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 deleterions 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 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.4

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References

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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