Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Adult-Onset Parkinsonism as Late Manifestation of *HIVEP2*-Associated Developmental Disorder

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There is accumulating, yet still limited evidence that variants in genes associated with neurodevelopmental disorders can lead to late-onset motor phenotypes such as parkinsonian syndromes resembling Parkinson's disease.[1] With *HIVEP2*, we report another example of a neurodevelopmental gene in which rare variants may result in adult parkinsonism as late disease manifestation.

The male patient was referred to us for evaluation of new-onset atypical parkinsonian features. At the age of 49 years, he developed progressive gait disturbances and balance difficulties; he noted tremor of the lower limbs while walking. L-Dopa was prescribed and provided moderate benefit. Screening for metabolic disorders and CSF analysis were unremarkable. Brain MRI showed non-specific microangiopathic changes, but no gross atrophy. On examination at age 57, the patient demonstrated generalized rigidity and hypokinesia; fine repetitive movements of the hands were slow and significantly decreased in amplitude as part of the parkinsonism (Video 1, Segment 1). There was no significant cerebellar involvement. Gait was unsteady and only possible with support (Video 1, Segment 2); there were freezing and postural instability with marked retropulsion on pull test. A mild action tremor of the upper limbs was present, but no rest tremor. Finger-to-nose test was only slightly dysmetric (Video 1, Segment 3). Past medical history was notable for delay in language development with poor acquisition of speech. Hyperactivity was present in childhood; he was suspected to have a mild form of intellectual disability. The patient received logopedic therapy and visited a special education center. Motor development was normal, with free walking at the age of 15 months. There was no family history for neurological diseases (Fig. 1). Thorough genetic investigation using whole-exome sequencing revealed a heterozygous loss-of-function (frameshift) variant (NM_006734.4:c.3678dup, p.(Gln1227Alafs*44)) in *HIVEP2*, classified as "likely pathogenic" according to ACMG criteria (PVS1, PM2). The variant was confirmed by Sanger sequencing. No alternative potentially pathogenic variants in established parkinsonism-related genes were found (an OMIM-generated list of the assessed genes associated with parkinsonism and intellectual disability is available as supplementary file). Sanger sequencing showed that the variant was not carried by the healthy mother and brother (deceased father unavailable for testing).

Variants in *HIVEP2* have been linked to a monogenic neurodevelopmental condition –"*intellectual developmental disorder, autosomal dominant 43*"– in OMIM (#616977). Most published cases were identified to have heterozygous loss-of-function variants, especially nonsense or frameshift alleles predicted to lead to nonsense-mediated decay,[2–4] in line with the variant type we observed in our patient. Constraint metrics indicate that *HIVEP2* is a highly loss-of-function intolerant gene (pLI:1; LOEUF:0,08; pHAPLO:1,0) and haploinsufficiency is suggested as mechanism of disease.[2] Common symptoms of *HIVEP2*-associated disease include developmental delay and intellectual disability, minor variable dysmorphic features such as prominent forehead or widely spaced eyes, and behavioral issues such as hyperactivity,

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Video 1. Neurological examination of the patient with atypical parkinsonian features. Segments 1, 2, and 3 show repetitive hand movements, gait, and finger-to-nose test, respectively. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14156

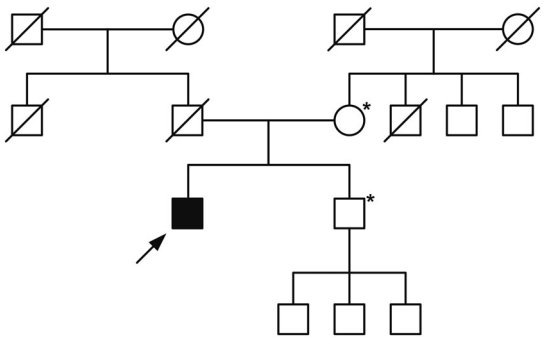

Figure 1. Pedigree without history for neurological diseases or intellectual disability; the index patient is indicated by the arrow. Sanger sequencing of available first-degree relatives (*mother and brother) for *HIVEP2* was negative.

impulsivity, and autism spectrum disorder. Some previously described individuals also showed movement and tone abnormalities, mainly hypotonia and mild-to-moderate motor delay; most affected subjects started to walk independently around the third year of life, and gait often remained wide-based or ataxic.[2–4] Other movement disorders such as dystonia or spasticity have been mentioned occasionally, without any further characterization in the published studies. Only one pediatric case, who was 10 years old at the time of reporting, was described as having tremor and potential parkinsonism.[3] As the reported individuals from the literature were all children or young adults, the clinical courses remained unknown and prognosis was indeterminate. Until today, the here-presented patient is the oldest individual with a disease-related variant in *HIVEP2*. He appears to share common features of the syndrome including developmental delay and intellectual impairment. Importantly, the onset of his movement disorder at the end of his forties suggests that this syndrome can also evolve into adult-onset parkinsonism.

This finding adds *HIVEP2* to an expanding group of genes which can be causally associated with late-onset movement disorders such as adult parkinsonism in addition to pediatric neurodevelopmental-disease pictures. Similar to the current observations, variants in *NR4A2* have been implicated in intellectual disability in childhood and adult-onset phenotypes with features of parkinsonism including bradykinesia and rigidity with L-Dopa response.[5] Intriguingly, the gene products of both *HIVEP2* and *NR4A2* act as transcription factors mediating expression of the dopamine transporter SLC6A3, essentially involved in reuptake of dopamine from the synapse in motor pathways.[6,7] Moreover, for both *HIVEP2* and *NR4A2*, critical roles in brain development and in maintenance of neuronal function have been documented.[2,8,9] Additional emerging examples of neurodevelopmental genes with dichotomic clinical outcomes including pediatric syndromes on the one hand and adult-onset parkinsonism or dystonia-parkinsonism on the other represent *NAA15*, *PLXNA1*, and *PPP2R5D*.[1] These observed genotype–phenotype relationships support the results from in-vitro and in-vivo experimental studies implying that not only neurodegenerative processes but also dysregulated neurogenesis may be implicated in the pathogenesis of parkinsonian syndromes and Parkinson's disease.[10] We encourage further research to better understand the neurodevelopmental basis of parkinsonian syndromes, which may facilitate stratification of patients according to etiological subtype and, thereby, offer paths to the design of more efficient therapies. Without functional data, a causal relationship between the *HIVEP2* variant and the observed parkinsonian features is not proven in our patient and an incidental co-occurrence cannot be excluded. However, not only the growing evidence suggesting a role for neurodevelopmental genes in late-onset motor manifestations but also the atypical clinical manifestation of the parkinsonism in our patient, not fitting to common Parkinson's disease, supports a causal association between the genetic variant in *HIVEP2* and the motor phenotype. Furthermore, this report highlights that genetic testing in adults and assessment of long-term outcomes of individuals with neurodevelopmental disorders are important to characterize the whole spectra of these diseases. Knowledge about prognosis and potential adult-onset manifestations of the conditions may influence treatment choices and care of affected individuals and their families.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

S.B.: 1A, 1C, 3A.
F.C.: 1A, 1C, 3B.
M.B.: 1C, 3B.
J.W.: 1B, 3B.
M.Z.: 1A, 1B, 1C, 3B.

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Disclosures

Ethical compliance statement: Genetic study and de-identified reporting of clinical and molecular data were performed in accordance with respective ethics review board approval (Technical University of Munich, Munich, Germany). Written informed consent was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Straka I, Svantnerova J, Minar M, Stankova S, Zech M. Neurodevelopmental gene-related dystonia-parkinsonism with onset in adults: a case with NAA15 variant. *Mov Disord* 2022;37(9):1955–1957.
2. Srivastava S, Engels H, Schanze I, et al. Loss-of-function variants in HIVEP2 are a cause of intellectual disability. *Eur J Hum Genet* 2016; 24(4):556–561.
3. Steinfeld H, Cho MT, Retterer K, et al. Mutations in HIVEP2 are associated with developmental delay, intellectual disability, and dysmorphic features. *Neurogenetics* 2016;17(3):159–164.
4. Quental R, Borges JP, Santos H, Leao M. Expanding the phenotypic Spectrum of HIVEP2-related intellectual disability: description of two Portuguese patients and review of the literature. *Mol Syndromol* 2022; 13(5):397–401.
5. Wirth T, Mariani LL, Bergant G, et al. Loss-of-function mutations in NR4A2 cause dopa-responsive dystonia parkinsonism. *Mov Disord* 2020; 35(5):880–885.
6. Zhao J, Chen C, Bell RL, Qing H, Lin Z. Identification of HIVEP2 as a dopaminergic transcription factor related to substance use disorders in rats and humans. *Transl Psychiatry* 2019;9(1):247.
7. Sacchetti P, Mitchell TR, Granneman JG, Bannon MJ. Nurr1 enhances transcription of the human dopamine transporter gene through a novel mechanism. *J Neurochem* 2001;76(5):1565–1572.
8. Jankovic J, Chen S, Le WD. The role of Nurr1 in the development of dopaminergic neurons and Parkinson's disease. *Prog Neurobiol* 2005; 77(1–2):128–138.
9. Takao K, Kobayashi K, Hagihara H, et al. Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia. *Neuropsychopharmacology* 2013;38(8):1409–1425.
10. Zagare A, Barmpa K, Smajic S, et al. Midbrain organoids mimic early embryonic neurodevelopment and recapitulate LRRK2-p.Gly2019 Ser-associated gene expression. *Am J Hum Genet* 2022;109(2):311–327.

Supporting Information

Supporting information may be found in the online version of this article.

TABLE S1.OMIM-listed Genes associated with Parkinson.