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LETTER

Haploinsufficiency of *ANKRD11* causes mild cognitive impairment, short stature and minor dysmorphisms

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Last year, in this journal, Willemsen *et al*[1,2] presented four patients with an interstitial deletion of chromosome band 16q24.3. The overlapping phenotypical features provided evidence for a novel microdeletion syndrome characterized by variable levels of intellectual disability, autistic features (ASD) and facial dysmorphisms. The shortest region of deletion overlap shared by these patients contained two potential candidate genes, *ANKRD11* and *ZNF778*. Here, we present two patients with cognitive impairment, short stature and dysmorphic features carrying a small deletion in the 16q24.3 region containing the *ANKRD11* gene. These observations confirm the findings of Willemsen *et al* and further strengthen the hypothesis that *ANKRD11* is a candidate gene for autosomal dominant (syndromic) intellectual disability.

The first patient, a female, was referred to the genetics department at the age of 6 years because of short stature, developmental delay and mild dysmorphic features. She was born after an *in vitro* fertilization triplet pregnancy of one girl and two boys at 37 weeks of gestation. Parents were non-consanguineous, and delivery was performed by caesarian section. She was born as the third child with a birth weight of 1880 g (−2.7 SDS), and the neonatal period was uneventful. One of her twin brothers was born with a unilateral cleft lip, hemivertebrae of L3, thirteenth rib and spina bifida occulta. The girl had none of those features but showed marked developmental delay, whereas her siblings had a normal psychomotor development. She started walking at 24 months of age and spoke her first words at 30 months. From the age of 4 years on, she received supportive therapy because of poor speech and motor development. She had a borderline intellectual disability (total IQ of 75 (WISC-R)), for which she attended special education.

Re-evaluation at the age of 15 years showed an adolescent with a weight of 50 kg (0 SDS), height of 152 cm (−2 SDS) and head circumference (OFC) of 54.5 cm (0 SDS). In addition to her short stature, dysmorphic features included mild synophrys, small nasal bridge, full nose with bulbous tip, broad mouth, pointed chin, bilateral clinodactyly of the fifth fingers, broad, flattened thorax, wide-spaced nipples and short neck (Figure 1). None of these features were present in other family members. Other characteristic features were her hoarse voice and a bilateral conductive hearing loss (moderate hearing loss of −35 dB). EEG and brain imaging were normal. There was no formal diagnosis of an autistic spectrum disorder, although mother mentioned her introvert personality and concentration problems. Initial genetic evaluation showed a normal female karyotype and *FMR1* analysis. Turner mosaïcism was ruled out by analyzing mucous tissue. High-resolution array analysis (180k Cytosure ISCA v2, Oxford Gene Technology, Oxford, UK) revealed a *de novo* 220-kb deletion at chromosome 16q24.3 harboring the complete *ANKRD11* gene and probably the 5′ end of the recessive *SPG7* gene (46, XX.arr 16q24.3 (87 871 394−88 093 157)×1, UCSC Human genome build 36; Figure 1).

The second patient, a male, was referred to the department of clinical genetics at the age of 19 years because of short stature. He was born to non-consanguineous parents at 37 weeks of gestation after an uneventful pregnancy. His birth weight was 2960 g (0 SDS) and length 45 cm (−1.7 SDS). He had a large fontanel with delayed closure. He had grand mal seizures for which he used medication until the age of 5 years. After this age, he was seizure free. His motor development was delayed, he walked at the age of 2 years. He had a normal speech development but was diagnosed with a borderline intellectual disability (total IQ of 77 (WISC-R) evaluated at the age of 9 years), whereas his younger brother had an IQ of above average. Furthermore, an attention deficit hyperactivity disorder was diagnosed, and he attended special education. He had normal vision, and his hearing was slightly impaired at one side. At physical examination at the age of 19 years, he had a height of 165 cm (−2.5 SDS), with a target height of 187.7 cm (+0.5 SDS), a sitting height/height ratio of +1.6 SDS and a head circumference of 57.9 cm (+0.3 SDS). His face showed a high and broad forehead, cowlicks, slightly deep-set eyes, mild synophrys, a broad nose with a short columella, protruding ears, a broad mouth and a prominent chin (Figure 1). He had short metacarpals of the fourth and fifth fingers of his left hand. Endocrinological analysis of the growth axis did not show abnormalities. A skeletal survey showed short metacarpals and short fifth middle phalanges. Analysis of the *FMR1* gene was normal. An Agilent 180k oligo-array (Agilent Technologies, Santa Clara, CA, USA) showed a *de novo* 138-kb intragenic deletion of the *ANKRD11* gene on chromosome 16q24.3 (46, XY.arr 16q24.3 (87 862 729−88 000 269)×1 UCSC Human genome build 36). This minimal deletion included exons 3–12, whereas exons 2 and 13 were located between the last non-deleted and the first deleted probes so they can be either deleted or not; exon 1 was not in the deletion (Figure 1). Two other variants were identified in the patient and his healthy father, a 500-kb duplication at 2q37.3 and a 223-kb duplication in the PAR2 region of the Y chromosome and were considered to be non-pathogenic.

Taking into account the *de novo* status in both patients and the previous report on the 16q24.3 microdeletion syndrome, we considered these deletions causal for the observed phenotype.[1,2]

When comparing the facial features of our patients with the previously described patients, some resemblance is noted: high forehead, a broad mouth and prominent chin.[1] Both patients also had a relatively small nasal bridge with mild synophrys and a bulbous nose tip, resembling patient 1 of the study of Willemsen *et al* at adult age. As in our patients, the stature of the reported patients is also relatively short compared with the other growth parameters. Interestingly, patient 3 described by Willemsen *et al*, who carried the largest deletion, had a hearing impairment. This is also identified in our first patient, and a slight unilateral impairment was mentioned in our second patient. We did not observe structural brain malformations or heterotopias in our first patient. Although epilepsy at childhood age was present in the second patient, a brain MRI has not been performed so far to rule out brain abnormalities.

Including our patients, a total of six patients have now been described with a (partial) *ANKRD11* deletion and variable levels

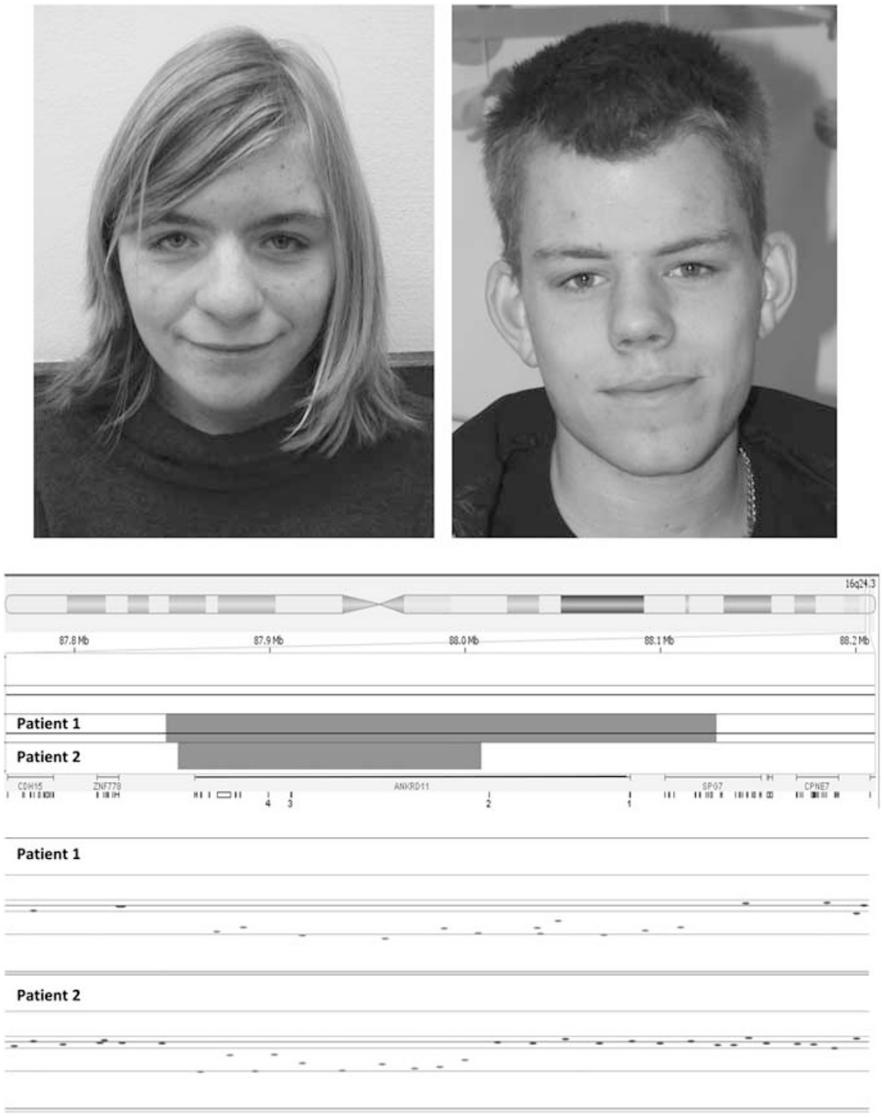

Figure 1 Upper panel: frontal view of the female patient at the age of 15 years and the male patient at the age of 19 years: features include mild synophrys, small nasal bridge, full nose with bulbous tip, broad mouth and pointed chin in the first patient, and a high and broad forehead, a mild synophrys, a broad nose with a short columella, a broad mouth and a prominent chin in the second patient. Lower panel: array results of the two patients. The top part shows an overview of the deletions, the boundaries are set halfway between the minimal and maximal deletion. The lower part shows the probe coverage on both arrays, clearly indicating that *ANKRD11* is deleted, whereas *ZNF778* is not.

of cognitive impairment, epilepsy, behavioral problems (autism spectrum and ADHD) and non-specific facial features. Although we cannot exclude a possible position effect of the respective deletions on nearby genes, the current data support the role of the *ANKRD11* gene in neurodevelopment (Figure 1). The ankyrin repeat domain-containing protein 11 is a member of a family of ankyrin repeat-containing cofactors, which has a role in transcriptional regulation through suppression of p160 receptor coactivators via recruitment of histone deacetylases.[3] Moreover, ANKDR11 was shown to be a potent p53 coactivator and was initially selected as a candidate breast cancer tumor suppressor gene because of its location within the 16q24.3 breast cancer loss of heterozygosity region.[4] This is not the first candidate tumor suppressor gene that might be involved in a constitutional disorder. Constitutional microdeletions on chromosome 17p13.1 containing other tumor suppressor genes have also been associated with intellectual impairment,[5] reinforcing the observation that tumor suppressor genes are involved in specific developmental transcriptional programs. At present, we do not know whether haploinsufficiency of *ANKRD11* confers an increased lifetime risk for (breast) cancer, but good clinical follow-up and surveillance of these patients seems warranted.

In summary, our data confirm the observation reported by Willemsen *et al* that *ANKRD11* constitutes a very valuable candidate to explain the neurocognitive phenotype present in these patients. Further functional studies are required to elucidate the exact role of *ANKRD11* in cognition, and additional patient reports will certainly advance the delineation of a specific phenotype caused by haploinsufficiency of *ANKRD11*.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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