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Short clinical report

A small *de novo* 16q24.1 duplication in a woman with severe clinical features

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ABSTRACT

We report here a *de novo* 16q24.1 interstitial duplication in a woman with a severe phenotype consistent with mental retardation, spastic paraplegia, severe epilepsy, a narrow and arched palate, malar hypoplasia, little subcutaneous fat and arachnodactyly. Although conventional karyotyping was found to be normal, array-CGH detected a small duplication on chromosome 16. Using QFM-PCR, we characterised its proximal and distal breakpoints. The duplication, which is approximately 250 kb, encompasses seven genes (*KIAA0182*, *GINS2*, *c16orf74*, *COX4NB*, *COX4I1*, *MIR1910* and *IRF8*). Several reports have previously described large 16q duplications, and some of these overlap with our region in 16q24.1.

Due to the variability of the described phenotypes, the characterisation of small 16q duplications may help to determine critical regions and the genes they contain that are associated with the components of complex phenotypes.

1. Introduction

Chromosomal abnormalities are a major cause of mental retardation. Unbalanced karyotypes are estimated to be present in 10–16% of children with intellectual disabilities with or without dysmorphic signs and malformations [1,2]. The recent application of molecular karyotyping in genomic medicine has strongly improved the detection of small chromosomal defects and has revealed new information about regions that are potentially involved in intellectual disabilities [3]. Although complete trisomies of chromosome 16 are associated with spontaneous abortions, partial duplications of 16q have been associated with different phenotypes such as mental retardation, dysmorphic features and limited post-natal survival [4].

Here, we report a woman with a small *de novo* duplication of 250 kb in the 16q24.1 region detected by chromosomal microarray and confirmed by quantitative fluorescence multiplex-PCR (QFM-PCR). Because our patient's clinical features are particularly severe considering the size of the duplication, we compared her phenotype with previously described cases of 16q trisomy [4–13]. Small chromosomal rearrangements such as the one found in this case may help to delineate the contribution of selected genes in larger 16q duplications.

2. Clinical report

2.1. Case report

The patient is a 26-year-old woman born to non-consanguineous and unaffected parents after an uncomplicated pregnancy. She is the second child, and her two brothers are healthy.

A marfanoid mental retardation syndrome (OMIM 248770) was suspected at 26 years old because of a 'typically' flat face and other marfanoid body habitus. Before the age of 2 years, she presented a developmental delay and dysmorphism that consisted of malar hypoplasia, a narrow and arched palate, micrognathia, long face, high forehead, anteverted nares, thick lip, large palpebral fissures, hollowed-out cheeks, arachnodactyly and little subcutaneous fat (Fig. 1). An optic atrophy was also observed but not confirmed afterwards. She was first treated by corticoids, but in the absence of improvement, she was treated by Rivotril. However, psychomotor difficulties were then amplified. In addition, she had an epicanthus and axial hypotonia, and her limbs were hypertonic. At 3 years old, her height was 105 cm (+2DS), weight was 15 kg (+1DS) and head circumference was 48 cm (−1DS). At 4 years, she was able to sit

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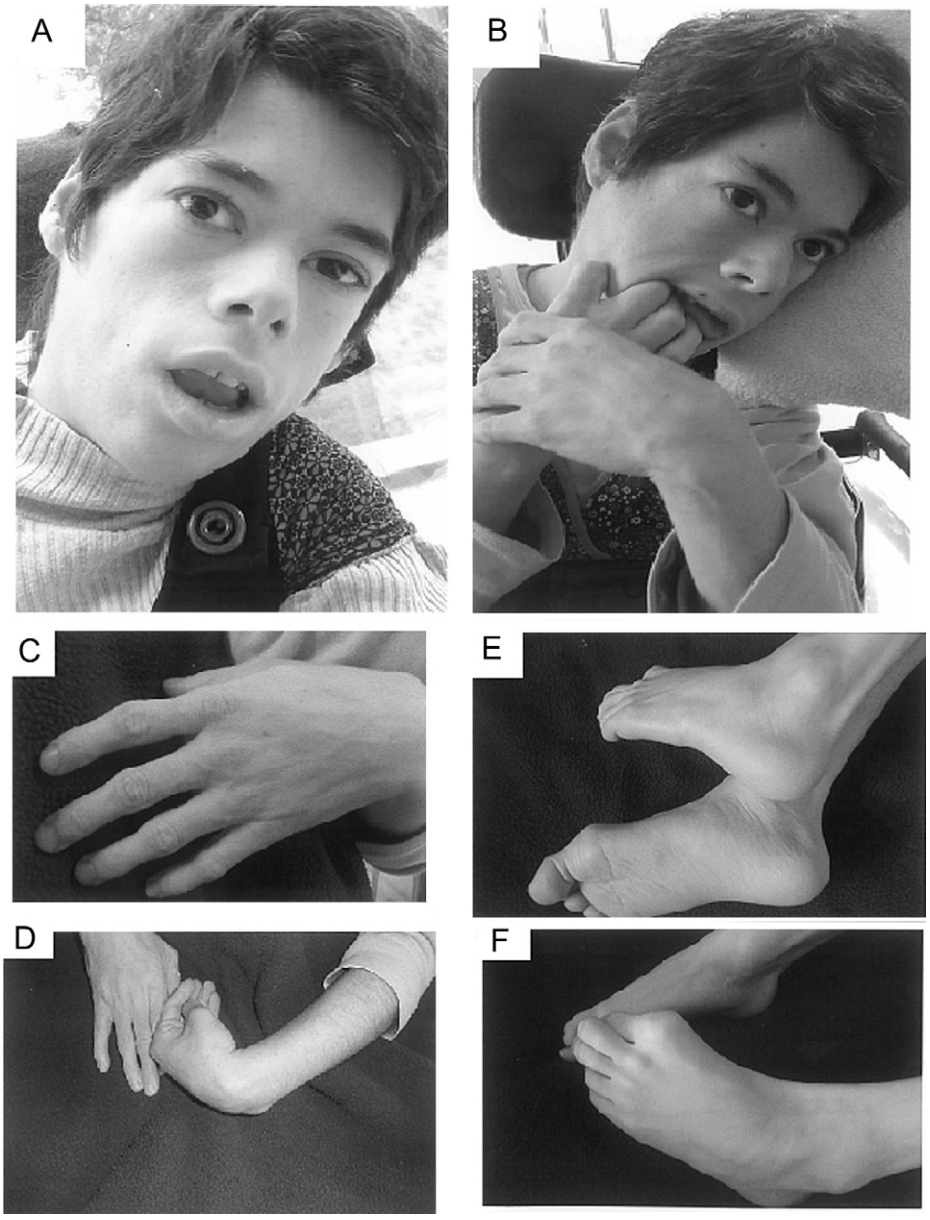

Fig. 1. Proband at 26 years old. [A, B] Note long face, large palpebral fissure, anteverted nares, small and attached lobe and thick lips. [C, D] Long and thin fingers and stiffness of the wrist/hand. [E, F] Talipes equinovarus deformity and stiffness of the feet.

alone, but she had severe communication difficulties (no language, shouting, laughing and crying without any reason). She was irritable and agitated. She still had a severe myopia without family history, a palpebral coloboma, and little subcutaneous fat associated with prominent muscles, in addition to joint hyperextensibility (hands, fingers and toes). At the age of 6 years, she was still unable to speak, walk, dress, eat or wash by herself. She had convulsive spasms every day. Between 7 and 12 years old, she could walk with assistance and grab objects. She had many infections and suffered from a scoliosis. At 20 years old, she was taking a combination of different sedatives. She suffered from spastic paraplegia and severe epilepsy.

A history of convulsive encephalopathy and spasms in flexion with hypsarrhythmia was shown with an electroencephalogram (EEG) analysis, and these required several hospitalisations. Other medical evaluations consisted of brain and spinal cord magnetic resonance imaging and blood amino acid and urine organic acid chromatographies, which were normal. CDG (congenital disorder of glycosylation) syndrome analysis was negative. Radiography revealed a hypertrophy at the tuft of the phalanx of the finger.

Seven years later, one of her brothers and his pregnant wife asked for genetic counselling. As no biological marker exists to confirm marfanoid mental retardation syndrome (OMIM 248770), an array-CGH was proposed to the propositi.

2.2. Oligonucleotide microarray

Chromosome analysis was performed on lymphocyte cultures using standard procedures with RHG banding.

Array-CGH analyses were performed using an Agilent Human Genome CGH microarray 105K consisting of 105,000 probes (Agilent Technologies, Santa Clara, CA). Experiments were performed with 1300 ng of DNA following the instructions provided by Agilent (Agilent Oligonucleotide Array-Based CGH for Genomic DNA Analysis, v.5.0, June 2007). Arrays were analysed using the