

Early-Onset Parkinson's Disease in a Patient With a De Novo Frameshift Variant of the *ANKRD11* Gene and KBG Syndrome

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Dear Editor,

Here we report the notable case of a patient with early-onset Parkinson's disease (PD) who was diagnosed with KBG syndrome.

The patient was a 41-year-old white male with a 2-year history of progressive bradykinesia, left-sided upper-limb tremor, rigidity, camptocormia, and gait impairment. He additionally experienced moderate hyposmia and constipation, with no indications of REM sleep behavior disorder. The patient was the second child of nonconsanguineous parents, and had an unremarkable family history and a healthy older brother. His antenatal and postnatal periods were uneventful. Remarkably the patient had no previous medical visits, but it was determined retrospectively that he had experienced early developmental delay and learning difficulties, with behavioral abnormalities including compulsive behavior, anxiety, and impaired communication skills predominating since early adulthood.

A clinical examination performed upon referral revealed a distinctive facial gestalt characterized by synophrys, hypertelorism, a prominent/high nasal bridge, long philtrum, thin upper lip, macrodontia, and moderate parkinsonism. The patient also exhibited mild intellectual disability, short stature, scoliosis, and clinodactyly (Supplementary Fig. 1 in the online-only Data Supplement). Brain magnetic resonance imaging (MRI) demonstrated multiple gray-matter (GM) heterotopias and hypoplasia of the corpus callosum. Additionally, volumetric MRI (SurferMagix Module, BrainMagix Software, Imagilys) revealed decreased cortical and subcortical GM volumes (Fig. 1).¹ DaTscan investigations revealed decreased dopamine-transporter uptake bilaterally, which was more pronounced in the right putamen. The findings of an extensive laboratory workup, electroencephalography, audiometry, bone density scan, transthoracic echocardiogram, and testicular ultrasound were all normal. Whole-exome sequencing revealed a heterozygous frameshift mutation [c.3770_3773delAAGA, p.(Lys1257fs*60)] in the *ANKRD11* (ankyrin repeat domain 11) gene (ClinVar: 560941), for which both parents and the brother of the patient tested negative (Supplementary Table 1 in the online-only Data Supplement). The patient was diagnosed with early-onset PD and KBG syndrome, and was started on treatment with rasagiline (1 mg orally once daily), which resulted in partial improvement of his motor symptoms.

Loss-of-function *ANKRD11* variants have been causally linked to KBG syndrome (OMIM #148050), which is a rare neurodevelopmental disorder characterized by intellectual disability and dental, craniofacial, and skeletal anomalies.² KBG has an autosomal-dominant inheritance pattern, with most cases occurring sporadically due to de novo mutations, either as heterozygous protein-truncating variants in *ANKRD11* or due to 16q24.3 microdeletions encompassing *ANKRD11*.^{3,4} The syndrome was first described in 1975 and named after the initials (K, B, and G) of the last names of the first three identified families.⁵ Approximately 200 KBG cases have subsequently been reported in the literature, but the exact prevalence remains unknown due to suspected underdiagnosis resulting from variable presentations,

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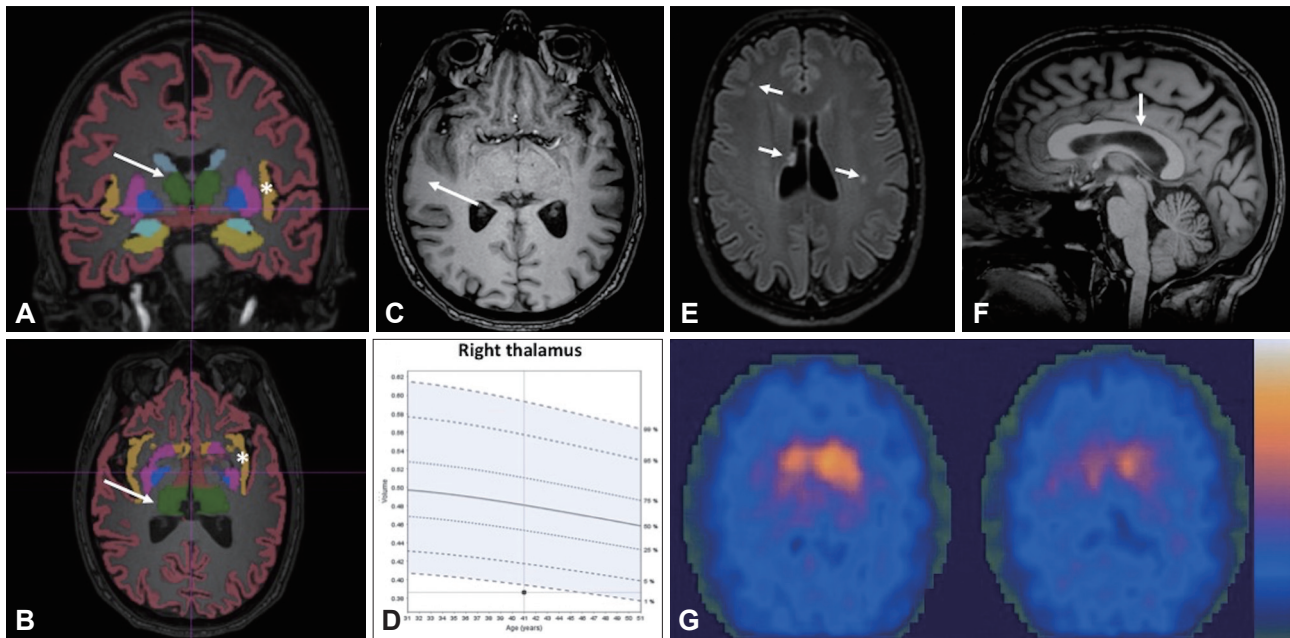


Fig. 1. Neuroimaging and DaTscan findings. Magnetic resonance imaging (MRI) volumetry (A and B) showed markedly reduced cortical and subcortical gray-matter volumes, with those of both hippocampi (yellow), cerebral cortex (coral), left insula (asterisk), and right thalamus (arrow) being below the 1st percentiles for the normative population (D). Normative curves were derived from a population of 1,800 healthy volunteers. The lines represent the percentiles of the volume of the right thalamus, normalized to the estimated total intracranial volume; for example, the 50th percentile corresponds to the median volume of the thalamus in the normal cohort. The dot indicates the corresponding measurement in our patient. Structural brain MRI revealed abnormal gyration and cortical thinning in the right temporal lobe (C, arrow), subependymal and subcortical heterotopias (E, arrow), and corpus-callosum hypoplasia (F, arrow). There were also abnormal DaTscan findings (G).

including mild clinical phenotypes.⁶ A KBG diagnosis in our patient was supported by genetic findings along with the presence of 1) neurodevelopmental delay/intellectual disability and 2) distinctive dental, craniofacial, and skeletal features.⁶ To the best of our knowledge, this is the second report of a patient with KBG harboring a loss-of-function variant in *ANKRD11* presenting with early-onset PD.⁷ Similarly to the present case, in the previous patient the PD onset had occurred before the age of 50 years and a de novo *ANKRD11* mutation had led to a KBG diagnosis. These two patients presented similar PD symptoms, neurocognitive deficits, and dental and craniofacial abnormalities (including hypertelorism, prominent/high nasal bridge, long philtrum, thin upper lip, and brachy-clinodactylous fifth finger); however, the cryptorchidism reported for the previous case was absent from our patient.

The neurobiological role of the transcriptional regulator *ANKRD11* has been receiving increasing attention, with animal studies highlighting its central role in neuronal development, particularly in dendritic growth and arborization.⁸ *ANKRD11* additionally regulates the BDNF/TrkB signaling pathways and the acetylation of the epigenetic molecules p53 and histone H3, all of which have been implicated in the pathogenesis of PD.⁸ There is research evidence that *ANKRD11* also regulates murine embryonic cortical neurogenesis, while conditional *ANKRD11* knockout in murine embryonic neu-

ral stem cells results in volume reductions of deep GM structures.⁹ To the best of our knowledge, this is the first report of decreased cortical and subcortical GM volumes detected using volumetric MRI, which has potential implications for a causal association of *ANKRD11* mutations with the pathogenesis of neurodevelopmental delay and PD in KBG. Consistent with our findings, previous studies have also identified cerebral abnormalities using structural MRI in approximately two-thirds of KBG patients.²

A recent comprehensive analysis of physician-reported data obtained from 36 adults with molecularly confirmed KBG syndrome combined with evidence from 154 adults with KBG syndrome in the literature disclosed gross and/or fine motor difficulties in approximately 40% of KBG patients, encompassing gait disturbances, dystonia, and hand tremor.¹⁰ To the best of our knowledge, our patient is among the oldest KBG patients reported in the literature. Although no patient included in the previous cohort was formally diagnosed with a movement disorder, the authors astutely commented that “movement disorders were rarely elaborated on in the literature.”¹⁰ Thus, it cannot be ascertained whether PD was absent from the previous cohort or was simply undiagnosed. Also, despite the intriguing putative associations with *ANKRD11*, the possibility of the incidental co-occurrence of KBG and early-onset PD cannot be excluded.⁷ Since previous cohort studies have

focused on pediatric KBG patients, our case highlights the need for longitudinal follow-up to determine whether PD represents an underrecognized facet of this rare genetic disorder in adulthood.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2024.0454>.

Ethics Statement

No ethics approval was required due to the study design. Written informed consent was obtained from the patient for the publication of this report and the accompanying images. We confirm that we have read the journal's guidelines for issues involved in ethical publication and affirm that this study was consistent with those guidelines.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

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