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Variants in *GBA, SNCA*, and *MAPT* Influence Parkinson Disease Risk, Age at Onset, and Progression

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Abstract

Multiple genetic variants have been linked to risk of Parkinson disease (PD), but known mutations do not explain a large proportion of the total PD cases. Similarly, multiple loci have been associated with PD risk by Genome-Wide Association Studies (GWAS). The influence that genetic factors confer upon phenotypic diversity remains unclear. Few studies have been performed to determine whether the GWAS loci are also associated with age at onset (AAO) or motor progression. We used two PD case-control datasets (Washington University and the Parkinson's Progression Markers Initiative) to determine whether polymorphisms located at the GWAS top hits (*GBA*, *ACMSD/TMEM163*, *STK39*, *MCCC1/LAMP3*, *GAK/TMEM175*, *SNCA*, and *MAPT*) show association with AAO or motor progression. We found associations between SNPs at the *GBA* and *MAPT* loci and PD AAO and progression. These findings reinforce the complex genetic basis of PD and suggest that distinct genes and variants explain the genetic architecture of PD risk, onset, and progression.

Keywords

Parkinson Disease; Age at Onset; Motor Progression; *GBA*; *SCNA*; *MAPT*

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INTRODUCTION

Parkinson disease (PD) is a neurodegenerative disorder with a complex etiologic basis including genetic and environmental factors. The discovery of mutations in a small number of genes associated with autosomal dominant and autosomal recessive forms of PD (including *SNCA, LRRK2, PRKN, PINK1, DJ-1*, and others) have shed considerable light on the pathophysiology of PD, but these disease-causing gene mutations only account for a small minority of PD cases [1-6]. Careful analysis of the remaining majority of PD cases that do not have a clear Mendelian inheritance pattern has demonstrated that variants in multiple genes may influence PD risk rather than cause disease. Over the last decade, multiple genome-wide association studies (GWAS) have identified more than twenty loci that each confer relatively small risk or protective effects [7-12]. Interestingly, several of these loci are near genes that cause autosomal forms of PD (e.g. *SNCA, LRRK2*), though the majority represent novel associations. Several of these loci are in close proximity to genes associated with other neurodegenerative diseases (*MAPT*), inflammation (*STK39*), or neurosecretory function (*MCCC1/LAMP3, SYT11/RAB25*), providing clues to their potential role in PD pathophysiology.

Despite the substantial progress in discovery of PD risk loci over the last decade, the risk attributable to identified genetic variants still does not entirely account for the genetic heritability observed in PD. This gap indicates that multiple genetic variants not yet described likely play a role in PD pathophysiology. Recently, Keller et al. used a statistical model termed genome-wide complex trait analysis (GCTA) to quantify so-called “missing heritability” in PD. They estimated that genetic factors could explain up to 27% of the PD cases, in contrast to the estimated 3-5% attributable to the top single nucleotide polymorphisms (SNPs) identified in GWAS studies to date [13]. This finding suggests that many more genetic variants yet to be discovered may influence PD risk and could represent novel therapeutic targets.

In addition to influencing risk of PD, genetic variants may also play a role in specific disease characteristics. Phenotypic diversity characterizes PD with variability of the pattern of motor manifestations, the range of age at onset, the difference in rate of progression, responsiveness to dopaminergic treatment, and the presence and progression of comorbid neuropsychiatric features including dementia and depression. Several studies have investigated the genetic basis of this diversity and have identified associations between multiple SNPs and disease phenotypes including age at onset, progression, and motor complications [14-24]. A recent analysis using a composite polygenic risk score compiled from multiple GWAS studies reported a significant association between higher polygenic risk scores and earlier age at onset [25]. Taken together these studies support the hypothesis that common genetic variants regulate specific PD phenotypes and underscore the need for further work in this area to identify trait-specific alleles.

In this study, we investigated the effect of common genetic variants on PD risk and other disease-related phenotypes: age at onset, and progression. We used data from the PDGene database to select 23 SNPs associated with PD. We then analyzed data from two studies of PD patients and healthy controls from the Washington University Movement Disorders

Center and the Parkinson's Progression Markers Initiative (PPMI) to determine associations between these SNPs and PD risk, age at onset, and rate of disease progression.

MATERIALS AND METHODS

Subjects

PD patients and healthy controls were recruited from the Washington University in Saint Louis Movement Disorder Center (WU). Appropriate written informed consent was obtained from all subjects and the study protocol was approved by the Institutional Review Board. A clinical diagnosis of PD satisfied United Kingdom Brain Bank criteria [26], modified for genetic studies [27]. Data from subjects in the Parkinson's Progression Markers Initiative (PPMI) study were obtained from the PPMI database (www.ppmi-info.org), accessed most recently on December 12, 2014. All individuals were of European descent and written consent was obtained from all participants.

Demographic characteristics have been described previously [28] and are listed in Table 1. The Washington University series contained 418 patients with clinical diagnoses of PD and 306 unaffected and unrelated control subjects. The mean age at onset was 60.4 ± 11.1 years for cases and the mean age at inclusion was 72.4.0 ± 15.1 years for controls. The PPMI series contained 368 patients with clinical diagnoses of PD and 150 unaffected and unrelated control subjects. The mean age at onset was 61.4 ± 9.9 years for cases and the mean age at inclusion was 60.9 ± 11.4 years for controls. In the Washington University series, 25% of cases reported a positive family history of PD, compared to 9% of cases in the PPMI series. Family history was defined as any family history and not restricted to first-degree relatives. The two series had a similar percentage of male cases, whereas the Washington University series had a higher percentage of female controls.

Genotyping and Selection of SNPs

All WU and PPMI samples were genotyped using the Illumina Immunochip and NeuroX. Prior to association analysis, all samples and genotypes underwent stringent QC. Genotype data was cleaned using PLINK v1.07 (http://pngu.mgh.harvard.edu/purcell/plink/) by applying a minimum call rate for SNPs and individuals (98%) and minimum minor allele frequencies (MAF=0.02) [29]. SNPs not in Hardy-Weinberg equilibrium ($P<1\times10^{-6}$) were excluded. We tested for unanticipated duplicates and cryptic relatedness (Pihat ≥0.5) using pairwise genome-wide estimates of proportion identity-by-descent using PLINK v1.07. When a pair of identical samples or a pair of samples with cryptic relatedness was identified, the sample with a higher number of SNPs that passed QC was prioritized. Eigenstrat was used for each cohort separately to calculate principal component factors for each sample and confirm the ethnicity of the samples. *GBA* coding variants were extracted from the NeuroX genotyping array. The NeuroX array underwent the same QC steps as the Immunochip, but removing variants based on the MAF.

Selection of SNPs for Analysis: We extracted data for 23 variants that showed significant association with PD risk based in part on recent large-scale meta-analysis of GWAS data [9]. The extracted SNPs tag genome-wide significance signals for the *GBA* (1q21), *ACMSD/*

TMEM163 (2q21), *STK39* (2q24), *MCCC1/LAMP3* (3q27), *GAK/TMEM175* (4p16), *SNCA* (4q21), and *MAPT* (17q21) loci.

Statistical Analyses

We used the PLINK whole genome association analysis toolset to analyze the association of variants with PD risk. Odds Ratios (OR) and p-values with risk for PD were calculated using logistic regression including APOE, sex, study site, and the two principal component factors as covariates. Association with AAO was carried out using the Kaplan-Meier method and tested for significant differences, using a log-rank test, with study site, sex, and family history included as covariates using the PROC LIFETEST model (SAS Institute, Inc., Cary, NC). Association with rate of disease progression was evaluated as described previously [30]. Briefly, progression of disease was measured by the change in Hoehn and Yahr stage or UPDRS score per year. Only individuals with at least three serial clinic visits spanning at least 1 year were included. The change in Hoehn and Yahr stage or UPDRS score per year fitted a linear model in both series and therefore we used a mixed linear model (PROC MIXED; SAS Institute Inc) to determine whether there is a relationship between the slope of the Hoehn and Yahr stage or UPDRS score and time as a function of genotype after controlling for study site, sex, family history, age at onset, and initial score included as covariates. The intra-class correlation coefficient for UPDRS measurements among raters in the WU study group was at least 0.85. The goal of this study is to analyze whether the genetic variants associated with PD risk associated with age at onset or progression. To do this we tested three different phenotypes: age at onset, change in UDPRS and change of H/Y scores. For this reason we performed a multiple test correction based on the number of phenotypes tested: $\alpha=0.05/3=0.0167$

RESULTS

Replication of Association between SNPs in *GBA, SNCA* and PD Risk

After combining the two datasets, we found significant association between PD risk and multiple SNPs that have been previously implicated in PD (Table 2, n=456 controls, 786 cases). Consistent with magnitudes reported in previous studies [9, 31], we found the largest risk effect for variants in *GBA*, with odds ratios of 4.46 and 4.975 for rs76763715 (N370S, MAF 0.00665) and rs75548401 (K26R, MAF 0.01173), respectively (Table 2). Four SNPs on chromosome 4 near the *SNCA* gene, rs356219, rs356220, rs356165 and rs2736990 were associated with increased PD risk (p=0.00467, 0.003729, 0.003201, and 0.002784, respectively, Table 2). We also report a trend towards increased PD risk for rs2390669, a SNP in an intron region of *STK39* that has been associated with PD risk in previous studies [9].

rs75548401 (*GBA*) and the H1/H2 *MAPT* Haplotype Influence Age at Onset

In a subgroup analysis of PD cases only (n=786), we found a significant association between rs75548401 in *GBA* and younger AAO (p=0.0126; Table 3 and Figure 1). We also found significant associations between older AAO and multiple SNPs on chromosome 17 (Table 3 and Figure 1). This genomic region is near *MAPT* and has recently also been linked to several other genes including *CRHR1* and *NSF*. In contrast with a previous study reporting

association with younger AAO in subjects with rs356165 (*SNCA*), we did not observe an association with this SNP and AAO in our study population [17].

rs76763715 (GBA) is associated with faster Motor Progression

We used serial assessments of Hoehn and Yahr stage to calculate rates of motor progression for PD cases. In the combined WU/PPMI dataset, Hoehn and Yahr scores were analyzed from 425 cases over a mean of 2.7 years. Carriers of the minor allele of rs76763715 (*GBA*) demonstrated a faster rate of progression of Hoehn and Yahr stage compared to non-carriers (Table 4 and Figure 2, $p=9.00 \times 10^{-4}$). We also analyzed serial measurements of UPDRS-III (motor subset) as another marker of disease progression. To eliminate the potentially confounding effect of dopaminergic medication, we restricted our analysis of UPDRS-III data to scores recorded in the OFF state only. In the WU dataset, UPDRS-III OFF-state scores were analyzed from 110 patients over a mean of 6.8 years. The rate of UPDRS-III progression did not relate to any of the SNPs we examined (Table 5). In similar analyses performed in the WU dataset using UPDRS-III scores measured in both the ON and OFF state, and in the PPMI cohort (in which ON/OFF state was not specified), UPDRS-III score progression also did not relate to any SNPs examined (data not shown). Given the strong contribution of postural stability on the Hoehn and Yahr stage, we performed a subset analysis for progression of UPDRS-III postural stability scores but we did not find an association between rs76763715 (GBA) and postural stability.

Discussion

Consistent with previous reports [7, 9, 15, 17-19, 31], we found nominal associations in the WU and PPMI datasets between SNPs in *GBA* and *SNCA* and PD risk. While we also observed a trend towards significance with a SNP near *STK39*, we found no relationship between PD risk in our population and other SNPs across multiple genes previously linked to PD in other populations, suggesting that our study is underpowered to replicate all the known risk loci. On the other hand, these findings indicate that *GBA* and *SNCA* present larger effect sizes than the other loci in this predominantly European-American population.

We also investigated the effect that common genetic variants have on specific phenotypic characteristics of PD, including age at onset and motor progression. Previous studies in multiple genetically diverse cohorts of PD patients have found associations between age at onset (AAO) of PD and SNPs in multiple genes including *GBA*, *SNCA*, *MAPT*, and *COMT* [15, 17-22]. A meta-analysis of GWAS data from three studies of both familial and idiopathic PD cases found several interesting (albeit non-significant at the genome-wide level) associations with AAO and several SNPs near genes implicated in melanin synthesis, protein misfolding pathways, and vesicular transport, all of which are important cell biological processes in PD and other neurodegenerative disorders [32]. A recent study using polygenic score for PD risk found that individuals with earlier onset also have higher polygenic risk, indicating that some of the genetic variants associated with PD risk also affect AAO [25].

Variants in the *GBA* gene, relatively common among PD patients although rare in the general population, have been shown to relate to earlier age at onset as well as prominent

non-motor symptoms in PD patients, including cognitive impairment, depression, sleep disturbance, and autonomic dysfunction [33]. Interestingly, the *GBA* variant rs76763715 (N370S), common in Ashkenazi Jews and one of the most frequently studied *GBA* variants, did not relate to AAO in our dataset. However, rs75548401 (K26R), first reported as a novel variant in a study of North African PD patients, was significantly associated in our dataset with both PD risk and younger AAO, but not progression [34].

Several groups have previously reported association between variants at the *MAPT* locus and AAO in populations of specific ethnic background, including Japanese and Indian subjects, and in families carrying mutations in *LRRK2* [20, 21, 35, 36]. To our knowledge, our study is the first to report an association between AAO and variants in *MAPT* in a non-*LRRK2*-associated Caucasian population. As in the *LRRK2* families, we found that the minor alleles of these *MAPT* SNPs (H2) were associated with older age at onset of PD. The implications of this finding are not immediately clear, but it should be noted that a recent large meta-analysis found a lower risk of PD with a *MAPT* variant, consistent with our finding that the H2 haplotype may play a protective role in PD [31]. The fact that we did not find an association between *MAPT* variants and PD risk in our dataset may suggest that *MAPT* has a larger effect on AAO than on overall PD risk, or that *MAPT* influences AAO in patients already at risk of PD due to variants in other genes.

Several studies have also reported that the H2 haplotype is protective for AD risk as well as in progressive supranuclear palsy and cortico-basal degeneration, both of which have pure tau pathology [37-39]. It is not immediately clear why the H2 haplotype is also protective in PD, which has primarily alpha-synuclein pathology with concurrent tau pathology in only a subset of patients [40]. A recent study identified some genetic overlap between AD and PD at the *MAPT* locus [41], although previous studies failed to identify any genetic overlap at the genome-wide level [42].

It is worth noting that there are several other genes in addition to *MAPT* located on chromosome 17q21, within the H1/H2 haplotype. While variants in *MAPT* likely explain the association between the H1 haplotype region and neurodegenerative disorders with prominent tau pathology including progressive supranuclear palsy and cortico-basal degeneration, it is possible that other genes within this region may be important in PD, in which pathological tau aggregates are occasionally present in conjunction with alpha-synuclein aggregates. The *CRHR1* gene encodes the corticotropin-releasing hormone receptor and a variant in *CRHR1* was recently shown to be associated with decreased PD risk in a large meta-analysis [31]. Brains from PD patients have reduced levels of CRF-like immunoreactivity [43], and urocortin, a CRF-like peptide, reduces nigrostriatal damage in an rat model of parkinsonism [44]. The *NSF* gene encodes N-ethylmaleimide sensitive fusion protein, an ATPase that plays an integral role in SNARE complex biology and synaptic neurotransmission. A growing literature supports an important link between alpha-synuclein and SNARE proteins [45, 46], and *NSF* may confer an independent genetic risk factor in PD [47]. Further work is required to clarify the role that genetic variation in *CRHR1* and *NSF* plays in PD.

Genetic variants have also been recently linked to motor progression in PD. A variant in the promoter region of *SNCA* was linked with faster progression of UPDRS-III scores in a California case-control study [23]. In a longitudinal, community-based study in the United Kingdom, a group of *GBA* variants (including N370S and L444P) were shown to relate to progression of Hoehn and Yahr stage, although individual analysis was not reported for each variant [24]. A similar but smaller study in a German population also reported more rapid progression of UPDRS-III scores and Hoehn and Yahr stage in patients carrying the same *GBA* variants, although results were again not reported for each variant individually [16]. In our dataset, we found an association with rs76763715 (N370S) and faster rate of progression of Hoehn and Yahr stage, but no relationship to UPDRS-III scores.

Motor progression is variable in PD and while genetic polymorphisms likely contribute to this variability, modeling these relationships is challenging. Clinical scores of motor symptoms (e.g. UPDRS-III) are routinely collected in movement disorders centers, and many academic centers including ours have good intra-rater and inter-rater reliability of these measurements [48, 49]. However, few studies have reported positive associations between genetic variants and motor progression. There are multiple potential explanations for this, including genetic diversity of the study population, length of follow-up and number of visits, and that disease progression is unlikely to remain linear. In our study, the length of follow up was variable and included subjects with relatively short follow up intervals, which may have compromised our ability to detect significant changes in UPDRS-III scores. Further work is needed to better understand the contribution of genetic variants to disease progression.

This study has several limitations. The number of individuals analyzed in our combined dataset from WU and PPMI is considerably smaller than recent meta-analyses from multicenter collaborations, and as such we were underpowered to detect some effects, particularly those with small effect size. Also, our analysis consisted of a single phase, in contrast to other studies which incorporated separate discovery and replication phases. Given that the variants we analyzed have been reported in previous studies, we feel that the lack of a two-phase approach does not significantly impair our conclusions.

Our data confirm the strong effect of *GBA* and *SNCA* on PD risk, and we report novel associations between variants in *GBA* and *MAPT* and specific disease phenotypes including AAO and motor progression. Our results also suggest that variants that tag the H1/H2 haplotype may influence AAO. When taken together with other recent reports, our data indicate that specific genes and variants differentially influence aspects of PD risk and phenotype. Certain variants appear to have a strong effect on disease risk, while other variants also modify age at onset or disease progression, suggesting that distinct aspects of PD have a specific genetic architecture. Focusing additional research on these different aspects of PD will likely lead to the discovery of additional genes and/or variants. Further work is necessary to better characterize the genetic architecture of PD, to determine whether disease risk, onset, and progression share common pathophysiologic mechanisms, and to help identify targets for diagnosis and therapeutic intervention.

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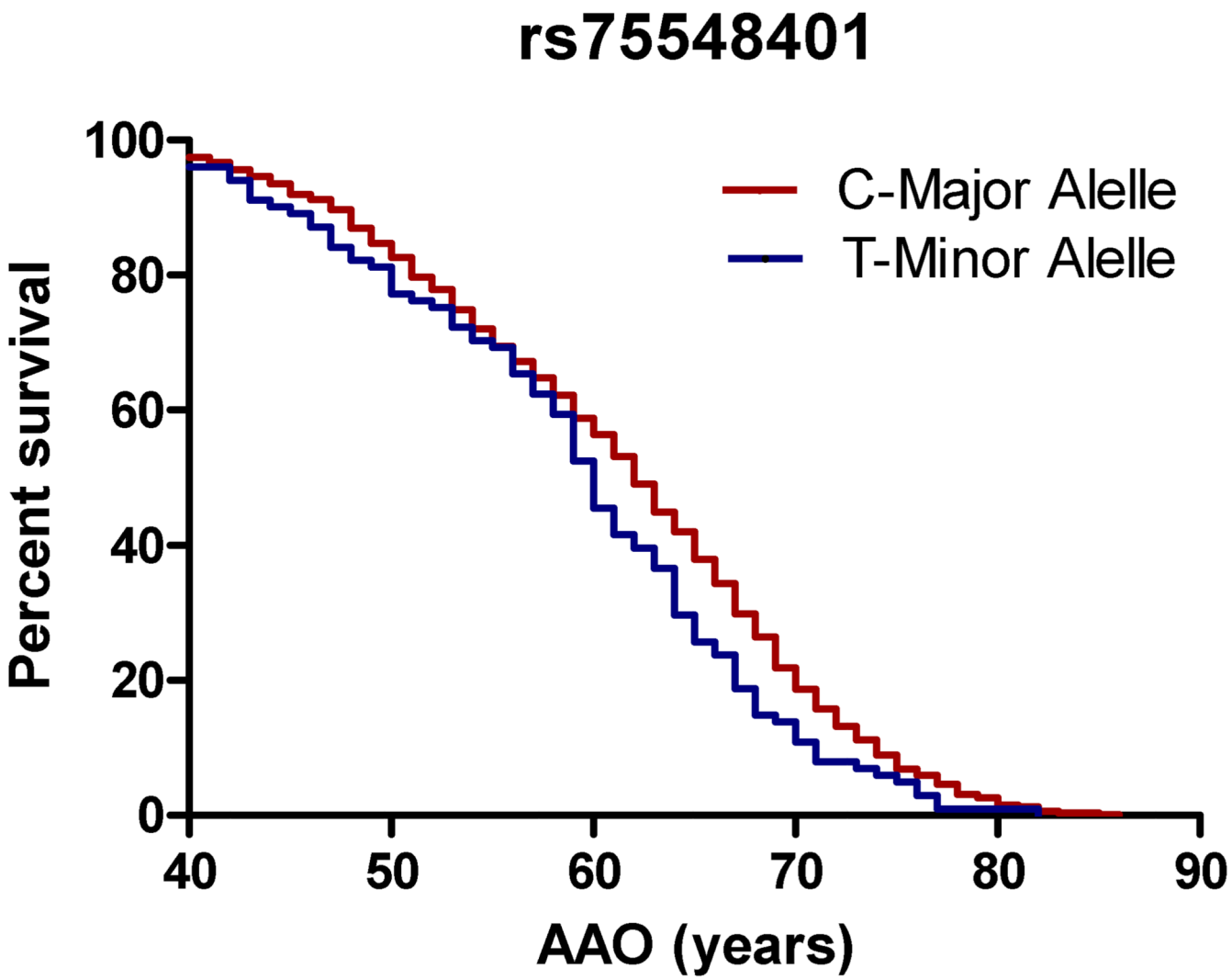
- Parkinson Disease (PD) has a complex genetic etiology.
- We identified variants in *GBA* and *SNCA* that contribute to PD risk.
- We identified variants in *GBA*, *SNCA*, and *MAPT* that influence disease phenotypes including age at onset and motor progression.
- Additional studies are likely to identify novel PD genes and facilitate new treatments.



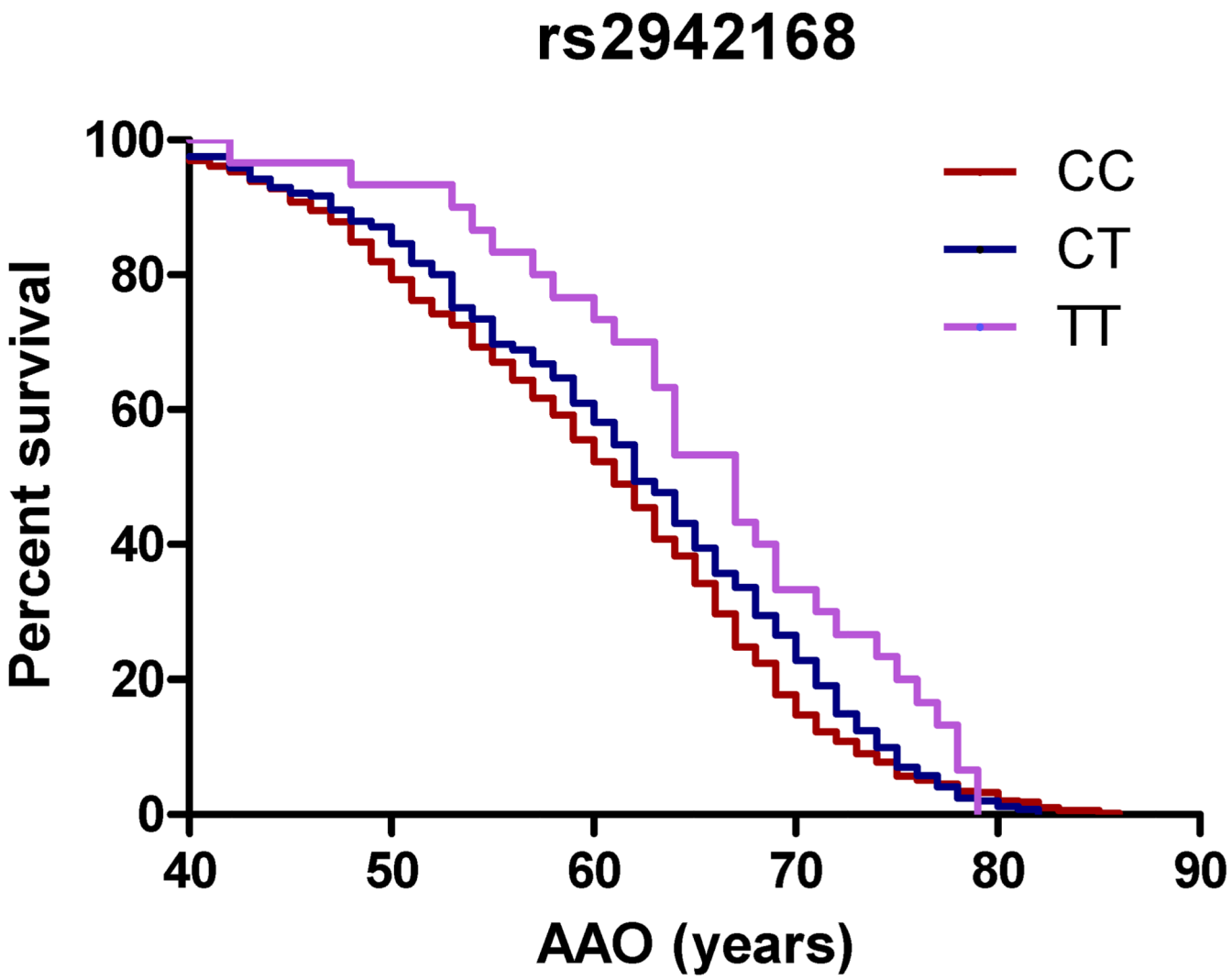


Figure 1. rs75548401 and multiple SNPs at the MAPT locus relate to age at onset

Kaplan-Meier survival curves for age at onset of Parkinson disease motor symptoms are shown for alleles of the GBA variant rs75548401 (a) and rs2942168 (b), a representative variant at the MAPT locus. Rs75548401: mean survival 62 vs 60 years. Hazard ratio: 0.7497 (0.509-0.9512), p=0.0126. Rs2942168: mean survival 61 vs. 62 vs. 67 years. Hazard ratio: 1.17 (1.007-1.36), p=0.0132.

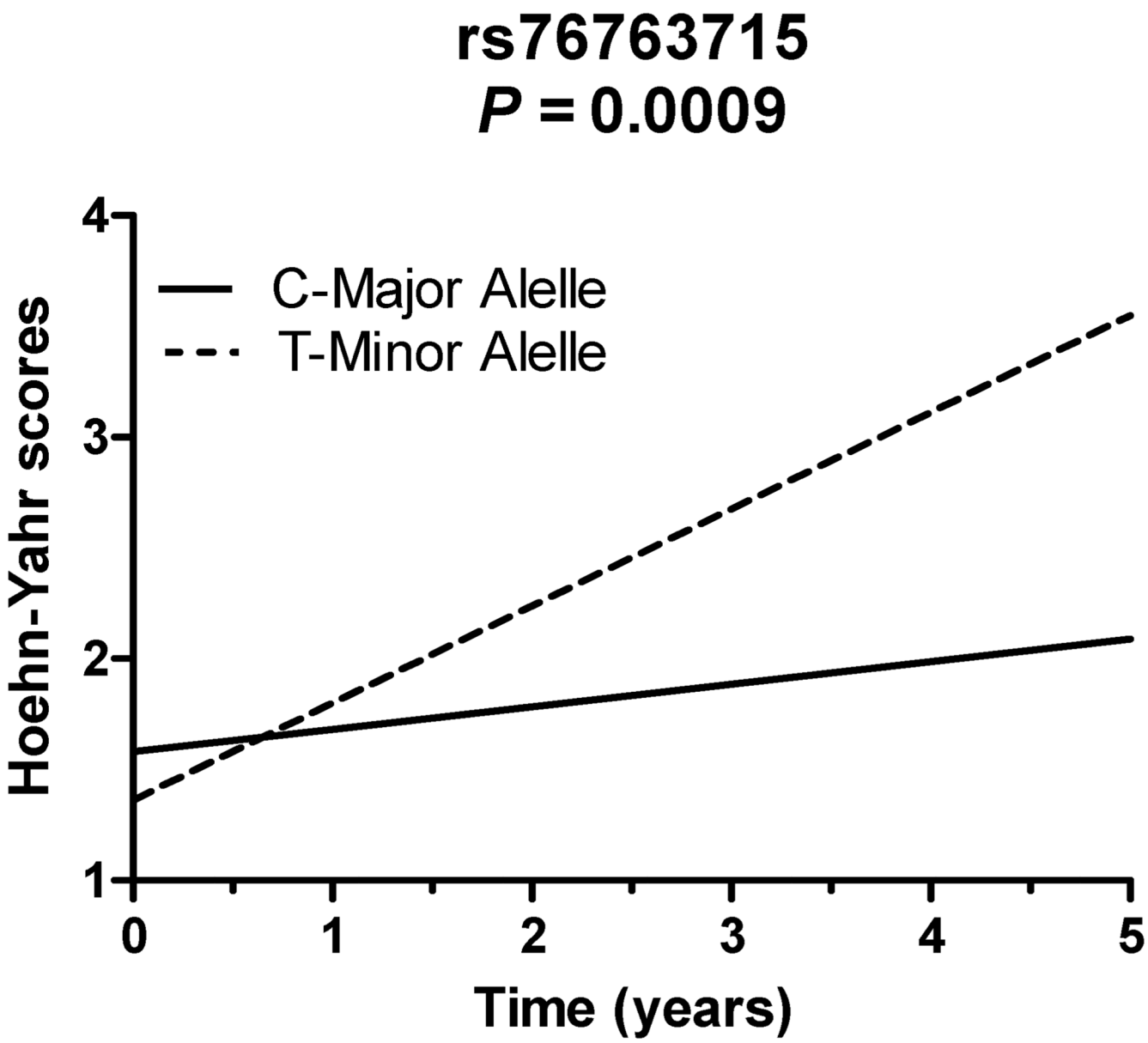


Figure 2.
rs76763715 relates to more rapid progression of Hoehn and Yahr stage

Table 1

Subject Characteristics

WU, Washington University; PPMI, Parkinson's Progression Markers Initiative

Demographic data for subjects in the Washington University (WU) and Parkinson's Progression Markers Initiative (PPMI) datasets are shown.

	WU		PPMI	
Sex, n (%)	**Controls**	**Cases**	**Controls**	**Cases**
Male	105 (34)	258 (62)	100 (67)	240 (65)
Female	201 (66)	160 (38)	50 (33)	128 (35)
Total	306	418	150	368
Age (years), mean (SD), range	**Controls (inclusion)**	**Cases (onset)**	**Controls (inclusion)**	**Cases (onset)**
	72.4 (15.1)	60.4 (11.1)	60.9 (11.4)	61.4 (9.9)
Ethnicity (%)	**Controls**	**Cases**	**Controls**	**Cases**
Caucasian	81.7	92.8	92.7	95.4
Hispanic	0.3	0.0	1.3	2.4
American Indian/Alaska Native	0.0	0.2	0.0	0.0
African American	0.0	0.0	6.0	1.6
Unknown	18.0	6.9	0.0	0.5
PD Family History (%)	**Controls**	**Cases**	**Controls**	**Cases**
Positive	0.0	25.1	0.0	9.2
Negative	88.6	67.9	99.3	90.2
Unknown	11.4	6.9	0.7	0.5

Table 2

Summary of significant loci

Location, nearest gene, and PD risk odds ratios for 22 variants in the combined WU and PPMI dataset. Variants with significant association ($p<0.05$) are indicated in bold. SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency; OR, odds ratio; 95% CI, confidence interval.

						PD Risk			
SNP	**Chr**	**Nearest Gene(s)**	**Position (bp)**	**Minor allele**	**Major allele**	**MAF**	**OR**	**95% CI**	**p value**
rs76763715	1	*GBA* (N370S)	155205634	C	T	0.007	4.46	0.99-19.88	0.050
rs75548401	**1**	***GBA* (K26R)**	**155206037**	**A**	**G**	**0.012**	**4.98**	**1.48-16.66**	**9.25E-03**
rs10928513	2	*ACMSD/TMEM163*	135173229	C	T	0.430	1.13	0.95-1.32	0.143
rs6723108	2	*ACMSD/TMEM163*	135196450	G	T	0.432	1.13	0.96-1.33	0.132
rs2390669	2	*STK39*	168800188	C	A	0.149	1.28	0.99-1.64	0.058
rs11711441	3	*MCCC1/LAMP3*	184303969	A	G	0.132	0.84	0.66-1.07	0.160
rs6599388	4	*GAK/TMEM175*	929087	T	C	0.328	1.12	0.94-1.32	0.207
rs356219	**4**	***SNCA***	**90856624**	**G**	**A**	**0.410**	**1.28**	**1.08-1.52**	**4.67E-03**
rs11931074	4	*SNCA*	90858538	T	G	0.099	1.00	0.75-1.31	0.983
rs356220	**4**	***SNCA***	**90860363**	**T**	**C**	**0.416**	**1.29**	**1.08-1.52**	**3.73E-03**
rs356165	**4**	***SNCA***	**90865909**	**A**	**G**	**0.464**	**1.30**	**1.09-1.54**	**3.20E-03**
rs3822086	4	*SNCA*	90883817	T	C	0.098	0.99	0.75-1.30	0.944
rs3857059	4	*SNCA*	90894261	G	A	0.098	0.99	0.75-1.30	0.944
rs2736990	**4**	***SNCA***	**90897564**	**T**	**C**	**0.497**	**0.78**	**0.65-0.91**	**2.78E-03**
rs2942168	17	*CRHR1/MAPT*	41070633	T	C	0.194	0.99	0.80-1.22	0.961
rs393152	17	*CRHR1/MAPT*	41074926	G	A	0.201	0.95	0.77-1.17	0.639
rs7215239	17	*CRHR1/MAPT*	41123556	C	T	0.221	0.96	0.78-1.16	0.672
rs1981997	17	*MAPT*	41412603	A	G	0.193	0.97	0.78-1.19	0.784
rs1052553	17	*MAPT*	41429726	G	A	0.194	0.98	0.79-1.20	0.826
rs17652121	17	*MAPT*	41429810	C	T	0.193	0.97	0.78-1.19	0.784
rs8070723	17	*MAPT*	41436901	G	A	0.195	0.96	0.78-1.18	0.734
rs199533	17	*NSF/MAPT*	42184098	T	C	0.183	0.94	0.754-1.16	0.547

Table 3
rs75548401 and multiple SNPs at the *MAPT* locus relate to age at onset

The age at onset of Parkinson disease motor symptoms was significantly associated with rs75548401 and with multiple SNPs at the *MAPT* locus. A positive test statistic indicates that the minor allele related to younger age at onset; a negative test statistic indicates that the minor allele related to older age at onset.

SNP	Chr	Nearest Gene(s)	Test Statistic	Standard Error	p value
rs76763715	1	*GBA* (N370S)	2.646	3.284	0.420
rs75548401	**1**	***GBA* (K26R)**	**9.185**	**3.681**	**0.013**
rs10928513	2	*ACMSD/TMEM163*	−4.540	18.923	0.810
rs6723108	2	*ACMSD/TMEM163*	−1.750	18.982	0.927
rs2390669	2	*STK39*	−3.667	13.287	0.783
rs11711441	3	*MCCC1/LAMP3*	−1.732	11.974	0.885
rs6599388	4	*GAK/TMEM175*	22.040	19.211	0.251
rs356219	4	*SNCA*	−0.537	17.916	0.976
rs11931074	4	*SNCA*	4.383	10.994	0.690
rs356220	4	*SNCA*	4.954	18.120	0.785
rs356165	4	*SNCA*	6.199	17.714	0.726
rs3822086	4	*SNCA*	3.757	10.984	0.732
rs3857059	4	*SNCA*	3.757	10.984	0.732
rs2736990	4	*SNCA*	−4.456	18.863	0.813
rs2942168	**17**	***CRHR1/MAPT***	**−38.813**	**15.662**	**0.013**
rs393152	**17**	***CRHR1/MAPT***	**−35.708**	**15.692**	**0.023**
rs7215239	17	*CRHR1/MAPT*	−28.984	15.795	0.067
rs1981997	17	*MAPT*	−38.052	15.650	0.015
rs1052553	**17**	***MAPT***	**−38.849**	**15.655**	**0.013**
rs17652121	17	*MAPT*	−38.052	15.650	0.015
rs8070723	**17**	***MAPT***	**−39.225**	**15.659**	**0.012**
rs199533	17	*NSF/MAPT*	−31.585	14.611	0.031

Table 4

rs76763715 relates to more rapid progression of Hoehn and Yahr stage

P values for association of Hoehn and Yahr stage for cases in the combined WU and PPMI dataset are shown. Cases with at least 3 scores measured over a minimum of 1 year were included.

SNP	Chr	Nearest Gene (s)	p value
rs76763715	**1**	***GBA* (N370S)**	**9.0E-04**
rs75548401	1	*GBA* (K26R)	0.682
rs10928513	2	*ACMSD/TMEM163*	0.576
rs6723108	2	*ACMSD/TMEM163*	0.599
rs2390669	2	*STK39*	0.107
rs11711441	3	*MCCC1/LAMP3*	0.495
rs6599388	4	*GAK/TMEM175*	0.206
rs356219	4	*SNCA*	0.575
rs11931074	4	*SNCA*	0.812
rs356220	4	*SNCA*	0.622
rs356165	4	*SNCA*	0.591
rs3822086	4	*SNCA*	0.820
rs3857059	4	*SNCA*	0.821
rs2736990	4	*SNCA*	0.287
rs2942168	17	*CRHR1/MAPT*	0.456
rs393152	17	*CRHR1/MAPT*	0.380
rs7215239	17	*CRHR1/MAPT*	0.461
rs1981997	17	*MAPT*	0.456
rs1052553	17	*MAPT*	0.456
rs17652121	17	*MAPT*	0.456
rs8070723	17	*MAPT*	0.465
rs199533	17	*NSF/MAPT*	0.744

Table 5

No association between genetic variants and progression of UPDRS scores

P values for association of serial measurements of UPDRS-III scores for cases in the WU group are shown for each variant. Cases with at least 3 scores measured over a minimum of 1 year were included. Only UPDRS-III scores measured in the OFF state were included in the final analysis. Inclusion of UPDRS-III scores measured in the ON state did not significantly change the results (not shown).

SNP	Chr	Nearest Gene(s)	p value
rs76763715	1	*GBA* (N370S)	N/A
rs75548401	1	*GBA* (K26R)	0.975
rs10928513	2	*ACMSD/TMEM163*	0.345
rs6723108	2	*ACMSD/TMEM163*	0.918
rs2390669	2	*STK39*	0.620
rs11711441	3	*MCCC1/LAMP3*	0.894
rs6599388	4	*GAK/TMEM175*	0.223
rs356219	4	*SNCA*	0.714
rs11931074	4	*SNCA*	0.801
rs356220	4	*SNCA*	0.768
rs356165	4	*SNCA*	0.768
rs3822086	4	*SNCA*	0.248
rs3857059	4	*SNCA*	0.455
rs2736990	4	*SNCA*	0.349
rs2942168	17	*CRHR1/MAPT*	0.741
rs393152	17	*CRHR1/MAPT*	0.741
rs7215239	17	*CRHR1/MAPT*	0.686
rs1981997	17	*MAPT*	0.741
rs1052553	17	*MAPT*	0.741
rs17652121	17	*MAPT*	0.741
rs8070723	17	*MAPT*	0.741
rs199533	17	*NSF/MAPT*	0.845