Table 1

Allelic Tests of SNPs Associated with Late-Onset PD

dbSNP Accession Number[a]	Gene	Chromosome	Position (Mbp)	Case[b]					Control[b]					Allelic Test		
				11	12	22	Sum	MAF[c]	11	12	22	Sum	MAF	OR (95% CI)	*P*[d]	Power (%)
rs7702187	*SEMA5A*	*5*	9.4	9	86	215	310	.168	8	83	217	308	.161	1.05 (.78–1.42)	.74	97
rs10200894		2	228.6	1	48	262	311	.080	3	66	238	307	.117	.66 (.45–.96)	.03	93
rs2313982		4	139.1	2	47	258	307	.083	4	45	256	305	.087	.95 (.64–1.42)	.81	96
rs17329669		7	36.6	10	73	224	307	.151	3	60	246	309	.107	1.49 (1.07–2.09)	.02	94
rs7723605		*5*	5.4	6	86	218	310	.158	*5*	70	232	307	.130	1.25 (.91–1.72)	.17	95
ss46548856		10	59.0	2	52	256	310	.090	4	61	241	306	.113	.78 (.54–1.13)	.19	92
rs16851009		2	166.5	6	53	251	310	.105	4	45	259	308	.086	1.24 (.85–1.82)	.26	94
rs2245218	*PRDM2*	1	13.9	12	64	234	310	.142	6	83	215	304	.156	.89 (.65–1.22)	.48	94
rs7878232:																
Male and female		X	150.5	...	...	...	307	.230	...	...	...	301	.244	.92 (.71–1.20)	.55	66
Female		...	...	13	47	101	161	.227	9	61	89	159	.248	.89 (.62–1.28)	.52	...
Male		...	...	...	...	...	146	.233	...	...	...	142	.239	.96 (.56–1.66)	.90	...
rs1509269		4	139.1	*5*	63	243	311	.117	7	65	235	307	.129	.90 (.64–1.26)	.55	92
rs11737074		4	125.4	16	116	178	310	.239	13	102	192	307	.208	1.19 (.91–1.56)	.20	90
rs7520966	*LOC200008*	1	54.4	16	117	175	308	.242	19	129	160	308	.271	.86 (.66–1.11)	.24	97

[a] The top 11 markers are presented in the same order as in table 4 in Maraganore et al.[1]
[b] Counts of genotype 11, 12, and 22.
[c] Minor-allele frequency.
[d] Two-sided *P* value for all strata and for female and male substrata in *rs7878232*.

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A Case-Control Association Study of the 12 Single-Nucleotide Polymorphisms Implicated in Parkinson Disease by a Recent Genome Scan

To the Editor:

To validate associations of SNPs that Maraganore et al.[1] reported as associated with Parkinson disease (PD [MIM 168600]), we constructed a case-control series from PD cases and matched population/convenience controls that are available through the National Institute of Neurological Disorders and Stroke (NINDS) Human Genetics Resources at the Coriell Institute. Cases met United Kingdom Brain Bank criteria for idiopathic PD,[2] and controls were neurologically normal. This series comprises 311 pairs of age- and sex-matched cases and controls. Cases had an age at disease onset ranging from 50 to 87 years (average [±SD] 63.8 ± 8.9 years) and were sampled at the age of 52–92 years (average [±SD] 70.1 ± 8.5 years). Controls were also sampled at the age of 52–92 years (average [±SD] 70.2 ± 8.5 years). All cases and controls are white, and each group includes 165 females (53.1%) and 146 males (46.9%), respectively. Cases in this series do not carry the Gly2019Ser mutation in *LRRK2* [MIM 609007], which may occur in idiopathic PD,[3] and several tests did not reveal evidence of significant population stratification for 78 individually genotyped null markers (data not shown). We individually genotyped the 11 SNPs that were reported significant and one of the two SNPs that map to the *PARK10* [MIM 606852] locus (the two reported-significant SNPs are highly correlated: $r^2 = 0.99$), using allele-specific real-time PCR in our PD case-control sample set. Cases and controls were run on the same plate in a blinded fashion. Our genotyping method has an overall accuracy of >99%.[4] As an additional indication of genotyping quality, we calculated deviation from Hardy-Weinberg equilibrium (HWE) in cases and controls. One marker had an HWE exact *P* value of <.05 (.017 for *rs2245218* in cases), but further examination of our genotype data did not reveal questionable calls. Therefore, these data were included in our analysis. All SNPs were tested for allelic association with PD with the use of χ^2 statistics to calculate two-sided *P* values (table 1). Power calculations were done for a sample size of 311 pairs for each SNP, with the use of a one-sided allelic χ^2-hypothesis test at a significance level of 0.05

and with the assumption that the control-allele frequencies of the unrelated controls and odds ratios (ORs) in table 4 in Maraganore et al.[1] are true population parameters. Power calculation for *rs7520966* was based on the tier 2 OR given in the text of Maraganore et al.,[1] since it did not appear in their table 4.

Two markers, *rs10200894* and *rs17329669,* were replicated in our sample set at $P < .1$ ($P = .03$ and $P = .02$, respectively) with the same risk alleles as in Maraganore et al.,[1] although with slightly lower ORs. *rs10200894* is an intergenic variant located on chromosome 2 near a linkage peak previously identified in late-onset PD,[5] and *rs17329669* is in an intergenic region on chromosome 7. Further investigations in these regions, including further genetic mapping and the identification of potential causative variants, are thus warranted. Indeed, several SNPs in the vicinity of *rs10200894* and *rs17329669* reached significance in the Maraganore et al.[1] discovery sample set ($P < .05$) but were not followed up because they did not reach their significance threshold of $P < .01$. *ELMO1* [MIM 606420], a gene whose product is predicted to be involved in apoptosis and cell migration, resides in a region that, according to the HapMap, is in high linkage disequilibrium with *rs17329669*. The more abundant splice variant of *ELMO1* appears to be exclusively expressed in brain[6] and, thus, constitutes an excellent biological candidate gene for PD. All other markers were not significant in our sample set at the 0.1 level, including the marker reported most significant in *SEMA5A* [MIM 609297] and the marker in *LOC200008,* which maps to the *PARK10* locus that appears to affect both disease risk and age of onset.[7–9] Our failure to replicate the majority of the associated markers may be due to false-positive results in the initial study or to locus heterogeneity. Although the power in our validation sample set is ⩾90% for 11 of the 12 tested SNPs, this may be an overestimation due to an OR inflation ("jackpot effect") in the original study. In addition, our sample set included only late-onset cases, commonly defined by age at onset >50 years, whereas the study by Maraganore et al. included both early- and late-onset cases.[1] Thus, it is possible that nonreplicated markers are associated with early-onset PD but make a lesser contribution to the more common, late-onset form of the disease. Additional studies are required to further assess the association of these markers with PD.

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Web Resources

The URLs for data presented herein are as follows:

dbSNP, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=snp
International HapMap Project, http://www.hapmap.org/
NINDS Human Genetics Resources at the Coriell Institute, http://locus.umdnj.edu/ninds
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PD, *LRRK2, PARK10, ELMO1,* and *SEMA5A*)

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