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Genetic Reports Abstracts

Role of sepiapterin reductase gene at the PARK3 locus in Parkinson's disease

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Abstract

Sepiapterin reductase (*SPR*) gene is an enzyme which catalyses the final step of tetrahydrobiopterin synthesis (BH4) and was implicated in Parkinson's disease (PD) pathogenesis as a candidate gene for PARK3 locus. A number of studies yielded association of the PARK3 locus with PD, and *SPR* knockout mice were shown to display parkinsonian features. To evaluate the role of *SPR* gene polymorphisms in diverse populations in PD, we performed collaborative analyses in the Genetic Epidemiology of Parkinson Disease (GEO-PD) Consortium. A total of 5 single nucleotide polymorphisms (3 in the promoter region and 2 in the 3′ untranslated region [UTR]) were genotyped. Fixed as well as random effect models were used to provide summary risk estimates of *SPR* variants. A total of 19 sites provided data for 6547 cases and 9321 controls. Overall odds ratio estimates varied from 0.92 to 1.01. No overall association with the *SPR* gene using either fixed effect or random effect model was observed in the studied population. I^2 Metric varied from 0% to 36.2%. There was some evidence for an association for participants of North European/Scandinavian descent with the strongest signal for rs1876487 (odds ratio = 0.82; p value = 0.003). Interestingly, families which were used to map the PARK3 locus, have Scandinavian ancestry suggesting a founder effect. In conclusion, this large association study for the *SPR* gene revealed no association for PD worldwide. However, taking the initial mapping of the PARK3 into account, the role of a population-specific effect warrants consideration in future studies.

Keywords: Parkinson disease; *SPR*; PARK3; PD genetic studies; PD-GWAS

1. Introduction

We performed a large multicenter collaborative study among the Genetic Epidemiology of Parkinson's Disease (GEO-PD) Consortium sites to assess the world-wide the role of common variation in the *SPR* gene in Parkinson's disease (PD). This large study includes over 15,868 subjects from 19 sites representing 14 countries from 4 continents (supplementary material).

2. Methods

A total of 19 teams representing 14 countries and 4 continents agreed to participate and contributed clinical and genotypic data for a total of 15,868 individuals (6547 cases and 9321 controls). A total of 5 single nucleotide polymorphisms (SNPs) were selected for genotyping: rs1396107, rs1567230, rs2421095, rs1876487, and rs1561244 listed in order from 5′ to 3′ end of the gene (Karamohamed et al., 2003; Sharma et al., 2006) (supplementary material).

3. Results

Nineteen sites contributed 6547 cases and 9321 controls. Characteristics of all participating sites are shown in Table 1 (supplementary material). The distribution of allele frequencies of each SNP per site is shown in Supplementary Table 2. The meta-analysis did not reveal nominal significant associations either by random or fixed effect models, with the tentative exception of rs1876487. The summary odds ratio (OR) for rs1876487 was 0.95 (95% confidence interval, 0.89–1.00) with a p value of 0.05, uncorrected for multiple testing (Table 1 and supplementary material).

4. Discussion

This very large association study of common variants in the *SPR* gene with PD has revealed no evidence of association world-wide and it excludes large effects for any of the tested variants (supplementary material). Although most genetic association studies typically consider all European populations to share some common ancestry, a recent study established direct correlation between genetic makeup and the geographic location from which samples are ascertained within the European continent. This has also been shown in PD genetics, where in a recently published Genome-Wide Association Study (GWAS) on PD the authors observed a frequency gradient and differential genetic impact for SNP rs3129882 within European population for human leukocyte antigen (HLA) locus (supplementary material). Thus it is conceivable that rs1876487 and/or rs1567230 (D' = 1.0; r^2 = 0.29) may modulate the disease susceptibility only in populations from Northern European descent. Furthermore, haploytpe analysis restricted to North European population showed suggestive evidence of association for haplotype (rs2421095-rs1876487-rs1561244; odds ratio, 0.57; p-value 0.07), again suggesting the role of founder effect for PARK3 locus in North European/Scandinavian populations. Acknowledging these caveats, our study is large enough to suggest that these variants are unlikely to be a clinically important determinant of PD risk world-wide and future efforts should focus specifically on Northern European populations.

Disclosure statement

All authors have reported no actual or potential conflict of interest.

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Table 1
Summary effect estimates and confidence interval for *SPR* gene

		Overall			North European/Scandinavian		
SNP	Site	RE OR (95% CI)	FE OR (95% CI)	Het p (I^2)	RE OR (95% CI)	FE OR (95% CI)	Het p (I^2)
rs1396107	17	0.97 (0.90–1.03)	0.97 (0.90–1.03)	0.80 (0%)	0.87 (0.76–0.99)	0.87 (0.76–0.99)	0.42 (0%)
rs1567230	18	0.93 (0.82–1.04)	0.92 (0.83–1.03)	0.29 (14%)	0.75 (0.59–0.94)	0.74 (0.60–0.91)*	0.31 (13%)
rs2421095	19	0.93 (0.84–1.04)	0.93 (0.85–1.01)	0.18 (21%)	0.78 (0.63–0.96)	0.78 (0.63–0.96)	0.68 (0%)
rs1876487	18	0.94 (0.89–1.00)	0.94 (0.89–1.00)	0.46 (0%)	0.83 (0.72–0.96)	0.82 (0.72–0.93)*	0.33 (12%)
rs1561244	17	1.01 (0.91–1.12)	1.00 (0.92–1.08)	0.07 (36%)	0.88 (0.72–1.08)	0.85 (0.73–1.00)	0.23 (30%)

Key: CI, confidence interval; FE, fixed effects; Het, heterogeneity (Q statistic); OR, odds ratio; RE, random effects.
* $p < 0.01$.

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Appendix: A. Supplementary data

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