Study of the genetic variability in a Parkinson's Disease gene: EIF4G1

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Recently, a new gene (EIF4G1) has been identified in one family with autosomal dominant late-onset Parkinson's Disease [2]. Linkage was ascribed to a region at chromosome 3q26–28 containing approximately 159 genes. Sequence analysis found only one novel coding variant (p.R1205H in the EIF4G1 gene) which segregated with disease, which was absent in 4050 controls and which was evolutionary conserved in mammals. Screening a cohort of about 4800 PD cases (familial and sporadic) identified nine additional patients of the p.R1205H mutation. Further molecular analysis of the EIF4G1 gene in a large case–control cohort (4500 cases and 3800 controls) identified another novel missense mutation (p.A502V) in three PD individuals, which was not found in controls. These data indicate that these variants are extremely rare in the PD population (0.2% for p.R1205H and 0.06% for p.A502V). Assignment of pathogenicity can be difficult when variants are very rare. With this background, we screened 150 familial PD cases from our UK familial Parkinson's Disease series, in which we have previously identified LRRK2, VPS35 and SNCA mutations [5,7] in order to determine whether we could provide further that this gene is indeed a PD-related locus. We also assessed these coding positions in a set of African samples (Table 1) from the Human Diversity series – a standard panel of African samples [1], as African samples have the greatest diversity and offer a rapid route to the identification of benign polymorphisms [4]. Briefly, exon 8 and exon 22 of the EIF4G1 gene (NM_182917.3) were PCR amplified and sequenced in the two cohorts for a total of 114 African samples and 150 familial PD cases.

To obtain a more exhaustive description of the pattern of variability in that gene we also extracted genotype data from the NHLBI exome sequencing project [Exome Variant Server, NHLBI Exome Sequencing Project (ESP), Seattle, WA (http://evs.gs.washington.edu/EVS)] [January 2011], which includes exome data for 3500 American individuals of European descent and 1850 African American. Frequencies were computed using VCFTools. We used the software ANNOVAR [8] to annotate the function of the variants.

We failed to identify any mutation previously reported to be associated with PD in our familial cohort, but we identified one coding change (P486S) in two PD individuals. The P486S variant is reported in dbSNP (rs112545306). Interestingly it has been observed in African-Americans (http://snp.gs.washington.edu/EVS), with a frequency of 0.15%.

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We identified six non-synonymous changes in exon 8 and in exon 22 in the African individuals. Of these, one is a novel change (P382L), the others are variants recently reported in dbSNP and found mainly in African populations (http://snps.gs.washington.edu/EVS). To predict the impact on protein function of these non-synonymous variants, we performed an in silico analysis using the software PolyPhen and SIFT [6] and all were predicted to be benign (Table 2).

Analysis of the NHLBI samples allowed us to detect the A502V variant in two European-American individuals (frequency of 0.02%). We identified 95 nonsynonymous SNP over 32 exons.
in total (NM_182917.3). Of note, 36 of them are located in exon 8 and exon 22 (Table 3). To investigate coding variability across the EIF4G1 gene we extracted the data from the NHLBI dataset and computed the average number of pairwise amino acid differences between two randomly selected European-American haplotypes from the NHLBI dataset (Methods). On average two such EIF4G1 sequences diverge by 0.45 amino acids. 82% of this variability (0.37 amino-acid differences) locates to exon 8, where the A502V lies. 9.8% of this variability locates to exon 22 (0.098 amino-acid differences). Combined with the identification of six coding variants in exons 8 and 22 in African samples, these data are consistent with a more limited selective pressure and a higher sequence variability in this region of the EIF4G1 protein.

These data, combined with the presence of the A502V in the NHLBI population with 0.02% frequency and our failure to identify any PD mutation carrier in our familial cohort, are consistent with the interpretation that either EIF4G1 variants are an extremely rare cause of familial PD in Caucasian cohorts, or that A502V is in fact a rare benign variant not involved in PD aetiology.

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Disclosure statement

Arianna Tucci, Gavin Charlesworth, Una-Marie Sheerin, Vincent Plagnol, Nick Wood, John Hardy report no disclosures.

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