PTRHD1 and Possibly *ADORA1* Mutations Contribute to Parkinsonism With Intellectual Disability

We recently published a genetic study on a family with autosomal-recessive Parkinsonism with cognitive decline.[1] Homozygous mutations in the adenosine A1 receptor gene (*ADORA1*; p.Gly279Ser) and the peptidyl-tRNA hydrolase domain containing 1 gene (*PTRHD1*; p.Cys52Tyr) that segregated with disease were identified. We suggested the *ADORA1* mutation is the stronger candidate causative mutation and labeled it as the "likely cause" of disease in the title of the article. Reasons for focus on the *ADORA1* gene included known associations between adenosine receptors and neurodegeneration, interactions between adenosine receptors and dopamine receptors, position of the mutated amino acid within a protein domain possibly important for receptor activation, analysis that marked the mutation as among the 0.2% most deleterious variations in the human genome, and its inclusion in the Parkinson disease 16 (PARK16) locus. With respect to the last item, the most recent update shows that *ADORA1* is located ~2.5 Mb upstream of PARK16.[2] Several months after the publication, Khodadadi and colleagues reported p.His53Tyr in *PTRHD1* as a cause of autosomal-recessive intellectual disability and Parkinsonism in a family.[3] In addition to genetic analysis, supportive evidences were *PTRHD1* inclusion within deletions associated with intellectual disability syndromes, p.His53 being within a ubiquitin-like domain-binding protein domain (peptidyl-tRNA hydrolase 2; PTH2) of the encoded protein, and, of course, our previous observation of a *PTRHD1* mutation. Most recently, Blauwendraat and colleagues, noting *ADORA1* as an interesting candidate gene for Parkinson's disease (PD) as well as DLB (dementia with Lewy bodies), searched for *ADORA1* mutations in exome data of 1,214 PD cases, 111 DLB cases, and 4,911 controls. They did not observe the p.Gly279Ser variation nor any homozygous or compound heterozygous coding variants in the data. The investigators also screened the data on European individuals from the Exome Aggregation Consortium database (ExAC; http://exac.broadinstitute.org/) and reported that, of >66,000 individuals investigated in total, only 1 individual with a homozygous missense variant was identified, marking such variants in *ADORA1* as "extremely rare."

As corresponding author of the original publication, I feel it is necessary on behalf of all authors to present a reassessment of the results of that study. The observation of a mutation in *PTRHD1* in a second family whose patients also present with Parkinsonism and intellectual disability argues that the p.Cys52Tyr in *PTRHD1* in our family did in fact contribute to disease status.[3] This consideration is notably strengthened by the fact that the mutations in the two families affect adjacent amino acids, that the encoded protein may be a ubiquitin-like domain binding protein, and that the mutated amino acids are within the PTH2 domain. On the other hand, because of considerations published in our article and summarized above, we cannot dismiss a possibility that the *ADORA1* mutation also contributed to disease status. The rarity of homozygous or compound heterozygous mutations coding sequence variations suggest that such variations may not be compatible with normal survival. Clearly, mutations in *ADORA1* are not a common cause of PD accompanied with cognitive decline. As already suggested, further studies may clarify whether *ADORA1* has a role in the etiology of Parkinsonism with cognitive decline.[2]

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Altered Gut Microbiome and Metabolome in Patients With Multiple System Atrophy

Emerging evidence links perturbations in the gut microbiota to neurological disease.[1,2] One recent publication

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