Letter to the Editor

Am. J. Hum. Genet. 78:1092, 2006

Response from Maraganore et al.

To the Editor:

In this issue, four independent research teams present new genetic association data for 13 SNPs previously reported by us to be potentially associated with Parkinson disease (PD [MIM 168600]).[1] Two groups[2,3] report statistically significant association between one or more of these SNPs and PD, whereas two groups[4,5] find no statistically significant association between PD and any of the SNPs investigated. In an accompanying letter,[6] Dr. Richard H. Myers provides his qualitative assessment of the implications of these new results.

We have performed a Mantel-Haenszel analysis, using 10 of the 13 SNPs not displaying linkage disequilibrium (LD) with each other—combining the data of Li et al.,[3] Farrer et al.,[4] and Goris et al.[5]—to provide an overall quantitative assessment of the new results. The odds ratios (ORs) are reported for the SNP alleles that increase the risk of PD[1] (table 1). The X-linked SNP *rs7878232* was not included in this analysis, since subgroup-level data for males and females were not reported by all groups. The results of Clarimon et al.[2] were also not included, given the significant difference in SNP allele frequency observed between the European and Taiwanese control samples. This analysis reveals that none of the 10 SNPs shows statistically significant association with PD (i.e., $P < .05$). As pointed out in many of the accompanying letters, this failure to replicate may be due, in part, to differences in sample ascertainment and demographics.

A Mantel-Haenszel analysis combining these new results with those from tier 2 of Maraganore et al. reveal five SNPs with $P < .05$ and smaller effect sizes than were originally reported[1] (table 1). Although we are aware that these low *P* values may, at least in part, be explained by multiple testing, additional data are required to determine if these SNPs truly confer PD susceptibility or if they represent false-positive associations. Despite the small ORs, the point estimates of attributable risk for PD in the total data is still quite large for two of these SNPs (*rs10200894* population-attributable risk 0.27, 95% CI 0.04–0.77; *rs7520966* population-attributable risk 0.21, 95% CI 0.1–0.39). If these are true associations, they may have substantial practical impact on PD.

We do not agree with Dr. Myers[6] that our failure to identify an association between the *LRRK2* gene and PD in our original study is evidence of a false-negative result. Farrer et al. have reported elsewhere that only a very small number of the individuals with PD studied in our original whole-genome scan have a mutation in the *LRRK2* (MIM 609007) gene.[7]

We also do not consider the positive association findings between SNP *rs7702187* and PD in a Taiwanese population by Clarimon et al.[2] to be a replication of our original study results, since the SNP allele associated with PD susceptibility is not the same in the two studies. However, further work to follow up these results in the Taiwanese population seems warranted.

It is gratifying that our hypotheses have been tested rapidly by many groups. The Michael J. Fox Foundation, which funded our original research, also has a large-scale replication study under way. Given the low heritability estimates for PD,[8] our initial study may have been underpowered for the detection of significant genetic associations, in part, because of the large number of genetic markers tested. Therefore, it may be prudent not to limit replication of our study to the 13 SNPs that we initially highlighted but to also consider additional SNPs and genes that had suggestive findings (as in the text files published in the online-only version of our original article).[1]

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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

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PD and *LRRK2*)

Table 1

Meta-Analysis of Genetic Association for 10 SNPs

dbSNP Accession Number	Alleles (High-Risk Allele)	Maraganore et al.[1] Tiers 1 and 2					Meta-Analysis (Replication Studies)					Meta-Analysis (Replication Studies and Maraganore et al.[1] Tier 2)				
		Cases	Controls	Allele Frequency (Controls)	OR (95% CI)	*P*	Cases	Controls	Allele Frequency (Controls)	OR (95% CI)	*P*	Cases	Controls	Allele Frequency (Controls)	OR (95% CI)	*P*
rs10200894	C/G (C)	772	772	.88	1.84 (1.38–2.45)	1.70×10^{-5}	1,566	1,546	.89	1.14 (.96–1.35)	.125	1,926	1,955	.89	1.25 (1.07–1.45)	.004
rs11737074	G/A (A)	764	764	.19	1.50 (1.21–1.86)	1.55×10^{-4}	1,563	1,542	.21	1.02 (.9–1.15)	.770	1,925	1,952	.21	1.09 (.97–1.21)	.142
rs16851009	C/T (T)	741	741	.08	1.84 (1.36–2.49)	4.17×10^{-5}	1,539	1,544	.1	.98 (.83–1.16)	.853	1,899	1,953	.1	1.08 (.93–1.26)	.312
rs17329669	A/G (G)	768	768	.12	1.71 (1.33–2.21)	2.30×10^{-5}	1,554	1,525	.12	1.13 (.97–1.32)	.102	1,914	1,933	.12	1.22 (1.06–1.39)	.004
rs2245218	A/G (G)	770	770	.12	1.67 (1.29–2.14)	4.61×10^{-5}	1,571	1,563	.16	.94 (.82–1.08)	.369	1,933	1,971	.16	1.02 (.9–1.16)	.752
rs2313982	C/T (T)	740	740	.07	2.01 (1.44–2.79)	1.79×10^{-5}	1,562	1,554	.09	.88 (.73–1.04)	.138	1,924	1,964	.09	1.01 (.86–1.18)	.935
rs7520966	C/T (C)	769	769	.7	.67 (.55–.81)	2.96×10^{-5}	1,563	1,550	.72	1.07 (.96–1.2)	.242	1,923	1,956	.72	1.15 (1.04–1.27)	.007
rs7702187	T/A (T)	761	761	.81	1.74 (1.36–2.24)	7.62×10^{-6}	1,541	1,541	.83	1.07 (.93–1.22)	.334	1,900	1,950	.82	1.14 (1.01–1.29)	.030
rs7723605	T/C (C)	773	773	.11	1.78 (1.35–2.35)	3.30×10^{-5}	1,567	1,571	.13	1.03 (.89–1.19)	.684	1,927	1,981	.13	1.12 (.98–1.28)	.105
ss46548856	G/C (G)	765	765	.9	1.88 (1.38–2.57)	3.65×10^{-5}	1,551	1,528	.9	1.12 (.94–1.33)	.196	1,913	1,933	.9	1.21 (1.03–1.42)	.016

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0002-9297/2006/7806-0024$15.00