Assessment of the Risk of Melanoma in Relatives of Patients with Parkinson's Disease

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Abstract

The goal of this pilot study was to describe the occurrence of melanoma among patients with PD in the Washington Parkinson's Disease Registry (WPDR), and their family members. Our evaluation has the following aims: 1) To determine whether there is a higher proportion of individuals with melanoma among those with PD compared to the general population; and 2) To determine whether there was a higher proportion of relatives with melanoma among those with PD than would be expected in the general population.

Eligible subjects were 839 individuals with PD enrolled in the WPDR. Data on melanoma and PD in relatives were based on self-report.

We found a significantly higher proportion of participants with melanoma in the WPDR than expected in the general population. Sixty-two (7.7%) of eight hundred and ten probands that responded to the melanoma questions on their surveys had melanoma, which was significantly higher than expected values. We found a higher, but not significantly higher, proportion of parents with melanoma (2.6%) in the WPDR than expected in the general White Population. We did not find a higher proportion of melanoma in siblings (1.5%) or children (0.6%) than expected in the WPDR than in the general White population.

Background

PD is an idiopathic neurodegenerative illness characterized by specific motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability. The motor symptoms of PD result from a significant loss of dopaminergic neurons, which are rich in neuromelanin. The U.S. is expected to have about 60,000 new cases of PD per year (Pan et al, 2011). The lifetime risk of PD for Whites, based on incidence rates of PD in Olmstead County, MN from 1976-1990 was 2.0% for men and 1.3% for women. PD incidence rates are highest in Hispanics and non-Hispanic Whites. Incidence rates between racial groups differ by about 2- 3 people per 100,000 person-years (Incidence rates were 16.6 per 100,000 person-years for Hispanics, 13.6 per 100,000 person-years for White, 11.3 for 100,000 person-years for Asians and 10.2 per 100,000 person-years in Blacks in Northern California, (VanDenEeden, 2003)).

Melanoma is a skin cancer in which the melanin-producing cells in the skin become malignant. It is more rare, yet causes more mortality than other forms of skin cancer. The U.S. is expected to have about 76,250 new cases of melanoma each year; the risk for melanoma, as reported in the SEER data, has increased 2.6% in the past 20 years (National Cancer Institute, 2012). However, the mortality rate has not increased in this same time period, possibly reflecting an increased surveillance and early detection of these cancers (National Cancer Institute, 2012). The National Cancer Institute estimated lifetime risks for melanoma based on 2000 – 2010 cross-sectional counts of incidence rates in the SEER database from 18 sites. Incidence rates were converted to probabilities for a hypothetical population based on census data (National Cancer Institute, 2013). Like PD, melanoma is most common in Whites; the estimated lifetime risk of melanoma is 2.04% in the general population, 2.38% in Whites, 0.09% in Blacks, 0.16% in Asians, 0.31% in American Indians / Alaskan Natives, and 0.51% in

Hispanics *(National Cancer Institute, 2013))*. Non-melanoma skin cancers, such as basal or squamous cell skin cancer, are more common (with an estimated lifetime risk of skin cancer in the U.S. at 20% (Robinson, 2005)) but are generally more slow moving and less invasive than melanoma.

At first glance, PD and melanoma do not seem to have many factors in common. The first connections between PD and melanoma were case reports of a few patients in the 1970s; these studies had speculated that PD treatment might cause melanoma. Case study reports in the 1970s had speculated that levodopa, a common drug used to treat PD, could contribute to melanoma risk since it is in the biochemical pathway that makes melanin (Fiala et al, 2003). However it was found in comprehensive reviews that the increased risk of melanoma also occurred before PD diagnosis (Fiala et al, 2003; Vemejj et al, 2009; Zanetti et al, 2006). For example, in a large population-based case-control study in Denmark, Olsen et al (2006) found a 44% increased risk for melanoma (Odds Ratio (OR) = 1.44, 95% Confidence Interval (CI) 1.03, 2.03) and a 26% increased risk of skin cancer (OR=1.26, 95% CI 1.11, 1.43) among 8,059 patients with PD compared to age- and sex-matched controls. In a review and critique of the earlier studies presuming a causal link between levodopa therapy and melanoma, Fiala et al (2003) found that many of the studies that claimed a causal relationship found increased risks of melanoma within a year of levodopa treatment. They pointed out that even a 3-5 year time span between levodopa therapy and development of melanoma would not be enough to infer a causal relationship between the medication and melanoma (Fiala et al, 2003). While it could be claimed that levodopa treatment would speed up the development of melanoma, medication itself could not explain why studies also find an increased risk in melanoma before PD diagnosis and treatment. In summary, it is unlikely that levodopa treatment increased risk for subsequent melanoma

development, but instead there may be shared unknown factors that contribute to risk of both diseases.

It has been observed that PD and melanoma co-occur more than might be expected by chance (Inzelberg et al, 2011; Liu et al, 2011; Rugbjerg et al, 2012). In general, PD patients tend to have a significantly decreased risk of other cancers (with the exception of a small increased risk in breast cancer (Bajaj et al, 2010; Olsen et al, 2005)), so this increased risk for melanoma and other skin cancers stands out. Currently, the reasons behind this comorbidity and the similar risk patterns observed in sex and race are unknown, though it is probably a combination of genes and the environment.

Recently data from several large studies in Europe and North America have supported the increased comorbid risk of both diseases. Most notable are the studies in Denmark, of more than 14,000 patients who had a primary diagnosis of PD from 1977-1998 and were identified through the Danish National Hospital Register by Olsen et al (2005). They found a significantly increased risk of melanoma among those with PD compared to age and sex matched controls without PD. Subjects free of PD at baseline were followed for up to 20 years; melanoma risk was almost doubled (RR=1.95; 95% CI 1.4, 2.6) in PD patients compared to age- and sex-matched controls without PD (Olsen et al, 2005). The same group followed up their study with an additional 6,000 PD patients, identified from the same national health registry, (resulting in over 20,000 subjects) diagnosed between 1977 and 2006 that were followed until 2008. They found a significantly higher risk of melanoma among those with PD (Standardized incidence ratio (SIR)=1.41, 95% CI 1.09, 1.80). Results were adjusted for age, sex, and calendar-specific rates in the general population without PD (Rugbjerg et al 2012)). In North America, a large case-control study on over 2,000 PD patients found that the 5-year prevalence of melanoma was over

two-fold higher than the 5-year prevalence in the U.S. SEER database in age- and sex- matched controls (Bertoni et al, 2010). Finally a meta-analysis of 12 studies in Europe, North America, and Australia by Liu et al (2002) found over a two-fold increased risk in melanoma among those with PD compared to those without PD (pooled OR = 2.11, 95% CI 1.26, 3.54). They did not find a significantly increased risk of non-melanoma skin cancer compared to the risk in the general population (Liu et al, 2011). Their meta-analysis found that while women have lower risks of melanoma than men, there was no evidence for a significant interaction with sex.

Family history of melanoma, rather than a subject's melanoma, has also been associated with a higher risk for PD. Gao et al (2009-1) looked at a cohort of 157,036 men and women in the Health Professional Follow-up Study and the Nurses Health study that were free of PD at baseline and followed for 14-20 years. Adjusting for age, smoking status, ethnicity, and caffeine intake, they found an 85% increased risk for PD (RR=1.85, 95% CI 1.2, 2.8) among those with a first-degree family history of melanoma, compared to those without a first-degree family history of melanoma (Gao et al, 2009-1). No association was found for colorectal, lung, prostate or other cancers. In a study using the Utah Population database, Kareus et al (2012) found a 29% increased risk among first-degree relatives (RR=1.29, 95% CI 1.27, 1.40) and a 18% increased risk in second-degree relatives (RR = 1.18, 95% CI 1.02, 1.23) comparing those with melanoma to age- and sex-matched controls. These studies provide additional evidence that there most likely exists a genetic factor that contributes to the increased risk of melanoma and PD, as a first-degree family history of melanoma was associated with an increased risk of PD in the proband.

While other studies have used family history of PD and melanoma as a covariate to determine the risk of comorbid skin-cancer in probands, as far as we know, there has only been one other study that looked other relatives' melanoma risk among probands with PD. This family

study by Kareus et al (2012) used death records in the Utah Genealogical Database, a rich epidemiological database with over 2 million people and a detailed family history. Among the 2,998 with PD listed on their death certificate, risk was almost two-fold higher for melanoma compared to age- and sex- matched controls without PD (RR=1.95, 95% CI 1.44, 2.59, ((Kareus et al, 2012). There was a 23% increased risk of melanoma among first-degree relatives of probands with PD (RR= 1.23, 95% CI 1.07, 1.40) and a 12% increase in risk among second-degree relatives (RR=1.12, 95% CI 1.02, 1.23) compared to age- and sex- matched controls without PD (Kareus et al, 2012). The reciprocal relationship, an increased risk of PD among those with melanoma, was also found. The risk for PD among 7,841 cases of melanoma was 65% greater (RR=1.65, 95% CI 1.22,2.19) compared to age- and sex- matched controls without melanoma. The risk for PD among first-degree relatives of those with melanoma was 29% greater (RR=1.29, 95% CI 1.12,1.48) for first-degree relatives and 18% greater (RR=1.18, 95% CI 1.07, 1.30) for second-degree relatives compared to age- and sex-matched controls without melanoma (Kareus et al, 2012).

The causal mechanisms for this increase in melanoma and PD risk are unknown, although there has been speculation of shared genetic factors. Since multiple studies have observed an increased risk of melanoma, but a significantly decreased risk of other cancers, the shared genetic pathways would most likely be unique to melanoma rather than cancer itself. Bertoni et al (2010) found that most of the PD patients with comorbid melanoma had common risk factors such as fair skin, blue eyes, blond or red hair, and severe blistering sunburns in childhood or early adulthood. Those with a fairer complexion have less melanin, which might be connected to the loss of dopaminergic neuromelanin cells in PD patients based on the melanin synthesis pathway (Figure 1, based on Pan et al, 2011). It has been speculated that the lower production of

dopamine in PD might cause an increase in melanin production and production of melanocytes, although this speculation has yet to be supported (Rugbjerg et al, 2012).

There are many genes that show a plausible connection between both diseases, but these results haven't been replicated. Enzymes and intermediaries in the melanin synthesis pathway (Figure 1) such as tyrosinase and tyrosine hydroxylase, dopamine decarboxylase (DDC), or levodopa (L-DOPA), may all be involved in shared risk patterns (Hernandez, 2010; Pan et al, 2011). Other possibilities are: 1) the cyclin dependent kinases, which are over-expressed in melanoma cells and involved in neuronal cell death; 2) *parkin,* a tumor suppressor that is known to increase risk of PD*; 3) α synuclein*, which is overexpressed in the dopamine producing cells in PD and has been found in malignant melanocytes (Liu et al, 2011); and 4) *LRRK2*, which increases neurotoxicity (Gao et al, 2009-1; Pan et al, 2011).

Another possible gene of interest, *MC1R*, codes for the melanocortin 1 receptor, which is involved in hair and skin pigmentation. Variations in these genes have been associated with melanoma. A nested case-control study of about 300 PD patients based on the Health Professionals Follow-Up Study and the Nurses Health Study, matched in a 4:1 ratio with randomly selected age- and sex- matched controls by Gao et al (2009-2), found that the variant in the gene associated with melanoma was also associated with PD. While the previously mentioned candidate gene study found a possible genetic connection between PD and melanoma, other genetic studies haven't found significant associations. A recent genome-wide association study by Meng et al (2012) tested 31 SNPs, which were previously found significantly associated with PD, in 2,297 melanoma patients matched 2:1 with controls. None of the SNPs that they tested were associated with melanoma. In addition, none of the SNPs that they found significant in these melanoma patients were associated with any PD-specific genes.

The environment most likely also contributes to both diseases. Environmental risk factors that are associated with PD include use of heavy metals, abuse of certain types of drugs, repeated head trauma, and pesticide or herbicide exposure. Environmental exposures that contribute to melanoma include multiple blistering sunburns, especially in childhood and early adulthood.

Methods

The WPDR is a large volunteer registry for subjects who desire to help out in PD research. It was started in 2007, and currently has 1,578 active participants. Subjects are primarily recruited through advertisements in local and national advocacy newsletters, at clinician and community educational programs, and in WPDR-specific brochures distributed to local clinics. Individuals with PD complete screening and enrollment in person or over the phone; subjects answer questions about symptoms, medications, surgical treatments, family history of PD, and possible confounding factors. Participants complete a yearly "Annual Update" form in which they update any changes in the past year, which may include diagnosis, medications, symptoms, and new family members with PD. In Spring of 2012, the WPDR added questions about melanoma to the Enrollment and Annual Update forms which ask if the patient has ever had melanoma (skin cancer), at what age the diagnosis was made, and if anybody in the patient's family has ever had a melanoma (skin cancer)[1]. A Melanoma Questionnaire was developed to capture more detailed information about personal and family of melanoma; this

[1] The form words the questions with "melanoma (skin cancer)" to capture the most patients

questionnaire was used to gather data when participants were contacted by phone. All questions are voluntary, and have been approved by the IRB of the VA Puget Sound Healthcare System.

Participants in the WPDR are sent updates every year, but these updates aren't always returned. The subject may have moved, not have returned the survey, or may not have been cognitively intact to answer the questions. Some people are lost to follow-up, and since the two survey questions about melanoma were only added to the Enrollment and Annual Update forms in 2012, we could not be certain that those who did not return the Annual Updates had a chance to answer the melanoma questions. Of the 1,578 people in the WPDR, 839 returned the Annual Update form or completed Enrollment, and therefore had a chance to answer the two survey questions about melanoma (Figure 2). Of the 839 whom had returned their Updates, 29 did not answer the two melanoma survey questions, 173 reported comorbid skin cancer or a family history of skin cancer, and 637 reported no skin cancer nor a family history of skin cancer. Subjects who reported either comorbid skin cancer or a family history of skin cancer were re-contacted to follow-up on their self-reported skin cancer diagnosis between March and June of 2013. The Melanoma Questionnaire was used to collect data on the proband and their family as part of this follow-up. In all 122/173 people (67.4%) were re-contacted and interviewed. After the interviews, there were 167 remaining subjects who reported comorbid skin cancer, or a family history of skin cancer (Figure 2). Through these phone interviews some designations changed: 10 people indicated they had a non-melanoma skin cancer rather than melanoma; 5 people indicated they did not have melanoma or any skin cancer; and 1 person indicated a first-degree relative did not have melanoma.

In order to compare the number of probands with comorbid melanoma to those without, we performed a two-sided exact test of deviations from an expected proportion of binary

outcomes (binomial probability test). The null hypothesis is that the observed proportion of binary outcomes matches the given expected proportion (StataCorp, 2011). The expected proportion is 0.0238 for Whites in the general population is based on the lifetime-risk of melanoma from the SEER database (National Cancer Institute, 2013). We compared proportions of subjects or relatives of subjects with melanoma to 2.38%, assuming that these proportions, especially among subjects (mean age 70.4 ± 10.0) and their relatives would match that of this lifetime risk.

The proportion of relatives with melanoma was calculated unadjusted and adjusted (Johnson and Leeman, 1977). Among those with comorbid melanoma, the proportions of relatives at each type were determined. Relatives without melanoma ("well" relatives) were adjusted for the 2.38% lifetime risk of melanoma in Whites reported from the National Cancer Institute (2013). Adjustment for well relatives was not made for grandparents, as most of these grandparents were already deceased. Proportions of relatives with melanoma were calculated for each relative type (Table 3). Proportion of relatives with melanoma was also calculated per proband, then averaged to get a mean per-family estimate.. When comparing average proportions of relatives with melanoma between covariates, analysis was limited to those with melanoma, rather than those with other forms of skin cancer.

STATA-12 software (Statacorp, Texas) were used for all analyses.

Results

Table 1 shows the demographics of the 839 individuals included in the study. Among the 810 who answered the melanoma questions, there were 167 individuals who reported comorbid

skin cancer or a family history of skin cancer, 643 individuals who had neither, and 29 that did not answer the questions. There were no significant differences in sex, race, or ethnicity between each of these subgroups or between each subgroup and the total dataset of 839 individuals. All of those who had either comorbid skin cancer or a family history of skin cancer identified as White and Non-Hispanic; these proportions were somewhat lower among the group that had no skin cancer or family history of skin cancer. Among the 167 probands, there were 62 with comorbid melanoma, 40 with comorbid non-melanoma skin cancer, and 65 with a family history of skin cancer. Family history of skin cancer included both melanoma and non-melanoma (Table 3). These three groups were also compared (Table 1). There were no significant differences between the groups in race, ethnicity, siblings, children, family history of PD, confirmation of diagnosis, age at PD diagnosis, or age at melanoma diagnosis between those with comorbid melanoma and those with a family history of melanoma. There were significantly fewer females among those with comorbid melanoma compared to those who had a family history of skin cancer ($p=0.0003$; 2 sided t-test). Those with comorbid melanoma were on average 4 years older than those with a family history of skin cancer ($p=0.03$; 2-sided t-test), although they were not significantly different in their age at PD diagnosis. There were no significant differences in any values between those with melanoma and those with non-melanoma skin cancers, or between those with non-melanoma and those with a family history of skin cancer ($p>0.10$ for all comparisons; 2-sided t-test).

Out of the 810 people who answered the melanoma questions, there were 62 with melanoma; this percentage, 7.7%, was significantly higher than expected in the general White population ($p<0.005$). If the analysis was limited to the 689 individuals who had no family

history of skin cancer, there were 42 with comorbid melanoma, which results in a significantly higher 6.1% proportion of melanoma ($p<0.005$).

On average, PD was diagnosed 4.0 ± 12.9 years after self reported incidence of melanoma, with a median of 3 years afterwards (Figure 3).

Table 2 gives the breakdown of skin cancer, divided into melanoma and non-melanoma among relatives of the probands. There were higher proportions of first-degree relatives, but not higher proportions of second-degree relatives with melanoma among the WPDR than would be expected in the general White population. We analyzed proportions of relatives by type. There was a significantly higher proportion of parents with melanoma among probands with melanoma compared to probands without melanoma or those with non-melanoma skin cancer ($p<0.05$, two-sided t-test). This suggested an increased proportion of melanoma among first-degree relatives (Table 3). The proportion of parents with melanoma was 2.6%, the proportion of mothers with melanoma was 3.2%, and the proportion of fathers with melanoma 2.8%. However, these proportions were not significantly greater than the 2.4% expected based on the SEER lifetime prevalence (National Cancer Institute, 2013). The proportion of siblings and children with melanoma, 1.5% and 0.6% respectively, was also less than expected. If the group that was analyzed was limited to probands without melanoma, the proportion of melanoma among parents was 2.5%, with 2.7% for mothers and 2.4% for fathers (Table 3). These numbers were not significantly greater than 2.4%, the expected proportion of individuals with melanoma.. While grandparents, but not other second-degree relatives, showed a higher proportion of melanoma than in the general population, the results were not significant, likely due to the small sample size (involving 10 individuals).

Previous studies had shown an increased risk of melanoma among relatives of those with melanoma. In order to determine if the presence of PD among the probands would affect this increased proportion of those with melanoma, we compared proportions of relatives with melanoma between those that did or did not have family members with melanoma. Among the probands, the proportion of those with melanoma and a family history of skin cancer was 21.5% (20/93) while the proportion of those with melanoma without a family history of skin cancer was 6.1% (42/689). Among probands without melanoma, the percentage of parents, siblings, and children with melanoma was 2.5%, 0.9% and 0.5%, while among probands with melanoma the percentage of parents, siblings, and children with melanoma was 6.5%, 4.5%, and 1.3%.

In order to see if a family history of PD increased the proportion of first-degree relatives with melanoma, we conducted a two-sided t-test on the proportion of first-degree relatives with melanoma calculated per proband (Table 4). There was a significantly higher proportion of melanoma among parents of probands with melanoma and a family history of PD compared to those who did not. This difference was on average 0.9% ($p=0.047$).

Discussion

In this pilot study, we found a significantly higher proportion of melanoma in those with PD than expected in the general white population. We also found a higher proportion of parents, but not first-degree relatives as a whole, with melanoma than expected in the White population. Comparisons were made to the lifetime risk of melanoma, assuming that that risk matched the proportion of relatives matched the proportion of individuals with melanoma by age groups in

the SEER database (National Cancer Institute, 2013). The proportion of first-degree relatives with melanoma was about 3 times greater if the probands had comorbid melanoma with their PD.

There were about three times more probands with melanoma than expected among the general White population ($p<0.005$; binomial probability test). This finding is consistent with studies showing increased risks of melanoma among those with PD in in large studies in Europe (Olsen et al, 2006; Rugbjerg et al, 2012), North America (Bertoni et al, 2010; Kareus et al, 2012), and Israel (Inzelberg et al, 2011). Both melanoma and PD are rare diseases; so finding melanoma at such a high proportion is significant, though our melanoma diagnoses were not confirmed by medical records and therefore may be an overestimate of melanoma, as discussed below in study limitations.

The previously mentioned study by Kareus et al (2012) estimated relatives' increased risk of melanoma among probands who were diagnosed with PD in Utah between 1904 -2008. They only included those who had at least three-generations of relatives in order to make a more precise comparison of relatives with melanoma. They found a significant 23% increased risk of melanoma (RR=1.23, 95% CI 1.07, 1.40) among first-degree relatives of those that had PD compared to age and sex-specific cancer rates in the cohort. Our results are consistent with Kareus et al (2012) and also show an increase in melanoma among relatives of those with PD. However, in contrast to Kareus et al, who found an increased proportion of melanoma in all first-degree relative types, we only found an 8% increased proportion of parents, not siblings and children, with melanoma compared to what was expected. While we relied on data from living probands, Kareus et al (2012) used medical record cohort data, determining numbers of relatives of each type for individuals that had died due to PD complications over a 100-year period. The average age of death from PD ranged in Kareus et al's (2012) study, from 71.2 in 1958-1967 to

80.3 in 1998-2008. In contrast, the average age of those in the WPDR was at 70.4. The older ages and the exclusion criteria of only including those with a complete three-generation family history of Kareus et al (2012) could allow them to find more relatives with melanoma than we found in the WPDR. We also may find more melanoma cases as subjects age, as we found that subjects with melanoma were, on average, 4 years older than those with a family history of melanoma ($p<0.05$), so more melanoma could occur in following years.

Many studies have shown an increased risk of melanoma in those with a family history of melanoma compared to those without a family history of melanoma. In a meta-analysis of 22 studies, Olsen et al (2010) found over a two-fold increase risk of melanoma comparing those who had a family history of melanoma to those who did not (RR=2.1, 95% CI 1.7,2.5), while a review of 14 studies by Chen et al (2013) found a 70% increased risk in melanoma comparing those who had a family history of melanoma to those who did not (RR = 1.7, 95% CI 1.4, 2.1). In a multisite study of 2,508 individuals in North America, Europe, and Australia, Begg et al (2004) found over a two-fold risk of melanoma comparing a family history of melanoma to a non-family history of melanoma (RR = 2.2, 95% CI 1.8, 2.9). Like the previous studies, we found a higher proportion of relatives with melanoma in those that had a family history of melanoma, though all of our individuals also had PD.

Other studies estimated risk to relatives of melanoma among those with melanoma compared to those without melanoma; most have found an increased risk of melanoma among those who have relatives with melanoma. Eldon et al (2010), in contrast to most other studies, did not find any added risk in first-, second- or third-degree relatives among 497 cases with melanoma compared to age and sex matched controls in the Iceland Cancer Registry, other studies. Two studies in the Utah Population Database found increased risks for melanoma in

family members of those with melanoma compared to an age- and sex- matched cohort without a family history of melanoma. Kerbert and O'Brien (2005) found a over two-fold increased risk of melanoma in first-degree relatives of 2,606 cases with melanoma compared to matched controls (RR = 2.5, 95% CI 1.8, 3.4), while Larsen et al (2007) found an even larger three-fold increased risk in melanoma (RR = 3.1, 95% CI 2.8, 3.6) for first-degree relatives of 4,079 cases with melanoma to an age-matched cohort. Finally, a study by Hemski et al (2004) looking at 24,818 verified melanoma cases in the Swedish Cancer Registry found a doubling or tripling of risk in probands if a relative had melanoma (SIR = 2.4, 95% CI 2.1, 2.7 if a parent had melanoma; SIR = 3.0, 95% CI 2.5, 3.1 if a sibling had melanoma), comparing those who had relatives with melanoma to those who did not have relatives with melanoma. In our study, the proportion of first-degree relatives in probands with melanoma compared to probands without melanoma were 2.6 times greater for parents (3.0 times greater for mothers, 2.0 times greater for fathers), 3.2 times greater for siblings, 3.3 times greater for children, and 2.8 times greater for all first-degree relatives. The increased proportions of relatives with melanoma comparing those with comorbid melanoma and PD to those with PD are consistent with previous studies that just compared those with melanoma to those without melanoma

There were several limitations in this study. Over 96% of the individuals in this study were Non-Hispanic White and, although both diseases have a higher incidence in this group, the information in this study may not be applicable to the general population. Our sample was limited to contacting the subset of the probands who reported skin cancer in them or their relatives in their Annual Updates or Enrollment forms. In the future we would want to collect the same information about melanoma among all participants in the WPDR.

The most important limitation in this study was the potential for misclassification. All information on melanoma, skin cancers, and PD were self-reported by the probands. Self-report of melanoma was shown in a study by Bergmann et al (1998) to have a low positive predictive value (0.34) and sensitivity (0.53) when compared to medical records in SEER or other cancer registries. If many people in the WPDR were misclassified as having melanoma that did not have it, we would be overestimating the prevalence of melanoma in the sample. Of the 122 probands contacted, there were 16 with discordant results between their survey and interview. If people who were contacted were a good representative of the WPDR population, this represents misclassification of about 4.9% for not having skin-cancer and 13.1%, if the misclassification of skin cancer type was included. There still is a 3-fold increased proportion of melanoma compared to the general population, if only the 48 that had a follow-up interview were considered. However, some of those that reported melanoma in both their survey and in the interview may not actually have melanoma, so the possibility of misclassification still exists. While this misclassification might reduce the proportion of subjects with melanoma, it is unlikely to fully account for the observed increased proportion of probands with melanoma. Some probands with melanoma may also have mis-reported their disease as skin cancer, and therefore would not be included in our melanoma estimates. In addition, probands could be more vigilant about screening for cancer, catching possible skin cancer before it became melanoma (some probands in interviews mentioned seeing a dermatologist regularly because they knew about the higher risk for melanoma). Therefore, the proportion of melanoma could also be an under-estimate as the proband would have removed a site before it became cancerous (in interviews with probands, some mentioned that they or relatives had suspected cancers

removed, but these were not reported as “skin cancer” on the Enrollment or Annual Update forms).

Age of the probands must also be considered for determining risk of melanoma to probands and their relatives. There was no difference in age or age at diagnosis of PD between any of the groups among the 810 who answered the melanoma questions so the differences in proportion of melanoma might not be reflective of age. It is possible that melanoma prevalence might change with different birth cohorts, with different rates between parents and probands/siblings, and between probands/siblings as people have become more aware of preventive measures but also may have different risk exposure patterns.. SEER data has shown that melanoma prevalence has increased by 4.6% in 1975-1985 and by 2.6% between 1985 and 2010 (National Cancer Institute, 2012). Through interviews with probands, some information on melanoma diagnosis age was obtained. The average age of melanoma diagnosis for parents (n=32) was 70.1 ± 12.3 years, for siblings (n=10) was 54.6 ± 10 years, for children (n=7) was 35.6 ± 8.0 years, and for second degree relatives (n=6) was 61.3 ± 14.4 years. This younger age at melanoma diagnosis in subsequent generations could reflect SEER reported trend in increased melanoma prevalence or may be because we are capturing those who get melanoma earlier in the younger generations. To further investigate this increased proportion of melanoma in probands with PD probands and relatives of probands, we would need to access medical records to determine if the self-reported melanoma diagnoses are accurate, especially given low reliability of melanoma self-reports.

Unlike some previous studies in which melanoma is diagnosed after PD diagnosis, in our study, the self-reported PD diagnosis age occurred about 4 years after the self-reported melanoma diagnosis. In a meta-analysis of 12 studies, Liu et al (2011) found a different pattern

than we found, with more risk for melanoma after PD diagnosis than before. They found over a three-fold increased risk of melanoma after PD diagnosis compared to a 44% increased risk before PD diagnosis compared to age- and sex- matched controls ((OR = 3.61, 95% CI 1.49, 8.77; OR = 1.44, 95% CI 1.06, 1.96, respectively) (Liu et al, 2011). In another meta-analysis of 14 studies, Rugbjerg et al (2012) found a 70% increased risk for melanoma comparing those with PD to age- and sex- matched controls (RR = 1.7, 95% CI 1.2, 2.4); there were no significant results for melanoma risk outside of that time window. Our study had a large range in the ages at diagnosis of PD and melanoma (Figure 3), and may not be directly comparable with these studies.

In the future, we may want to investigate possible genetic and environmental links that could explain the comorbidity of these two diseases. In order to do this, we would focus on those families with younger onset of melanoma and / or PD as well as families with multiple affected individuals for genetic analysis. It is possible there is a connection between the two diseases in the melanin pathway (Figure 1) or in other genes of interest. While Meng et al (2012) did not find any significant SNPs shared between those with PD and those with melanoma in a GWAS, a family study with carefully selected families using linkage analysis or sequencing might be able to better elucidate genetic contributions to the increased risk for both diseases.

Other studies have found a significantly increased risk of melanoma in PD patients associated with risk factors such as fair skin, red hair, blue eyes, and blistering sunburns (Bertoni et al, 2010; Pan et al, 2011). We did not have information on these types of melanoma risk factors beyond race and ethnicity in our analysis, but might want to collect this information in the future. Gao et al (2009-2) found an increased risk of PD with decreasing hair darkness in a

cohort analysis of 38,461 men and 93,661 women who were free of PD in 1986 in the Health Professional's Follow-up study and in 1980 Nurses Health Study. Each group was followed until 2002. They also conducted a nested case-control analysis of the previously mentioned *MC1-R* gene. 298 PD cases were matched 4:1 to randomly selected cohort members by birth year, sex, and DNA collection method. The same variants in *MC1-R* that were associated with red hair and a lighter complexion were also associated with an over three-fold risk of PD (RR = 3.2, 95% CI 1.1, 9.4) (Gao et al, 2009-2). The authors proposed that a connection between *MC1-R* and PD could be that the gene variant is associated with fewer neuromelanin dopamine producing cells.

If we do find genetic risk factors for melanoma and /or PD in the future, we would need to determine when, if ever, to communicate those results to patients or their families. In a study by Vadaparampil et al (2007), 48% of first-degree relatives of probands with melanoma were interested in a genetic test for melanoma risk, even if that test was only approved for research not clinical use. Most had positive responses to the possibility of genetic testing (such as better informed healthcare decisions) compared to negative responses (such as fears of insurance discrimination). Melanoma is a severe cancer, but can be easily treated if caught early enough. Rather than giving a genetic test, it would probably be more effective to continue to inform those with PD that they have a higher risk for melanoma and to be more vigilant about skin surveillance and also to be certain to use sun protection.

However, not all diseases have as clear or effective preventative measures as melanoma; this is the case with both PD and Alzheimer's disease, another neurological disease. Tan et al (2007) found positive attitudes towards genetic testing among relatives of probands with PD, although there were fears of healthcare discrimination. While there might not be as many clear preventative measures for PD as for melanoma, finding out a genetic predisposition to PD might

reduce anxiety and allow patients to try preventative measures such as exercise or diet change that, while they may not prevent onset of disease, are not harmful and contribute to better health. In studies of another neurological disease with limited prevention measures, Alzheimer's disease, researchers found that those who learned that they carried the higher risk allele were more likely to participate in health-positive behaviors (Chao et al, 2008) and did not have a significantly increased risk of depression or other short or long-term negative symptoms (Roberts et al, 2005). Therefore, we might consider reporting information on genes that increase risk for PD and / or melanoma if they might encourage health-positive behaviors.

There is speculation that contextual factors, such as socioeconomic status (SES), might confound the relationship between PD and melanoma. A case control study in over 2,500 people with melanoma found a significant association between higher income compared to lower income, and white collar work compared to blue collar work (OR = 1.58, 95% CI 1.33, 1.88, and 1.33, 95% CI 1.17, 1.51, respectively $p<0.001$) among age- and race-matched men, but not women (Pion et al, 1995). In this study, income and type of work was used as a proxy for SES. It is speculated that those with higher income are more likely to take vacations that involve intermittent sun exposure, including the risk of blistering sunburn (Pion et al, 1995). The connection between SES and these two diseases could involve behaviors that these groups engage in. Smoking reduces risk of PD, a connection that has been confirmed in many studies, while infrequent sun exposure resulting in tanning or burning results in a higher melanoma risk. Smoking is more common in those with a lower SES (reduced risk for PD), and infrequent tanning is more common in higher SES (increased risk of melanoma). In order to investigate whether SES confounds the relationship between melanoma and PD, we would collect SES proxies, such as an estimated income and / or education, as well as data on the proposed

proximal risk factors such as smoking and sunburns and adjust analysis for these potential confounders.

Conclusion

This study found 3 times more probands with melanoma that would be expected in the general White population without PD. Proportions of parents with melanoma were 8% higher than expected in the general White population. This increase in the proportion of those with melanoma was significant for probands, but not first-degree relatives.

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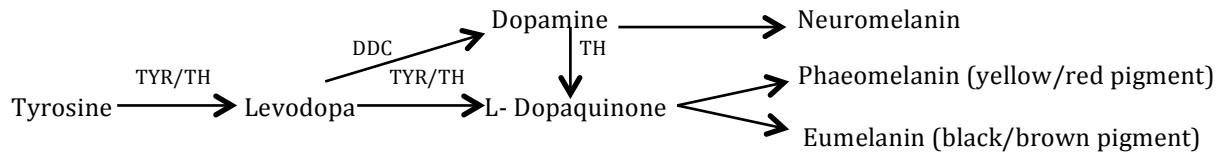
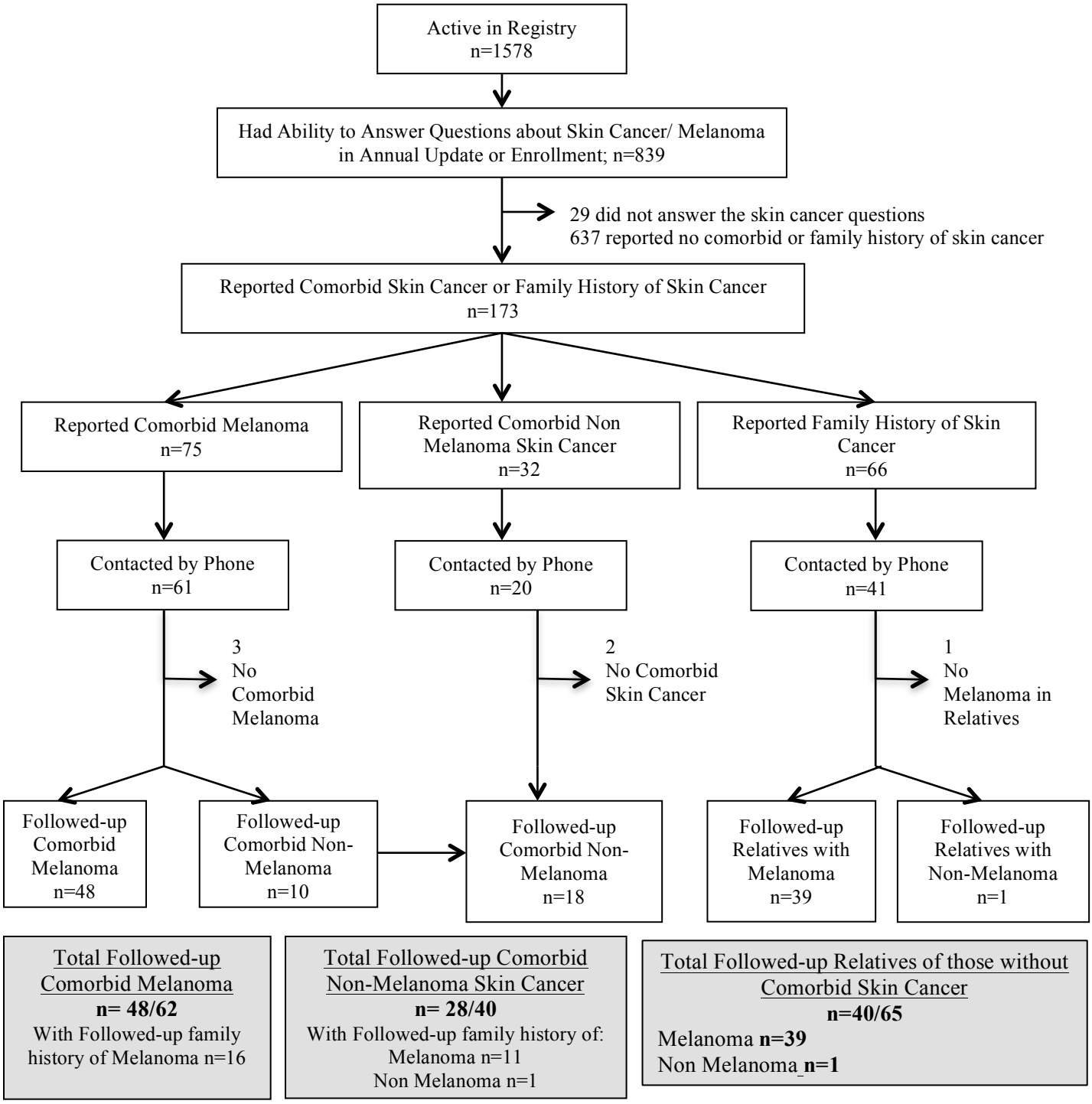
Figure 1: Synthesis of melanin and neuromelanin involves a shared pathway[2].



[2] Neuromelanin cells die in Parkinson's, and melanin-producing cells become cancerous in melanoma. It has been proposed that the connection between these two diseases may lie in this pathway. (based on Pan et al, 2011)

Figure 2: Flowchart of the study and contact with those in the WPDR.[3]



[3] The 173 probands who reported comorbid skin cancer or a family history of skin cancer were called between March 2013 and June 2013. Gray boxes give the total number of followed up probands. After follow-up there were 643 individuals who did not have co-morbid skin cancer or a family history of skin cancer.

Table 1: Demographics within Study, broken up by groups.[4]

	Had Opportunity to Answer Melanoma Questions in Annual Update or Enrollment n=839	
	n	%
Female	276	32.9
White Race	816	97.3
Non Hispanic Ethnicity	833	99.3
Age: Mean ± SD	69.8 ± 9.2	
Age at PD Diagnosis: Mean± SD	62.1 ± 10.4	

	Comorbid Skin Cancer or Family History of Skin Cancer (n=167)		No Comorbid Melanoma or Family History of Skin Cancer (n=643)		Did Not Answer the Skin Cancer Questions (n=29)	
	n	%	n	%	n	%
Female	52	31.1	217	33.7	7	24.1
White Race	167	100	621	96.6	28	96.6
Non Hispanic Ethnicity	167	100	637	99.1	29	100
Age: Mean ± SD	69.7 ± 9.8		69.7 ± 9.3		71.8 ± 7.2	
Age at PD Diagnosis: Mean± SD	62.2 ± 11.5		62.2 ± 10.4		62.1 ± 11.0	

Probands with Comorbid Skin Cancer or Family History of Skin Cancer (n=167)	Comorbid Melanoma (n=62)		Comorbid Skin Cancer (n=40)		No Comorbid Skin Cancer but Family History of Skin Cancer (n=65)	
	n	%	n	%	n	%
Female	**11**	**17.8**	12	30	**35**	**46.1**
White Race	62	100	40	100	65	100
Non Hispanic Ethnicity	62	100	40	100	65	100
Age Mean ± SD	**71.4 ± 9.5**		70.8 ± 8.6		**67.6 ± 9.9**	
With Siblings	55	88.7	36	90.0	72	94.7
With Children	55	88.7	35	87.5	65	85.5
With Full Second Degree Relatives	10	16.1	6	15.0	10	13.1
With Full Third Degree Relatives	5	8.6	6	15.0	5	6.8
Family History of PD	17	27.4	15	37.5	30	39.5
1st	11	17.7	11	27.5	19	25.0
2nd	14	22.6	7	17.5	12	15.8
Family History Melanoma	20	32.3	13	32.5	63	96.9
1st	17	27.4	13	32.5	51	78.5
2nd	5	8.1	0	0	13	20.0
Family History Skin Cancer	20	32.3	14	35.0	65	100
1st	17	27.4	14	35.0	53	81.5
2nd	5	8.1	0	0	15	23.1
Melanoma Diagnosis Followed-up	48	77.4	28	70.0	49	64.5
Age at PD Diagnosis Mean ± SD	62.4 ± 11.3		65.5 ± 10.6		60.7 ± 11.6	
Age at Skin Cancer Diagnosis Mean ± SD	58.4 ± 12.7		61.1 ± 12.9		X	

[4] White race was compared to non-white, and non-Hispanic ethnicity to Hispanic ethnicity. In paired t-tests, the only significant differences between groups are indicated in bold. Comorbid melanoma and no-comorbid skin cancer groups were significantly different in proportion of females and age ($p<0.05$).

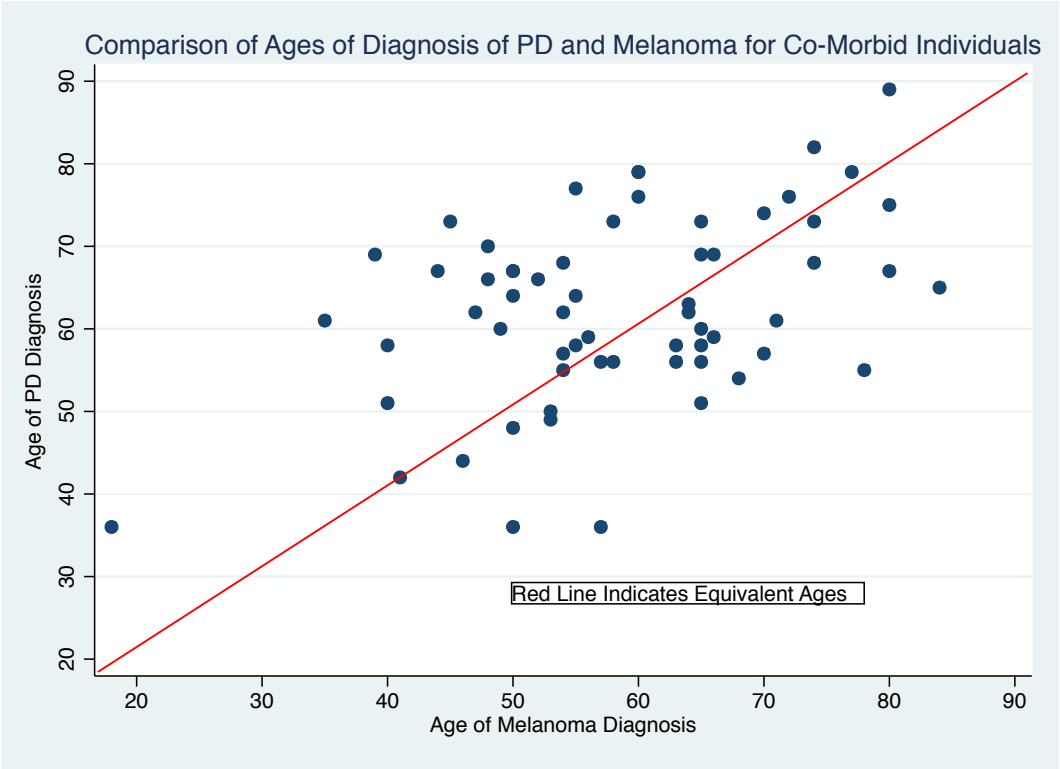


Figure 3: Difference in reported Parkinson's Diagnosis Age and Melanoma Diagnosis Age among those with comorbid skin cancer in the WPDR

Table 2: Melanoma in First Degree Relatives of Probands[5]

Probands		Parents			Siblings			Children		
Type	n	Total	With Melanoma n(%)	With Non-Melanoma Skin Cancer n(%)	Total	With Melanoma n(%)	With Non-Melanoma Skin Cancer n(%)	Total	With Melanoma n(%)	With Non-Melanoma Skin Cancer n(%)
All	**810**	**1620**	**47(2.6%)**	**10(0.6%)**	**1908**	**28 (1.5%)**	**1 (0.05%)**	**1801**	**11(0.6%)**	**2(0.1%)**
Comorbid Melanoma	62	124	8 (6.5%)	0 (0%)	133	6 (4.5%)	0 (0%)	149	2 (1.3%)	1 (0.7%)
Comorbid Non-melanoma Skin Cancer	40	80	3 (0.4%)	7 (0.9%)	106	7 (0.7%)	1 (0.1%)	87	1 (0.1%)	1 (0.1%)
No Comorbid Skin Cancer	708	1416	36 (2.5%)	3 (0.2%)	1669	24 (1.4%)	0 (0%)	1565	9 (0.6%)	0 (0%)

[5] Absolute numbers and percentages for those with comorbid melanoma and those without comorbid melanoma are given. There were a larger proportion of parents, siblings, and children with melanoma among probands with comorbid melanoma compared to probands without comorbid melanoma

Table 3: Proportion of Relatives with Melanoma[6].

Proband	Degree	Relative	Total	Proband	Melanoma n Disease	Melanoma n Well	Melanoma Proportion of Relatives	Adj Well	Adjusted Proportion of Relatives
Comorbid Melanoma	First	Parents	124	62	8	116	0.065	113.2	0.066
		Mothers	62	62	5	57	0.081	55.6	0.082
		Fathers	62	62	3	59	0.048	57.6	0.049
		Siblings	133	55	6	127	0.045	123.9	0.046
		Children	150	55	3	147	0.020	143.5	0.020
		Total	407	62	17	390	0.042	380.6	0.043
	Second	Grandparents	40	10	2	38	0.025	38	0.025
		Aunts/Uncles	69	10	1	68	0.014	66.4	0.015
		Nieces/Nephews	49	10	0	49	0	47.8	0
		Total	158	10	3	155	0.019	152.2	0.019
	Third	Cousins	42	5	1	42	0.024	40.1	0.024
No Comorbid Melanoma	First	Parents	1416	708	36	1380	0.025	1347.2	0.026
		Mothers	708	708	19	689	0.027	672.6	0.027
		Fathers	708	708	17	691	0.024	674.6	0.024
		Siblings	1669	643	24	1645	0.014	1605.8	0.015
		Children	1565	595	9	1556	0.006	1519.0	0.006
		Total	4650	708	69	4581	0.015	4472.0	0.015

[6] Adjusted proportions with melanoma was calculated by dividing the total number of relatives of each type with melanoma by adjusted well + relatives with melanoma. Only probands with full secondary relatives information were used to estimate proportion of secondary relatives with melanoma.

Table 4: Comparison of proportion of melanoma in first-degree relatives of probands with comorbid melanoma[7].

	Proportion of Relatives with Melanoma					
		No Family History of PD			Family History of PD	
Relatives	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI
Parents	**45**	**0.067 (0.172)**	**(0.015, 0.118)**	**17**	**0.058 (0.166)**	**(-0.026, 0.144)**
Siblings	39	0.094 (0.278)	(0.004, 0.184)	16	0.016 (0.063)	(-0.018, 0.050)
Children	39	0.012 (0.081)	(-0.013, 0.039)	16	0.0625 (0.25)	(-0.071, 0.196)
Total	45	0.048 (0.087)	(0.022, 0.074)	45	0.034 (0.071)	(-0.002, 0.071)

[7] The proportion of melanoma was calculated per proband with comorbid melanoma (n=62) and averaged, then compared by a 2-sided t-test with unequal variances. There were significantly less parents with melanoma among probands who had a family history of PD, compared to those who did not have a family history of PD ($p<0.05$ for t-test with unequal variances)