Paroxysmal kinesigenic dyskinesia (PKD) (MIM# 128200) is a movement disorder characterized by brief episodes of involuntary movements consisting of dystonia, chorea, or myoclonus, usually triggered by sudden voluntary movements. Pathogenic variants in \textit{PRRT2} (MIM# 614386), located on chromosome 16p11.2, have been identified as the most common cause of PKD. Most of the reported patients (approximately 80%) had the frameshift pathogenic variant c.649dupC (p. Arg217Profs*8), which causes a premature stop codon. Other reported variants are nonsense, frameshift, or rarely missense that are predicted to cause a truncated protein, absence of protein product through nonsense-mediated mRNA decay, or nonfunctional protein. Isolated PKD is typically associated with heterozygous intragenic variants in \textit{PRRT2}. Symptomatic PKD has been reported in 6 patients with 16p11.2 microdeletion syndrome (MIM# 611913). PKD is thus postulated to result from \textit{PRRT2} haploinsufficiency. The reciprocal chromosome 16p11.2 duplication syndrome (MIM# 614671) is associated with autism, ADHD, developmental delay, intellectual disability, epilepsy, hypotonia, congenital anomalies, and microcephaly but has not until now been associated with PKD.

Case

Identical twin brothers presented to our clinic at age 5 years for the evaluation of episodic involuntary movements. They were born at 33 weeks' gestation by Cesarean section because of premature labor and breech presentation. Family history was significant for learning disability in both parents and mental health problems in the father. The pregnancy was complicated by prenatal diagnosis of talipes equinovarus deformity, which prompted amniocentesis and prenatal chromosomal microarray (CMA) that revealed a 674 kilobase interstitial microduplication at 16p11.2 (29,517,699–30,191,895) x3 (hg19).

Developmental delay became apparent at age 18 months, when they were unable to sit independently or speak single words. Both twins had impaired social interaction and impulsive behavior and were diagnosed with autistic spectrum disorder and started applied behavior analysis. Their foot anomaly was complicated by tendo-Achilles contractures and treated with serial casting and bilateral heel cord tenotomies. They subsequently walked independently at age 26 months.

Shortly after age 2 years, 1 twin developed 30- to 40-second episodes of dystonic posturing and athetosis of the upper and lower limbs (Video 1, links.lww.com/NXG/A358), triggered by sudden voluntary movements. At age 4 years, he developed generalized tonic-clonic seizures (GTCS), for which he started oxcarbazepine (OXC). At age 5 years, the episodes of involuntary movements occurred multiple times per day. Trihexyphenidyl partially controlled the symptoms.
Investigations including brain and whole-spine MRI, urine organic acids, serum amino acids, and copper and ceruloplasmin levels were unremarkable. On our initial examination, he had mild generalized hypotonia without hyperreflexia or dysmorphic features. He was diagnosed with PKD. OXC was increased and trihexyphenidyl was discontinued. Ultimately, both the seizures and PKD episodes were controlled with OXC 32 mg/kg/d. Of note, a higher dose was needed to control the episodes of PKD than to control his seizures.

The other twin brother experienced GTCS at age 3 years, which subsided without any treatment, and experienced milder episodes of PKD that were controlled completely with OXC 13 mg/kg/d.

At age 8 years, both developed persistent urinary retention, and lumbar spine MRI revealed a tethered cord, which was surgically released with subsequent improvement in bladder and bowel function. Postnatal CMA revealed a 660 kilobase microduplication at 16p11.2 (29,517,698–30,177,240) x3 (hg19) (figure), which was almost identical to the result of the prenatal CMA. Targeted sequencing of PRRT2 did not identify pathogenic variants.

Discussion

We report monozygotic twins with chromosome 16p11.2 microduplication manifesting symptomatic PKD. Although 16p11.2 microduplication and deletion have many common clinical features, cases of 16p11.2 microduplication have not been reported in association with PKD. Some of the twins’ symptoms such as developmental delay, autistic spectrum disorder, hypotonia, and epilepsy commonly occur in 16p11.2 duplication carriers, but other clinical features of the syndrome such as skin lesions (e.g., café-au-lait spots and sacral dimples), cranial nerve abnormalities, hyper or hyporeflexia, tremor, tics, abnormal agility, abnormal brain MRI findings, or microcephaly were not observed in our patients.

The PRRT2-related phenotypes such as PKD are caused by loss of function in 16p11.2 deletion and PRRT2 sequence variants. A mouse model of PRRT2 deficiency demonstrated that loss of function in PRRT2 deletion can be associated with abnormal synaptic transmission by altering soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein function and behavioral episodes resembling PKD.

The occurrence of PKD in our patients with 16p11.2 microduplication syndrome suggests that PRRT2 haploinsufficiency is not the only possible mechanism underlying PKD, as has been previously hypothesized. Although we cannot exclude the possibility that a hypomorphic allele in the regulatory region of PRRT2 exists as a second hit, our case suggests that dosage of PRRT2 is important and that 16p11.2 microduplication, presumably associated with PRRT2 gain of function may also cause PKD. The remarkably reduced penetrance for PKD in 16p11.2 rearrangements may relate to common polymorphisms on the remaining hemizygous allele, different genotypes elsewhere in the genome, or sex-dependent penetrance because all patients reported so far with PKD and these 16p11.2 alterations were men. Although PRRT2 haploinsufficiency can be the mechanism for dosage sensitivity in 16p11.2 deletion, the pathogenicity in the reciprocal microduplication is not clear, but the surplus of PRRT2 may interfere with the dosage balance required for the SNARE protein.

Study Funding

No targeted funding reported.

Disclosure

The authors report no financial conflicts of interest. Go to Neurology.org/NG for full disclosures.

Publication History

Received by Neurology: Genetics August 17, 2020. Accepted in final form October 29, 2020.
References


Appendix

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<tr>
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<th>Location</th>
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Neurol Genet 2021;7;
DOI 10.1212/NXG.0000000000000549

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