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Early-Onset Parkinsonism Is a Manifestation of the *PPP2R5D* p.E200K Mutation

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Author Contributions

W.C. contributed to the overall conception and design of the study. C.K., T.W., C.H., A.N., V.O., M.A., N.D., C.T., G.R., J.C., K.T.B., C.B., J.P.V., E.C., R.A., and W.C. contributed to the acquisition and analysis of data. C.K., T.W., and J.P.V. contributed to drafting of the text. T.W. and J.P.V contributed to preparation of the figures.

Potential Conflict of Interest

The authors report no conflicts of interest.

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Abstract

PPP2R5D-related neurodevelopmental disorder is characterized by a range of neurodevelopmental and behavioral manifestations. We report the association of early-onset parkinsonism with the *PPP2R5D* p.E200K mutation. Clinical characterization and exome sequencing were performed on three patients, with postmortem neuropathologic examination for one patient. All patients had mild developmental delay and developed levodopa-responsive parkinsonism between the ages of 25 and 40 years. The *PPP2R5D* c.598G>A (p.E200K) mutation was identified in all patients. Neuropathologic examination demonstrated uneven, focally severe neuronal loss and gliosis in the substantia nigra pars compacta, without Lewy bodies. Our findings suggest the *PPP2R5D* p.E200K mutation to be a possible new cause of early-onset parkinsonism.

Introduction

PPP2R5D, primarily expressed in brain, encodes the regulatory subunit B566 of PP2A, a serine–threonine phosphatase playing a crucial regulatory role in multiple cellular processes, including proliferation, apoptosis, and signal transduction.[1] Recurring de novo missense mutations in *PPP2R5D* have been associated with neurodevelopmental delay, intellectual disability, macrocephaly, motor and coordination deficits, epilepsy, visual impairment, and autism spectrum disorders (Mendelian Inheritance in Man (MIM) number 616355).[2,5] Mast of these mutations, including p. E200K, occur in a hotspot coding for a conserved acidic ltxjp enabling B56δ to bind the scaffolding and catalytic PP2A subunits.[6] p.E200K might impair this binding, perturbing the holoenzyme formation and hindering dephosphorylation of the normal PP2A substrates through a dominant-negative effect[3] The associated phenotype of p. E200K appears to be milder, with greater functional capacity than other mutations, but with limited certainty given the condition's rarity. Additionally, given that most confirmed genetic diagnoses of *PPP2R5D-related* disorder are in children, its natural history after 20 years of age remains largely unknown. We report clinical courses for three adults carrying the *PPP2R5D* p.E200K mutation with mild intellectual disability who developed early-onset parkinsonism. We report postmortem neuropathologic examination for one patient.

Patients and Methods

Cases 1 and 2 were identified through Movement Disorders clinics. Case 3 was identified through an overgrowth study.[4] Genomic DNA was extracted from whole blood. Whole

exome sequencing (WES) and Sanger confirmations [4,7,8] and neuropathologic analysis[9] were performed as previously described.

All participation was voluntary. Signed informed consent was obtained from each patient or representative before genetic testing. Patients were enrolled in institutional research studies, approved by the Columbia University Institutional Review Board, Strasbourg Ethics Committee,[10] and London Multicentre Ethics Committee, respectively.

Results

Clinical Summaries

Case 1: The patient had mild developmental motor and language delays. At 40 years of age, he developed gait difficulty and bradykinesia. Brain magnetic resonance imaging (MRI) demonstrated T2 white matter hyperintensities (Fig 1A). He had co-morbid hypertension and diabetes mellitus. Motor symptoms improved with dopaminergic therapy, gradually complicated by motor and nonmotor fluctuations. Treatment with dopamine agonists was limited by impulse control disorders. At 57 years of age, he underwent implantation for deep brain stimulation, with unclear benefit. He died at 61 years of age from aspiration pneumonia.

Case 2: The patient had no motor delay but had intellectual disability. At 27 years of age, he developed rest tremor and myoclonus, evolving to akinetic rigid parkinsonism. Brain MRI was normal (Fig 1B). Motor symptoms improved with levodopa, limited by motor and nonmotor fluctuations, controlled with carbidopa/levodopa intestinal gel. Treatment with dopamine agonists was complicated by impulse control disorders. Early nonmotor features of parkinsonism were noted.

Case 3: The patient was previously reported (case COG0328).[4] She was suspected to have Sotos syndrome based on overgrowth features; however, no mutations in *NSDJ* or *NFIX* were identified. She had delays in motor development and language acquisition, with mild intellectual disability. By 22 years of age, she developed rest tremor, incoordination, and parkinsonism with good levodopa responsiveness, ultimately complicated by motor fluctuations including dyskinesias.

Birth history was unremarkable in all cases. No family members were affected. Details of clinical courses are provided in Table and as Supplemental Material (Video SI examination).

Genetic Findings

In Case 1, the variant *PPP2R5D* c.598 G>A;p.E200K (NM_006245.3) was identified by proband-only WES,confirmed with Sanger sequencing as present in the patient and absent from his unaffected older sister. This variant was reported as pathogenic by multiple institutions in ClinVar (https://www.ncbi.nlm.nih.gOv/clinvar/variation/217456/). Assessment for likely gene-disrupting or deleterious missense variants in known Parkinson's disease (PD) genes was negative. A heterozygous variant in PARK7 c.70delG; p.Asp24fs (NM_007262) was identified in the prohand and his unaffected sister.

The same *PPP2R5D* variant, c.598G>A;p.E200K, was identified through WES in both Cases 2 and 3. The mutation was confirmed by Sanger sequencing in both cases and was absent from both parents in Case 2. Although the parents were unavailable for testing in Case 3, the mutation was presumed de novo because they were reported to be clinically unaffected. No other likely pathogenic variants in genes associated with PD or early-onset parkinsonism[10] were identified in Case 2. Known PD genes were not assessed specifically in Case 3.

Neuropathology (Case 1)

The external brain surface (l,792.2g) was normal except for the presence of bilateral frontal electrodes and atheromatous plaques involving the large arteries of the base (maximum 50% luminal stenosis). Bilateral electrode tracks extended from the cortex to the zona incerta. Transverse slices from the brainstem revealed marked depigmentation of the substantia nigra bilaterally, contrasting with the well-pigmented nucleus coeruleus. Microscopic assessment of the substantia nigra was performed using two levels: one near the red nucleus, the other near the decussation of the superior cerebellar peduncle (Fig 2). Bilateral, uneven loss of pigmented neurons, reactive gliosis, and the presence of scant, small macrophage clusters with pigmented cytoplasmic debris were notable. The density of pigmented neurons was either apparendy normal or mildly to moderately decreased in patches, flanked by areas showing severe loss of pigmented neurons with loose, glioric parenchyma Sections from the rostral level were less involved than the caudal. In the left pars compacta, loss of pigmented neurons prevailed medially. In contrast, on the right, loss was severe laterally but moderate medially. The pars reticulata was unremarkable. The dorsal nucleus of the vagus was normal bilaterally. Neither Lewy body-containing neurons nor Lewy neuritis was detected throughout the myelencephalon, mesencephalon, diencephalon, basal forebrain, or cerebral cortex. The nucleus coeruleus showed no abnormality. Marked criblures involved the polar subcortical white matter and lenticular nuclei; athero-arteriolosderosis was likewise marked.

Discussion

The association of parkinsonism with a unique recurring de novo mutation, *PPP2R5D* p.E200K, is noteworthy. Although the association between the p.E200K mutation and impaired neurodevelopment is well established, our report is the first linking it to neurodegeneration, which represents an important advance in understanding of the natural history of this condition. The clinical courses of all three patients are notable for mild intellectual disability and early-onset parkinsonism, with onset from ages 25 to 40 years and variable rates of progression. This phenotype of stable intellectual disability during childhood with subsequent adult-onset parkinsonism has been described with mutations in only a few genes previously.[8,11] All *PPP2R5D* p.E200K cases demonstrated levodopa responsiveness with motor fluctuations; two were complicated by impulse control disorders.

Incidence of the *PPP2R5D* neurodevelopmental disorder is estimated at 2.32 to 2.87 per 100,000 births.[12] The mutation frequency in early-onset PD is unknown. We explored public PD genetic databases for the presence of the p.E200K mutation and did not identify any PD or control carriers, suggesting the variant to be extremely rare in the general population

(JJ Kim; MB Makarious; S Bandres Ciga; JR Gibbs; J Ding; D Hernandez; J Brooks; F Grenn; H Iwaki; A Singleton; MA Nalls; G Blauwendraat; and International Parkinson's Disease Genomics Gonsortium, https://pdgenetics.shinyapps.io/VariantBrowser/, manuscript in preparation). Notably, current databases do not distinguish between early-onset, familial, and other PD. We searched for *PPP2R5D* in a University of Strasbourg cohort of 122 patients with parkinsonism, including 60 early-onset and 35 familial cases; we did not identify any pathogenic or likely pathogenic variants. Further clarification will require study of a larger early-onset cohort.

The association of other *PPP2R5D* mutations with neurodegeneration is unknown. Parkinsonism has not been reported in association with other mutations to our knowledge. Increased screening (eg, inclusion of *PPP2R5D* in a genetic panel for early-onset parkinsonism) and longitudinal follow-up of *PPP2R5D* mutation carriers would allow better delineation of phenotype–genotype correlation. Biochemical/functional studies are reported in another manuscript currendy under review and suggest alteration in targets of phosphorylation with the mutation. Identification of the downstream targets of different mutations should help to elucidate the molecular mechanisms underlying neurological manifestations.

The neuropathologic findings represent the first such characterization in a *PPP2R5D* mutation carrier, to our knowledge. Focally severe substantia nigra atrophy and the absence of Lewy body pathology are notable. The absence of α-synuclein pathology is reminiscent of *Parkin-associated* PD[13] or l-methyl-4-phenyl-l,2,3,6-tetrahydropyridine-related parkinsonism,[14] both of which are thought to be primarily attributable to mitochondrial impairment.[14,15] In contrast to most idiopathic PD cases, the nucleus coeruleus was unaffected here, the sparing of which is also reported in most *Parkin-associated* PD.[13] PP2A-B56δ plays an important role in regulating phosphatidylinositol 3-kinase/protein kinase B and glycogen synthase kinase-3 beta-mediated growth control and tau phosphorylation, but tau deposits were not induced in a *PPP2R5D* knockout mouse model.[16,17] Thus, although neurofibrillary tangles were not noted, we cannot exclude the possibility that altered dephosphorylation of tau might have contributed to the observed neurodegeneration.

We suspect that the noted vascular changes involving the subcortical white matter reflect incidental microvascular disease secondary to the patient's vascular risk factors. Notably, brain MRI in Gase 2 was reassuring for significant white matter abnormalities (Fig 1B). Gase 1 is notable for a heterozygous *DJ-1* frameshift variant, very likely to be incidental, given that his asymptomatic sister is also a carrier, only recessive mutations in *DJ-1* have been linked to PD, and all *DJ-1* PD cases with published neuropathology have demonstrated Lewy body pathology,[18,19] absent here.

Rare neurogenetic conditions associated with intellectual disabilities, autism, and epilepsy are rapidly being identified, meriting further natural history data in adults. Although many will be static, identification of those associated with neurodegeneration or other systemic phenotypes is important. Understanding the precise molecular genetic basis for neurological conditions will allow individualized prognostication and, ultimately, treatment.

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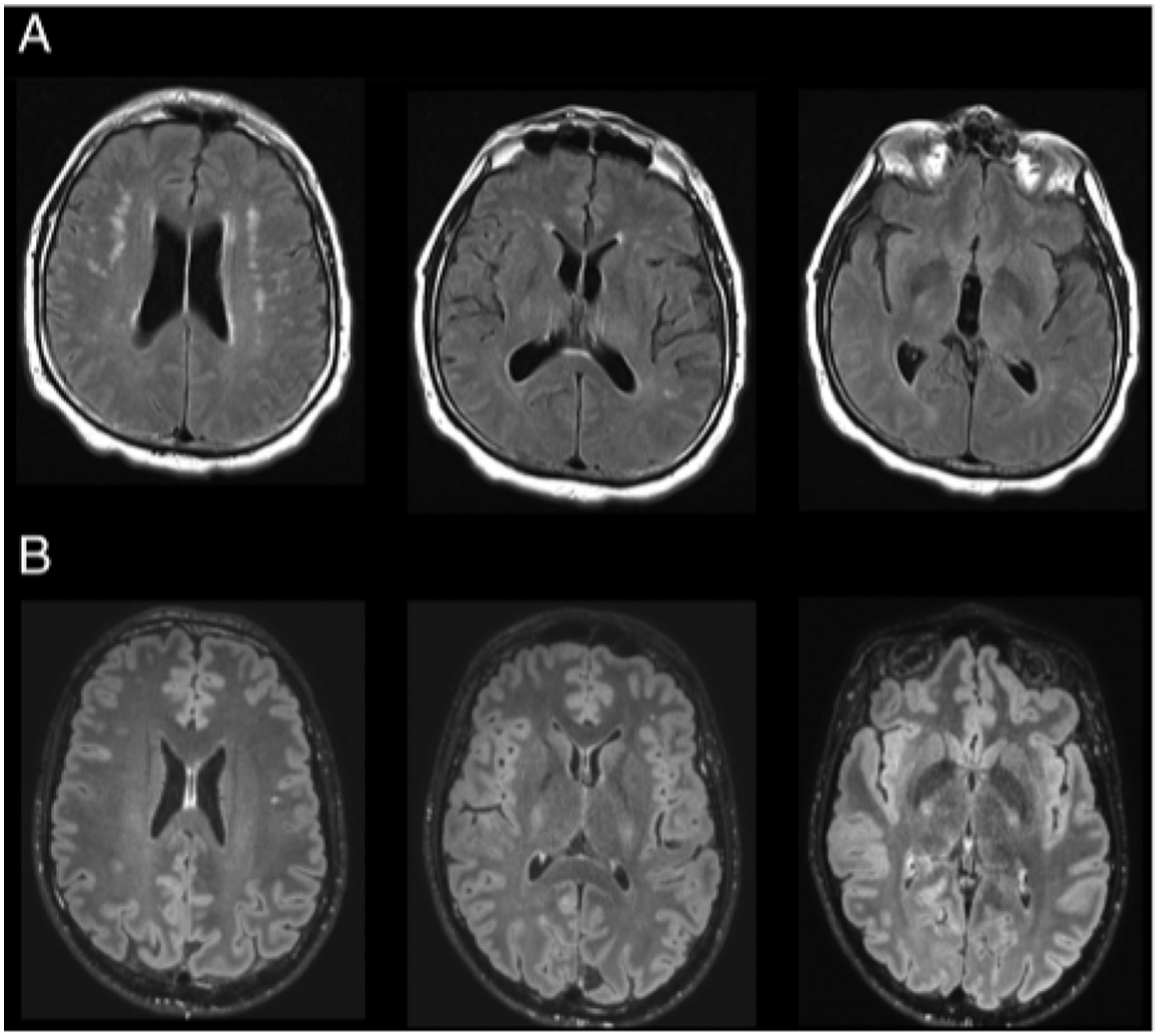

FIGURE 1:
Neuroimaging: Cases 1 and 2. (A) Case 1: magnetic resonance imaging (MRI) brain T2 fluid-attenuated inversion recovery (FLAIR) images demonstrating hyperintensities in subcortical white matter bilaterally. (B) Case 2: MRI brain T2 FLAIR images demonstrating relative paucity of white matter signal abnormality.

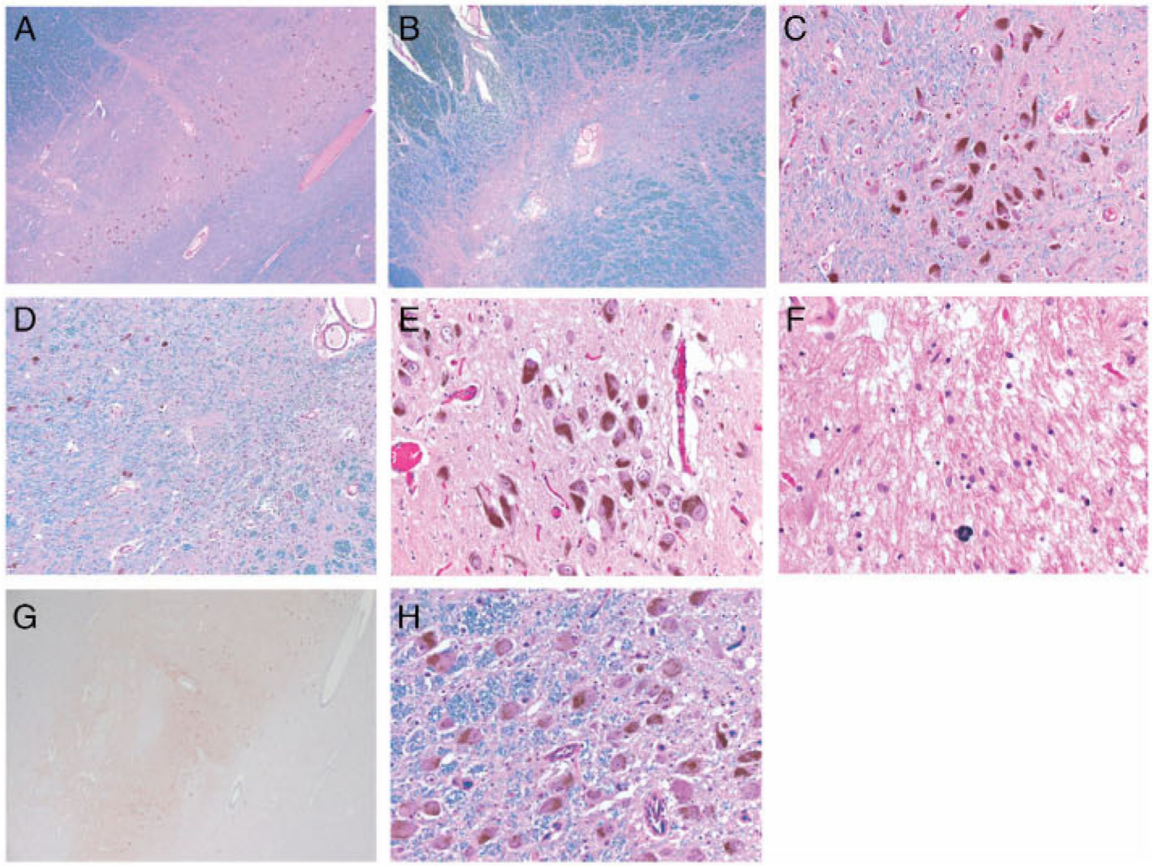

FIGURE 2:

(A–D) Photomicrographs of the left substantia nigra: rostral, medial levels in A and C; caudal in B; and caudal, medial levels in D. The loss of pigmented neurons is uneven and prevails at the caudal levels. Relatively sharp demarcation between foci without or with resilient neurons in D. (E–H) Photomicrographs of the caudal levels of the right substantia nigra in E–G and of the nucleus coeruleus in H. (E) The density of pigmented neurons is apparently normal within the medial third. (F) The loss is subtotal within the lateral third. (G) Neither Lewy body-containing neurons nor Lewy neurites were detected. (H) The neuronal density of the nucleus coeruleus is normal. Staining: Luxol Fast Blue counterstained with Hematoxylin and Eosin in A–D and H; Hematoxylin and Eosin in E and F; and a-synudein in G. Original magnification: ×25 in A, B, and G; ×100 in D; ×200 in C, E, and H; and ×400 in F.

Video S1.

TABLE.

Parkinsonism in *PPP2R5D* (NM_006245.3) p.E200K Mutation Carriers: Clinical Features

Characteristic	Case 1	Case 2	Case 3
Ancestry	European	European	European
Sex	Male	Male	Female
Age at last visit	61 years	34 years	44 years
Genetic test	Exome sequencing	Exome sequencing	Exome sequencing
Developmental history	Term birth. Motor delay: walked at 2–3 years. Language delayed. Mild intellectual disability: special education classes; graduated from vocational high school	Term birth: possible amniotic fluid aspiration. No motor delay. Language delayed. Severe learning disability: stopped schooling at 15 years	Term birth. Motor delay: sat at 9–10 months; cruised at 2 years. I Iypotonia. Language delayed. Mild intellectual disability
Seizures	No	No	No
Past medical history	Diabetes mellitus type 2, hypertension, sensorimotor neuropathy	None	Overgrowth (height 97th percentile by 2.5 years; macrocephaly)
Parkinsonism: age at onset	40 years	27 years	22 years
Motor features	Onset of gait difficulty, generalized hradykinesia; subsequent freezing of gait. Atrcmulous	Onset of right arm rest tremor; subsequently, predominantly akinetic–rigid. Postural instability	Onset of asymmetric rest tremor; subsequent freezing of gait, postural instability, cervical dystonia
Nonmotor features	Autonomic: non motor off symptoms (sweats, urinary urgency). No cognitive decline	Autonomic: constipation, urinary urgency. Rapid eye movement sleep behavior disorder. Depression, anxiety. Early cognitive decline	Autonomic: none. Sleep disturbance: none. Visual hallucinations
Atypical features	None	Myoclonus; oculomotor abnormalities	None
Rate of progression	Fluctuations: 9 years after onset. Freezing of gait: 10 years after onset. Wheelchair bound: 17 years after onset	Fluctuations: 3 years after onset. Postural instability: 5 years after onset. Remains ambulatory without aids	Slow progression since onset (neady 20 years)
Diagnostic studies	Magnetic resonance imaging of brain without contrast: subcortical white matter T2 hyperintensities(Fig 1A)	Dopamine transporter imaging scan: abnormal. Magnetic resonance imaging of brain without contrast: normal (Fig 1B). Electromyography/Nerve conduction study: normal	None
Levodopa and other treatment response	Levodopa responsive. Deep brain stimulation (subthalamic nuclei, 17 years after onset): unclear benefit	Levodopa responsive	Levodopa responsive
Complications of therapy	Motor and nonmotor off symptoms. Impulse control disorders (gambling, overeating) with dopamine agonist	Motor and nonmotor off symptoms. Impulse control disorders (gambling, hypersexuality) with dopamine agonist	Fluctuations: motor off symptoms (marked rigidity); dopamine-induced dyskinesias
Agc/causc of death	61 years/aspiration pneumonia	Not applicable	Not applicable