.93-2.54)	86/217	1.67 (1.02-2.73)	0.02	
Alcohol Consumption, g/day										
0	88/399	1.00 (ref.)	107/356	1.37 (0.97-1.94)	121/344	1.74 (1.24-2.45)	163/375	2.03 (1.45-2.82)	< 0.0001	0.99
0-5	58/342	1.00 (ref.)	90/345	1.64 (1.10-2.44)	117/339	2.18 (1.47-3.22)	165/348	2.78 (1.91-4.04)	< 0.0001	<i>Categorical</i>
>= 5	67/275	1.00 (ref.)	91/294	1.42 (0.95-2.14)	99/307	1.43 (0.96-2.14)	135/298	2.03 (1.38-3.00)	0.0005	<i>Continuous</i>
History of Benign Breast Disease										
No	177/859	1.00 (ref.)	210/862	1.29 (1.00-1.67)	255/803	1.82 (1.42-2.34)	304/770	2.18 (1.71-2.78)	< 0.0001	0.94
Yes	57/229	1.00 (ref.)	110/223	2.06 (1.34-3.17)	115/284	1.74 (1.14-2.64)	184/316	2.48 (1.66-3.70)	0.0001	
Body Mass Index, kg/m²										
< 25	72/416	1.00 (ref.)	166/565	1.72 (1.21-2.44)	177/566	1.98 (1.40-2.79)	213/531	2.50 (1.77-3.53)	< 0.0001	0.51
25-30	93/339	1.00 (ref.)	95/300	1.22 (0.84-1.75)	122/332	1.31 (0.92-1.86)	166/334	1.71 (1.22-2.40)	0.002	<i>Categorical</i>
>= 30	65/322	1.00 (ref.)	51/200	1.42 (0.87-2.33)	60/173	2.42 (1.50-3.88)	101/202	3.06 (1.98-4.72)	< 0.0001	0.07
First-Degree of Family History of Breast Cancer										
No	174/905	1.00 (ref.)	241/936	1.44 (1.13-1.84)	288/914	1.89 (1.49-2.40)	353/890	2.35 (1.87-2.96)	< 0.0001	0.25
Yes	50/132	1.00 (ref.)	63/118	1.52 (0.91-2.52)	64/143	1.26 (0.75-2.10)	87/159	1.76 (1.08-2.86)	0.05	
Nulliparity										
Nulliparous	18/95	1.00 (ref.)	34/100	2.53 (1.20-5.33)	56/129	3.28 (1.62-6.65)	66/141	2.86 (1.45-5.65)	0.006	0.84
Parous	210/983	1.00 (ref.)	281/975	1.40 (1.12-1.77)	306/945	1.65 (1.31-2.07)	415/940	2.21 (1.77-2.75)	< 0.0001	
Parity²										
1	15/76	1.00 (ref.)	30/120	1.81 (0.78-4.21)	42/111	2.48 (1.09-5.64)	57/105	3.65 (1.65-8.10)	0.0004	0.20
2	62/314	1.00 (ref.)	85/346	1.23 (0.81-1.85)	112/355	1.57 (1.06-2.34)	160/382	2.06 (1.41-3.00)	< 0.0001	
3+	133/593	1.00 (ref.)	166/509	1.53 (1.14-2.06)	152/479	1.62 (1.20-2.19)	198/453	2.16 (1.61-2.90)	< 0.0001	
Age at 1st Child, yrs²										
<= 25.5	124/618	1.00 (ref.)	158/564	1.48 (1.10-2.00)	161/521	1.62 (1.20-2.19)	241/551	2.33 (1.75-3.10)	< 0.0001	0.93
> 25.5	86/368	1.00 (ref.)	125/412	1.29 (0.90-1.85)	148/425	1.68 (1.18-2.38)	176/389	2.09 (1.48-2.95)	< 0.0001	
Breast Feeding History²										
No	52/264	1.00 (ref.)	74/229	1.68 (1.06-2.66)	82/245	1.84 (1.18-2.88)	102/232	2.70 (1.73-4.23)	< 0.0001	0.64
Yes	153/704	1.00 (ref.)	204/728	1.37 (1.05-1.79)	223/683	1.67 (1.28-2.17)	307/691	2.14 (1.66-2.76)	< 0.0001	
Physical Activity, METs/week										
< 4.5	60/277	1.00 (ref.)	75/266	1.26 (0.81-1.95)	78/221	1.79 (1.15-2.77)	123/254	1.89 (1.24-2.87)	0.001	0.90
4.5 - 12	56/249	1.00 (ref.)	68/255	1.32 (0.85-2.04)	109/273	1.87 (1.24-2.83)	125/254	2.28 (1.52-3.43)	< 0.0001	<i>Categorical</i>
12 - 25.5	46/279	1.00 (ref.)	79/234	2.24 (1.43-3.51)	78/261	2.03 (1.30-3.17)	114/281	2.92 (1.90-4.49)	< 0.0001	0.80
>= 25.5	56/243	1.00 (ref.)	71/276	1.26 (0.81-1.96)	85/291	1.47 (0.96-2.28)	113/269	2.03 (1.34-3.09)	0.0005	<i>Continuous</i>
Smoking Status										
Never	109/560	1.00 (ref.)	180/622	1.72 (1.27-2.34)	206/605	2.13 (1.58-2.88)	257/638	2.33 (1.74-3.14)	< 0.0001	0.68
Past	112/429	1.00 (ref.)	113/390	1.06 (0.75-1.48)	142/399	1.37 (0.98-1.90)	194/369	2.00 (1.46-2.73)	< 0.0001	
Current	13/95	1.00 (ref.)	26/71	3.29 (1.27-8.55)	21/79	2.75 (1.01-7.49)	37/79	4.86 (1.91-12.38)	0.002	
Menopausal Hormone Therapy Use³										
Never	46/174	1.00 (ref.)	33/151	0.75 (0.42-1.33)	37/132	0.96 (0.53-1.71)	43/128	1.06 (0.58-1.91)	0.78	0.002*
Past	33/140	1.00 (ref.)	41/138	1.10 (0.60-2.02)	39/139	1.27 (0.69-2.35)	53/120	1.94 (1.10-3.43)	0.02	
Current	46/253	1.00 (ref.)	72/278	1.53 (0.97-2.41)	137/294	2.51 (1.65-3.83)	181/313	3.16 (2.09-4.77)	< 0.0001	

Age at Menopause³										
< 50	40/199	1.00 (ref.)	62/226	1.32 (0.79-2.20)	81/238	1.66 (1.01-2.74)	103/220	2.30 (1.42-3.73)	0.0003	0.92
50 - 55	84/342	1.00 (ref.)	79/303	1.09 (0.74-1.62)	124/280	1.81 (1.25-2.62)	151/297	2.09 (1.46-3.01)	<0.0001	
>= 55	8/26	1.00 (ref.)	6/26	0.64 (0.14-2.96)	10/37	0.71 (0.17-3.02)	21/22	3.22 (0.82-12.62)	0.06	
Non-dense Area⁴										
< 67.12 cm²			67.12-104.59 cm²		104.59-155.67 cm²		>= 155.67 cm²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	85/190	1.00 (ref.)	83/262	0.65 (0.44-0.97)	88/255	0.59 (0.39-0.90)	92/316	0.42 (0.26-0.69)	0.0008	0.79
12-13	242/661	1.00 (ref.)	207/604	0.89 (0.69-1.13)	198/633	0.88 (0.68-1.15)	165/605	0.69 (0.50-0.94)	0.04	
> 13	85/233	1.00 (ref.)	68/217	0.71 (0.46-1.09)	54/193	0.55 (0.34-0.91)	39/162	0.36 (0.19-0.69)	0.001	
Alcohol Consumption, g/day										
0	118/326	1.00 (ref.)	108/330	0.85 (0.61-1.18)	118/371	0.77 (0.55-1.08)	135/447	0.58 (0.39-0.87)	0.008	0.72
0-5	129/341	1.00 (ref.)	115/337	0.83 (0.60-1.16)	102/355	0.73 (0.51-1.03)	84/341	0.59 (0.39-0.90)	0.01	<i>Categorical</i>
>= 5	136/347	1.00 (ref.)	109/347	0.65 (0.47-0.90)	92/272	0.74 (0.51-1.07)	55/208	0.47 (0.30-0.76)	0.005	<i>Continuous</i>
History of Benign Breast Disease										
No	252/774	1.00 (ref.)	234/811	0.77 (0.61-0.97)	239/847	0.74 (0.59-0.95)	221/862	0.55 (0.41-0.73)	< 0.0001	
Yes	162/312	1.00 (ref.)	125/276	0.82 (0.60-1.14)	102/239	0.76 (0.52-1.10)	77/225	0.58 (0.37-0.93)	0.02	
Body Mass Index, kg/m²										
< 25	305/866	1.00 (ref.)	189/662	0.77 (0.61-0.98)	99/410	0.71 (0.53-0.95)	35/140	0.82 (0.52-1.29)	0.02	0.11
25-30	85/181	1.00 (ref.)	132/330	0.81 (0.56-1.17)	164/417	0.83 (0.58-1.19)	95/377	0.49 (0.33-0.72)	0.0006	<i>Categorical</i>
>= 30	16/25	1.00 (ref.)	29/79	0.57 (0.24-1.32)	69/242	0.39 (0.18-0.82)	163/551	0.38 (0.18-0.79)	0.01	0.01* <i>Continuous</i>
First-Degree of Family History of Breast Cancer										
No	318/938	1.00 (ref.)	262/922	0.77 (0.63-0.95)	265/899	0.79 (0.64-0.99)	211/886	0.55 (0.42-0.71)	< 0.0001	0.86
Yes	73/128	1.00 (ref.)	74/140	0.83 (0.53-1.31)	61/152	0.53 (0.32-0.88)	56/132	0.58 (0.33-1.04)	0.03	
Nulliparity										
Nulliparous	54/132	1.00 (ref.)	50/119	0.95 (0.57-1.60)	40/87	0.77 (0.42-1.42)	30/127	0.28 (0.12-0.63)	0.008	0.14
Parous	357/946	1.00 (ref.)	299/952	0.76 (0.62-0.94)	296/993	0.73 (0.59-0.91)	260/952	0.59 (0.46-0.76)	<.0001	
Parity²										
1	47/115	1.00 (ref.)	43/98	1.05 (0.59-1.89)	32/92	0.70 (0.36-1.38)	22/107	0.36 (0.16-0.81)	0.02	0.91
2	124/387	1.00 (ref.)	98/330	0.85 (0.60-1.21)	111/357	0.98 (0.69-1.40)	86/323	0.83 (0.54-1.28)	0.57	
3+	186/444	1.00 (ref.)	158/524	0.66 (0.50-0.88)	153/544	0.58 (0.43-0.79)	152/522	0.49 (0.34-0.69)	<.0001	
Age at 1st Child, yrs²										
<= 25.5	187/502	1.00 (ref.)	170/573	0.71 (0.54-0.94)	168/612	0.68 (0.51-0.90)	159/567	0.58 (0.41-0.81)	0.002	0.65
> 25.5	171/446	1.00 (ref.)	132/381	0.83 (0.61-1.12)	129/381	0.80 (0.58-1.11)	103/386	0.60 (0.40-0.89)	0.02	
Breast Feeding History²										
No	78/239	1.00 (ref.)	73/216	0.89 (0.58-1.37)	83/221	1.07 (0.69-1.66)	76/294	0.61 (0.36-1.01)	0.14	0.44
Yes	277/700	1.00 (ref.)	220/720	0.73 (0.58-0.92)	208/746	0.64 (0.50-0.82)	182/640	0.58 (0.43-0.79)	0.0001	
Physical Activity, METs/week										
< 4.5	83/191	1.00 (ref.)	85/222	0.85 (0.57-1.28)	82/283	0.60 (0.39-0.92)	86/322	0.54 (0.33-0.89)	0.006	0.48
4.5 - 12	102/257	1.00 (ref.)	87/252	0.81 (0.56-1.18)	91/239	0.91 (0.61-1.36)	78/283	0.58 (0.36-0.92)	0.06	<i>Categorical</i>
12 - 25.5	95/290	1.00 (ref.)	86/270	0.81 (0.56-1.19)	73/260	0.89 (0.60-1.32)	63/235	0.66 (0.41-1.07)	0.16	0.77
>= 25.5	117/309	1.00 (ref.)	79/294	0.68 (0.48-0.98)	72/264	0.61 (0.41-0.91)	57/212	0.43 (0.26-0.73)	0.0009	<i>Continuous</i>
Smoking Status										
Never	224/637	1.00 (ref.)	183/621	0.78 (0.61-1.01)	192/590	0.77 (0.59-1.01)	153/577	0.51 (0.37-0.72)	0.0004	0.82
Past	159/369	1.00 (ref.)	145/387	0.76 (0.56-1.03)	135/410	0.71 (0.52-0.98)	122/421	0.61 (0.42-0.88)	0.009	
Current	31/79	1.00 (ref.)	31/78	0.98 (0.47-2.05)	12/83	0.60 (0.24-1.49)	23/84	0.56 (0.20-1.54)	0.19	
Menopausal Hormone Therapy Use³										
Never	39/97	1.00 (ref.)	25/142	0.37 (0.19-0.74)	45/160	0.57 (0.30-1.07)	50/186	0.34 (0.16-0.72)	0.03	0.27
Past	34/134	1.00 (ref.)	40/121	1.20 (0.66-2.20)	47/136	1.36 (0.73-2.51)	45/146	0.91 (0.45-1.86)	0.93	
Current	168/337	1.00 (ref.)	127/303	0.87 (0.63-1.19)	76/269	0.60 (0.41-0.87)	65/229	0.61 (0.39-0.96)	0.006	
Age at Menopause³										
< 50	79/223	1.00 (ref.)	75/218	0.91 (0.60-1.38)	69/234	0.88 (0.56-1.37)	63/208	0.79 (0.46-1.36)	0.40	0.76
50 - 55	141/303	1.00 (ref.)	111/299	0.76 (0.54-1.07)	100/304	0.63 (0.43-0.91)	86/316	0.42 (0.27-0.66)	0.0002	
>= 55	13/23	1.00 (ref.)	12/35	0.47 (0.13-1.69)	6/24	0.76 (0.16-3.63)	14/29	0.68 (0.15-3.10)	0.90	

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Analysis conducted among parous women only. *Parity and age at 1st birth* were removed from the set of adjusting factors in the regression model. *Number of Children* (1, 2, 3+), *Age at 1st Child* (before/after 25 yrs-old) and *History of breast feeding* (Binary) were further adjusted for, with exception of the covariate used for stratification.

³Conducted among menopausal women only. *Menopausal status* was removed from the covariate set for adjustment. *Age at menopause* (Continuous) was further adjusted for, with exception of the covariate used for stratification.

⁴Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls.

*Statistically significant with p-value < 0.05

Supplementary Table 1.7 Associations of percent mammographic density, absolute dense and non-dense area with ER-negative breast cancer risk by breast cancer risk factors¹.

<i>Percent Density</i>	< 10%		10 - 25% (Ref.)		25 - 49%		≥ 50%		P for Trend	P for Interaction
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)		
Age at Menarche, yrs										
< 12	11/221	1.12 (0.48-2.61)	24/377	1.00 (ref.)	38/328	2.50 (1.29-4.84)	11/97	3.61 (1.53-8.52)	0.002	0.29
12 - 13	13/425	0.57 (0.27-1.17)	43/840	1.00 (ref.)	75/888	1.81 (1.16-2.82)	41/350	2.46 (1.47-4.14)	< 0.0001	
> 13	5/139	0.57 (0.19-1.69)	18/225	1.00 (ref.)	24/319	1.14 (0.52-2.50)	9/122	1.03 (0.37-2.89)	0.36	
Alcohol Consumption, g/day										
0	12/305	0.72 (0.33-1.55)	35/530	1.00 (ref.)	45/459	1.76 (1.01-3.05)	18/180	2.21 (1.10-4.43)	0.003	0.81
0 - 5	12/257	0.98 (0.46-2.12)	24/429	1.00 (ref.)	45/517	1.81 (1.03-3.20)	22/171	2.93 (1.48-5.77)	0.002	Categorical
≥ 5	5/166	0.42 (0.14-1.30)	22/370	1.00 (ref.)	39/452	1.66 (0.91-3.02)	21/186	1.79 (0.87-3.67)	0.007	0.04*
History of Benign Breast Disease										
No	22/642	0.73 (0.42-1.28)	62/1140	1.00 (ref.)	95/1125	2.04 (1.37-3.05)	32/387	2.12 (1.26-3.59)	< 0.0001	0.51
Yes	7/146	0.68 (0.26-1.75)	24/308	1.00 (ref.)	43/416	1.30 (0.73-2.31)	30/182	2.31 (1.21-4.44)	0.004	
Body Mass Index, kg/m²										
< 25	6/153	0.71 (0.26-1.89)	30/577	1.00 (ref.)	77/918	1.65 (1.02-2.67)	45/430	2.15 (1.26-3.68)	0.001	0.44
25-30	13/275	1.04 (0.48-2.24)	27/492	1.00 (ref.)	41/437	1.94 (1.09-3.46)	14/101	2.78 (1.31-5.92)	0.003	Categorical
≥ 30	10/350	0.61 (0.27-1.38)	25/359	1.00 (ref.)	18/158	1.98 (0.96-4.09)	3/30	1.92 (0.50-7.38)	0.005	0.17
First-Degree of Family History of Breast Cancer										
No	22/658	0.69 (0.40-1.18)	60/1212	1.00 (ref.)	111/1289	1.78 (1.24-2.55)	49/486	2.14 (1.38-3.32)	< 0.0001	0.47
Yes	6/83	1.08 (0.37-3.17)	15/186	1.00 (ref.)	20/212	1.84 (0.79-4.26)	10/71	3.77 (1.36-10.46)	0.02	
Nulliparity										
Nulliparous	0/76	NA	6/125	1.00 (ref.)	17/188	2.03 (0.62-6.63)	7/76	3.34 (0.82-13.55)	0.006	0.20
Parous	29/706	0.82 (0.51-1.33)	80/1309	1.00 (ref.)	119/1337	1.74 (1.23-2.45)	55/491	2.23 (1.46-3.40)	< 0.0001	
Parity										
1	4/69	0.99 (0.22-4.42)	6/126	1.00 (ref.)	11/155	1.60 (0.46-5.51)	6/62	2.31 (0.57-9.41)	0.24	0.83
2	7/221	0.61 (0.26-1.48)	29/464	1.00 (ref.)	46/497	1.44 (0.82-2.51)	25/215	1.96 (1.04-3.71)	0.006	
3+	18/416	0.84 (0.44-1.61)	45/719	1.00 (ref.)	62/685	1.94 (1.21-3.12)	24/214	2.16 (1.15-4.07)	0.001	
Age at 1st Child, yrs²										
≤ 25.5	17/435	0.82 (0.43-1.56)	50/802	1.00 (ref.)	76/752	2.13 (1.36-3.33)	30/265	2.55 (1.45-4.49)	< 0.0001	0.40
> 25.5	12/272	0.82 (0.39-1.73)	30/511	1.00 (ref.)	43/584	1.21 (0.70-2.08)	25/227	1.84 (0.97-3.50)	0.04	
Breast Feeding History²										
No	6/200	0.45 (0.16-1.24)	23/318	1.00 (ref.)	36/323	1.89 (0.99-3.63)	17/129	1.91 (0.85-4.31)	0.004	0.38
Yes	23/492	1.05 (0.60-1.83)	55/967	1.00 (ref.)	82/988	1.73 (1.14-2.61)	38/359	2.31 (1.40-3.82)	0.0009	
Physical Activity, METs/week										
< 4.5	7/234	0.83 (0.30-2.33)	17/357	1.00 (ref.)	44/321	4.07 (2.02-8.24)	11/106	2.46 (0.97-6.27)	0.0009	0.03*
4.5 - 12	8/184	0.74 (0.29-1.90)	21/343	1.00 (ref.)	33/385	1.57 (0.79-3.11)	21/119	4.43 (2.02-9.72)	0.0002	Categorical
12 - 25.5	6/190	0.74 (0.27-2.01)	18/314	1.00 (ref.)	23/384	1.20 (0.59-2.47)	15/167	1.82 (0.80-4.11)	0.08	0.045*
≥ 25.5	8/153	0.71 (0.29-1.77)	25/372	1.00 (ref.)	32/394	1.30 (0.71-2.38)	15/160	1.42 (0.65-3.09)	0.15	Continuous
Smoking Status										
Never	17/403	0.83 (0.45-1.55)	51/795	1.00 (ref.)	79/888	1.79 (1.15-2.78)	35/339	2.43 (1.44-4.12)	0.0001	0.99
Past	11/310	0.79 (0.35-1.78)	27/547	1.00 (ref.)	51/540	1.97 (1.12-3.44)	26/190	2.91 (1.49-5.69)	0.0003	
Current	1/72	0.15 (0.02-1.50)	8/102	1.00 (ref.)	8/110	0.87 (0.25-3.05)	1/40	NA	0.71	
Menopausal Hormone Therapy Use³										
Never	3/172	0.28 (0.07-1.05)	17/231	1.00 (ref.)	15/152	1.07 (0.43-2.64)	6/30	1.73 (0.32-9.37)	0.06	0.46
Past	6/132	1.02 (0.33-3.18)	11/203	1.00 (ref.)	8/163	1.17 (0.42-3.20)	8/39	2.94 (0.75-11.57)	0.29	
Current	8/231	0.85 (0.33-2.21)	23/387	1.00 (ref.)	48/403	2.65 (1.39-5.04)	18/117	3.55 (1.62-7.77)	0.0001	

Age at Menopause³										
< 50	6/202	0.47 (0.16-1.37)	24/317	1.00 (ref.)	25/294	1.58 (0.79-3.17)	10/70	2.22 (0.87-5.66)	0.006	0.94
50 - 55	13/304	0.89 (0.40-1.97)	24/447	1.00 (ref.)	37/375	2.02 (1.07-3.83)	16/96	4.04 (1.75-9.36)	0.0007	
>= 55	0/25	NA	4/44	1.00 (ref.)	7/33	1.70 (0.09-30.60)	1/9	0.98 (0.02-55.51)	0.88	
<i>Dense Area⁴</i>	< 18.85 cm ²		18.85-31.32 cm ²		31.32-48.09 cm ²		≥ 48.09 cm ²			
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	12/285	1.00 (ref.)	18/262	1.22 (0.54-2.78)	19/228	1.61 (0.71-3.68)	35/248	2.80 (1.36-5.78)	0.002	0.33
12-13	20/595	1.00 (ref.)	29/631	1.58 (0.82-3.07)	53/660	2.68 (1.45-4.93)	70/617	3.76 (2.09-6.77)	< 0.0001	
> 13	12/202	1.00 (ref.)	11/190	1.06 (0.39-2.87)	13/196	1.30 (0.51-3.30)	20/217	1.62 (0.66-3.98)	0.25	
Alcohol Consumption, g/day										
0	17/399	1.00 (ref.)	24/356	1.32 (0.61-2.86)	29/344	2.28 (1.14-4.57)	40/375	2.72 (1.38-5.34)	0.0009	0.72
0-5	13/342	1.00 (ref.)	17/345	1.33 (0.61-2.93)	29/339	2.30 (1.11-4.78)	44/348	3.44 (1.73-6.86)	< 0.0001	<i>Categorical</i>
≥ 5	13/275	1.00 (ref.)	16/294	1.26 (0.57-2.78)	21/307	1.33 (0.61-2.92)	37/298	2.32 (1.13-4.79)	0.01	<i>Continuous</i>
History of Benign Breast Disease										
No	33/859	1.00 (ref.)	40/862	1.27 (0.75-2.17)	59/803	2.05 (1.24-3.37)	79/770	2.63 (1.63-4.25)	< 0.0001	0.63
Yes	11/229	1.00 (ref.)	19/223	1.46 (0.63-3.39)	26/284	1.85 (0.85-4.05)	48/316	3.26 (1.57-6.81)	0.0003	
Body Mass Index, kg/m²										
< 25	17/416	1.00 (ref.)	34/565	1.44 (0.75-2.76)	51/566	2.39 (1.29-4.42)	56/531	2.74 (1.48-5.07)	0.0002	<i>Categorical</i>
25-30	18/339	1.00 (ref.)	17/300	0.99 (0.44-2.20)	20/332	1.23 (0.59-2.60)	40/334	2.33 (1.20-4.51)	0.005	
>= 30	8/322	1.00 (ref.)	8/200	1.50 (0.52-4.31)	11/173	2.27 (0.80-6.46)	29/202	4.76 (1.99-11.40)	0.0002	<i>Continuous</i>
First-Degree of Family History of Breast Cancer										
No	31/905	1.00 (ref.)	48/936	1.51 (0.92-2.47)	69/914	2.11 (1.32-3.37)	94/890	2.92 (1.86-4.57)	< 0.0001	0.87
Yes	10/132	1.00 (ref.)	5/118	0.49 (0.14-1.68)	11/143	1.18 (0.44-3.17)	25/159	2.13 (0.89-5.13)	0.02	
Nulliparity										
Nulliparous	1/95	1.00 (ref.)	4/100	NA	10/129	NA	15/141	NA	0.005	0.16
Parous	43/983	1.00 (ref.)	55/975	1.18 (0.75-1.87)	74/945	1.72 (1.12-2.64)	111/940	2.50 (1.67-3.75)	< 0.0001	
Parity²										
1	2/76	1.00 (ref.)	4/120	1.83 (0.29-11.51)	5/111	2.02 (0.32-12.94)	16/105	7.17 (1.37-37.54)	0.004	0.26
2	15/314	1.00 (ref.)	15/346	0.72 (0.32-1.63)	35/355	1.88 (0.96-3.69)	42/382	2.04 (1.06-3.93)	0.003	
3+	26/593	1.00 (ref.)	36/509	1.61 (0.89-2.91)	34/479	1.62 (0.89-2.96)	53/453	2.57 (1.47-4.48)	0.001	
Age at 1st Child, yrs²										
<= 25.5	24/618	1.00 (ref.)	36/564	1.48 (0.81-2.71)	47/521	2.38 (1.35-4.18)	66/551	2.92 (1.69-5.03)	< 0.0001	0.69
> 25.5	19/368	1.00 (ref.)	19/412	0.86 (0.43-1.75)	27/425	1.04 (0.53-2.03)	45/389	2.00 (1.09-3.69)	0.008	
Breast Feeding History²										
No	10/264	1.00 (ref.)	20/229	2.65 (1.06-6.61)	22/245	2.95 (1.20-7.22)	30/232	3.72 (1.53-9.04)	0.005	0.69
Yes	33/704	1.00 (ref.)	34/728	0.84 (0.49-1.45)	52/683	1.41 (0.85-2.31)	79/691	2.14 (1.35-3.39)	< 0.0001	
Physical Activity, METs/week										
< 4.5	11/277	1.00 (ref.)	13/266	0.77 (0.29-2.05)	22/221	2.45 (1.08-5.56)	33/254	2.87 (1.31-6.26)	0.0005	0.07
4.5 - 12	13/249	1.00 (ref.)	11/255	1.00 (0.40-2.52)	22/273	1.54 (0.66-3.57)	37/254	2.99 (1.39-6.43)	0.0008	
12 - 25.5	5/279	1.00 (ref.)	12/234	2.56 (0.86-7.64)	19/261	3.05 (1.06-8.72)	26/281	4.77 (1.75-12.98)	0.001	0.01*
>= 25.5	15/243	1.00 (ref.)	20/276	1.43 (0.66-3.09)	19/291	1.44 (0.66-3.12)	26/269	1.70 (0.80-3.62)	0.20	<i>Continuous</i>
Smoking Status										
Never	27/560	1.00 (ref.)	32/622	0.93 (0.51-1.69)	53/605	1.78 (1.05-3.02)	70/638	2.14 (1.29-3.55)	0.0002	0.57
Past	16/429	1.00 (ref.)	19/390	1.51 (0.70-3.23)	28/399	1.88 (0.90-3.91)	52/369	3.75 (1.91-7.38)	< 0.0001	
Current	1/95	1.00 (ref.)	8/71	11.25 (1.21-104.82)	4/79	7.43 (0.71-77.41)	5/79	5.06 (0.49-52.65)	0.39	
Menopausal Hormone Therapy Use³										
Never	6/174	1.00 (ref.)	9/151	2.07 (0.68-6.30)	11/132	1.13 (0.32-3.98)	15/128	2.29 (0.75-7.03)	0.27	0.20
Past	5/140	1.00 (ref.)	10/138	1.76 (0.55-5.62)	4/139	0.89 (0.22-3.56)	14/120	2.10 (0.65-6.83)	0.39	
Current	10/253	1.00 (ref.)	20/278	1.54 (0.62-3.84)	23/294	1.75 (0.74-4.15)	44/313	3.43 (1.54-7.61)	0.0007	

Age at Menopause³										
< 50	9/199	1.00 (ref.)	17/226	1.58 (0.56-4.45)	14/238	1.81 (0.65-5.04)	25/220	2.67 (1.02-7.00)	0.03	0.72
50 - 55	14/342	1.00 (ref.)	20/303	1.66 (0.77-3.59)	18/280	1.22 (0.53-2.82)	38/297	2.82 (1.37-5.79)	0.008	
>= 55	1/26	1.00 (ref.)	3/26	NA	3/37	NA	5/22	NA	0.39	
Non-dense Area⁴										
< 67.12 cm² 67.12-104.59 cm² 104.59-155.67 cm² >= 155.67 cm²										
Breast Cancer Risk Factors	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	Cases/Controls	OR (95% CI)	P for Trend	P for Interaction
Age at Menarche, yrs										
< 12	17/190	1.00 (ref.)	22/262	0.87 (0.43-1.78)	21/255	0.57 (0.26-1.25)	24/316	0.49 (0.20-1.24)	0.08	0.80
12-13	69/661	1.00 (ref.)	37/604	0.64 (0.41-1.00)	30/633	0.49 (0.29-0.82)	36/605	0.52 (0.29-0.94)	0.008	
> 13	16/233	1.00 (ref.)	18/217	1.12 (0.50-2.53)	14/193	0.84 (0.33-2.13)	8/162	0.68 (0.22-2.11)	0.47	
Alcohol Consumption, g/day										
0	33/326	1.00 (ref.)	26/330	0.76 (0.42-1.39)	24/371	0.51 (0.26-1.00)	27/447	0.48 (0.22-1.04)	0.03	0.55
0-5	35/341	1.00 (ref.)	22/337	0.66 (0.37-1.18)	21/355	0.49 (0.26-0.94)	25/341	0.72 (0.35-1.46)	0.16	<i>Categorical</i>
>= 5	31/347	1.00 (ref.)	27/347	0.82 (0.45-1.49)	16/272	0.65 (0.32-1.32)	13/208	0.48 (0.19-1.19)	0.09	<i>Continuous</i>
History of Benign Breast Disease										
No	63/774	1.00 (ref.)	48/811	0.77 (0.50-1.19)	49/847	0.60 (0.38-0.96)	51/862	0.49 (0.28-0.86)	0.007	
Yes	41/312	1.00 (ref.)	29/276	0.71 (0.41-1.23)	16/239	0.43 (0.21-0.87)	18/225	0.79 (0.36-1.69)	0.15	
Body Mass Index, kg/m²										
< 25	76/866	1.00 (ref.)	47/662	0.77 (0.51-1.15)	24/410	0.54 (0.31-0.94)	11/140	0.90 (0.43-1.89)	0.09	0.99
25-30	25/181	1.00 (ref.)	21/330	0.54 (0.27-1.06)	32/417	0.56 (0.30-1.08)	17/377	0.36 (0.17-0.75)	0.01	<i>Categorical</i>
>= 30	1/25	1.00 (ref.)	9/79	2.65 (0.30-23.30)	8/242	0.69 (0.08-6.01)	38/551	1.32 (0.17-10.51)	0.76	<i>Continuous</i>
First-Degree of Family History of Breast Cancer										
No	89/938	1.00 (ref.)	58/922	0.74 (0.51-1.06)	45/899	0.55 (0.36-0.84)	50/886	0.58 (0.35-0.95)	0.007	0.20
Yes	13/128	1.00 (ref.)	13/140	0.90 (0.37-2.22)	13/152	0.51 (0.19-1.38)	12/132	0.51 (0.17-1.55)	0.16	
Nulliparity										
Nulliparous	11/132	1.00 (ref.)	8/119	0.85 (0.28-2.56)	7/87	0.81 (0.23-2.88)	4/127	0.13 (0.02-0.91)	0.08	0.54
Parous	92/946	1.00 (ref.)	69/952	0.74 (0.52-1.06)	57/993	0.55 (0.36-0.82)	65/952	0.62 (0.39-0.98)	0.01	
Parity²										
1	7/115	1.00 (ref.)	7/98	1.27 (0.38-4.24)	6/92	1.05 (0.26-4.24)	7/107	0.94 (0.19-4.76)	0.92	0.93
2	42/387	1.00 (ref.)	28/330	0.73 (0.42-1.27)	15/357	0.37 (0.18-0.76)	22/323	0.66 (0.31-1.37)	0.05	
3+	43/444	1.00 (ref.)	34/524	0.72 (0.43-1.21)	36/544	0.64 (0.37-1.12)	36/522	0.61 (0.31-1.17)	0.11	
Age at 1st Child, yrs²										
<= 25.5	55/502	1.00 (ref.)	42/573	0.63 (0.40-1.00)	32/612	0.41 (0.24-0.70)	44/567	0.55 (0.30-0.98)	0.009	0.40
> 25.5	37/446	1.00 (ref.)	27/381	0.92 (0.52-1.62)	25/381	0.86 (0.46-1.60)	21/386	0.74 (0.35-1.59)	0.45	
Breast Feeding History²										
No	24/239	1.00 (ref.)	29/216	1.34 (0.70-2.55)	14/221	0.58 (0.26-1.30)	15/294	0.39 (0.15-1.02)	0.02	0.20
Yes	68/700	1.00 (ref.)	39/720	0.57 (0.37-0.89)	42/746	0.56 (0.35-0.89)	49/640	0.76 (0.45-1.30)	0.15	
Physical Activity, METs/week										
< 4.5	22/191	1.00 (ref.)	23/222	0.87 (0.44-1.72)	15/283	0.39 (0.17-0.89)	19/322	0.58 (0.24-1.41)	0.08	0.17
4.5 - 12	31/257	1.00 (ref.)	16/252	0.51 (0.25-1.01)	18/239	0.43 (0.20-0.95)	18/283	0.39 (0.16-0.94)	0.02	<i>Categorical</i>
12 - 25.5	24/290	1.00 (ref.)	12/270	0.59 (0.27-1.28)	12/260	0.68 (0.31-1.50)	14/235	0.79 (0.31-2.00)	0.51	0.38
>= 25.5	24/309	1.00 (ref.)	25/294	1.10 (0.58-2.09)	17/264	0.83 (0.40-1.72)	14/212	0.62 (0.24-1.61)	0.32	<i>Continuous</i>
Smoking Status										
Never	67/637	1.00 (ref.)	40/621	0.61 (0.39-0.95)	35/590	0.45 (0.27-0.76)	40/577	0.48 (0.27-0.88)	0.004	0.89
Past	32/369	1.00 (ref.)	31/387	0.95 (0.54-1.66)	25/410	0.71 (0.38-1.34)	27/421	0.74 (0.36-1.54)	0.30	
Current	5/79	1.00 (ref.)	6/78	1.44 (0.31-6.78)	5/83	0.90 (0.17-4.63)	2/84	0.24 (0.02-2.36)	0.25	
Menopausal Hormone Therapy Use³										
Never	8/97	1.00 (ref.)	15/142	2.80 (0.70-11.20)	7/160	1.87 (0.42-8.29)	11/186	2.06 (0.42-10.07)	0.71	0.10
Past	12/134	1.00 (ref.)	5/121	0.60 (0.17-2.12)	7/136	0.98 (0.30-3.13)	9/146	1.12 (0.30-4.15)	0.78	
Current	44/337	1.00 (ref.)	20/303	0.45 (0.23-0.86)	20/269	0.47 (0.23-0.93)	13/229	0.38 (0.16-0.93)	0.01	
Age at Menopause³										
< 50	21/223	1.00 (ref.)	19/218	0.67 (0.31-1.43)	18/234	0.56 (0.25-1.26)	7/208	0.35 (0.12-1.05)	0.05	0.43
50 - 55	34/303	1.00 (ref.)	15/299	0.53 (0.25-1.10)	15/304	0.55 (0.26-1.16)	26/316	0.91 (0.41-2.04)	0.63	
>= 55	3/23	1.00 (ref.)	6/35	0.83 (0.02-30.77)	3/24	0.62 (0.003-148.21)	0/29	NA	0.32	

¹Multivariate adjusted logistic regression models were adjusted for the following covariates, with exception of the covariate used for stratification: *Race* (White/Non-white); *Age at diagnosis* (Continuous); *BMI at diagnosis* (Continuous); *Age at menarche* (Continuous); *Parity and age at 1st birth* (Nulliparous, Any number of children and 1st birth no later than 25 yrs-old, Any number of children and 1st birth after 25 yrs-old); *Menopausal status* (Premenopausal, Postmenopausal); *Menopausal hormone therapy use* (Never, Past, Current); *First-degree family history of breast cancer* (Binary); *History of benign breast disease* (Binary); *Alcohol consumption* (0, 0-5, >=5 g/day); *Smoking status* (Never, Past, Current); *Physical activity* (Continuous, METs/week).

²Analysis conducted among parous women only. *Parity and age at 1st birth* were removed from the set of adjusting factors in the regression model. *Number of Children* (1, 2, 3+), *Age at 1st Child* (before/after 25 yrs-old) and *History of breast feeding* (Binary) were further adjusted for, with exception of the covariate used for stratification.

³Conducted among menopausal women only. *Menopausal status* was removed from the covariate set for adjustment. *Age at menopause* (Continuous) was further adjusted for, with exception of the covariate used for stratification.

⁴Categorization of absolute area of dense and non-dense tissue was based on their distribution among all controls.

*Statistically significant with p-value < 0.05

Supplementary Table 2.1 Information, sample size and the distributions of key variables, by study included in the GWAS analysis.

Study Name	Country	Study Design	Sample Size	MD Phenotypes Available	Genotyping Platform	Age, yrs Mean (SD)	BMI, kg/m ² Mean (SD)	PMD, % Mean (SD)	DA, cm ² Mean (SD)	NDA, cm ² Mean (SD)
ABCFS	Australia	Family-based study	100	DA, NDA, PMD	iCOGs + OncoArray	39.5 (6.3)	23.6 (3.8)	45.4 (23.0)	48.2 (30.2)	64.7 (44.7)
BBCC	Germany	Case-control	361	DA, NDA, PMD	iCOGs	57.1 (10.4)	25.5 (4.6)	38.2 (20.1)	71.2 (37.7)	138.4 (88.8)
BCEES	Australia	Case-control	697	DA, NDA, PMD	OncoArray	59.9 (7.6)	27.1 (5.4)	10.3 (11.9)	11.0 (12.8)	111.6 (43.4)
BREOGAN	Spain	Case-control	376	DA, NDA, PMD	OncoArray	52.6 (12.5)	26.2 (4.9)	22.6 (14.1)	29.6 (19.0)	118.1 (61.7)
CBCS	Canada	Population-based cohort study	1,122 (DA)	DA, NDA, PMD	OncoArray	57.1 (9.8)	25.7 (5.1)	17.7 (13.1)	20.8 (16.1)	117.2 (64.6)
			1,128 (NDA)							
			1,105 (PMD)							
FHRISK	UK	Family-based study	371	PMD	OncoArray	45.6 (8.2)	25.4 (5.0)	39.9 (21.0)	-	-
KCONFAB	Australia	Family-based study	52 (DA)	DA, NDA, PMD	iCOGs	51.9 (8.7)	26.6 (4.4)	27.1 (19.6)	27.7 (24.7)	85.3 (47.8)
			53 (NDA)							
			51 (PMD)							
MCBCS	USA	Case-control	1,434 (DA)	DA, NDA, PMD	iCOGs + OncoArray	59.4 (11.5)	27.5 (5.6)	17.8 (12.4)	24.5 (16.9)	138.8 (64.3)
			1,435 (PMD)							
			1,468 (NDA)							
MCCS	Australia	Nested Case-control	692	DA, NDA, PMD	iCOGs + OncoArray	58.5 (7.3)	26.5 (4.7)	18.2 (16.6)	21.3 (21.7)	133.6 (66.9)
MEC	USA	Nested Case-control	101	DA, NDA, PMD	iCOGs	56.0 (8.5)	25.3 (6.3)	28.3 (24.2)	28.9 (24.3)	103.8 (77.1)
MMHS	USA	Nested Case-control	3,150 (DA, PMD)	DA, NDA, PMD	iCOGs + OncoArray	54.2 (12.8)	27.5 (6.2)	20.5 (14.5)	26.7 (18.4)	127.7 (71.4)
			3,209 (NDA)							
NBCS	Norway	Case-control	39 (DA, PMD)	DA, NDA, PMD	iCOGs	64.5 (5.5)	27.1 (4.8)	15.7 (9.8)	25.4 (16.1)	152.8 (62.4)
			40 (NDA)							
NC-BCFR	USA	Family-based study	58	DA, NDA, PMD	OncoArray	50.0 (8.6)	24.4 (5.5)	37.7 (18.6)	41.2 (23.7)	81.9 (57.9)
NHS	USA	Nested Case-control	185	DA, NDA, PMD	OncoArray	52.1 (6.9)	24.6 (4.1)	34.5 (20.4)	47.5 (31.8)	104.8 (68.4)
NHS2	USA	Nested Case-control	1,249	DA, NDA, PMD	OncoArray	45.8 (4.7)	26.2 (6.0)	38.4 (17.7)	42.6 (24.3)	76.5 (47.3)
OFBCR	Canada	Family-based study	155 (DA, PMD)	DA, NDA, PMD	iCOGs + OncoArray	50.4 (7.7)	26.3 (4.8)	36.2 (16.7)	47.4 (27.1)	96.0 (55.1)
			159 (NDA)							
PBCS	Poland	Case-control	125 (DA, PMD)	DA, NDA, PMD	OncoArray	54.9 (9.9)	27.7 (5.2)	28.8 (15.0)	40.7 (25.6)	115.1 (61.9)
			128 (NDA)							
PROCAS	UK	Population-based cohort study	2,030	PMD	OncoArray	59.6 (6.8)	26.9 (5.3)	29.2 (17.3)	-	-
SASBAC	Sweden	Case-control	1,634 (DA)	DA, NDA, PMD	iCOGs	62.8 (6.3)	25.6 (4.0)	16.1 (14.1)	25.5 (23.2)	145.1 (56.6)
			1,636 (NDA)							
			1,635 (PMD)							
SEARCH	UK	Case-control	1,042 (DA, NDA)	DA, NDA, PMD	iCOGs	59.8 (8.5)	27.3 (5.0)	20.0 (15.9)	24.5 (19.6)	163.5 (71.9)
			1,959 (PMD)							
UKBGS	UK	Nested Case-control	1,233 (DA, NDA)	DA, NDA, PMD	iCOGs + OncoArray	58.6 (5.7)	25.9 (4.3)	26.9 (18.8)	34.1 (24.5)	106.5 (56.3)
			1,252 (PMD)							
Total			13,805 (DA)		~6,566 iCOGs	56.6 (10.3)	26.5 (5.3)	23.4 (17.6)	28.5 (23.5)	120.4 (67.1)
			13,915 (NDA)		~10,560 OncoArray					
			17,126 (PMD)							

Supplementary Table 2.2 Information and sample size of previous GWASs with summary statistics collected.

Study Name	Country	Study Design	Sample Size	MD Measures Available	Genotyping Platform
AMDTSS	Australia	Family-based study	2,485	DA, NDA, PMD	OncoArray
DDM-Spain	Spain	Cross-sectional	274	DA, NDA, PMD	Infinium Human610-Quad BeadChips
LAMBDA	USA	Family-based study	1,472	DA, NDA, PMD	Affymetrix 500k
MCOCS	USA	Non-Breast Cancer Case-control	356	DA, NDA, PMD	Illumina 610k
Mayo-VTE	USA	Non-Breast Case-control	317	DA, NDA, PMD	Illumina 660W
MBCFS	USA	Family-based breast cancer study	595	DA, NDA, PMD	Illumina 660W Quad
NHS	USA	Nested Breast Cancer Case-control	2,856	DA, NDA, PMD	Affymetrix 500k (147 Controls); Illumina HumanHap 550 (951 Cases + 962 Controls); Illumina OmniExpress (151 Cases + 645 Controls)
SASBAC	Sweden	Breast Cancer Case-control	1,274	DA, NDA, PMD	Illuminal HumanHap 300 (528 Cases); Illumina HumanHap 550 (746 Controls)
SIBS	UK	Population-based cohort study	1,145	DA, NDA, PMD	Illumina HumanCytoSNP-12
Total			10,774		

Supplementary Table 2.4 Association between genome-wide significant SNPs of NDA (p-value < 5E-08) and BMI (N = 13,915)

SNP	chr	Position ¹	REF/ALT	Sample Size_NDA	Pval_NDA	Sample Size_BMI	Pval_BMI
rs78395856	1	119495096	A/C	24689	3.29E-08	13915	2.62E-01
rs413472	5	80930992	T/C	24689	2.84E-08	13915	2.59E-01
rs16885613	8	36848357	T/C	24689	1.92E-37	13915	2.49E-01
rs2138555	10	64220494	A/G	24689	3.63E-09	13915	9.58E-01
rs61938093	12	96026737	T/C	24689	8.68E-12	13915	1.11E-01
rs73169097	22	41027870	T/C	24688	1.83E-09	13915	6.76E-01
¹ Genomic positions based on build GRCh37/hg19							

Supplementary Table 2.6 Associations between previously reported independent breast cancer significant SNPs(N = 205) and mammographic density phenotypes (DA, NDA and PMD)

SNP	chr	Position	Minor Allele	MAF	Ref	Alt	DA_Zscore	DA_Pvalue	NDA_Zscore	NDA_Pvalue	PMD_Zscore	PMD_Pvalue
rs10864459	1	10563609	A	0.284	a	g	0.479	6.32E-01	0.642	5.21E-01	-0.337	7.36E-01
rs616488	1	10566215	G	0.297	a	g	-1.113	2.66E-01	-2.439	1.47E-02	0.699	4.85E-01
rs2992756	1	18807339	T	0.487	t	c	1.479	1.39E-01	-0.309	7.58E-01	0.998	3.18E-01
rs4233486	1	41380440	C	0.354	t	c	0.595	5.52E-01	-0.564	5.73E-01	0.211	8.33E-01
rs79724016	1	42137311	G	0.04	t	g	-0.621	5.35E-01	-0.392	6.95E-01	-0.241	8.09E-01
rs1707302	1	46600917	A	0.336	a	g	0.567	5.71E-01	2.141	3.23E-02	-0.671	5.02E-01
rs140850326	1	50846032	C	0.472	ggccaagatctc	c	-4.090	4.32E-05	1.575	1.15E-01	-3.576	3.49E-04
rs17426269	1	88156923	A	0.149	a	g	1.869	6.16E-02	-0.428	6.68E-01	1.038	2.99E-01
rs11552449	1	114448389	T	0.158	t	c	2.127	3.34E-02	1.143	2.53E-01	1.595	1.11E-01
rs7529522	1	118230221	C	0.242	t	c	0.054	9.57E-01	0.181	8.56E-01	-0.542	5.88E-01
rs11249433	1	121280613	G	0.417	a	g	2.020	4.34E-02	-0.627	5.31E-01	1.312	1.90E-01
rs12405132	1	145644984	T	0.359	t	c	2.289	2.21E-02	-0.322	7.47E-01	1.857	6.33E-02
rs12048493	1	149927034	C	0.36	a	c	-6.346	2.21E-10	-0.792	4.28E-01	-4.902	9.48E-07
rs4971059	1	155148781	A	0.316	a	g	0.165	8.69E-01	-1.433	1.52E-01	0.660	5.09E-01
rs35383942	1	201437832	T	0.049	t	c	-2.802	5.08E-03	-2.535	1.12E-02	-1.210	2.26E-01
rs17489300	1	202179042	C	0.392	a	c	-2.427	1.52E-02	-0.264	7.92E-01	-2.060	3.94E-02
rs6678914	1	202187176	A	0.399	a	g	2.227	2.60E-02	0.010	9.92E-01	2.065	3.89E-02
rs4951011	1	203766331	G	0.156	a	g	-0.451	6.52E-01	0.196	8.44E-01	0.901	3.67E-01
rs4245739	1	204518842	C	0.261	a	c	1.129	2.59E-01	1.435	1.51E-01	0.485	6.28E-01
rs11117758	1	217220574	A	0.211	a	g	0.723	4.70E-01	2.333	1.97E-02	-0.001	1.00E+00
rs72755295	1	242034263	G	0.034	a	g	1.165	2.44E-01	0.182	8.56E-01	1.647	9.96E-02
rs113577745	2	10135681	G	0.096	c	g	-0.400	6.89E-01	-0.023	9.82E-01	-1.246	2.13E-01
rs12710696	2	19320803	T	0.41	t	c	4.238	2.25E-05	-1.557	1.19E-01	4.010	6.07E-05
rs200648189	2	24739694	C	0.19	ct	c	0.060	9.52E-01	-0.651	5.15E-01	0.619	5.36E-01
rs6725517	2	25129473	G	0.391	a	g	0.680	4.97E-01	2.325	2.01E-02	-0.744	4.57E-01
rs67073037	2	29119585	T	0.217	a	t	-0.192	8.47E-01	-2.710	6.73E-03	0.544	5.87E-01
rs4577244	2	29120733	T	0.219	t	c	-0.025	9.80E-01	2.705	6.84E-03	-0.759	4.48E-01
rs6734079	2	29160421	A	0.216	a	t	0.009	9.93E-01	2.643	8.23E-03	-0.675	5.00E-01
rs71801447	2	111925731	C	0.06	cttatggt	c	-0.148	8.83E-01	0.960	3.37E-01	-1.000	3.17E-01
rs11903787	2	121088182	A	0.259	a	g	-6.549	5.80E-11	-3.103	1.92E-03	-3.582	3.41E-04
rs4849887	2	121245122	T	0.106	t	c	-1.002	3.17E-01	-4.000	6.34E-05	0.904	3.66E-01
rs2016394	2	172972971	A	0.473	a	g	0.051	9.59E-01	-3.284	1.02E-03	1.451	1.47E-01
rs1550623	2	174212894	G	0.142	a	g	0.435	6.64E-01	0.733	4.63E-01	-0.180	8.57E-01
rs74943274	2	201717014	A	0.019	a	g	0.348	7.28E-01	-0.599	5.49E-01	0.390	6.96E-01
rs188686860	2	201733341	T	0.02	t	c	0.840	4.01E-01	-1.430	1.53E-01	1.126	2.60E-01
rs115635831	2	201743594	G	0.019	a	g	-0.401	6.88E-01	0.534	5.94E-01	-0.368	7.13E-01
rs114962751	2	201935871	A	0.02	a	t	0.451	6.52E-01	-0.580	5.62E-01	0.439	6.60E-01
rs1830298	2	202181247	C	0.308	t	c	-0.638	5.24E-01	1.899	5.75E-02	-1.290	1.97E-01
rs4442975	2	217920769	T	0.465	t	g	0.515	6.06E-01	0.535	5.92E-01	0.848	3.97E-01
rs34005590	2	217963060	A	0.046	a	c	1.196	2.32E-01	2.406	1.61E-02	0.180	8.57E-01
rs16857609	2	218296508	T	0.259	t	c	-2.726	6.41E-03	2.648	8.10E-03	-4.631	3.65E-06
rs12479355	2	227226952	G	0.217	a	g	-1.148	2.51E-01	0.390	6.96E-01	-0.930	3.52E-01
rs6762644	3	4742276	G	0.338	a	g	-0.736	4.62E-01	-0.990	3.22E-01	-0.048	9.62E-01
rs4973768	3	27416013	C	0.487	t	c	-1.279	2.01E-01	0.539	5.90E-01	-1.811	7.01E-02
rs12493607	3	30682939	C	0.36	c	g	2.311	2.08E-02	-0.263	7.93E-01	1.818	6.91E-02
rs6796502	3	46866866	A	0.095	a	g	3.266	1.09E-03	0.005	9.96E-01	3.117	1.83E-03
rs1053338	3	63967900	G	0.136	a	g	-0.158	8.74E-01	-0.546	5.85E-01	0.904	3.66E-01
rs6805189	3	71532113	C	0.466	t	c	-0.953	3.41E-01	-0.256	7.98E-01	0.247	8.05E-01

rs13066793	3	87037543	G	0.082	a	g	-1.093	2.74E-01	-0.998	3.18E-01	-0.896	3.70E-01
rs9833888	3	99723580	T	0.213	t	g	-0.289	7.73E-01	2.354	1.86E-02	-2.497	1.25E-02
rs34207738	3	141112859	C	0.38	ctt	c	-0.570	5.68E-01	0.573	5.67E-01	-0.482	6.30E-01
rs58058861	3	172285237	A	0.205	a	g	-1.728	8.40E-02	0.493	6.22E-01	-0.873	3.83E-01
rs6815814	4	38816338	C	0.288	a	c	-0.657	5.11E-01	2.147	3.18E-02	-1.077	2.82E-01
c4_84370124	4	84370124	TA	0.47	ta	taa	-0.693	4.89E-01	-0.912	3.62E-01	0.517	6.05E-01
rs10022462	4	89243818	T	0.46	t	c	0.351	7.26E-01	0.691	4.90E-01	-0.617	5.37E-01
rs9790517	4	106084778	T	0.259	t	c	-2.974	2.94E-03	0.614	5.39E-01	-2.432	1.50E-02
rs77528541	4	126843504	T	0.127	t	g	2.457	1.40E-02	-1.161	2.46E-01	3.123	1.79E-03
rs6828523	4	175846426	A	0.102	a	c	0.979	3.27E-01	-0.753	4.51E-01	1.593	1.11E-01
rs116095464	5	345109	C	0.051	NA	NA	NA	NA	NA	NA	NA	NA
rs10069690	5	1279790	T	0.27	t	c	-0.037	9.71E-01	-0.341	7.34E-01	-0.427	6.69E-01
rs2242652	5	1280028	A	0.2	a	g	0.412	6.80E-01	-0.797	4.25E-01	0.065	9.48E-01
rs7726159	5	1282319	A	0.352	a	c	0.710	4.78E-01	0.405	6.85E-01	0.123	9.02E-01
rs3215401	5	1296255	A	0.298	a	ag	-0.845	3.98E-01	-0.460	6.45E-01	-0.259	7.96E-01
rs2736108	5	1297488	T	0.287	t	c	0.641	5.21E-01	0.546	5.85E-01	0.254	8.00E-01
rs13162653	5	16187528	T	0.449	t	g	0.032	9.74E-01	0.610	5.42E-01	0.319	7.50E-01
rs2012709	5	32567732	C	0.489	t	c	1.236	2.17E-01	0.803	4.22E-01	1.328	1.84E-01
rs10941679	5	44706498	G	0.253	a	g	1.148	2.51E-01	-0.753	4.51E-01	2.176	2.96E-02
rs72749841	5	49641645	C	0.155	t	c	-1.738	8.22E-02	-1.382	1.67E-01	-2.285	2.23E-02
rs35951924	5	50195093	AT	0.309	a	at	-2.470	1.35E-02	1.116	2.64E-01	-2.447	1.44E-02
rs62355902	5	56053723	T	0.159	a	t	0.028	9.77E-01	-0.262	7.93E-01	-0.105	9.16E-01
rs10472076	5	58184061	C	0.37	t	c	2.266	2.35E-02	0.127	8.99E-01	2.267	2.34E-02
rs1353747	5	58337481	G	0.087	t	g	-1.057	2.90E-01	0.576	5.65E-01	-1.315	1.88E-01
rs7707921	5	81538046	T	0.265	a	t	-1.225	2.21E-01	-0.295	7.68E-01	-0.791	4.29E-01
rs10474352	5	90732225	T	0.169	t	c	1.117	2.64E-01	1.129	2.59E-01	-0.127	8.99E-01
rs6882649	5	111217786	G	0.354	t	g	1.825	6.80E-02	-0.243	8.08E-01	1.062	2.88E-01
rs6596100	5	132407058	T	0.23	t	c	1.328	1.84E-01	1.464	1.43E-01	-0.320	7.49E-01
rs1432679	5	158244083	C	0.425	t	c	1.826	6.78E-02	-2.662	7.77E-03	3.504	4.59E-04
rs4562056	5	169591487	T	0.36	t	g	-2.912	3.59E-03	-1.650	9.90E-02	-3.015	2.57E-03
rs11242675	6	1318878	C	0.338	t	c	0.019	9.85E-01	-0.726	4.68E-01	-0.488	6.25E-01
rs9348512	6	10456706	A	0.354	a	c	-1.099	2.72E-01	-0.980	3.27E-01	0.874	3.82E-01
rs204247	6	13722523	G	0.431	a	g	0.139	8.90E-01	-0.892	3.73E-01	1.193	2.33E-01
rs3819405	6	16399557	T	0.307	t	c	4.555	5.25E-06	-1.977	4.80E-02	5.806	6.42E-09
rs2223621	6	20621238	T	0.399	t	c	1.117	2.64E-01	0.067	9.47E-01	0.451	6.52E-01
rs71557345	6	26680698	A	0.055	a	g	0.271	7.86E-01	-0.536	5.92E-01	1.079	2.81E-01
rs9257408	6	28926220	C	0.442	c	g	-0.409	6.82E-01	0.366	7.14E-01	-0.366	7.14E-01
rs12207986	6	81094287	G	0.479	a	g	-1.569	1.17E-01	-2.571	1.01E-02	0.630	5.29E-01
rs17529111	6	82128386	C	0.234	t	c	0.265	7.91E-01	-0.830	4.07E-01	1.010	3.12E-01
rs6569648	6	130349119	C	0.22	t	c	-0.637	5.24E-01	-0.399	6.90E-01	0.634	5.26E-01
rs9485372	6	149608874	A	0.189	a	g	4.988	6.10E-07	-2.917	3.54E-03	6.798	1.06E-11
rs12662670	6	151918856	G	0.083	t	g	5.514	3.51E-08	1.128	2.59E-01	4.708	2.50E-06
rs3757322	6	151942194	G	0.323	t	g	6.633	3.28E-11	0.332	7.40E-01	5.732	9.94E-09
rs11155804	6	151946152	A	0.34	a	t	-6.504	7.81E-11	0.263	7.93E-01	-6.076	1.23E-09
rs9397437	6	151952332	A	0.075	a	g	-7.846	4.29E-15	-0.432	6.66E-01	-7.243	4.40E-13
rs2747652	6	152437016	T	0.492	t	c	-0.808	4.19E-01	-1.913	5.57E-02	-0.488	6.25E-01
rs7971	7	21940960	G	0.35	a	g	-1.724	8.47E-02	-0.305	7.60E-01	-1.167	2.43E-01
rs17156577	7	28356889	C	0.122	t	c	1.649	9.92E-02	-0.182	8.55E-01	1.069	2.85E-01
rs6964587	7	91630620	T	0.416	t	g	0.026	9.79E-01	-1.067	2.86E-01	0.620	5.36E-01
rs17268829	7	94113799	C	0.272	t	c	-0.303	7.62E-01	2.546	1.09E-02	-1.772	7.64E-02

rs71559437	7	101552440	A	0.104	a	g	-2.283	2.24E-02	0.190	8.50E-01	-2.815	4.87E-03
rs4593472	7	130667121	T	0.314	t	c	-0.488	6.25E-01	-1.034	3.01E-01	-0.587	5.57E-01
rs11977670	7	139942304	A	0.445	a	g	-0.901	3.68E-01	0.696	4.86E-01	-1.312	1.90E-01
rs720475	7	144074929	A	0.247	a	g	0.053	9.58E-01	3.164	1.55E-03	-1.488	1.37E-01
rs66823261	8	170692	C	0.23	t	c	1.246	2.13E-01	0.204	8.38E-01	0.727	4.67E-01
rs9693444	8	29509616	A	0.331	a	c	-0.991	3.22E-01	2.444	1.45E-02	-1.502	1.33E-01
rs13365225	8	36858483	G	0.231	a	g	-0.168	8.67E-01	-12.392	2.87E-35	6.263	3.78E-10
rs6472903	8	76230301	G	0.17	t	g	-1.896	5.80E-02	0.585	5.59E-01	-1.163	2.45E-01
rs2943559	8	76417937	G	0.092	a	g	-0.385	7.00E-01	0.724	4.69E-01	-0.146	8.84E-01
rs514192	8	102478959	A	0.334	a	t	0.951	3.41E-01	1.416	1.57E-01	0.656	5.12E-01
rs12546444	8	106358620	T	0.092	a	t	0.182	8.56E-01	-0.826	4.09E-01	0.521	6.03E-01
rs13267382	8	117209548	A	0.365	a	g	-2.219	2.65E-02	-1.243	2.14E-01	-0.965	3.34E-01
rs58847541	8	124610166	A	0.152	a	g	5.994	2.05E-09	-0.212	8.32E-01	4.868	1.13E-06
rs17350191	8	124757661	T	0.34	t	c	3.124	1.78E-03	0.557	5.78E-01	2.254	2.42E-02
rs13281615	8	128355618	G	0.449	a	g	0.560	5.76E-01	1.474	1.40E-01	-1.041	2.98E-01
rs11780156	8	129194641	T	0.208	t	c	-2.492	1.27E-02	0.547	5.84E-01	-2.002	4.53E-02
rs1011970	9	22062134	T	0.158	t	g	0.036	9.71E-01	-2.240	2.51E-02	0.562	5.74E-01
rs10759243	9	110306115	A	0.333	a	c	-0.661	5.09E-01	0.288	7.73E-01	-0.685	4.93E-01
rs10816625	9	110837073	G	0.066	a	g	-0.183	8.54E-01	-1.505	1.32E-01	-0.672	5.02E-01
rs13294895	9	110837176	T	0.164	t	c	0.625	5.32E-01	-0.442	6.59E-01	-0.322	7.48E-01
rs676256	9	110895353	C	0.337	t	c	0.105	9.17E-01	0.002	9.98E-01	-0.510	6.10E-01
rs1895062	9	119313486	G	0.378	a	g	-4.249	2.15E-05	-1.051	2.93E-01	-3.445	5.71E-04
rs10760444	9	129396434	G	0.423	a	g	3.657	2.56E-04	-1.047	2.95E-01	3.116	1.83E-03
rs8176636	9	136151579	T	0.214	t	aggaaaaaattgt	-2.856	4.29E-03	1.533	1.25E-01	-2.619	8.81E-03
rs2380205	10	5886734	T	0.432	t	c	1.099	2.72E-01	-0.610	5.42E-01	1.245	2.13E-01
rs67958007	10	9088113	T	0.131	t	tg	0.891	3.73E-01	-2.547	1.09E-02	1.168	2.43E-01
rs7072776	10	22032942	A	0.322	a	g	-0.757	4.49E-01	-0.580	5.62E-01	-0.403	6.87E-01
rs11814448	10	22315843	C	0.021	a	c	0.660	5.09E-01	-0.823	4.11E-01	1.963	4.97E-02
rs10995190	10	64278682	A	0.164	a	g	8.892	6.00E-19	-2.706	6.82E-03	10.326	5.37E-25
rs10995201	10	64299890	G	0.169	a	g	-8.854	8.44E-19	2.763	5.73E-03	-10.141	3.62E-24
rs704010	10	80841148	T	0.367	t	c	-0.756	4.49E-01	1.357	1.75E-01	-1.264	2.06E-01
rs140936696	10	95292187	CA	0.163	caa	c	0.393	6.94E-01	0.937	3.49E-01	0.820	4.12E-01
rs7904519	10	114773927	G	0.471	a	g	-0.746	4.56E-01	0.245	8.07E-01	-1.633	1.03E-01
rs6585202	10	114782803	C	0.471	t	c	-0.756	4.50E-01	0.114	9.10E-01	-1.568	1.17E-01
rs11199914	10	123093901	T	0.349	t	c	-0.049	9.61E-01	-0.851	3.95E-01	0.195	8.45E-01
rs2981578	10	123340311	T	0.496	t	c	-0.924	3.56E-01	-2.195	2.82E-02	0.054	9.57E-01
rs45631563	10	123349324	T	0.052	a	t	0.182	8.55E-01	0.607	5.44E-01	-0.836	4.03E-01
rs6597981	11	803017	A	0.492	a	g	0.136	8.92E-01	-1.392	1.64E-01	1.209	2.27E-01
rs4980383	11	1902097	T	0.459	t	c	-7.228	4.90E-13	-0.364	7.16E-01	-5.860	4.62E-09
rs3817198	11	1909006	C	0.352	t	c	6.121	9.30E-10	1.072	2.84E-01	4.886	1.03E-06
rs3903072	11	65583066	T	0.494	t	g	-0.528	5.97E-01	-0.532	5.94E-01	-0.627	5.31E-01
rs554219	11	69331642	G	0.149	c	g	-1.380	1.68E-01	0.981	3.27E-01	-1.669	9.51E-02
rs75915166	11	69379161	A	0.066	a	c	2.047	4.07E-02	1.364	1.73E-01	1.265	2.06E-01
rs11374964	11	108345515	GA	0.42	g	ga	0.909	3.63E-01	1.578	1.15E-01	0.780	4.36E-01
rs74911261	11	108357137	A	0.02	a	g	-2.307	2.11E-02	-0.518	6.04E-01	-1.734	8.30E-02
rs11820646	11	129461171	T	0.36	t	c	0.672	5.02E-01	0.319	7.50E-01	0.516	6.06E-01
rs12422552	12	14413931	C	0.264	c	g	-2.418	1.56E-02	1.800	7.19E-02	-2.742	6.11E-03
rs10771399	12	28155080	G	0.102	a	g	-4.134	3.57E-05	-3.209	1.33E-03	-2.599	9.34E-03
rs7297051	12	28174817	T	0.24	t	c	6.166	7.01E-10	2.570	1.02E-02	4.082	4.46E-05
rs202049448	12	85009437	C	0.314	t	c	-1.944	5.20E-02	0.358	7.21E-01	-2.052	4.02E-02
rs17356907	12	96027759	G	0.274	a	g	2.154	3.13E-02	6.623	3.52E-11	-1.729	8.38E-02
rs1292011	12	115836522	G	0.404	a	g	0.580	5.62E-01	-2.437	1.48E-02	2.029	4.25E-02
rs206966	12	120832146	T	0.17	t	c	-0.313	7.55E-01	0.887	3.75E-01	-1.279	2.01E-01
rs11571833	13	32972626	T	0.007	a	t	-1.203	2.29E-01	-1.165	2.44E-01	-0.415	6.78E-01
rs12870942	13	73806982	C	0.313	t	c	3.400	6.74E-04	1.229	2.19E-01	2.700	6.93E-03
rs17181761	13	73811471	C	0.312	a	c	3.374	7.41E-04	1.107	2.68E-01	2.680	7.35E-03

rs9573140	13	73813803	G	0.312	a	g	3.437	5.88E-04	1.036	3.00E-01	2.792	5.23E-03
rs6562760	13	73957681	A	0.244	a	g	5.055	4.31E-07	1.456	1.45E-01	2.830	4.65E-03
rs2181965	13	73960952	A	0.245	a	g	5.000	5.75E-07	1.499	1.34E-01	2.806	5.02E-03
rs8002929	13	73964519	A	0.244	a	g	4.946	7.58E-07	1.325	1.85E-01	2.855	4.30E-03
rs2236007	14	37132769	A	0.206	a	g	4.327	1.51E-05	-0.899	3.69E-01	4.091	4.30E-05
rs2588809	14	68660428	T	0.196	t	c	1.962	4.97E-02	-1.871	6.14E-02	2.484	1.30E-02
rs999737	14	69034682	T	0.199	t	c	3.869	1.09E-04	-1.559	1.19E-01	3.432	6.00E-04
rs941764	14	91841069	G	0.351	a	g	-1.004	3.15E-01	0.236	8.14E-01	-0.631	5.28E-01
rs11627032	14	93104072	C	0.266	t	c	3.819	1.34E-04	1.489	1.37E-01	2.825	4.72E-03
rs10623258	14	105212261	CT	0.458	ctt	c	1.492	1.36E-01	0.019	9.85E-01	0.534	5.93E-01
rs2290203	15	91512067	A	0.211	a	g	-0.953	3.41E-01	0.787	4.31E-01	-1.656	9.77E-02
rs11076805	16	4106788	A	0.25	a	c	0.491	6.24E-01	0.583	5.60E-01	0.649	5.17E-01
rs4784227	16	52599188	T	0.279	t	c	-3.051	2.28E-03	0.363	7.17E-01	-3.559	3.72E-04
rs17817449	16	53813367	G	0.441	t	g	-4.640	3.49E-06	3.099	1.94E-03	-5.845	5.06E-09
rs11075995	16	53855291	A	0.241	a	t	2.182	2.91E-02	0.766	4.44E-01	1.771	7.66E-02
rs28539243	16	54682064	A	0.484	a	g	-3.370	7.52E-04	0.997	3.19E-01	-3.750	1.77E-04
rs2432539	16	56420987	A	0.415	a	g	1.141	2.54E-01	-1.149	2.51E-01	2.153	3.13E-02
rs13329835	16	80650805	G	0.245	a	g	-1.162	2.45E-01	0.467	6.40E-01	-1.179	2.39E-01
rs4496150	16	87085237	A	0.262	a	c	2.731	6.32E-03	-0.200	8.42E-01	1.914	5.56E-02
rs72826962	17	40836389	T	0.012	t	c	-0.351	7.25E-01	0.298	7.66E-01	0.043	9.66E-01
rs2532263	17	44252468	A	0.175	a	g	1.014	3.10E-01	1.280	2.01E-01	0.032	9.75E-01
rs2787486	17	53209774	C	0.285	a	c	-1.555	1.20E-01	1.107	2.68E-01	-1.824	6.81E-02
rs745570	17	77781725	G	0.486	a	g	-1.549	1.21E-01	-2.623	8.72E-03	-0.352	7.25E-01
rs527616	18	24337424	C	0.395	c	g	0.492	6.23E-01	-0.151	8.80E-01	0.547	5.84E-01
rs1436904	18	24570667	G	0.375	t	g	-0.585	5.59E-01	0.520	6.03E-01	-1.126	2.60E-01
rs36194942	18	25401204	AT	0.3	a	at	0.470	6.39E-01	0.582	5.61E-01	0.669	5.04E-01
rs117618124	18	29977689	C	0.043	t	c	-4.277	1.90E-05	0.006	9.95E-01	-3.053	2.27E-03
rs6507583	18	42399590	G	0.063	a	g	-1.143	2.53E-01	1.321	1.86E-01	-1.430	1.53E-01
rs322144	19	11423703	G	0.47	c	g	0.054	9.57E-01	0.268	7.89E-01	0.081	9.35E-01
rs78269692	19	13158277	C	0.053	t	c	-1.119	2.63E-01	0.486	6.27E-01	-1.507	1.32E-01
rs2594714	19	13954571	A	0.2	a	g	1.098	2.72E-01	1.105	2.69E-01	0.743	4.58E-01
rs8170	19	17389704	A	0.184	a	g	1.012	3.11E-01	0.154	8.77E-01	0.384	7.01E-01
rs56069439	19	17393925	A	0.291	a	c	0.510	6.10E-01	-0.487	6.27E-01	0.130	8.97E-01
rs67397200	19	17401404	G	0.293	c	g	-0.484	6.28E-01	0.649	5.16E-01	-0.249	8.03E-01
rs4808801	19	18571141	G	0.301	a	g	-2.224	2.62E-02	0.730	4.65E-01	-2.053	4.01E-02
rs2965183	19	19545696	A	0.352	a	g	-0.418	6.76E-01	0.320	7.49E-01	-0.243	8.08E-01
rs113701136	19	30277729	T	0.32	t	c	-0.359	7.20E-01	-0.190	8.49E-01	-0.781	4.35E-01
rs3760982	19	44286513	A	0.456	a	g	0.368	7.13E-01	0.497	6.19E-01	0.217	8.28E-01
rs71338792	19	46183031	AT	0.255	a	at	0.708	4.79E-01	-1.809	7.04E-02	1.068	2.86E-01
rs16991615	20	5948227	A	0.072	a	g	0.061	9.52E-01	1.056	2.91E-01	-0.473	6.36E-01
rs2284378	20	32588095	T	0.293	t	c	-1.647	9.95E-02	1.874	6.09E-02	-2.664	7.71E-03
rs6122906	20	48945911	G	0.184	a	g	4.274	1.92E-05	0.104	9.17E-01	2.812	4.93E-03
rs2823093	21	16520832	A	0.271	a	g	-1.673	9.43E-02	-1.705	8.81E-02	-0.744	4.57E-01
rs17879961	22	29121087	G	0.014	a	g	1.637	1.02E-01	1.645	1.00E-01	0.706	4.80E-01
rs132390	22	29621477	C	0.037	t	c	0.955	3.40E-01	-0.419	6.75E-01	1.480	1.39E-01
rs738321	22	38568833	G	0.382	c	g	-4.642	3.45E-06	1.651	9.88E-02	-4.676	2.92E-06
rs_39359355_Cf	22	39359355	CNO	0.096	CNO	c	-0.864	3.87E-01	1.256	2.09E-01	-0.666	5.06E-01
rs6001930	22	40876234	C	0.127	t	c	-8.590	8.71E-18	-5.616	1.96E-08	-4.624	3.76E-06
rs73161324	22	42038786	T	0.067	t	c	5.988	2.12E-09	2.324	2.01E-02	3.221	1.28E-03
rs28512361	22	46283297	A	0.117	a	g	-1.345	1.79E-01	-1.426	1.54E-01	-0.274	7.84E-01

Supplementary Table 2.7 LD-score regression estimated the enrichment of heritability of DA, NDA and PMD

Phenotype	Category	Prop_SNPs	Prop_h2	Prop_h2_std_error	Enrichment	Enrichment_std_error	Enrichment_p	Coefficient	Coefficient_std_error	Coefficient_z-score
DA	H3K27ac_HniszL2_0	0.3891	0.8762	0.0692	2.2520	0.1778	7.10E-11	1.50E-07	1.42E-07	1.0560
DA	H3K27ac_Hnisz.extend.5	0.4205	0.8352	0.0756	1.9862	0.1797	2.96E-08	-8.06E-08	1.42E-07	-0.5662
DA	SuperEnhancer_Hnisz.ex	0.1704	0.4243	0.0477	2.4904	0.2797	2.93E-07	1.75E-07	5.23E-07	0.3336
DA	SuperEnhancer_HniszL2	0.1672	0.4139	0.0471	2.4753	0.2816	9.07E-07	-1.55E-07	5.29E-07	-0.2922
DA	CpG_Content_50kbl2_0	0.0101	0.0122	0.0004	1.2161	0.0427	7.00E-06	3.04E-08	1.36E-06	0.0223
DA	MAF_Adj_LLD_AFRL2_0	0.0028	-0.3655	0.0598	-130.7020	21.3758	7.19E-06	1.97E-09	5.33E-09	0.3703
DA	GERP.NSL2_0	1.7453	3.1882	0.4012	1.8267	0.2299	1.30E-04	-3.79E-10	1.15E-08	-0.0330
DA	DGF_ENCODE.extend.50	0.5385	0.9881	0.1277	1.8351	0.2371	5.37E-04	5.92E-08	4.95E-08	1.1965
DA	H3K4me3_Trynka.extend.5	0.2551	0.6631	0.1200	2.5989	0.4703	1.01E-03	9.72E-08	7.86E-08	1.2368
DA	Repressed_Hoffman.ext	0.7185	0.5053	0.0696	0.7033	0.0968	1.50E-03	2.62E-08	4.03E-08	0.6509
DA	Enhancer_Hoffman.exte	0.0898	0.3885	0.0909	4.3245	1.0112	1.68E-03	2.04E-07	1.58E-07	1.2941
DA	H3K9ac_Trynka.extend.5	0.2299	0.5681	0.1060	2.4716	0.4610	1.71E-03	-1.12E-08	8.92E-08	-0.1257
DA	FetalDHS_TrynkaL2_0	0.0839	0.5637	0.1683	6.7164	2.0048	2.32E-03	2.10E-07	1.75E-07	1.2012
DA	DHS_TrynkaL2_0	0.1662	0.8112	0.2280	4.8809	1.3720	2.50E-03	1.44E-07	1.64E-07	0.8755
DA	DHS_Trynka.extend.500	0.4960	0.9385	0.1516	1.8920	0.3056	2.92E-03	2.32E-08	6.39E-08	0.3623
DA	Conserved_LindbladToh	0.0257	0.3456	0.1144	13.4539	4.4544	3.54E-03	5.70E-07	3.03E-07	1.8788
DA	MAFbin9L2_0	0.1011	0.2074	0.0397	2.0519	0.3924	5.03E-03	9.21E-08	2.21E-08	4.1603
DA	H3K4me1_peaks_Trynka	0.1698	0.7889	0.2138	4.6452	1.2587	5.53E-03	2.43E-07	1.28E-07	1.8998
DA	H3K27ac_PGC2.extend.5	0.3352	0.6393	0.1080	1.9072	0.3222	6.03E-03	9.49E-08	1.08E-07	0.8763
DA	TFBS_ENCODE.extend.5	0.3412	0.6736	0.1308	1.9740	0.3834	1.19E-02	-2.96E-08	7.03E-08	-0.4210
DA	Recomb_Rate_10kbl2_0	1.5524	2.4958	0.3313	1.6077	0.2134	1.23E-02	6.53E-09	3.98E-09	1.6411
DA	DHS_peaks_TrynkaL2_0	0.1106	0.5614	0.1931	5.0769	1.7465	1.39E-02	7.17E-09	1.82E-07	0.0394
DA	H3K9ac_TrynkaL2_0	0.1254	0.4516	0.1370	3.6005	1.0925	1.53E-02	1.58E-07	1.48E-07	1.0673
DA	H3K4me1_TrynkaL2_0	0.4237	0.7686	0.1487	1.8142	0.3510	1.72E-02	-6.30E-08	8.85E-08	-0.7113
DA	Conserved_LindbladToh	0.3304	0.6363	0.1269	1.9258	0.3842	1.81E-02	-1.58E-10	5.07E-08	-0.0031
DA	MAF_Adj_Predicted_Alle	0.0000	-0.2748	0.1196	-81014.9043	35242.9372	2.72E-02	-1.30E-08	8.62E-09	-1.5094
DA	UTR_3_UCSC.extend.50	0.0265	0.1579	0.0658	5.9688	2.4876	4.30E-02	6.65E-08	2.09E-07	0.3188
DA	FetalDHS_Trynka.extend	0.2834	0.6245	0.1700	2.2038	0.6000	4.32E-02	-8.18E-08	7.88E-08	-1.0374
DA	WeakEnhancer_Hoffma	0.0888	0.2966	0.1064	3.3405	1.1983	5.15E-02	1.26E-07	1.10E-07	1.1432
DA	TFBS_ENCODEL2_0	0.1312	0.4837	0.1973	3.6858	1.5034	6.22E-02	1.17E-07	1.48E-07	0.7853
DA	GERP.RSup4L2_0	0.0081	0.1104	0.0559	13.5419	6.8592	6.64E-02	2.39E-07	4.62E-07	0.5174
DA	Transcr_Hoffman.extend	0.7621	0.6113	0.0856	0.8022	0.1123	7.59E-02	-5.74E-08	3.51E-08	-1.6329
DA	Repressed_HoffmanL2_0	0.4609	0.2365	0.1284	0.5131	0.2786	7.81E-02	3.63E-08	4.42E-08	0.8218
DA	Backgrd_Selection_Statt	0.1777	0.1984	0.0122	1.1164	0.0687	7.97E-02	2.07E-08	2.99E-08	0.6931
DA	Transcr_HoffmanL2_0	0.3460	0.5359	0.1121	1.5491	0.3240	8.62E-02	1.01E-07	4.00E-08	2.5151
DA	H3K4me1_Trynka.extend	0.6058	0.7532	0.0846	1.2433	0.1397	8.70E-02	-7.85E-08	6.29E-08	-1.2490
DA	Super_Enhancer_Vahedi	0.0207	0.0536	0.0200	2.5859	0.9656	9.76E-02	2.26E-06	1.38E-06	1.6408
DA	Nucleotide_Diversity_10	4.6087	4.2858	0.1995	0.9299	0.0433	1.03E-01	-5.72E-10	2.47E-09	-0.2313
DA	CTCF_HoffmanL2_0	0.0239	-0.1046	0.0786	-4.3808	3.2938	1.05E-01	-5.56E-07	2.64E-07	-2.1089
DA	Coding_UCSCL2_0	0.0143	0.1147	0.0640	8.0380	4.4826	1.18E-01	1.53E-08	6.33E-07	0.0241
DA	MAFbin1L2_0	0.1024	0.0479	0.0368	0.4677	0.3591	1.35E-01	2.79E-09	2.18E-08	0.1284
DA	H3K4me3_TrynkaL2_0	0.1330	0.3320	0.1370	2.4964	1.0300	1.42E-01	-1.25E-07	1.31E-07	-0.9564
DA	TSS_Hoffman.extend.50	0.0344	0.1358	0.0710	3.9536	2.0655	1.53E-01	1.09E-07	2.37E-07	0.4604
DA	Enhancer_AnderssonL2_0	0.0043	0.0566	0.0376	13.0700	8.6855	1.63E-01	8.63E-07	5.84E-07	1.4770
DA	Intron_UCSCL2_0	0.3875	0.3149	0.0524	0.8127	0.1352	1.66E-01	6.47E-08	3.50E-07	0.1848
DA	H3K27ac_PGC2L2_0	0.2688	0.4417	0.1275	1.6434	0.4745	1.80E-01	-1.85E-07	1.23E-07	-1.5021
DA	MAFbin10L2_0	0.0985	0.0548	0.0339	0.5565	0.3439	1.94E-01	1.12E-08	2.10E-08	0.5322
DA	Promoter_UCSC.extend.	0.0381	0.1039	0.0548	2.7307	1.4400	2.25E-01	1.85E-08	4.06E-07	0.0456
DA	UTR_3_UCSCL2_0	0.0112	0.1340	0.1035	11.9762	9.2535	2.37E-01	5.40E-07	9.80E-07	0.5510
DA	MAFbin3L2_0	0.0996	0.0686	0.0262	0.6883	0.2632	2.45E-01	1.63E-08	1.65E-08	0.9855
DA	Enhancer_HoffmanL2_0	0.0420	0.1633	0.1104	3.8894	2.6293	2.59E-01	-1.70E-07	2.73E-07	-0.6213
DA	MAFbin4L2_0	0.1007	0.1396	0.0374	1.3863	0.3713	3.00E-01	5.37E-08	2.39E-08	2.2450
DA	Promoter_UCSCL2_0	0.0307	0.0897	0.0587	2.9264	1.9160	3.08E-01	-1.46E-08	4.92E-07	-0.0297
DA	PromoterFlanking_Hoffr	0.0083	-0.0404	0.0482	-4.8570	5.7973	3.17E-01	-4.31E-07	4.60E-07	-0.9390
DA	TSS_HoffmanL2_0	0.0178	0.0779	0.0604	4.3698	3.3889	3.20E-01	-8.16E-08	3.43E-07	-0.2379
DA	H3K4me3_peaks_Trynka	0.0416	0.1475	0.1153	3.5418	2.7673	3.44E-01	5.96E-08	2.10E-07	0.2840
DA	DGF_ENCODEL2_0	0.1360	0.3280	0.2221	2.4113	1.6327	3.72E-01	-1.15E-07	1.29E-07	-0.8954
DA	Super_Enhancer_Vahedi	0.0212	0.0351	0.0160	1.6579	0.7572	3.85E-01	-2.26E-06	1.35E-06	-1.6757
DA	MAFbin2L2_0	0.0999	0.1336	0.0441	1.3382	0.4415	4.49E-01	5.02E-08	2.82E-08	1.7778
DA	Typical_Enhancer_Vahedi	0.0261	0.0614	0.0510	2.3477	1.9499	4.86E-01	3.95E-07	6.49E-07	0.6083
DA	Intron_UCSC.extend.50	0.3968	0.3659	0.0464	0.9222	0.1170	5.04E-01	-8.97E-08	3.50E-07	-0.2564
DA	MAFbin8L2_0	0.1002	0.0779	0.0342	0.7776	0.3417	5.16E-01	2.18E-08	2.00E-08	1.0915
DA	Enhancer_Andersson.ex	0.0190	-0.0159	0.0578	-0.8352	3.0367	5.47E-01	-4.27E-07	2.36E-07	-1.8064
DA	MAFbin7L2_0	0.0997	0.0804	0.0323	0.8060	0.3243	5.50E-01	2.31E-08	1.95E-08	1.1874
DA	Coding_UCSC.extend.50	0.0637	0.1127	0.0976	1.7697	1.5337	6.10E-01	-1.33E-07	9.62E-08	-1.3814
DA	MAFbin6L2_0	0.0996	0.0800	0.0394	0.8024	0.3956	6.18E-01	2.34E-08	2.24E-08	1.0433
DA	UTR_5_UCSC.extend.50	0.0269	0.0582	0.0643	2.1662	2.3924	6.23E-01	9.85E-08	1.65E-07	0.5970
DA	MAFbin5L2_0	0.0983	0.1098	0.0317	1.1169	0.3221	7.16E-01	3.86E-08	1.90E-08	2.0308
DA	WeakEnhancer_Hoffma	0.0210	-0.0071	0.0791	-0.3380	3.7694	7.20E-01	-4.03E-07	2.71E-07	-1.4848
DA	H3K9ac_peaks_TrynkaL2	0.0385	-0.0019	0.1139	-0.0492	2.9604	7.23E-01	-3.60E-07	2.48E-07	-1.4519
DA	PromoterFlanking_Hoffr	0.0332	0.0203	0.0690	0.6104	2.0789	8.50E-01	-5.63E-08	1.94E-07	-0.2905
DA	UTR_5_UCSCL2_0	0.0055	-0.0008	0.0346	-0.1465	6.3043	8.56E-01	-3.33E-07	4.61E-07	-0.7220
DA	CTCF_Hoffman.extend.5	0.0708	0.0805	0.0966	1.1361	1.3637	9.20E-01	1.33E-07	1.30E-07	1.0246
DA	Typical_Enhancer_Vahedi	0.0219	0.0229	0.0237	1.0465	1.0843	9.66E-01	-4.61E-07	6.55E-07	-0.7039

Phenotype	Category	Prop_SNPs	Prop_h2	Prop_h2_std_error	Enrichment	Enrichment_std_error	Enrichment_p	Coefficient	Coefficient_std_error	Coefficient_z-score
NDA	H3K27ac_HniszL2_0	0.3891	0.8193	0.0900	2.1058	0.2313	9.71E-07	8.10E-08	1.27E-07	0.6359
NDA	SuperEnhancer_HniszL2_0	0.1672	0.3862	0.0567	2.3094	0.3389	6.34E-05	6.97E-07	4.55E-07	1.5307
NDA	H3K4me3_Trynka.extend.5	0.2551	0.7126	0.1195	2.7930	0.4685	6.92E-05	8.79E-08	6.02E-08	1.4603
NDA	CpG_Content_50kbL2_0	0.0101	0.0118	0.0004	1.1710	0.0411	1.08E-04	-1.93E-08	1.15E-06	-0.0168
NDA	H3K27ac_Hnisz.extend.5	0.4205	0.7667	0.0907	1.8233	0.2157	1.46E-04	-5.21E-08	1.28E-07	-0.4081
NDA	H3K9ac_TrynkaL2_0	0.1254	0.5599	0.1189	4.4648	0.9482	1.88E-04	1.55E-07	1.05E-07	1.4735
NDA	H3K4me1_TrynkaL2_0	0.4237	1.0663	0.1797	2.5168	0.4241	2.06E-04	1.54E-07	7.47E-08	2.0621
NDA	H3K9ac_Trynka.extend.5	0.2299	0.6644	0.1207	2.8906	0.5252	2.13E-04	1.10E-09	7.06E-08	0.0156
NDA	SuperEnhancer_Hnisz.ex	0.1704	0.3326	0.0488	1.9518	0.2865	8.43E-04	-7.15E-07	4.49E-07	-1.5917
NDA	MAF_Adj_LLD_AFR_L2_0	0.0028	-0.3693	0.0846	-132.0660	30.2446	8.92E-04	-3.58E-09	5.51E-09	-0.6492
NDA	H3K27ac_PGC2.extend.5	0.3352	0.6796	0.1065	2.0274	0.3176	1.85E-03	1.50E-08	1.04E-07	0.1441
NDA	Recomb_Rate_10kbL2_0	1.5524	2.9422	0.4328	1.8952	0.2788	4.45E-03	8.66E-09	3.69E-09	2.3449
NDA	Conserved_LindbladToH	0.0257	0.2853	0.0986	11.1068	3.8374	6.60E-03	3.85E-07	1.97E-07	1.9494
NDA	GERP_NSL2_0	1.7453	2.6768	0.3501	1.5337	0.2006	7.37E-03	-9.61E-10	9.79E-09	-0.0982
NDA	DGF_ENCODE.extend.50	0.5385	0.9488	0.1558	1.7621	0.2894	7.38E-03	2.92E-08	4.81E-08	0.6072
NDA	Enhancer_Hoffman.exte	0.0898	0.3254	0.0932	3.6220	1.0368	1.14E-02	-3.54E-08	1.13E-07	-0.3123
NDA	Typical_Enhancer_Vahed	0.0219	0.1031	0.0345	4.7158	1.5777	1.51E-02	3.85E-07	3.92E-07	0.9822
NDA	Enhancer_AnderssonL2_0	0.0043	-0.0909	0.0431	-21.0148	9.9510	2.06E-02	-1.19E-06	5.27E-07	-2.2617
NDA	CTCF_HoffmanL2_0	0.0239	-0.1983	0.1029	-8.3105	4.3123	2.28E-02	-4.86E-07	2.51E-07	-1.9403
NDA	TFBS_ENCODE.extend.5	0.3412	0.6993	0.1564	2.0494	0.4585	2.51E-02	4.87E-08	6.24E-08	0.7805
NDA	H3K27ac_PGC2L2_0	0.2688	0.5980	0.1432	2.2247	0.5327	2.54E-02	-4.27E-08	1.17E-07	-0.3637
NDA	Nucleotide_Diversity_10	4.6087	4.0695	0.2394	0.8830	0.0519	2.55E-02	-3.95E-09	2.10E-09	-1.8782
NDA	Enhancer_HoffmanL2_0	0.0420	0.2647	0.1025	6.3034	2.4422	2.75E-02	2.05E-07	1.85E-07	1.1098
NDA	Repressed_Hoffman.ext	0.7185	0.5628	0.0715	0.7833	0.0995	2.82E-02	1.96E-08	3.80E-08	0.5163
NDA	DHS_Trynka.extend.500	0.4960	0.8336	0.1704	1.6805	0.3435	4.55E-02	-8.03E-09	6.14E-08	-0.1307
NDA	TSS_Hoffman.extend.50	0.0344	0.1636	0.0722	4.7635	2.1016	7.62E-02	1.42E-07	1.97E-07	0.7224
NDA	MAFbin1L2_0	0.1024	0.0298	0.0441	0.2907	0.4305	8.25E-02	-1.86E-08	2.05E-08	-0.9080
NDA	Typical_Enhancer_Vahed	0.0261	0.0832	0.0380	3.1812	1.4541	1.28E-01	-2.70E-07	3.62E-07	-0.7463
NDA	FetalDHS_Trynka.extend	0.2834	0.5285	0.1683	1.8650	0.5941	1.53E-01	1.40E-08	6.44E-08	0.2177
NDA	H3K4me3_TrynkaL2_0	0.1330	0.2999	0.1195	2.2545	0.8985	1.64E-01	-1.04E-07	9.76E-08	-1.0679
NDA	Super_Enhancer_Vahedi	0.0207	0.0454	0.0191	2.1917	0.9209	1.95E-01	5.29E-07	1.14E-06	0.4620
NDA	Coding_UCSCL2_0	0.0143	0.0836	0.0583	5.8569	4.0848	2.19E-01	2.27E-07	2.29E-07	0.9911
NDA	GERP_RSsup4L2_0	0.0081	0.0880	0.0656	10.8020	8.0457	2.24E-01	1.45E-07	3.91E-07	0.3699
NDA	Conserved_LindbladToH	0.3304	0.4715	0.1261	1.4270	0.3817	2.66E-01	-1.53E-08	3.69E-08	-0.4149
NDA	H3K4me1_peaks_Trynka	0.1698	0.3972	0.2332	1.3737	0.3261	3.26E-01	-3.01E-08	1.05E-07	-0.2867
NDA	Super_Enhancer_Vahedi	0.0212	0.0398	0.0201	1.8780	0.9510	3.55E-01	-5.26E-07	1.13E-06	-0.4638
NDA	UTR_3_UCSC.extend.50	0.0265	-0.0143	0.0443	-0.5400	1.6737	3.55E-01	-1.77E-07	1.23E-07	-1.4390
NDA	UTR_5_UCSC.extend.50	0.0269	0.0782	0.0559	2.9122	2.0809	3.57E-01	1.76E-07	1.36E-07	1.2900
NDA	H3K9ac_peaks_TrynkaL2	0.0385	0.1363	0.1097	3.5432	2.8527	3.74E-01	-2.04E-08	1.65E-07	-0.1233
NDA	MAFbin5L2_0	0.0983	0.0646	0.0387	0.6572	0.3940	3.84E-01	-1.65E-09	1.81E-08	-0.0911
NDA	CTCF_Hoffman.extend.5	0.0708	-0.0160	0.1034	-0.2254	1.4598	3.97E-01	7.19E-08	1.18E-07	0.6108
NDA	MAFbin4L2_0	0.1007	0.1342	0.0395	1.3323	0.3920	4.01E-01	2.49E-08	2.05E-08	1.2132
NDA	Promoter_UCSCL2_0	0.0307	0.0883	0.0683	2.8794	2.2271	4.04E-01	4.46E-07	3.94E-07	1.1295
NDA	MAFbin10L2_0	0.0985	0.1310	0.0421	1.3308	0.4274	4.30E-01	2.67E-08	1.93E-08	1.3843
NDA	H3K4me1_Trynka.extend	0.6058	0.6848	0.1043	1.1304	0.1721	4.51E-01	-1.32E-07	5.40E-08	-2.4453
NDA	UTR_5_UCSCL2_0	0.0055	-0.0192	0.0332	-3.5044	6.0479	4.57E-01	-4.94E-07	2.99E-07	-1.6508
NDA	PromoterFlanking_Hoffr	0.0332	0.0810	0.0662	2.4407	1.9934	4.70E-01	-7.08E-08	1.34E-07	-0.5285
NDA	UTR_3_UCSCL2_0	0.0112	0.0400	0.0405	3.5719	3.6238	4.73E-01	1.70E-07	2.56E-07	0.6654
NDA	DHS_TrynkaL2_0	0.1662	0.3168	0.2280	1.9061	1.3718	5.14E-01	6.75E-08	1.57E-07	0.4303
NDA	DGF_ENCODEL2_0	0.1360	0.2871	0.2334	2.1113	1.7162	5.14E-01	2.44E-08	1.13E-07	0.2167
NDA	Repressed_HoffmanL2_0	0.4609	0.3537	0.1688	0.7676	0.3663	5.26E-01	-3.52E-08	4.28E-08	-0.8227
NDA	FetalDHS_TrynkaL2_0	0.0839	-0.0169	0.1704	-0.2020	2.0305	5.50E-01	-2.05E-07	1.60E-07	-1.2846
NDA	PromoterFlanking_Hoffr	0.0083	0.0451	0.0619	5.4259	7.4515	5.54E-01	1.24E-07	3.84E-07	0.3234
NDA	TSS_HoffmanL2_0	0.0178	0.0548	0.0626	3.0712	3.5124	5.59E-01	-7.89E-08	2.87E-07	-0.2754
NDA	Backgrd_Selection_StatL	0.1777	0.1846	0.0126	1.0386	0.0708	5.75E-01	3.04E-08	1.80E-08	1.6882
NDA	Transcr_Hoffman.extend	0.7621	0.7075	0.0973	0.9284	0.1276	5.81E-01	1.16E-08	3.23E-08	0.3589
NDA	Transcr_HoffmanL2_0	0.3460	0.2704	0.1563	0.7817	0.4517	6.29E-01	-4.42E-08	4.30E-08	-1.0270
NDA	Intron_UCSC.extend.50	0.3968	0.4171	0.0451	1.0512	0.1136	6.51E-01	2.36E-10	2.92E-07	0.0008
NDA	WeakEnhancer_Hoffmai	0.0210	-0.0175	0.0868	-0.8358	4.1343	6.55E-01	-9.46E-08	2.30E-07	-0.4119
NDA	Enhancer_Andersson.ext	0.0190	0.0427	0.0539	2.2449	2.8332	6.58E-01	2.27E-07	1.94E-07	1.1667
NDA	MAF_Adj_Predicted_Alle	0.0000	0.0739	0.1853	21784.2230	54632.7701	6.86E-01	9.06E-09	8.93E-09	1.0151
NDA	Coding_UCSC.extend.50	0.0637	0.0399	0.0622	0.6262	0.9776	7.01E-01	-1.18E-07	7.39E-08	-1.6042
NDA	DHS_peaks_TrynkaL2_0	0.1106	0.1828	0.2004	1.6534	1.8119	7.20E-01	2.04E-08	1.73E-07	0.1177
NDA	Intron_UCSCL2_0	0.3875	0.3653	0.0625	0.9427	0.1612	7.21E-01	-2.31E-09	2.92E-07	-0.0079
NDA	H3K4me3_peaks_Trynka	0.0416	0.0759	0.1271	1.8227	3.0527	7.88E-01	-3.71E-08	1.76E-07	-0.2106
NDA	MAFbin2L2_0	0.0999	0.1125	0.0473	1.1268	0.4741	7.90E-01	1.51E-08	2.34E-08	0.6432
NDA	Promoter_UCSC.extend	0.0381	0.0253	0.0647	0.6647	1.2902	7.95E-01	-4.10E-07	3.23E-07	-1.2711
NDA	MAFbin8L2_0	0.1002	0.1117	0.0444	1.1148	0.4433	7.96E-01	1.68E-08	2.04E-08	0.8273
NDA	MAFbin9L2_0	0.1011	0.1121	0.0438	1.1088	0.4332	8.01E-01	1.72E-08	2.00E-08	0.8623
NDA	MAFbin7L2_0	0.0997	0.1074	0.0424	1.0773	0.4252	8.56E-01	1.55E-08	1.98E-08	0.7828
NDA	MAFbin3L2_0	0.0996	0.0933	0.0402	0.9366	0.4034	8.75E-01	9.11E-09	1.80E-08	0.5064
NDA	WeakEnhancer_Hoffmai	0.0888	0.1010	0.0971	1.1379	1.0939	9.00E-01	-6.49E-08	8.53E-08	-0.7605
NDA	MAFbin6L2_0	0.0996	0.1034	0.0433	1.0372	0.4343	9.32E-01	1.34E-08	2.00E-08	0.6706
NDA	TFBS_ENCODEL2_0	0.1312	0.1190	0.1859	0.9066	1.4167	9.47E-01	-7.36E-08	1.09E-07	-0.6738

Phenotype	Category	Prop_SNPs	Prop_h2	Prop_h2_std_error	Enrichment	Enrichment_std_error	Enrichment_p	Coefficient	Coefficient_std_error	Coefficient_z_score
PMD	H3K27ac_HniszL2_0	0.3891	0.8650	0.0785	2.2232	0.2019	7.71E-10	2.08E-07	1.19E-07	1.7496
PMD	GERP.NSL2_0	1.7453	3.7341	0.3805	2.1395	0.2180	2.23E-08	2.08E-08	9.61E-09	2.1659
PMD	SuperEnhancer_Hnisz.ex	0.1704	0.4059	0.0470	2.3823	0.2756	1.02E-06	2.18E-07	4.32E-07	0.5049
PMD	CpG_Content_50kbl2_0	0.0101	0.0118	0.0004	1.1786	0.0378	8.12E-06	1.67E-06	9.72E-07	1.7143
PMD	SuperEnhancer_HniszL2_	0.1672	0.3925	0.0491	2.3473	0.2935	8.59E-06	-2.12E-07	4.39E-07	-0.4823
PMD	H3K27ac_Hnisz.extend.5	0.4205	0.7627	0.0806	1.8139	0.1916	2.97E-05	-1.61E-07	1.18E-07	-1.3598
PMD	Conserved_LindbladToh	0.0257	0.4208	0.1053	16.3846	4.0998	1.54E-04	6.41E-07	2.24E-07	2.8637
PMD	H3K27ac_PGC2.extend.5	0.3352	0.6297	0.1001	1.8786	0.2987	2.05E-03	1.38E-08	1.04E-07	0.1330
PMD	H3K9ac_TrynkaL2_0	0.1254	0.5083	0.1305	4.0528	1.0404	2.31E-03	1.85E-07	1.09E-07	1.6972
PMD	H3K4me3_Trynka.exten	0.2551	0.5961	0.1152	2.3362	0.4513	2.55E-03	6.52E-08	6.05E-08	1.0786
PMD	H3K4me1_TrynkaL2_0	0.4237	0.8796	0.1550	2.0762	0.3658	2.91E-03	3.55E-08	7.51E-08	0.4727
PMD	Enhancer_Hoffman.exte	0.0898	0.3276	0.0843	3.6461	0.9384	3.83E-03	1.05E-07	1.07E-07	0.9837
PMD	MAF_Adj_LLD_AFRL2_0	0.0028	-0.2608	0.0788	-93.2750	28.1842	5.99E-03	-6.47E-10	4.64E-09	-0.1396
PMD	H3K9ac_Trynka.extend.5	0.2299	0.5389	0.1131	2.3445	0.4922	6.52E-03	-3.94E-08	7.22E-08	-0.5461
PMD	DHS_peaks_TrynkaL2_0	0.1106	0.6026	0.1912	5.4493	1.7287	6.55E-03	1.44E-07	1.48E-07	0.9754
PMD	FetalDHS_TrynkaL2_0	0.0839	0.5086	0.1829	6.0592	2.1788	1.29E-02	1.70E-07	1.65E-07	1.0278
PMD	DHS_Trynka.extend.500	0.4960	0.8702	0.1527	1.7543	0.3078	1.49E-02	3.23E-08	5.44E-08	0.5940
PMD	Repressed_Hoffman.ext	0.7185	0.5599	0.0671	0.7793	0.0934	1.62E-02	2.61E-08	3.89E-08	0.6714
PMD	H3K4me1_peaks_Trynka	0.1698	0.6356	0.1929	3.7429	1.1357	1.70E-02	9.83E-08	8.96E-08	1.0972
PMD	DHS_TrynkaL2_0	0.1662	0.6540	0.2151	3.9349	1.2941	1.77E-02	-5.54E-08	1.35E-07	-0.4116
PMD	CTCF_HoffmanL2_0	0.0239	-0.1889	0.0914	-7.9139	3.8291	1.84E-02	-5.42E-07	2.62E-07	-2.0679
PMD	DGF_ENCODE.extend.50	0.5385	0.8586	0.1340	1.5945	0.2489	2.20E-02	8.94E-09	4.25E-08	0.2104
PMD	Transcr_Hoffman.exten	0.7621	0.5662	0.0892	0.7429	0.1170	2.90E-02	-6.12E-08	3.16E-08	-1.9405
PMD	TFBS_ENCODE.extend.5	0.3412	0.6298	0.1402	1.8457	0.4110	4.11E-02	1.36E-08	5.70E-08	0.2393
PMD	Coding_UCSCL2_0	0.0143	0.1349	0.0597	9.4506	4.1809	4.59E-02	1.99E-07	4.04E-07	0.4923
PMD	Backgrd_Selection_Statt	0.1777	0.1988	0.0116	1.1186	0.0651	5.15E-02	3.44E-08	2.04E-08	1.6805
PMD	MAFbin9L2_0	0.1011	0.1819	0.0430	1.7994	0.4254	5.79E-02	5.52E-08	2.14E-08	2.5773
PMD	H3K27ac_PGC2L2_0	0.2688	0.5482	0.1456	2.0396	0.5416	6.15E-02	-4.03E-08	1.23E-07	-0.3278
PMD	DGF_ENCODEL2_0	0.1360	0.4515	0.1882	3.3194	1.3838	8.49E-02	6.46E-09	9.95E-08	0.0649
PMD	TSS_Hoffman.extend.50	0.0344	0.1448	0.0661	4.2161	1.9227	9.15E-02	2.23E-07	1.90E-07	1.1731
PMD	H3K4me3_peaks_Trynka	0.0416	0.2134	0.1110	5.1244	2.6640	1.07E-01	1.85E-07	1.64E-07	1.1262
PMD	MAFbin3L2_0	0.0996	0.0480	0.0321	0.4820	0.3221	1.11E-01	-6.10E-09	1.66E-08	-0.3676
PMD	UTR_3_UCSC.extend.50	0.0265	0.1097	0.0527	4.1466	1.9932	1.14E-01	3.63E-08	1.43E-07	0.2542
PMD	CTCF_Hoffman.extend.5	0.0708	-0.0662	0.0897	-0.9347	1.2660	1.23E-01	4.02E-08	1.16E-07	0.3465
PMD	FetalDHS_Trynka.extend	0.2834	0.5613	0.1841	1.9809	0.6496	1.27E-01	-6.57E-08	6.82E-08	-0.9632
PMD	Intron_UCSCL2_0	0.3875	0.3017	0.0561	0.7786	0.1448	1.27E-01	5.50E-08	3.14E-07	0.1750
PMD	Promoter_UCSC.extend.	0.0381	0.1180	0.0520	3.1009	1.3665	1.27E-01	3.11E-07	3.55E-07	0.8783
PMD	MAFbin5L2_0	0.0983	0.1489	0.0342	1.5145	0.3481	1.32E-01	4.01E-08	1.79E-08	2.2386
PMD	H3K4me3_TrynkaL2_0	0.1330	0.2905	0.1074	2.1839	0.8072	1.46E-01	-1.66E-07	9.59E-08	-1.7290
PMD	MAFbin1L2_0	0.1024	0.0493	0.0383	0.4815	0.3742	1.60E-01	-7.57E-09	2.10E-08	-0.3599
PMD	Recomb_Rate_10kbl2_0	1.5524	2.1255	0.3846	1.3692	0.2478	1.61E-01	2.64E-09	3.46E-09	0.7623
PMD	TFBS_ENCODEL2_0	0.1312	0.3454	0.1618	2.6323	1.2328	1.71E-01	3.56E-08	1.09E-07	0.3256
PMD	UTR_3_UCSCL2_0	0.0112	0.1072	0.0717	9.5857	6.4137	1.83E-01	2.72E-07	5.61E-07	0.4849
PMD	Conserved_LindbladToh	0.3304	0.4946	0.1261	1.4968	0.3818	1.90E-01	-5.78E-08	3.60E-08	-1.6067
PMD	Transcr_HoffmanL2_0	0.3460	0.5137	0.1299	1.4847	0.3753	1.94E-01	7.42E-08	3.68E-08	2.0150
PMD	Super_Enhancer_Vahedi	0.0207	0.0434	0.0178	2.0924	0.8578	2.01E-01	1.59E-06	1.12E-06	1.4222
PMD	GERP.RSsup4L2_0	0.0081	0.0839	0.0599	10.2944	7.3438	2.05E-01	-9.58E-08	3.80E-07	-0.2520
PMD	Enhancer_Andersson.ex	0.0190	-0.0474	0.0529	-2.4879	2.7769	2.14E-01	-3.30E-07	1.85E-07	-1.7789
PMD	Enhancer_HoffmanL2_0	0.0420	0.1611	0.1003	3.8377	2.3884	2.30E-01	-8.63E-08	1.91E-07	-0.4527
PMD	H3K4me1_Trynka.exten	0.6058	0.7111	0.0901	1.1738	0.1488	2.52E-01	-9.05E-08	5.29E-08	-1.7095
PMD	Nucleotide_Diversity_10	4.6087	4.3942	0.1896	0.9535	0.0411	2.61E-01	3.90E-10	1.91E-09	0.2038
PMD	Repressed_HoffmanL2_0	0.4609	0.2960	0.1531	0.6423	0.3322	2.82E-01	1.63E-08	4.24E-08	0.3832
PMD	WeakEnhancer_Hoffma	0.0888	0.1724	0.1003	1.9418	1.1297	4.06E-01	3.13E-08	8.35E-08	0.3749
PMD	PromoterFlanking_Hoffr	0.0332	0.0828	0.0629	2.4950	1.8958	4.35E-01	2.38E-09	1.40E-07	0.0169
PMD	UTR_5_UCSC.extend.50	0.0269	0.0680	0.0539	2.5308	2.0061	4.44E-01	1.29E-07	1.27E-07	1.0181
PMD	MAFbin8L2_0	0.1002	0.0736	0.0374	0.7339	0.3735	4.79E-01	6.24E-09	1.77E-08	0.3531
PMD	Typical_Enhancer_Vahe	0.0261	0.0496	0.0367	1.8956	1.4053	5.23E-01	4.90E-08	3.57E-07	0.1374
PMD	WeakEnhancer_Hoffma	0.0210	-0.0283	0.0773	-1.3466	3.6833	5.24E-01	-3.02E-07	2.19E-07	-1.3760
PMD	Typical_Enhancer_Vahe	0.0219	0.0381	0.0285	1.7430	1.3021	5.68E-01	-6.36E-08	3.73E-07	-0.1703
PMD	Intron_UCSC.extend.50	0.3968	0.3701	0.0474	0.9328	0.1194	5.71E-01	-7.32E-08	3.14E-07	-0.2329
PMD	MAFbin10L2_0	0.0985	0.0833	0.0373	0.8456	0.3787	6.83E-01	1.24E-08	1.97E-08	0.6331
PMD	Enhancer_AnderssonL2_	0.0043	0.0191	0.0369	4.4048	8.5200	6.90E-01	3.00E-07	4.79E-07	0.6263
PMD	UTR_5_UCSCL2_0	0.0055	0.0171	0.0293	3.1185	5.3461	6.92E-01	-1.98E-07	3.26E-07	-0.6090
PMD	Super_Enhancer_Vahedi	0.0212	0.0279	0.0176	1.3186	0.8294	7.01E-01	-1.60E-06	1.11E-06	-1.4473
PMD	Promoter_UCSCL2_0	0.0307	0.0541	0.0679	1.7643	2.2145	7.30E-01	-3.59E-07	4.36E-07	-0.8246
PMD	MAFbin7L2_0	0.0997	0.1112	0.0361	1.1150	0.3616	7.50E-01	2.33E-08	1.91E-08	1.2235
PMD	Coding_UCSC.extend.50	0.0637	0.0409	0.0756	0.6426	1.1870	7.61E-01	-2.01E-07	7.51E-08	-2.6810
PMD	MAF_Adj_Predicted_Alle	0.0000	-0.0478	0.1563	-14101.3723	46082.9775	7.62E-01	4.73E-10	8.60E-09	0.0550
PMD	TSS_HoffmanL2_0	0.0178	0.0347	0.0579	1.9481	3.2453	7.70E-01	-3.55E-07	2.61E-07	-1.3613
PMD	MAFbin4L2_0	0.1007	0.1112	0.0399	1.1041	0.3962	7.94E-01	2.17E-08	2.10E-08	1.0327
PMD	MAFbin6L2_0	0.0996	0.0891	0.0453	0.8939	0.4544	8.16E-01	1.32E-08	2.21E-08	0.5994
PMD	H3K9ac_peaks_TrynkaL2	0.0385	0.0555	0.1116	1.4440	2.9028	8.78E-01	-2.14E-07	1.94E-07	-1.1045
PMD	PromoterFlanking_Hoffr	0.0083	0.0136	0.0502	1.6356	6.0361	9.16E-01	-1.17E-07	3.54E-07	-0.3316
PMD	MAFbin2L2_0	0.0999	0.1036	0.0400	1.0376	0.4007	9.25E-01	1.74E-08	2.18E-08	0.7993

Supplementary Table 2.8 Statistically significant TWAS results of association between genetically predicted gene expression and DA, NDA or PMD

MD Trait	Gene Name	CHR	Gene End Position	Heritability	Heritability P	# of SNP	# of SNP in Model	Model Used	TWAS Zscore	TWAS P-value
DA	MTMR11	1	149936866	0.198	3.54E-05	955	3	lasso	-6.59	4.45E-11
DA	SMIM25	20	50267485	0.224	1.75E-05	2436	5	lasso	5.39	7.02E-08
DA	EP300	22	41091785	0.084	2.22E-03	1506	1506	blup	-4.96	6.89E-07
NDA	NTN4	12	95791151	0.115	9.47E-03	3044	3044	susie	-6.46	1.04E-10
NDA	SHOX2	3	158106502	0.168	9.83E-07	2400	2400	blup	-4.79	1.68E-06
NDA	RP11-419C23.1	8	37069417	0.255	2.10E-07	1684	1684	susie	-4.60	4.15E-06
PMD	MTMR11	1	149936866	0.198	3.54E-05	955	3	lasso	-5.54	3.05E-08
PMD	CRISPLD2	16	84819983	0.262	8.56E-05	4164	4164	susie	4.66	3.14E-06

Supplementary Table 2.9 Fine-mapping generated credible sets of mammographic dense area (DA) GWAS loci covering 95% of the posterior probability of causality

Region	Lead SNP			95% Credible Sets				
	rs ID	CHR	Position	rs ID	CHR	Position	GWAS Zscore	Posterior_Prob
1q21.2	rs11205303	1	149906413	rs11205303	1	149906413	-6.772	0.7213
				rs1868992	1	149908108	6.556	0.1791
				rs12048493	1	149927034	-6.346	0.0483
				rs67807996	1	149995265	6.202	0.0201
2q14.2	rs17625845	2	121089731	rs17625845	2	121089731	7.949	0.9649
4q13.3	rs6851733	4	75518708	rs6851733	4	75518708	6.874	0.9996
5q11.2	rs150249911	5	52119132	rs150249911	5	52119132	-5.928	0.9959
5q23.2	rs335189	5	122446856	rs335189	5	122446856	6.655	0.9960
5q35.1	rs2042239	5	169566329	rs2042239	5	169566329	6.485	0.2140
				rs13169329	5	169571480	6.478	0.2048
				rs17562499	5	169570889	6.474	0.1997
				rs2879278	5	169572731	6.314	0.0742
				rs11134615	5	169556934	6.250	0.0503
				rs2112670	5	169557594	-6.250	0.0503
				rs13163248	5	169553186	6.156	0.0286
				rs35733404	5	169556907	6.126	0.0239
				rs7733443	5	169514685	-6.078	0.0180
				rs7729559	5	169568846	-6.050	0.0153
				rs1006634	5	169518545	-5.970	0.0096
				rs17072121	5	169567992	5.923	0.0073
				rs35709472	5	169575620	5.920	0.0072
				rs17562083	5	169512748	-5.913	0.0069
				rs56251929	5	169523866	-5.905	0.0066
				rs12516022	5	169537130	-5.905	0.0066
rs12656442	5	169582216	5.889	0.0060				
rs13169384	5	169578628	5.871	0.0054				
rs55788424	5	169555028	5.868	0.0054				
rs2338815	5	169541551	-5.840	0.0046				
rs13189237	5	169587799	5.830	0.0043				
rs6880991	5	169545642	5.826	0.0042				
6q25.1	rs9397436	6	151952002	rs9397436	6	151952002	7.951	0.1878
				rs9397435	6	151951220	7.936	0.1674
				rs58343273	6	151953180	7.875	0.1050
				rs9397068	6	151953859	-7.867	0.0988
				rs60954078	6	151955914	7.848	0.0855
				rs9397437	6	151952332	-7.846	0.0842
				rs9383590	6	151953765	7.845	0.0835
				rs6912323	6	151958612	-7.797	0.0581
				rs12173562	6	151957570	-7.788	0.0543
rs9383937	6	151957119	7.773	0.0485				

7p11.2	rs10155920	7	55308930	rs10155920	7	55308930	5.755	0.9461
				rs4947993	7	55305966	-5.064	0.0254
8q24.13	rs58847541	8	124610166	rs58847541	8	124610166	5.994	0.9109
				rs35542655	8	124563705	-5.392	0.0331
				rs17253058	8	124559709	5.316	0.0223
10q21.2	rs10995187	10	64273026	rs10995187	10	64273026	8.933	0.1567
				rs4746419	10	64275261	-8.911	0.1296
				rs34511355	10	64276964	-8.894	0.1119
				rs10995189	10	64278181	8.892	0.1100
				rs10995190	10	64278682	8.892	0.1100
				rs10995191	10	64278874	8.891	0.1091
				rs10995201	10	64299890	-8.854	0.0794
				rs10995194	10	64288130	8.843	0.0723
				rs11524313	10	64283656	8.820	0.0594
				rs10995193	10	64288082	-8.813	0.0559
11p15.5	rs4980383	11	1902097	rs4980383	11	1902097	-7.228	0.6738
				rs1810199	11	1886306	-6.912	0.0776
				rs909116	11	1941946	-6.822	0.0426
				rs4980389	11	1892585	6.792	0.0350
				rs686722	11	1891722	6.771	0.0305
				rs562434	11	1892930	6.744	0.0256
				rs569550	11	1887068	-6.701	0.0193
				rs4980386	11	1895708	6.640	0.0130
				rs576603	11	1914139	6.608	0.0106
				rs735955	11	1943120	6.595	0.0098
				rs1973765	11	1898664	-6.561	0.0079
				rs3781962	11	1907609	-6.540	0.0069
12p12.1	rs11836164	12	26446625	rs11836164	12	26446625	6.028	0.1670
				rs35723060	12	26447931	-6.017	0.1567
				rs12822659	12	26448513	-6.012	0.1522
				rs12822258	12	26448400	6.010	0.1504
				rs12813761	12	26450396	5.988	0.1324
				rs11836653	12	26452481	5.955	0.1094
				rs7968305	12	26451545	5.940	0.1004
12p11.2	rs7297051	12	28174817	rs7297051	12	28174817	6.166	0.7612
				rs7976725	12	28183286	-5.803	0.0930
				rs812020	12	28151609	-5.763	0.0744
				rs2590275	12	28166067	-5.612	0.0324
12q23.2	rs833472	12	103005100	rs833472	12	103005100	7.134	0.0660
				rs61941038	12	102989316	-7.133	0.0656
				rs703556	12	103011894	-7.126	0.0625
				rs703557	12	103012049	-7.126	0.0625
				rs1096914	12	103001065	-7.109	0.0556
				rs833463	12	103007185	-7.091	0.0491
				rs61941039	12	102989606	-7.090	0.0488
				rs61941040	12	102989710	-7.089	0.0484

				rs17032884	12	102995192	-7.087	0.0478
				rs1070208	12	103008745	-7.085	0.0471
				rs703551	12	103009144	7.085	0.0471
				rs17032899	12	102997164	-7.084	0.0468
				rs703555	12	103011455	7.078	0.0449
				rs703553	12	103010139	7.059	0.0394
				rs61937479	12	102977074	7.054	0.0381
				rs1840959	12	102982041	7.047	0.0363
				rs61937482	12	102980979	-7.041	0.0349
				rs11611928	12	102979757	-7.021	0.0304
				rs61937477	12	102972154	6.996	0.0257
				rs703560	12	103014414	-6.996	0.0257
				rs833469	12	103002657	-6.979	0.0229
				rs78693353	12	102965986	6.925	0.0159
19q13.33	rs1231281	19	49239200	rs1231281	19	49239200	6.860	0.1930
				rs12462111	19	49171306	6.811	0.1395
				rs973579	19	49241976	-6.752	0.0948
				rs427248	19	49241015	6.749	0.0929
				rs8111874	19	49168942	6.741	0.0882
				rs418464	19	49239026	-6.737	0.0859
				rs35866622	19	49218060	6.734	0.0843
				rs380743	19	49241014	6.722	0.0779
				rs281381	19	49214748	6.539	0.0241
				rs281380	19	49214470	6.536	0.0236
				rs281386	19	49217305	6.520	0.0214
				rs281378	19	49214066	-6.513	0.0204
				rs204248	19	49216224	-6.472	0.0158
20q13.13	rs17789629	20	48892374	rs17789629	20	48892374	-5.478	0.0990
				rs6020413	20	48896445	-5.422	0.0737
				rs6020414	20	48896783	-5.412	0.0699
				rs6125970	20	48911064	-5.346	0.0496
				rs8119240	20	48899892	-5.335	0.0469
				rs7354606	20	48899908	5.334	0.0466
				rs6095858	20	48900511	5.332	0.0461
				rs6020423	20	48909667	-5.318	0.0429
				rs6020424	20	48910141	-5.314	0.0420
				rs6122896	20	48901652	5.304	0.0399
				rs6095863	20	48908979	-5.301	0.0393
				rs6012893	20	48910103	5.292	0.0376
				rs62208627	20	48892508	5.286	0.0364
				rs56261730	20	48907760	5.274	0.0343
				rs6020417	20	48899352	5.260	0.0319
				rs17196808	20	48909280	-5.257	0.0314
				rs6063497	20	48907120	-5.254	0.0309
				rs6125967	20	48904044	-5.233	0.0278
				rs871750	20	48908140	-5.209	0.0246

				rs746426	20	48938580	-5.160	0.0193
				rs2869981	20	48939095	5.157	0.0190
				rs7263249	20	48975329	-5.128	0.0164
				rs6067395	20	48913586	5.062	0.0119
				rs6020445	20	48939863	5.061	0.0118
				rs1889236	20	48905967	-5.048	0.0111
				rs6125971	20	48915766	4.958	0.0072
				rs3088220	20	48894756	-4.901	0.0055
22q13.1	rs34066050	22	38612604	rs34066050	22	38612604	-5.534	0.0973
				rs9622757	22	38613768	-5.510	0.0856
				rs2235264	22	38609950	-5.487	0.0757
				rs4821767	22	38614129	-5.478	0.0722
				rs2064103	22	38608227	5.441	0.0594
				rs8139952	22	38606989	-5.420	0.0532
				rs13055114	22	38607394	-5.331	0.0335
				rs2267374	22	38600595	5.295	0.0278
				rs9607518	22	38605133	-5.277	0.0254
				rs5995556	22	38642494	-5.214	0.0184
				rs11914181	22	38602140	5.181	0.0156
				rs3761448	22	38595571	-5.165	0.0144
				rs2018805	22	38642343	-5.165	0.0144
				rs2413507	22	38593428	5.118	0.0114
				rs9607517	22	38596100	-5.114	0.0112
				rs9610915	22	38611080	5.108	0.0109
				rs9619728	22	38652566	-5.097	0.0103
				rs9610924	22	38652339	-5.084	0.0096
				rs5750558	22	38582497	-5.073	0.0091
				rs9622764	22	38650731	5.064	0.0087
				rs9622763	22	38650644	-5.061	0.0086
				rs3761444	22	38580371	-5.059	0.0085
				rs2899298	22	38603186	5.057	0.0084
				rs9610923	22	38649783	5.032	0.0075
				rs9610927	22	38653689	-5.031	0.0074
				rs3761447	22	38595539	-5.023	0.0072
				rs2413505	22	38592967	-5.011	0.0067
				rs133019	22	38573035	-4.994	0.0062
				rs2413510	22	38638597	-4.958	0.0052
				rs2267382	22	38644195	-4.946	0.0049
				rs738320	22	38568715	4.944	0.0049
				rs133014	22	38571087	-4.931	0.0046
				rs2413503	22	38568944	-4.930	0.0046
				rs133022	22	38573589	-4.928	0.0045
				rs4385	22	38573229	-4.922	0.0044
				rs2267381	22	38634388	4.922	0.0044
				rs133023	22	38573629	-4.921	0.0044
				rs133024	22	38574066	-4.918	0.0043

				rs4379	22	38569171	-4.917	0.0043
				rs9306326	22	38649153	4.916	0.0043
				rs738322	22	38569006	-4.914	0.0042
				rs5995558	22	38647639	-4.906	0.0041
				rs4820329	22	38646063	4.905	0.0041
				rs5756986	22	38640841	-4.902	0.0040
				rs5750571	22	38640312	-4.898	0.0039
				rs133009	22	38569653	4.895	0.0039
				rs2284072	22	38633666	-4.892	0.0038
				rs2092180	22	38571563	-4.891	0.0038
				rs75387	22	38572057	4.888	0.0037
				rs2267373	22	38600542	-4.888	0.0037
				rs133021	22	38573338	-4.887	0.0037
				rs133016	22	38572582	4.886	0.0037
				rs133018	22	38572761	4.883	0.0037
				rs4380	22	38569529	-4.882	0.0036
				rs6001038	22	38570585	-4.882	0.0036
				rs133012	22	38570721	4.881	0.0036
				rs4381	22	38570791	-4.881	0.0036
				rs4382	22	38570842	-4.881	0.0036
				rs133013	22	38570912	4.880	0.0036
				rs4383	22	38570927	-4.880	0.0036
				rs133017	22	38572637	-4.880	0.0036
				rs4820324	22	38599857	-4.876	0.0035
				rs4821764	22	38599364	-4.875	0.0035
				rs9610922	22	38646460	4.873	0.0035
				rs5995554	22	38630272	-4.870	0.0034
				rs2267375	22	38601231	-4.868	0.0034
				rs7289126	22	38628306	4.866	0.0034
				rs2277844	22	38577515	-4.865	0.0034
				rs2267380	22	38631768	-4.863	0.0033
				rs132972	22	38562056	-4.861	0.0033
				rs9306325	22	38649142	-4.855	0.0032
				rs2092076	22	38637676	-4.851	0.0031
				rs4820325	22	38599978	-4.849	0.0031
				rs6001068	22	38639314	4.839	0.0030
				rs7290372	22	38628388	-4.833	0.0029
				rs4820328	22	38635679	4.832	0.0029
				rs3761445	22	38595411	-4.807	0.0026
				rs2899297	22	38594668	-4.804	0.0025
				rs6001063	22	38637842	4.801	0.0025
				rs133010	22	38570189	-4.793	0.0024
				rs9610926	22	38653575	4.789	0.0024
				rs4384	22	38572440	4.780	0.0023
				rs5756968	22	38595240	-4.780	0.0023
				rs4608623	22	38597378	-4.776	0.0022

				rs2012725	22	38536861	-4.774	0.0022
				rs9610921	22	38638897	4.771	0.0022
				rs133015	22	38572526	-4.770	0.0022
				rs4820318	22	38570313	4.763	0.0021
				rs5750561	22	38595260	4.756	0.0020
				rs3761449	22	38595615	-4.749	0.0020
				rs145125237	22	38954208	-0.779	0.0017
				rs13056506	22	38580917	-4.697	0.0015
				rs3827355	22	38538121	-4.680	0.0014
				rs5756946	22	38570219	-4.674	0.0014
				rs132971	22	38561911	-4.669	0.0014
				rs2267376	22	38628739	-4.667	0.0013
				rs5750542	22	38534507	-4.666	0.0013
				rs84473	22	38557326	-4.663	0.0013

22q13.2	rs6001939	22	40892794	rs6001939	22	40892794	8.791	0.0471
				rs73167080	22	40885498	-8.709	0.0235
				rs73167030	22	40819013	-8.669	0.0168
				rs12158872	22	40832501	8.658	0.0153
				rs6001911	22	40825193	-8.650	0.0143
				rs6001912	22	40828361	-8.648	0.0141
				rs56150793	22	40824087	8.646	0.0139
				rs73167039	22	40833146	-8.643	0.0135
				rs73167082	22	40885499	-8.636	0.0128
				rs73169071	22	41014472	8.633	0.0124
				rs73169060	22	40994744	-8.631	0.0122
				rs17001915	22	40842466	8.630	0.0121
				rs17001907	22	40834346	-8.622	0.0114
				rs73167044	22	40842405	-8.622	0.0114
				rs6001979	22	40999766	-8.620	0.0112
				rs3827381	22	40881402	-8.614	0.0106
				rs73169058	22	40992235	-8.614	0.0106
				rs73169072	22	41016681	8.611	0.0104
				rs6001980	22	41004384	-8.608	0.0101
				rs6001983	22	41023304	-8.604	0.0098
				rs6001974	22	40979164	-8.603	0.0097
				rs73169083	22	41022503	-8.602	0.0096
				rs17002019	22	40965336	8.598	0.0093
				rs6001981	22	41017425	8.597	0.0092
				rs6001910	22	40824009	-8.595	0.0091
				rs6001950	22	40906635	-8.592	0.0088
				rs17002030	22	40989374	-8.591	0.0088
				rs6001930	22	40876234	-8.590	0.0087
				rs55719110	22	41005749	-8.584	0.0083
				rs6001915	22	40840614	-8.582	0.0081

				rs55669535	22	41012819	8.580	0.0080
				rs10483206	22	40901345	8.579	0.0079
				rs6001946	22	40903421	-8.578	0.0079
				rs28567076	22	40984798	-8.576	0.0077
				rs55997921	22	41006612	8.576	0.0077
				rs6001982	22	41019948	8.575	0.0077
				rs17002026	22	40982581	8.574	0.0076
				rs73169057	22	40990950	-8.574	0.0076
				rs6001973	22	40977556	-8.572	0.0075
				rs6001984	22	41025380	-8.572	0.0075
				rs59047419	22	41011279	8.569	0.0073
				rs73169051	22	40979648	-8.567	0.0072
				rs17002024	22	40975268	8.565	0.0071
				rs73167076	22	40879843	8.564	0.0070
				rs6001937	22	40887085	-8.563	0.0070
				rs5995867	22	40888136	-8.562	0.0069
				rs74767555	22	40826733	8.560	0.0068
				rs73167097	22	40895706	8.560	0.0068
				rs28444678	22	40974252	-8.560	0.0068
				rs73167045	22	40842923	-8.559	0.0067
				rs55662398	22	40948875	-8.558	0.0067
				rs141597790	22	40994998	-8.558	0.0067
				rs147759720	22	40935623	8.556	0.0066
				rs73167098	22	40895810	8.555	0.0065
				rs6001913	22	40836753	8.554	0.0065
				rs6001942	22	40893866	-8.546	0.0060
				rs6001935	22	40886993	-8.545	0.0060
				rs5995876	22	40972056	8.544	0.0059
				rs73167031	22	40821818	-8.540	0.0057
				rs73169078	22	41019767	8.540	0.0057
				rs1106673	22	40825814	8.537	0.0056
				rs2294352	22	40827319	8.537	0.0056
				rs12160047	22	40967695	-8.536	0.0056
				rs112880707	22	40884662	8.535	0.0055
				rs12159970	22	40819154	8.534	0.0055
				rs73167073	22	40879408	-8.534	0.0055
				rs6001962	22	40949210	-8.533	0.0054
				rs5995856	22	40849062	8.523	0.0050
				rs17002034	22	40996367	8.519	0.0048
				rs5995881	22	41015883	-8.519	0.0048
				rs6001932	22	40877635	8.517	0.0048
				rs3827382	22	40881403	8.514	0.0046
				rs55674424	22	40957013	8.513	0.0046
				rs6001931	22	40877514	8.512	0.0046
				rs17001920	22	40849495	-8.511	0.0045
				rs73167034	22	40826534	-8.510	0.0045

				rs55853923	22	40987113	-8.508	0.0044
				rs73169056	22	40986258	8.507	0.0044
				rs17002027	22	40984571	-8.506	0.0043
				rs2072857	22	40816841	8.504	0.0043
				rs73169097	22	41027870	8.501	0.0042
				rs6001965	22	40960867	8.500	0.0041
				rs57705902	22	40977121	8.499	0.0041
				rs78694459	22	41027354	-8.499	0.0041
				rs73169096	22	41027716	8.499	0.0041
				rs56283550	22	40831888	8.498	0.0041
				rs192603101	22	41014253	-8.498	0.0041
				rs117669949	22	41026775	-8.496	0.0040
				rs56108505	22	41024650	-8.495	0.0040
				rs73169087	22	41024846	8.495	0.0040
				rs73169089	22	41024854	-8.495	0.0040
				rs73169091	22	41026018	-8.494	0.0039
				rs145351698	22	41018451	8.493	0.0039
				rs5995875	22	40960692	8.490	0.0038
				rs73169084	22	41022805	8.489	0.0038
				rs17002036	22	40997111	8.487	0.0037
				rs10483203	22	40829953	-8.485	0.0037
				rs718193	22	41024064	-8.485	0.0037
				rs10483205	22	40883599	8.484	0.0036
				rs17001974	22	40877384	8.481	0.0035
				rs73169032	22	40956816	8.481	0.0035
				rs56051217	22	41049402	8.481	0.0035
				rs142127948	22	40995290	8.480	0.0035
				rs17002038	22	41000964	8.480	0.0035
				rs73169077	22	41018507	8.480	0.0035
				rs73169098	22	41031027	8.477	0.0034
				rs56124626	22	40907951	-8.475	0.0034
				rs73167067	22	40875199	-8.474	0.0033
				rs17001993	22	40900077	8.474	0.0033
				rs8141330	22	41052794	-8.474	0.0033
				rs113966362	22	40899836	8.473	0.0033
				rs17001994	22	40900818	8.473	0.0033
				rs73169003	22	40900856	-8.473	0.0033
				rs17001977	22	40880213	8.470	0.0032
				rs56047425	22	40968152	-8.468	0.0032
				rs113409089	22	40885600	8.466	0.0031
				rs74278065	22	40885710	-8.466	0.0031
				rs5995886	22	41033801	8.465	0.0031
				rs73167093	22	40893789	-8.463	0.0031
				rs5995864	22	40866763	-8.462	0.0030
				rs73167089	22	40887648	8.462	0.0030
				rs138175438	22	40893900	8.462	0.0030

				rs79799751	22	40977346	8.462	0.0030
				rs5995860	22	40852671	-8.461	0.0030
				rs28419341	22	40854456	8.461	0.0030
				rs77426923	22	40889908	8.461	0.0030
				rs112375848	22	40855011	-8.458	0.0029
				rs73167079	22	40883088	-8.457	0.0029
				rs73167090	22	40888363	8.457	0.0029
				rs73169043	22	40973610	8.455	0.0029
				rs4140512	22	41032863	-8.455	0.0029
				rs73167092	22	40892127	-8.452	0.0028
				rs73167041	22	40837964	8.448	0.0027
				rs28552449	22	40854814	8.448	0.0027
				rs56135013	22	40887074	8.446	0.0027
				rs73167096	22	40894463	-8.446	0.0027
				rs12159787	22	40870699	-8.445	0.0026
				rs73169028	22	40954094	8.443	0.0026
				rs17002020	22	40965443	-8.443	0.0026
				rs61675795	22	40839696	8.442	0.0026
				rs73167072	22	40879105	8.442	0.0026
				rs73167042	22	40840610	8.441	0.0025
				rs138476044	22	40972176	8.436	0.0024
				rs16985899	22	40963402	8.433	0.0024
				rs117423948	22	40970711	8.433	0.0024
				rs10483204	22	40870794	-8.431	0.0023
				rs73169040	22	40969989	-8.430	0.0023
				rs17001997	22	40905072	8.429	0.0023
				rs5995893	22	41062014	-8.429	0.0023
				rs149683271	22	40944385	-8.428	0.0023
				rs73169036	22	40967688	8.426	0.0023
				rs73171013	22	41051935	8.426	0.0023
				rs8142396	22	41052756	-8.426	0.0023
				rs73169026	22	40953763	8.425	0.0022
				rs6002000	22	41051109	8.424	0.0022
				rs17002067	22	41050306	-8.423	0.0022
				rs5995871	22	40922332	-8.422	0.0022
				rs6001954	22	40921680	-8.420	0.0021
				rs6001949	22	40904486	8.417	0.0021
				rs5995870	22	40921816	-8.414	0.0020
				rs73167069	22	40878253	-8.413	0.0020
				rs733999	22	41050335	-8.409	0.0020
				rs73167052	22	40847848	-8.407	0.0019
				rs73167062	22	40864848	8.406	0.0019
				rs12158399	22	41048941	8.406	0.0019
				rs55916800	22	41049315	-8.406	0.0019
				rs12159974	22	41046757	8.404	0.0019
				rs56411183	22	40968616	8.400	0.0018

Supplementary Table 2.10 Fine-mapping generated credible sets of mammographic non-dense area (NDA) GWAS loci covering 95% of the posterior probability of causality

Region	Lead SNP			95% Credible Sets				
	rs ID	CHR	Position	rs ID	CHR	Position	GWAS Zscore	Posterior_Prob
1p12	rs78395856	1	119495096	rs78395856	1	119495096	5.525	0.4362
				rs190709029	1	119719773	5.312	0.1428
				rs77261529	1	119680851	5.259	0.1089
				rs188862021	1	119625891	5.224	0.0912
				rs75990303	1	119780123	5.147	0.0619
				rs191382641	1	119707077	-5.057	0.0397
				rs7522839	1	119542855	5.044	0.0373
				rs1779445	1	119508412	5.029	0.0347
5q14.1	rs413472	5	80930992	rs413472	5	80930992	5.551	0.8685
				rs446696	5	80936563	4.854	0.0260
				rs2917542	5	80883110	4.687	0.0120
				rs2917544	5	80906583	-4.607	0.0084
				rs2917540	5	80900719	4.541	0.0063
				rs420202	5	80999768	-4.454	0.0043
				rs374479	5	80998915	-4.448	0.0042
				rs403795	5	81001981	-4.439	0.0040
				rs365241	5	81002004	-4.437	0.0040
				rs389860	5	80993221	-4.436	0.0040
				rs420412	5	81001867	-4.433	0.0039
				rs425897	5	80999222	-4.420	0.0037
				rs424844	5	80998260	-4.419	0.0037
				8p11.23	rs16885613	8	36848357	rs16885613
rs10110651	8	36847115	-12.763					0.1699
rs28735403	8	36848038	-12.749					0.1430
rs7816345	8	36846109	12.734					0.1188
rs10096213	8	36853213	12.734					0.1188
rs10955009	8	36851901	12.709					0.0873
rs10095380	8	36853217	12.703					0.0811
10q21.2	rs2138555	10	64220494					rs2138555
12q22	rs61938093	12	96026737	rs61938093	12	96026737	-6.827	1.0000
22q13.2	rs73169097	22	41027870	rs5750915	22	40642368	-1.030	0.0351
				rs73169097	22	41027870	6.012	0.0319
				rs6001982	22	41019948	5.991	0.0283
				rs6001979	22	40999766	-5.983	0.0270
				rs6001981	22	41017425	5.977	0.0261
				rs6001983	22	41023304	-5.976	0.0259
				rs73169071	22	41014472	5.975	0.0258
				rs73169083	22	41022503	-5.975	0.0258
				rs55669535	22	41012819	5.967	0.0246
				rs73169072	22	41016681	5.963	0.0240
				rs59047419	22	41011279	5.955	0.0230

rs28444678	22	40974252	-5.954	0.0228
rs6001974	22	40979164	-5.954	0.0228
rs6001984	22	41025380	-5.950	0.0223
rs17002024	22	40975268	5.940	0.0211
rs17002026	22	40982581	5.935	0.0205
rs73169051	22	40979648	-5.934	0.0203
rs28567076	22	40984798	-5.934	0.0203
rs73169058	22	40992235	-5.933	0.0202
rs12160047	22	40967695	-5.932	0.0201
rs6001973	22	40977556	-5.930	0.0199
rs6001954	22	40921680	-5.929	0.0198
rs6001980	22	41004384	-5.927	0.0195
rs73169060	22	40994744	-5.926	0.0194
rs5995871	22	40922332	-5.925	0.0193
rs5995876	22	40972056	5.925	0.0193
rs55997921	22	41006612	5.918	0.0186
rs5995881	22	41015883	-5.918	0.0186
rs6001962	22	40949210	-5.912	0.0179
rs6001965	22	40960867	5.903	0.0170
rs55719110	22	41005749	-5.900	0.0167
rs5995875	22	40960692	5.896	0.0164
rs141597790	22	40994998	-5.888	0.0156
rs6001949	22	40904486	5.815	0.0103
rs5995870	22	40921816	-5.766	0.0079
rs192603101	22	41014253	-5.684	0.0050
rs145351698	22	41018451	5.681	0.0049
rs73169078	22	41019767	5.678	0.0048
rs147759720	22	40935623	5.674	0.0047
rs139903991	22	40924662	-5.667	0.0045
rs112034576	22	40918712	5.663	0.0044
rs73169026	22	40953763	5.648	0.0041
rs73169091	22	41026018	-5.644	0.0040
rs117669949	22	41026775	-5.643	0.0040
rs57705902	22	40977121	5.642	0.0040
rs78694459	22	41027354	-5.642	0.0040
rs73169096	22	41027716	5.642	0.0040
rs73169028	22	40954094	5.638	0.0039
rs17002027	22	40984571	-5.637	0.0039
rs73169057	22	40990950	-5.637	0.0039
rs73169056	22	40986258	5.636	0.0038
rs55853923	22	40987113	-5.636	0.0038
rs73169098	22	41031027	5.635	0.0038
rs56047425	22	40968152	-5.634	0.0038
rs718193	22	41024064	-5.632	0.0038
rs73169087	22	41024846	5.631	0.0037
rs73169089	22	41024854	-5.631	0.0037
rs73169077	22	41018507	5.630	0.0037

rs73169084	22	41022805	5.630	0.0037
rs56108505	22	41024650	-5.630	0.0037
rs55993771	22	40919559	5.624	0.0036
rs116973859	22	40973612	5.621	0.0035
rs56411183	22	40968616	5.620	0.0035
rs6001930	22	40876234	-5.616	0.0034
rs73169036	22	40967688	5.615	0.0034
rs73169043	22	40973610	5.613	0.0034
rs73169040	22	40969989	-5.611	0.0033
rs117423948	22	40970711	5.611	0.0033
rs17002020	22	40965443	-5.610	0.0033
rs138476044	22	40972176	5.610	0.0033
rs932379	22	40952534	-5.608	0.0033
rs79799751	22	40977346	5.605	0.0032
rs6001920	22	40850066	-5.600	0.0032
rs17002036	22	40997111	5.589	0.0030
rs55662398	22	40948875	-5.588	0.0030
rs17002019	22	40965336	5.586	0.0029
rs17002038	22	41000964	5.586	0.0029
rs73169032	22	40956816	5.583	0.0029
rs17002030	22	40989374	-5.580	0.0028
rs142127948	22	40995290	5.575	0.0028
rs56092708	22	40962808	5.574	0.0027
rs17002034	22	40996367	5.572	0.0027
rs55960299	22	40932066	5.568	0.0027
rs55849114	22	40932003	5.566	0.0026
rs73169017	22	40936288	5.544	0.0023
rs149683271	22	40944385	-5.540	0.0023
rs55674424	22	40957013	5.539	0.0023
rs55722862	22	40932041	-5.538	0.0023
rs5995856	22	40849062	5.532	0.0022
rs112375848	22	40855011	-5.525	0.0021
rs5995862	22	40857793	-5.516	0.0020
rs6001942	22	40893866	-5.504	0.0019
rs16985899	22	40963402	5.498	0.0018
rs5995860	22	40852671	-5.497	0.0018
rs5995864	22	40866763	-5.496	0.0018
rs56051217	22	41049402	5.496	0.0018
rs6001950	22	40906635	-5.493	0.0018
rs73167097	22	40895706	5.492	0.0018
rs12159787	22	40870699	-5.489	0.0017

Supplementary Table 2.11 Fine-mapping generated credible sets of percent mammographic density (PMD) GWAS loci covering 95% of the posterior probability of causality

Region	Lead SNP			95% Credible Sets				
	rs ID	CHR	Position	rs ID	CHR	Position	GWAS Zscore	Posterior_Prob
1q21.2	rs1868992	1	149908108	rs1868992	1	149908108	5.517	0.3908
				rs4926399	1	149924299	-5.245	0.0948
				rs12058281	1	149928679	5.154	0.0600
				rs6684987	1	149929342	5.150	0.0588
				rs12022928	1	149994954	5.108	0.0477
				rs3767628	1	149938745	5.095	0.0448
				rs11205309	1	149956342	5.080	0.0416
				rs12023748	1	149941228	5.070	0.0396
				rs12082689	1	149972358	5.062	0.0381
				rs11205303	1	149906413	-5.054	0.0366
				rs3936952	1	149978552	-5.034	0.0332
				rs3738320	1	149982626	5.026	0.0319
				rs6660842	1	149918619	4.925	0.0196
				rs12048493	1	149927034	-4.902	0.0176
5q23.2	rs335189	5	122446856	rs335189	5	122446856	6.196	0.2511
				rs151283	5	122446619	-6.133	0.1724
				rs335145	5	122444585	6.091	0.1345
				rs509256	5	122490489	5.764	0.0206
				rs419771	5	122478931	5.727	0.0168
				rs335160	5	122478676	5.726	0.0167
				rs335175	5	122479838	5.712	0.0154
				rs374621	5	122480261	5.712	0.0154
				rs412584	5	122473432	-5.646	0.0107
				rs391555	5	122473457	-5.645	0.0107
				rs441446	5	122473514	5.645	0.0107
				rs602648	5	122473190	-5.643	0.0106
				rs432604	5	122472817	5.642	0.0105
				rs412232	5	122473199	-5.642	0.0105
				rs335158	5	122475779	5.628	0.0097
				rs186749	5	122454305	-5.620	0.0093
				rs335173	5	122480902	-5.616	0.0091
				rs393761	5	122472792	5.611	0.0089
				rs443382	5	122484529	-5.609	0.0088
				rs335172	5	122481271	-5.607	0.0087
				rs233174	5	122483142	5.606	0.0086
				rs335154	5	122485659	-5.605	0.0086
				rs335153	5	122485679	5.605	0.0086
				rs372478	5	122483855	5.604	0.0086
				rs412618	5	122475196	5.603	0.0085
				rs383705	5	122472386	5.599	0.0083
				rs335152	5	122485731	-5.599	0.0083

			rs372212	5	122472098	5.596	0.0082	
			rs335169	5	122483513	-5.595	0.0081	
			rs335149	5	122486729	-5.594	0.0081	
			rs335148	5	122487045	5.591	0.0080	
			rs335150	5	122486143	-5.590	0.0079	
			rs430148	5	122470831	-5.589	0.0079	
			rs335171	5	122481928	-5.589	0.0079	
			rs412742	5	122470647	5.588	0.0078	
			rs382718	5	122472077	5.585	0.0077	
			rs335151	5	122485955	-5.584	0.0077	
			rs394782	5	122487404	-5.584	0.0077	
			rs406157	5	122470763	5.579	0.0075	
			rs335155	5	122485629	5.576	0.0073	
			rs170838	5	122454845	-5.569	0.0071	
			rs189191	5	122453420	-5.568	0.0070	
			rs173028	5	122487549	-5.547	0.0063	
			rs187341	5	122454354	-5.533	0.0058	
			rs398028	5	122454550	-5.533	0.0058	
5q31.1	rs76876329	5	131237759	rs76876329	5	131237759	5.530	0.6058
				rs3776027	5	130802970	-4.889	0.0239
				rs2074808	5	131329591	-4.728	0.0113
				rs12659474	5	130801304	-4.706	0.0102
				rs244739	5	130806874	-4.705	0.0102
				rs1468303	5	130804400	-4.689	0.0095
				rs17167760	5	130782699	-4.688	0.0094
				rs11242077	5	130771037	4.686	0.0093
				rs11242078	5	130792035	-4.686	0.0093
				rs56228197	5	130805475	4.686	0.0093
				rs3776028	5	130789750	4.683	0.0092
				rs10463887	5	130776854	4.680	0.0091
				rs3776030	5	130776738	-4.677	0.0090
				rs76753180	5	130763701	-4.676	0.0089
				rs739952	5	130796568	-4.670	0.0087
				rs6895841	5	130773534	4.668	0.0086
				rs58895212	5	130797057	4.668	0.0086
				rs1422081	5	130776053	4.663	0.0084
				rs683749	5	131283376	4.651	0.0080
				rs72793242	5	131242506	-4.645	0.0078
				rs12656936	5	130788642	-4.643	0.0077
				rs804059	5	131270136	-4.611	0.0067
				rs491624	5	131270222	-4.611	0.0067
				rs257390	5	130740617	4.605	0.0065
				rs145025650	5	131233225	4.594	0.0062
				rs27663	5	130741438	-4.589	0.0060
				rs28537859	5	131237277	-4.589	0.0060
				rs142958719	5	131232959	4.586	0.0060
				rs12520906	5	131224804	-4.577	0.0057

				rs56081930	5	131235274	-4.574	0.0057
				rs58016983	5	131235275	-4.570	0.0056
				rs7733731	5	131223402	4.553	0.0052
				rs4493667	5	131247218	4.535	0.0048
				rs27708	5	130743541	4.532	0.0047
				rs60847707	5	131252554	4.527	0.0046
				rs27421	5	130743771	4.522	0.0045
				rs4996522	5	130761470	4.521	0.0045
				rs12654593	5	130756867	4.520	0.0045
				rs59808242	5	130754894	4.519	0.0044
				rs12521320	5	130755920	-4.511	0.0043
				rs2158428	5	130751481	4.510	0.0043
				rs7710536	5	131231535	-4.507	0.0042
				rs72793241	5	131240885	4.504	0.0042
				rs687816	5	131262077	4.487	0.0039
				rs55945538	5	131228421	4.480	0.0037
				rs7708140	5	131252396	4.464	0.0035
				rs615305	5	131291856	-4.406	0.0027
				rs600661	5	131290894	-4.385	0.0025
				rs510434	5	131292503	4.384	0.0025
				rs139620728	5	131228670	-4.346	0.0021
				rs10075660	5	131240843	4.317	0.0019
				rs476428	5	131301615	4.277	0.0016
				rs17171380	5	131020095	-4.253	0.0014
				rs79392931	5	131285115	4.245	0.0014
				rs76386054	5	131023158	4.229	0.0013
				rs75544080	5	130885515	-4.226	0.0013
				rs559971	5	131316164	4.224	0.0013
				rs4277907	5	131227713	4.222	0.0013
				rs635164	5	131312874	4.219	0.0012
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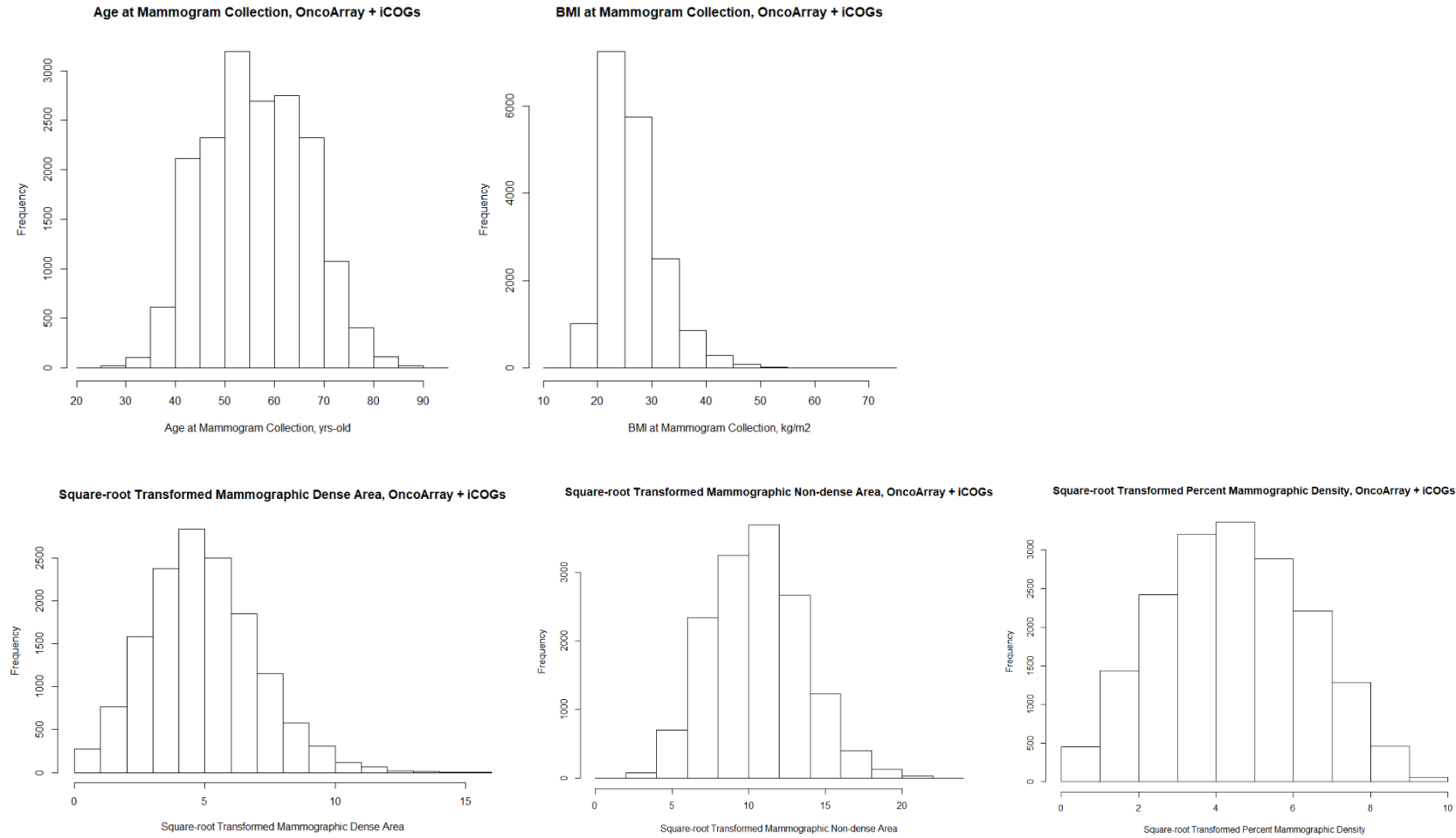
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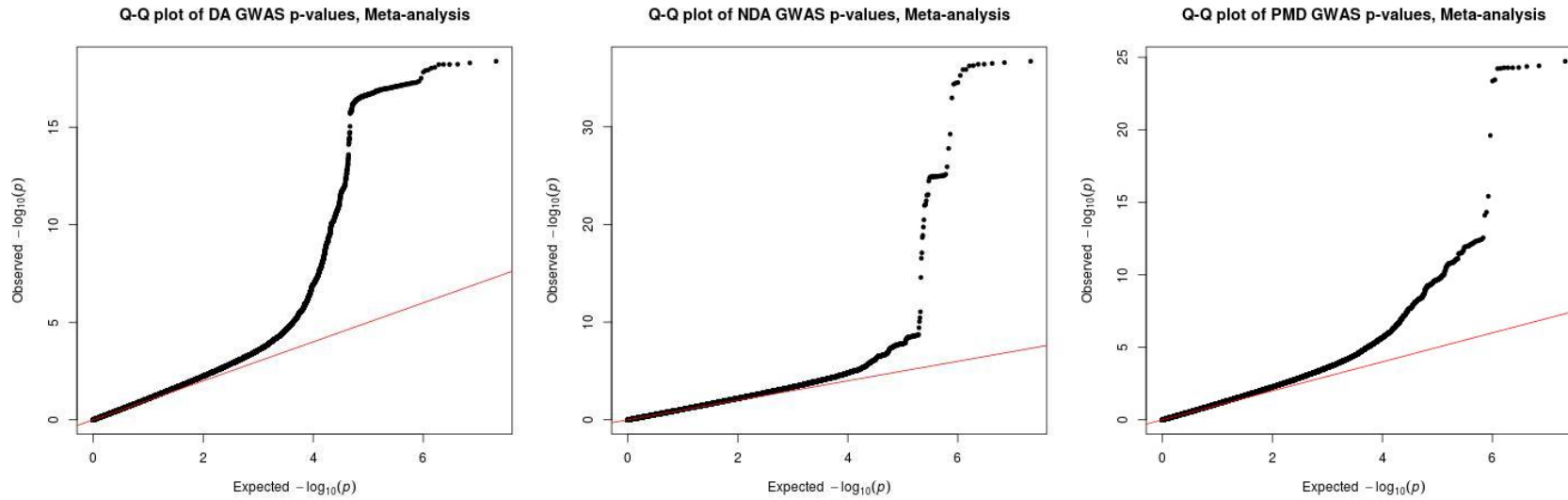
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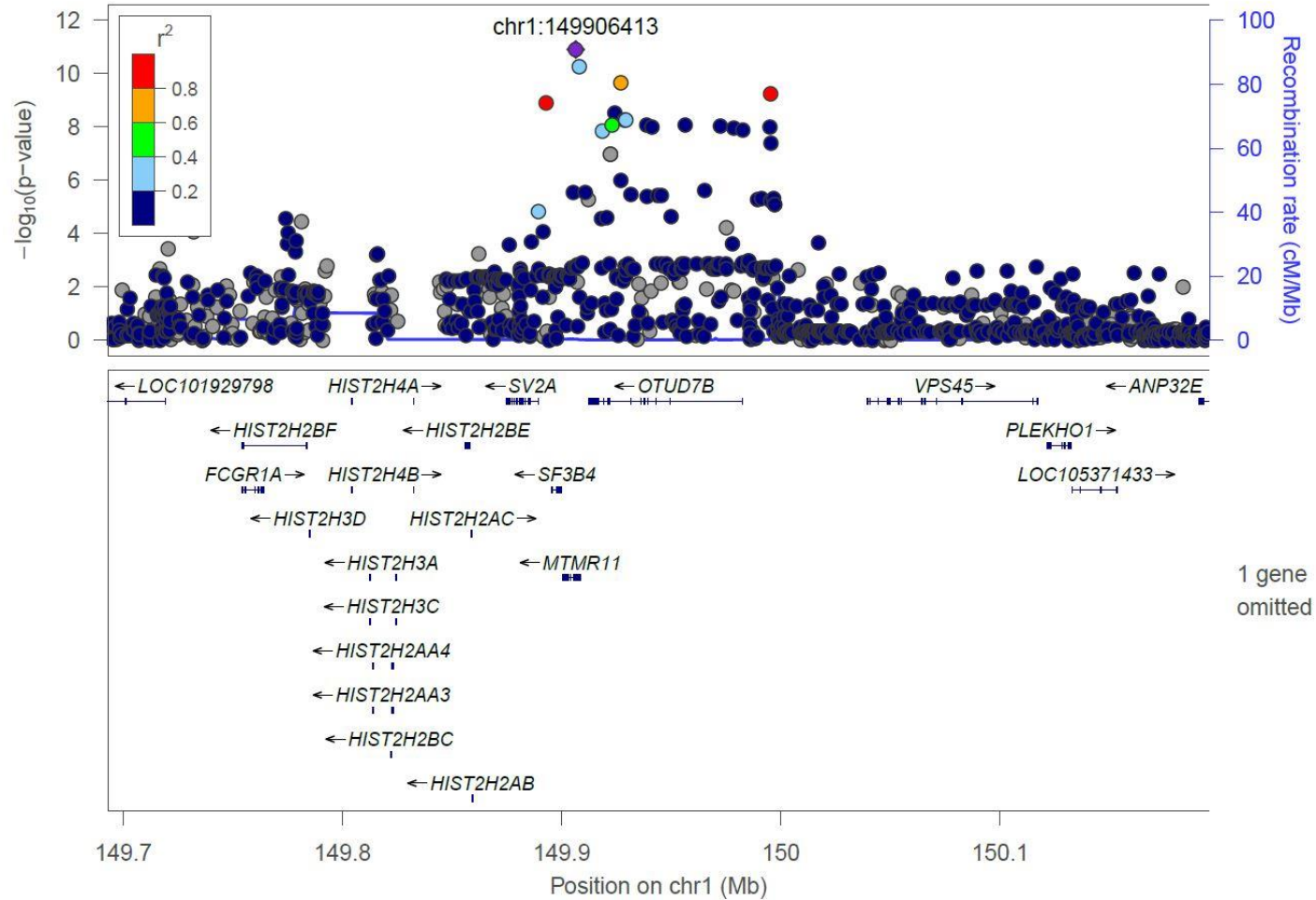
Supplementary Figure 2.1. Distribution of age (left, N = 17,162) and BMI (right, N = 17,162) at mammogram collection (top panel), and square-root transformed mammographic density measures (DA (left), NDA (middle) and PMD (right), bottom panel). Only individuals included in the final analyses were used to generate the distribution of DA, NDA, and PMD, which had a sample size of 13,805, 13,915, and 17,126, respectively.



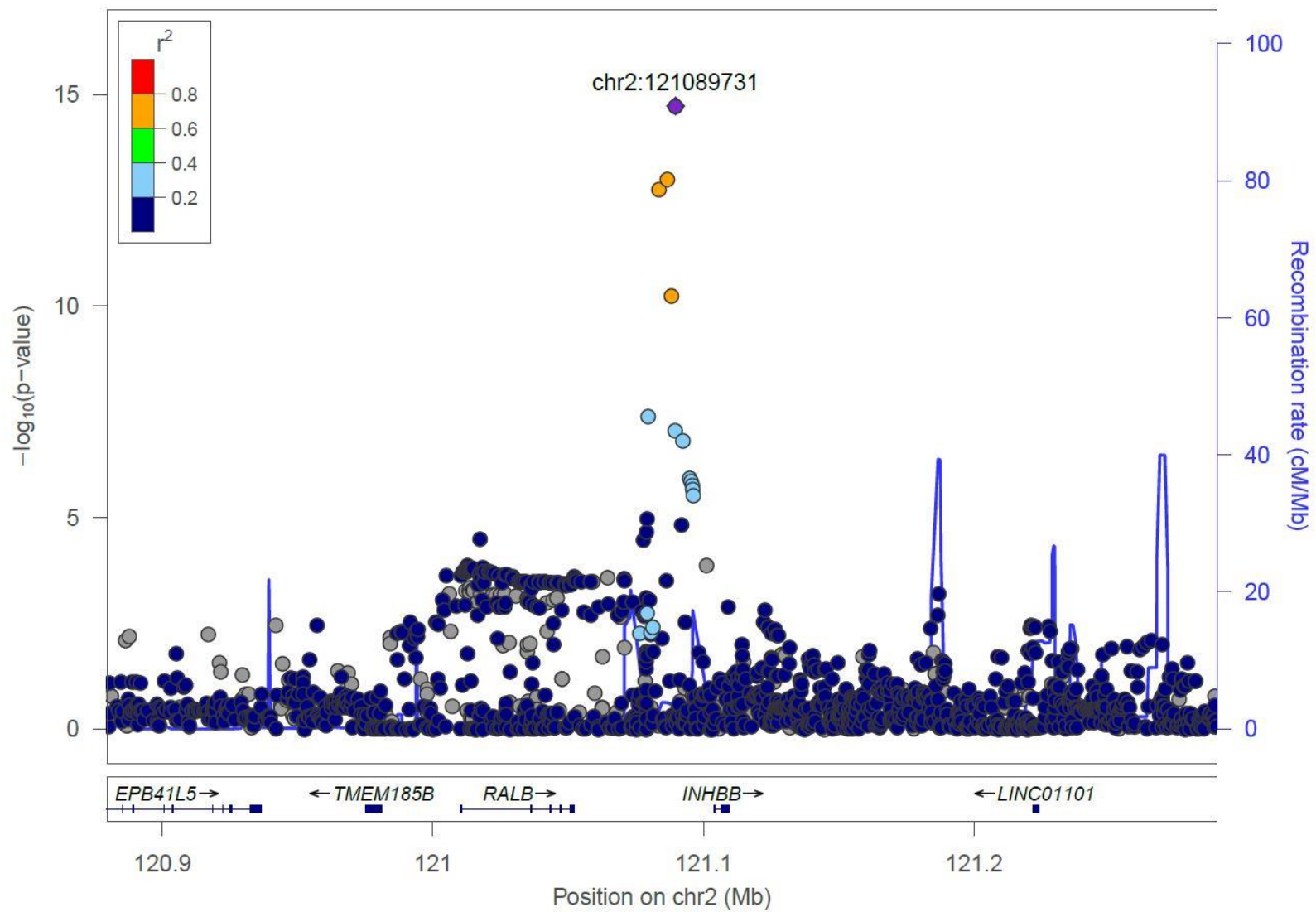
Supplementary Figure 2.2. Quantile-Quantile plots of the GWAS meta-analysis results for mammographic dense area, DA; non-dense area, NDA; and percent mammographic density, PMD. The genomic inflation factors (λ_{GC}) were estimated as 1.11, 1.11 and 1.13 for the meta-analysis results of DA, NDA and PMD, respectively.

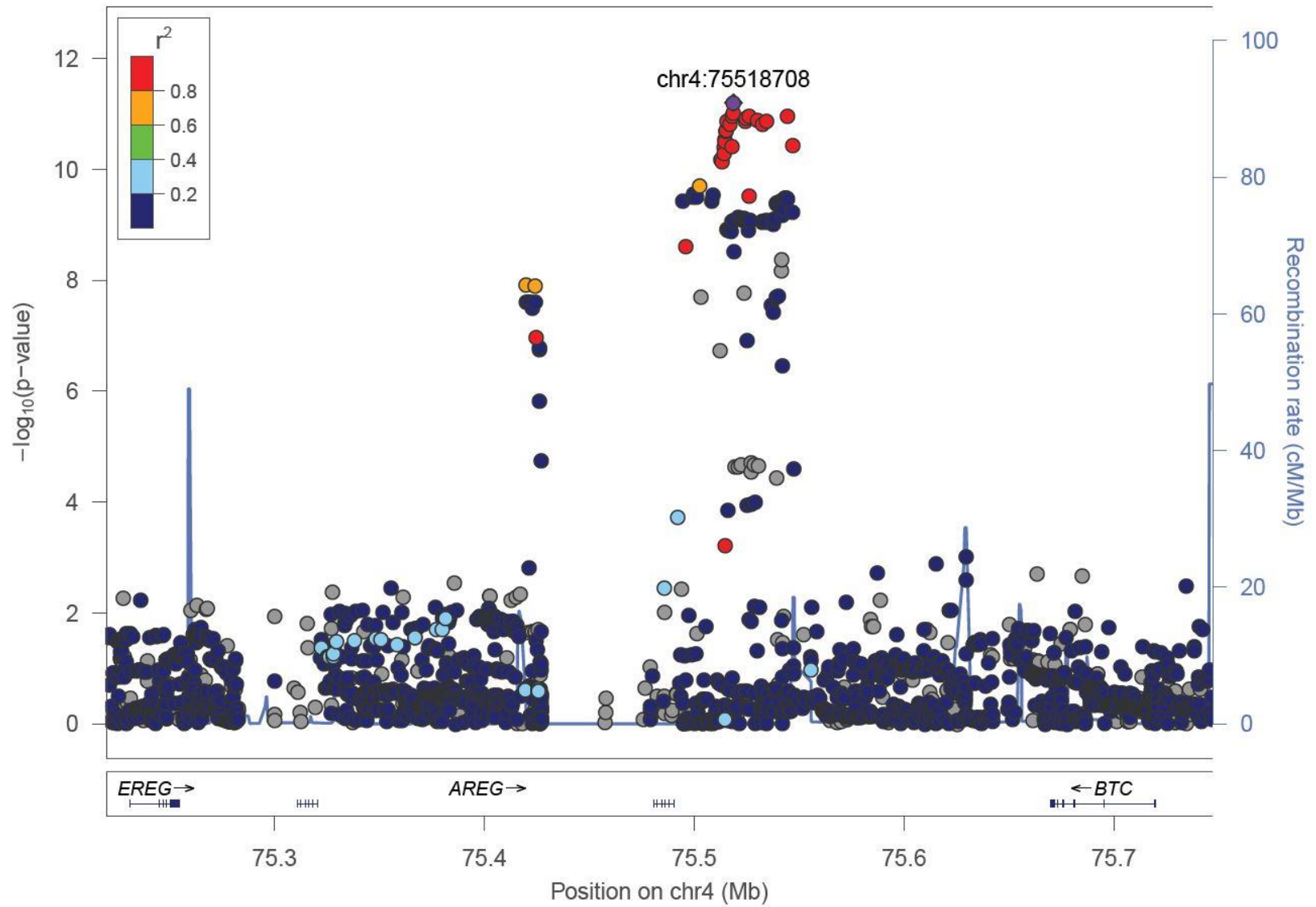


Supplementary Figure 2.3. Regional association plots for 18 genome-wide significant loci of DA. The European ancestry population (EUR) in the 1000 Genomes project was used as the reference panel for linkage disequilibrium (LD) estimates (shown as r^2). Color of the dots indicated the extent of LD. Recombination rates were estimated using EUR samples in 1000 Genomes. Physical positions were based Genomic build hg19.

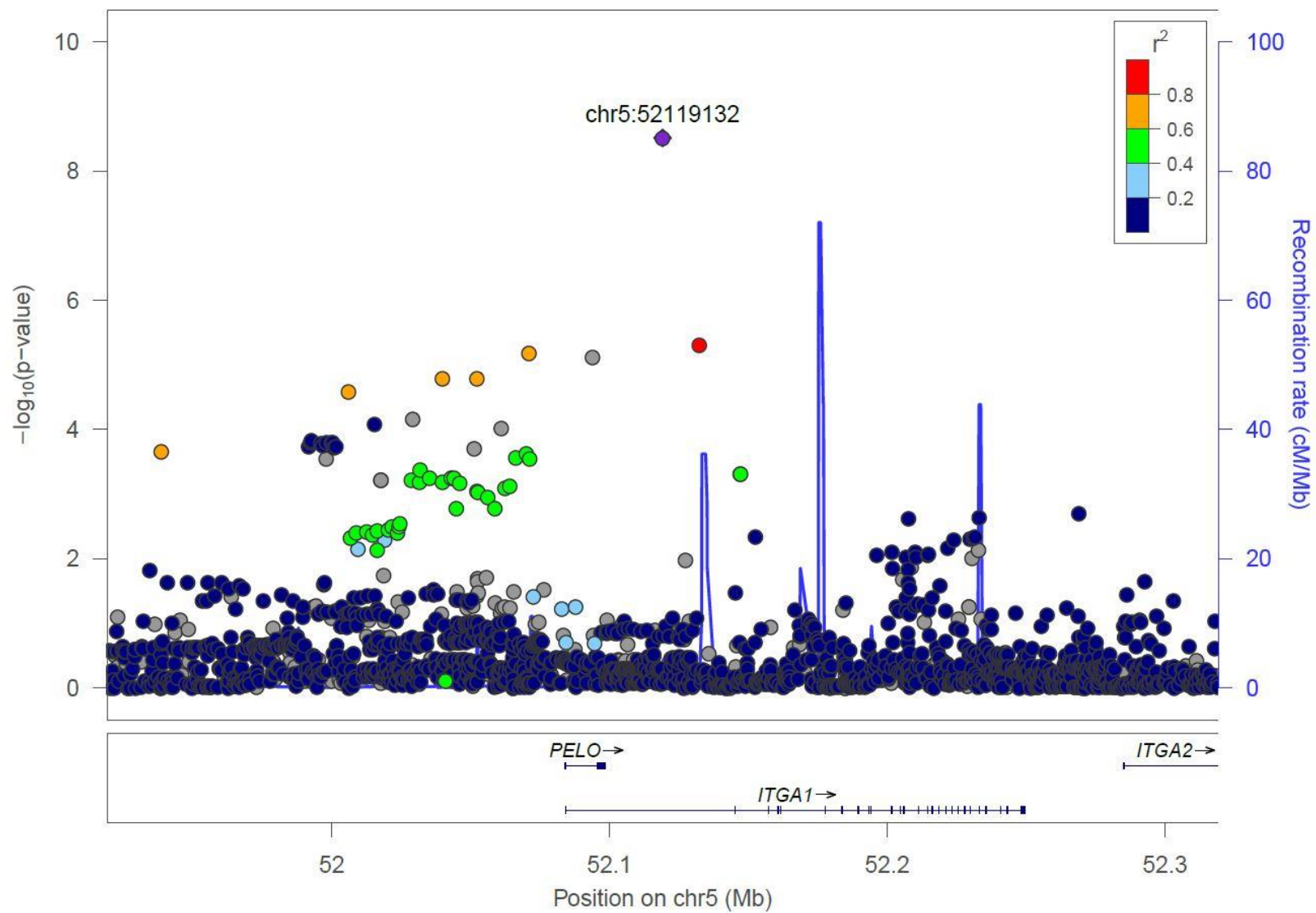


1q21.2

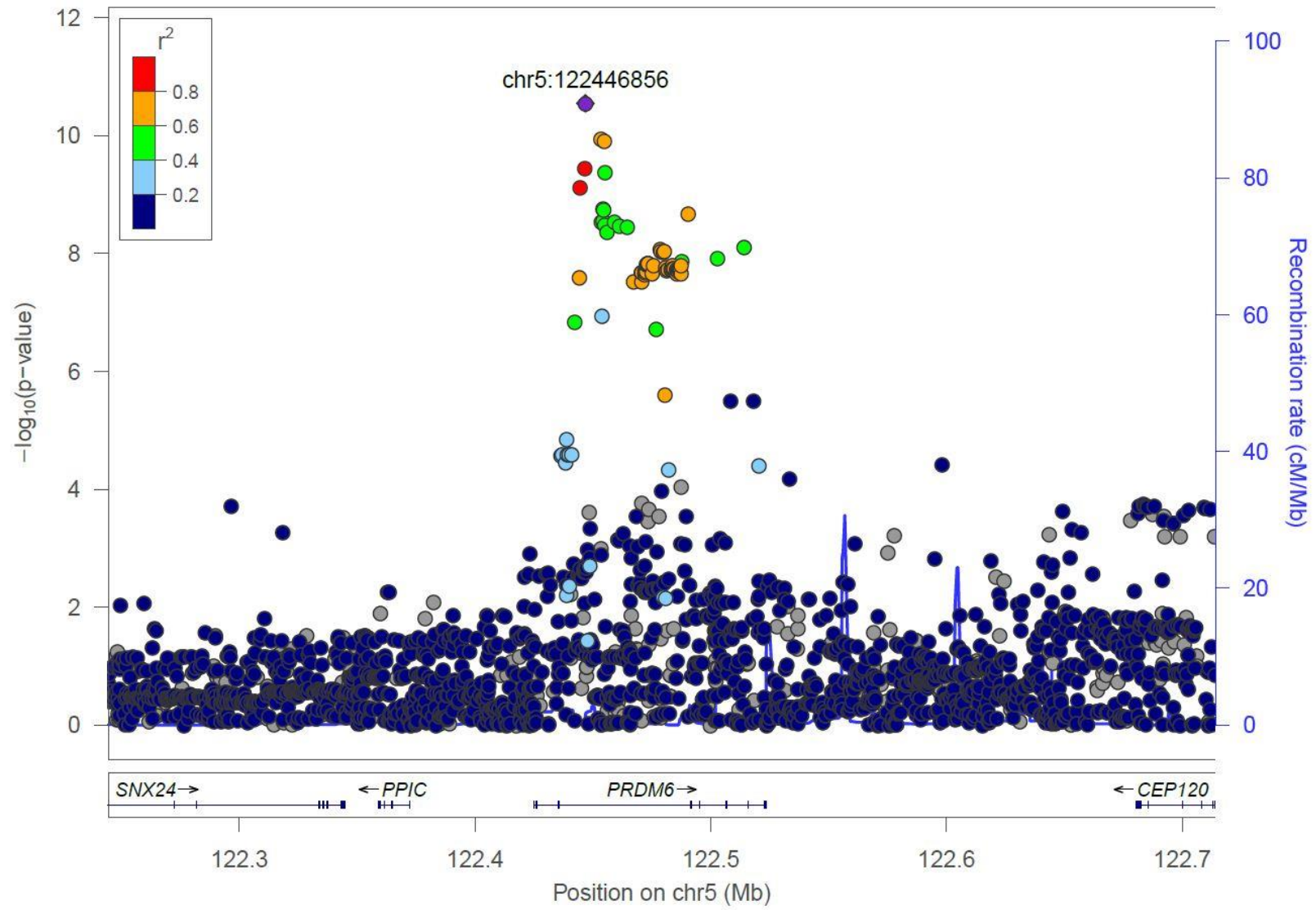
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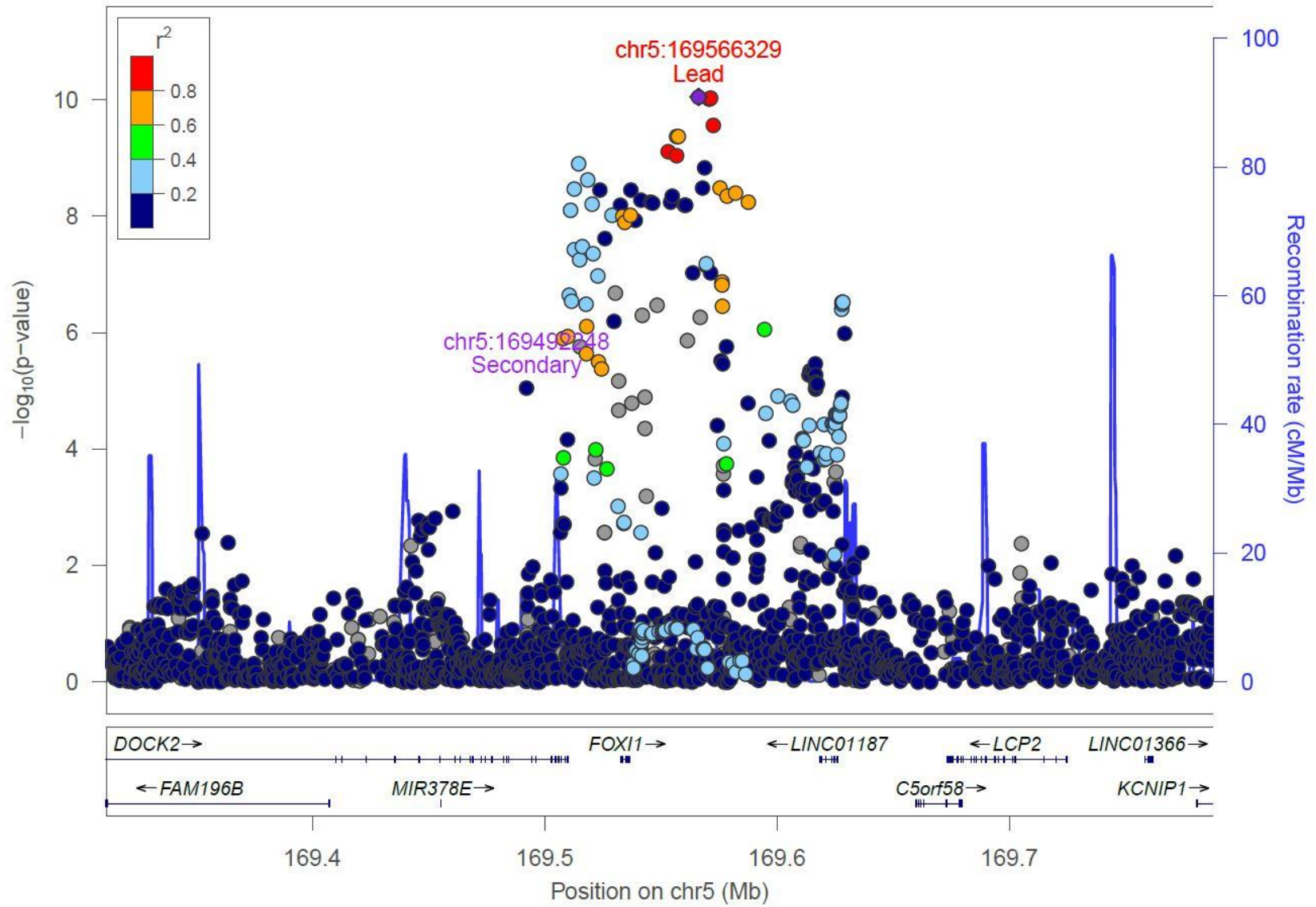
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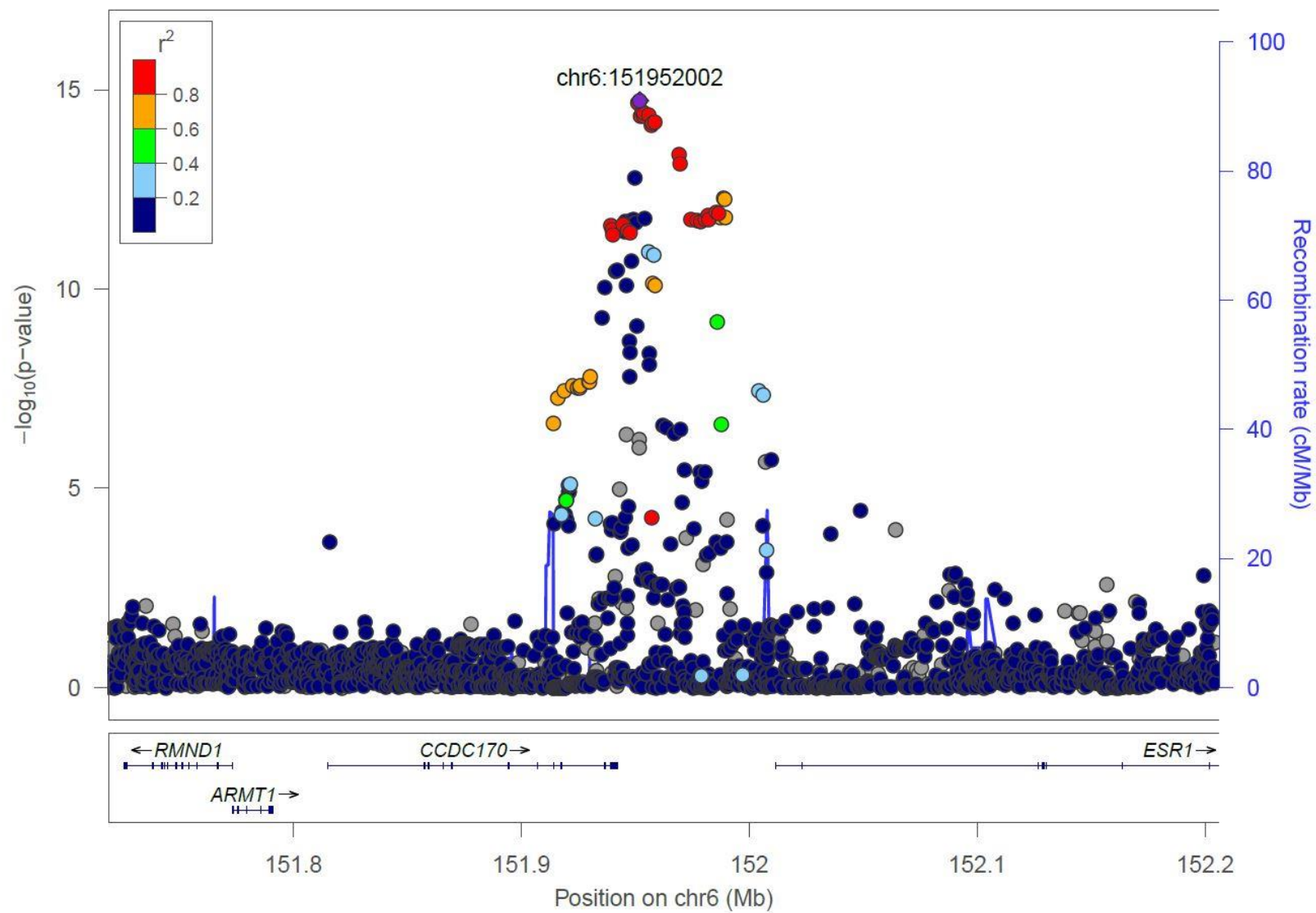
5q11.2



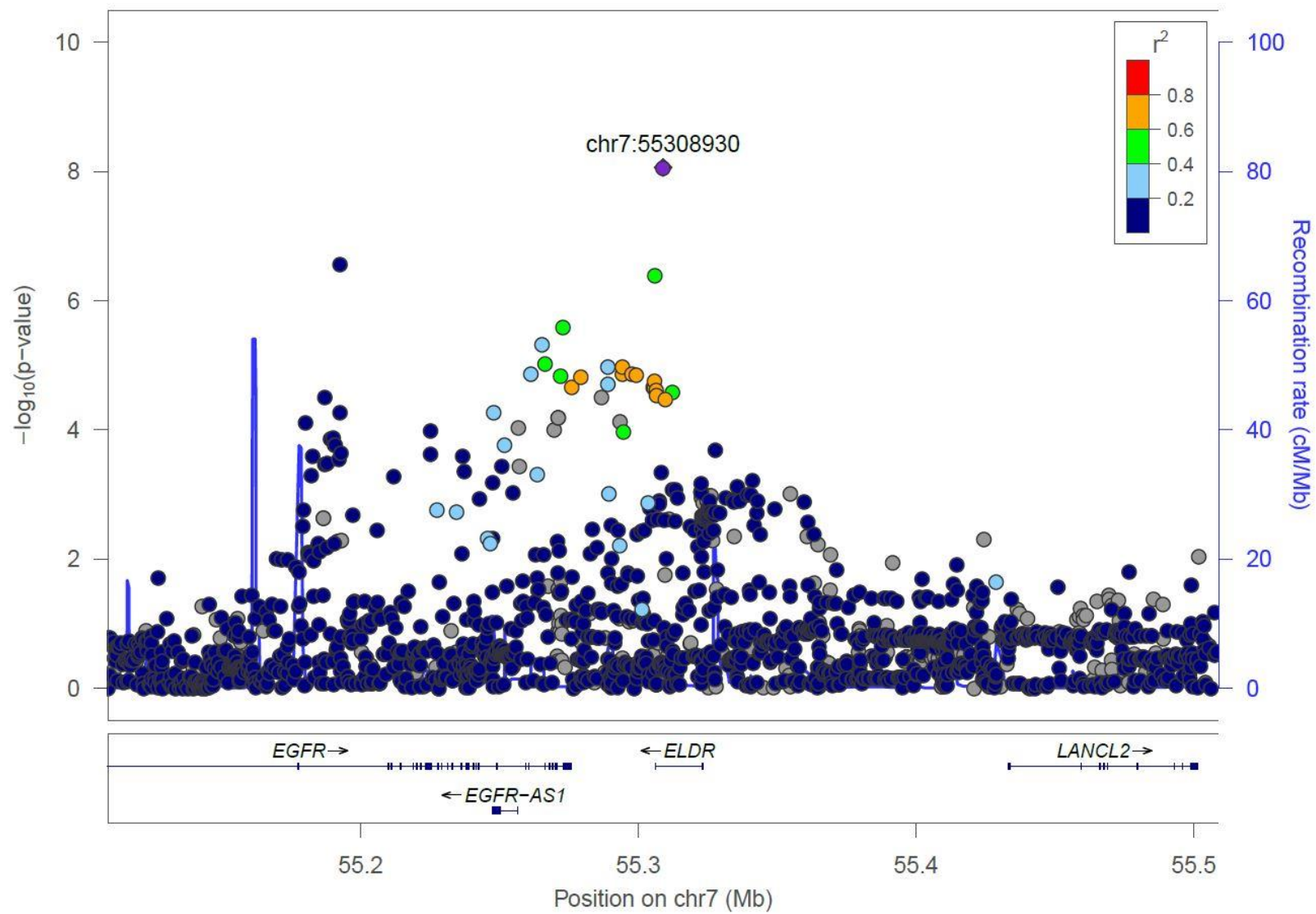
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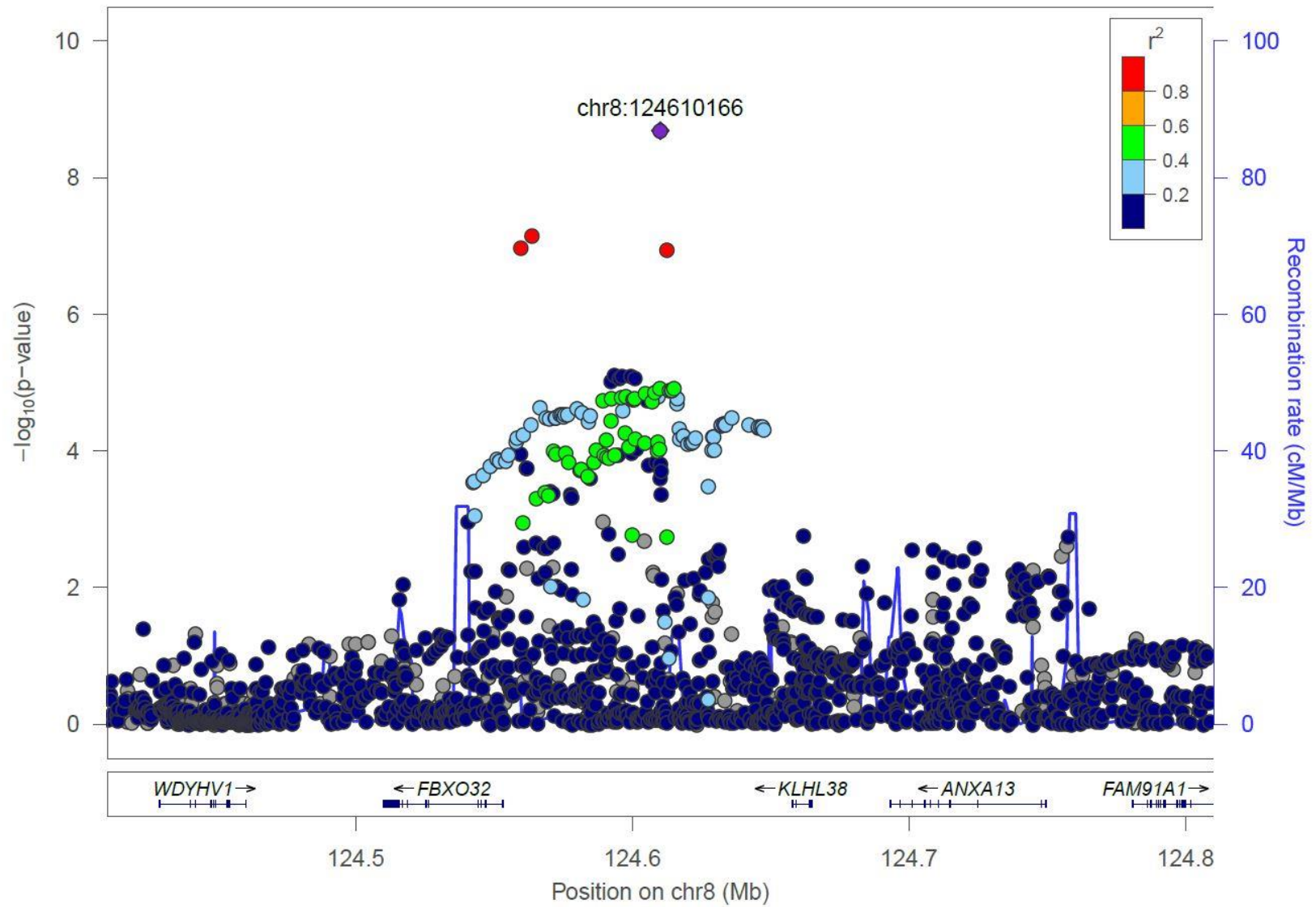
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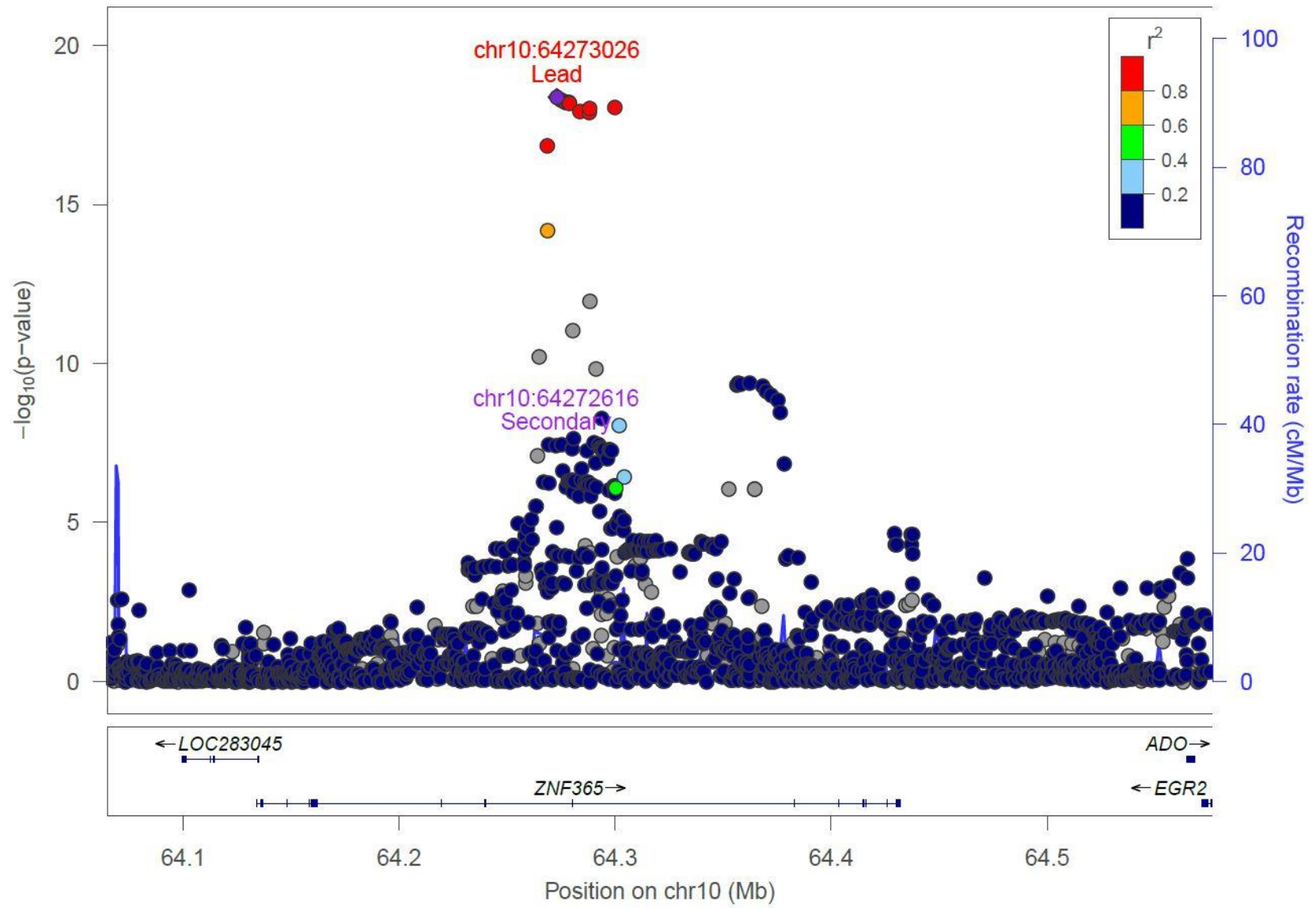


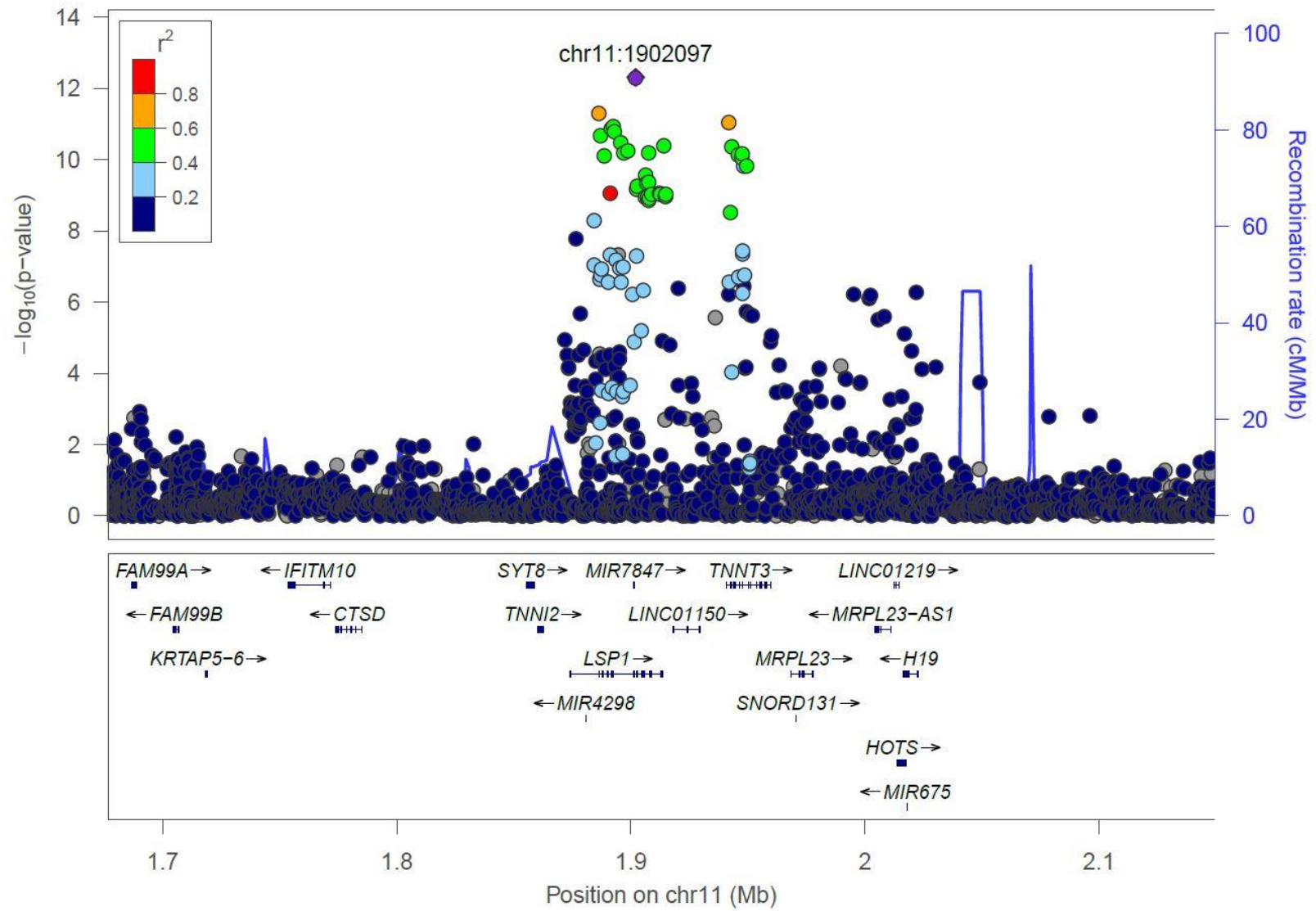
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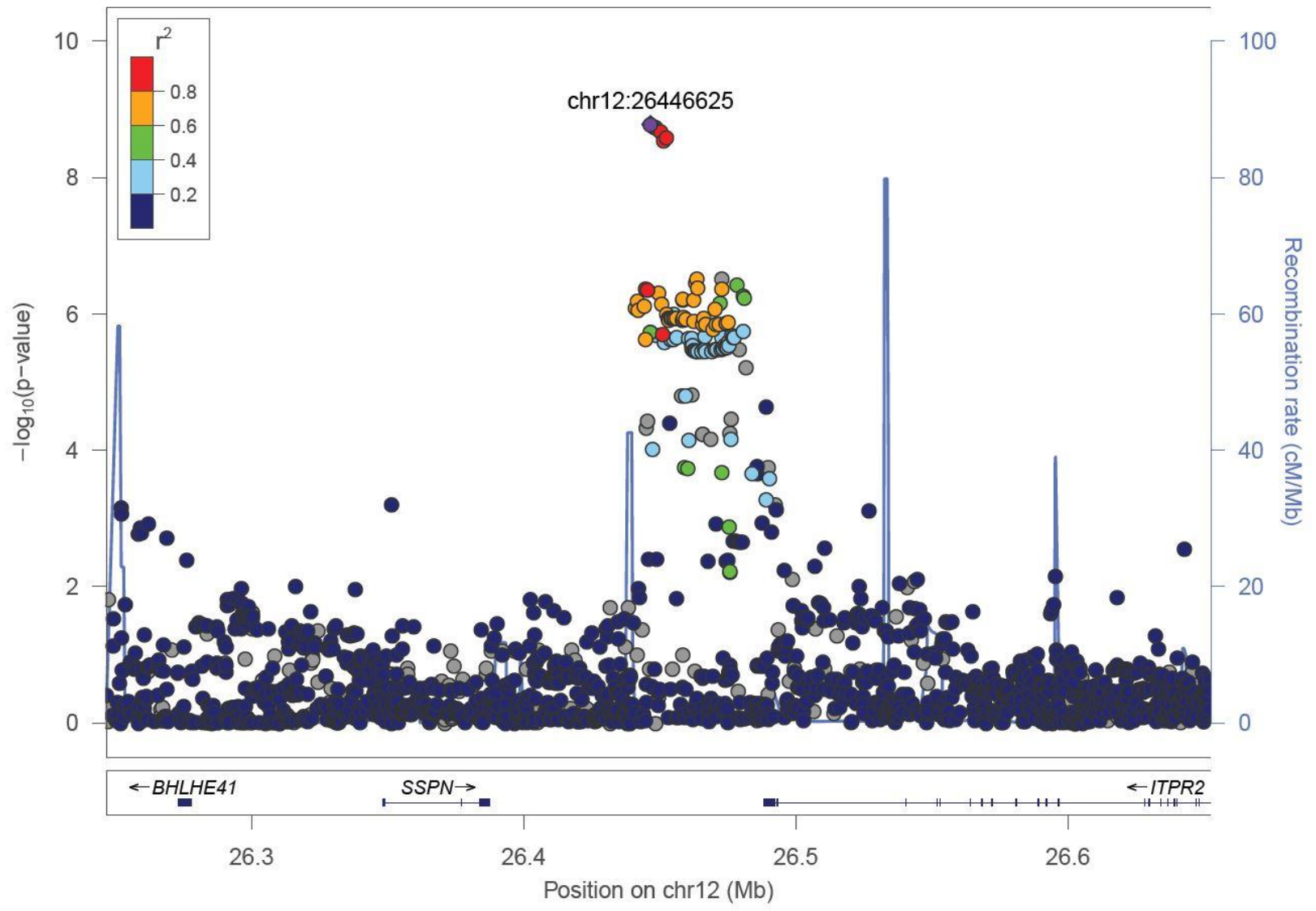


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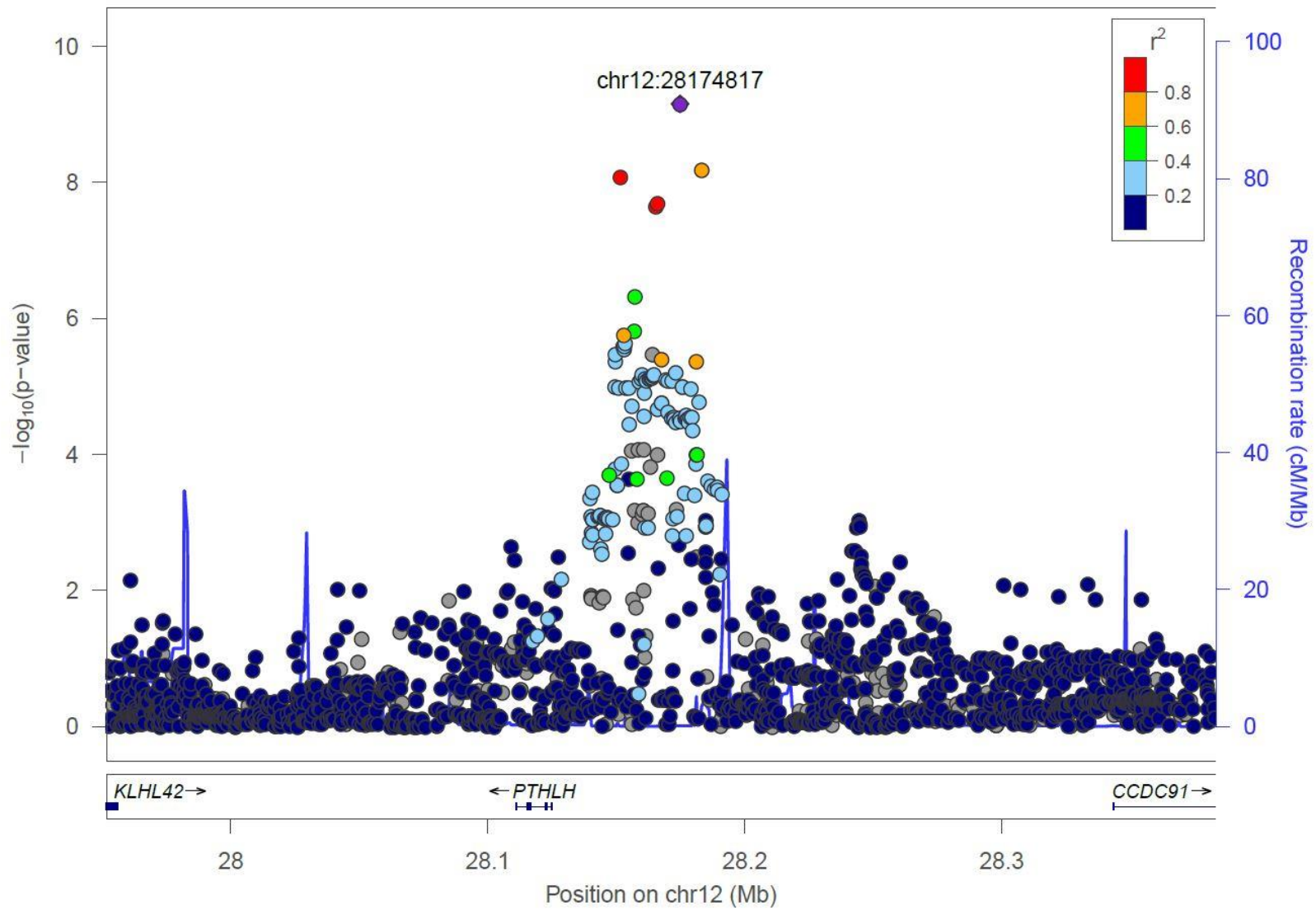
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**10q21.2**

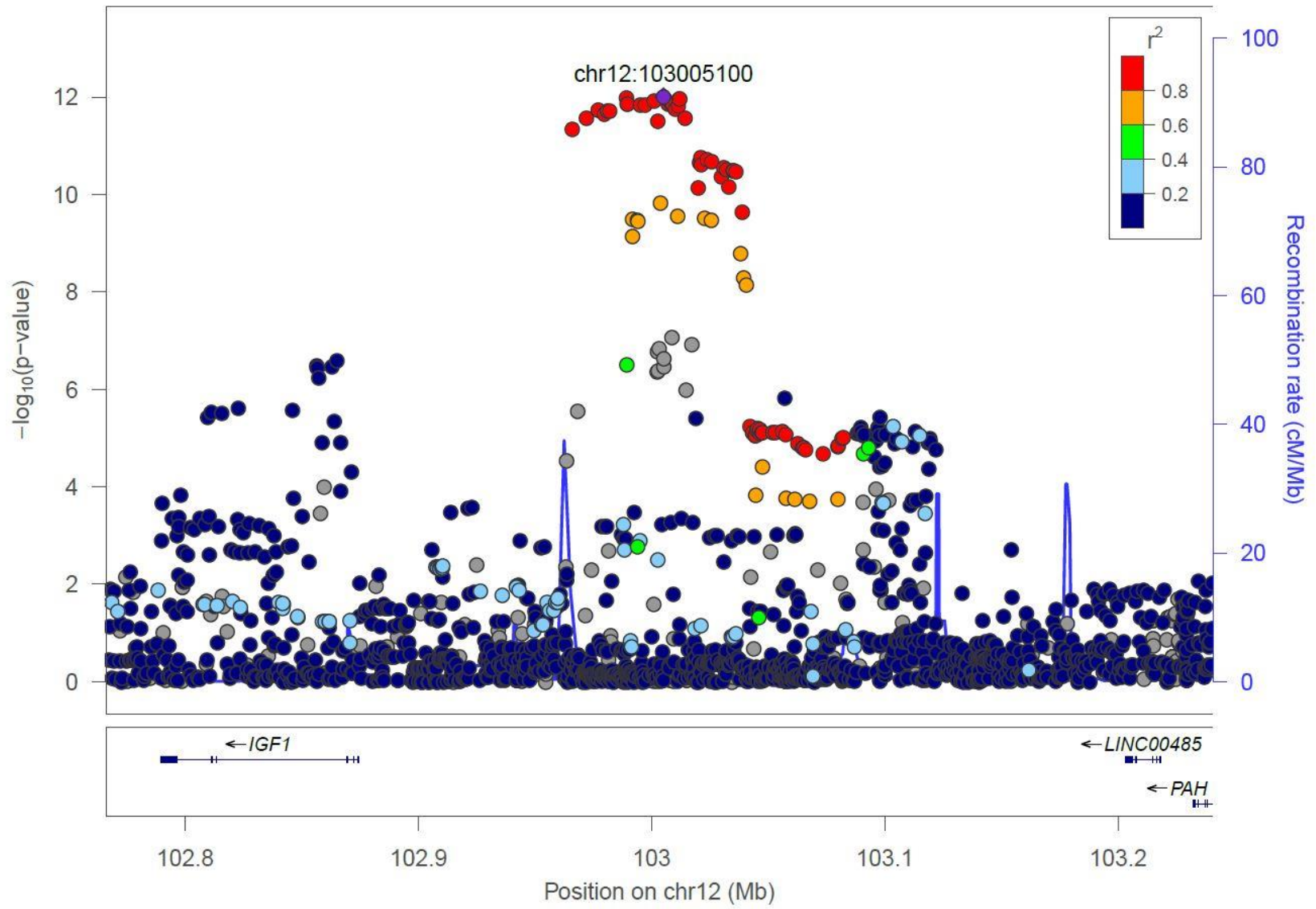
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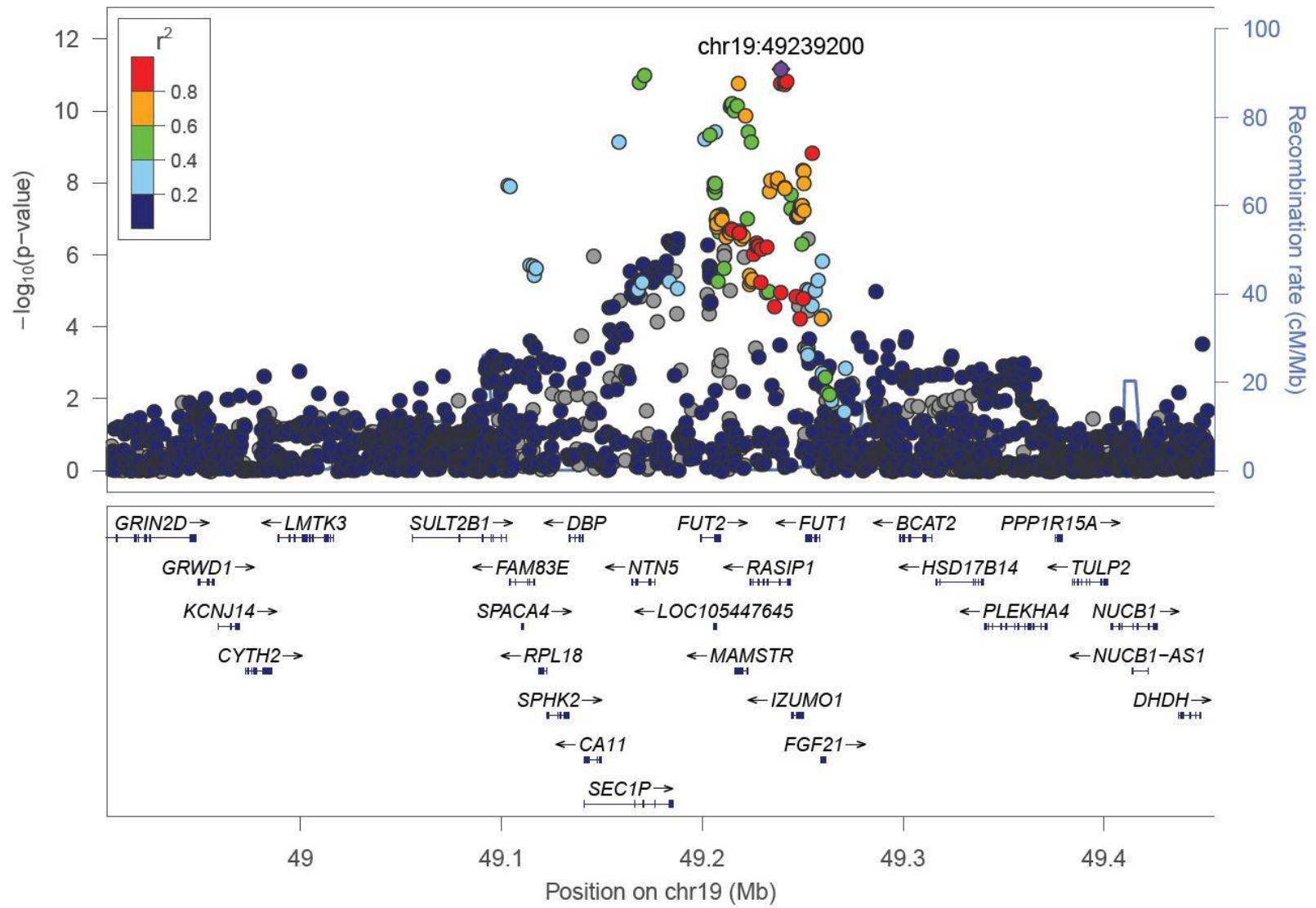


12p12.1

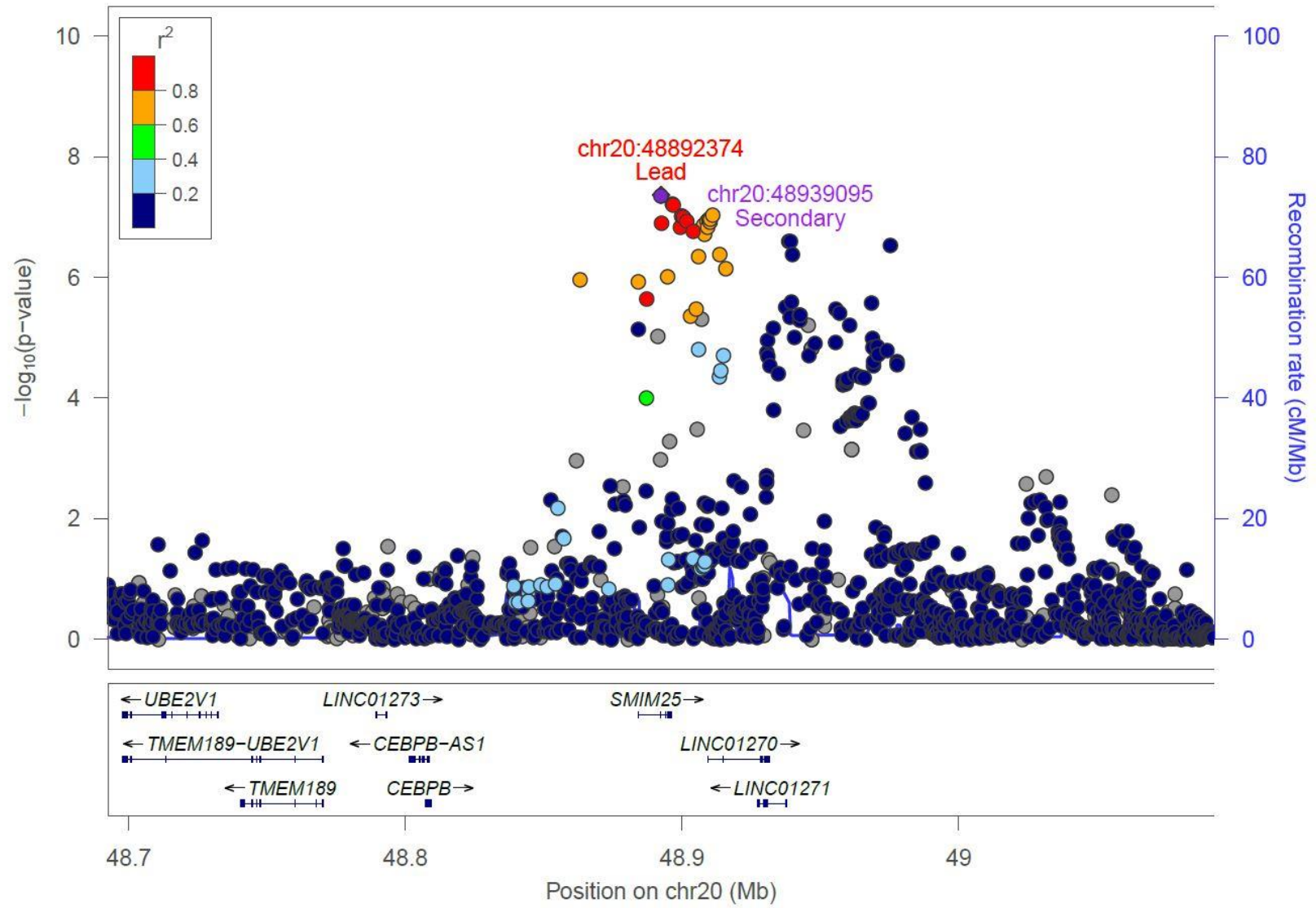


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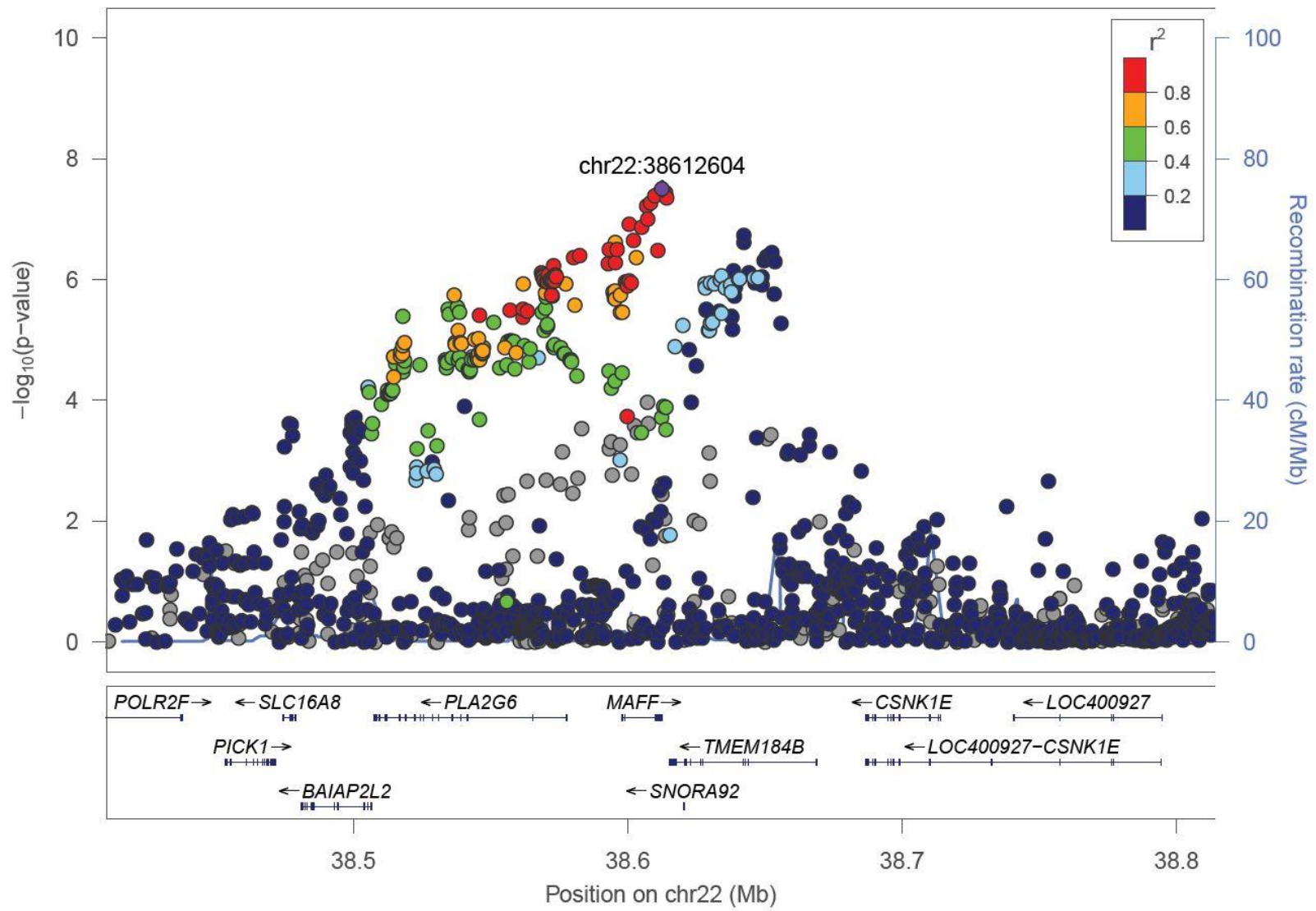
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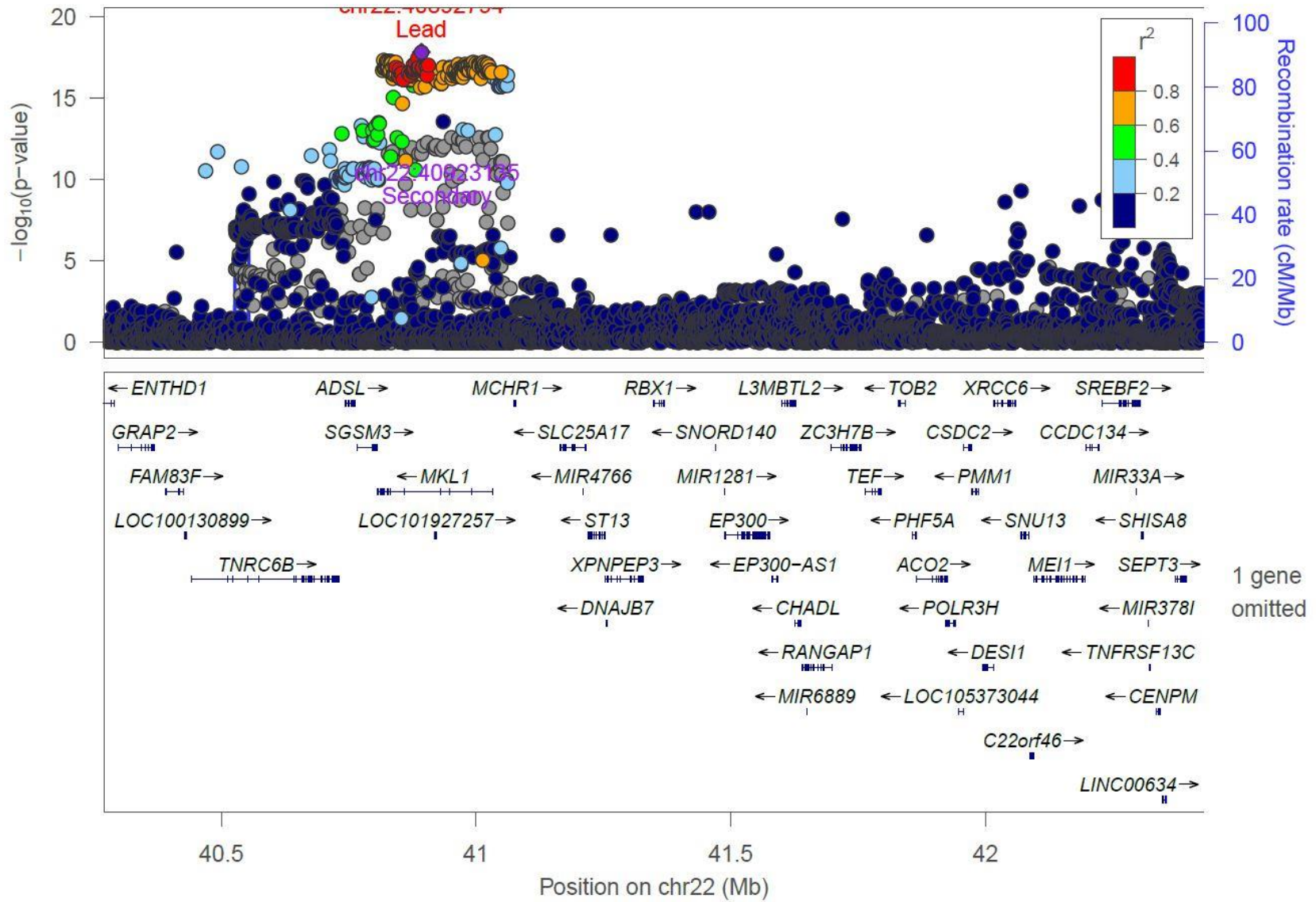
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20q13.13

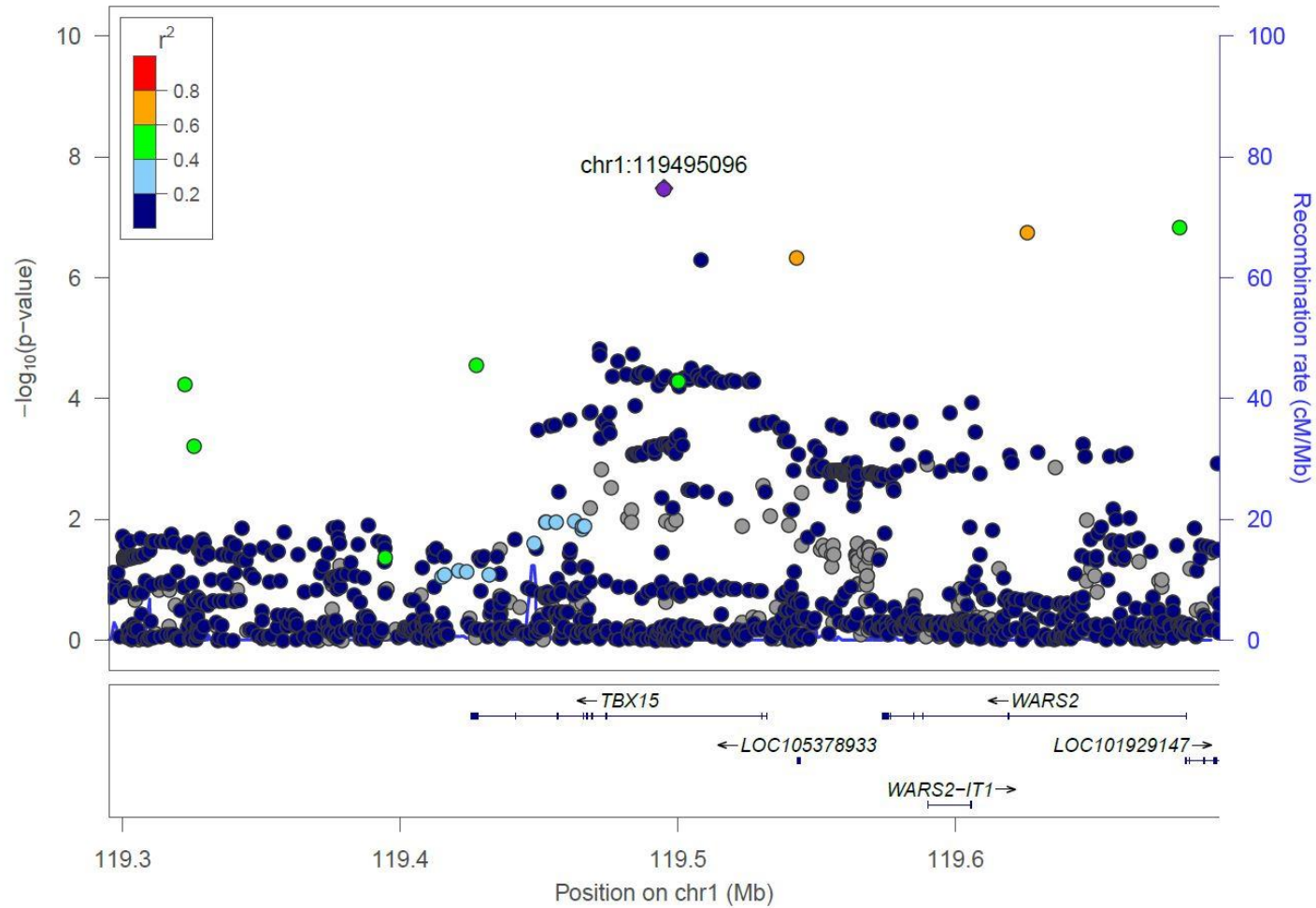


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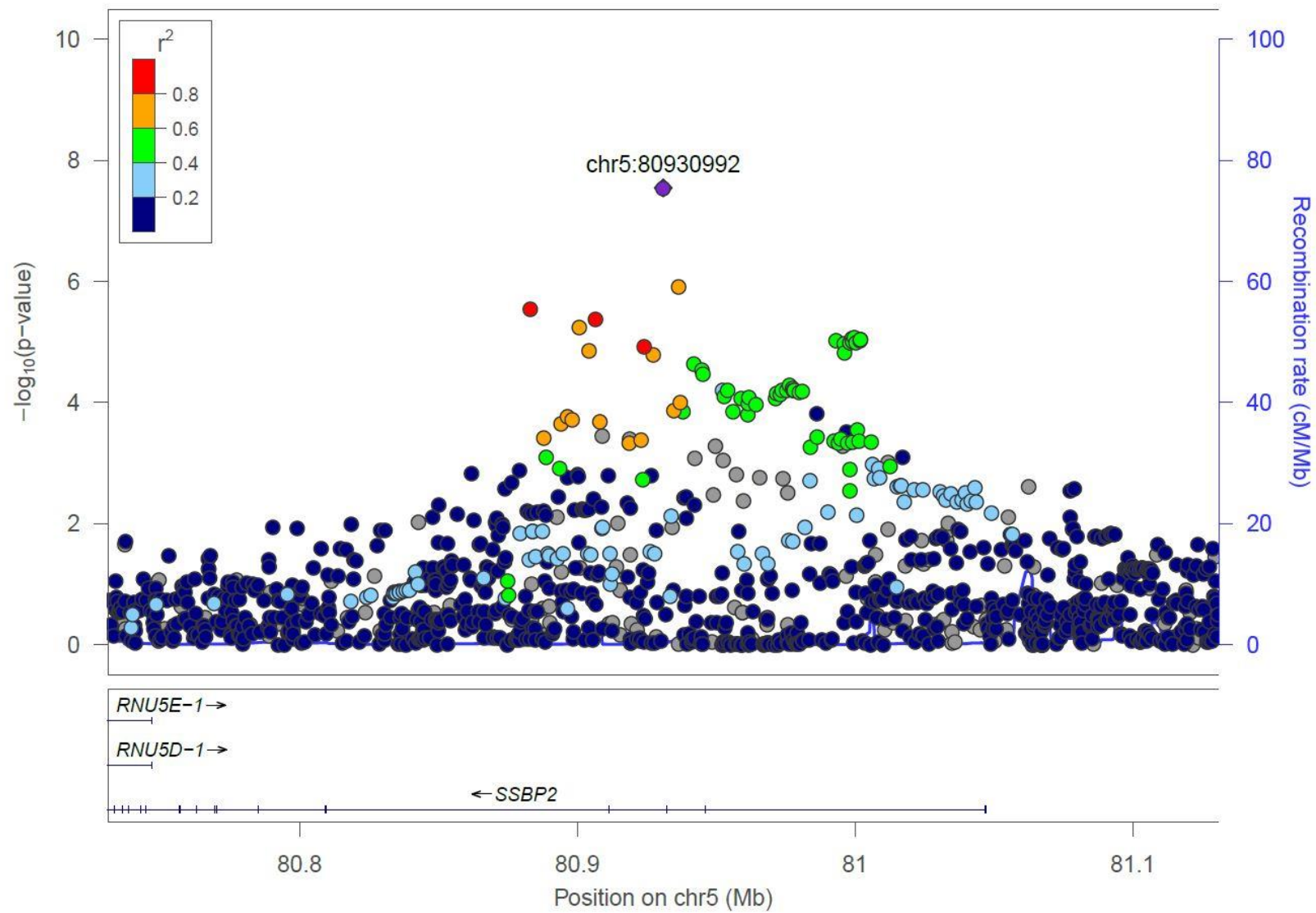


22q13.2

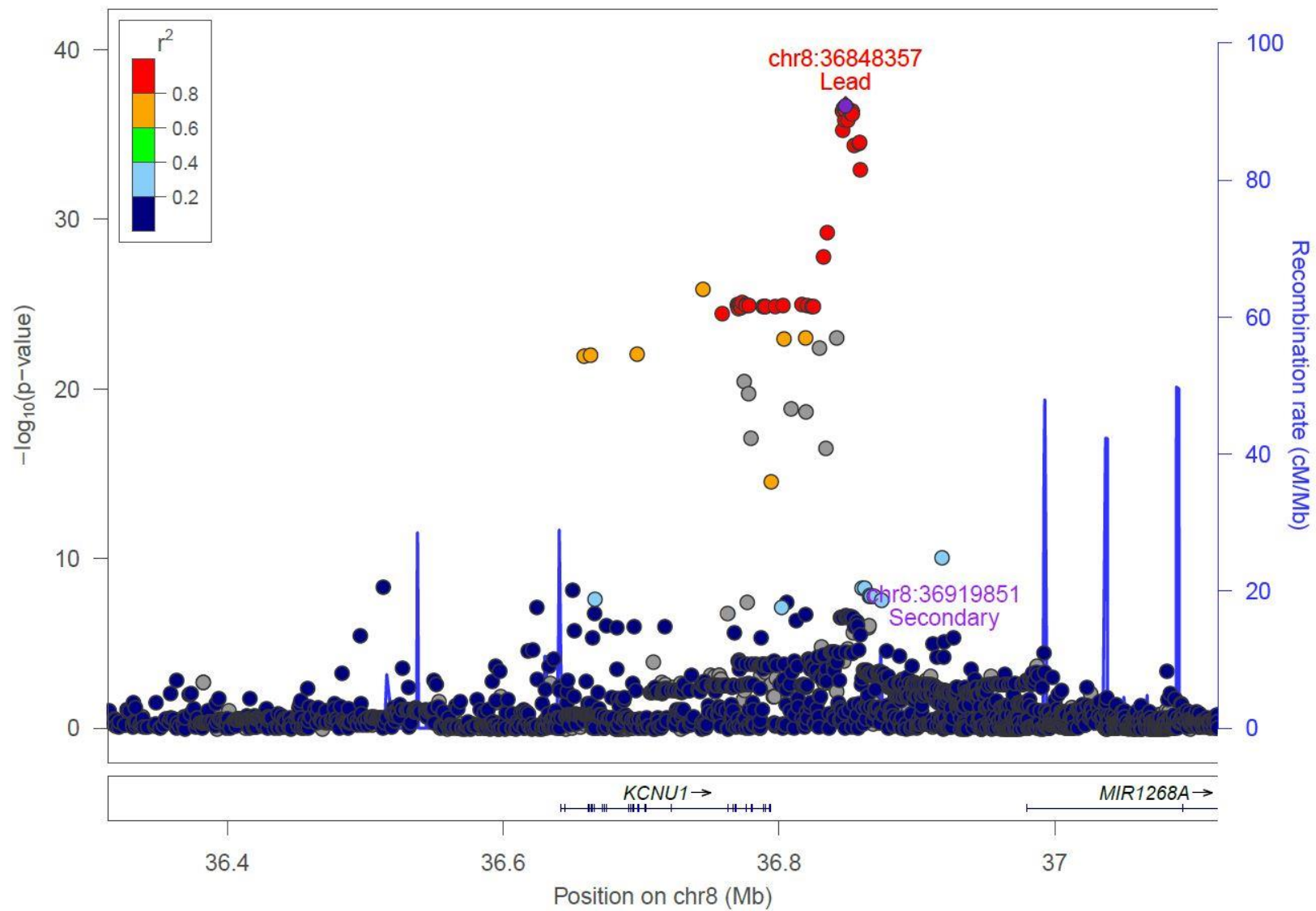
Supplementary Figure 2.4. Regional association plots for six genome-wide significant loci of NDA. The European ancestry population (EUR) in the 1000 Genomes project was used as the reference panel for linkage disequilibrium (LD) estimates (shown as r^2). Color of the dots indicated the extent of LD. Recombination rates were estimated using EUR samples in 1000 Genomes. Physical positions were based Genomic build hg19.

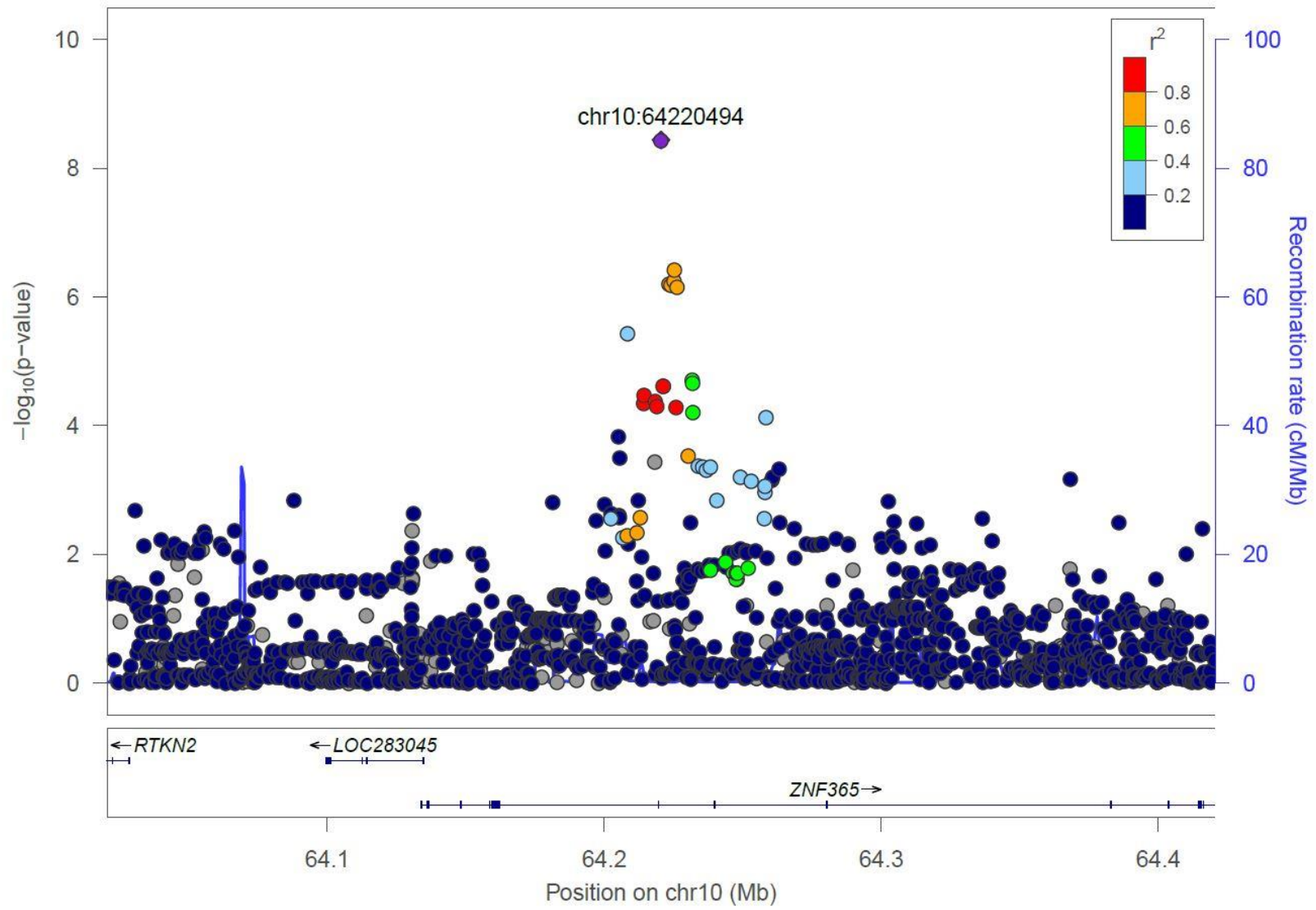


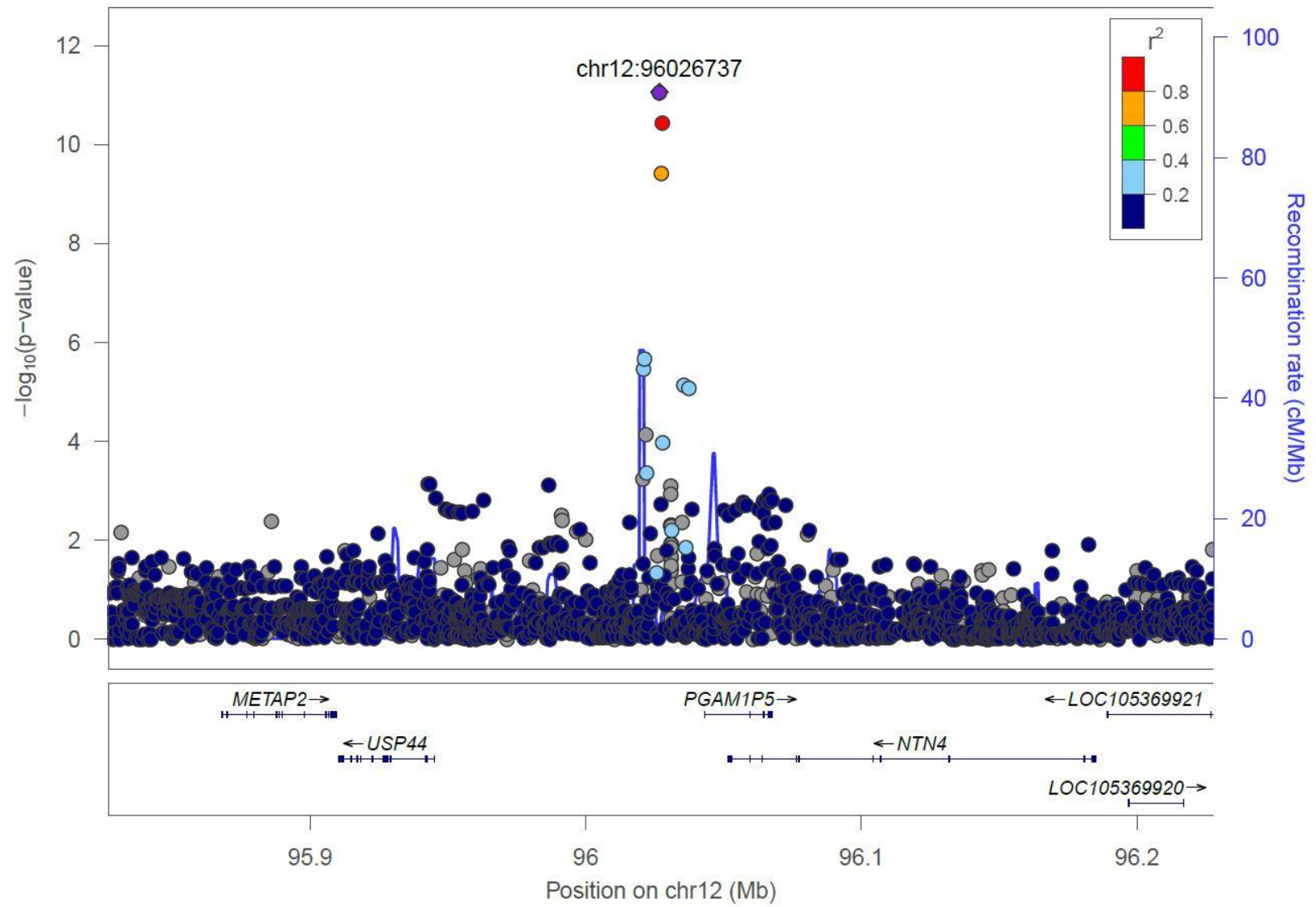
1p12



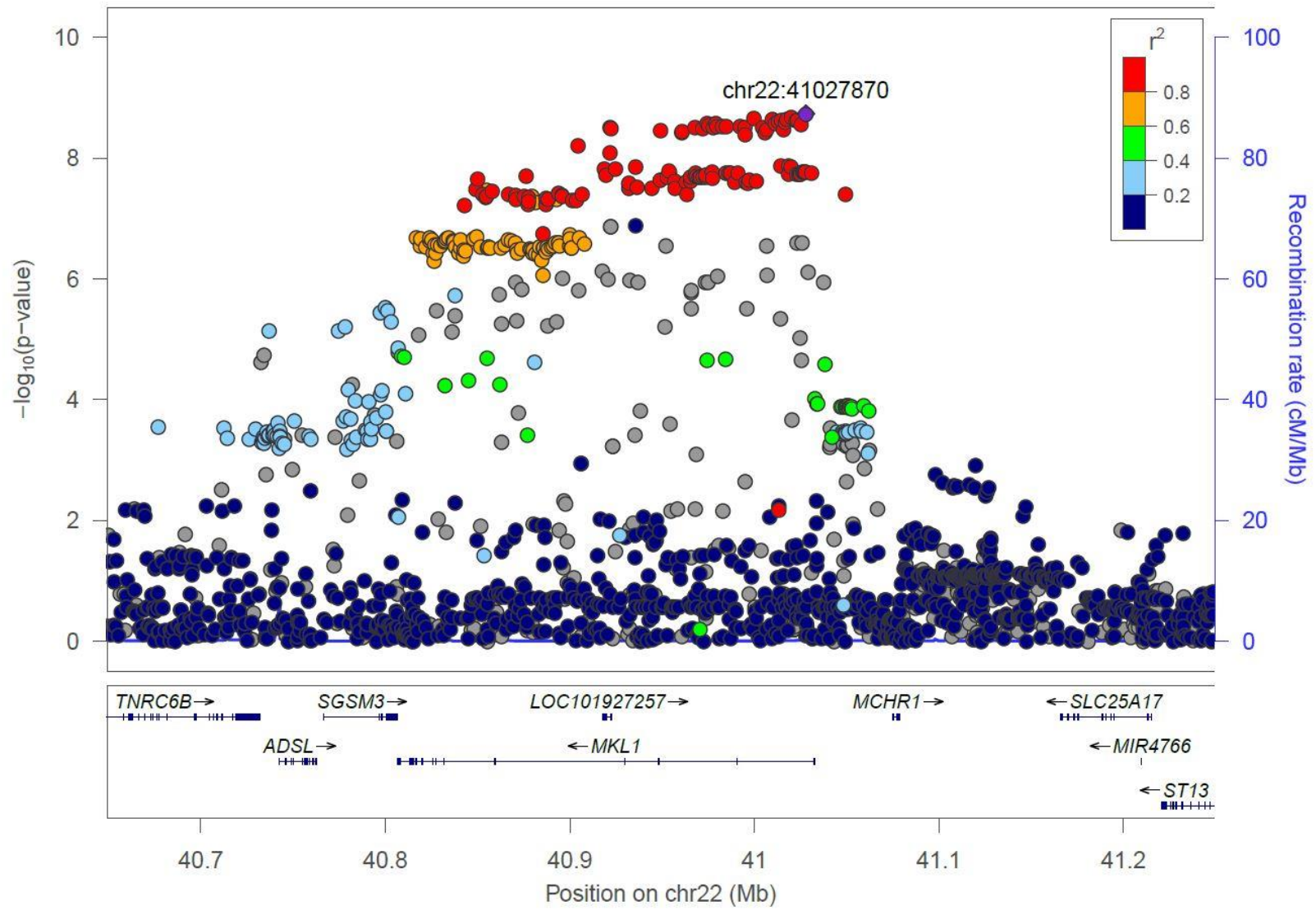
5q14.1

**8p11.23**

**10q21.2**

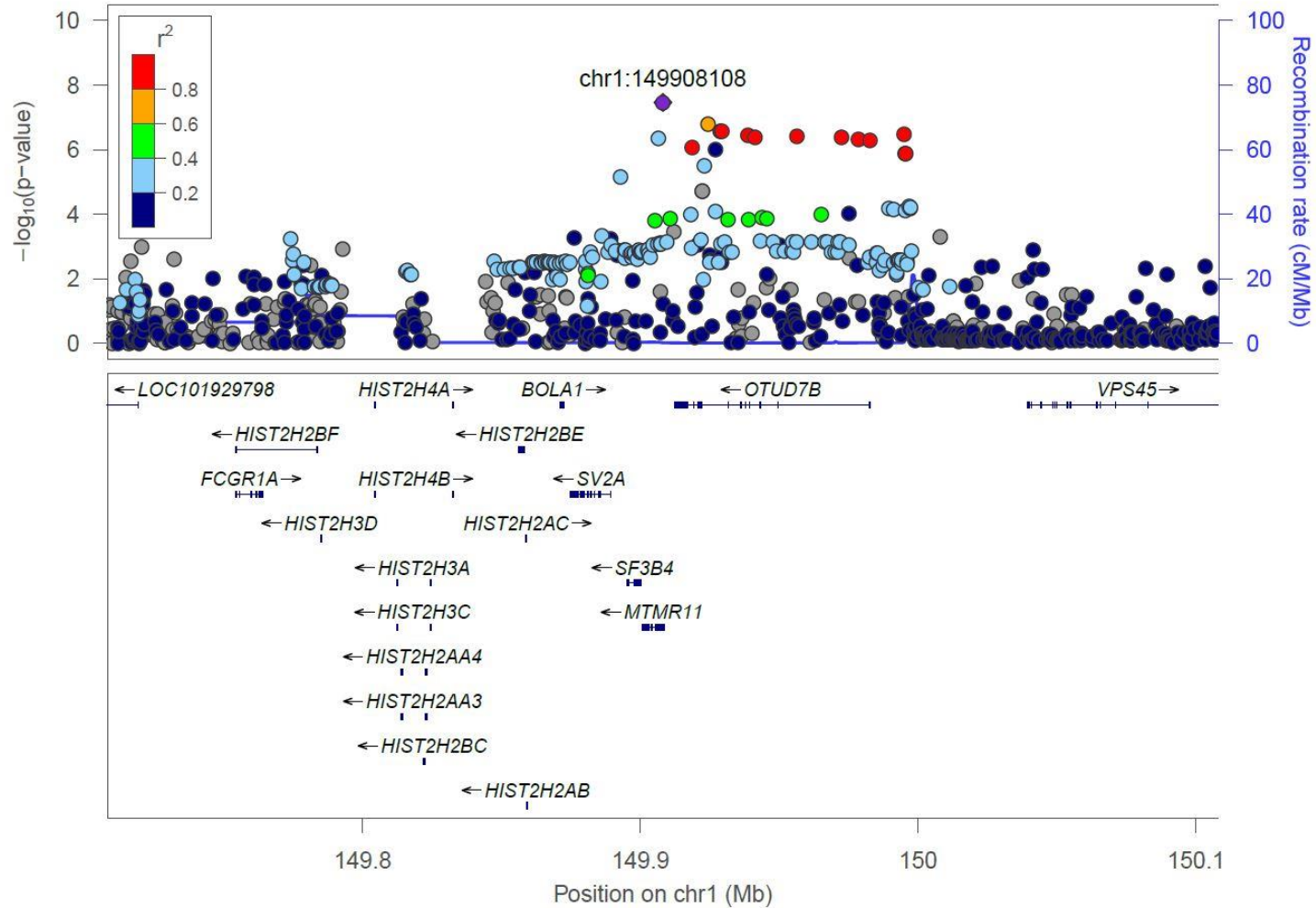


12q22

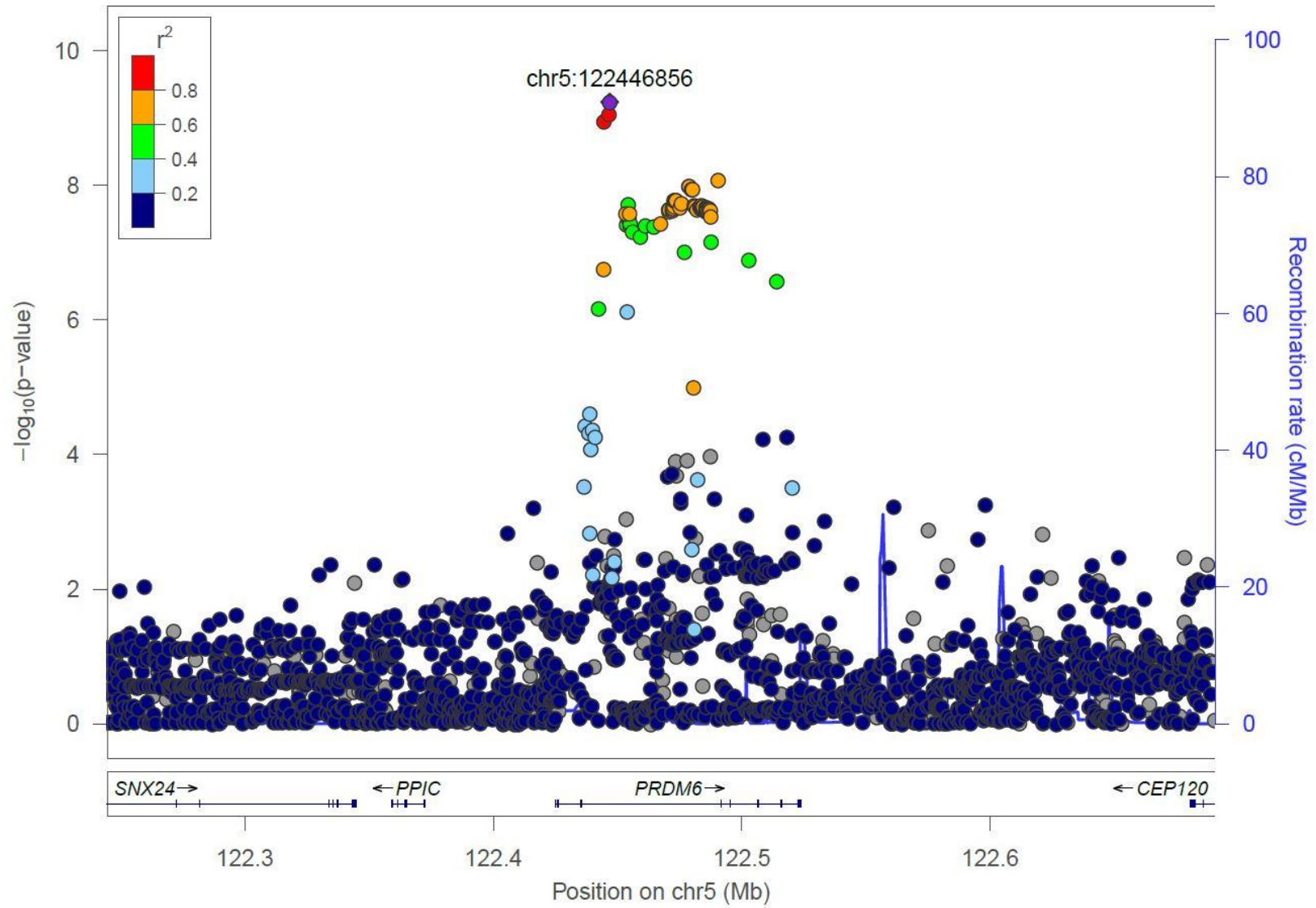


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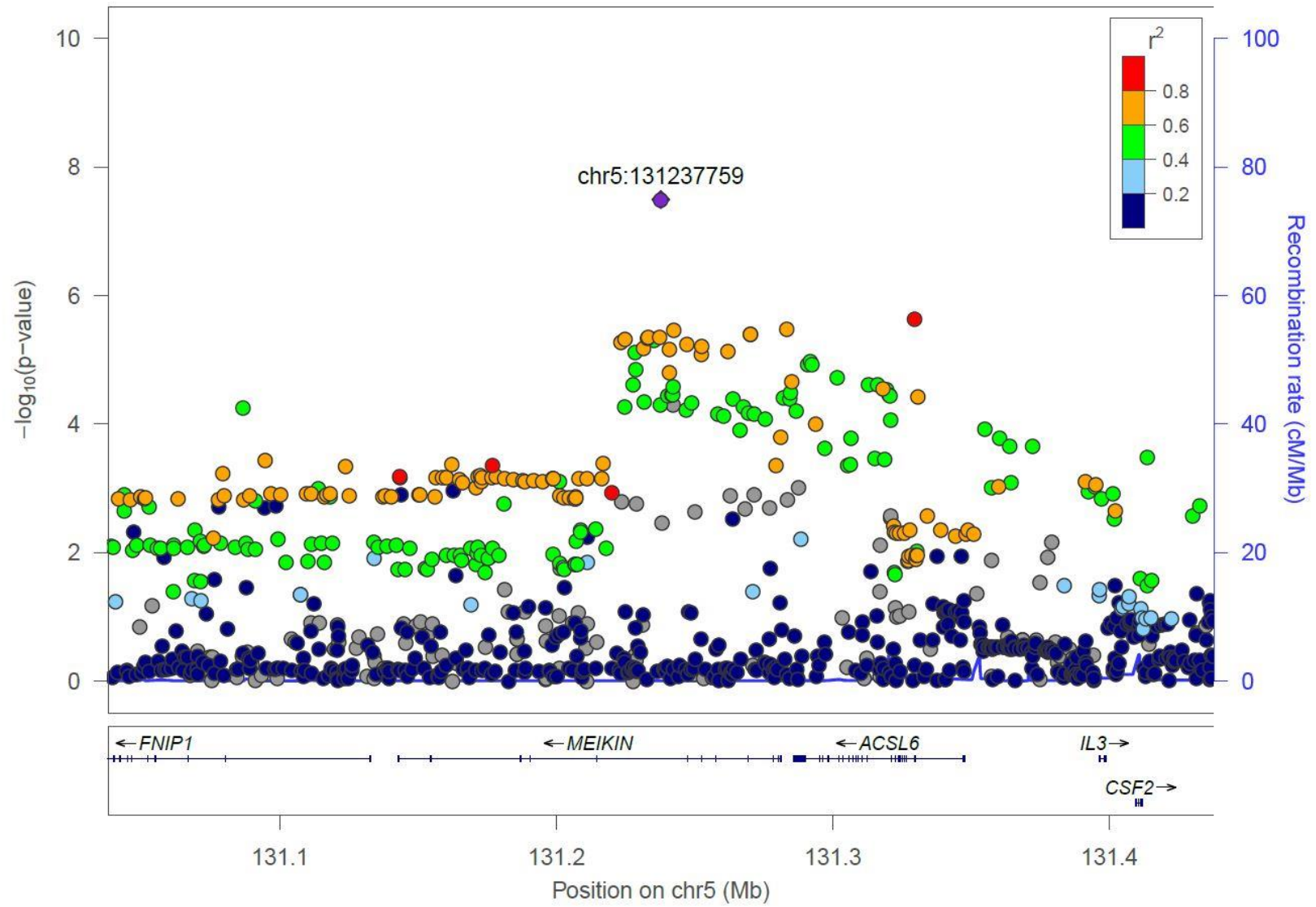
Supplementary Figure 2.5. Regional association plots for 15 genome-wide significant loci of PMD. The European ancestry population (EUR) in the 1000 Genomes project was used as the reference panel for linkage disequilibrium (LD) estimates (shown as r^2). Color of the dots indicated the extent of LD. Recombination rates were estimated using EUR samples in 1000 Genomes. Physical positions were based Genomic build hg19.



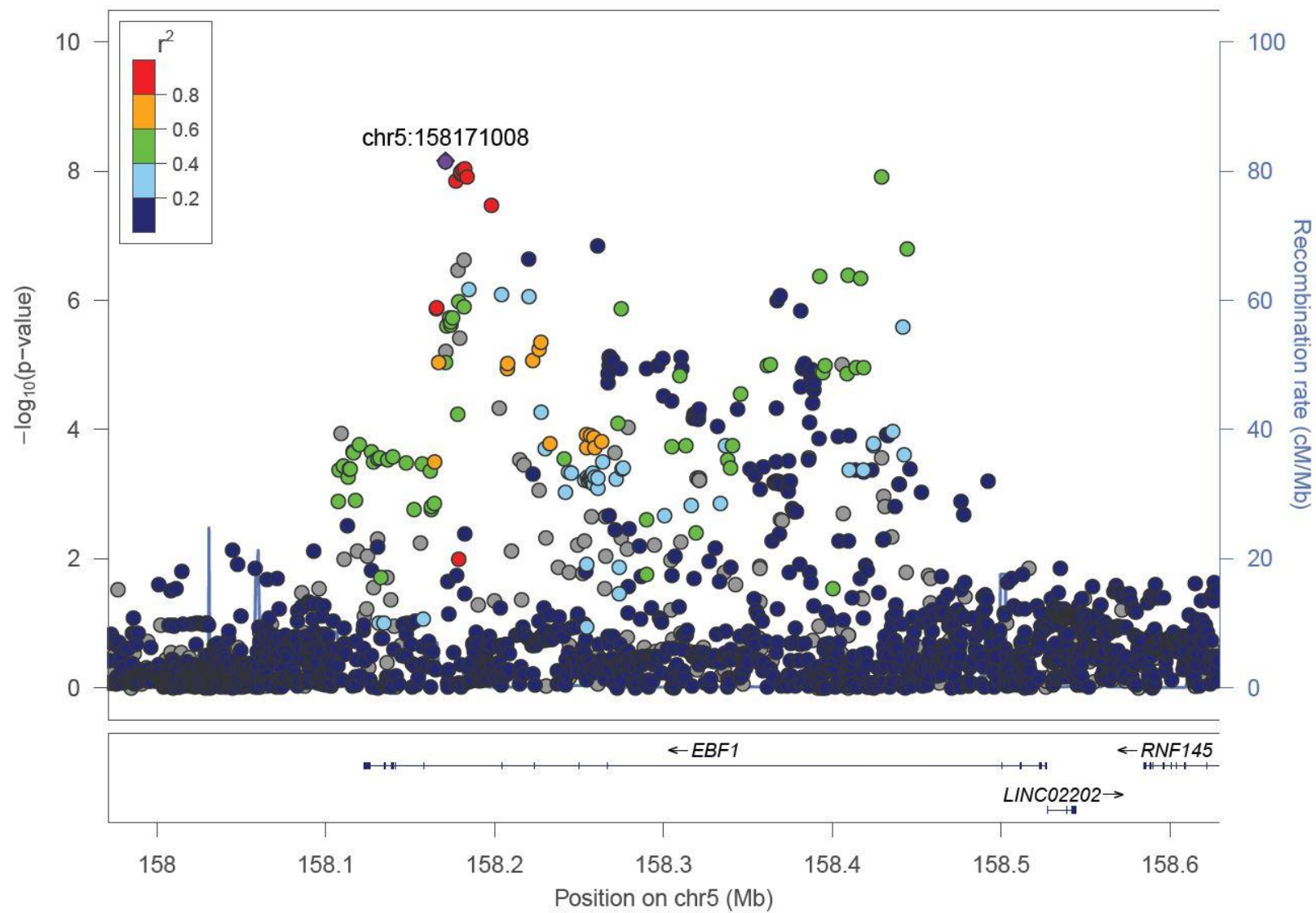
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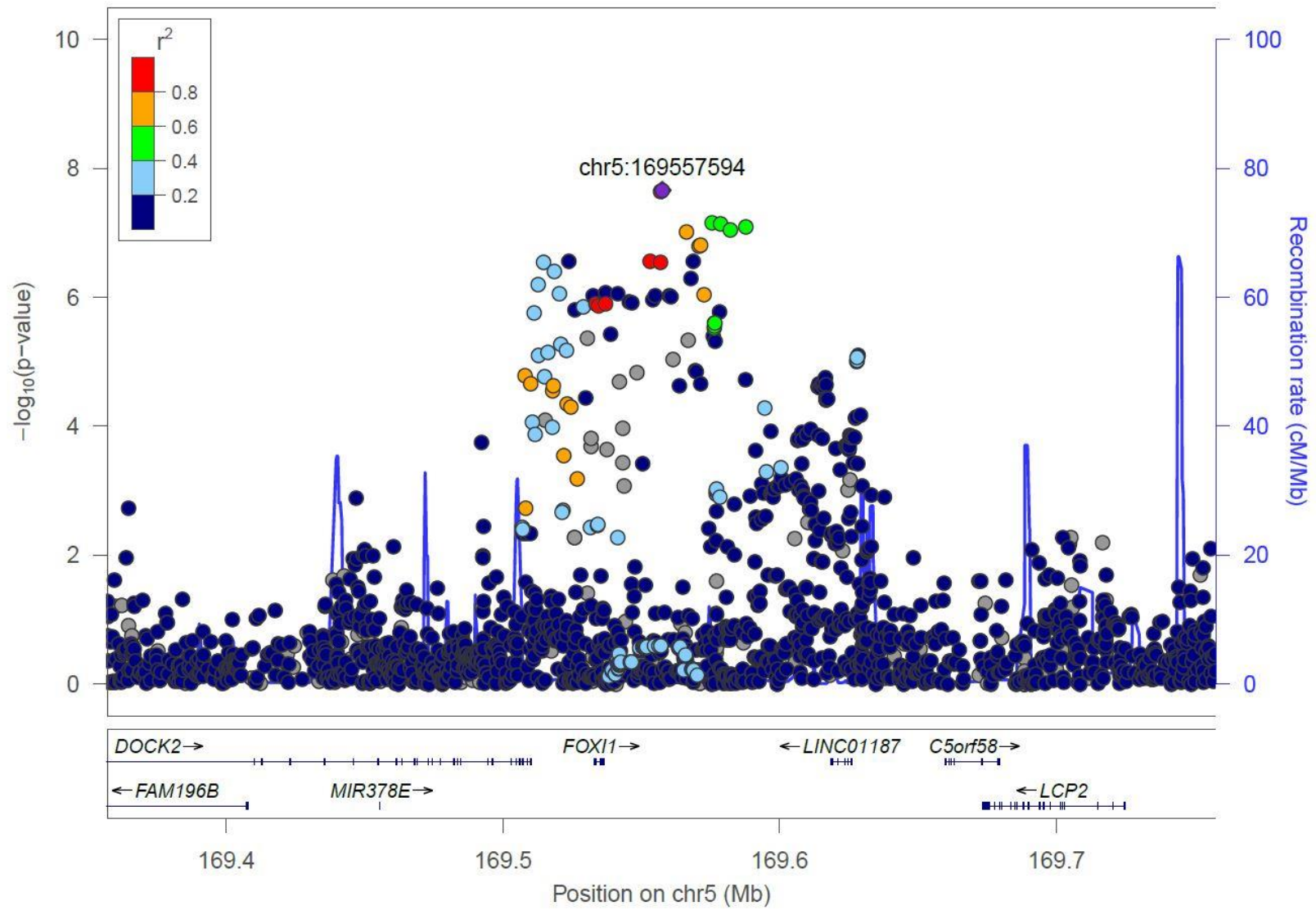
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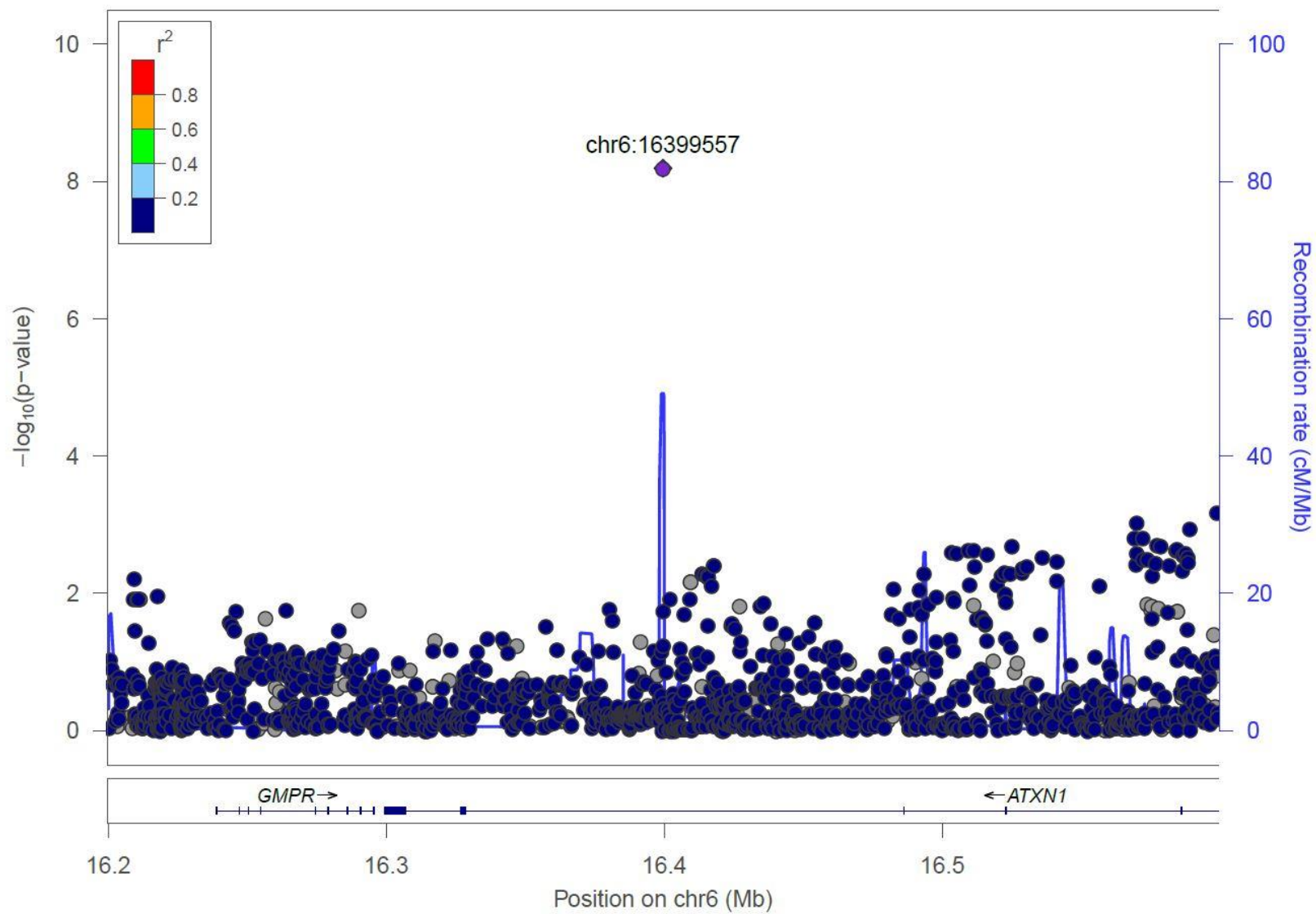
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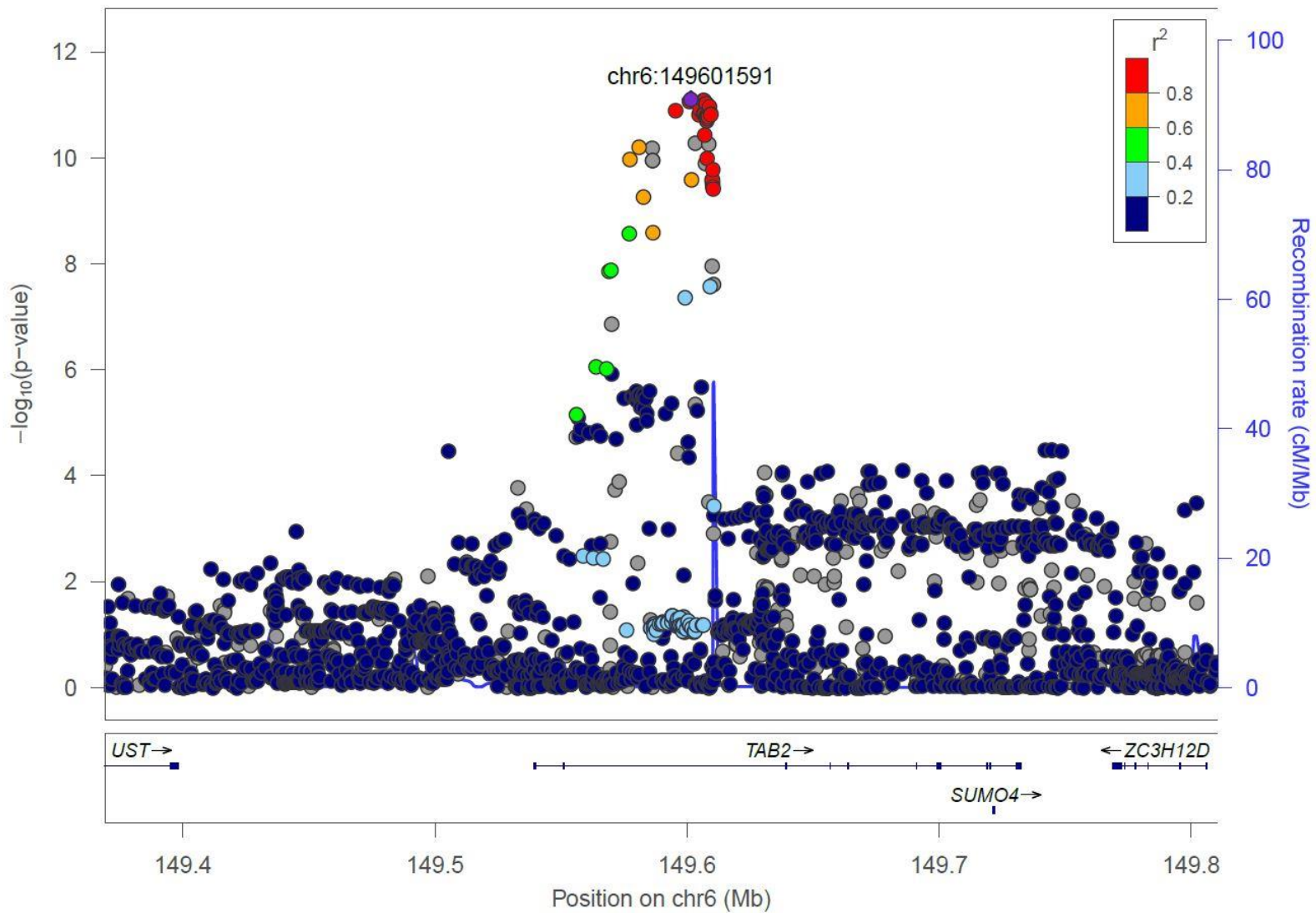
5q33.3



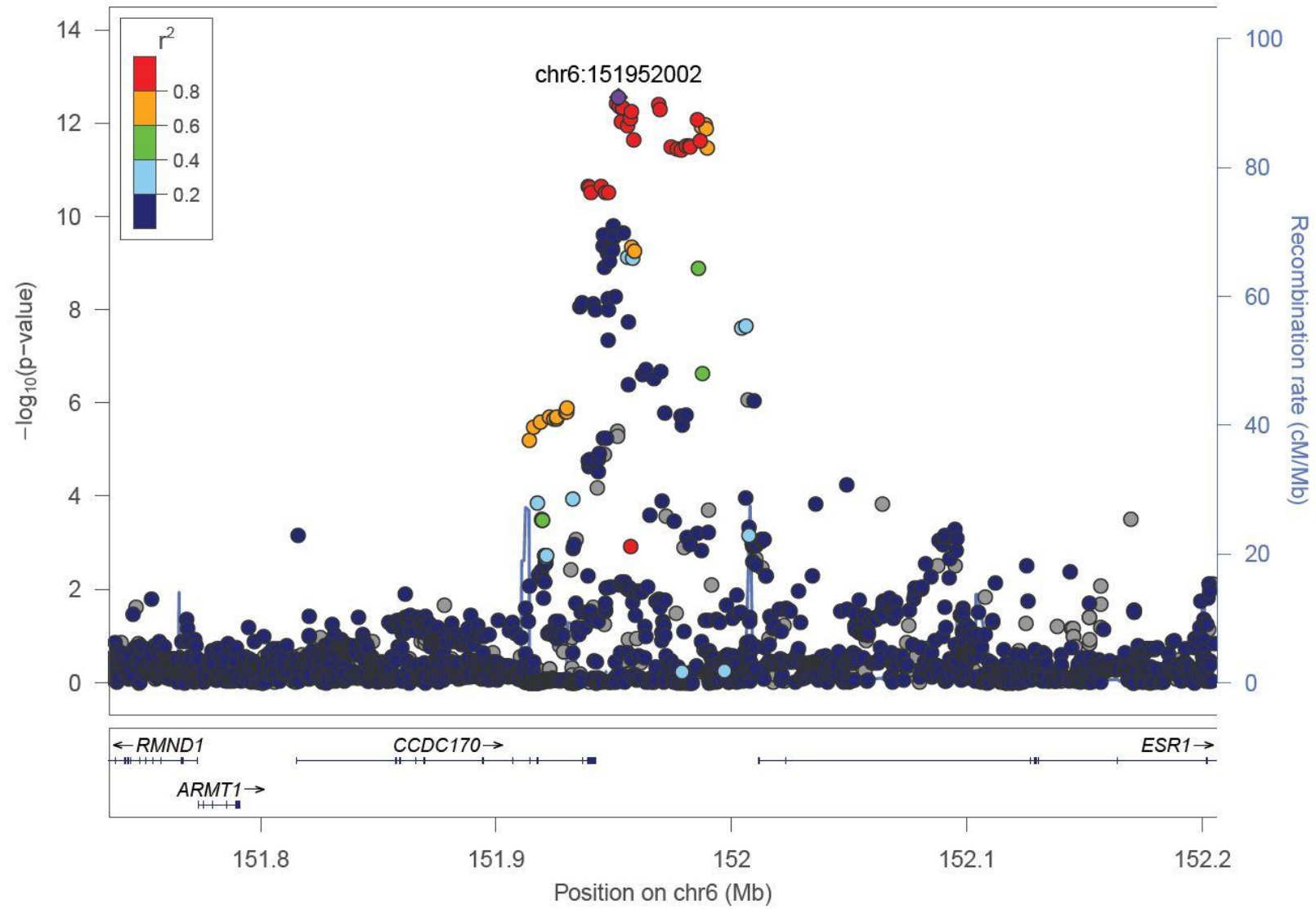
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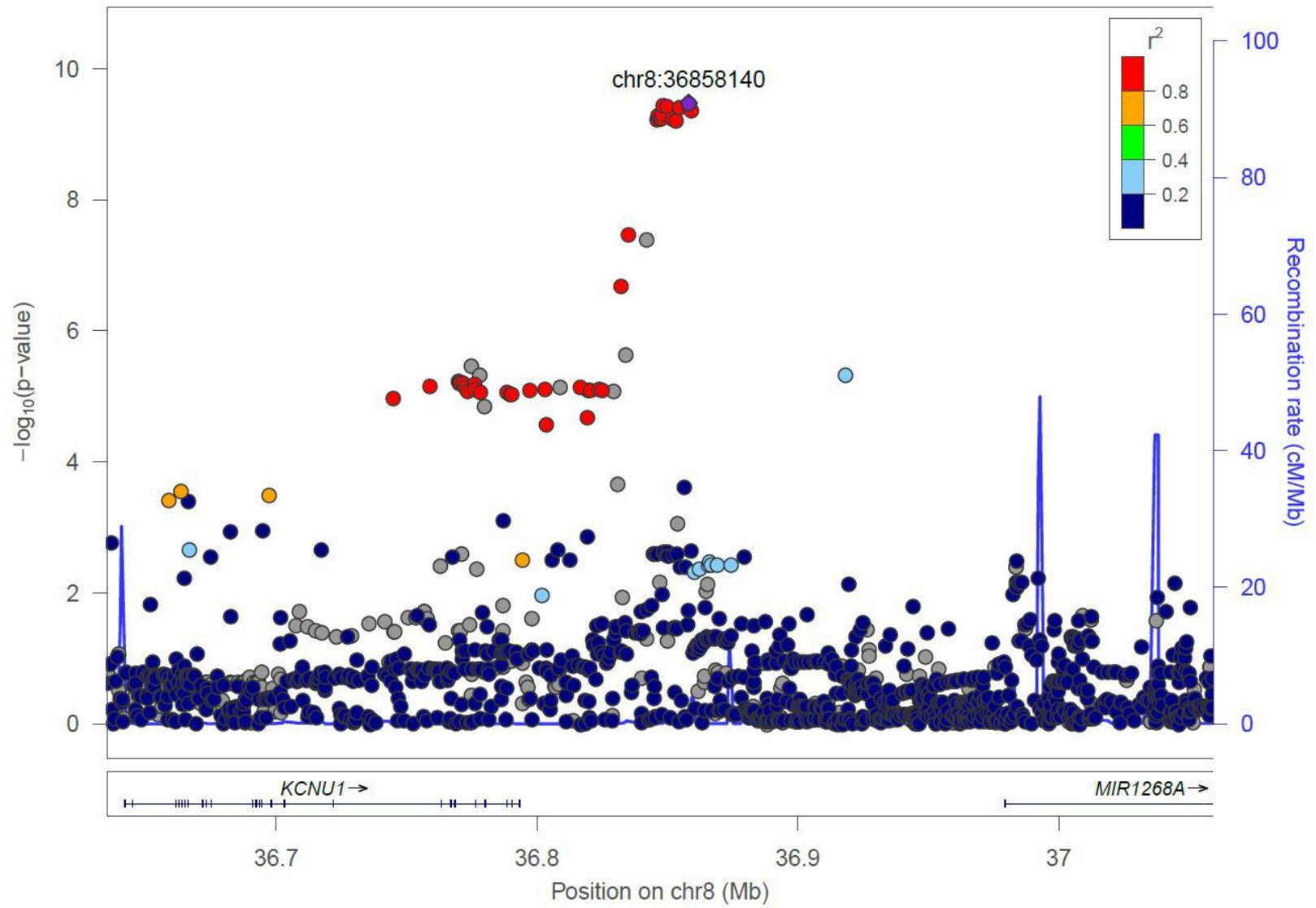


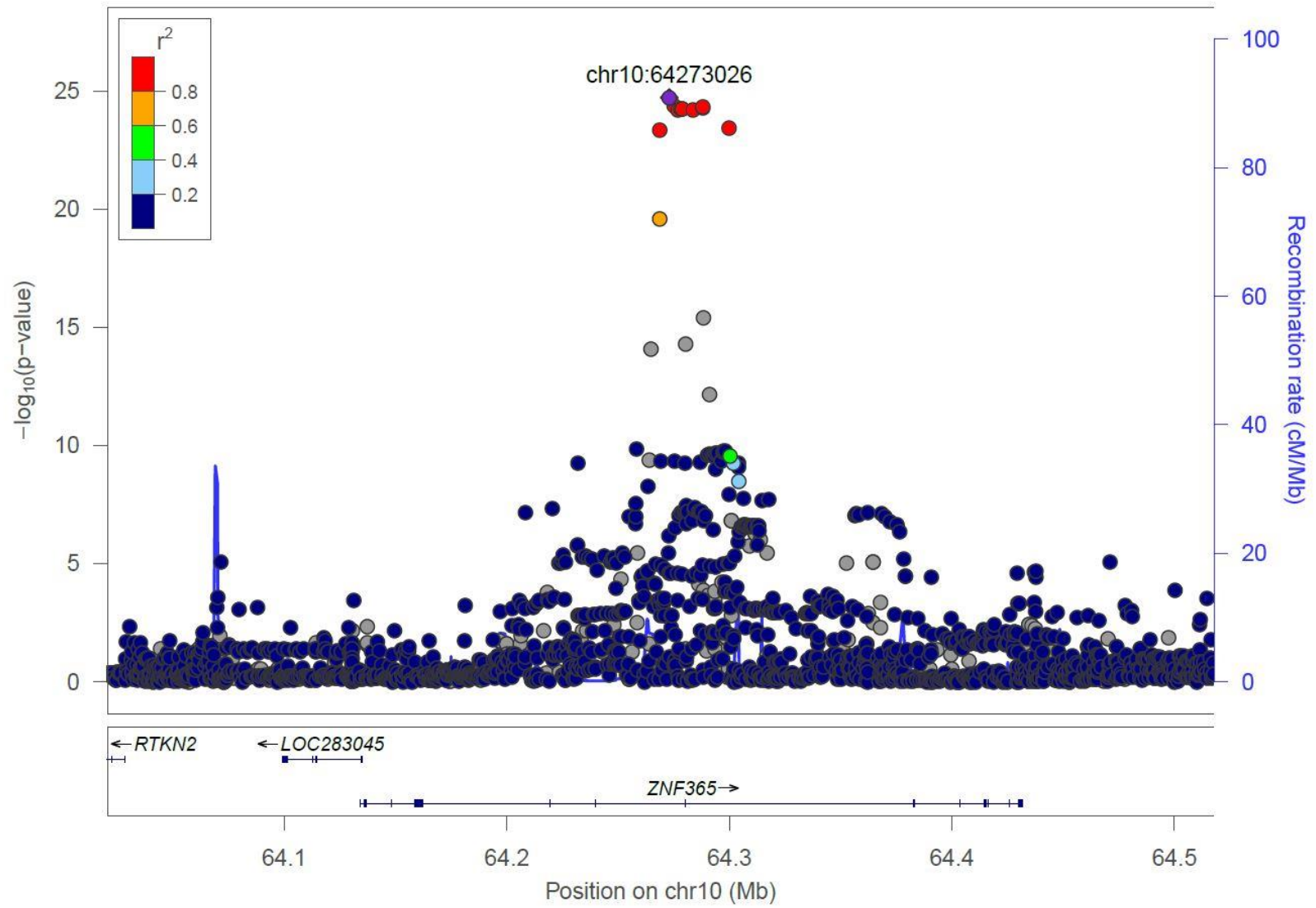
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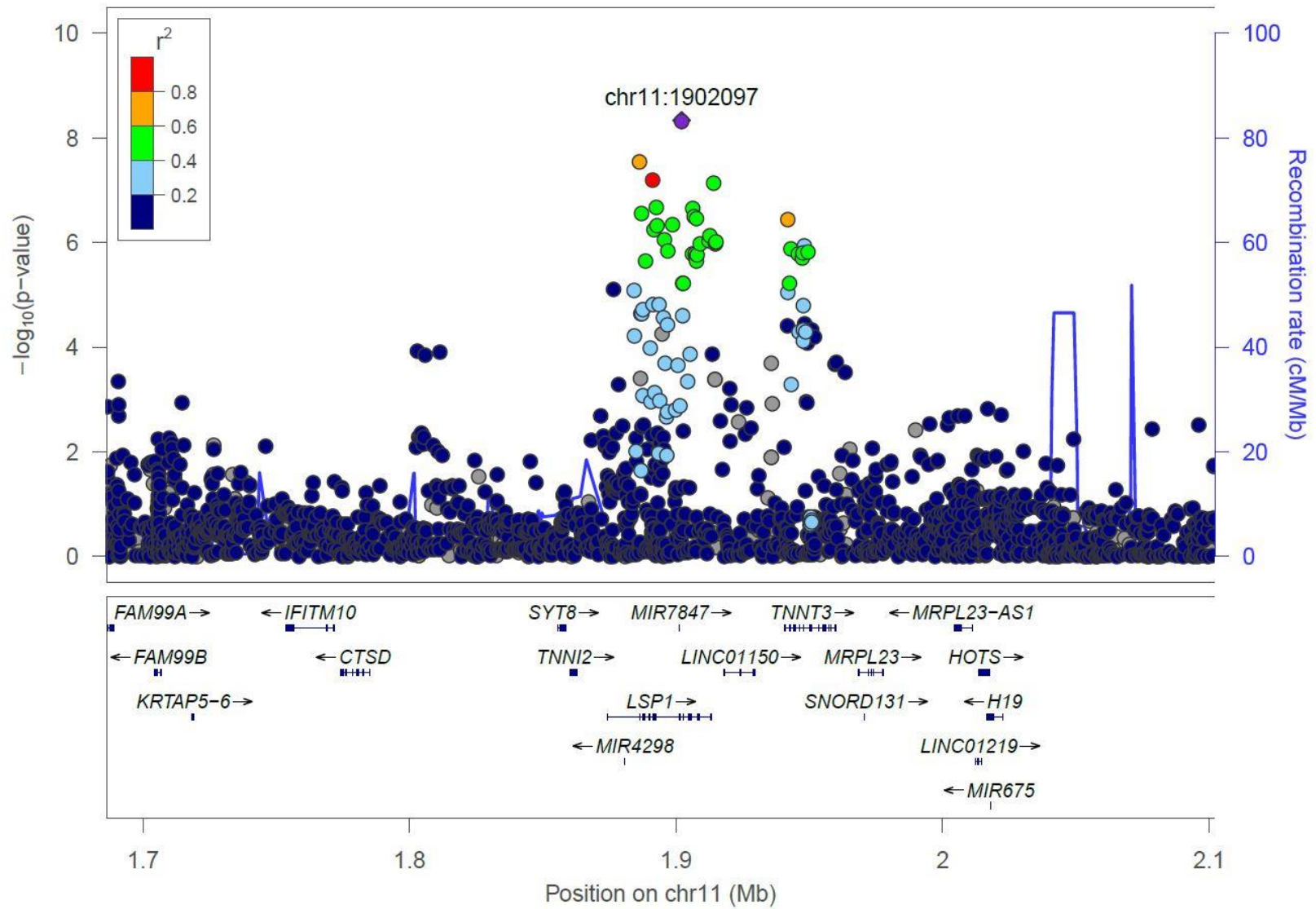


6q25.1 (1)

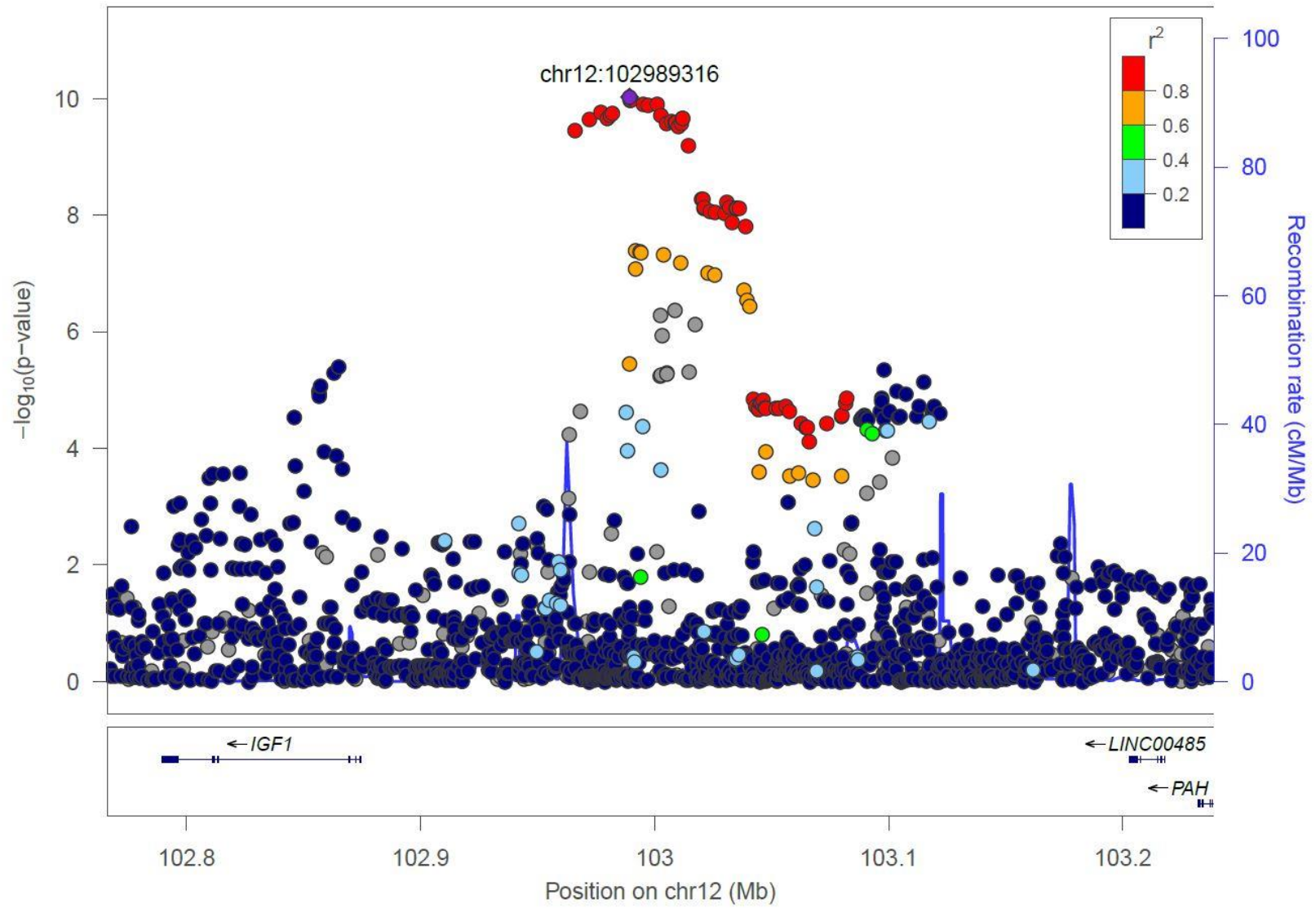
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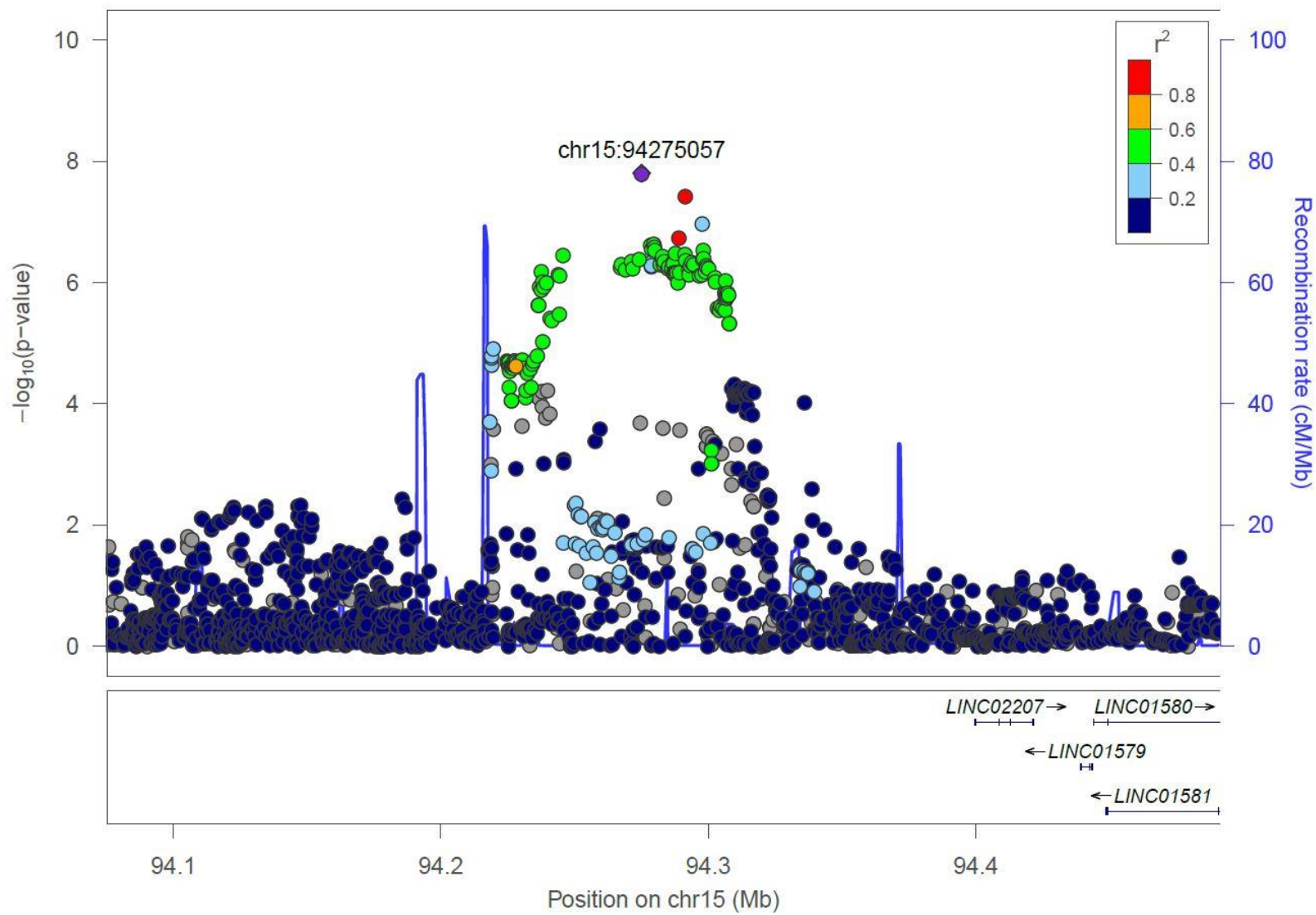
**8p11.23**

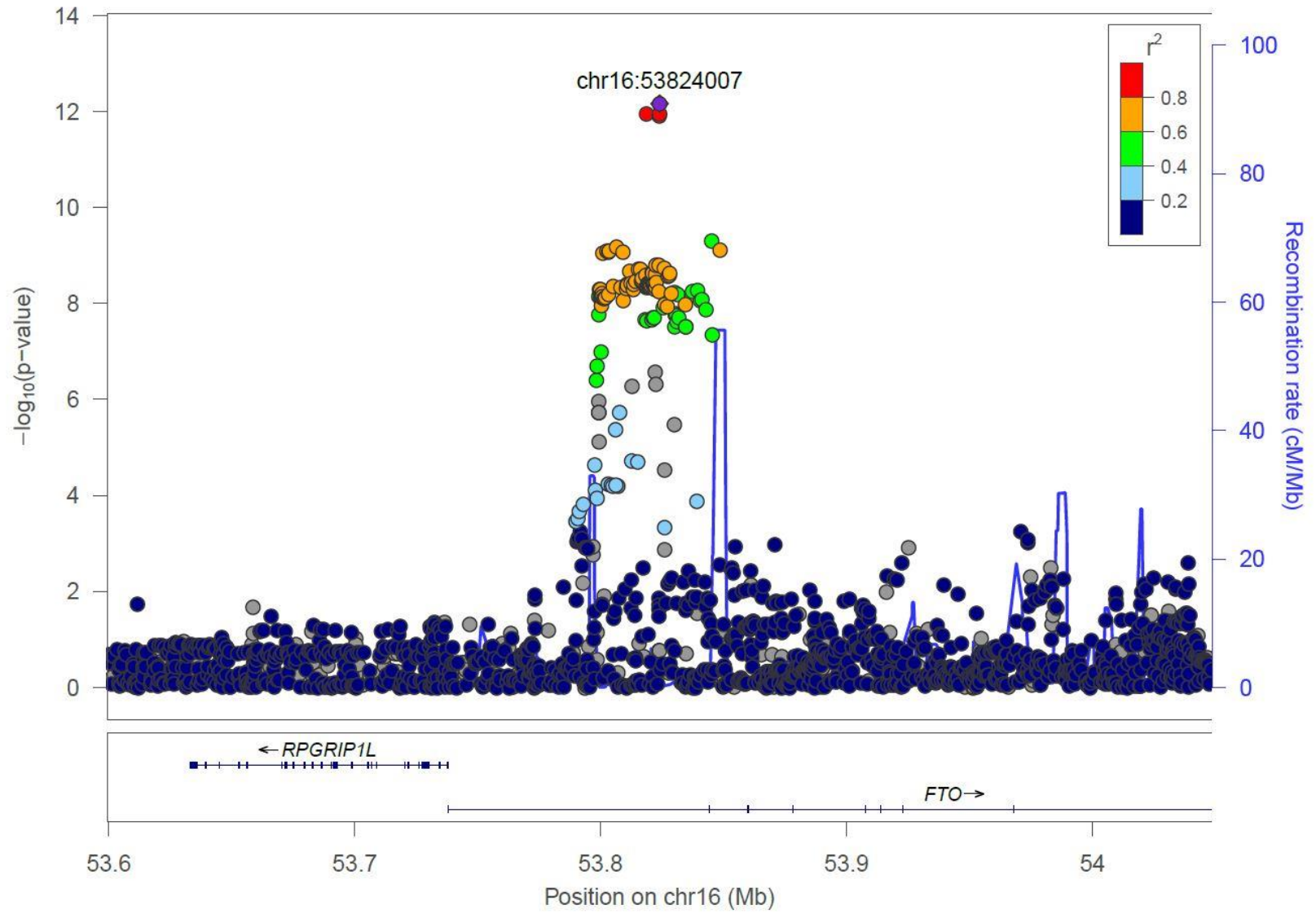
**10q21.2**



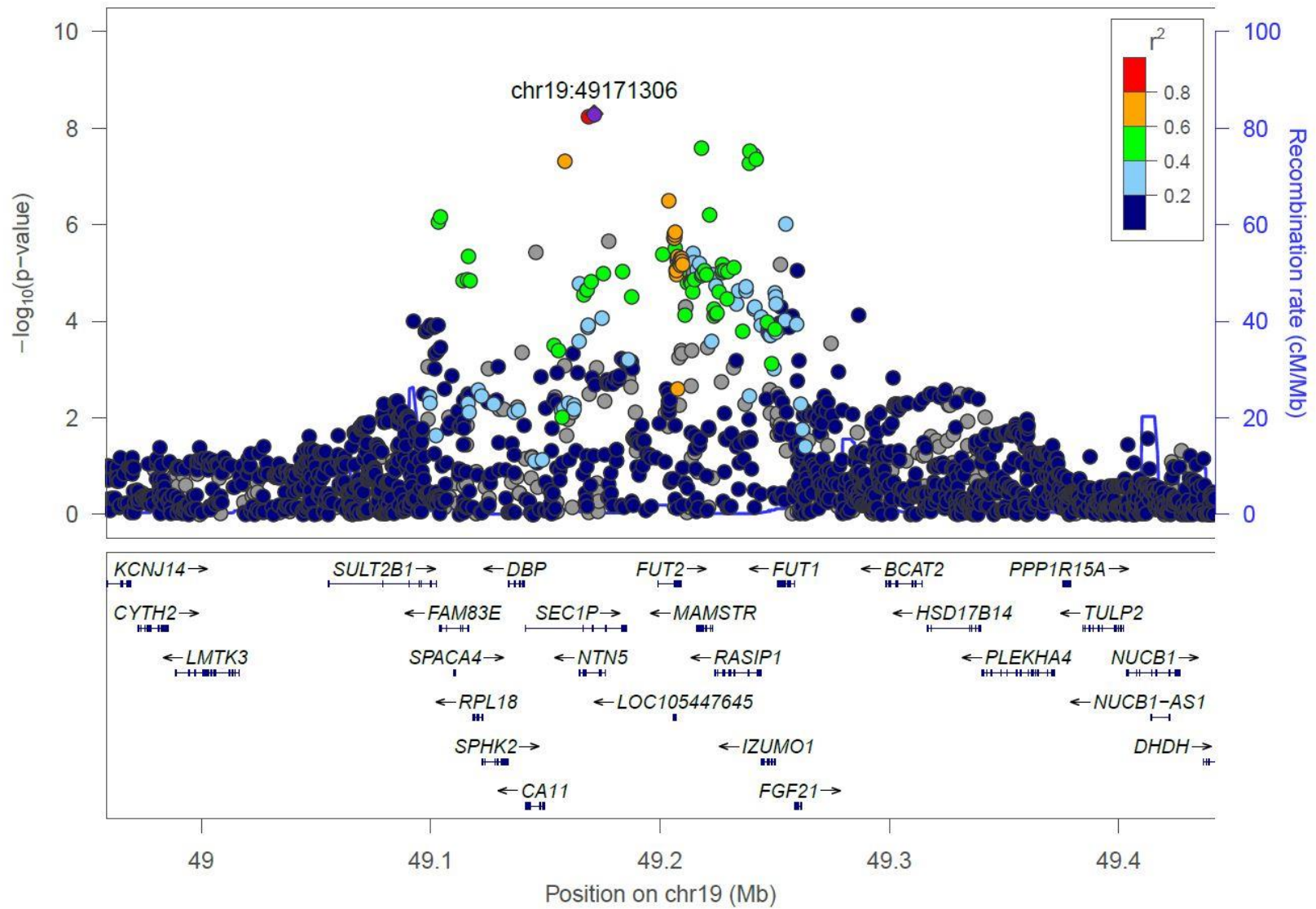
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**12q23.2**

**15q26.1**

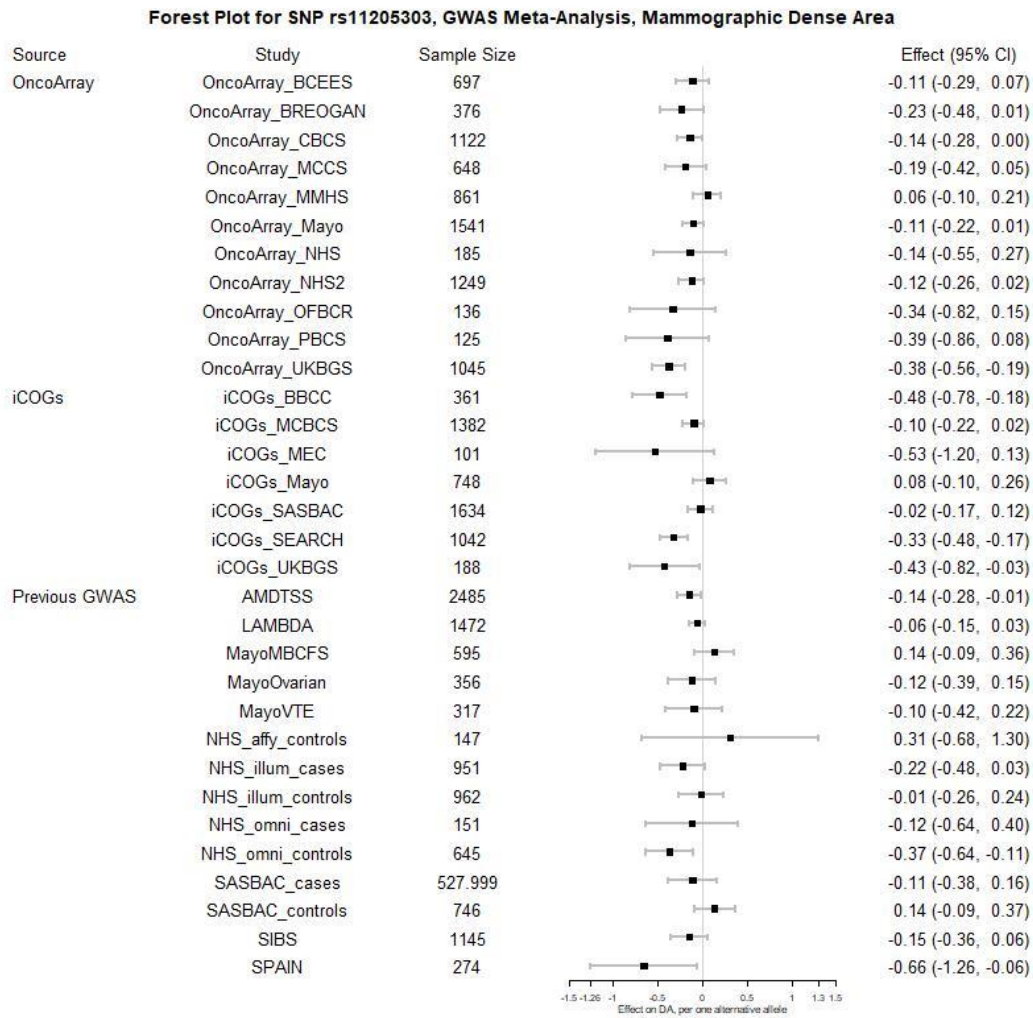


16q12.2

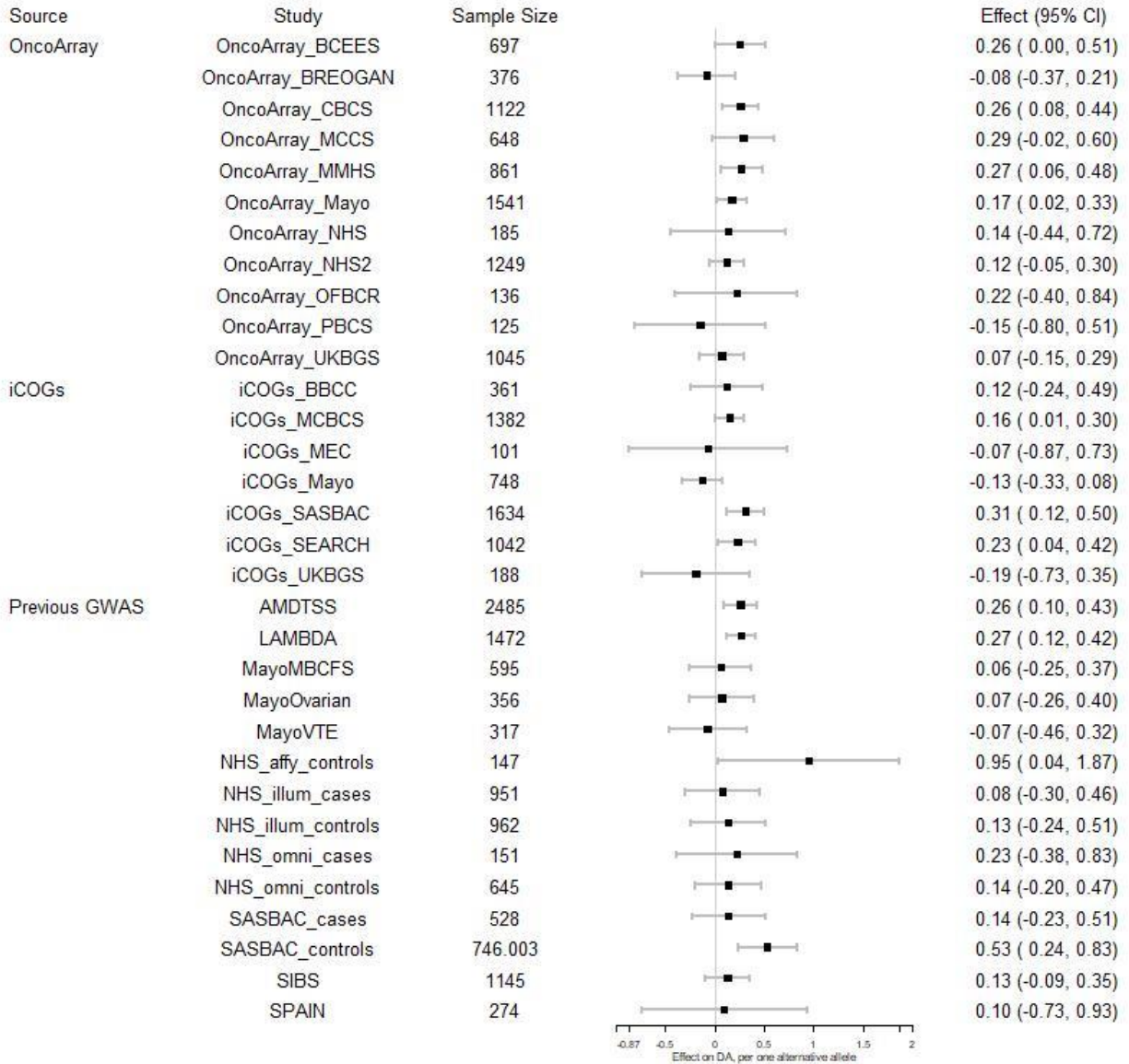


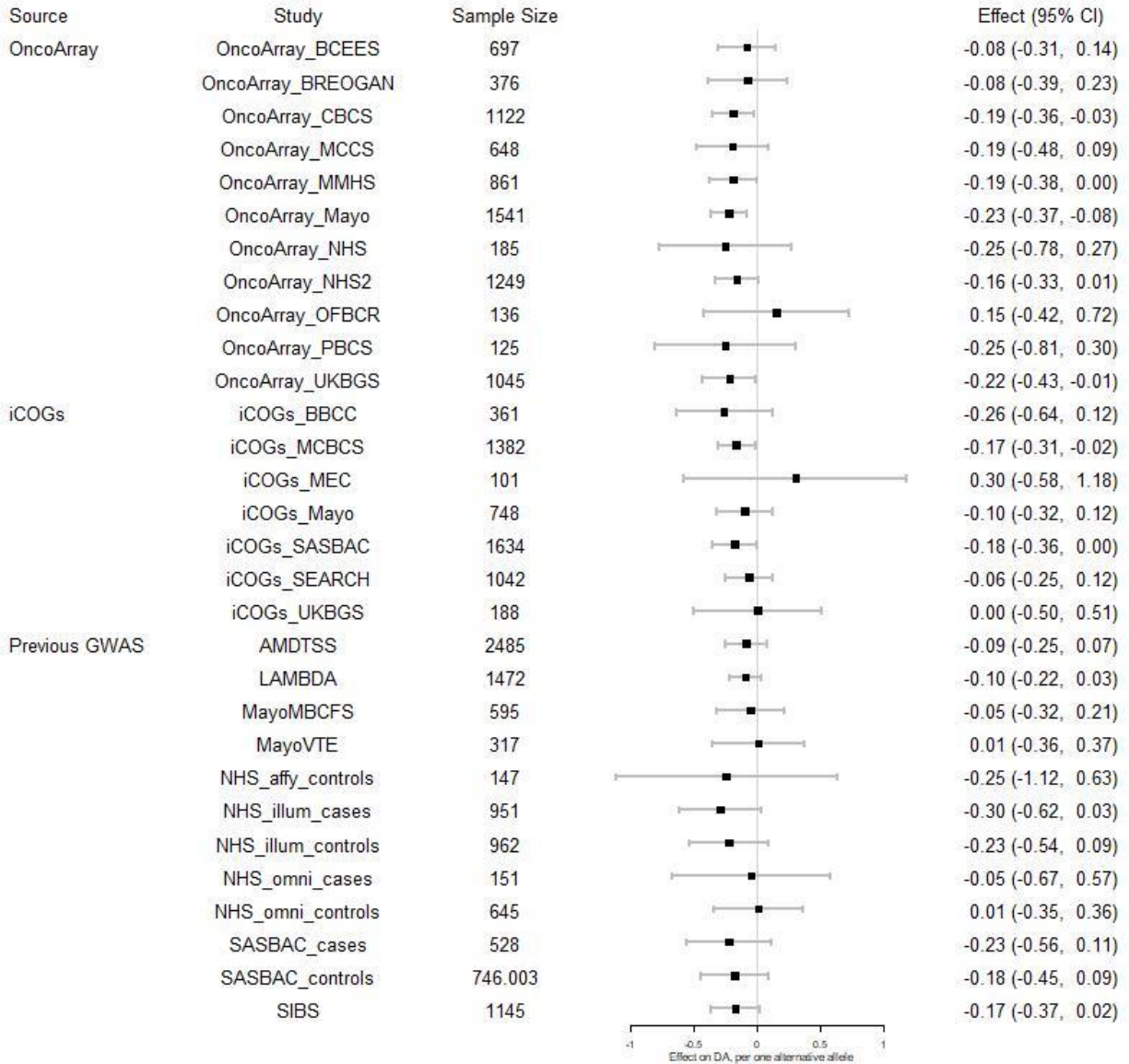
19q13.33

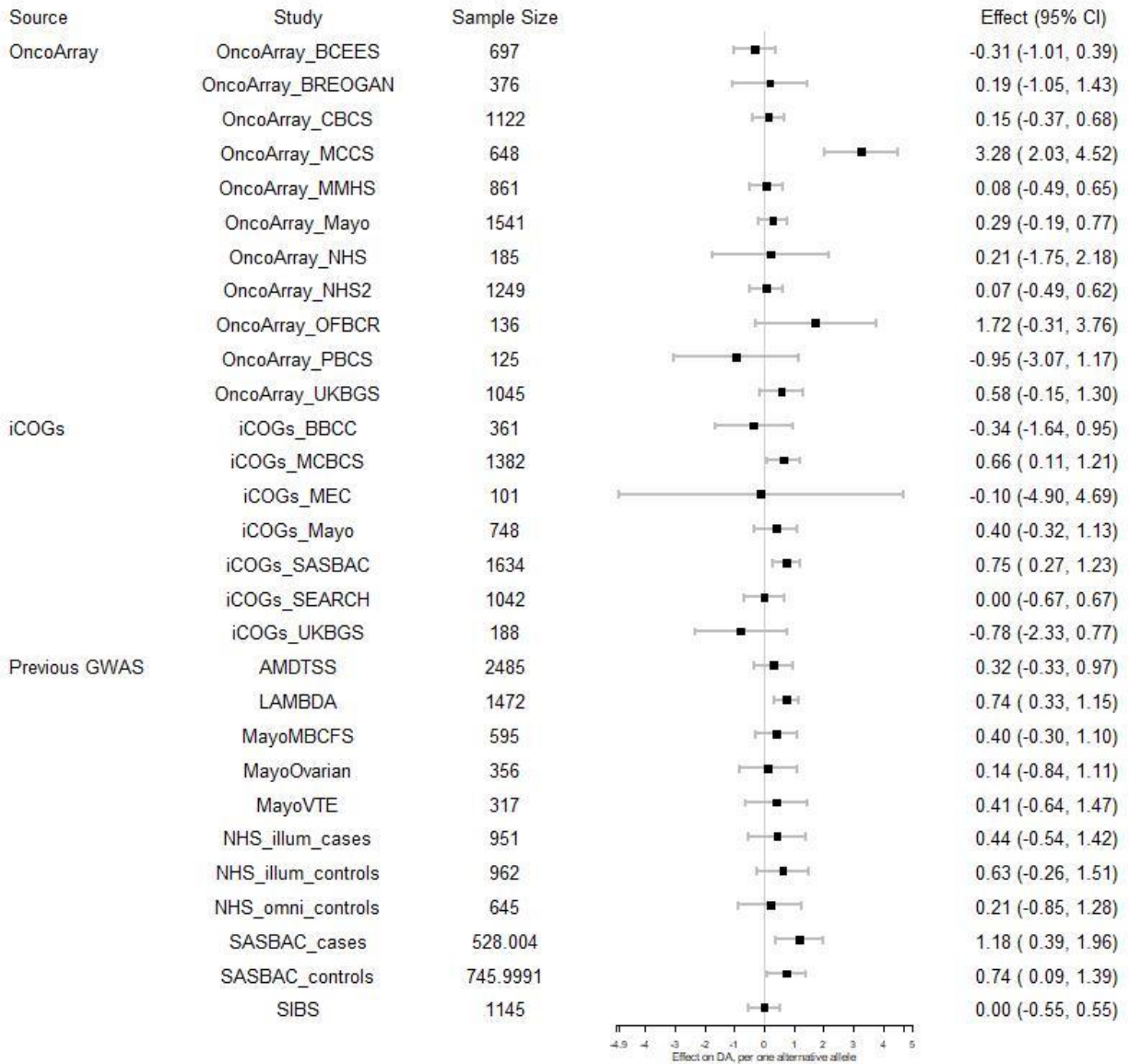
Supplementary Figure 2.6. Forest plots presenting the GWAS meta-analysis results of the lead SNP of eighteen genome-wide significant loci of DA. In each plot, the study name, sample size, beta estimate and 95% confidence interval for each participating study is shown. Studies with less than 100 individuals are not shown on the forest plots, although they were still included in the meta-analysis.



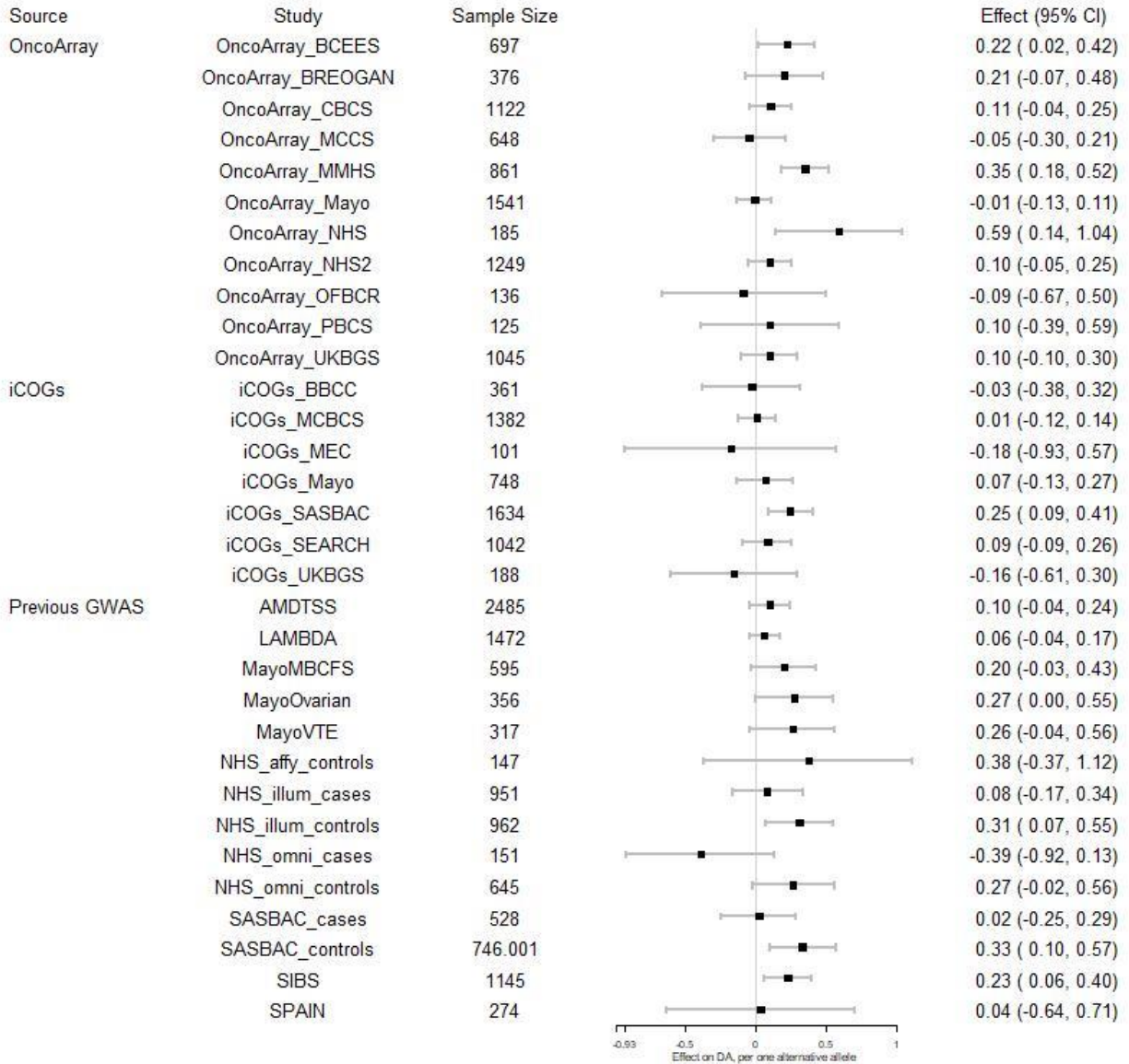
Forest Plot for SNP rs17625845, GWAS Meta-Analysis, Mammographic Dense Area

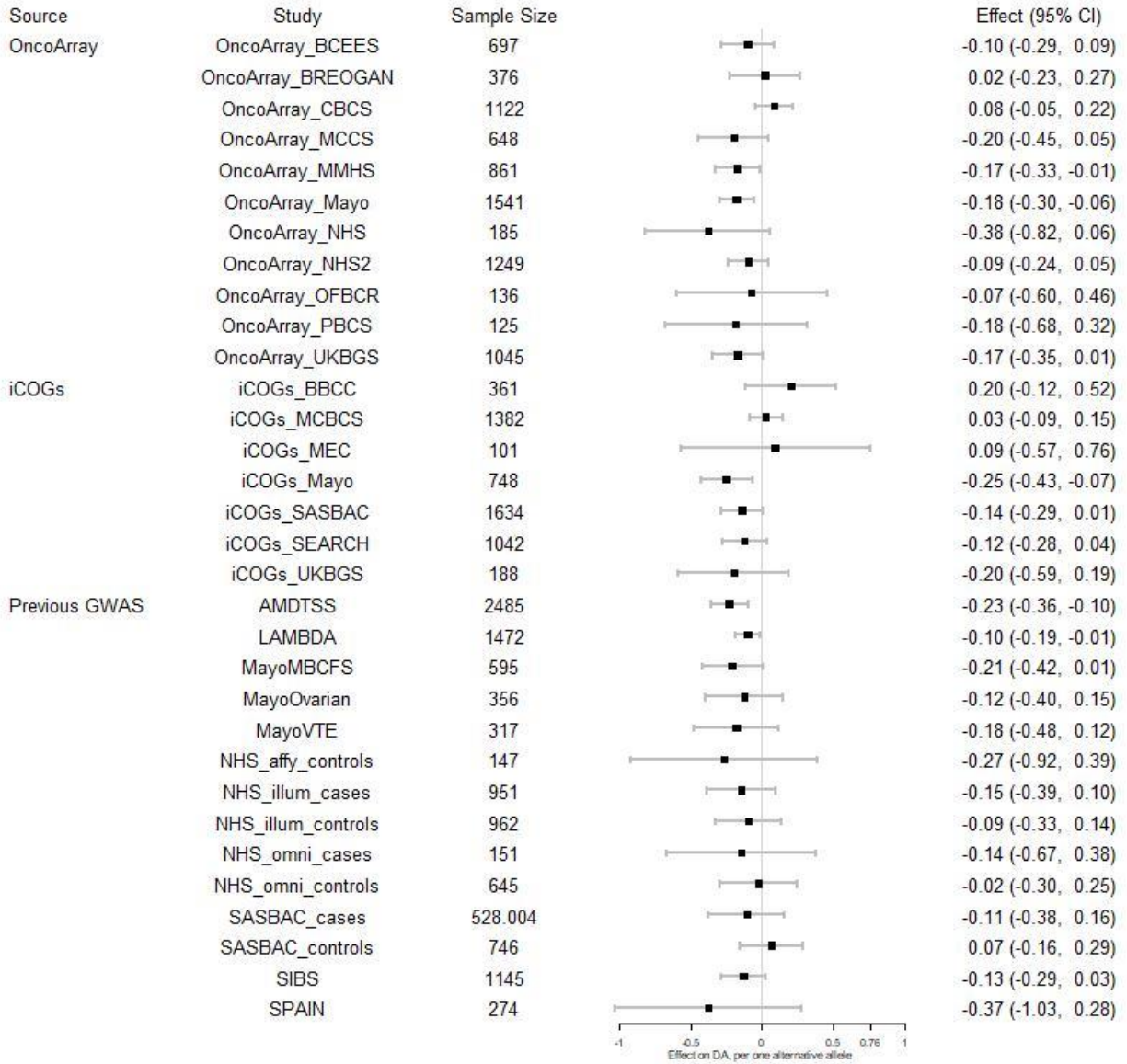


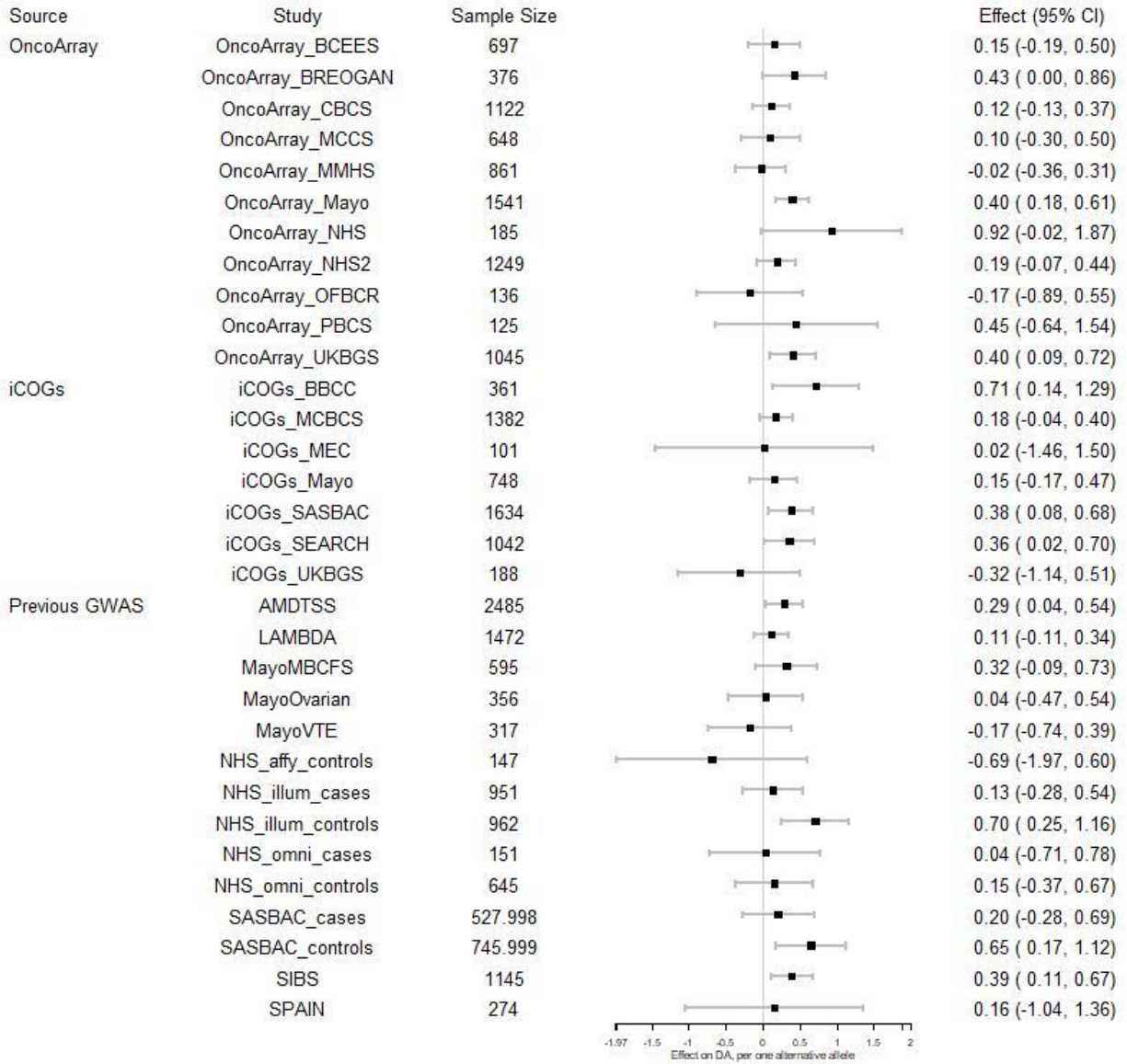
Forest Plot for SNP rs6851733, GWAS Meta-Analysis, Mammographic Dense Area


Forest Plot for SNP rs150249911, GWAS Meta-Analysis, Mammographic Dense Area


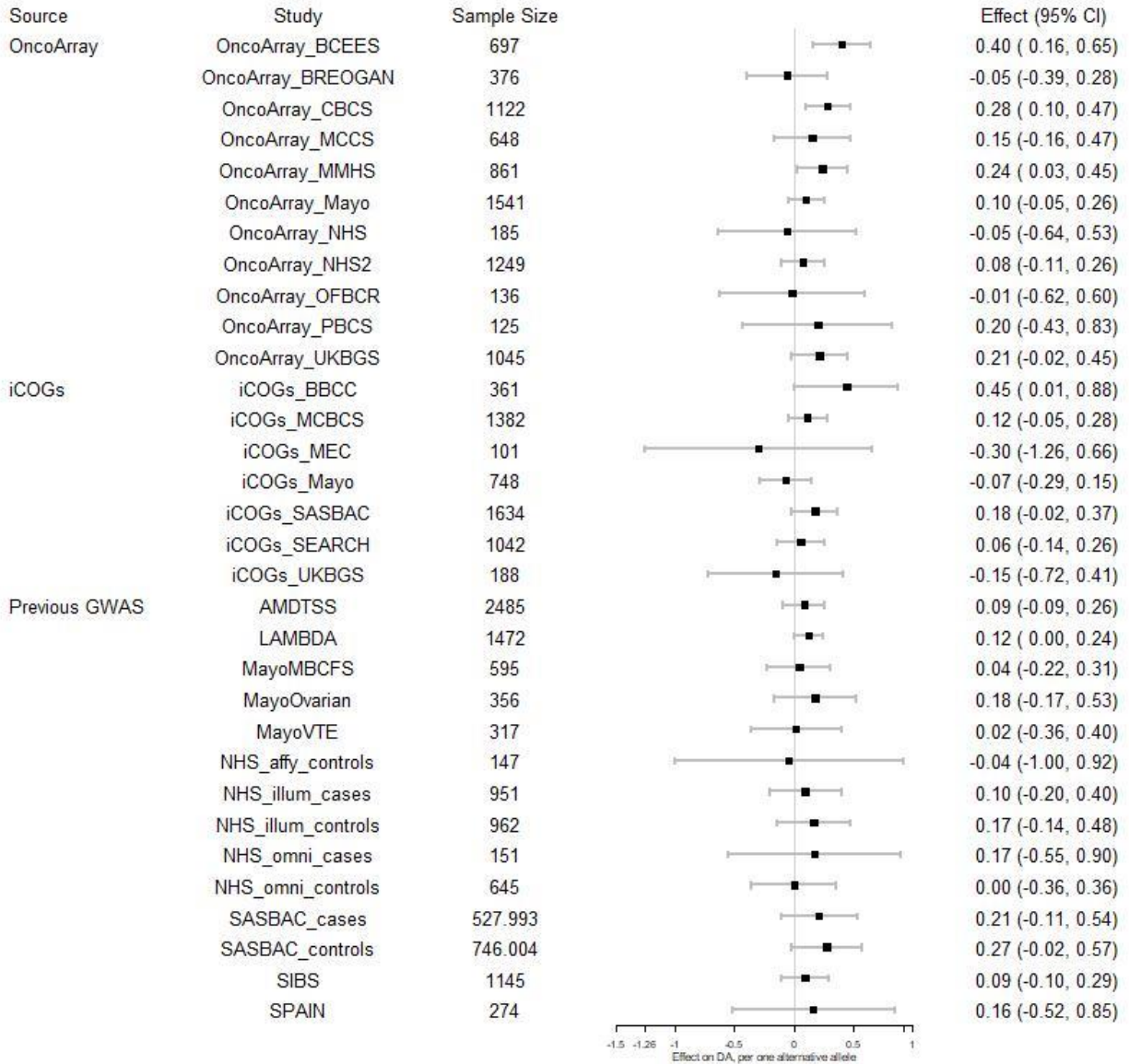
Forest Plot for SNP rs335189, GWAS Meta-Analysis, Mammographic Dense Area



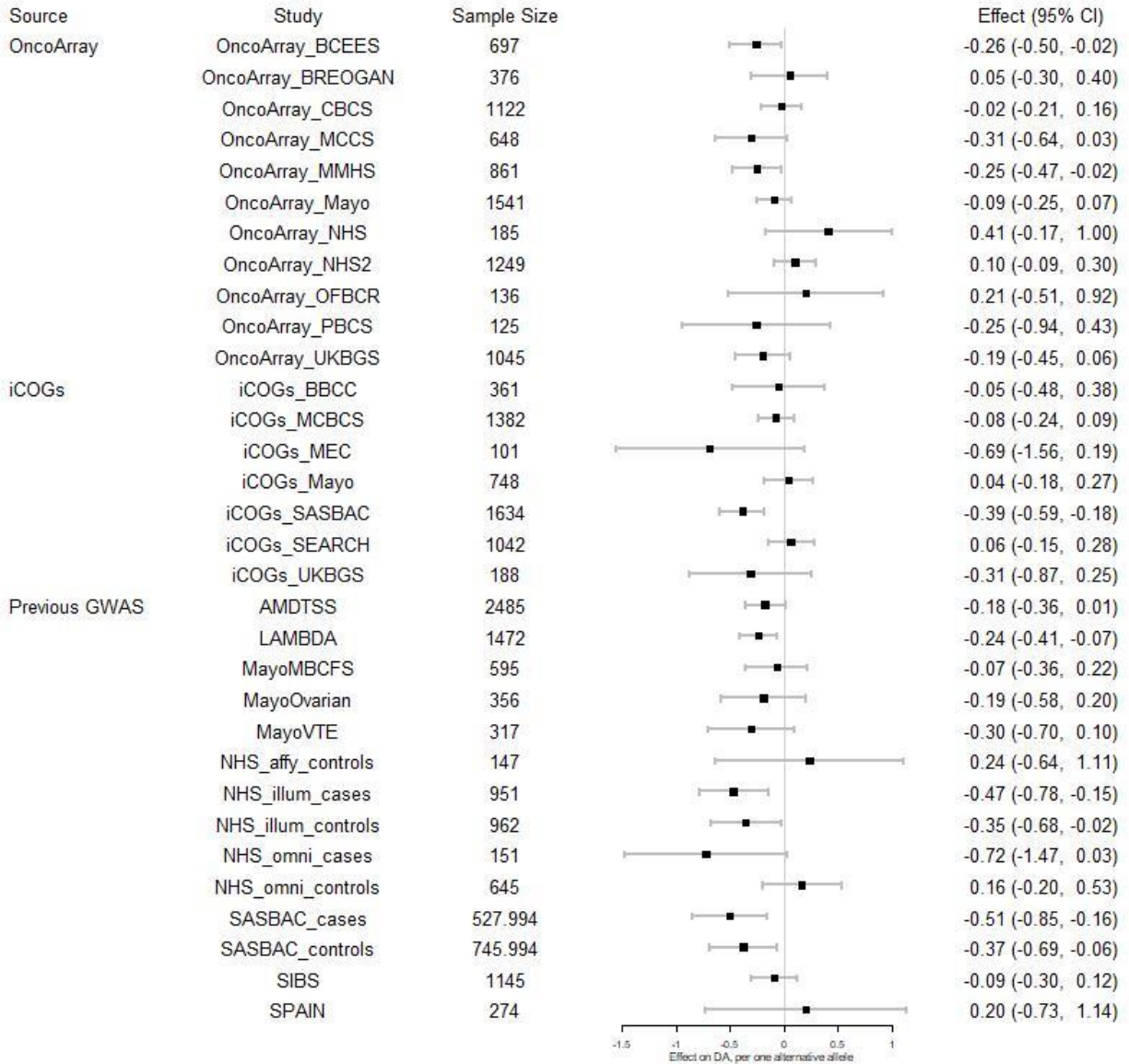
Forest Plot for SNP rs2042239, GWAS Meta-Analysis, Mammographic Dense Area


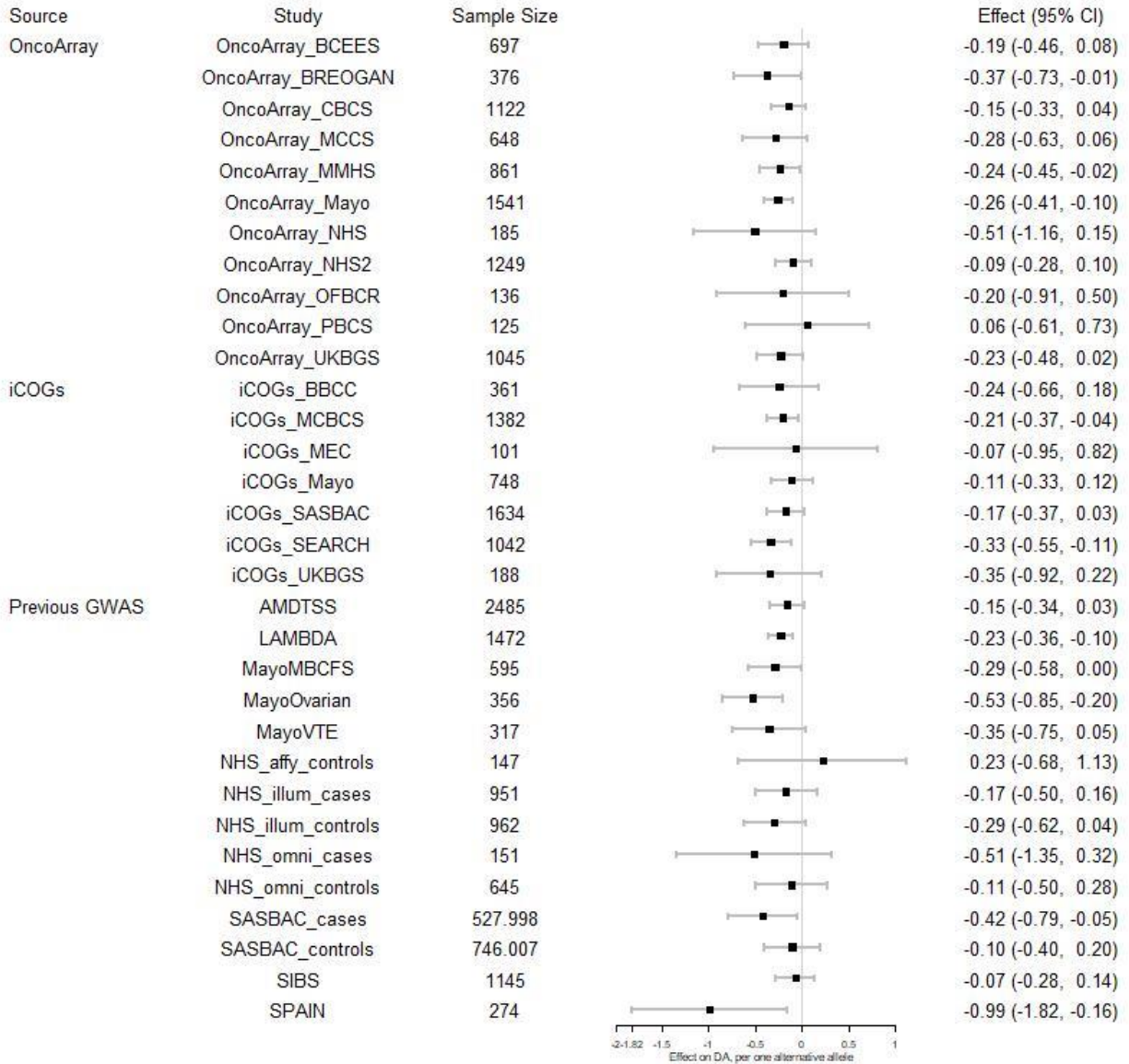
Forest Plot for SNP rs9397436, GWAS Meta-Analysis, Mammographic Dense Area


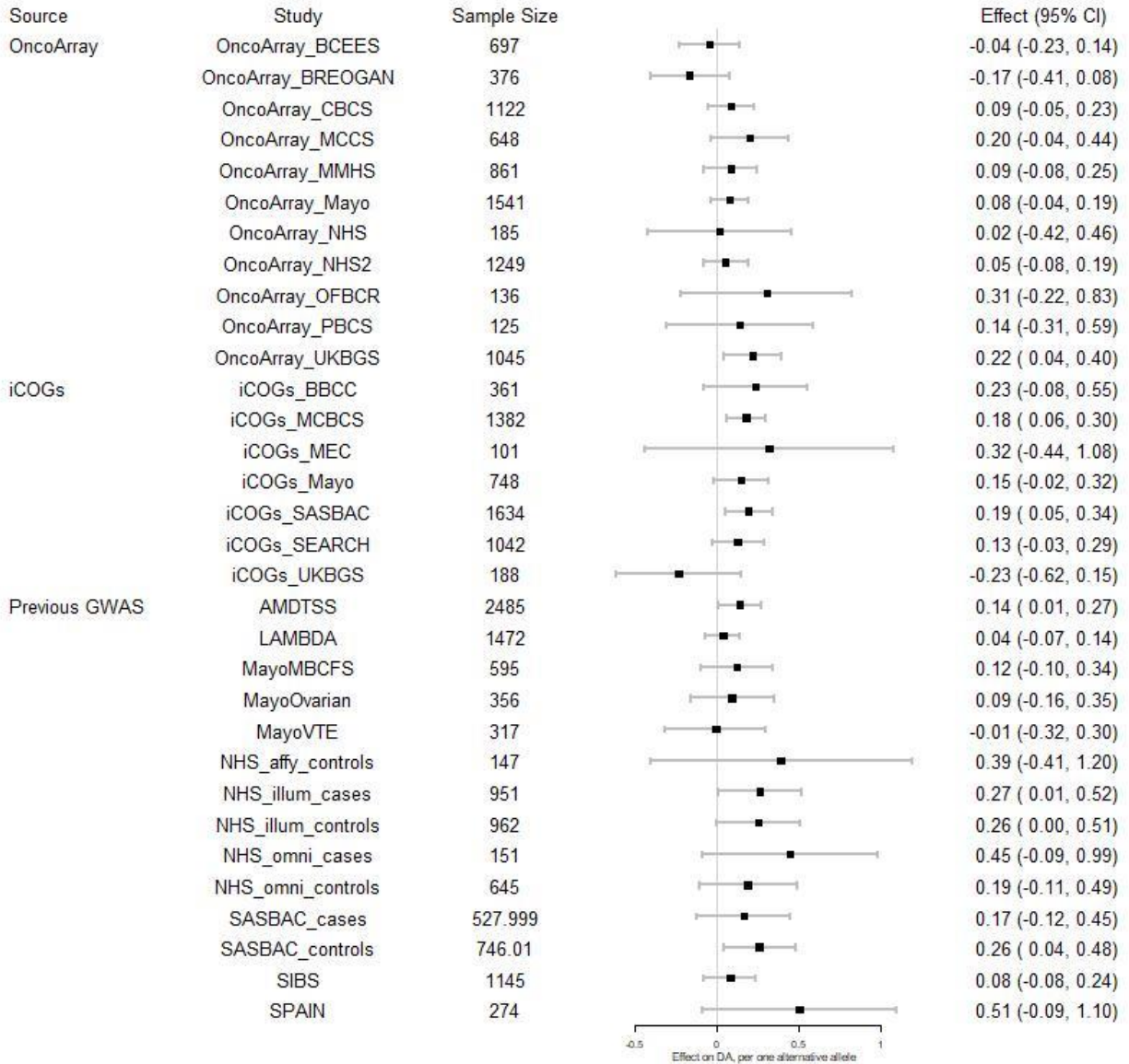
Forest Plot for SNP rs10155920, GWAS Meta-Analysis, Mammographic Dense Area



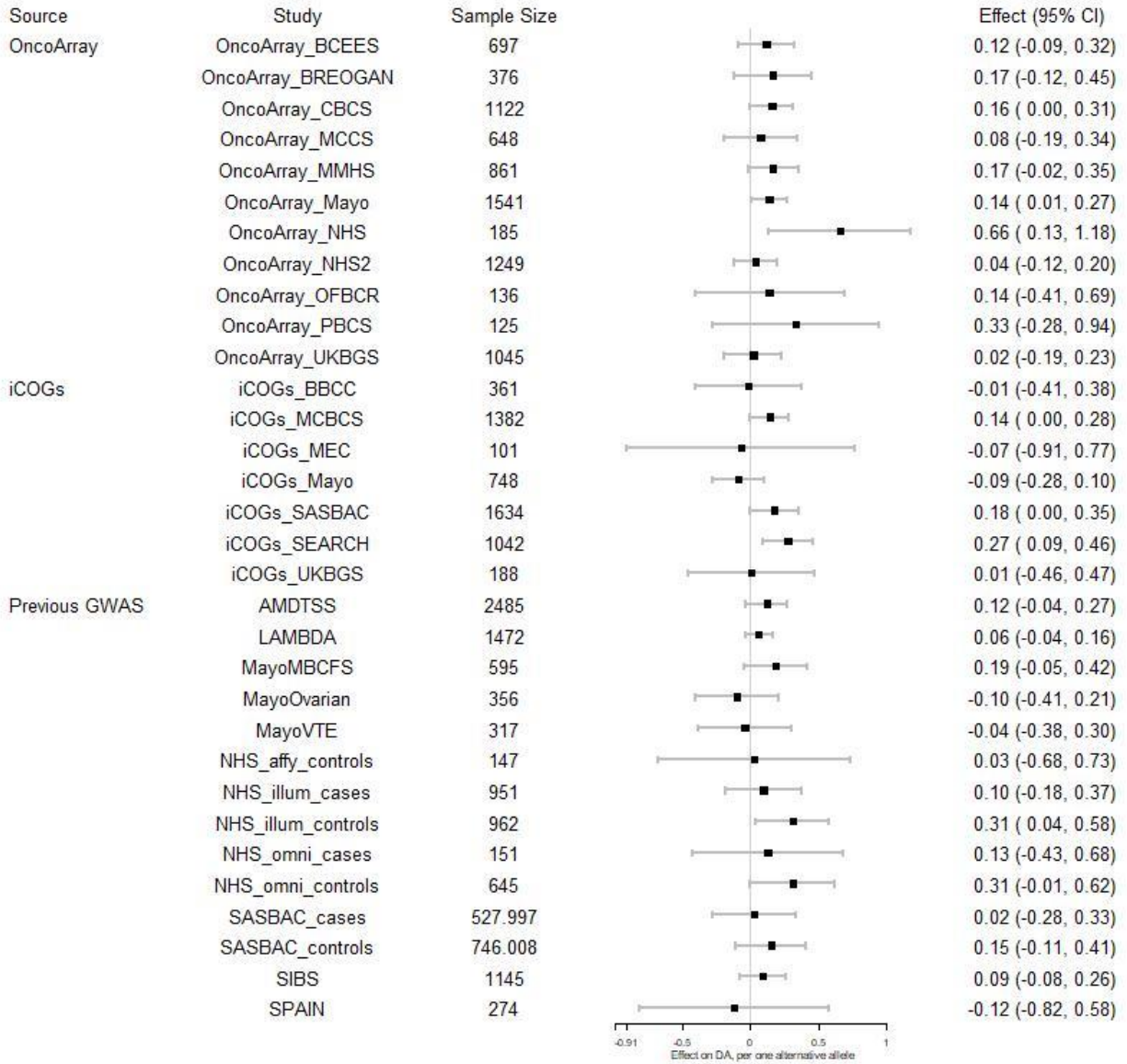
Forest Plot for SNP rs58847541, GWAS Meta-Analysis, Mammographic Dense Area



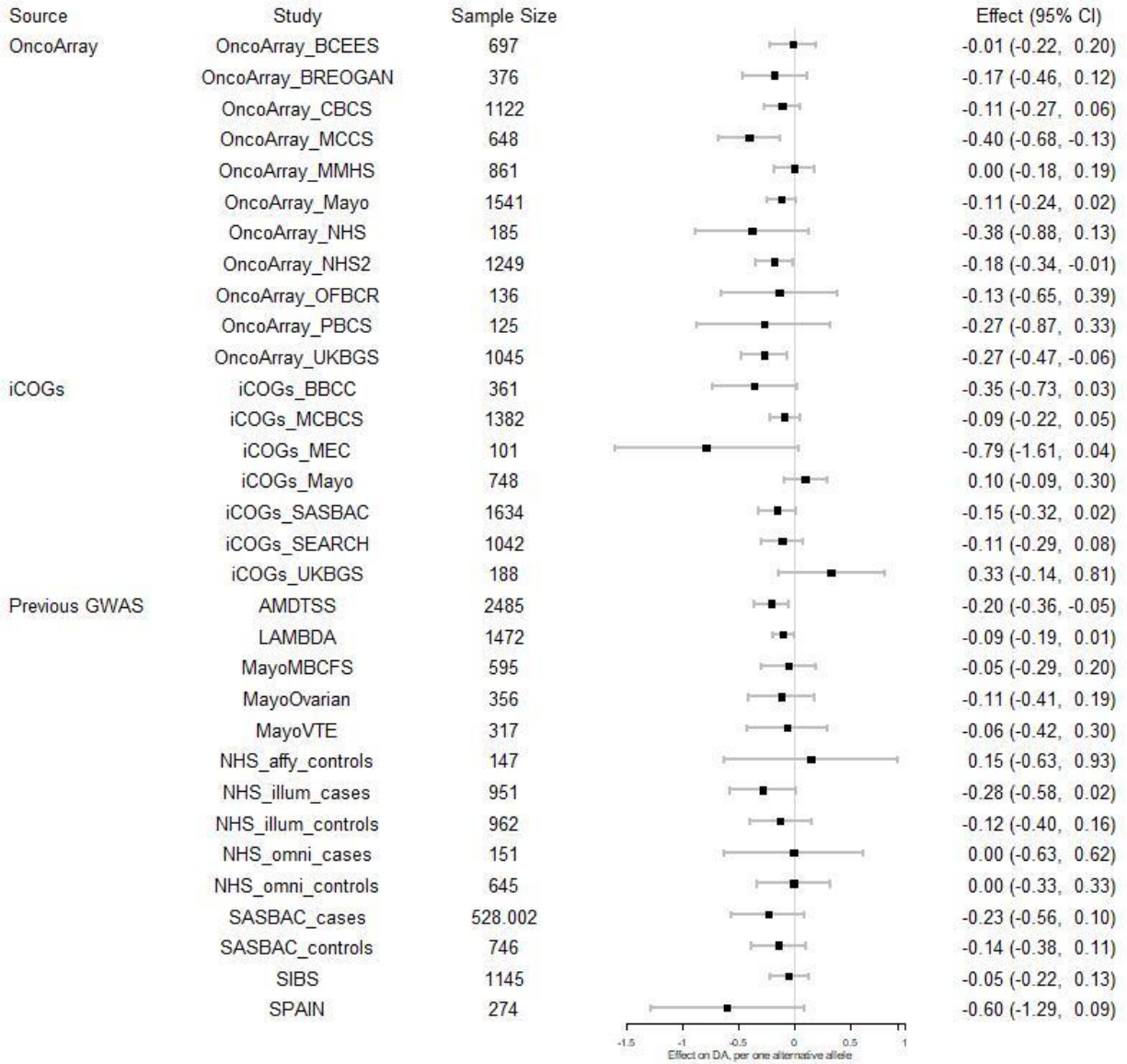
Forest Plot for SNP rs10995187, GWAS Meta-Analysis, Mammographic Dense Area


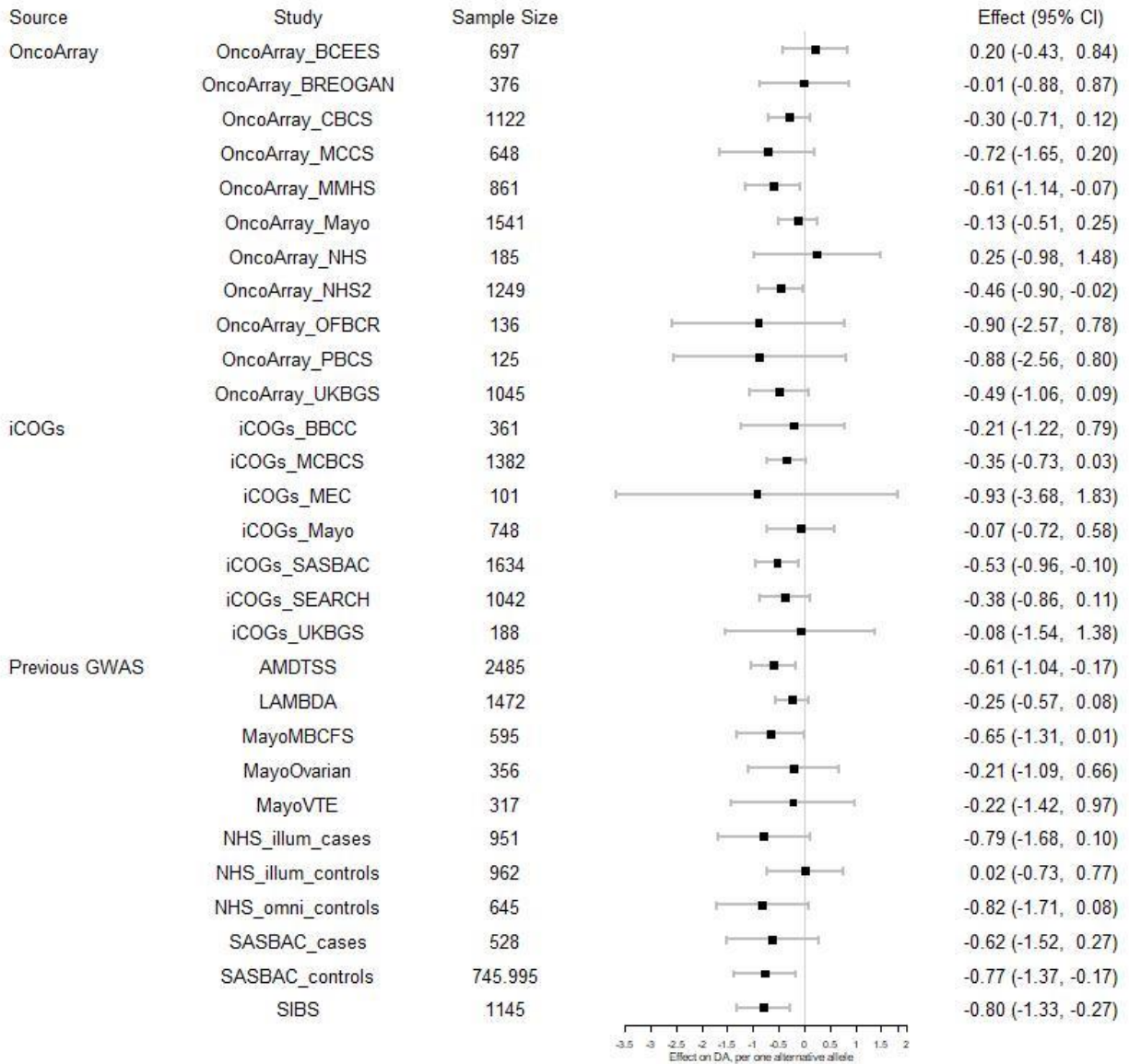
Forest Plot for SNP rs4980383, GWAS Meta-Analysis, Mammographic Dense Area


Forest Plot for SNP rs11836164, GWAS Meta-Analysis, Mammographic Dense Area

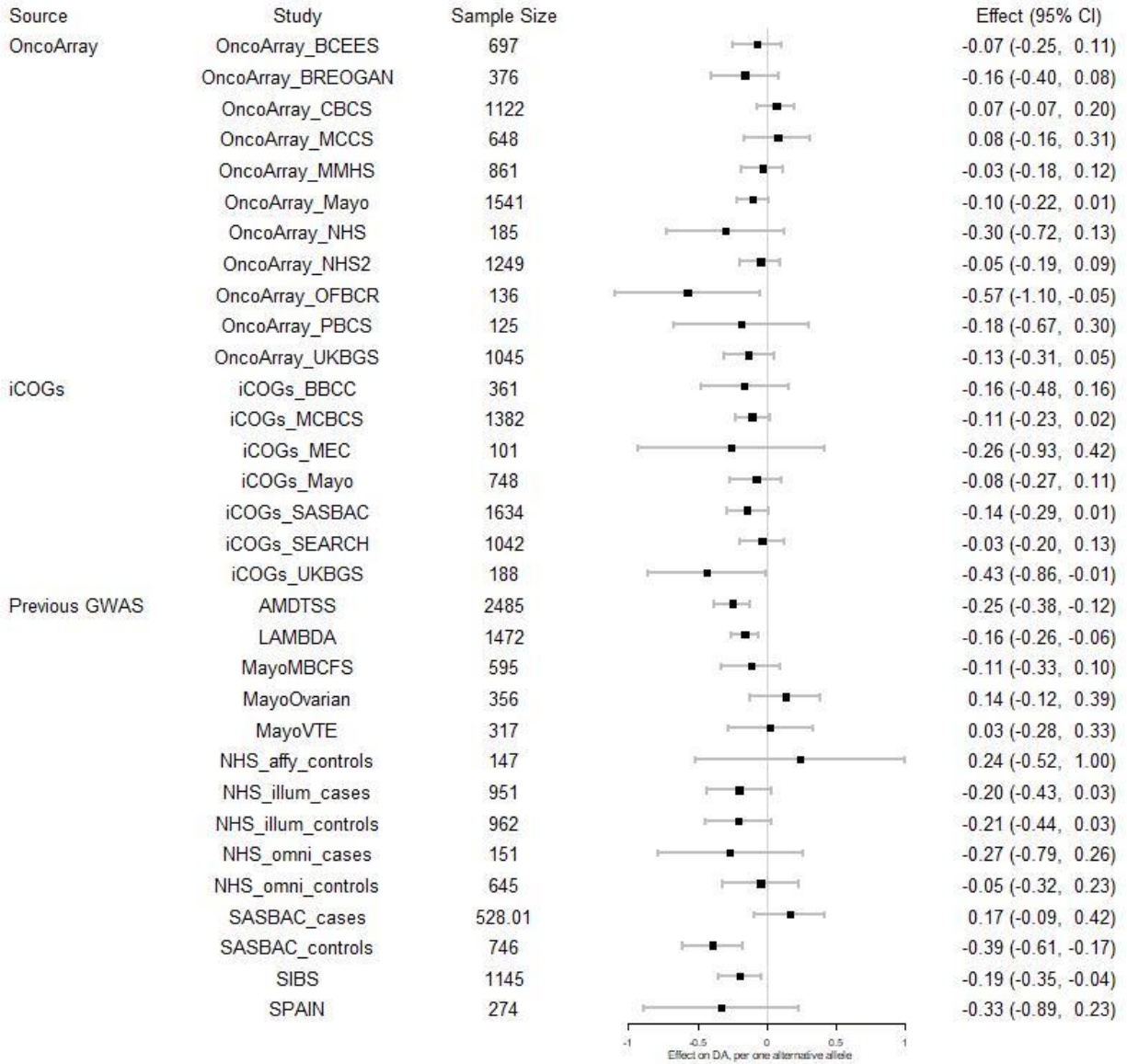


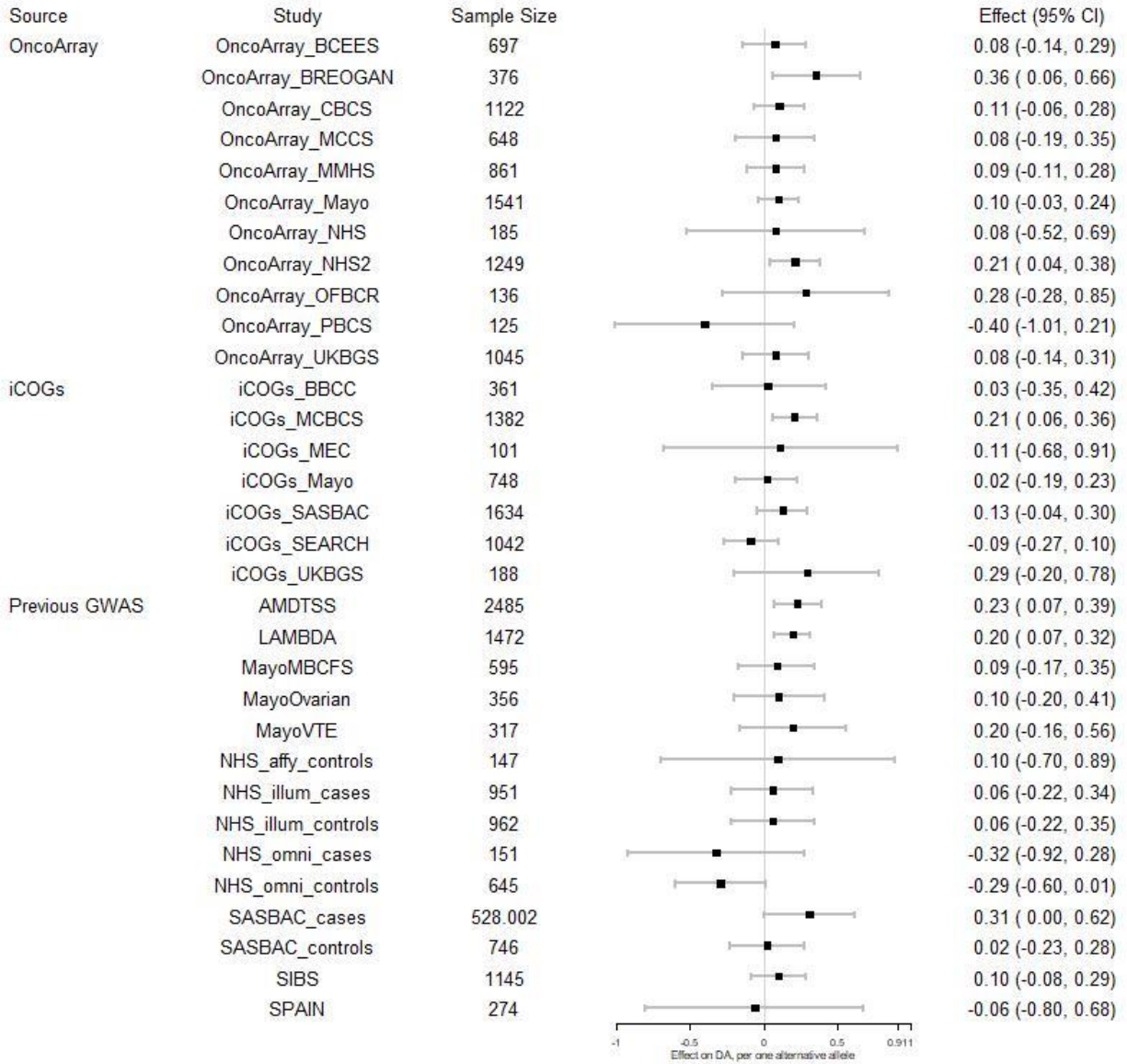
Forest Plot for SNP rs7297051, GWAS Meta-Analysis, Mammographic Dense Area



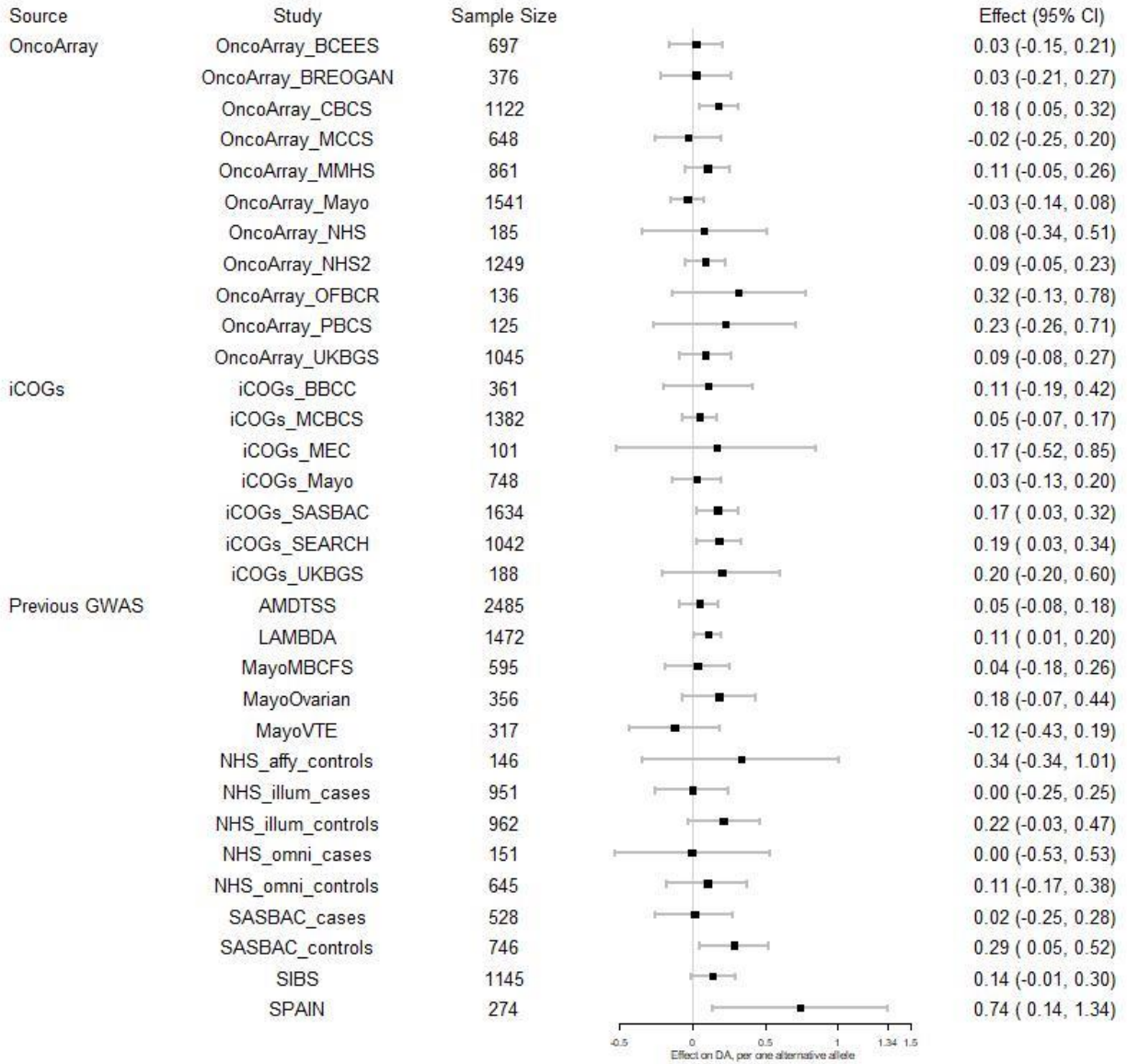
Forest Plot for SNP rs833472, GWAS Meta-Analysis, Mammographic Dense Area


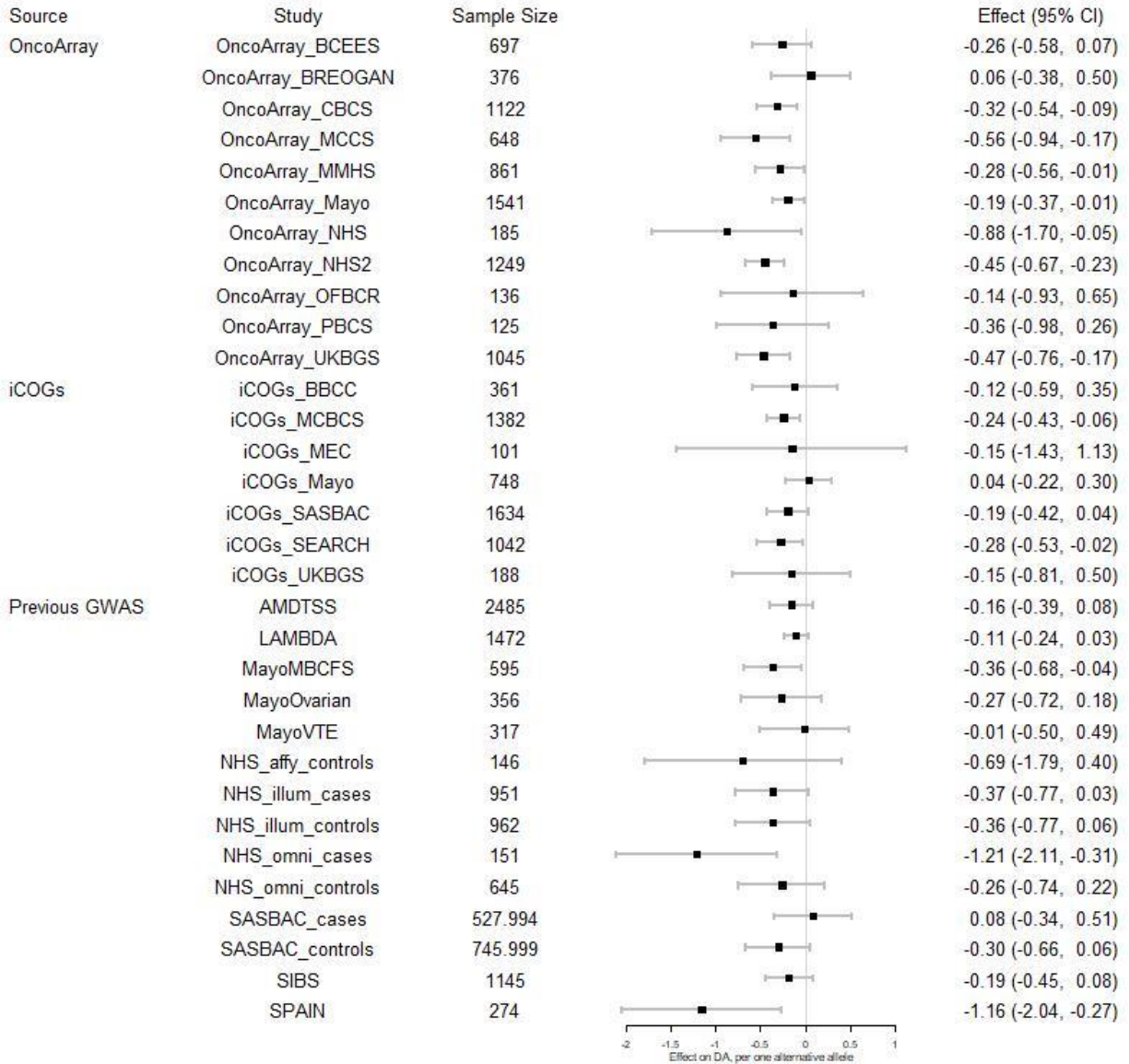
Forest Plot for SNP rs1231281, GWAS Meta-Analysis, Mammographic Dense Area



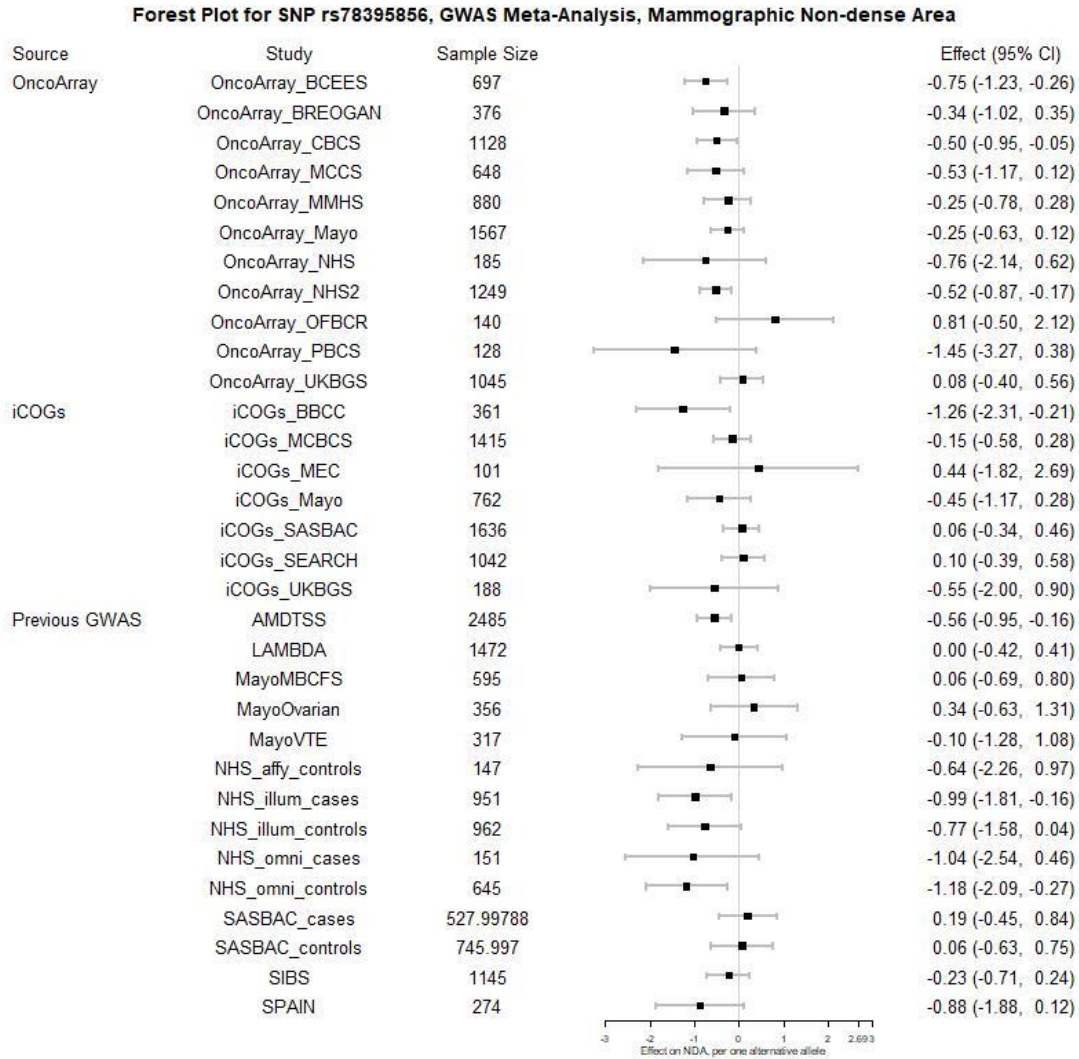
Forest Plot for SNP rs17789629, GWAS Meta-Analysis, Mammographic Dense Area


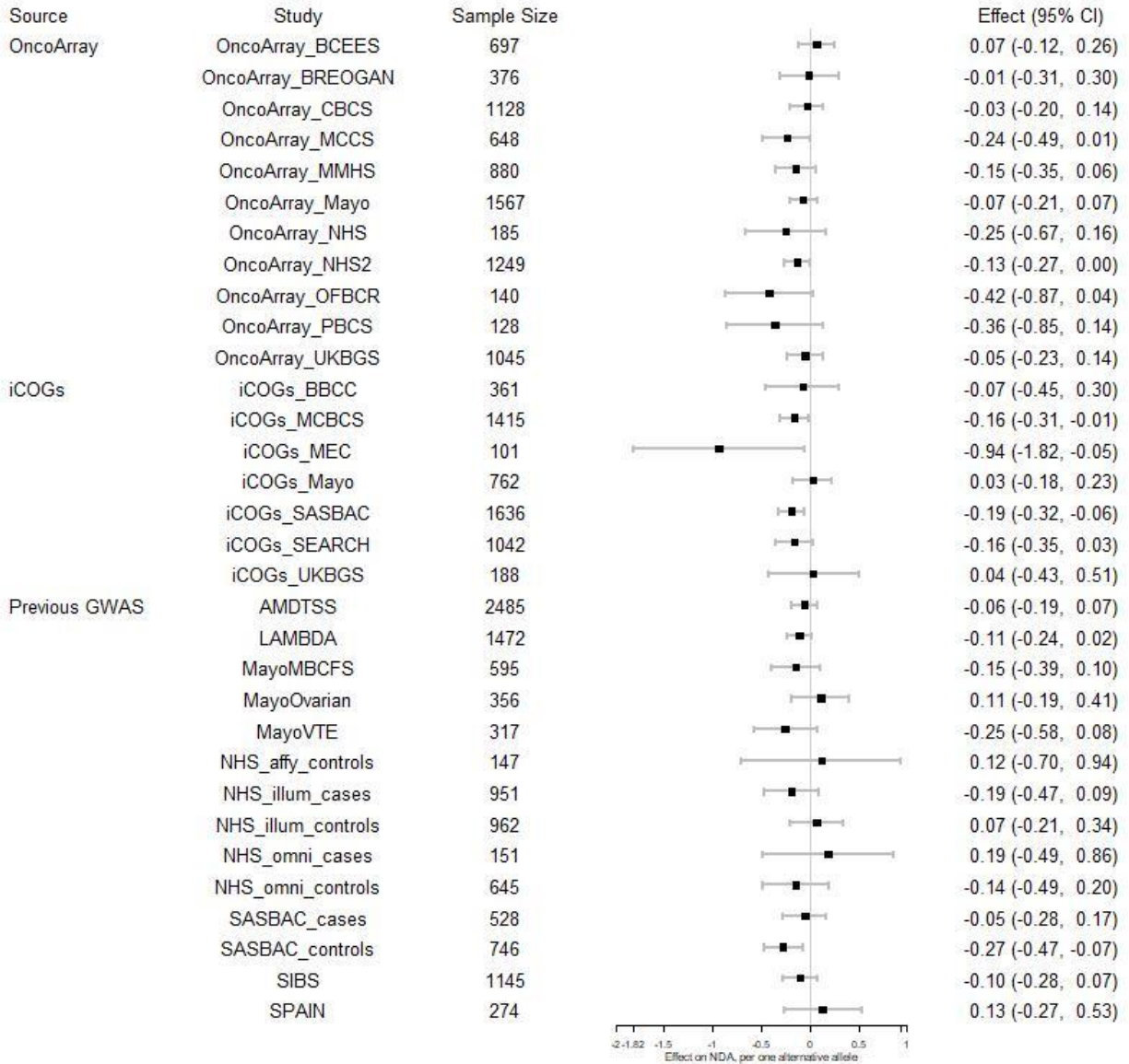
Forest Plot for SNP rs34066050, GWAS Meta-Analysis, Mammographic Dense Area



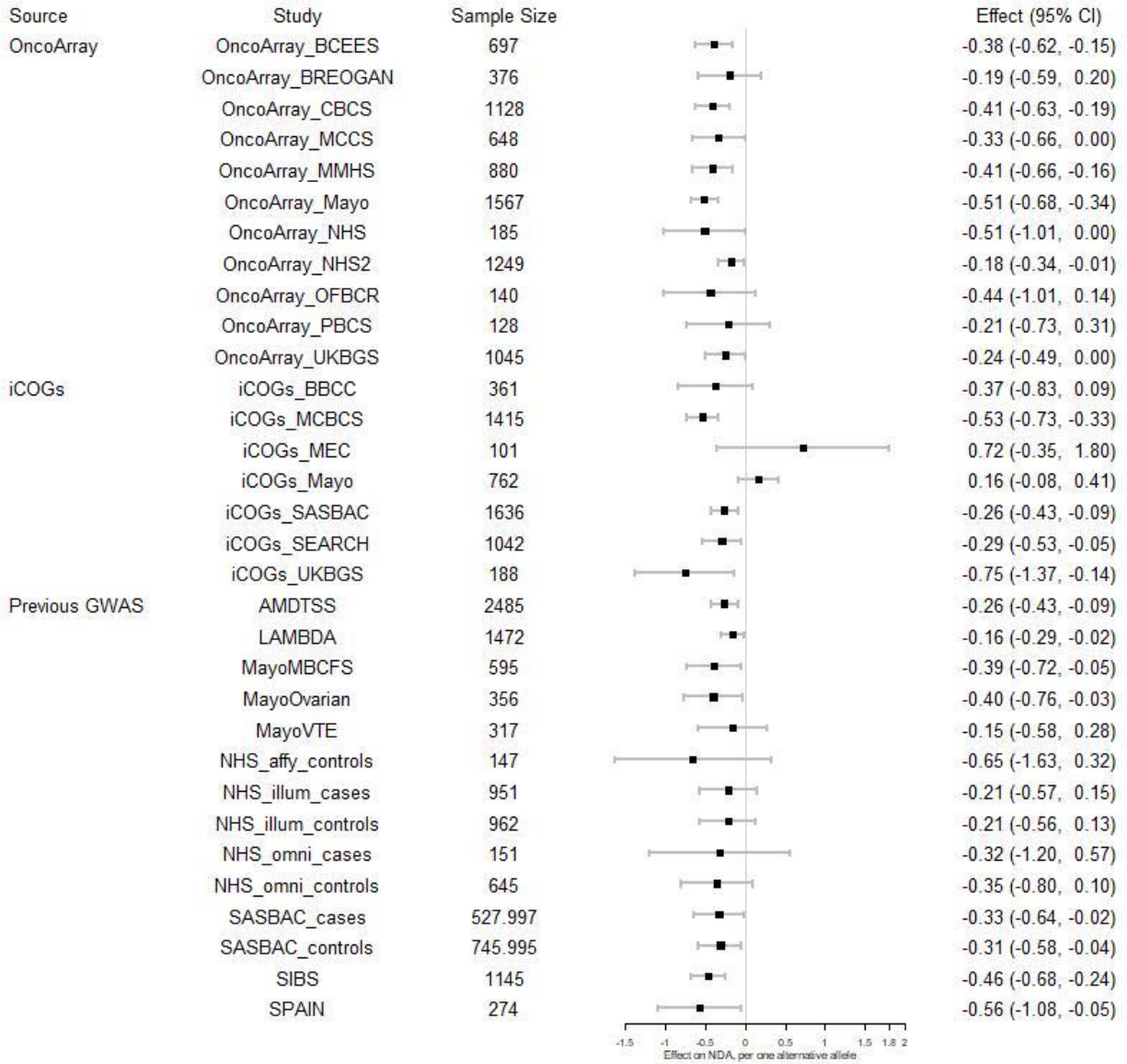
Forest Plot for SNP rs6001939, GWAS Meta-Analysis, Mammographic Dense Area


Supplementary Figure 2.7. Forest plots presenting the GWAS meta-analysis results of the lead SNP of six genome-wide significant loci of NDA. In each plot, the study name, sample size, beta estimate and 95% confidence interval for each participating study is shown. Studies with less than 100 individuals are not shown on the forest plots, although they were still included in the meta-analysis.

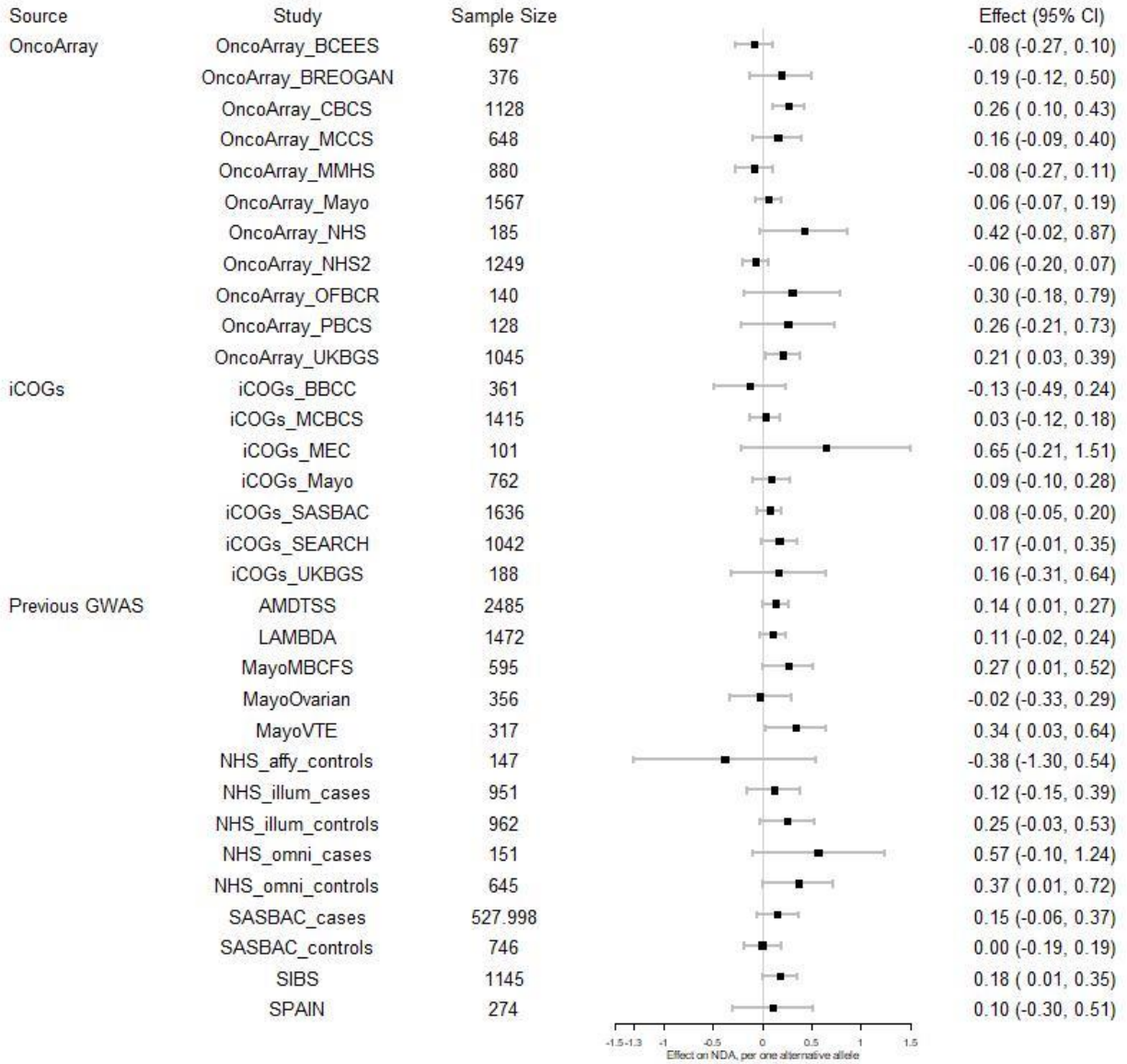


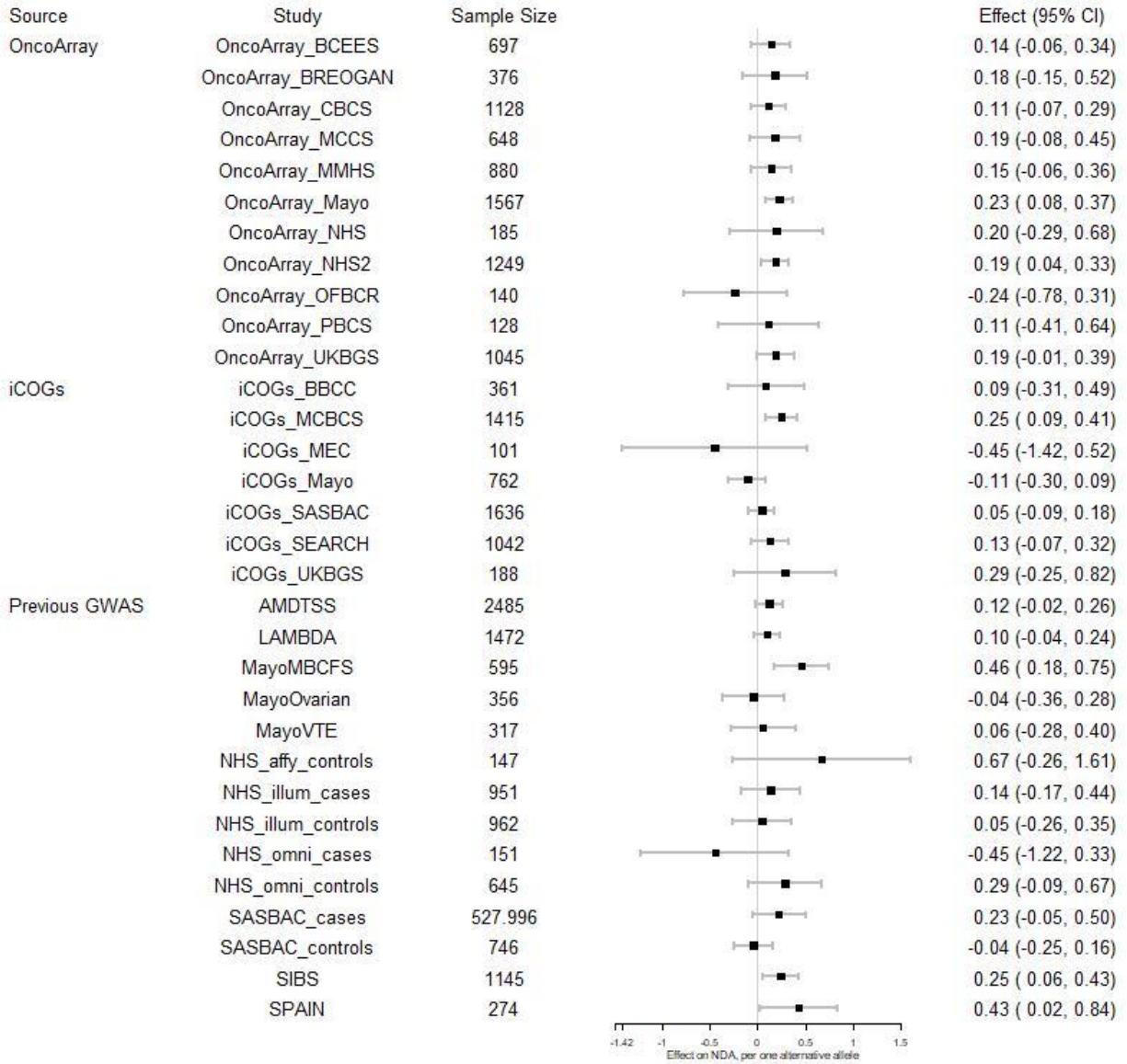
Forest Plot for SNP rs413472, GWAS Meta-Analysis, Mammographic Non-dense Area


Forest Plot for SNP rs16885613, GWAS Meta-Analysis, Mammographic Non-dense Area

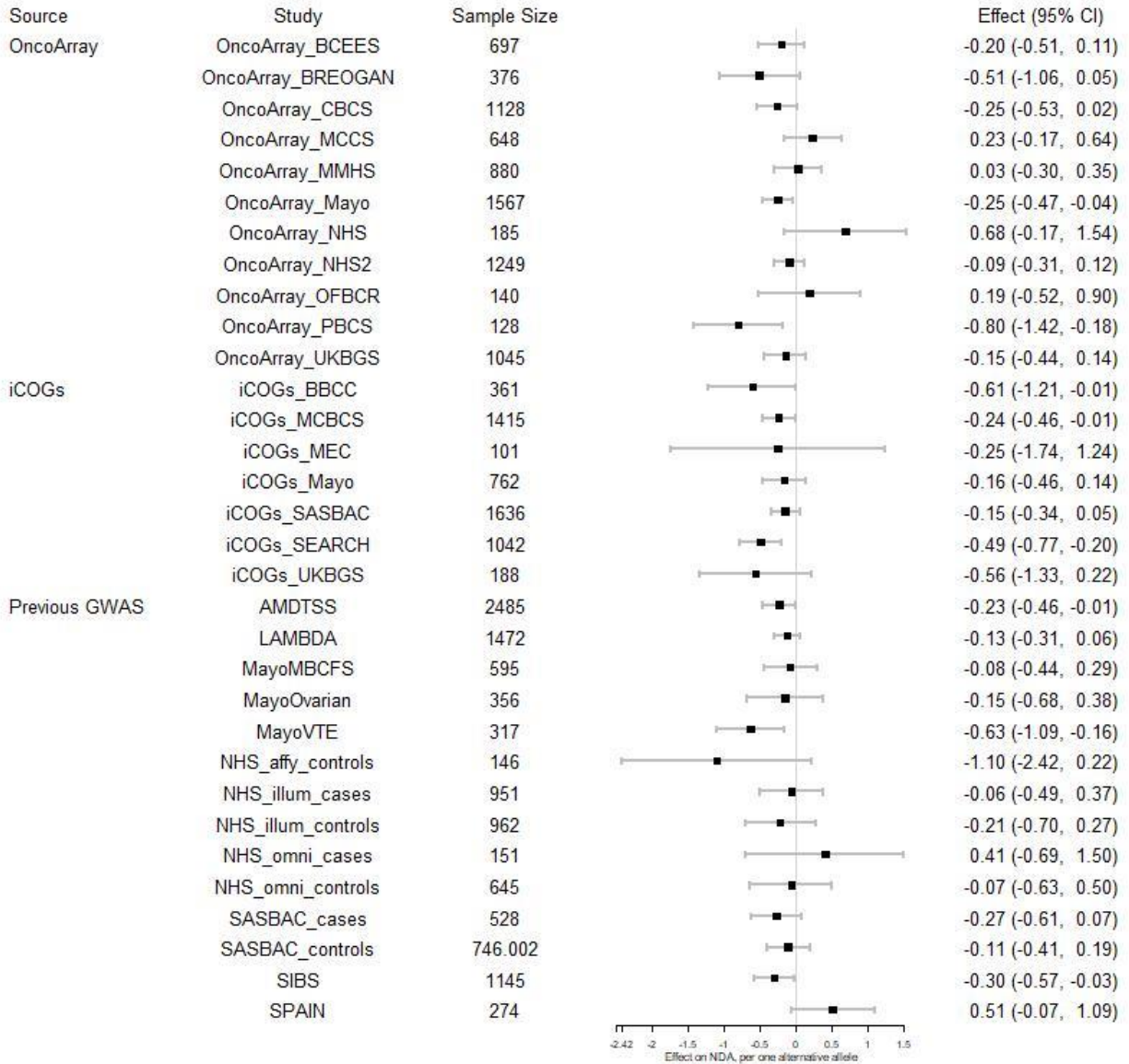


Forest Plot for SNP rs2138555, GWAS Meta-Analysis, Mammographic Non-dense Area

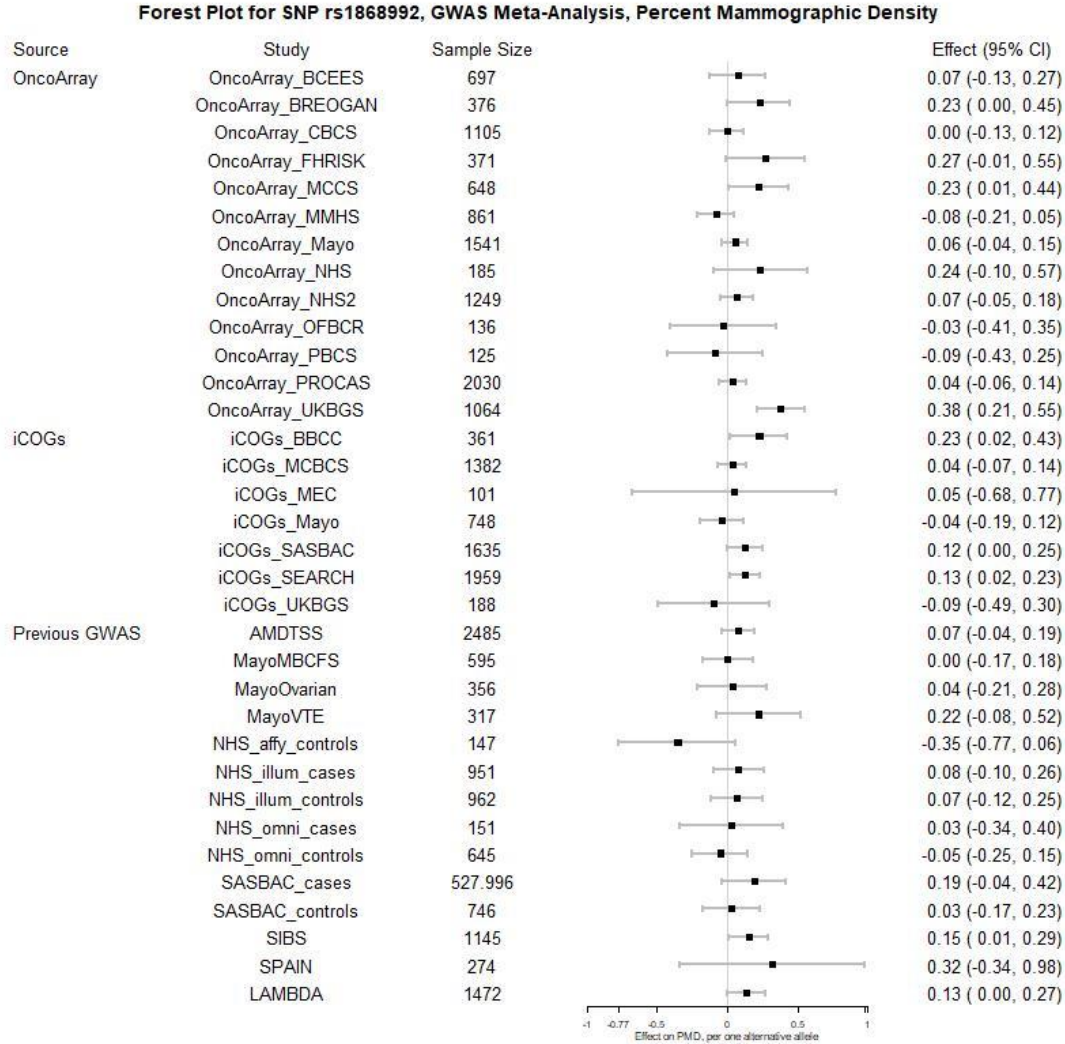


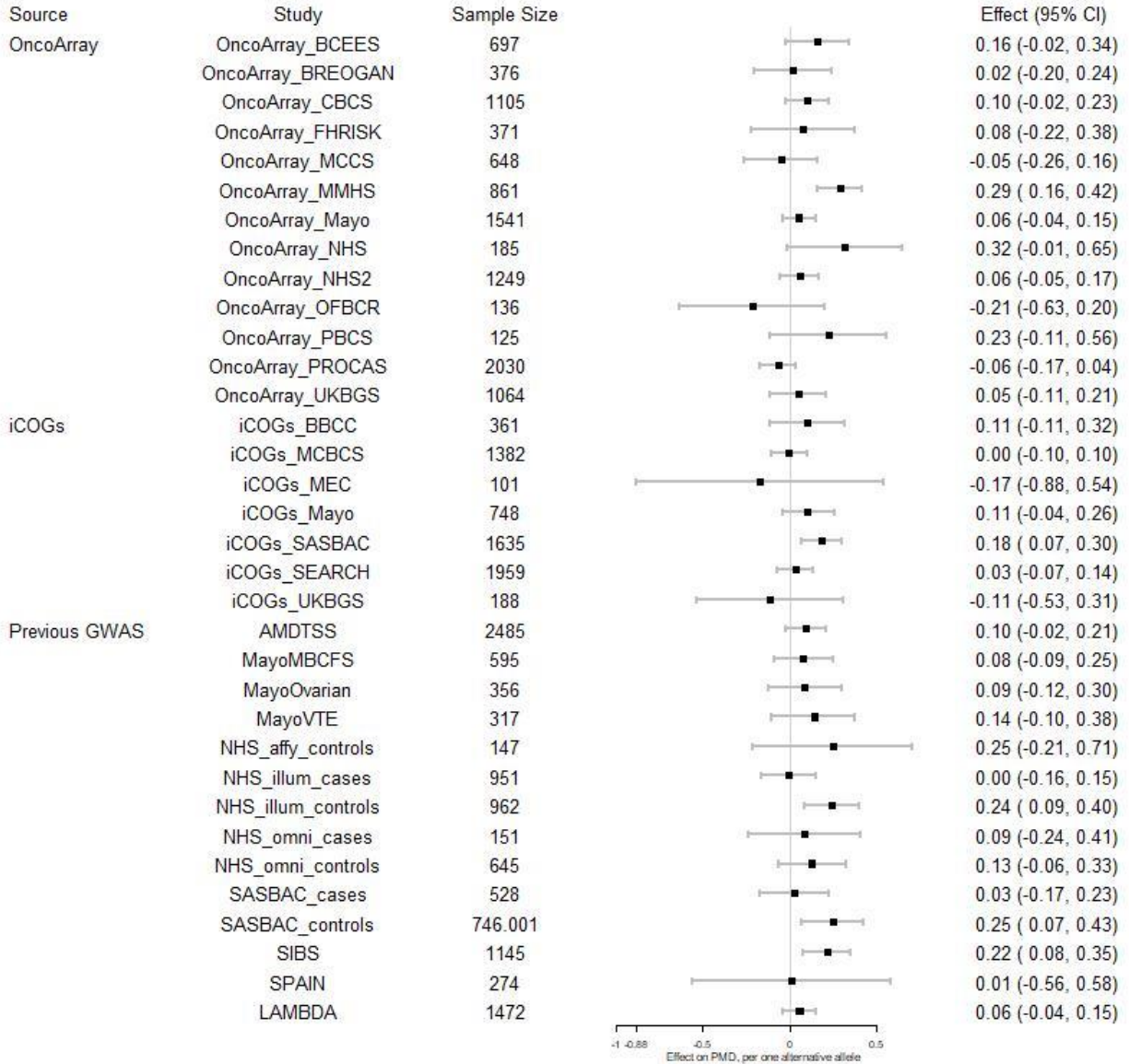
Forest Plot for SNP rs61938093, GWAS Meta-Analysis, Mammographic Non-dense Area


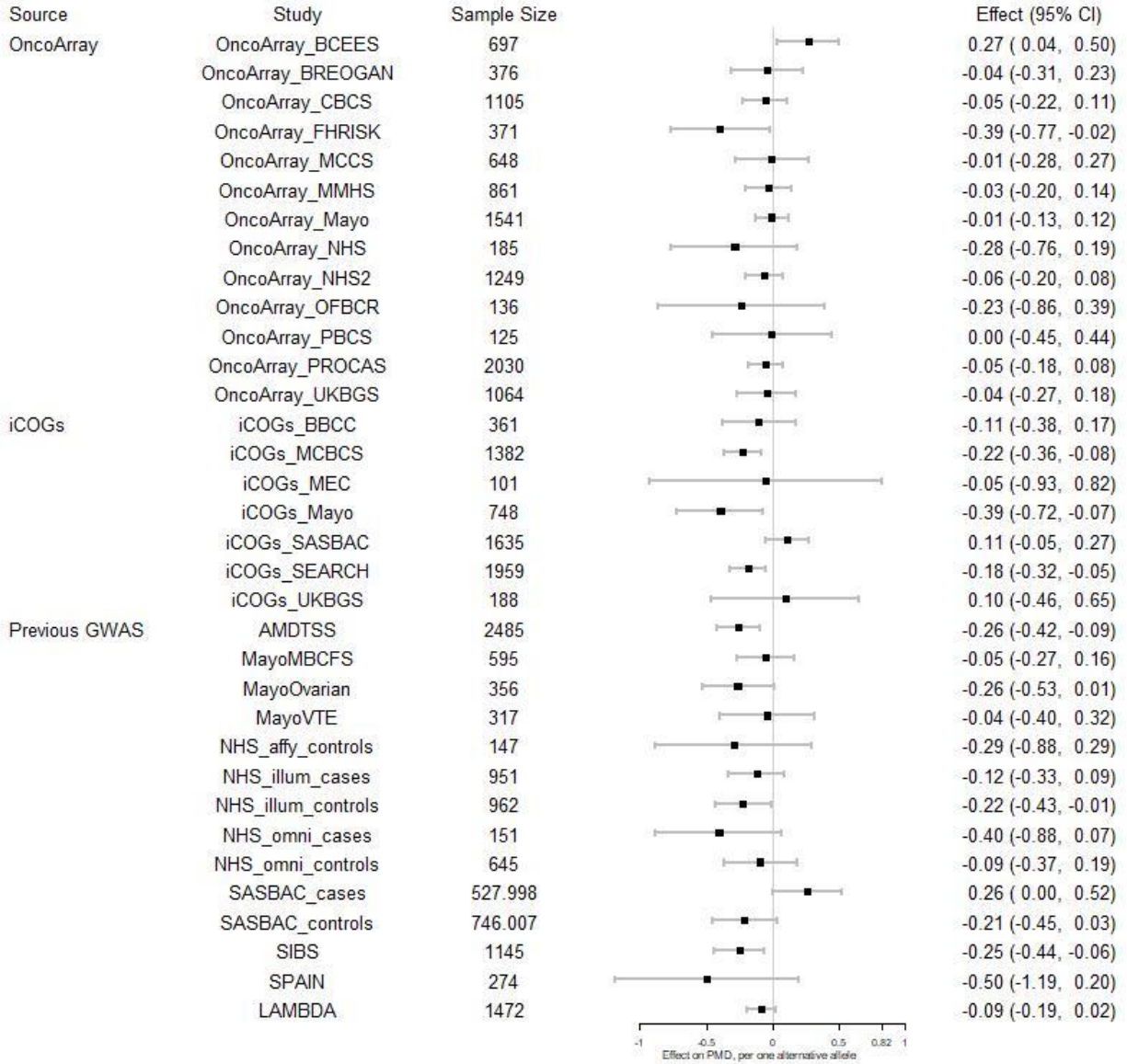
Forest Plot for SNP rs73169097, GWAS Meta-Analysis, Mammographic Non-dense Area

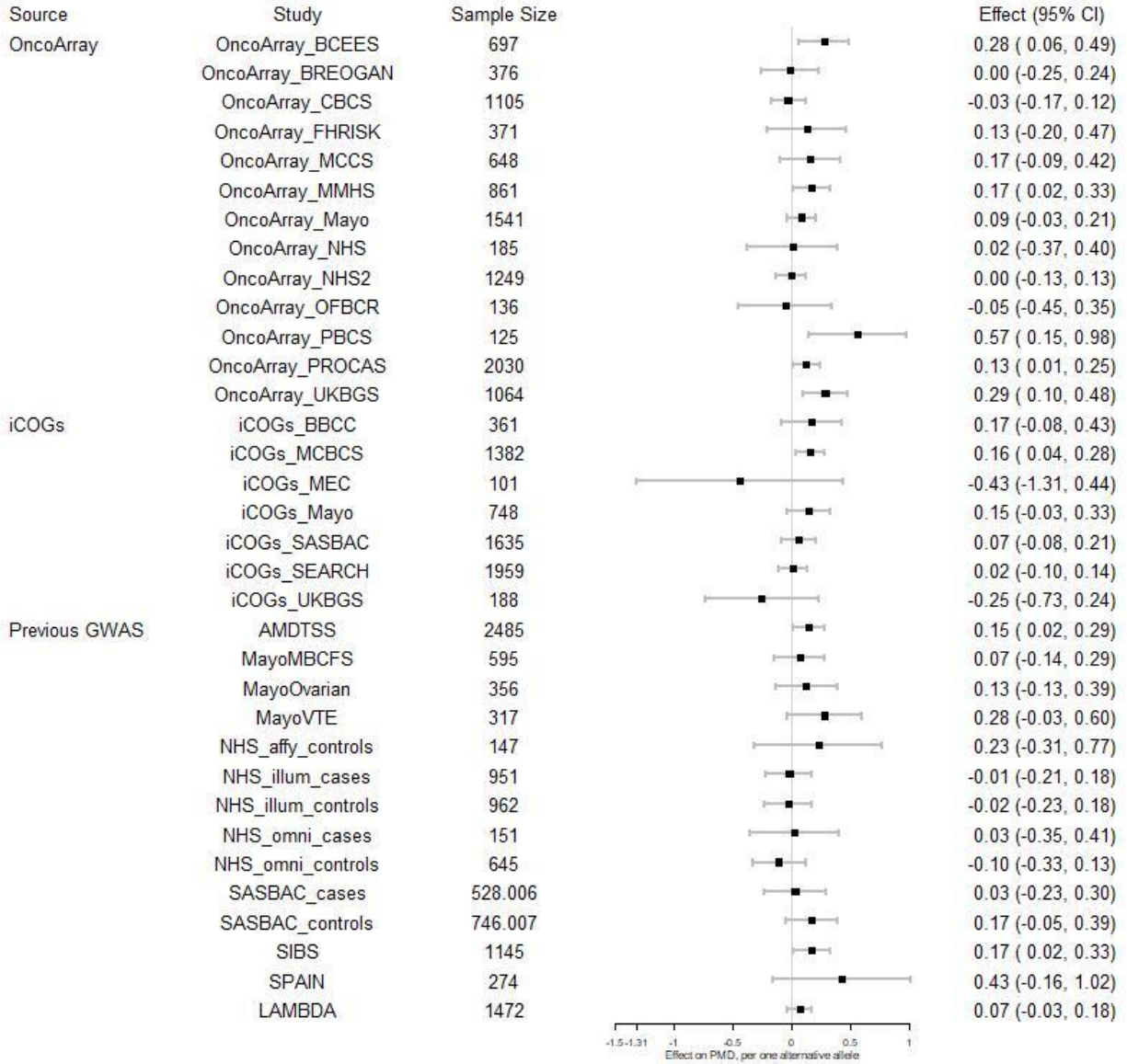


Supplementary Figure 2.8. Forest plots presenting the GWAS meta-analysis results of the lead SNP of fifteen genome-wide significant loci of PMD. In each plot, the study name, sample size, beta estimate and 95% confidence interval for each participating study is shown. Studies with less than 100 individuals are not shown on the forest plots, although they were still included in the meta-analysis.

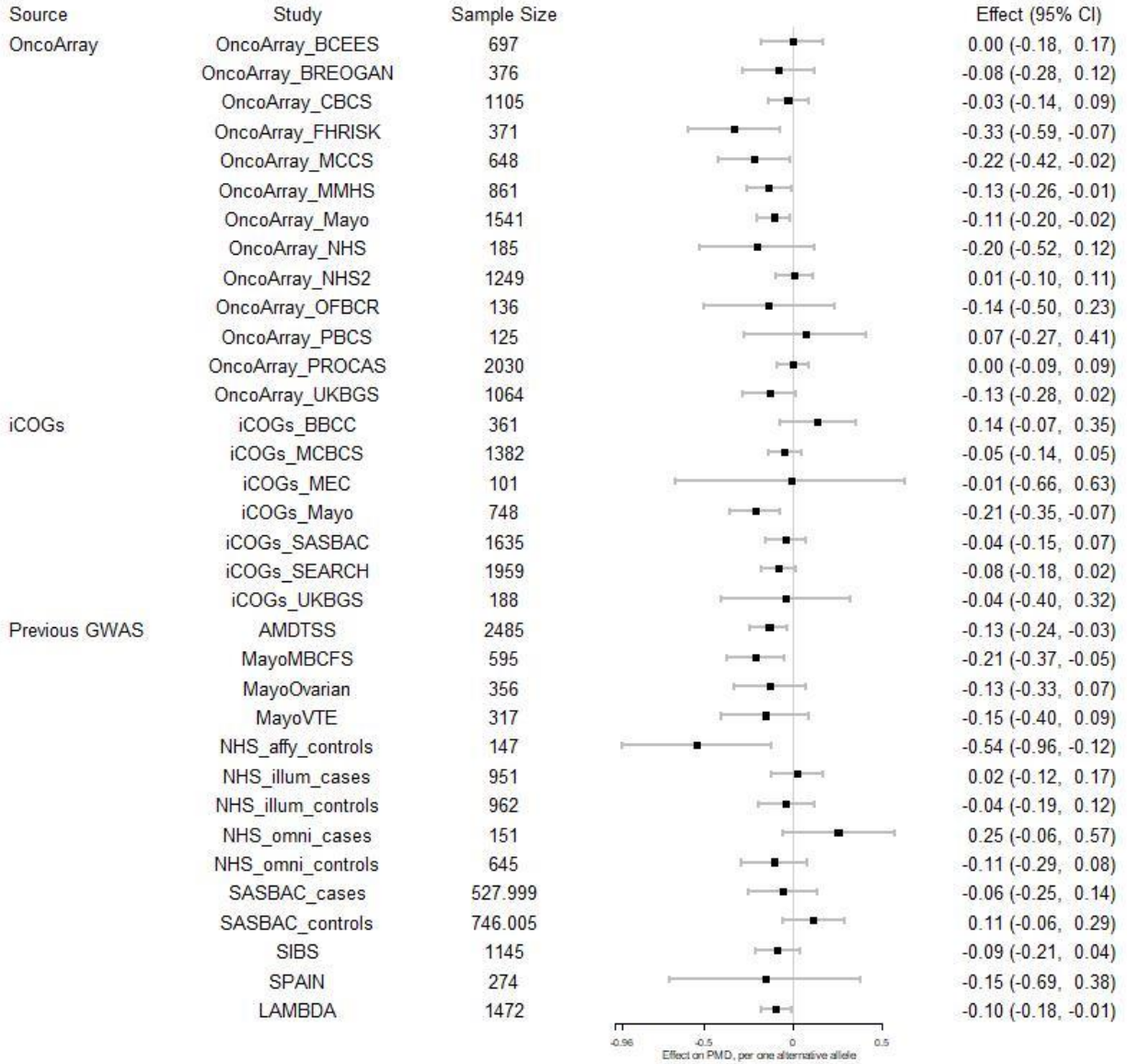


Forest Plot for SNP rs335189, GWAS Meta-Analysis, Percent Mammographic Density


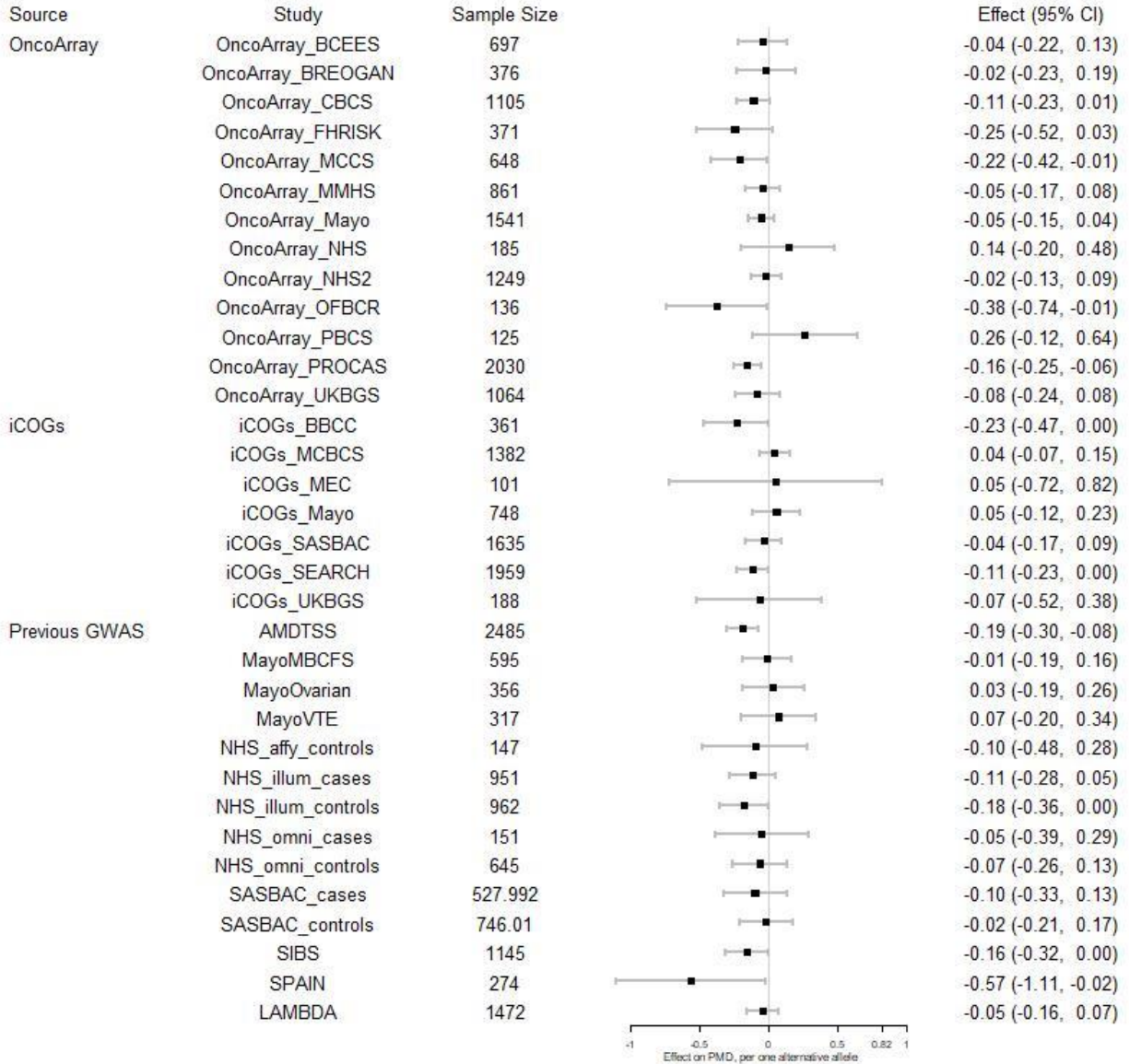
Forest Plot for SNP rs76876329, GWAS Meta-Analysis, Percent Mammographic Density


Forest Plot for SNP rs11745230, GWAS Meta-Analysis, Percent Mammographic Density


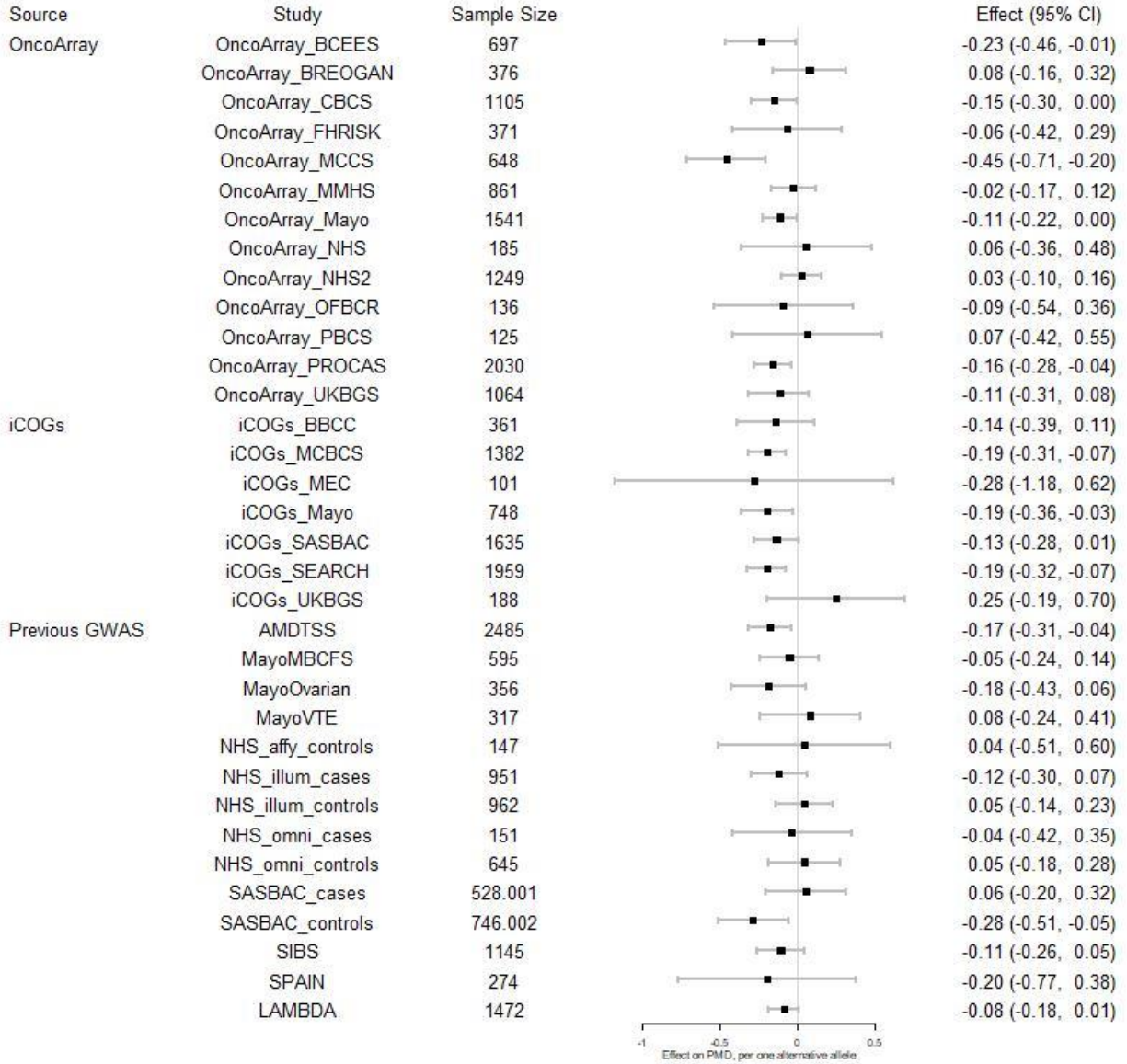
Forest Plot for SNP rs2112670, GWAS Meta-Analysis, Percent Mammographic Density

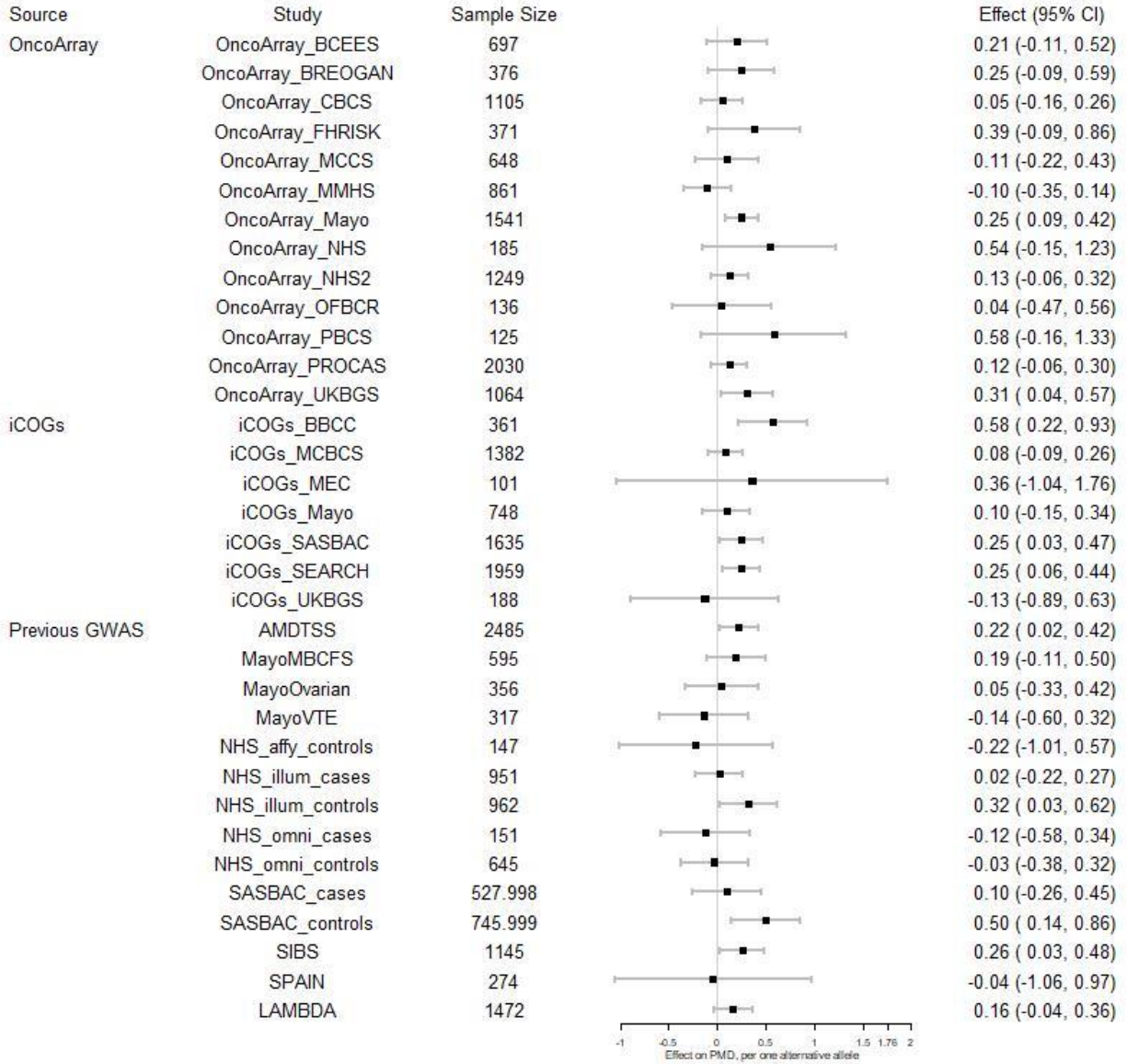


Forest Plot for SNP rs3819405, GWAS Meta-Analysis, Percent Mammographic Density

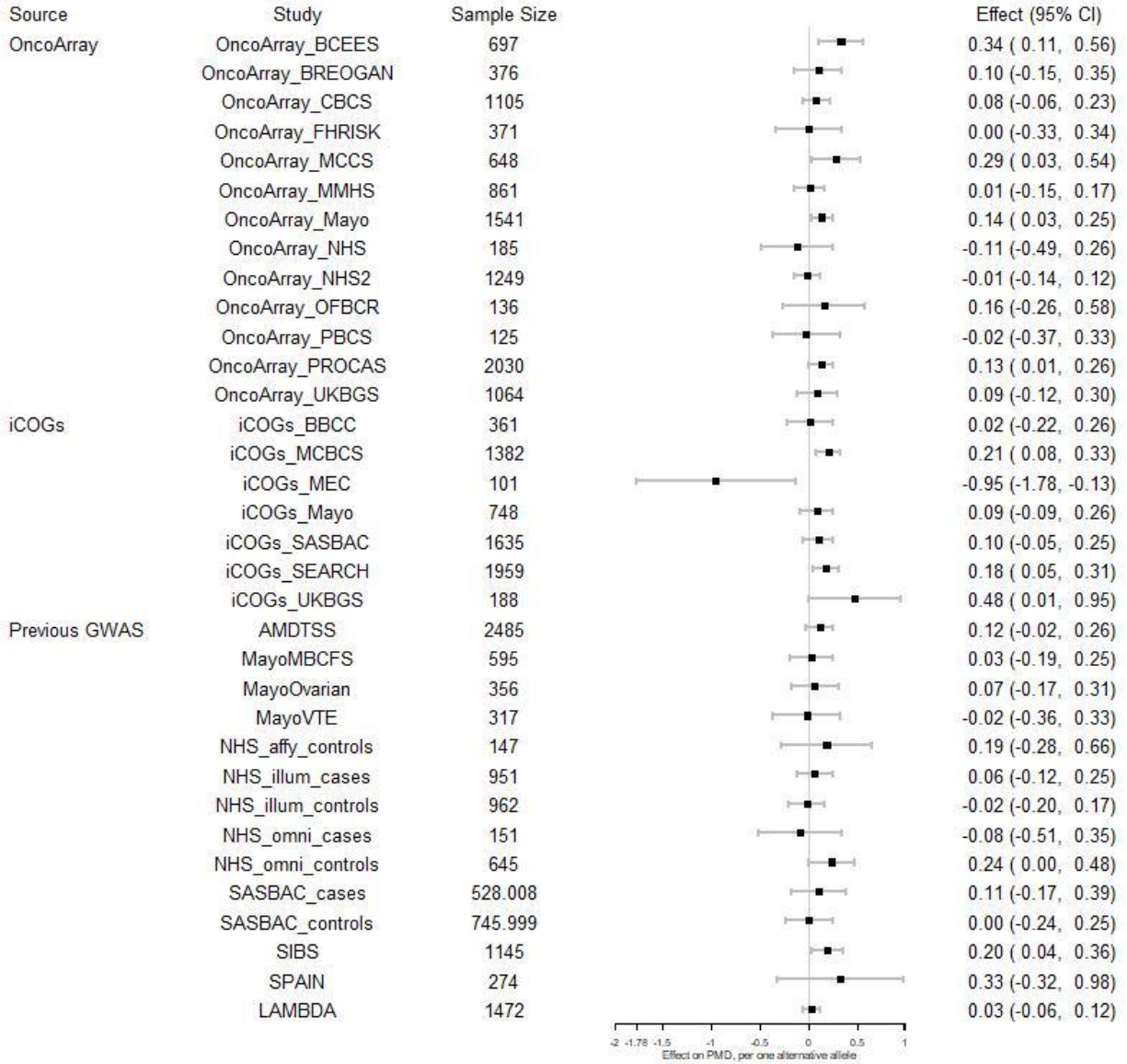


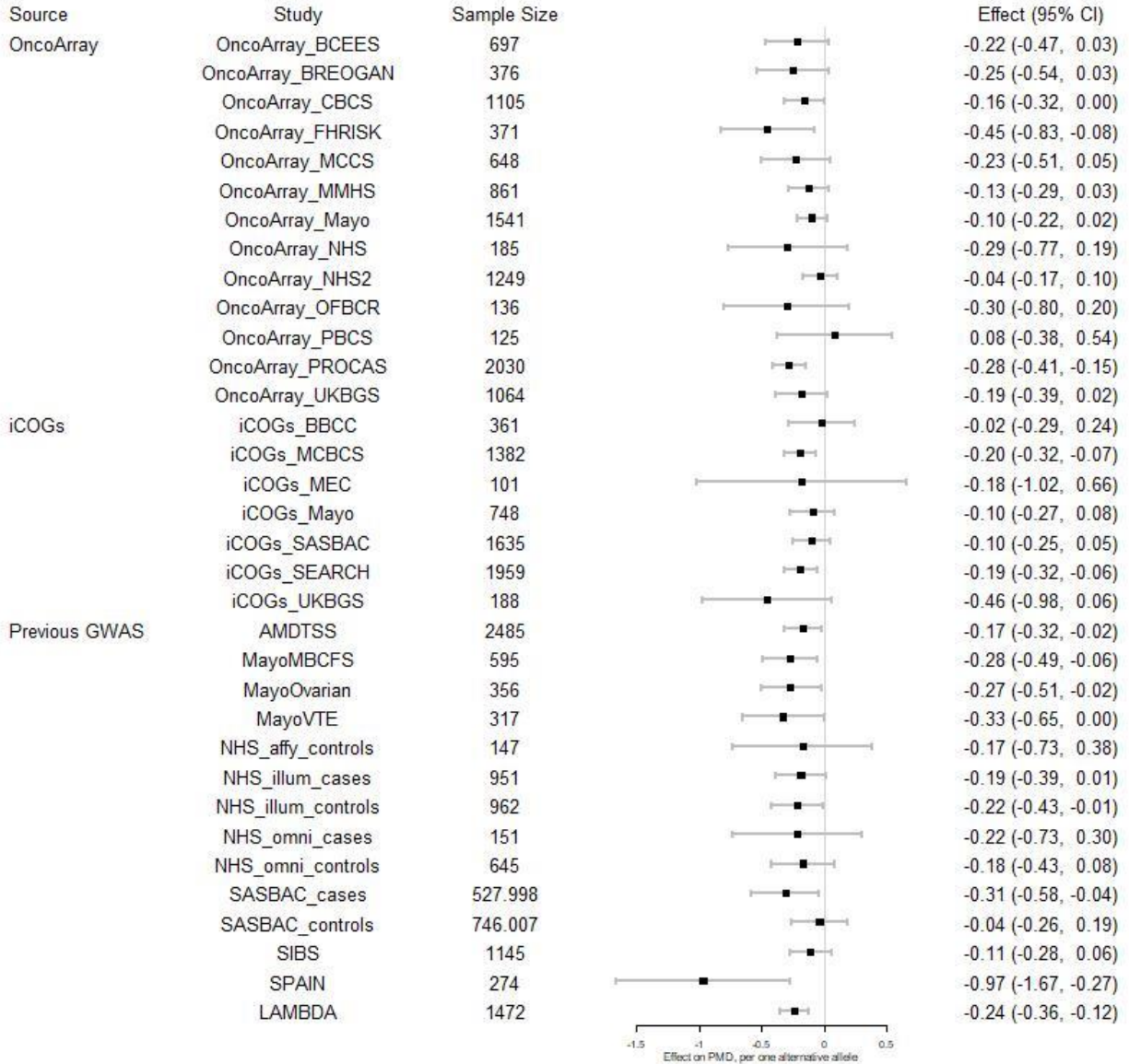
Forest Plot for SNP rs4897107, GWAS Meta-Analysis, Percent Mammographic Density

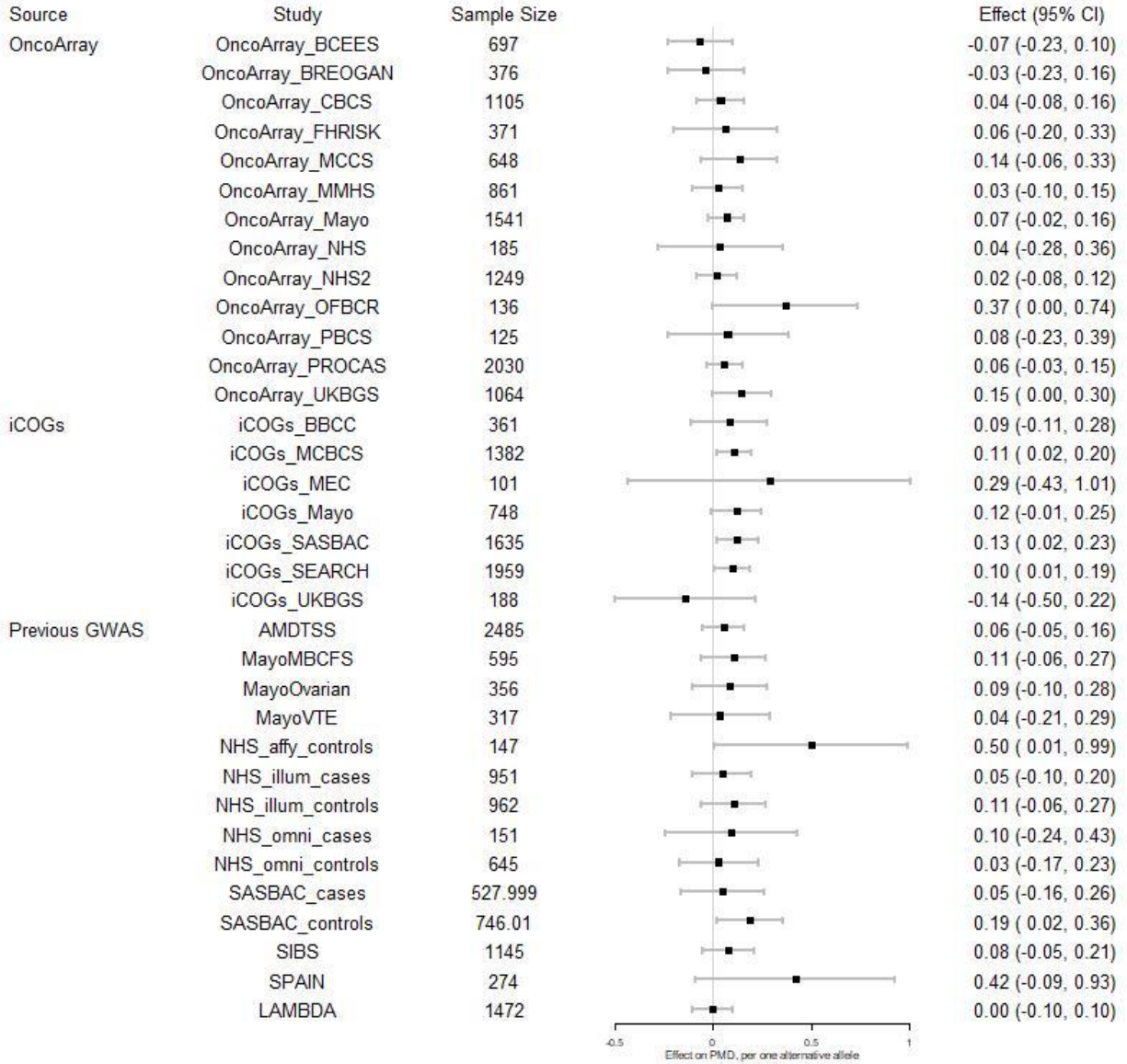


Forest Plot for SNP rs9397436, GWAS Meta-Analysis, Percent Mammographic Density


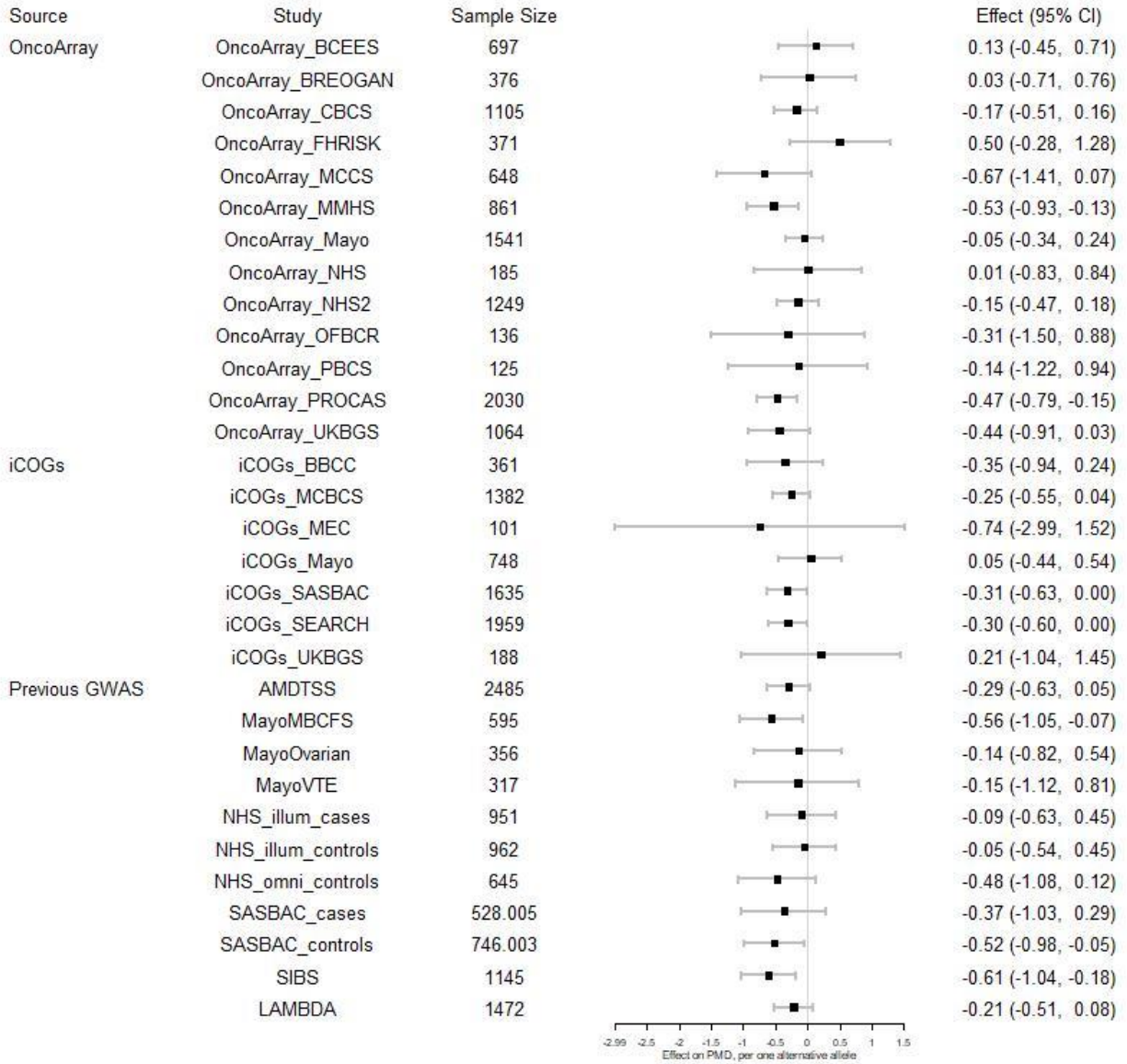
Forest Plot for SNP rs10087804, GWAS Meta-Analysis, Percent Mammographic Density



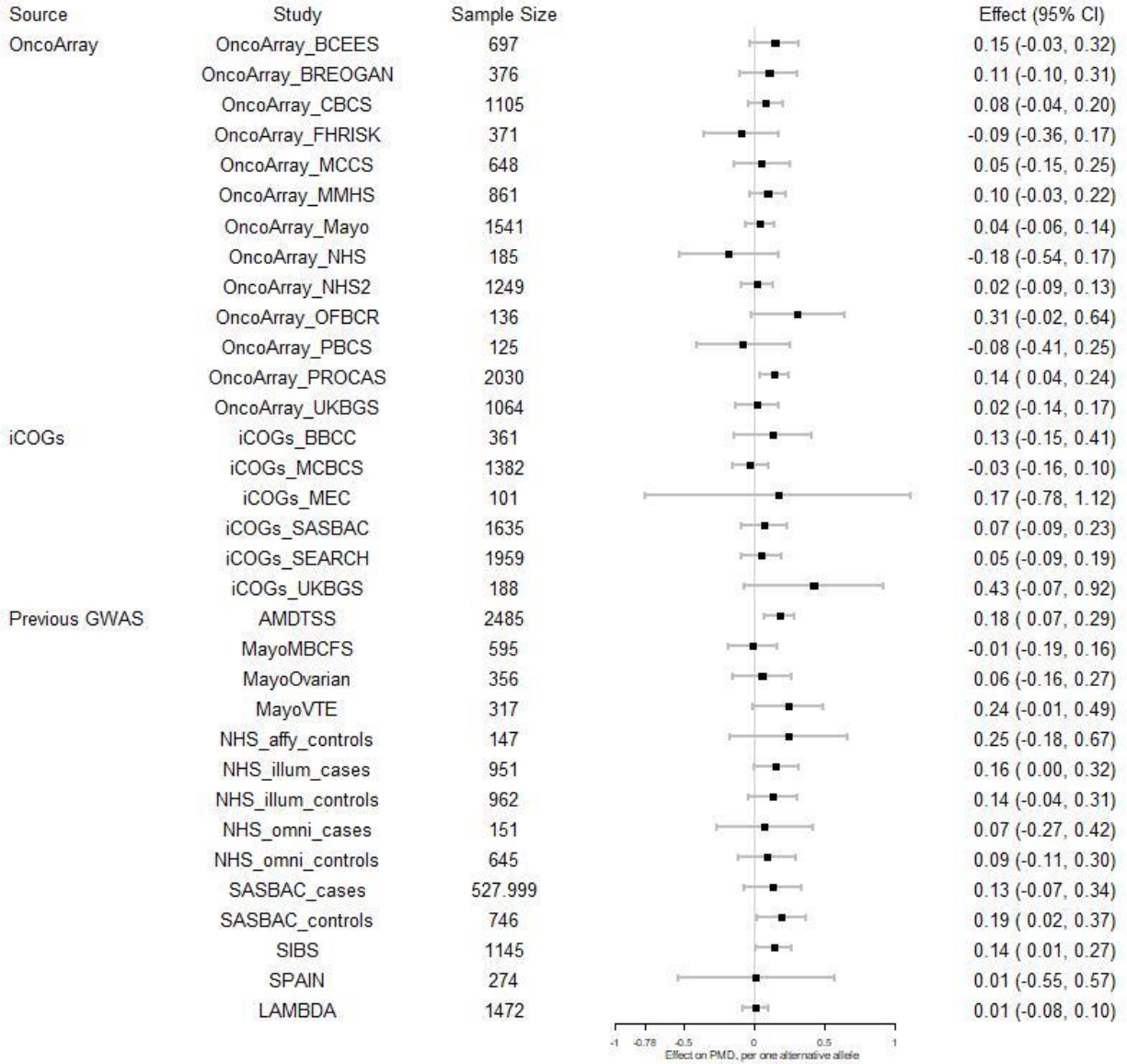
Forest Plot for SNP rs10995187, GWAS Meta-Analysis, Percent Mammographic Density


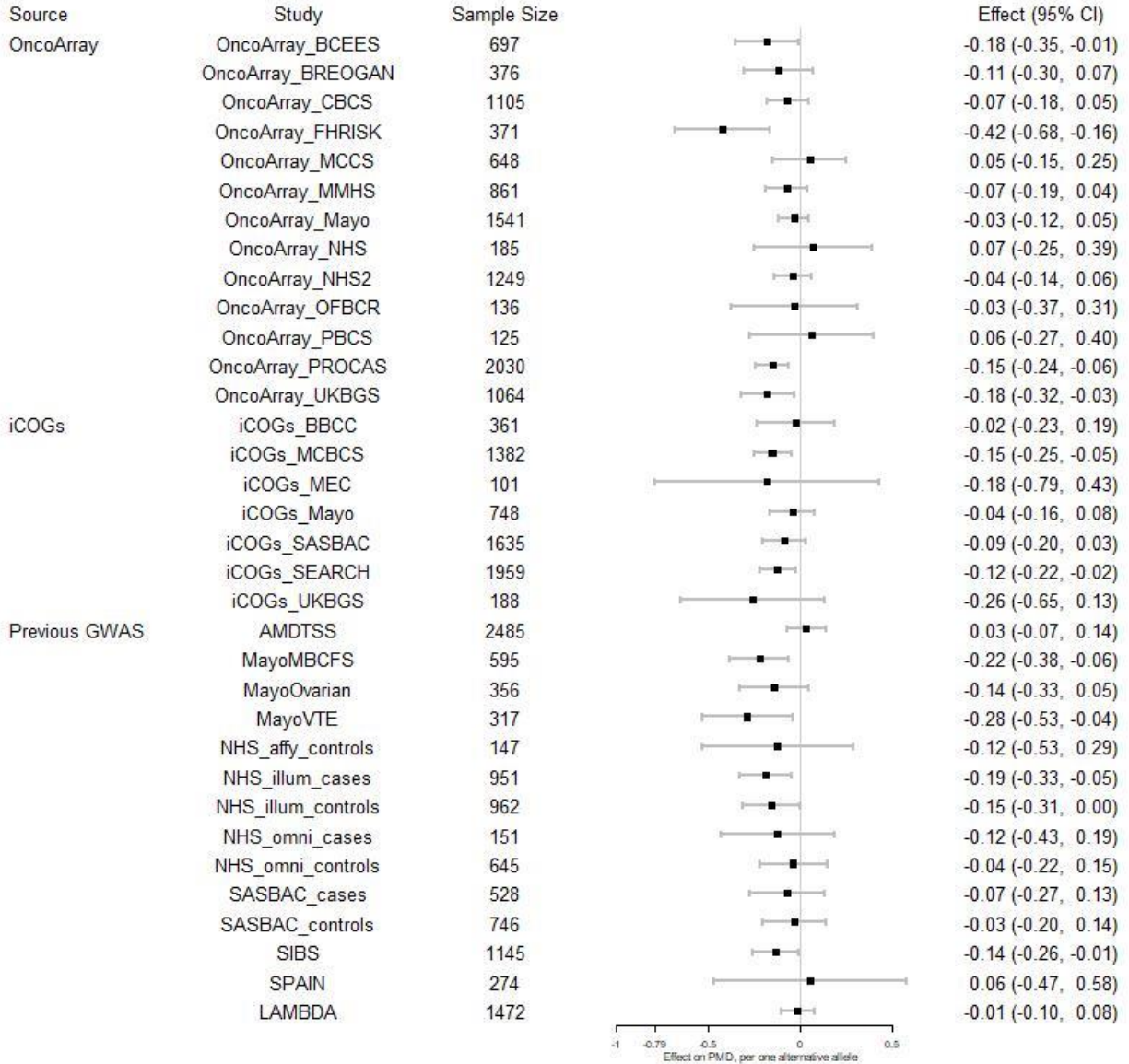
Forest Plot for SNP rs4980383, GWAS Meta-Analysis, Percent Mammographic Density


Forest Plot for SNP rs61941038, GWAS Meta-Analysis, Percent Mammographic Density

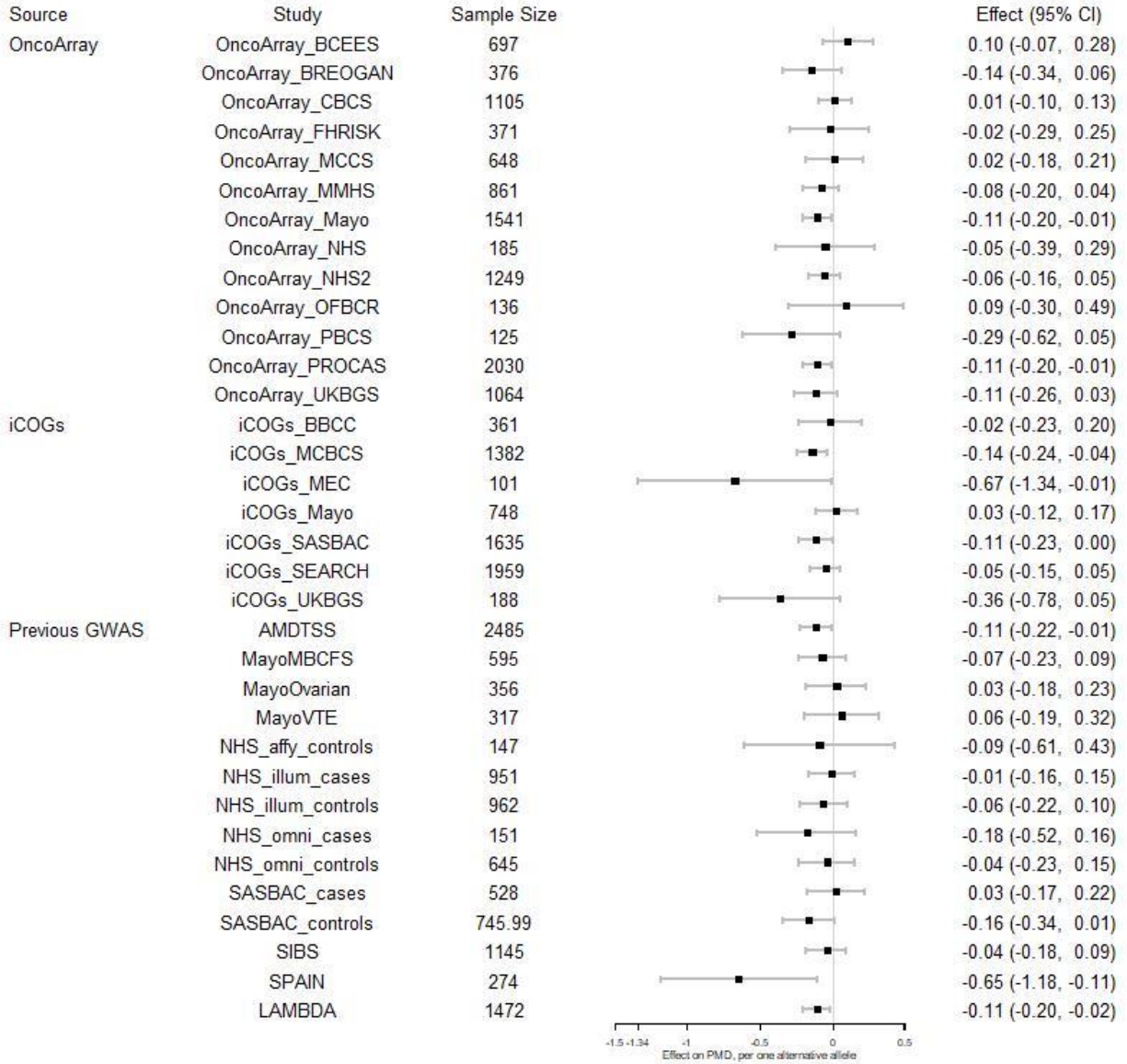


Forest Plot for SNP rs4499190, GWAS Meta-Analysis, Percent Mammographic Density

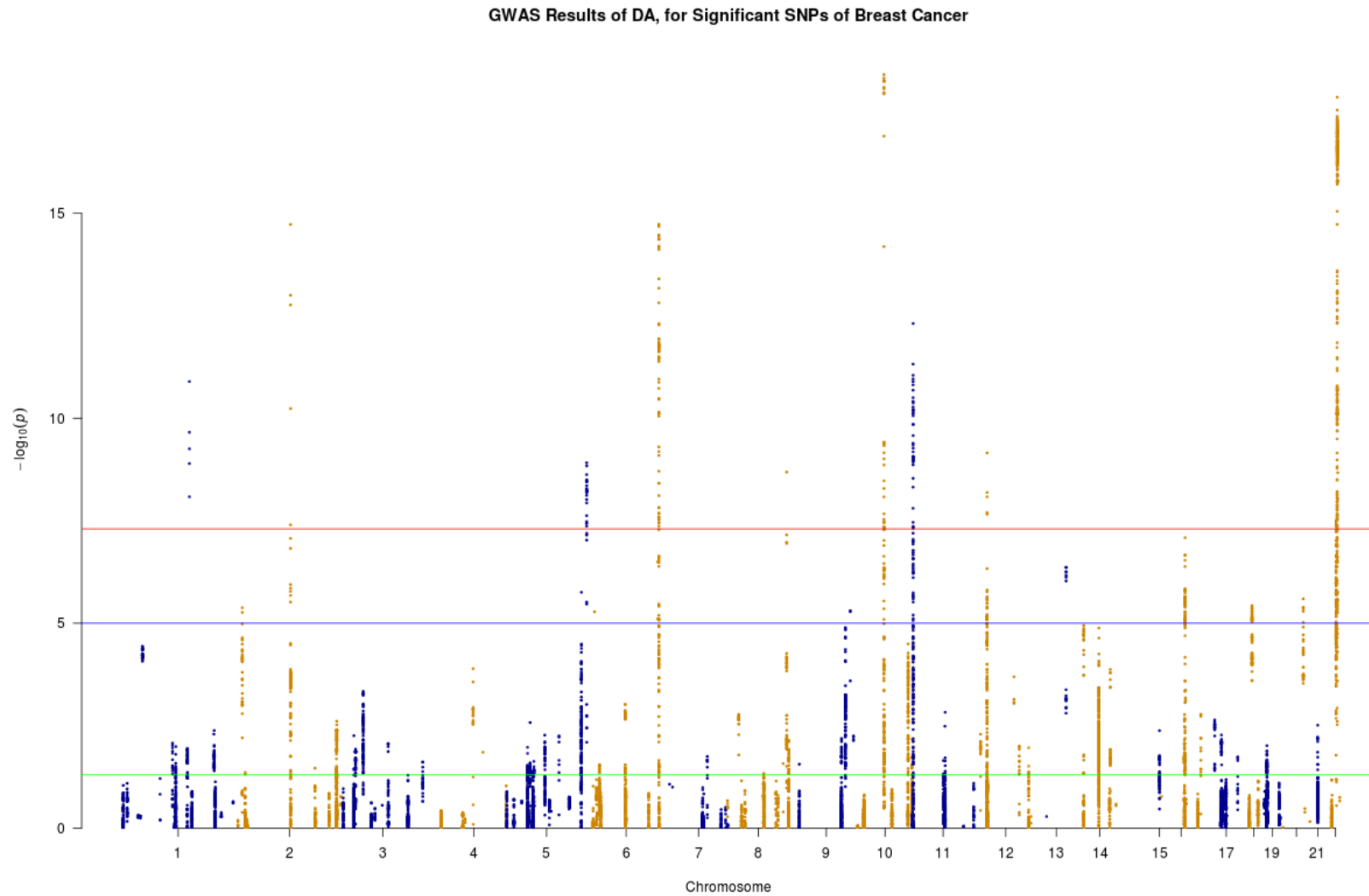


Forest Plot for SNP rs11646715, GWAS Meta-Analysis, Percent Mammographic Density


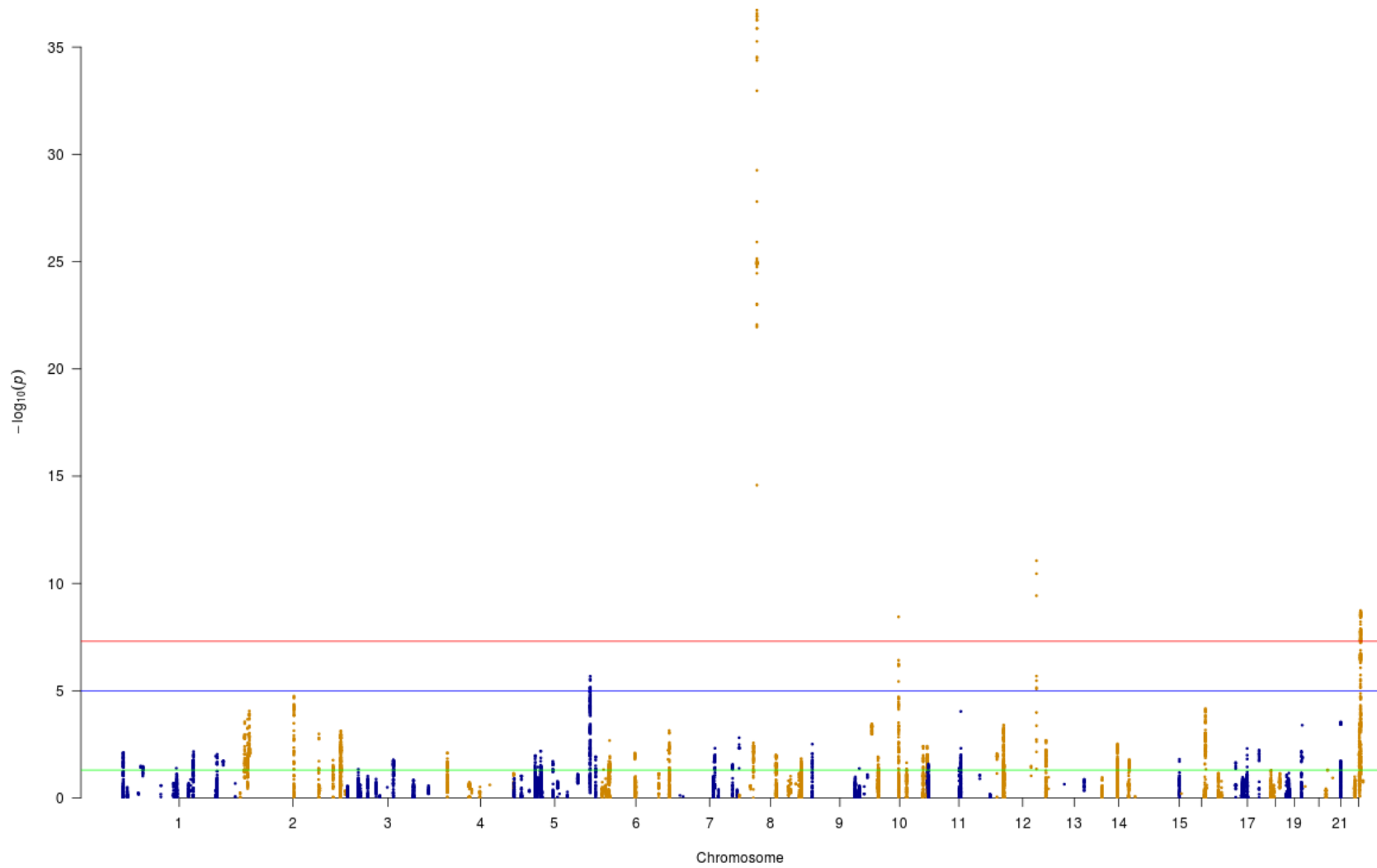
Forest Plot for SNP rs12462111, GWAS Meta-Analysis, Percent Mammographic Density



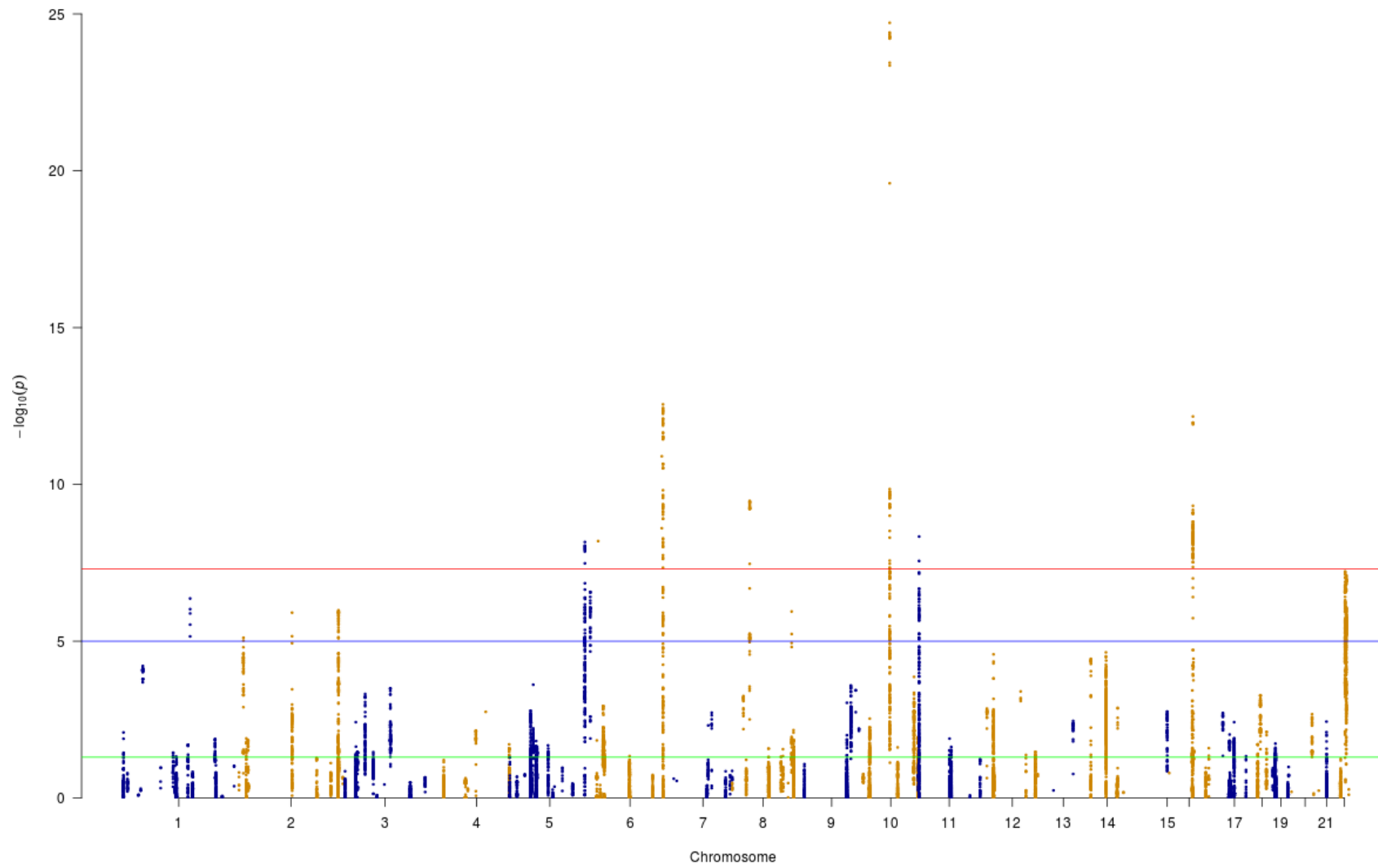
Supplementary Figure 2.9. Manhattan-like plots showing the association between previously identified breast cancer (overall, ER-positive and/or ER-negative) significant SNPs and the three MD phenotypes. P-value thresholds for genome-wide significance ($p < 5 \times 10^{-8}$, red line), suggestive significance ($p < 10^{-5}$, blue line) and nominal significance ($p < 0.05$, green line) are shown as horizontal lines.



GWAS Results of NDA, for Significant SNPs of Breast Cancer

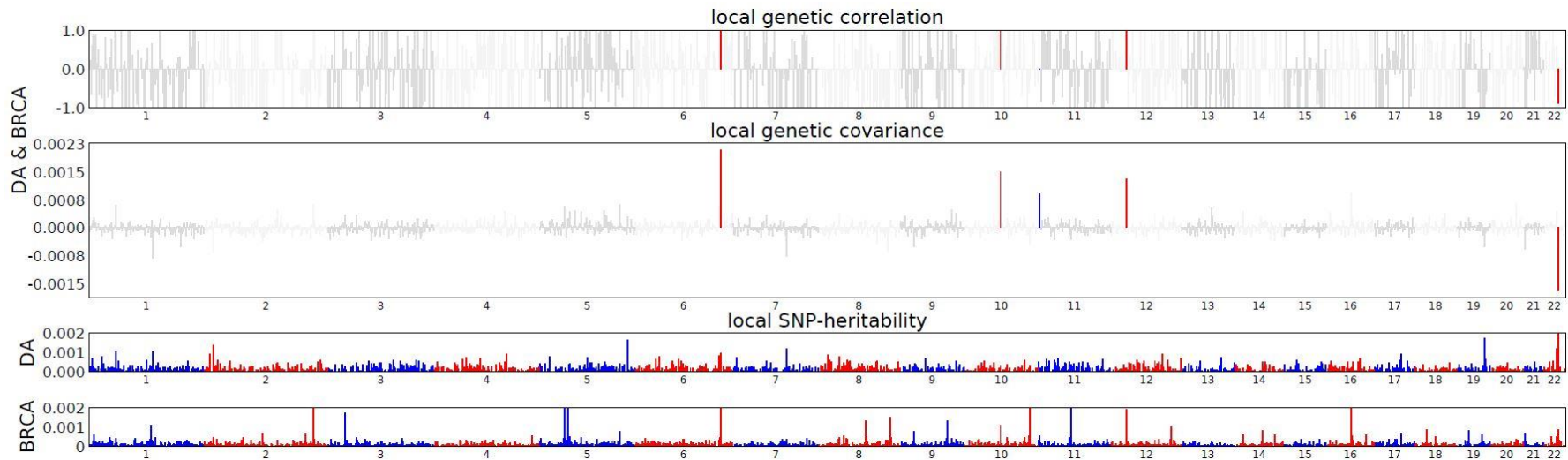


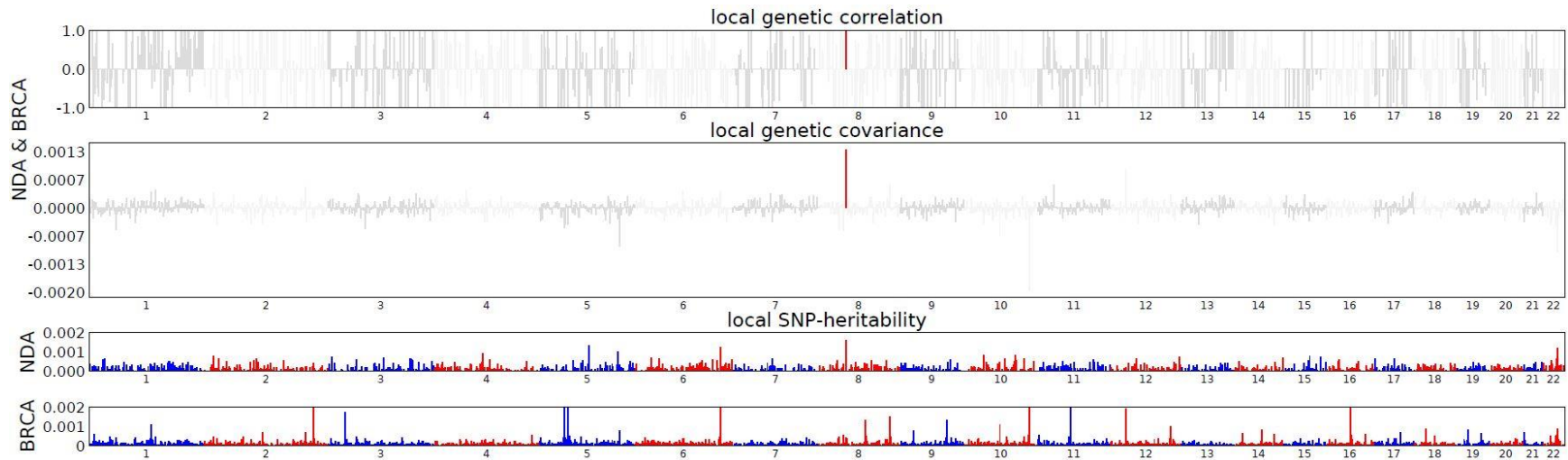
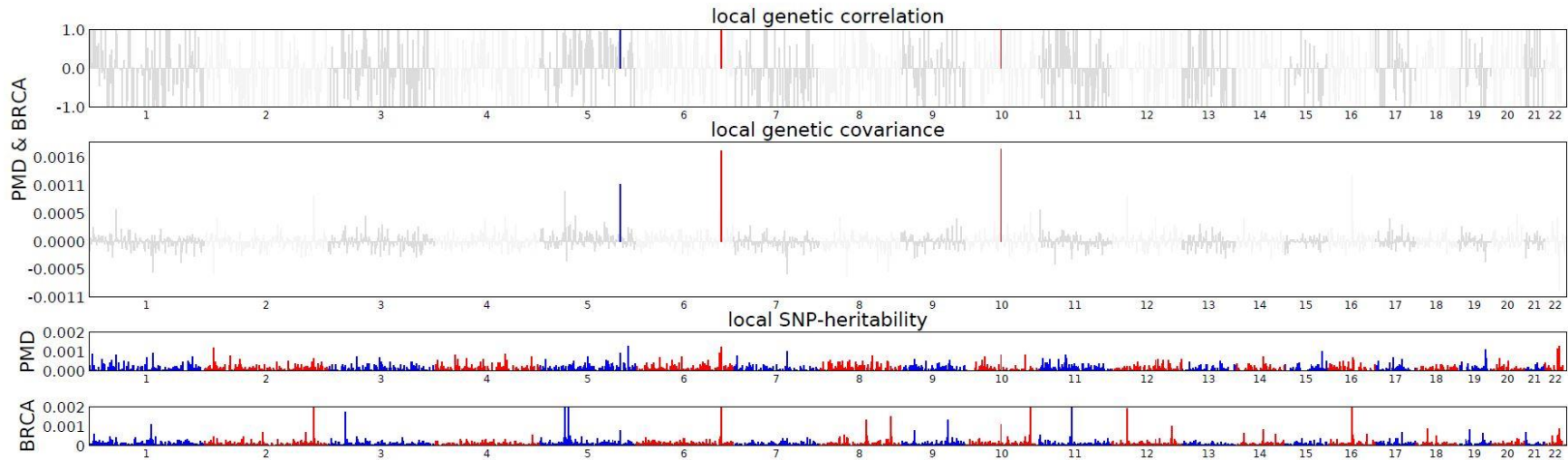
GWAS Results of PMD, for Significant SNPs of Breast Cancer



Supplementary Figure 2.10. Local genetic correlation estimates between the three MD phenotypes and overall breast cancer. For the analysis of each traits pair, the whole genome was partitioned into 1,703 regions. SNP-heritability shared by the two traits was estimated, and then used to estimate the local genetic covariance and correlation. Regions with statistically significant local genetic correlation (after adjusting for multiple comparison) is highlighted in blue or red.

Local genetic correlation between DA and Overall breast cancer



Local genetic correlation between NDA and Overall breast cancer**Local genetic correlation between PMD and Overall breast cancer**

Supplementary Figure 2.11. Manhattan-like plots showing the TWAS Z-scores of association between genetically determined expression level of 7,882 genes and three MD phenotypes (DA, NDA and PMD). Z-score threshold (Z-score = +/- 4.515) corresponding to the statistical significance after adjusting for multiple comparison using Bonferroni correction ($p = 0.05/7,882 = 6.34 \times 10^{-6}$) is shown by the horizontal red line. Significant genes are annotated.

