

A 3.9-Mb Deletion on 2p11.2 Comprising the *REEP1* Gene Causes Early-Onset Atypical Parkinsonism

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Deletions of 2p11.2-p12 are exceedingly rare with few reported cases.^{1,2} Most patients display a mild-to-moderate developmental delay and intellectual disability. Additional manifestations are happy disposition, tendency to obesity, and minor dysmorphic features, such as short stature, prominent forehead, hypertelorism, broad nasal bridge, or large low-set ears. Occasionally congenital malformations are present, such as chest and spine abnormalities, urogenital malformations, or atrial septal defect.¹ In this study, we report a patient presenting with early-onset atypical parkinsonism carrying a heterozygous 3.9-Mb deletion on 2p11.2.

The proband, a 35-year-old White woman, was referred to our clinic for further study of parkinsonism. She reported a 2-year history of tremor, generalized stiffness, and progressive gait difficulty. She is the second child of nonconsanguineous parents. She was born preterm by cesarean section because of transverse presentation. Psychomotor development was slightly delayed, but she achieved all milestones without assistance. Medical history was significant for strabismus, amblyopia, and ear surgery for prominent ears. Scoliosis was diagnosed at age 12 years and treated with a brace.

At age 35 years (Video 1), she displayed mild dysmorphic features, such as short stature, high forehead, and mandibular prognathism. Facial expression was markedly reduced with lower face dystonic gesture. Smooth pursuit was impaired, and saccades were slow and inaccurate. Speech was hypophonic and dysarthric. She exhibited high-frequency, low-amplitude tremor, probably with a superimposed distal jerky compound, and severe bradykinesia and rigidity. Dystonic postures emerged with arms outstretched. Inferior limb spasticity, brisk reflexes, and bilateral ankle clonus were observed. Plantar reflexes were equivocal. Gait was unsteady with bilateral flexed-elbow deformity and absent arm swing. When walking, truncal hyperextension and a tendency to invert the left foot appeared. Neuropsychological evaluation was normal. She did not report REM sleep behavior disorder, anosmia, or autonomic symptoms. Dopamine agonists and trihexyphenidyl were not beneficial, but she achieved partial improvement with carbidopa/levodopa 250 mg qid. This dose was stable for the past 5 years without the development of motor fluctuations or dyskinesias. As the disease progressed, foot dystonia worsened, and she received botulinum toxin injections.

A thorough laboratory investigation was conducted, including thyroid stimulating hormone, B₁₂ and E vitamins, anti-nuclear antibodies, serum copper, ceruloplasmine, 24-hour urine copper, acanthocytes, plasma amino acids, alpha-fetoprotein, homocysteine, cholestanol, and glucocerebrosidase and sphingomyelinase enzymatic activities, without findings. A nerve conduction study was unremarkable. Brain and spine MRI findings were normal (Figure, A). Presynaptic

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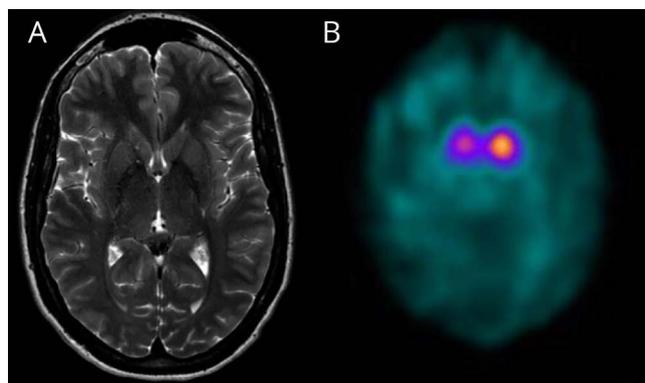
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Figure Neuroimaging Findings



(A) Normal cranial MRI T2 axial image. (B) 123-ioflupane (DatScan) reveals bilateral asymmetrical denervation with right striate showing markedly reduced uptake, contralateral to the most affected side.

nigrostriatal imaging with 123-ioflupane confirmed presynaptic denervation (Figure, B). Genes associated with parkinsonism were first screened (*PANK2*, *ATP13A2*, *PLA2G6*, *FBXO7*, *SPG11*, *PRKRA*, *ATP1A3*, and *SLC6A3*) using the Ion AmpliSeq Neurological Research Panel (Thermo Fisher Scientific, Waltham, MA) and *MAPT* by Sanger sequencing. Copy number variations (CNVs) were then investigated by multiplex ligation-dependent probe amplification analysis (MLPA) (SALSA P051/P052 Parkinson, MRC Holland, Amsterdam, the Netherlands), which included *PARK2*, *PINK1*, *DJ1/PARK7*, *LRRK2*, *UCHL1*, *ATP13A2*, *LPA*, *TNFRSF9*, *CAV2*, *CAV1*, and *GCHI*. Subsequently, the patient was studied using the panel MovDisord-498,³ which detected the whole *REEP1* deletion, later confirmed by MLPA (SALSA P213). The deletion was delineated by SNP-based array analysis (CytoScan HD, Affymetrix Inc., Santa Clara, CA), and a heterozygous 3.9-Mb microdeletion was identified: arr [hg19]2p11.2 (chr2: 83,335,425-87,271,924)x1. Parents were studied, and the deletion was confirmed to be de novo.

Patients carrying 2p11.2-p12 deletions exhibit neurodevelopmental delay, minor dysmorphic features, and congenital malformations.^{1,2} Our patient showed early-onset atypical parkinsonism with dystonia and lower limb spasticity. She displayed subtle facial dysmorphism, short stature, and scoliosis, but no congenital malformations nor cognitive impairment.

The size of the 2p11.2-2p12 deletion was smaller than that previously reported, ranging from 7.5 to 11.4 Mb.¹ Among the 47 genes included in the deleted region, the most remarkable were *POLRIA*, involved in the Cincinnati type of acrofacial dysostosis (AFDCIN; MIM 616462) and *REEP1* in spastic paraplegia type 31 (SPG31; MIM 610250), both autosomal dominant conditions (eTable, [links.lww.com/NXG/A496](https://www.lww.com/NXG/A496)). Our proband's phenotype seemed to be closer to SPG31-associated phenotypes. Most patients manifest a pure SPG, although SPG31 complex clinical pictures can include

peripheral neuropathy, cerebellar ataxia, tremor, and cognitive impairment.^{4,5} Moreover, *REEP1* variations may be responsible for distal hereditary motor neuropathy and congenital spinal muscular atrophy with respiratory distress type 1.⁶ No cases with movement disorders are known, likely because of delayed expression of additional clinical features.⁴ Nevertheless, recent evidence suggests that *REEP1* variations may impair the function of DRP1, a mitochondrial protein involved in Parkinson disease pathogenesis.⁷ Identification of 2p11.2-p12 cases and complex SPG31 is needed to unravel genotype-phenotype correlations and further delineate the *REEP1* biological role.

In conclusion, this case expands the 2p11.2-p12 deletion-associated phenotypes, including parkinsonism, and underscores that CNVs must be considered when analyzing next-generation sequencing data.

Ethical Compliance Statement

Written informed consent was obtained from the proband, and this study was approved by the ethic committee of the Hospital U. i P. La Fe (2019/0052).

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Disclosure

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Appendix (continued)

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