PARK7-Related Early Onset Parkinson Disease in the Setting of Complete Uniparental Isodisomy of Chromosome 1

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Approximately 10% of Parkinson disease (PD) has a monogenic basis. PARK7 is a rare recessive form of early-onset PD caused by mutations in the gene PARK7 (formerly DJ1).1 As expected for a recessive disorder, PARK7 patients usually inherit 1 mutant allele from each parent; in fact, most reported cases have occurred in consanguineous families. We report an adult with early onset PD who inherited 2 identical pathogenic PARK7 variants from her asymptomatic father, a carrier for the same variant, via complete uniparental isodisomy (UPD) of chromosome 1.

UPD occurs when an offspring inherits 2 copies of a chromosome or segments of a chromosome from 1 parent and none from the other. In UPD, the abnormally inherited chromatin segments are identical. UPD can result from meiotic nondisjunction when an abnormal gamete forms either a monosomic or trisomic zygote followed by either duplication of the monosomic chromosome (monosomy rescue) or loss of the trisomic chromosome (trisomy rescue).2 Mechanisms of disease in the context of UPD include overexpression or underexpression of imprinted genes or, because in this case, emergence of homozygosity for pathogenic variants contributed by the segments of chromatin involved. Advanced maternal age is the only established risk factor for UPD.

Case

A 38-year-old woman was referred to the NIH Undiagnosed Diseases Program after seeking medical attention for progressive dysphonia since age 31. Her examination was notable for hypophonia, masked facies, bradykinesia, asymmetric upper extremity rigidity, micrographia, and resting tremor consistent with parkinsonism. She had brisk reflexes throughout with no other pyramidal features. She had a history of depression treated with antidepressants, although at the time of psychiatry evaluation she did not meet criteria for any psychiatric diagnosis. She endorsed mild subjective forgetfulness, inattentiveness, and apathy with previously unremarkable neurocognitive testing. She did not endorse olfactory changes or constipation. An overnight polysomnogram demonstrated severe obstructive sleep apnea without signs of parasomnias. Trials of levodopa/carbidopa and pramipexole improved symptoms but were poorly tolerated because of gastrointestinal side effects. MRI (Figure 1) and EMG were normal.

Her parents were unrelated, and there was no family history of PD.

Her history was also notable for progressive vision loss in her twenties. Ophthalmologic evaluation uncovered changes consistent with Stargardt macular dystrophy (eFigure 1, links. lww.com/NXG/A438) as well as mild cataracts. Birth and developmental history were within normal limits. Her physical examination was also notable for joint hypermobility (Beighton
score 6/9, scoliosis, micrognathia, elevated palate, pectus excavatum, and mild sensorineural hearing loss.

A nuclear family single nucleotide polymorphism (SNP) microarray study identified complete UPD of the entire chromosome 1 (Figure 1). Genome sequencing revealed a homozygous truncating PARK7 mutation (c.331delG, p.A111LfsX7) of paternal origin as well as homozygosity for a previously reported ABCA4 variant (c.1805 G > A, p.R406Q). Both variants were validated by Sanger sequencing and interpreted as causative of the phenotype.
as pathogenic by American College of Medical Genetics criteria. The proband’s father, but not her mother, was heterozygous for both variants (Figure 1).

Discussion

Early-onset PD due to PARK7 is rare. A comprehensive review of the literature in 2018 identified 30 cases in 18 families, with most cases involving homozygous mutations. The mechanism by which PARK7 mutations lead to parkinsonism is unclear; PARK7 is thought to play roles as a chaperone with protease activity, a mitochondrial stabilizer, a reduction-oxidation sensor, and a transcriptional regulator, and an oncogenic agent. The incidence of PARK7 remains unknown, although it is estimated to account for less than 1 percent of patients with early onset of PD in the United States. Both missense mutations and truncating mutations have been reported, with studies demonstrating functionally inactive or complete lack of DJ1 expression. Our patient’s variant has not been previously reported, and this is the report of PARK7 early onset PD emerging from UPD.

Our patient’s phenotype additionally includes macular dystrophy, hearing loss, micrognathia, scoliosis, and pectus excavatum. The same mechanism leading to homozygosity in PARK7 also led to homozygosity for a pathogenic variant in ABCA4, supporting a diagnosis of Stargardt macular dystrophy. While our evaluation did not identify definite explanations for her remaining findings, homozygous variants of unclear significance were identified in short stature genes on chromosome 1.

The incidence of UPD in the general population is estimated at 1:2,500, and most individuals with UPD in nonimprinted chromosomes are phenotypically normal. The likelihood of unmasking a given recessive condition by UPD is contingent on the joint probability of a particular UPD event and the carrier frequency for disease-causing variants in the implicated gene.

Disease-specific gene panel testing for PD or macular dystrophy would have identified homozygous PARK7 or ABCA4 changes. However, to provide full account of the phenotype and fully understand the inheritance mechanism, parental segregation, chromosomal microarray, or genomic sequencing would have been required to provide a unified explanation for her complex presentation. Considering UPD and its potential systemic implications is relevant even in specialty clinics, particularly when encountering rare recessive homozygous mutations in the absence of consanguinity or when complex phenotypes and rare genetic diagnoses aggregate in 1 individual.

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References

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