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CORRESPONDENCE

PARK16 haplotypes and the importance of protective genetic factors in Parkinson's disease

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Recent studies suggest that there are at least 28 risk factors for Parkinson's disease (PD) in 24 loci across the human genome,[1] and additional genes cause PD or Parkinsonian syndromes in an autosomal dominant, autosomal recessive or X-linked manner.[2] Moreover, the contribution of hereditary factors for PD development is probably more than 30%, emphasizing the importance of genetic factors in PD pathogenesis.[3,4] However, when reading the recent literature on PD genetics and its potential mechanisms, it seems that, although the genes and risk factors that cause PD or increase the risk for PD are being extensively studied, not enough attention is being given to protective genetic factors. Of course, for each genetic loci increasing PD risk there is its opposite, a protective one. For example, carriers of *GBA* mutations are at increased risk for PD; therefore, non-carriers are at decreased risk as compared with carriers. Yet, these non-carriers have an average population-level risk for PD. However, there are genetic factors that significantly reduce the risk for PD below the average population risk. Studying these naturally occurring protective variations may prove useful for finding new therapeutic targets.

In their recent study, Pihlstrøm *et al.*[5] analyzed the protective *PARK16* region, which was initially identified in the Japanese population[6] and was later replicated in other populations worldwide. Single nucleotide polymorphisms (SNPs) in this region were associated with reduced risk for PD, and a haplotype that includes functional SNPs[7] in the 5′ UTR and promoter region of *RAB7L1* (now officially termed *RAB29*) was previously associated with a 10-fold risk reduction for PD in the Ashkenazi-Jewish population.[8] This is probably the strongest protective genetic factor found to date in PD. Similarly, Pihlstrøm *et al.* also identified a haplotype in the 5′ UTR of *RAB7L1* with about twofold reduced risk for PD in the Scandinavian population. This haplotype included two of the three markers that were analyzed for haplotypes in the Ashkenazi-Jewish population, rs1572931 and rs947211,[5,8] which allows a partial comparison with the Ashkenazi-Jewish population (Table 1). Interestingly, a specific combination of markers of these two SNPs, T allele of rs1572931 and G allele of rs947211, which were part of the 10-fold protective haplotype among Ashkenazi-Jews, did not exist in the Scandinavian population, or had a frequency of <0.01. Of note, the T allele of rs1572931 was also a part of yet another, independent protective haplotype in the Ashkenazi-Jewish population, which was associated with about 25% reduced risk for PD.[8] Among Scandinavians, it were the C allele of rs1572931 and the G allele of rs947211 that were part of the strongest protective haplotype (Table 1). These observations, together with results from other studies,[1,5,7–9] suggest that there are several independent haplotypes around the *RAB7L1* promoter associated with reduced risk for PD.

As coding variants in the genes within the *PARK16* locus were not associated with PD among Scandinavians (although these results need to be confirmed in additional populations), it is likely that the effect of *PARK16* is related to regulatory variants. The existence of several independent protective haplotypes around the *RAB7L1* 5′ UTR and promoter region, together with important functional studies linking *RAB7L1* and the disease causing *LRRK2* and *VPS35* genes,[7,10] suggest that *RAB7L1* is the culprit in the *PARK16* locus. Moreover, these data may suggest that any variation that affects the expression or splicing of *RAB7L1* can influence PD risk. It is therefore imperative to further study the *PARK16/RAB7L1* region in depth, and understand all of the genetic and epigenetic factors in both coding and regulatory regions that convey protection from PD.

Basically, *PARK16* is just one out of several protective genetic regions and genes across the human genome that are associated with a

Table 1 rs1572931 and rs947211 in protective and increased risk haplotypes among Ashkenazi-Jews and in the Scandinavian population

	Protective haplotype[a]			*Risk haplotype*[b]		
Population	*Genotype*[c]	*MAF*	*OR (95% CI)*	*Genotype*[c]	*MAF*	*OR (95% CI)*
Ashkenazi-Jewish	T-G-$_{(T)}$	0.013	0.10 (0.02–0.44)	C-G-$_{(C)}$	0.72	1.95 (1.25–3.04)
Scandinavian	C-G-$_{(C)}$	0.028	0.51 (0.33–0.77)	C-G-$_{(T)}$	0.72	1.18 (1.04–1.33)

Abbreviations: CI, confidence interval; MAF, minor allele frequency (in the respective control population); OR, odds ratio.
[a]The haplotype with the lowest ORs in each population.
[b]The haplotype with the highest ORs in each population.
[c]The first two nucleotides correspond to the genotypes of rs1572931 and rs947211, respectively. In parentheses, the nucleotide represents the third SNP of the haplotype, in the Ashkenazi-Jewish population it was rs1772153 and in the Scandinavian population it was rs1775143.

reduced risk for PD, such as *SCARB2*, *MAPT* and others.[1] Considerable effort is needed for studying these protective genes and their effects. Even if we do not fully understand the pathogenic mechanism leading to PD, by properly defining and perhaps manipulating these protective genetic factors we may find the long-awaited treatment for PD.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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