

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. www.nhlbi.nih.gov/health/NIHtopics/stargardt-macular-dystrophy) as well as mild cataracts. Birth and developmental history were within normal limits. Her physical examination was also notable for joint hypermobility (Beighton

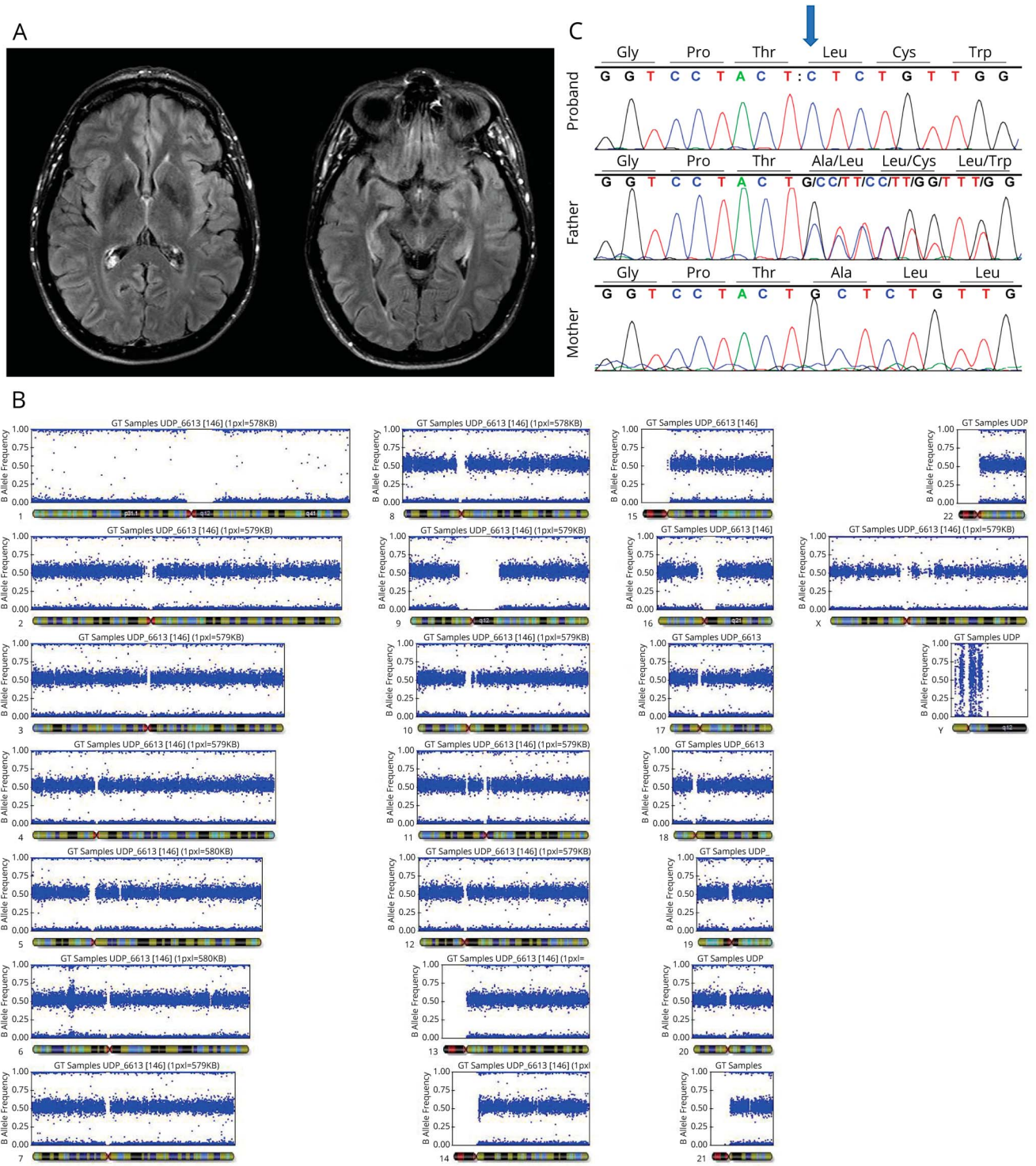
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Figure 1 Imaging and Genetic Testing Results



(A) MRI fluid-attenuated inversion recovery shows normal striatum (left) and midbrain (right). (B) Single nucleotide polymorphism microarray (SNP array) data for all chromosomes show loss of heterozygosity in chromosome 1 in an otherwise normal background. (C) Sanger sequencing confirmed deletion in the proband, heterozygosity in father, and no deletion in the mother.

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 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.³ 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, a transcriptional regulator, and an oncogenic agent.⁴ 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.³ Both missense mutations and truncating mutations have been reported, with studies demonstrating functionally inactive or complete lack of DJ1 expression.⁵ 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.⁶ 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.⁷ 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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Disclosure

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Appendix Authors

Name	Location	Contribution
Changrui Xiao, MD	National Human Genome Research Institute, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Thomas Markello, MD	Office of the Clinical Director, National Human Genome Research Institute, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content, and major role in the acquisition of data
Wadih M. Zein, MD	National Eye Institute, Bethesda, MD	Major role in the acquisition of data and analysis or interpretation of data
Rachel Bishop, MD	National Eye Institute, Bethesda, MD	Major role in the acquisition of data
Catherine Groden, APN	NIH Undiagnosed Diseases Program, National Human Genome Research Institute, Bethesda, MD	Major role in the acquisition of data
William Gahl, MD	NIH Undiagnosed Diseases Program, National Human Genome Research Institute, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Camilo Toro, MD	NIH Undiagnosed Diseases Program, National Human Genome Research Institute, Bethesda, MD	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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