

Peripheral synucleinopathy in a *DJ1* patient with Parkinson disease, cataracts, and hearing loss

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Whereas Parkinson disease (PD) is usually sporadic, PD with onset under 50 years old can be associated with genetic abnormalities, including rare biallelic mutations in the *DJ1* gene (*PARK7*).¹ The *DJ1* phenotype is incompletely described and has been presumed to be similar to the Parkin (*PARK2*) phenotype, in which atypical clinical features are usually absent, and, in contrast to idiopathic PD, synucleinopathy is lacking and olfaction preserved.² Whether *DJ1* patients have peripheral synucleinopathy and olfactory dysfunction has been unknown.

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Video

Methods

For immunofluorescence microscopy, 3-mm punch biopsies from the C2 area of the posterior neck were fixed in Zamboni fixative, cryosectioned into 10- μ m slices, and immunostained for tyrosine hydroxylase (Pel-Freez Biologicals, Rogers, AR) (red), α -synuclein (Santa Cruz Biotechnology, Santa Cruz, CA) (green), and smooth muscle actin (ACTA2; Santa Cruz Biotechnology) (blue). Fibroblast cell lines were also established. A colocalization index for α -synuclein and tyrosine hydroxylase was calculated from confocal images using Fiji (NIH, Bethesda, MD). Normalized mean deviation product (nMDP) values for colocalization were tabulated from -0.1 to $+1.0$, and the colocalization index calculated as $\log(0.1 + \sum \text{nMDP} [0.3\text{--}1.0])$.

Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent before participation in the research study, which was approved by the National Institute of Neurological Disorders and Stroke institutional review board.

Results

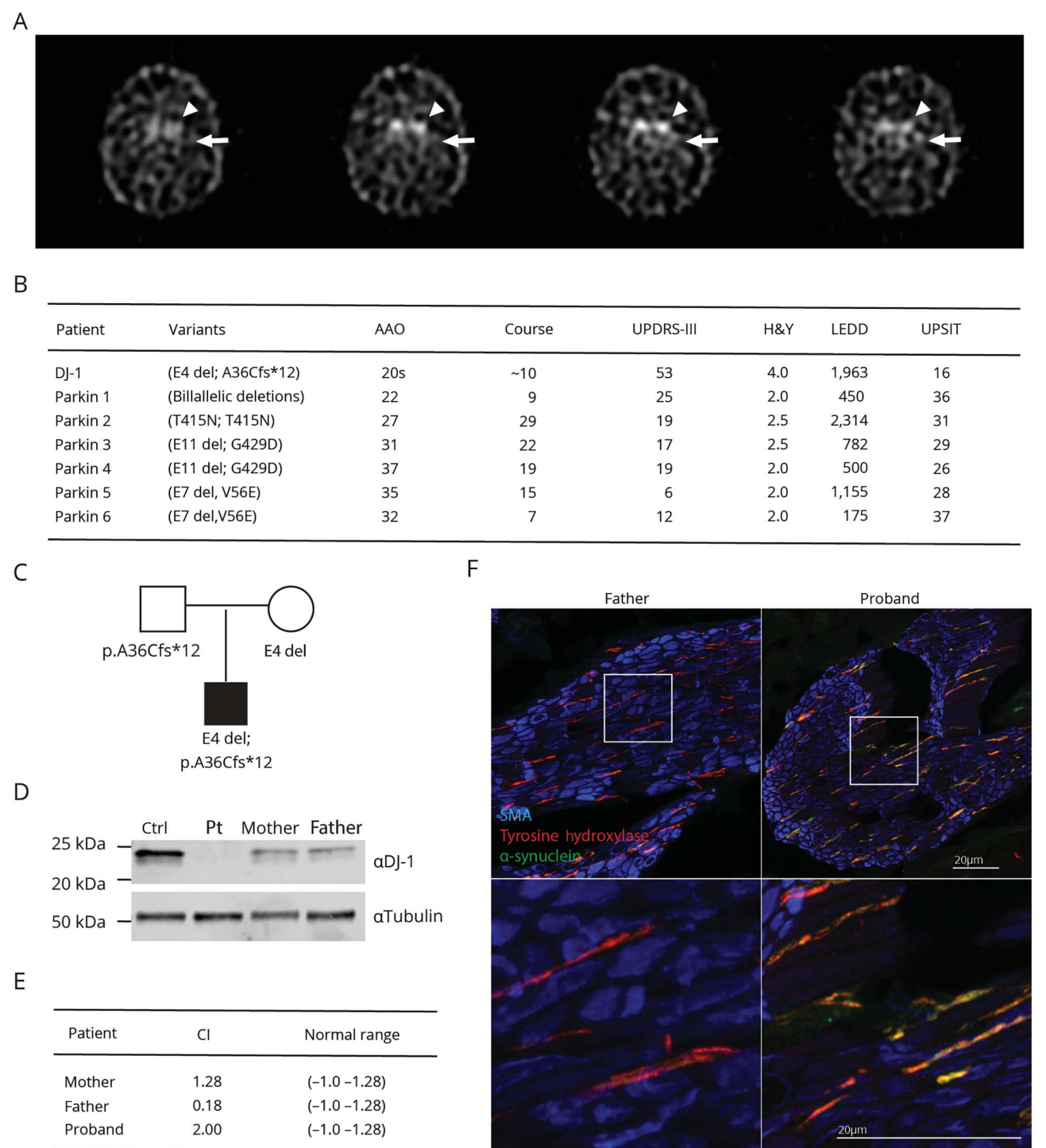
We report a 35-year-old man with PD and compound heterozygous *DJ1* mutations. In his mid-20s, he developed a left-hand resting tremor that progressed over years, followed by loss of mobility, disability, and speech difficulties. His symptoms responded to levodopa, prompting a diagnosis of PD, supported by DaT imaging (figure, A). At the time of evaluation, the patient had resting tremor, bradykinesia, rigidity, postural instability, motor fluctuations, and dyskinesia. The patient's examination was notable also for eyelid opening apraxia, hyperreflexia, extensor plantar reflex responses bilaterally, and pseudobulbar affect (video 1). The patient was anosmic by the University of Pennsylvania Smell Identification Test (UPSIT; score 16/40). Six patients with early-onset PD from our clinic cohort with biallelic Parkin mutations had higher UPSIT scores (mean 32.8; range 26–38; figure, B). In addition to his neurologic presentation, he had sensorineural hearing loss on audiometry and visual difficulties that improved after bilateral cataract surgery at the age of 33.

Testing for a panel of PD-related genes (Next-Generation Sequencing, Invitae, CA) revealed 2 previously unreported *DJ1* variants (deletion [exon 4]; c.105dupT [p.Ala36Cysfs*12] [NM_007262.4]). Parental testing showed these were on opposite chromosomes (figure, C). No *DJ1*

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Figure Peripheral synucleinopathy and anosmia in a patient with early-onset Parkinson disease with biallelic *DJ1* mutations



(A) Consecutive axial FP-CIT SPECT images demonstrate absent signal in the region of the putamen (arrows) and decreased signal in caudate heads, bilaterally (arrowheads). (B) Clinical characteristics of the *DJ1* patient and 6 biallelic *Parkin* patients for whom University of Pennsylvania Smell Identification Test (UPSIT) data were available. (C) Pedigree of *DJ1* family. Filled in symbol indicates affected individual. (D) fibroblast lysates from a control adult dermal fibroblast line (ATCC), the affected patient, and his unaffected parents were separated on sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) gels and immunoblotted for *DJ1* (MBL International, Woburn, MA). (E, F) Representative confocal images (F) and quantification (E) of α -synuclein (green) within sympathetic noradrenergic nerve fibers (red) innervating dermal piloerector muscles (blue). Normal range is based on measurements from 4 healthy controls and 7 patients with multiple system atrophy.³ Scale bar = 20 μ m. AAO = age at onset; H&Y = Hoehn & Yahr; LEDD = levodopa equivalent daily dose; UPDRS = Unified Parkinson's Disease Rating Scale.

protein was detectable in lysates from the patient's fibroblasts. Lysates from each parent had half of the normal DJ1 protein, establishing pathogenicity of the variants (figure, D).

Immunofluorescence microscopy of skin biopsies from the patient demonstrated substantial deposition of α -synuclein within tyrosine hydroxylase-positive fibers. The calculated

colocalization index, 2.0, was above the control range in our series (−1.0 to 1.3, n = 11; figure, E and F); and within the range of idiopathic PD (0.9–4.9, n = 9).³

Discussion

We identified novel compound heterozygous *DJ1* mutations in a patient with early-onset PD. A prior report of a *DJ1* case noted postmortem Lewy body pathology in the brain.⁴ Here we report deposition of α -synuclein in sympathetic noradrenergic nerves in biopsied skin from a living patient. Together these reports support the view that *DJ1/PARK7* involves synucleinopathy within both the brain and the sympathetic nervous system. We also provide evidence that olfaction can be severely compromised in *DJ1/PARK7*. Data on peripheral synucleinopathy and olfaction, key phenotypic features that distinguish most patients with *Parkin* from patients with idiopathic PD,² were previously missing for *DJ1/PARK7* on review of the 32 reported cases (appendix e-1: doi.org/10.5061/dryad.nv892mp). These findings suggest that the *DJ1* phenotype resembles that of idiopathic PD more closely than that of *Parkin/PARK2* PD.

This case and review of the literature also underscore atypical features of the *DJ1/PARK7* clinical phenotype. Early cataracts were present in 3 cases (9.1%), 2 of whom also had sensorineural hearing loss (6.1%).^{5,6} The triad of early-onset PD, cataracts, and sensorineural hearing loss may be specific for *DJ1/PARK7*, as we are unaware of their co-occurrence in other PD cases. Recent studies suggest that *DJ1* is a deglycase, repairing cellular damage from reactive aldehydes and protecting against oxidative damage. Reactive aldehydes and oxidative damage are implicated in cataractogenesis, pointing to a possible mechanism for premature cataract development in *DJ1/PARK7*.⁷

We expand the *DJ1* phenotype to include autonomic synucleinopathy and impaired olfaction, distinguishing it from the *Parkin/PARK2* phenotype. In addition, we suggest that the clinical triad of early-onset PD, cataracts, and sensorineural hearing loss may be specific for *DJ1/PARK7*.

Author contributions

D.P. Narendra: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision, obtaining funding. R. Isonaka: drafting/revising the manuscript, data acquisition, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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