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LETTER TO THE EDITOR

Parkinsonism in GTP cyclohydrolase 1 mutation carriers

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Sir,

We read with great interest the article by Mencacci and colleagues (2014) reporting a significantly higher frequency of GTP cyclohydrolase 1 (*GCH1*) variants in patients with Parkinson's disease compared to controls. Whole-exome sequencing of a large case-control cohort showed that rare *GCH1* coding variants are associated with a 7-fold increased risk of Parkinson's disease.

Heterozygous loss-of-function mutations in *GCH1*, a crucial enzyme for dopamine production in nigrostriatal neurons (Kaufman, 1959; Nagatsu *et al.*, 1964), are the most common cause of DOPA-responsive dystonia (DRD) (Ichinose *et al.*, 1994). DRD is a rare hereditary disease characterized by childhood-onset, generalized dystonia and a dramatic long-lasting response to levodopa (Segawa *et al.*, 1976). The disease may also manifest in adulthood with parkinsonism as the sole or dominant clinical feature (Hjermind *et al.*, 2006; Momma *et al.*, 2009). *GCH1* mutations have been shown to segregate in pedigrees with multiple individuals affected by isolated parkinsonism, a phenotype that is likely due to nigrostriatal degeneration (Kikuchi *et al.*, 2004; Hjermind *et al.*, 2006; Eggers *et al.*, 2012; Mencacci *et al.*, 2014). Herein, we report *GCH1* variability in patients with Parkinson's disease ($n = 361$, 68.7% male, mean age 69.9 ± 12.8 years; mean age at onset 58.3 ± 12.9 years), atypical parkinsonism ($n = 167$, male 61.7%, mean age 77.5 ± 12.2 years; mean age at onset 66.3 ± 11.2 years, including diagnostic categories of dementia with Lewy bodies, progressive supranuclear palsy and multiple system atrophy) and control subjects ($n = 290$, 59% male; mean age 73.3 ± 11.2 years).

Sequencing of *GCH1* coding regions, performed on the SOLiD 5500xl platform (Life Technologies), identified four rare heterozygous non-synonymous coding substitutions including: (i) a novel missense variation (p.A99D); (ii) the known DRD pathogenic mutation (p.K224R); and (iii) two benign variants (p.P23L and p.P69L) (Jarman *et al.*, 1997; Mencacci *et al.*, 2014). The p.A99D mutation was identified in a male patient with typical late-onset Parkinson's disease (age at onset 61 years) with an extensive family history of dementia and parkinsonism. This amino acid position is highly conserved, and substitution of a hydrophobic non-polar (alanine) to a negatively charged (glutamic acid) amino acid is likely to perturb the amphipathic alpha-helical structure of this domain. The mutation has not been reported in the publically available Exome Variant Server data set (http://evs.gs.washington.edu/EVS/), which suggests it is unlikely to be a benign, albeit rare, variant. The p.K224R mutation, previously described in pedigrees with dominantly inherited DRD (Leuzzi *et al.*, 2002), was detected in two unrelated Canadian patients. One had asymmetrical tremor onset parkinsonism (age at onset 82 years) and good levodopa response. She died at 90 years and brain pathology showed

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tau-immunoreactive neurofibrillary tangles consistent with a diagnosis of progressive supranuclear palsy. However, immunohistochemistry for α-synuclein revealed immunopositive staining in the brainstem, suggesting the concomitant presence of Lewy body pathology. The other carrier has typical late-onset Parkinson's disease (age at onset 76 years). Her affected sister, diagnosed with Parkinson's disease (age at onset 64 years) also carries the p.K224R mutation and her deceased father had Parkinson's disease.

Overall, the frequency of *GCH1* pathogenic mutations in patients is 0.57% (3/528), whereas only two benign variants were identified in one control subject, consistent with the recently published results (frequency in patients with Parkinson's disease 0.75% versus controls 0.1%) (Mencacci *et al.*, 2014) and may concur with a mega meta-analysis of genome-wide association data which have highlighted *GCH1* as a low-risk susceptibility locus for Parkinson's disease (Nalls *et al.*, 2014). Taken together these data suggest that *GCH1* genetic variability should be considered as a risk factor for parkinsonism.

Past studies investigating the role of GCH1 variability in early-onset Parkinson's disease have reported negative results (Hertz *et al.*, 2006; Cobb *et al.*, 2009), although they were performed in relatively small cohorts insufficiently powered to assess the contribution of rare variants. To confirm pathogenicity, segregation analysis of putative *GCH1* mutations within extended pedigrees is warranted; whether *GCH1* parkinsonism is more penetrant in females, as for DRD (Furukawa *et al.*, 1998) may also be qualified. Moreover the presence of *GCH1* copy number variants may be as frequent and should be assessed (Wider *et al.*, 2008). Additional autopsy studies may address whether post-mortem tauopathy is an incidental finding, merely concurrent, or a consequence of *GCH1* mutations. Insight into the pathogenic mechanism may help elucidate the role of dopamine metabolism in nigrostriatal degeneration and parkinsonism, and to develop new therapeutic targets.

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