Rare genetic variants support mitochondrial dysfunction in Lewy body disorders

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Parkinson disease (PD) and other Lewy body disorders are common neurodegenerative conditions manifesting with progressive motor and nonmotor symptoms. Although their pathogenesis remains to be fully elucidated, a number of genetic findings have helped better understand the molecular mechanisms involved.[1] Mutations in genes causing PD that are inherited in a Mendelian fashion as well as genetic variants that modify disease risk have been identified, some overlapping with those involved in other Lewy body disorders. Recently, mutations in a gene named coiled-coil-helix-coiled-coil-helix domain containing 2 (*CHCHD2*) were found in Japanese patients from families with autosomal dominantly inherited PD.[2] Moreover, a patient-control analysis suggested that variants in *CHCHD2* associate with increased risk for sporadic, late-onset PD.[2] These findings have raised strong interest given that (1) the CHCHD2 protein is localized in mitochondria and (2) mitochondrial dysfunction plays an important role in PD, particularly early-onset PD due to mutations in *PINK1* and *PARKIN*.[3]

In this issue of *Neurology*®, Ogaki et al.[4] investigate thoroughly the role of *CHCHD2* genetic variants in large series of Caucasian patients from the United States, Ireland, and Poland with clinically diagnosed PD (n = 1,627), pathologically confirmed Lewy body disease (LBD, n = 610), and control individuals (n = 1,432). In an initial discovery stage, all 4 *CHCHD2* exons were sequenced in the US series (PD, LBD, and controls). Subsequently, exons 1 and 2 were sequenced in the Irish and Polish series. Four common variants were found that did not associate with disease risk in any of the series. However, the authors identified 19 rare variants (i.e., found at a frequency <1%), of which 9 were localized in coding/exonic regions (p.P2L, p.G4R, p.P14S, p.A16A, p.V31V, p.P34L, p.A37V, p.A49V, and p.A93V). The 9 exonic variants were found in 7 patients with PD, 6 patients with LBD, and only 1 control individual. Of note, the control individual was examined at an early age and, therefore, could still develop disease later in life. Because the 9 exonic variants were rare, there was insufficient power for single variant comparisons. Instead, the authors used a gene burden assessment method, whereby the presence of any rare variant is compared between patients and controls. When combining all PD and LBD patients, the occurrence of rare exonic *CHCHD2* variants was significantly more frequent in patients compared with controls (0.6% vs 0.1%, $p = 0.013$). The results were driven largely by the US series, with no rare variants in the Irish series and only one patient with PD harboring a rare variant in the Polish series. Additionally, although not reaching statistical significance, rare *CHCHD2* variants were more frequent in patients with PD than in controls. It is important to note that even when collapsing across rare variants, the gene burden test yielded only slightly significant or borderline results; therefore, the risk of false-negative errors must be taken into account.

Interestingly, 8 of the 9 rare exonic variants are within the mitochondrial targeting sequence (MTS) of the CHCHD2 protein. This supports the hypothesis that mitochondrial dysfunction could be the link between *CHCHD2* genetic variants and disease occurrence. Various software prediction tools were used to assess putative pathogenicity, and all rare variants but one were predicted to be damaging (i.e., likely pathogenic) by at least one of these tools. Two of the 7 patients with PD harboring a rare *CHCHD2* variant had a positive family history of PD (uncle) or dementia (mother), but no DNA was available from those family members for analysis. Overall, patients displayed a classical PD phenotype, although one had limited response to levodopa and another had dementia early in the disease course.

Five brain samples from patients with LBD with *CHCHD2* variants (p.P2L, p.G4R, p.A37V, and p.A93V) were assessed for CHCHD2 expression using immunohistochemistry. Not surprisingly, most Lewy bodies and pale bodies did not stain for CHCHD2. There was a suggestion that CHCHD2 expression was reduced in patients with LBD with variants compared to controls and to patients with

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LBD without variants. Interestingly, this was not observed for the patient harboring the only variant not lying within the MTS (p.A93V).

Establishing the pathogenicity of the rare *CHCHD2* variants reported in the present study will require either their identification in large, multi-incident families or careful functional studies of these variant proteins. With the exception of the p.P2L variant observed at a very low frequency (total 4 individuals), the present study did not replicate the findings of the Japanese report,[2] likely indicating ethnic specificity. This is further supported by recent studies in other Caucasian populations where the Japanese findings were not replicated.[5–8] In contrast, 1 of the 9 rare variants identified by Ogaki et al. (p.P34L) was also found in another patient with PD of Caucasian descent.[7] In the latter study, 2 other rare *CHCHD2* exonic variants (p.A32T and p.I80V) were found in Caucasian patients with PD, further supporting *CHCHD2* variants as a risk factor for PD. As for replication in Asian populations, 1 study in a Chinese series confirmed the p.P2L variant as an important risk factor for PD.[9]

The study by Ogaki et al. highlights the importance of rare genetic variants as risk factors for PD and LBD and provides additional support for mitochondrial dysfunction in the pathogenesis of these disorders. For clinicians, increased availability of clinical exome sequencing poses a challenge when confronted with rare variants of unknown importance, emphasizing the need for more replicative data. After over a decade of genome-wide association studies of common variants, which have pointed to loci associated with disease, the field is moving toward identifying rare variants that will likely account for some of the missing heritability in PD.

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REFERENCES

1. Trinh J, Farrer M. Advances in the genetics of Parkinson disease. Nat Rev Neurol 2013;9:445–454.
2. Funayama M, Ohe K, Amo T, et al. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. Lancet Neurol 2015;14:274–282.
3. Haelterman NA, Yoon WH, Sandoval H, Jaiswal M, Shulman JM, Bellen HJ. A mitocentric view of Parkinson's disease. Annu Review Neuroscience 2014;37:137–159.
4. Ogaki K, Koga S, Heckman MG, et al. Mitochondrial targeting sequence variants of the *CHCHD2* gene are a risk for Lewy body disorders. Neurology 2015;85:2016–2025.
5. Liu G, Li K. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14:679–680.
6. Iqbal Z, Toft M. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14:680–681.
7. Jansen IE, Bras JM, Lesage S, et al. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14:678–679.
8. Puschmann A, Dickson DW, Englund E, Wszolek ZK, Ross OA. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14:679.
9. Foo JN, Liu J, Tan EK. CHCHD2 and Parkinson's disease. Lancet Neurol 2015;14:681–682.