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ANKRD11 gene deletion in a 17-year-old male

Erin L. Youngs, Jessica A. Hellings, and Merlin G. Butler

Departments of Psychiatry and Behavioral Sciences and Pediatrics, Kansas University Medical Center, Kansas City, Kansas, USA

List of key features

Autism; Mental retardation; Prominent forehead; Pointed chin; Abnormal philtrum

Introduction

The 16q24.3 microdeletion syndrome has been recognized only recently with one previous report of four patients with autism and variable cognitive impairment (Willemsen *et al.*, 2009). Herein we report an additional patient with autism and intellectual disability with a small 180-kb deletion of chromosome 16q24.3 band (located at 87.92–88.10 Mb from pterminus) containing the ankyrin repeat domain-containing protein 11 (*ANKRD11*) gene identified by the chromosomal microarray analysis.

Clinical report

Our patient was the second child of a 26-year-old mother and the product of a full-term gestation after a difficult prolonged vaginal delivery. There were several episodes of decreased fetal heart rate and a calcified placenta was noted. His birth weight was 2.61 kg (5th centile) and birth length was 47 cm (5th centile). He went home on the second day of life. Recurrent ear and sinus infections were observed during infancy and early childhood, but were resolved without pressure equalization ear tube placement. He had delayed development with walking at 3 years of age. He was nonverbal, but used several basic signs for communication. He had no history of seizures. On account of his developmental delays and behavioral problems, brain MRIs on two separate occasions were performed and were interpreted as normal.

A psychiatric evaluation showed autism, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety, self-injury, and mild-to-moderate mental retardation. The Global Assessment of Functioning Scale was used to determine his overall level of functioning and the ability to carry out activities for daily living (American Psychiatric Association, 2000). A score of 60 was found, which is consistent with moderate difficulty in social, occupational, or school functioning. The family history was unremarkable with no other family members affected with autism, mental retardation, birth defects, consanguinity,

or miscarriages over three generations. The mother reported a Raynaud's phenomenon of her extremities during childhood that improved with age.

Our patient presented at 17 years of age for genetic evaluation of his behavioral and learning problems. He was cooperative at the time of evaluation but did avoid eye contact. On physical examination, his height was 151.2 cm (< 3rd centile), weight was 37 kg (< 3rd centile), and head circumference was 51.8 cm (< 3rd centile). Inner canthal distance was 2.7 cm (20th centile) and outer canthal distance was 8.0 cm (10th centile). He had two disorganized posterior hair whorls, bilaterally attached ear lobes with an ear length of 6.5 cm (75th centile), a prominent forehead, downslanting palpebral fissures, long eye lashes, anteverted nares, a wide appearing philtrum with increased distance between the pillars of the columella, a tented upper lip, a pointed chin (Fig. 1), and a high-arched palate with anterior dental crowding. Plantar creases were noted bilaterally. Cutis marmorata was noted particularly of his feet. His hands were erythematous with decreased temperature (right greater than left) consistent with Raynaud's phenomenon. The rest of the examination was unremarkable.

Our proband had a cytogenetic study performed previously that showed a 46,XY karyotype. We performed a high-resolution chromosomal microarray study using a 105-K Oligo HD Scan (CMDX Laboratory, Irvine, California, USA) to rule out DNA deletions or duplications. The microarray study identified a small 180-kb deletion of chromosome 16q24.3 band (located at 87.92–88.10 Mb from pterminus) containing the *ANKRD11* gene (Fig. 2). The microarray study did not identify other copy number variation accounting for his condition. Microarray study on the mother was normal. The father was not available for analysis.

Discussion

The *ANKRD11* gene encodes a member of the ankyrin repeat-containing cofactors that interacts with p160 nuclear receptor coactivators that inhibits ligand-dependent transcriptional activation (Zhang *et al.*, 2004). Marshall *et al.* (2008) later proposed that *ANKRD11* is a candidate gene for autism. Willemsen *et al.* (2009) further reported four unrelated individuals with 16q24.3 deletions of varying size, but with an approximate 90-kb region of overlap (located at about 87.80–87.90 Mb from pterminus) including the *ANKRD11* and zinc finger 778 (*ZNF778*) genes. Clinical characteristics of their patients included an autism spectrum disorder, variable cognitive impairment, facial dysmorphisms (prominent forehead, large ears, smooth philtrum, pointed chin, and wide mouth), seizures, and brain anomalies. The *ANKRD11* and *ZNF778* genes were reported as candidates for the autism phenotype in their patients. The 16q24.3 microdeletion in our patient was more distally positioned compared with the smallest region of overlap in the four previously reported patients with a deletion by Willemsen *et al.* (2009), but involved only a portion of the 3' end of the *ANKRD11* gene. The chromosomal microarray finding in our patient further supports a role of the *ANKRD11* gene in the clinical findings of a prominent forehead, an abnormal philtrum, a pointed chin, autism, and cognitive impairment with involvement. No other gene was found to be deleted in the 16q24.3 region in our patient or in any other chromosome region analyzed using microarray technology; however, the

deletion could alter the *cis* regulation of neighboring genes, which may also contribute to the phenotype seen in the proband.

Chromosome microarray hybridization is useful in identifying microdeletions or microduplications, and provides a precise description of size, location, and genes involved in a genetic lesion allowing for genotype–phenotype correlations, genetic counseling, and medical care management. The investigators encourage the reporting of additional patients with this cytogenetic deletion using new tools for genetic testing to precisely identify the chromosomal abnormality.

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Fig. 1. Frontal views of the patient at ages 3, 8, and 15 years showing a prominent forehead, downslanting palpebral fissures, wide philtrum, long eye lashes, tented upper lip, pointed chin, and lack of eye contact.

Fig. 2. Chromosome microarray hybridization showing the location of the 180-kb deletion of the 16q24.3 region occurring at 87.92–88.10 Mb from the pterminus, which includes a partial deletion of the *ANKRD11* gene. The arrow shows the deleted segment.