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Developmental delay and connective tissue disorder in four patients sharing a common microdeletion at 6q13-14

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Abstract

Interstitial deletions of the long arm of chromosome 6 are rare, and most of the reported cases represent large, cytogenetically detectable deletions. The implementation of array comparative genome hybridisation in the diagnostic work-up of patients presenting with congenital disorders including developmental delay has enabled the identification of many patients with smaller chromosomal imbalances. Here we present 4 patients with a *de novo* interstitial deletion of chromosome 6q13-14, resulting in a common microdeletion of 3.7 Mb. All patients present with developmental delay, mild dysmorphism and signs of lax connective tissue. Interestingly, the common deleted region harbours 16 genes of which the *COL12A1* represents a good candidate for the connective tissue pathology.

Introduction

A detailed phenotypic description of small interstitial 6q deletions is hampered by the scarcity of such patients and most of the reported cases represent large, cytogenetically detectable deletions [1]. The widespread use of array comparative genome hybridisation (array-CGH) in the diagnostic work-up of patients presenting with congenital disorders including developmental delay has enabled the identification of many patients with smaller chromosomal imbalances [2]. It moreover permitted the identification and delineation of new microdeletion and microduplication syndromes, allowing a more detailed assessment of the phenotypic consequences associated with specific chromosomal imbalances. The present report describes the genotypic and phenotypic delineation of four patients with a *de novo* interstitial deletion of chromosome 6q13-14, resulting in a common microdeletion of 3.7 Mb. All patients present with developmental delay, mild dysmorphism and signs of lax connective tissue. Interestingly, the COL12A1 gene that maps within the common deleted region constitutes a good candidate for the connective tissue pathology.

Clinical description

Patient 1

The girl was born at 35 weeks gestation by spontaneous delivery after an uncomplicated pregnancy to healthy, unrelated parents. Family history is unremarkable. At birth, both feet were in an extreme dorsiflexion position and she had a fibromatosis colli, both necessitating physiotherapy. Initially, feeding was difficult because of general hypotonia with poor sucking. Motor development was delayed because of this hypotonia as well as the presence of hyperlaxity in hips and large joints. She sat with her thighs internally rotated and her knees flexed. She started to crawl at 21 months. In addition, her speech development was delayed with the use of only a few words at the age of two. At her last clinical examination, at the age of 2 years, the growth parameters were all within the normal range. She has mild motor delay and moderate language delay (level of 18 months at age 24 months). She has a high-pitched voice and shows good social contact. Hyperlaxity is still present and she has a pronounced lordosis and bilateral pes plani. She also has mild dysmorphic features including a high forehead, long philtrum with thin upper vermillion, broad neck and sacral dimples (Figure 1A). Brain imaging and EMG were normal, but on radiographs of the spine an anterolisthesis L2-L3 was seen. Because of the hyperlaxity and developmental delay, Larsen syndrome was initially suspected.

Patient 2

This boy was born at 37 weeks of pregnancy. He was hospitalized on the neonatal ward because of low birth weight (2300 g) and repetitive hypoglycemia. He was the first and only child of unrelated healthy parents. Family history revealed borderline mental impairment present in the brother of the father and in his maternal uncle. At the age of 3 years an inguinal unilateral hernia was surgically corrected. His psychomotor development was characterized by walking at 22 months and delayed speech development. He was referred at the age of 5 years because of his delay with an IQ of 50-55. Clinical examination at that age showed a boy with growth parameters in the high-normal range. Hyperlaxity was present in fingers, wrists and elbows together with bilateral pes plani with short toes and a mild pectus excavatum. He had mild dysmorphic features including long philtrum with thin upper vermillion, large earlobes, mild synophris and a metopic ridge (Figure 1B). Brain imaging, EEG, echocardiography, radiograph of the spine and metabolic work-up were all normal.

Patient 3

This girl was born at term after an uneventful pregnancy. The neonatal period was complicated by a necrotizing enterocolitis. Because of facial dysmorphism, she was seen by a clinical geneticist at the age of 2 months. Several dysmorphic signs were noted: low frontal hair line, high nasal bridge, long philtrum with thin upper lip, low-set posterior rotated ears, high palate and retrognathia. Her thorax was short and an umbilical hernia was present. She had bilateral tri-phalangeal thumbs and broad distal phalanges. She presented with a bilateral nystagmus, axial hypotonia and hands in a fist position. Re-examination at the age of 5 months showed axial hypotonia as well as hyperlaxity, and length and weight below the third centile. She suffered from recurrent respiratory infections. A bilateral sensorineural hearing loss of 55 dB was documented. Ultrasound of the brain showed a small periventricular hemorrhage. Ultrasound of the abdomen showed bilateral small kidneys. Radiograph of the skull and spine were normal. She died at the age of 8 months of unknown cause, post-mortem examination was refused by the parents.

Patient 4

This boy is the second child of healthy unrelated parents, with no family history of note. He was born after an unremarkable pregnancy at 38 weeks gestation by planned Caesarian, because of breech position. He was noted to have undescended testes and hypotonia. Chromosome analysis was performed at 20 months of age because of motor delay and dysmorphic features. This showed an apparently balanced translocation, 46,XY t(2:6)(q31;q15). When he was seen in clinic he was noted to have marked joint laxity, a smooth philtrum, thin upper vermillion, upturned nose with anteverted nostrils, large ears, pointed chin and 5th finger clinodactyly (Figure 1 C,D). At the age of 6 years he was found to have hypogonadotrophic hypogonadism (not Kallman's) and was referred back to the

genetics clinic. At that time his parents reported that he was making slow but steady progress. He attended a special school and had some difficulties with fine motor skills. His biggest problem was walking; he had begun to walk at 3 ½ years but still frequently fell due to eversion at the ankles. On examination, his facial features were as described before. He continued to have generalized joint laxity and had mild truncal obesity. His feet appeared small for his size with bilateral pes cavus. He held his feet in eversion with both halluces pointing upwards. A hard swelling was present on the lateral side of each foot which has been ascribed to the fact that his weight bears along the lateral side of the feet. Ophthalmological examination was normal.

Methods

The protocol was approved by the appropriate Institutional Review Board of the University Hospitals of Leuven and Ghent in Belgium, and the Institute of Child Health London, and informed consent was obtained from the parents of the affected patients. Written consent was given to the authors for publication of the patient's images in print and online. Genomic DNA of each patient and the parents was isolated according to standard procedures.

Standard cytogenetic analysis showed normal karyotypes for patients 1, 2 and 3. In patient 4 an apparently balanced *de novo* translocation, 46,XY,t(2:6)(q31;q15) was detected.

The genomic DNA of patients 1 and 4 was analyzed on the total genome 1Mb BAC array. Clone preparation, hybridization and data analysis were performed as previously described [3]. Both patients 2 and 3 were analyzed using the Agilent Human Genome CGH 44k array [2]. All genome coordinates mentioned in this study are according to human genome build 18 (NCBI 36.1). The inheritance of each of these deletions was investigated by analyzing parental samples using microarrays (patients 1 and 2) or karyotyping and FISH analysis (patients 3 and 4).

Results

In the absence of an etiological diagnosis in patients 1, 2 and 3, array-CGH analysis was performed. Regarding patient 4, array analysis was performed to query the balanced nature of the chromosomal rearrangement. Table 1 summarizes the clinical and molecular findings in the 4 patients. All patients carry overlapping deletions of variable size spanning the 6q13-14 region (Figure 1F). The shortest region of overlap (SRO) is defined by the proximal breakpoint at 72.65 Mb in patient 2 and the distal breakpoint at 76.31 Mb in patient 1. This critical region is 3.66 Mb in size and contains 16 annotated genes (Table 2, supplementary). All deletions have arisen *de novo*.

Discussion

Since the introduction of array-CGH technology, the rate of discovery of novel genomic imbalances has increased dramatically. New disorders are described by their genomic rearrangement and subsequently, clinical features are compared among patients when a common imbalance is identified. In this regard, the use of worldwide databases of chromosomal imbalances such as DECIPHER, has greatly facilitated the identification of additional patients, as in our cases [4].

Interstitial deletions involving chromosome 6q13-14 are rare with eight patients reported to date [5-12]. Here, we present four more patients that were analyzed by array-CGH because of developmental delay and facial dysmorphism. By comparing the facial features, we could distinguish some common features, namely long philtrum, thin upper vermillion, pointed chin and large ear lobes (Figure 1). All patients presented with developmental delay with hypotonia, the latter symptom especially in the first years of life. In the older reported patients language and motor delay were noted, with severity correlating with the deletion sizes.

Interestingly, in each patient marked joint laxity was noticed by the respective clinical geneticist, and in patient 1 even the diagnosis of Larsen syndrome was suggested. This hyperlaxity was also noted in some of the older reported patients, with dislocation of the hips in three patients, and flatfeet in two [5-7, 10-12]. In addition, in the majority of patients, other features of loose connective tissue were present, including umbilical and inguinal hernia and thorax and foot deformities. Within the SRO deletion, the *COL12A1* gene is present, which encodes the alpha chain of type XII collagen, a member of the FACIT (fibril-associated collagens with interrupted triple helices) collagen family. Type XII collagen is a homotrimer found in association with type I collagen, an association that is thought to modify the interactions between collagen I fibrils and the surrounding matrix. Expression analysis in zebrafish showed that collagen type XII is broadly expressed in many connective tissues including fascia and basement membranes [13]. Moreover, sequence variants within *COL12A1* have recently been associated with increased risk of ligament ruptures in a case-control genetic association study [14]. To date, *COL12A1* has not been implicated in human disease, to our knowledge, and no mouse model is available. Our finding might represent the first association between haploinsufficiency of the *COL12A1* gene and a possible human phenotype. Further sequencing analysis in a large group of patients with similar connective tissue pathology as well as the development of a mouse model will enable us to confirm these results and open the way to exactly define the phenotype associated with this collagen gene.

Other interesting genes within the common defined deletion are *KCNQ5*, a voltage dependent potassium channel and member of a very large family of potassium channels of which some have been linked to diseases including cardiac arrhythmias, deafness and epilepsy [15] and *SLC17A5* (Table

| Patient | 1 | 2 | 3 | 4 | Lespinasse et al.[12] | Older published cases [5-11] |
|----------------------------------|-------------------------------------|-----------------------|---|---------------------------------------|--|------------------------------|
| DECIPHER | | 00002719 | 00000863 | 00000140 | | |
| Sex | F | M | F | M | F | 3 M/4 F |
| size deletion | 68213162-76318818 | 72654054-76925922 | 72157311-97184863 | 72157311-80953422 | 73112000-80988000 | |
| Birth | 35 weeks | 37 weeks | term | 38 weeks | 39 weeks | |
| weight | 3005 g | 2300 g | 2350 g | NI | 3780 g | |
| length | 47 cm | 47.5 cm | 47cm | NI | 53 cm | |
| OFC | 34 cm | NI | 35 cm | NI | 37 cm | |
| Age at first clinical exam | 16 months | 5 years | 2 months | 23 months | 30 months | |
| Developmental delay | + | + | + | + | + | 7/7 |
| Motor delay, hypotonia | + | + | + | + | + | 7/7 |
| Mental level | mild delay | IQ = 55 | too young to assess | moderate delay | IQ = 70 | |
| Facial dysmorphism | | | | | | 6/7 |
| thin upper lip | + | + | + | + | | |
| smooth long philtrum | + | + | + | + | | |
| low frontal hair line | | | + | | | |
| high palate | + | | + | | | |
| retrognathia | | | + | | + | |
| high nasal bridge | + | | + | | | |
| low set ears | + | + | + | | + | |
| other | | | | epicanthus, prominent ears | epicanthus, hypotelorism | |
| Growth parameters/age | 16 months | 5 years | 2 months | 23 months | 10 years | |
| weight | 10.5 kg (P50) | 18.2 kg (P75) | 3220 g (< P3) | 14.5 kg (P90) | 40 kg (>P90) | |
| length | 81 cm (P75) | 108.5 cm (P50) | 50 cm (<P3) | 81 cm (P3) | 149 cm (>P90) | |
| OFC | 47 cm (P50) | 52 cm (P90) | 37.4 cm (P25) | 49 cm (P10) | 54 cm (>P90) | |
| Joint laxity (all joints) | + | + | + | + | + | |
| thorax | | mild pectus excavatum | short | | pectus excavatum | |
| loose connective tissue | talipes equinovarus | inguinal hernia | umbilical hernia | pes cavus | umbilical hernia cubitus valgus flat valgus feet | 5/7 |
| Urogenital anomalies | VUR grade 2-3 | | small kidneys | cryptorchidism | | 3/7 |
| Other | high pitched voice sacral dimple | sacral dimple | neonatal enterocolitis nystagmus died at 8 months recurrent respiratory infections | hypogonadotr. hypogonadism obesity | | |

2). Mutations in the latter gene cause an autosomal recessive lysosomal free sialic acid storage disease [16]. Lespinasse and co-authors suggested that the *5-HT1B* gene could be responsible for the mental retardation and language delay observed in 6q13-14del patients [12]. This gene encodes a hydroxytryptamine receptor and these type of receptors have been implicated in a variety of neuropsychiatric disorders [17]. It maps 2 Mb telomeric to the common defined deleted region and is deleted in two of our patients. We can not exclude a role for this gene in the developmental delay of these patients, but given the fact that the two other patients also clearly exhibit a developmental delay, another gene(s) within the SRO should also be involved. In this regard the *FILIP* gene encoding a Filamine A-interacting protein involved in cortical cell migration represents an interesting candidate [18]. Yet, neither of our patients shows neuronal migration defects on MRI scan of the brain.

Another feature present in the majority of patients is urogenital anomalies with cryptorchidism reported in three out of the five male patients. In patient 4, this cryptorchidism is probably due to the documented hypogonadotropic hypogonadism.

Our analysis of four cases of 6q13-14 microdeletion defines a novel site of copy number variation associated with developmental delay, distinct facial features and connective tissue pathology. The latter feature in particular may constitute a good clinical handle to identify additional patients.

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Legends to the figures

Figure 1

A-D: Clinical pictures of patient 1 at the age of 21 months (A), patient 2 at the age of 5 years (B), and patient 4 at the age of 6 years (C,D). Note the facial features they have in common: long philtrum, thin upper vermillion, high nasal bridge, short and upturned nose, epicanthal folds, pointed chin and large ears with large earlobes.

Lower panel: Schematic overview of the 6q13-14 region and different overlapping deletions.

Black bars indicate the microdeletion in the respective patient, grey bar indicates the breakpoint containing region; the shortest region of overlap (SRO) is indicated by the arrow; the patient reported by Lespinasse [12] is indicated by a grey bar; lower part shows a view of the UCSC genome browser (NCBI build 36.1, March 2006) illustrating the genes that map within the SRO.

Written consent was given to the authors for publication of the patient's images in print and online.

Table 1

Overview of molecular and clinical data of the new and reported patients with a microdeletion 6q13-14. Reported patients are referenced in [5-12]. Abbreviations: F: female; M: male; +: present; NI: no information; LL: lower limbs; UL: upper limbs; VUR: vesico-uretral reflux; hypogonadotr.: hypogonadotrophic. Genome coordinates are according to human genome build 18 (NCBI 36.1), except for the patient reported by Lespinasse et al. (human genome build 17, NCBI35).

Table 2 Supplementary

List of the reference genes present in the shortest region of deletion overlap at 6q13-q14.1, based on human genome build 18 (NCBI 36.1).

