

Genetic-epidemiological confirmation of top hits of GWAS of Parkinson disease: A large multi-centre collaborative study.

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Background

Replication of top hits of GWAS is a prerequisite to claim or refute the validity of findings. Lack of replication can be attributed to small sample size, genetic heterogeneity, population admixture and liberal use of test statistic. It was suggested that lack of consistency in association could be due to unrecognised interaction with non genetic factors and incorporation of such interactions are expected to substantially improve power to dissect the disease aetiology. Therefore, this proposal aims to replicate the top snps (cut off $p < 10^{-4}$) from recently published GWAS on PD by simultaneously considering the role of non genetic factors as risk modifiers.

Aims

Our proposal aims to assess the joint effects (genetic/non genetic factors) of top hits of our recently published GWAS.

1. To assess the potential interaction of smoking, coffee drinking and pesticide exposure with the risk conferred by SNPs in SNCA and MAPT in modulating the susceptibility to PD.
2. To confirm the role of PARK16 as a new susceptibility locus for PD across different populations.

PRELIMINARY STUDIES

Recently, we published one of the largest GWAS studies so far in PD (5). This study clearly established the role of SNCA and MAPT in the pathogenesis of PD. Our study had 80% power to detect variants conferring an odds ratio (OR) of 1.3 with an allele frequency of 10% (5). It is unlikely that common alleles of large effect sizes have been missed. Though it is plausible to assume that SNPs which were selected to genotype in the replication stage might have missed the statistical stringency (Bonferroni threshold) to detect effect sizes of variants < 1.2 , because of inadequate sample size (3). Indeed, out of 345 SNPs selected to genotype in the replication cohort, only 9 SNPs passed the genome wide threshold. Moreover, another 75 variants showed an uncorrected p value $< 10^{-4}$. This includes the role of a new locus, designated as *PARK16*, on chromosome 1 described in the Japanese population (6). The observation that signals on chr 1 with low minor allele frequency ($< 3\%$) in the Caucasian population, showed consistent association as in the Asian population suggests that the locus on chr 1 may be a true disease locus and indicates that validation of the *PARK16* is highly warranted.

STUDY DESIGNS AND METHODS

A total of 75 SNPs will be genotyped for which necessary funding will be sought through charitable foundations. We will perform pooled analysis to fulfil above mentioned objectives. Our proposed study will include demographic, clinical and environmental exposure data to meet our objectives. Participating GEO-PD sites will share de-identified data, including, site-specific study characteristics such as sources of PD cases, clinical diagnostic criteria employed, age at onset of first motor symptom or sign, age at examination, gender, race and ethnicity, family history of PD (at least one affected first degree relative, ye/no), levodopa therapy (yes/no), smoking (ever/never), coffee drinking (yes/no), pesticide exposure (ever/never) and raw genotypes of 75 SNPs.

DNA samples will be coded with study-specific laboratory identification numbers. If the sites would like to genotype at their own sites, a control plate of 12 standard DNA samples from patient with PD will be provided to centres and the results will be then analyzed at Hertie Institute for Clinical Brain Research, Tuebingen, Germany. Those sites which will provide us DNA samples genotyping will be performed using Sequenome iPLEX chemistry using

MALDI-TOF. The PI will be responsible for coordinating data sharing and statistical analysis. Data quality will be assessed by the statistical core. This will include heterozygosity checks, assessment of goodness-of-fit of Hardy-Weinberg equilibrium (HWE) in controls. Effect estimates based on major vs minor allele contrast will be computed. Results will be then synthesised across different sites using both fixed effect and random effect models. Cochran's Q and I^2 statistic will be used to test for heterogeneity.

Significance

Our proposed study, apart from validating genetic effects, will for the first time delineate the role of non-genetic component from selected variants. Defining the role of genetic variants based on the involvement of non genetic factors will enable us to develop a set of genetic markers which will be used directly in clinical practices for genetic testing to predict a risk to PD. This is an important step which will be followed by quantification of the effect in different populations based on the GEO-PD.

TIMELINE

1. Interested sites will email Dr. Manu Sharma (manu.sharma@uni-tuebingen.de) form letter of intent by *November 30, 2009*. Interested sites will fill in site-specific information, to include the name and email address of the global site PI and also the names of global site co-investigators.
2. Preliminarily approved sites will provide data to Tuebingen team with de-identified, individual-level non genetic data (using a standardized Excel spreadsheet) by *December 31, 2009*. If the sites would like to avail our genotype facility, they will inform Dr. Manu Sharma latest by 15th December 2009.
3. Genotyping will be completed within next three months. It is expected that those sites which will perform genotyping will provide the genotype data to Tuebingen team, latest by Feb 2010. On March 2010 Tuebingen will start analyzing the complete data.
4. At the April 2010 GEO-PD meeting (to be held in Toronto, Canada), Dr. Sharma will present preliminary results of the fully approved sites.
5. Dr. Sharma will have the data analyzed and a manuscript will be ready for circulation/publication by the August 2010.
6. When the paper is accepted for publication, Dr. Sharma will share site-specific data with their PIs.

CONTACT INFORMATION

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