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Progressive Parkinsonism in *PPP2R5D*-Related Neurodevelopmental Disorder

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ABSTRACT

PPP2R5D-related neurodevelopmental disorder (Houge–Janssens syndrome type 1) is a rare autosomal dominant condition characterized by macrocephaly, intellectual disability, and epilepsy. Progressive parkinsonism is an emerging adult phenotype that neurologists should be aware of since timely genetic diagnosis opens the door to disease-modifying therapies currently in clinical trials. We describe a 33-year-old woman with this condition who developed progressive mixed-tremor parkinsonism in early adulthood. Dopamine transporter imaging confirmed presynaptic nigrostriatal dysfunction. Whole-genome sequencing identified the recurrent de novo pathogenic missense variant PPP2R5D p.Glu198Lys. The clinical triad of macrocephaly, intellectual disability, and early-onset parkinsonism is specific for this condition and should prompt targeted genetic evaluation even in adults with a longstanding diagnosis of a neurodevelopmental disorder.

1 | Introduction

Neurologists in general adult practice can find themselves caught off guard when a patient with a longstanding neurodevelopmental disorder develops a progressive movement disorder in adulthood. The instinct is often to treat the two problems independently: the childhood condition on one hand, and what looks like early-onset Parkinson's disease on the other. *PPP2R5D*-related neurodevelopmental disorder, also known as Jordan's syndrome or Houge–Janssens syndrome type 1, is a rare condition that should shift this instinct because the parkinsonism is not coincidental: it is part of the syndrome. More importantly, a correct genetic diagnosis now opens the door to emerging disease-modifying treatments.

2 | Case Report

A 33-year-old woman was referred for progressive gait instability and worsening hand tremor. She had been born at term with no neonatal complications. There was no family history of neurodevelopmental or movement disorders. Her background included macrocephaly, global developmental delay, and later moderate intellectual disability, severe myopia, and childhood-onset epilepsy. She had attended special education, and no genetic evaluation had previously been performed. A brain MRI in childhood was reported as normal. Motor milestones were delayed from infancy, and independent ambulation was achieved at age 4 years, when a mild action tremor and impaired fine motor skills were first noted. Motor

function did not normalize but remained relatively stable through adolescence.

Epilepsy consisted of a single seizure in infancy and a cluster of generalized seizures at ages 14–15, which responded to carbamazepine and later lamotrigine. At the time of her evaluation, she had been seizure-free off medication for more than a decade.

Motor symptoms worsened slowly through her twenties before accelerating subacutely at age 30. She developed a high-amplitude mixed rest and action tremor interfering with fine motor tasks, gait freezing, frequent falls, and persistent left foot inversion—initially attributed to an orthopedic problem. By the time of referral, she needed a posterior walker or physical assistance for all walking (Figure 2).

Examination (Video 1) showed macrocephaly (62.5 cm, Z ~ +4.3) and dysmorphic facial features including mild hypertelorism and frontal bossing. Speech was hypophonic and dysarthric. Oculomotor examination was normal, with no supranuclear gaze palsy. There was moderate rigidity (left greater than right) and bradykinesia in all limbs, and a complex high-amplitude tremor with resting, postural, and intention components. Mild orofacial, facial, and cervical dystonia were present, along with sustained plantar flexion and inversion of the left foot during walking. Deep tendon reflexes were 2+ throughout with downgoing plantar responses.

Routine investigations, including complete blood counts, serum electrolytes, renal and hepatic function, thyroid function, inflammatory markers, ceruloplasmin, and 24-h urinary copper, were all normal. Brain MRI showed T2 signal shortening and increased susceptibility in the globi pallidi and putamina, and subtle callosal dysgenesis (Figure 1A–B). Dopamine transporter (DAT) imaging showed asymmetrically reduced striatal uptake in the putamina, confirming presynaptic nigrostriatal dysfunction (Figure 1C).

A trial of carbidopa/levodopa (25/100 mg, titrated to 1.5 tablets three times daily) produced a mild subjective improvement in bradykinesia, documented over time in Video 2, but overall functional independence was not restored. Treatment was discontinued after she developed a severe perioral erythematous rash, a rare potential side effect.

The distinctive combination of macrocephaly, moderate intellectual disability, childhood epilepsy, and early-onset progressive parkinsonism with DAT imaging evidence of nigrostriatal dysfunction suggested a genetic etiology, prompting enrolment in a gene discovery study (NCT05354622). Whole-genome sequencing identified a *de novo* heterozygous missense variant in *PPP2R5D* (NM_006245.4:c.592G>A, p.Glu198Lys), classified as pathogenic, establishing the diagnosis of *PPP2R5D*-related neurodevelopmental disorder (OMIM #616355). The clinical course is summarized in Figure 2.

3 | Discussion

PPP2R5D encodes the B56δ regulatory subunit of protein phosphatase 2A (PP2A), a critical regulator of neuronal development and intracellular signaling. All known pathogenic variants are missense and cluster in the substrate-binding pocket of B56δ, arising almost exclusively de novo, causing autosomal dominant disease [1]. In a published cohort of 72 individuals, core features included hypotonia (75%), macrocephaly (67%), epilepsy (46%), language disorder (60%), and autism spectrum disorder (26%). Independent walking is typically achieved late, between 18 months and 9 years of age. More than 150 individuals have been reported, and p.Glu198Lys is among the most common and most severe variants in terms of cognitive outcome. The prevalence of parkinsonism among p.Glu198Lys carriers cannot yet be estimated from published cohorts, as most reported individuals are of pediatric age and have not reached the expected age of onset for this feature [1–3].

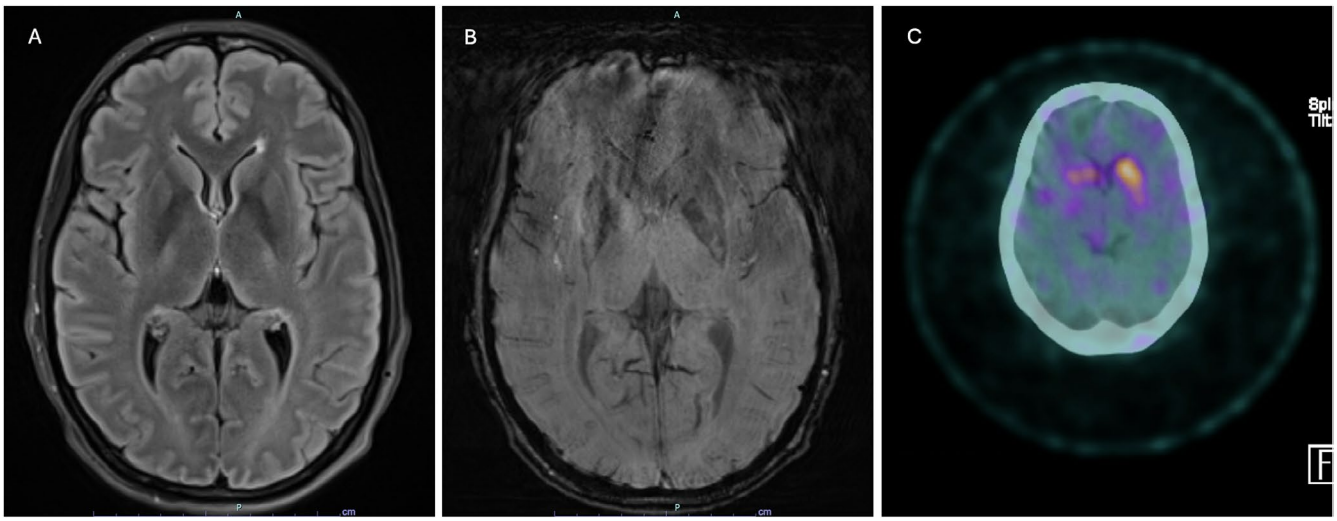

FIGURE 1 | Neuroimaging. (A) Axial FLAIR MRI: Non-specific T2 signal shortening in the globi pallidi and lateral putamina. (B) Axial susceptibility-weighted imaging (SWI): Increased susceptibility in the corresponding regions, without "eye-of-the-tiger" sign or extensive iron overload. (C) Dopamine transporter (DAT) SPECT: Asymmetrically reduced striatal uptake in the putamina (right greater than left), consistent with presynaptic nigrostriatal dysfunction and correlating with the patient's left-sided symptom predominance.

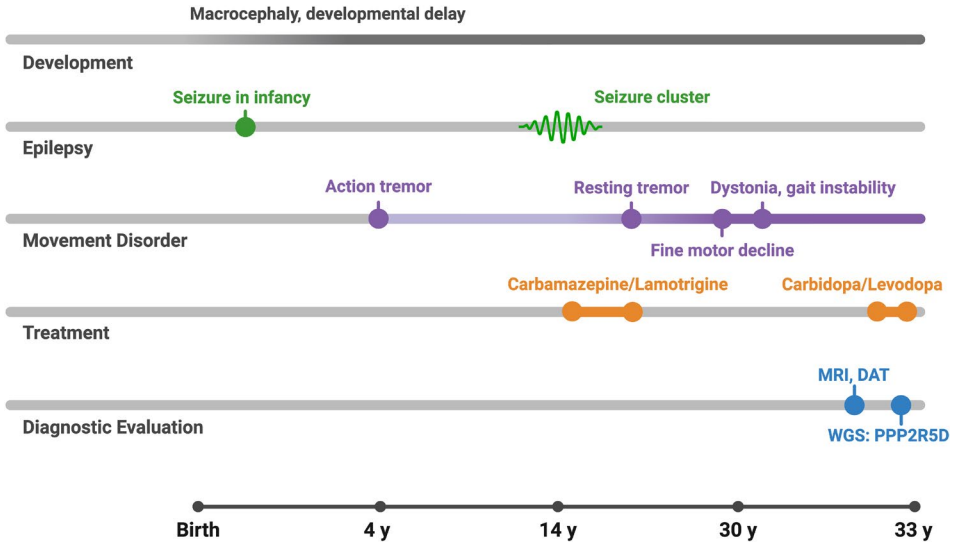

FIGURE 2 | Clinical timeline from birth to age 33 years, summarizing the evolution of neurodevelopmental features, epilepsy, movement disorder, treatments, and diagnostic milestones.

3.1 | Movement Disorders in PPP2R5D-Related Disease

Movement disorder features follow a recognizable developmental arc: uncoordinated gait in childhood, hand tremors in adolescence, and early-onset parkinsonism in adulthood—a progression that clinicians may not recognize as a continuum if they encounter the patient for the first time in adulthood. Kim et al. first described levodopa-responsive parkinsonism in individuals with the recurrent p.Glu200Lys variant [4], and Hetzelt et al. documented parkinsonism with p.Glu198Lys—the same variant as our patient [5]. Compared with prior reports, our case extends the clinical characterization of the p.Glu198Lys phenotype by documenting the temporal sequence of motor symptom evolution, delineating a complex profile of mixed tremor and dystonia, and contextualizing this presentation within the emerging therapeutic landscape. Neuropathological analysis revealed focal neuronal loss and gliosis in the substantia nigra pars compacta without Lewy bodies, distinguishing this from idiopathic Parkinson's disease [4]. Our patient's DAT imaging provides in vivo confirmation of presynaptic dopaminergic degeneration and extends the imaging characterization of this phenotype. The observed clinical deterioration most likely reflects natural progression of nigrostriatal neurodegeneration rather than primary drug failure, a conclusion consistent with the neuropathological findings of Kim et al. [4]. The limited levodopa response additionally raises the possibility of concomitant postsynaptic dysfunction—an open question that warrants investigation with postsynaptic imaging in future cases.

3.2 | A Clinically Recognizable Syndrome

Macrocephaly and the preceding history of developmental delays and intellectual disability without regression are the key discriminating features. This is absent from virtually every other cause of early-onset parkinsonism—including *PRKN*, *PINK1*, *DJ-1*, *ATP13A2* (Kufor–Rakeb), beta-propeller protein-associated neurodegeneration (BPAN), and hereditary spastic paraplegia types 11 and 15. The presence of macrocephaly alongside intellectual disability and early-onset parkinsonism should immediately prompt genetic testing for *PPP2R5D*. Other features that argue against other genetic causes of parkinsonism are the longstanding childhood neurodevelopmental course without evolution of additional neurological symptoms; for example, the absence of a pyramidal syndrome (against *SPG11/ZFYVE26*) [6] or supranuclear gaze palsy (against Kufor–Rakeb syndrome) [7].

Brain MRI is often non-diagnostic or shows only subtle changes (ventriculomegaly, callosal dysgenesis, or non-specific basal ganglia signal change). DAT imaging is a practical next step when the diagnosis is uncertain, and a positive result supports initiation of dopaminergic therapy and strengthens the case for genetic evaluation. A differential diagnosis of early-onset genetic parkinsonism is summarized in Table S1.

When this condition is on the differential, whole-genome or whole-exome sequencing is the most efficient diagnostic route. Standard gene panels for Parkinson's disease or movement disorders will not include *PPP2R5D*. Adult neurologists should be aware that testing may face insurance authorization challenges and that referral to a genetics service or specialist center experienced in rare genetic disorders may facilitate a genetic diagnosis [8]. We concur with Kim et al. that inclusion of *PPP2R5D* in gene panels for early-onset parkinsonism and neurodevelopmental disorders would facilitate earlier diagnosis, particularly in settings where comprehensive genomic testing is unavailable.

3.3 | Management and Therapeutic Considerations

Published management guidelines for this condition explicitly recommend a levodopa trial for parkinsonism [9]. Benefit can be meaningful, though as in our case a perioral rash from carbidopa is an uncommon but recognized adverse effect [10]. Alternative dopaminergic strategies (dopamine agonists, MAO-B inhibitors) are under consideration for patients who cannot tolerate levodopa.

This report is limited by the absence of formal motor rating scale assessments (e.g., MDS-UPDRS) before and after levodopa initiation; prospective standardized motor evaluations should be incorporated in future cases to better characterize treatment response. Deep brain stimulation is a potential option for refractory motor symptoms, but requires careful multidisciplinary evaluation including formal neuropsychological assessment: patients with pre-existing intellectual disability may carry additional risk for postoperative cognitive and behavioral complications.

Beyond symptomatic treatment, the diagnostic stakes have risen significantly. Young et al. demonstrated that allele-specific antisense oligonucleotides targeting the pathogenic E198K allele fully rescued neurite phenotypes in patient-derived neurons [2] representing a compelling proof-of-principle for targeted genetic therapy. In parallel, a phase 1/2 clinical trial of zatolmilast (BPN14770), a phosphodiesterase-4D inhibitor, is currently recruiting (NCT06717438). The DBSMatchMaker platform supports clinician collaboration for those considering deep brain stimulation in ultra-rare disorders, such as this one [11, 12].

It is also worth proactively screening for associated features that are easy to overlook when parkinsonism dominates the referral. In published cohorts these include: behavioral difficulties such as anxiety, aggression, and attention deficit (present in the majority, except in those with residue 251 variants); GI dysmotility, gastro-esophageal reflux, and constipation (~24%); ophthalmologic abnormalities including strabismus and astigmatism (~45%); scoliosis and hip dysplasia; and endocrine features including precocious puberty [9]. A diagnosis also opens the door to disease registries, natural history studies, and family counseling, in addition to the emerging therapeutic trials.

4 | Conclusion

This case illustrates that adults with a history of neurodevelopmental delay who experience progressive motor symptoms warrant systematic re-evaluation for genetic etiologies rather than assumption of an idiopathic diagnosis or attribution to cerebral palsy. The combination of macrocephaly, intellectual disability, and early-onset parkinsonism is a distinctive and relatively specific clinical constellation that should prompt immediate targeted genetic evaluation for *PPP2R5D*. Early diagnosis enables anticipatory co-morbidity surveillance, enrollment in clinical trials, access to emerging targeted therapies, and informed family counseling. As disease-modifying treatments advance toward clinical translation, timely genetic diagnosis will be increasingly critical for optimizing long-term outcomes.

Author Contributions

D.E.-F. contributed to the conception and design of the study; K.B., E.G.S.-D., J.R., B.A., S.M., K.Y., and D.E.-F. contributed to the acquisition and analysis of data; K.B. drafted the manuscript. All authors reviewed and approved the final version.

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Ethics Statement

This study was approved by the Boston Children's Hospital Institutional Review Board (IRB-P00039630).

Consent

Written informed consent was obtained from the patient's legal guardians for participation in research and for publication of all clinical information, including neuroimaging and video material.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Differential diagnosis of early-onset parkinsonism in the context of PPP2R5D-related neurodevelopmental disorder. **Video S1:** Examination at the time of referral showing rest, postural, and action-induced tremor of moderate frequency and high amplitude, with bradykinesia, rigidity, orofacial and cervical dystonia, and dystonic left foot posturing. **Video S2:** Gait at two labeled time points. Time point 1 ('Shortly after levodopa initiation'): broad-based shuffling gait with intermittent need for support and postural instability on turning. Time point 2 ('Several months later'): clinical deterioration with full assistance required for ambulation, despite mild subjective improvement in upper limb bradykinesia as reported by the patient and family.