

Familial Aggregation of component traits of Metabolic Syndrome:

The GENNID study

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Abstract

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Introduction: Metabolic Syndrome (MetS) is defined as a constellation of cardiovascular and metabolic risk factors (elevated blood pressure, lower plasma HDL cholesterol, elevated plasma triglycerides [TG], higher blood glucose and abdominal obesity). The clustering of MetS components among individuals suggests shared etiologies and underlying pathophysiologic mechanisms, including genetic susceptibility factors. Despite strong evidence for genetic determinants of MetS and its components, studies have been unable to conclusively find genetic variations that account for significantly higher risk of MetS. Understanding aggregation patterns of traits will enhance the effort to find underlying genes contributing to the clustering of traits.

Objective: The objective of the study was to investigate the within and across family aggregation of MetS traits in families with type 2 diabetes across four ethnic groups.

Methods: The study was conducted among a total of 1701 subjects which included 758 Caucasian Americans (CA), 569 Mexican Americans (MA), 253 African Americans (AA), and 121 Japanese Americans (JA) from the Genetics of Non-Insulin Dependent Diabetes (GENNID) study. The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) criteria was used to define the presence of MetS among subjects. Aggregation of MetS within (number of MetS affected individuals with a given trio of traits in the family divided by the

number of MetS affected family members) and across families (number of families with at least half of the family members affected by a given MetS trait trio divided by the total number of MetS affected families in that ethnic group) was examined by evaluating prevalence estimates of individual traits and all possible three trait clusters of MetS.

Results: The most prevalent trait trio in the within family analysis was high glucose-abdominal obesity –low HDL cholesterol. However, the prevalence of this trait trio was significantly different across the different populations (prevalence of 54.4%, 69.2%, 43.8% and 70.7% among AA, CA, JA and MA, respectively). The most prevalent trio of MetS traits across families in AA, CA and MA was high glucose-abdominal obesity –low HDL cholesterol (prevalence of 58.9%, 60.2% and 63.3% among AA, CA, and MA, respectively). Among JA families, high glucose - hypertriglyceridemia-low HDL cholesterol was the most prevalent (prevalence of 46.8%).

Conclusion: We observed variation in the clustering patterns of MetS traits both within and across families. Understanding the underlying clustering of MetS traits may be helpful in future genetic studies for the identification of genes that are involved in the etiology of MetS.

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INTRODUCTION:

Metabolic syndrome (MetS) is defined as a cluster of interrelated risk factors for cardiovascular disease (CVD) and type-2 diabetes mellitus (T2DM) occurring in the same individual. The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) criteria, typically used in the U.S. for clinical diagnosis of MetS, defines MetS as the presence of at least three out of the following five risk factors (Alberti et al, 2009): elevated blood pressure (BP), raised triglycerides (TG), lowered HDL-cholesterol (HDL-cholesterol), raised fasting glucose and abdominal obesity. People with MetS are at increased risk for cardiovascular disease (Isomaa et al, 2001) as well as all cause, and cause specific (cardiovascular) mortality (Trevisan et al, 1998). In addition, an increase in the prevalence of MetS components has been observed in the population. From 1999 and 2000 to 2009 and 2010, there has been an increase in age-adjusted prevalence of MetS components: 12% increase in mean TG, 17-27% increase in plasma cholesterol, a 12% increase in mean body mass index, and doubled prevalence of obesity (Beltrán-Sánchez et al, 2013). Therefore, MetS is an important public health problem.

The individual components of MetS are all well-established heritable traits. Studies have shown high heritability of MetS and its components in family studies. In a study of Japanese American families, significant genetic influences were noted in every MetS component, of which around 50% of the variance was attributable to genetic influences (Austin et al, 2004). Similar high estimates were reported from other studies (van Dongen et al, 2013, Luo et al, 2010, Lin H-F et al, 2006). Various lines of evidence from twin and family studies have also suggested significant underlying genetic factors in occurrence of different combinations of MetS components. A review of 9 twin and 19 family studies found that genetic correlations were strongest (i.e., genetic pleiotropy was highest) between waist circumference and Homeostasis model

assessment- estimated insulin resistance (HOMA-IR), HDL cholesterol and TG, and between adiponectin and MetS (Povel et al, 2011). Further, studies have found associations between all-cause mortality and certain component-combinations of MetS (Guize et al, 2007). In sum, these observations underline the fact that MetS is a heterogeneous syndrome with potentially different underlying risk factors (including genetic risk factors) and pathogenetic mechanisms that lead to different combinations of MetS components.

Several genetic studies have been carried out recently to understand the genetic susceptibility of MetS. A genome scan performed in 507 Caucasian nuclear families demonstrated a strong link between 3q27 and 6 MetS traits with LOD scores ranging from 2.4 to 3.5 (Busfield et al, 2002). On the other hand, the chromosome locus of 16p13 (LOD = 3.06) was related to MetS among an Indian study population (Francke et al, 2001). Similar suggestive linkage has been observed for regions in chromosomes 2, 7, 12, 14, and 15 (Tang et al, 2003) and MetS among subjects from the National Heart Lung and Blood Institute (NHLBI) Family Heart Study. Differences in finding across the different ethnic populations may reflect variation in allelic diversity.

One other contributing factor for observed inconsistencies and limited congruence of previous investigations, may, at least in part, be differing familial aggregation of MetS components in different families from different racial groups. Understanding differential patterns of clustering in MetS components may help guide future genetic/epigenetic studies and elucidate underlying pathologic processes that lead to clustering of combinations of MetS components. Therefore, the goal of my thesis was to investigate differential aggregation of the component traits of MetS – both within and across families from four ethnic groups.

METHODS

Study setting and study population: Subjects from the GENNID (Genetics of NIDDM) study were used for the purpose of this study. GENNID is a multicenter study established by the American Diabetes Association in 1993 and comprises a comprehensive, well-characterized resource of Type II Diabetes families from four ethnic groups [Caucasian Americans (CA), Mexican Americans (MA), African Americans (AA), and Japanese Americans (JA)].

Raffel et al have previously described the aims, study design, ascertainment scheme and measurements of the GENNID study in detail (Raffel et al, 1996). Briefly, with a goal of determining genes for commonly occurring forms of NIDDM, the enrollment criteria for GENNID required the availability of at least two siblings (the index cases) affected with NIDDM, using the National Diabetes Data Group criteria, either a fasting plasma glucose concentration of ≥ 7.8 mmol/l [≥ 40 mg/dl] on more than one occasion or a plasma glucose concentration of ≥ 11.1 mmol/l [≥ 200 mg/dl] in the 2-h sample and in at least one other sample during oral glucose tolerance test. Between 1993 and 1995, enrollment also required at least three available additional first degree relatives of either of these affected individuals (regardless of diabetes status) and one non diabetic ethnically matched individual to act as control. The GENNID study included a total of 5,665 subjects- 565 AA (252 males and 313 females), 1,688 CA (831 males and 857 females), 173 JA (92 males and 81 females) and 3,239 MA (1658 males and 1581 females). Study protocols were approved by IRB of the participating institutions and all participants provided informed consent.

Data Collection

Data were collected for the study using standardized questionnaires (including a medical history questionnaire for data on age, gender, self-reported ethnicity, diabetes and medication use (anti-hypertensive and hypoglycemic)), a family history questionnaire, physical examinations (for height, weight, waist circumference and systolic and diastolic blood pressure measurements), fasting blood samples (for laboratory testing of glucose, insulin, high density lipoprotein (HDL) and triglycerides), and a diabetes history form (for detailed questions specific to their diabetes status).

Subjects with missing plasma glucose, triglyceride, HDL cholesterol, blood pressure or waist circumference measurements were excluded from the analysis. After applying the exclusion criteria, a total of 1,701 participants had complete information for the study variables and were included in the analytic population. They included 253 AA (86 males and 167 females), 758 CA (333 males and 425 females), 121 JA (65 males and 57 females) and 569 MA (210 males and 359 females).

Definition of Metabolic Syndrome:

MetS was defined in this study based on the NCEP ATP III guidelines as the presence of three or more of the five components of the MetS¹. The five components of the MetS defined by the 2009 Joint Scientific Statement ATP III and their biological thresholds were: 1) Abdominal obesity [waist circumference ≥ 102 cm (males adults) and ≥ 88 cm (female adults)] 2) Atherogenic dyslipidemia [triglycerides >150 mg/ dl] 3) Atherogenic dyslipidemia [high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl (male adults) and <50 mg/dl (female adults)] 4) Elevated blood

¹ NCEP ATP III

pressure [blood pressure of 130/85 mm Hg] and 5) Raised fasting glucose [fasting plasma glucose >100 mg/dl].

Statistical analysis:

Descriptive statistics used to characterize the study population included means and standard errors (SEs) for continuous variables and counts and percentages for categorical variables. Our main analyses focused on examining the distributions (both individual and combinations) of the five components of the MetS within and across families. MetS (presence or absence) was defined as the presence in an individual of at least three out of five traits described above using the ATPIII criteria for MetS. All possible three-trait combinations of the five traits were generated for analysis. For within family clustering analysis, the number of individuals affected with a given trait combination was expressed as a proportion of all MetS affected individuals in the family (i.e. number of MetS affected individuals with a given trio of traits in the family divided by the number of MetS affected family members). The across family analysis analyzed the proportion of families where a large number (at least half) of the family members were affected with a given trait combination (i.e., number of families with at least half of the family members affected by a given MetS trait trio divided by the total number of MetS affected families in that ethnic group). Since medication use can result in variability in MetS trait levels, it may affect MetS trait aggregation patterns. Therefore, proportion of medication use among different groups of study subjects was evaluated. All analyses were performed using the statistical software R 3.1.0.

Table-1. Descriptive variables of 1,701 GENNID study subjects with complete information on all five MetS traits.

		Variables									
Race	Sex	N** (%)	Age*	Diabetes** (%)	MetS** (%)	HDL*	TG*	Glucose*	SBP*	DBP*	Waist circumference*
AA	Female	167 (66.0)	52.29±1.1	101 (74.8)	99 (79.8)	48.13±0.88	103.66±6.18	148.26±5.94	128.22±1.61	79±0.83	100.38±1.30
	Male	86 (33.9)	42.95±1.6	34 (25.2)	23 (20.2)	45.17±1.45	106.8±7.68	141.04±7.68	128.43±1.84	80.07±1.14	95.09±1.40
	Total	253 (14.8)	51.18±0.95	135 (17.5)	124 (49.0)	47.13±0.77	104.73±7.00	145.81±4.71	128.29±1.23	79.36±0.67	98.58±1.00
CA	Female	425 (56.1)	55.52±0.87	153 (44.9)	242 (54.1)	43.7±0.55	148.53±6.67	132.94±2.86	127.97±1.01	76.57±0.50	100.22±0.82
	Male	333 (43.9)	54.37±0.8	188 (55.1)	205 (45.9)	34.52±0.49	158.51±5.94	138.83±3.28	130.07±0.89	79.73±0.52	102.94±0.75
	Total	758 (44.6)	55.02±0.56	341 (44.3)	447 (58.9)	39.67±0.41	152.92±4.56	135.53±2.16	128.89±0.71	77.96±0.37	101.42±0.57
JA	Female	57 (47.1)	53.83±2.1	10 (31.2)	21 (44.7)	51.91±1.87	131.23±15.8	106.69±3.54	119.47±2.46	69.37±1.42	83.95±1.51
	Male	65 (53.7)	58.53±3.6	22 (68.8)	26 (55.3)	38.95±1.32	139.66±11.2	125.31±4.48	124.67±2.25	75.19±1.49	92.50±1.12
	Total	121 (7.1)	56.34±1.4	32 (4.1)	47 (38.8)	45.01±1.27	135.72±9.55	116.61±3.04	122.24±1.68	72.47±1.06	88.51±1.01
MA	Female	359 (63.0)	51.44±0.84	173 (66.3)	239 (65.5)	41.07±0.53	163.31±7.37	149.33±3.96	125.00±1.03	72.90±0.55	101.95±0.79
	Male	210 (36.9)	52.34±1.03	88 (33.7)	126 (34.5)	36.28±0.68	165.03±8.21	154.83±5.49	126.70±1.22	77.26±0.74	101.52±0.83
	Total	569 (33.5)	51.77±0.66	261 (33.9)	365 (64.1)	39.30±0.43	163.95±5.55	151.36±3.22	125.63±0.79	74.51±0.45	101.79±0.59
	Total	1701 (100)	53.40±1.3	769 (100)	983 (100)	41.03±0.79	148.2±7.21	141.37±3.82	127.24±1.1	76.66±0.79	100.2±0.92

HDL = High density lipoprotein (mg/dl); TG = triglyceride (mg/dl); SBP = systolic blood pressure (mmHg); DBP = Diastolic blood pressure (mmHg).

*values are mean±SE **number of observation

= African Americans; CA = Caucasian Americans; JA = Japanese Americans; MA = Mexican Americans.

RESULTS:

Overall, 57.79% of the participants (N=769) had MetS using the ATP III definition comprised of 124 AAs (49.0%), 447 CAs (58.9%), 47 JAs (38.8%) and 365 MAs (64.1%) (Table 1). There was a higher proportion of female subjects in all ethnicities except in JA. The greatest proportion of subjects were of CA origin whereas the smallest number of subjects were of JA origin. The mean age of the overall sample was 53.4 years. On average, female subjects were older than male subjects in AA and CA, but were younger on average, compared to males, in JA and MA. Among MA and AA, considerably more women self-reported as diabetic than men, whereas the opposite was true for JA. MA had the highest number of subjects affected with MetS; more women were diagnosed with MetS in every ethnic group except in JA. HDL levels were lower on average among subjects of CA and MA origin and as expected were on average higher among women than men in all groups. AA had the lowest TG levels while MA had the highest with similar levels in women and men. Plasma glucose level was highest amongst MA and on average higher in men than women in CA, JA and MA, but lower in AA. Systolic and diastolic BP were slightly lower in JA compared to other ethnic groups with no major sex specific differences. JA had the lowest prevalence of abdominal obesity and women were less obese across all ethnic groups.

Table-2: Prevalence of MetS traits among 1,701 GENNID subjects by ethnicity.

	High Glucose	Abdominal obesity	High TG	Low HDL Cholesterol	High BP
AA	67.98	60.08	13.83	52.17	50.59
CA	62.80	63.59	35.49	73.88	46.31
JA	61.16	23.14	32.23	52.07	28.93
MA	67.66	68.37	42.36	76.45	42.71

All values are percentages.

AA= African Americans, CA= Caucasian Americans, JA=Japanese Americans, MA=Mexican Americans.

High glucose= >100 mg/dl; Abdominal obesity= ≥ 102 cm (males) and ≥ 88 cm (females); High TG= >150 mg/ dl 3)

Low HDL cholesterol= <40 mg/dl (male adults) and <50 mg/dl (female adults); High BP= $\geq 130/85$ mm Hg;

The prevalence (%) of individual components meeting the ATP III criteria for MetS are listed in Table 2. On average, 64% of participants were above the threshold for blood glucose, with the highest proportion in AAs and lowest in JAs. Prevalence of abdominal obesity and high blood pressure was lowest in JA compared to other ethnicities and the prevalence of high plasma TG was lowest in AA. CA were similar to MA in terms of the prevalence of individual MetS components.

Table-3: Prevalence of Metabolic syndrome traits among individuals with MetS (N=983) by ethnicity.

	MetS affected* (%)	High Glucose* (%)	Abdominal obesity* (%)	High TG* (%)	Low HDL Cholesterol* (%)	High Blood pressure* (%)
African-Americans	124 (49.0)	115 (93.5)	109 (87.9)	97 (77.4)	94 (75.8)	94 (75.8)
Caucasian-Americans	447 (58.9)	381 (85.2)	367 (82.1)	256 (57.3)	409 (91.5)	298 (66.7)
Japanese-Americans	47 (38.8)	43 (91.5)	24 (51.1)	29 (61.7)	42 (89.4)	23 (48.9)
Mexican Americans	365 (64.1)	327 (89.6)	301 (82.5)	229 (62.7)	322 (88.2)	205 (56.2)

*Number of subjects with given trait out of all affected with MetS.

High glucose= >100 mg/dl; Abdominal obesity= ≥102 cm (males) and ≥88 cm (females); High TG= >150 mg/ dl 3)
Low HDL cholesterol= <40 mg/dl (male adults) and <50 mg/dl (female adults); High BP=≥130/85 mm Hg;

Amongst individuals affected with MetS, the most prevalent trait in AA, JA and MA was high glucose while low HDL cholesterol was the most prevalent trait in CA. The second most common trait was abdominal obesity in all ethnic groups except in JAs, where low plasma HDL ranked second (Table-3).

Table-4: Proportion of MetS patients and their underlying number of defective traits used for diagnosis of MetS.

	%with 5 traits	%with 4 traits	%with 3 traits
AA	12.9	35.5	55.6

CA	22.1	39.8	48.3
JA	8.50	25.5	70.2
MA	20.8	39.5	47.9

AA= African Americans, CA= Caucasian Americans, JA=Japanese Americans, MA=Mexican Americans.

Table-4 shows the proportion of MetS patients who were diagnosed using 5, 4 or 3 underlying positive traits. JA had a substantially lower proportion of subjects with all 5 traits (8.5%) and considerably higher proportion of patients who had 3 defective traits (70.2%). On the other hand, MA and CA had the highest proportion (20.8 and 22.1%, respectively) of patients with 5 defective traits and lowest proportion of patients with 3 defective traits (47.9% and 48.3%, respectively).

Table-5: Proportion of antihypoglycemic and antihypertensive medication use among self-reported diabetics and hypertensives respectively.

	AA			CA			JA			MA		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Oral hypoglycemic/insulin use*	89.3	90.6	90.3	84.9	99.8	93.6	79.3	45.1	67.2	97.8	86.1	91.1
Antihypertensive use**	91.3	98.9	97.1	88.0	87.4	87.6	83.3	73.7	76.1	83.3	89.7	88.2

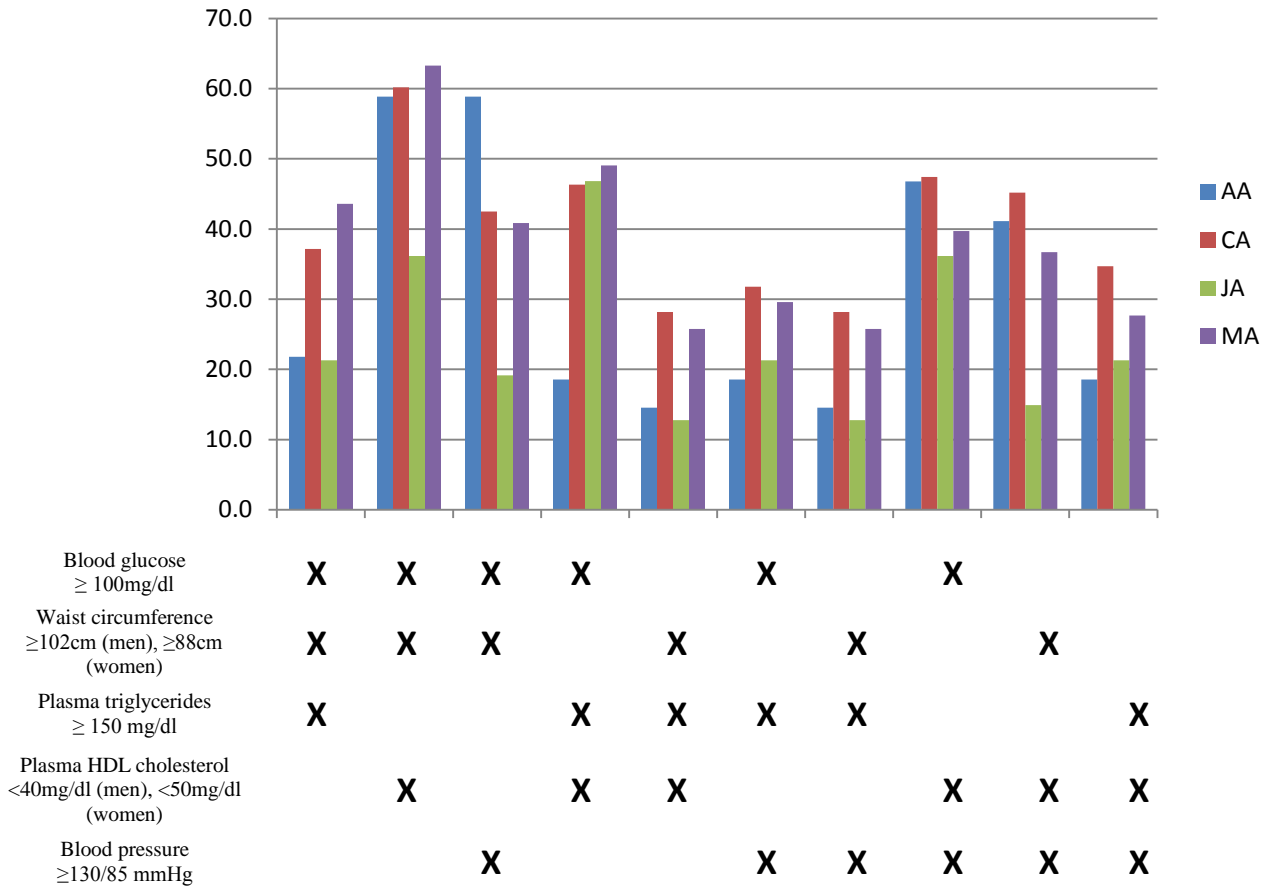
*Proportion of oral hypoglycemic/Insulin users among self-reported diabetics

**Proportion of antihypertensive medication users among self-reported hypertensives

AA= African Americans, CA= Caucasian Americans, JA=Japanese Americans, MA=Mexican Americans.

Report of oral hypoglycemic use by diabetic subjects differed (Table 5) across ethnicities with the highest use reported by CA women (98%) and lowest by JA women (40%). Compared to other ethnic groups, insulin use was significantly lower in JA whereas AA females reported the highest use. Use of antihypertensive medication was generally high among participants who self-reported as hypertensive in all ethnicities with AA females reporting the highest use. Overall, a consistently high proportion of subjects with diabetes and hypertension reported using medication in all ethnic groups.

Figure 1: Prevalence of three trait combinations among affected individuals across ethnicities.



AA= African Americans, CA= Caucasian Americans, JA=Japanese Americans, MA=Mexican Americans.

The most prevalent trait trio across families in AA, CA and MA was high glucose-abdominal obesity –low HDL cholesterol (58.9%, 60.2%, and 63.3% among AA, CA, and MA respectively) except in JA where high glucose -hypertriglyceridemia-low HDL cholesterol was most prevalent (46.8%). Among AA, another trait combination, High glucose-Abdominal Obesity-High Blood Pressure was equally prevalent (58.9%) (Figure 1).

Table 6: Proportion of families where at least half of the family members are affected with a given trait combination.

Trait combination	AA	CA	JA	MA
higluc-hiwaist-hitg	20.6	38.5	12.5	51.5
lohdl-hiwaist-higluc	54.4	69.2	43.8	70.7
hibp-hiwaist-higluc	55.9	47.4	6.3	46.5

lohdl-hitg-higluc	22.1	50.6	37.5	55.6
lohdl-hitg-hiwaist	11.8	29.5	6.3	24.2
hibp-hitg-higluc	16.2	34.0	25.0	27.3
hibp-hitg-hiwaist	11.8	30.1	12.5	25.3
hibp-lohdl-higluc	42.6	51.3	37.5	43.4
hibp-lohdl-hiwaist	35.3	52.6	0.0	36.4
hibp-lohdl-hitg	17.6	35.9	18.8	25.3

AA= African Americans, CA= Caucasian Americans, JA=Japanese Americans, MA=Mexican Americans.
Proportion= number of family members with a given trait combination out of all MetS affected family members within a family

Table 6 shows the proportion of families where a large number (at least half) of the family members were affected with a given trait combination. Contrary to findings from the across family analyses, the within family analysis shows that High glucose-Abdominal obesity –Low HDL aggregates in all ethnicities. However, the prevalence estimates for this combination of MetS components were significantly different across ethnic populations (prevalence of 54.4%, 69.2%, 43.8% and 70.7% in AA, CA, JA and MA respectively). In addition, the within family analysis demonstrates heterogeneity in prevalences of MetS trait combinations across families of ethnic groups. In AA, besides the most prevalent trait trio, other highly prevalent traits include high BP-low HDL-high glucose (42.6%) and high BP-low HDL- high abdominal obesity (35.3%). Similarly, in CA families, four other trait trios are nearly equally prevalent. In JA families certain trait trios are completely non-existent (high BP-low HDL-high abdominal obesity) whereas others are more prevalent. Likewise variations in prevalence of trait trios were observed in MA families with low HDL–high TG-high abdominal obesity being the least prevalent (24.2%).

DISCUSSION:

This study identified heterogeneity in the clustering of MetS traits within and across families of four ethnic groups. The most prevalent trio of MetS traits across families in AA, CA

and MA was high glucose-abdominal obesity –low HDL cholesterol (58.9%, 60.2% and 63.3% respectively). Among JA families, high glucose -high TG-low HDL cholesterol was the most prevalent (46.8%). Within family analysis showed that high glucose-abdominal obesity –low HDL cholesterol was the most prevalent cluster in all ethnicities although the prevalence of this MetS trait trio varied considerably among ethnic groups (54.4%, 69.2%, 43.8% and 70.7% in AA, CA, JA and MA respectively).

Our observations of the different prevalent MetS trait trio combination among JA, compared with the other ethnic groups, in the across family analyses may be driven by the following factors. The low number of high abdominal obesity in the aggregating MetS trait trio in JA may be because the NCEP criteria for obesity are not suitable for the Japanese (Zhang et al, 2005). Tan et al., 2004) suggested that the NCEP definition of MetS underestimates its prevalence in Asian populations, because it embodies an unsuitable threshold of central obesity for Asians (Tan et al, 2004). With use of appropriate biologic threshold for traits, one can expect better agreement in clustering of MetS across ethnic groups, i.e., clustering of high glucose-high abdominal obesity –low HDL cholesterol trait combination in all ethnicities. The difference in within and across family clustering pattern in JA may also be partially driven by the group's smaller sample size compared to AA, CA and MA- the 3 biggest groups in terms of sample size, which all have the same clustering. There were five JA families in our study (22 diagnosed with low HDL cholesterol-high glucose-high abdominal obesity in the within-family analyses versus 17 with high glucose-high TG- low HDL cholesterol in the across family analyses). Consequently, if ethnicity appropriate biologic thresholds are used for MetS traits, studies should expect minimal variation in aggregation patterns of MetS across ethnic groups.

Although similar MetS components aggregate across ethnic groups, there is considerable variability in the prevalence estimates of the prevalent trait trios within any given ethnic group as well as prevalence of the other trait trio combinations. As seen in Figure 1, the second most prevalent trait combination in AA, CA and JA was High blood pressure-Low HDL cholesterol-High glucose and in MA, it was High glucose-High Abdominal obesity-High TG. Therefore, while the most prevalent trait combination is concordant across ethnic groups, differences still exist in prevalence of other trait combinations across families within an ethnic group. These aggregation patterns underlying MetS are important for genetic studies, because they show possible underlying genetic differences which cause MetS. If genetic differences truly underlie the clustering of MetS traits, combining such heterogeneous families in linkage studies will likely reduce evidence for linkage. Using properly defined MetS phenotype to allow for trait aggregates and conducting cluster stratified genetic studies may be beneficial in understanding the genetics of MetS.

Use of oral hypoglycemic medication and insulin could have resulted in an underestimation of subjects with elevated plasma glucose thereby affect the aggregation patterns. However, subjects on antihypoglycemics continued to meet the threshold for diabetes across all ethnicities and therefore potentially had minimal influence on familial aggregation patterns (across all ethnicities 99.2% of medication users met the threshold for elevated plasma glucose). Similarly, substantial proportion of subjects continued to meet the high BP threshold after antihypertensive medication use in AA, CA and MA (73.9%, 71.1% and 70.7% respectively) and, lower but still substantial, proportion in JA subjects (52.9%). Despite this difference, most of these subjects had none or only one other defective MetS trait, and therefore they would not

have been MetS positive by reaching the NCEP threshold for BP trait alone, and therefore would not influence the observed aggregation patterns.

If we compare the prevalence of MetS in our study (57.8%) and a 21.7% of US MetS prevalence reported by Ford et al (2002) during the 1988–1994 period using data from NHANES, it is evident that our GENNID samples have a higher prevalence of MetS than the general US population (Ford et al, 2002). This observation is explained by the study's recruitment criterion that was based on NIDDM status. As a result a large proportion (94.4%) of our study participants were positive for at least one of the MetS components. Similar results were observed when selection for a component trait resulted in higher prevalence estimates in a multinational study, Genetic Epidemiology of Metabolic Syndrome Project. This study has revealed a prevalence of 76% of MetS out of 1,436 participants, as result of selecting for atherogenic dyslipidemia (Wyszynsk et al, 2005).

A limitation of the present study is the lack of complete data on all five traits for the entire GENNID population. Subjects who were missing data on any one of the five MetS traits were excluded from the analysis; the majority of such subjects were of MA origin (68.7%) and more specifically MA males (36.5%) whereas JA had the lowest rate of missingness (i.e. complete information was available for 70% of JAs). Although, the excluded subjects did not differ in any other manner from those included in the analysis (data not shown) availability of complete information on subjects with missing data may have affected the observed clustering patterns.

Among affected individuals, the top component contributor of MetS in AA, JA and MA was high plasma glucose, whereas low HDL cholesterol was most prevalent in CA (Figure 2-5). The

high prevalence of elevated plasma glucose in study participants is due to the ascertainment scheme used in GENNID study. While the aggregation patterns are true for this population, it would be unwise to extrapolate these data to the general population as study participants had been selected for diabetes status. However, the aggregation patterns found in this study suggest that ethnic differences in aggregation of MetS traits across families exist. Our results indicate the critical importance of using appropriate and comparable phenotypic definition of MetS for future genetic studies that involve different study populations. More specifically, prior studies have not looked at clustering of MetS phenotypes in clinical or research populations and as a result, none of the aggregation patterns we identified have been previously reported.

In summary, a novel finding of the present study is that high glucose-abdominal obesity –low HDL cholesterol traits strongly aggregate in subjects with MetS, although prevalence for this trait trio differed substantially across ethnic groups. In addition, we observed significant differences in prevalence of other trait combinations that constitute MetS across different ethnic groups. It is important to take this phenotypic heterogeneity into consideration while designing and conducting future genetic and gene-environment interaction studies.

Figure-2: Clustering of Metabolic syndrome components across families in African Americans.

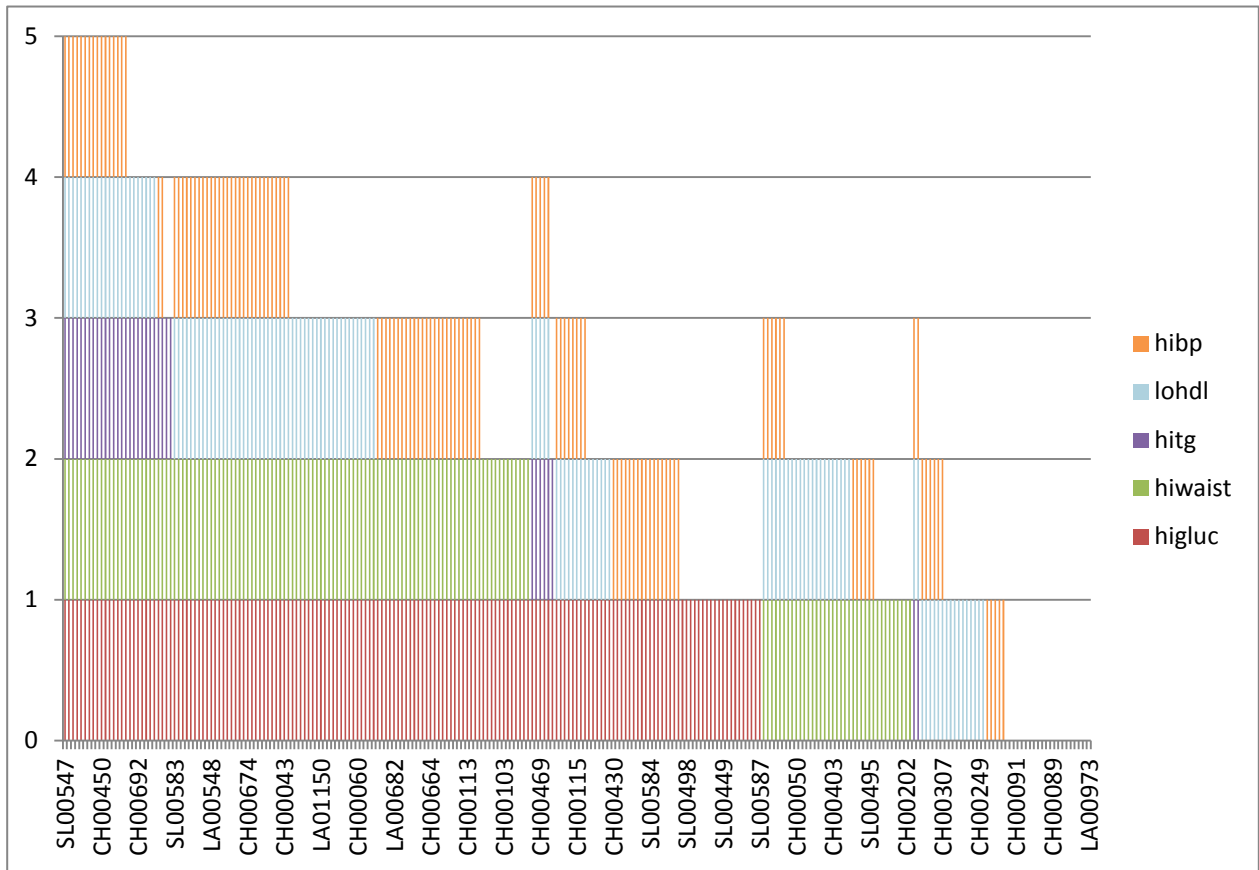


Figure-3: Clustering of Metabolic syndrome components across families in Caucasian Americans.

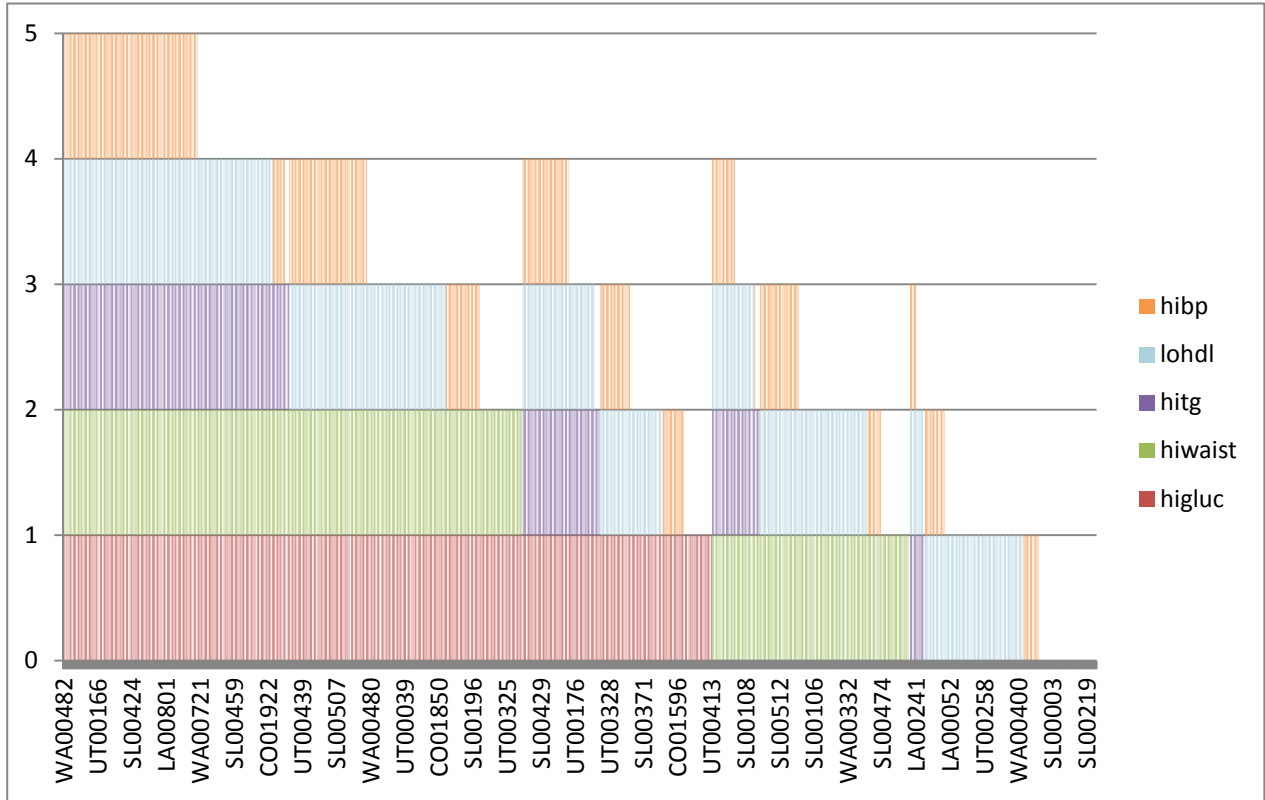


Figure-4: Clustering of Metabolic syndrome components across families in Japanese Americans.

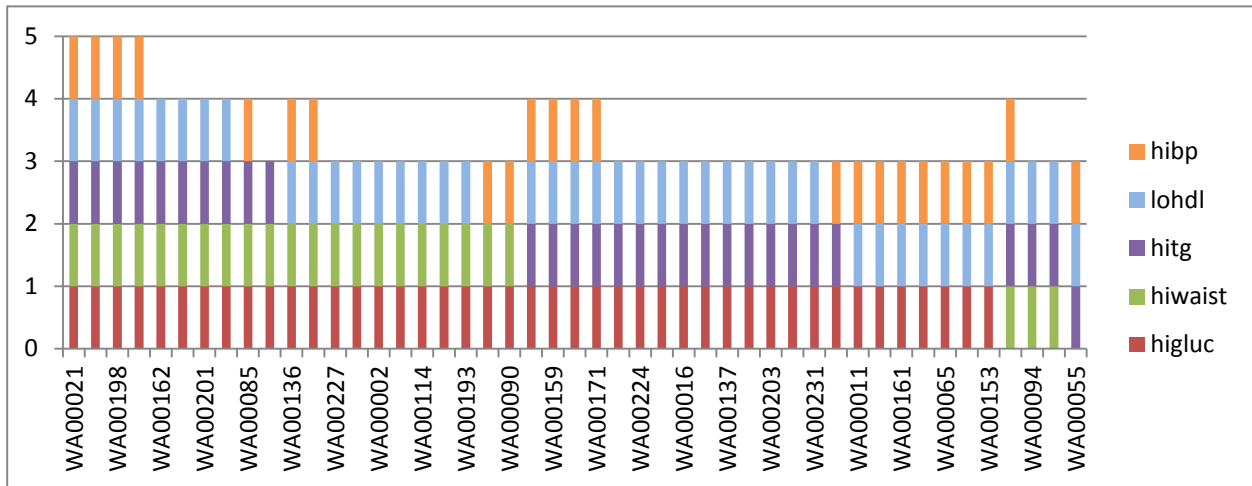
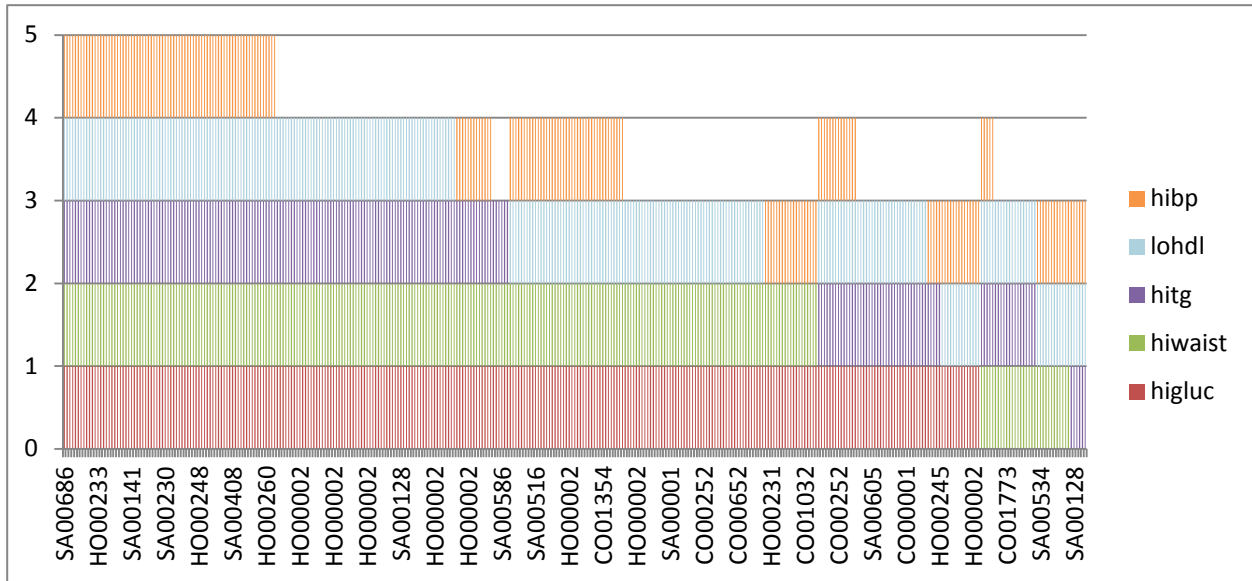


Figure-5: Clustering of Metabolic syndrome components across families in Mexican Americans.



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