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Congenital diaphragmatic hernia is part of the new 15q24 microdeletion syndrome

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ABSTRACT

The recurrent microdeletion 15q24 syndrome is rare with only 5 cases reported thus far. Here we describe an additional patient with this deletion, presenting with many features common to this syndrome, including developmental delay, loose connective tissue, digital and genital anomalies and a distinct facial gestalt. Interestingly, in addition, this patient has a large congenital diaphragmatic hernia, as was described in one other patient with a 15q24 microdeletion, indicating that this feature might be part of the syndrome. Chromosome 15q24 has a highly polymorphic architecture that is prone to genomic rearrangements underlying this novel microdeletion syndrome.

1. Introduction

The implementation of array comparative genome hybridization (array CGH) in diagnostics has revolutionized clinical genetics, as the number of new recurrent microdeletion and microduplication syndromes is gradually increasing. The 15q24 microdeletion syndrome was first described in 2007, in four individuals, sharing several major anomalies and overlapping deletion intervals [8]. These anomalies include mental retardation, digital anomalies, genital anomalies and similar facial features (high forehead, broad medial eyebrows, hypertelorism, downslanting palpebral fissures, broad base of the nose and long philtrum). The microdeletions in these four cases are between 1.7 and 3.9 Mb in size, creating a common deletion interval of 1.7 Mb (72.15–73.85 Mb). Further high resolution mapping studies, using oligonucleotide-array, showed that the breakpoints of these deletions co-localize to highly identical segmental duplications, suggesting non-allelic homologous recombination (NAHR) as underlying mechanism. Recently, a fifth patient with the 15q24 microdeletion was published that overlaps with the previously reported cases clinically and molecularly [5].

We report on a 33 year old male patient carrying a 15q24 microdeletion and presenting with severe mental retardation, significant behavioral problems and digital and facial dysmorphisms, highly resembling the other cases. Moreover, this man was recently hospitalized for dyspnea and severely reduced physical tolerance, leading to the diagnosis of congenital diaphragmatic hernia with massive herniation of abdominal organs. We compare this case with the other reported cases and try to establish a genotype–phenotype correlation.

2. Material and methods

2.1. Clinical report

The patient is the first child of healthy non-related parents, born at term with normal birth parameters (birth weight 3.300 g) after an uneventful pregnancy. Family history revealed a maternally related cousin with Angelman syndrome. The younger brother of the patient is healthy but followed primary school with special educational help because of learning problems. Both parents followed normal high school and are employed. At birth, bilateral inguinal hernias were present that were surgically corrected. Also facial dysmorphisms were noted with broad nasal bridge, hypertelorism and large ears. At that time a standard karyotype was performed and reported to be normal. His psychomotor development was severely delayed with severe hypotonia. He started to walk independently at 3½ years and his speech was very limited with echolalia and unclear articulation. He was seen several times at our center during follow-up visits. He followed school with special educational needs and always showed a hyperactive and chaotic behavior with aggressive outbursts. Because of this difficult

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behavior he was institutionalized from the age of 16 onwards. He progressively developed a scoliosis and talipes equinovarus. Over the last year he became dyspnoeic and had a severely reduced physical tolerance necessitating the use of a wheel-chair. Because of retrosternal chest pain he was further investigated at the age of 33 and a diaphragmatic hernia was seen on X-ray, with herniation of the small intestines and part of the colon compressing the heart and right lung. Upon surgical correction a congenital anterior retrosternal diaphragmatic hernia type Morgagni was diagnosed. A recent re-examination at the age of 33 years showed an obese and tall man (weight 94 kg for height 185 cm) with head circumference of 60.5 cm (>97th centile). He has convergent strabismus, downslanting, small palpebral fissures and hypertelorism (Fig. 1). He has a long face with high forehead, broad medial eyebrows, long philtrum, a small maxilla with high palate and bifid uvula, and a large mandible. His voice is high pitched. He has long slender fingers with distal tapering. His genitals are small with cryptorchidism at the right side. His behavior remained unchanged and is still very difficult to handle, even under psychopharmacological therapy.

2.2. Methods

The protocol was approved by the appropriate Institutional Review Board of the University Hospital of Leuven, Belgium, and informed consent was obtained from the parents of the affected patient.

Routine G-band karyotyping was performed according to routine protocol.

Initially, we used the arrays constructed for total genome coverage using a 1 Mb clone set. Clone preparation, hybridization and data analysis were performed as previously described [9]. To validate the result and to determine the exact size of the deletion, we subsequently used a chromosome 15 tiling BAC array containing 866 BAC and PAC targets obtained from BACPAC Resources Children's Hospital, Oakland, USA. Hybridization and data analysis were performed as described [7].

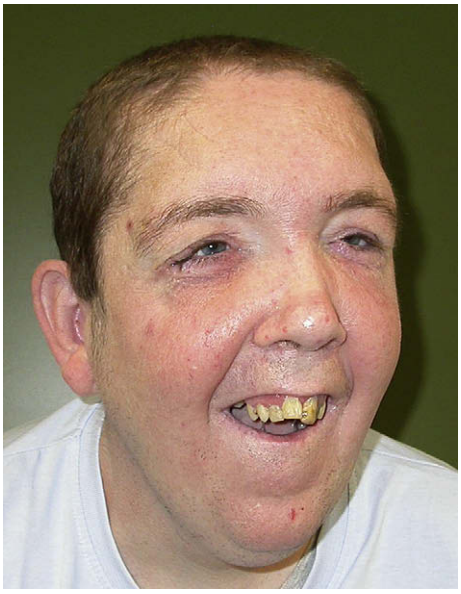

Fig. 1. Clinical picture of the patient at the age of 33 years. Note the typical facial features: high forehead, long face, broad medial eyebrows, hypertelorism, downslanting small palpebral fissures, low set ears, long smooth philtrum, large mandible and full cheeks.

3. Results

Repeated standard karyotyping revealed no abnormalities. In the absence of an etiological diagnosis, array CGH analysis using the 1 Mb clone set was performed, showing a microdeletion of approximately 4.3 Mb flanked by clones RP11-2I17 (70.3 Mb) and RP11-78M2 (74.6 Mb), giving normal ratio's, respectively (Ensembl release 52, December 2008). In order to define the breakpoints more precisely and to confirm the deletion, we hybridized the patient's genomic DNA to a chromosome 15 full tiling array. The proximal breakpoint maps within clone RP11-422O2, that showed an intermediate $\log_2$ normalized ratio of −0.38, and maps between clones RP11-612A9 (present) and RP11-361M10 (deleted) (70.6 Mb). The distal breakpoint maps between clones RP11-586G22 (deleted) and RP-1249A09 (present) (73.7 Mb), reducing the size of the deletion to 3.1 Mb. In comparison with the 5 published cases, the proximal breakpoint maps very closely to the proximal breakpoint of patient IMR371 as reported by Sharp et al. [8] (Fig. 2). According to the UCSC Genome Browser (http://genome.ucsc.edu), the proximal breakpoint maps within a segmental duplication cluster. The distal breakpoint in our patient coincides with BP2, as defined by Sharp et al. also within a segmental duplication cluster (Fig. 2) [8]. The segmental duplication clusters that flank the deletion in our patient show about 93% sequence identity (http://genome.ucsc.edu; http://humanparalogy.gs.washington.edu/build36/chr.htm). Besides the deletion at 15q24, which is *de novo* in the patient, we also detected a maternally inherited microduplication on chromosome 3 with a maximum size of 1 Mb flanked by clones RP11-767N9 and RP11-611C4, giving normal ratios, respectively. This duplication is not registered as a known genomic variant and therefore we do not know the pathological relevance of this finding. Besides the patients' mother, also his younger brother carries this small duplication.

4. Discussion

The 15q24 microdeletion is very rare, with only 6 patients reported so far, including the presented patient. Three patients have apparent identical deletions, while the other three have overlapping deletions, leading to a common deleted region of 1.7 Mb [8]. As shown in Fig. 2, the distal breakpoint in our patient coincides with the recurrent breakpoint BP2 defined by Sharp et al., while the proximal breakpoint is different [8]. Both breakpoints map within segmental duplication clusters. Chromosome 15 is rich in inter- and intrachromosomal segmental duplications clusters (http://humanparalogy.gs.washington.edu/build36/chr.htm), mediating a number of different rearrangements. These duplicated sequences predispose to NAHR most likely underlying the 15q24 deletion, as well as the recently identified reciprocal 15q24 microduplication [3].

Our patient has a lot of phenotypical features in common with the reported cases, including mental retardation, digital and genital abnormalities, loose connective tissue and distinct facial features (Table 1). However, in our case, as well as in the case reported by Klopocki et al., there is no growth retardation, neither microcephaly which were present in three of the four cases described by Sharp et al. [8]. Also growth hormone deficiency, bowel anomalies, as well as hearing loss are absent in our patient. As more cases will be recognized and diagnosed, the cardinal features of this microdeletion syndrome will become more delineated. Nevertheless, the facial gestalt is very distinct in all cases and can be used as a diagnostic handle for the clinical geneticist: high forehead, long face, broad medial eyebrows, downslanting palpebral fissures, low set ears, long smooth philtrum and full cheeks (Table 1, Fig. 1).