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CORRESPONDENCE

Segregation of *ATP10B* variants in families with autosomal recessive parkinsonism

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Martin et al. [2] recently reported that biallelic missense and stop-gain variants in *ATP10B* are associated with Parkinson's disease (PD) and dementia with Lewy bodies (DLB). They identified double-heterozygous variants demonstrated to be located in *trans* in three of seven isolated cases (six with PD and one with DLB). These variants had a minor allele frequency (MAF) < 5% in the public Genome Aggregation Database (GnomAD) (https://gnomad.broadinstitute.org). Using cell function assays, they showed that nine of the ten variants tested resulted in ATPase activity and lipid translocation decreases and a lower level of cell protection against rotenone exposure, consistent with a loss of ATP10B function. Overall, this study indicates that biallelic *ATP10B* missense variants increase the risk of PD. However, the relatively high frequency of several of these *ATP10B* variants (> 2%), and the presence of healthy carriers homozygous for these variants in GnomAD raised questions about their pathogenicity. In a large case–control study, Real et al. [3] also questioned the implication of *ATP10B* variants as risk factors in the pathogenesis of PD. However, in their reply Smolders and Van Broeckhoven [4] pointed out that Real et al. [3] did not assess the phasing and therefore could not conclude that *ATP10B* was involved in their cohort but agreed that analyses of large number of trios are necessary to estimate the frequency of PD carriers of homozygous or compound heterozygous *ATP10B* variants.

We assessed the presence of biallelic *ATP10B* variants in families with PD and their segregation with the disease, by analyzing whole-exome sequencing (WES) data from 17 PD families with autosomal recessive (AR) inheritance including at least two affected siblings (Supplementary information for patients and methods).

Setting the MAF threshold at 5%, as used in Martin et al.'s paper, we identified six rare *ATP10B* missense variants, including three previously reported [2], in two of the 17 families. In the consanguineous Algerian FDP-167 family, the reported p.L1421F and p.I540T variants were both present in the three affected siblings, with ages at onset ranging from 30 to 35 years (Fig. 1a). Segregation analysis provided evidence for a *cis* location of the two variants, both inherited from the mother, who was unaffected at age 58, suggesting that they cannot be causal for PD, given the AR transmission of the disease. In the consanguineous Turkish family PD-IST-154 with typical PD (Supplementary information), the index case (IV-6) carried the p.V219M, p.G671R, and p.N865K variants in the homozygous state. The p.G671R and p.N865K variants have previously been reported to occur in *cis* [2]. Segregation analysis revealed that the affected sister (IV-4) carried the same variants, but in the heterozygous state, whereas the 52 year-old unaffected sister (IV-5) carried the same three variants in the homozygous state (Fig. 1b). As expected, both unaffected parents were heterozygous carriers of the three variants, whereas the father (III-1) carried another rare missense variant, p.T1019S, on the same haplotype. Segregation analysis alone is sufficient to exclude these variants as the cause of PD within this family. Moreover, we previously identified a homozygous p.L34R mutation in *FBXO7* that segregated with the disease in this family (Fig. 1b) [1]. This variant is

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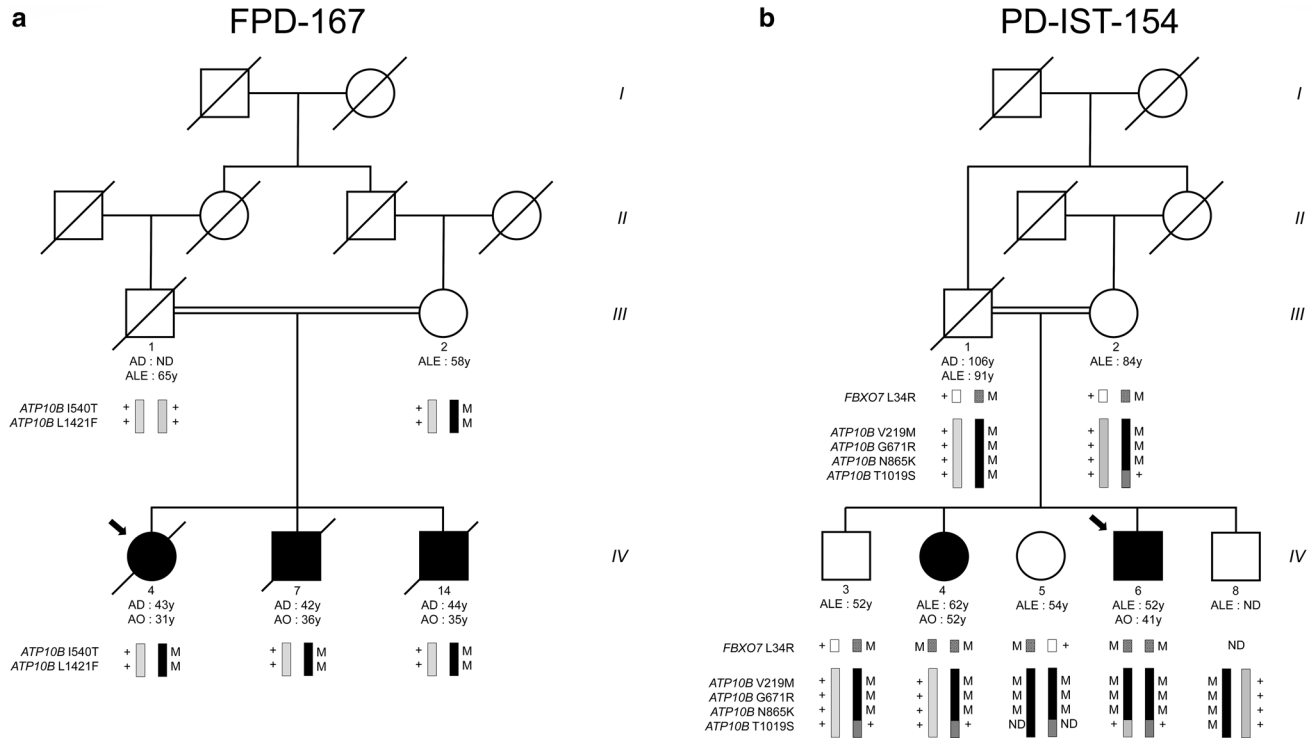

Fig. 1 Segregation of *ATP10B* variants. **a** Segregation of *ATP10B* variants in the FPD-167 family, both are inherited from the unaffected mother. **b** Segregation of *FBXO7* mutation and *ATP10B* variants in the PD-IST-154 family. The *FBXO7* mutation segregates with the disease, whereas the *ATP10B* p.V219M, p.G671R and p.N865K variants are present in the homozygous state in the unaffected individual IV.5 and in the heterozygous state in affected individual IV.4. *AD* age at death, *ALE* age at last examination, *AO* age at onset, + wild type, *M* mutated, *ND* not determined

absent from GnomAD and affects a well-conserved amino acid located at the N-terminal ubiquitin-like domain of FBXO7 and associated with its nuclear localization. Another known mutation of *FBXO7,* p.T22M, affecting the same domain, leads to FBXO7 mislocalization to the cytoplasm [5]. Taken together, these data suggest that the homozygous *FBXO7* p.L34R mutation, which segregates with PD, is responsible for the disease in this family, whereas the three rare *ATP10B* variants, do not, in absence of co-segregation.

Even though specific functional assays revealed a deleterious impact of the variants on ATP10B function [2], suggesting potential pathogenicity, our data did not support this hypothesis. Co-segregation analysis, revealing a PD case carrying *ATP10B* variants in the heterozygous state and an unaffected with homozygous variants, in a family in which a *FBXO7* mutation had already been shown to segregate with the disease, is not consistent with a causal role of these *ATP10B* variants in PD. In addition, several variants of *ATP10B* seem to be located in *cis*, as observed in both the families we studied. Therefore, genetic studies in multiplex pedigrees remain crucial for assessing the pathogenicity of rare variants which are increasingly frequently encountered with the use of next-generation sequencing. In addition, the demonstration of a biological effect of the protein encoded by a missense variant is, by no means, a direct proof of its pathogenicity. Even if these variants affect protein function [2], it cannot be assumed that they cause PD.

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