Potocki–Lupski syndrome mimicking a connective tissue disorder

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List of main features

Wide forehead
Downslanting palpebral fissures
Long philtrum
Large earlobes
Micrognathia
Hypoplastic nails
Long toes
High arched palate
Hypotonia
Thoracic kyphosis
Global developmental delay

Summary

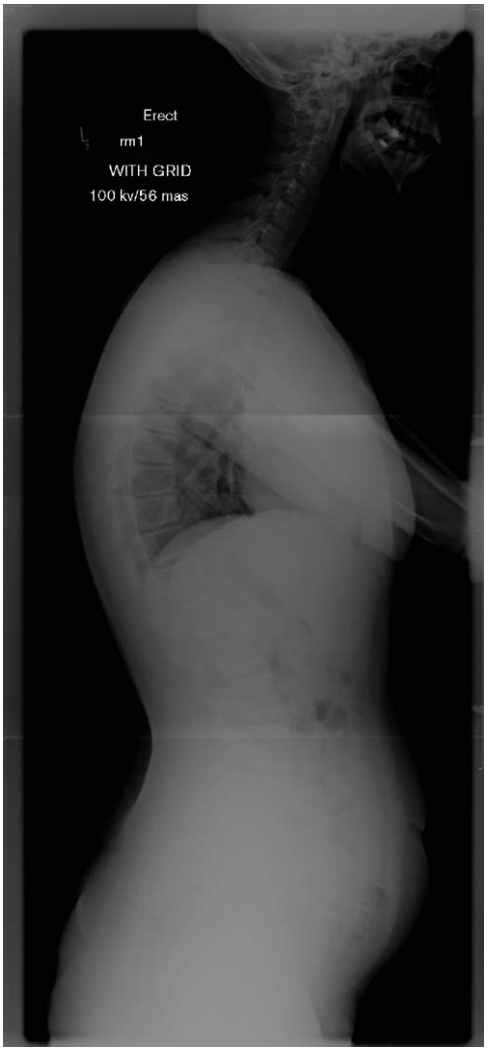
We report the case of a 16-year-old boy with 17p11.2 duplication (Potocki–Lupski syndrome, PTLS) and thoracic kyphosis. He was first referred to Clinical Genetics at the age of $2\frac{1}{2}$ years following a diagnosis of global developmental delay and benign hypotonia. He was noted to be a tall boy (height on the 90th centile and head circumference on the 97th centile) with long toes.

He is the second child of non-consanguineous parents. Pregnancy was unremarkable, and he was born at full term by emergency Caesarean section for a brow presentation. He was a large baby with a birth weight of 3.8 kg. He was noted to be floppy and slow to feed soon after birth. At 4 months of age, following normal electromyography and nerve conduction studies, he was diagnosed with benign hypotonia, which later resolved spontaneously.

His development was delayed globally. He first walked at 18 months and at the age of 6 years, he was noted to have difficulties with coordination. His first spoken words came only at the age of 6 years. He was a hyperactive child and had episodes of breath holding until the age of 5 years.

At 16 years, his behaviour is immature. He has some autistic traits such as a dislike for changes in his routine and a tendency to repeat himself. He has some sleep disturbances including sleep walking and talking in his sleep. He has learning disability and has attended a

Fig. 1



Lateral radiograph of spine showing thoracic kyphosis.

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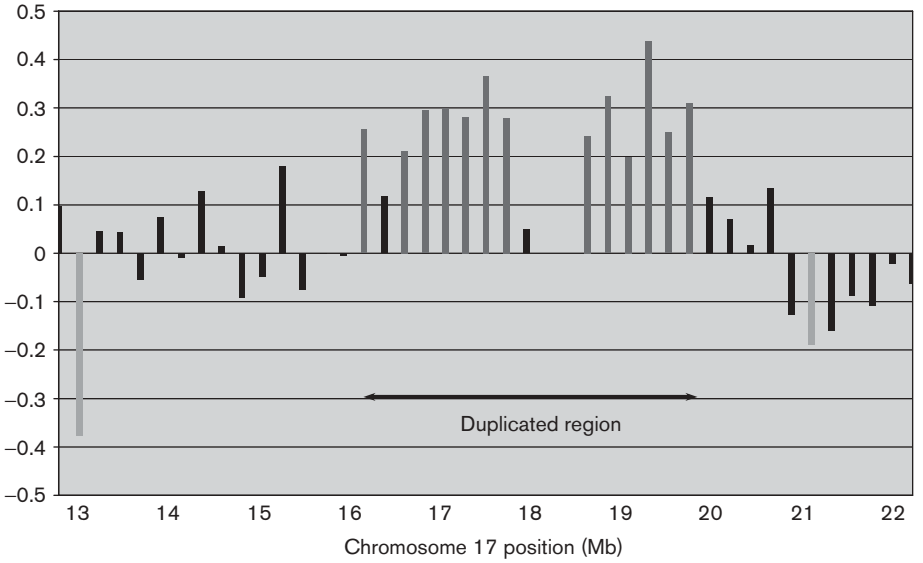
Fig. 2



Array CGH results chart for our patient showing the log2 ratio (*y*-axis) for bacterial artificial chromosome probes mapping to chromosome 17 region 13–22 Mb, human genome build 35 (*x*-axis). Deviations of probe log2 ratios from 0 are depicted as coloured bars. Probe log2 ratios exceeding a threshold of 1.5 standard deviations from the mean probe ratio are coloured dark grey and light grey to represent relative gains and losses, respectively. Bars coloured black do not exceed the threshold. The ~3.8 Mb duplication encompassing the Potocki–Lupski syndrome region is clearly visible.

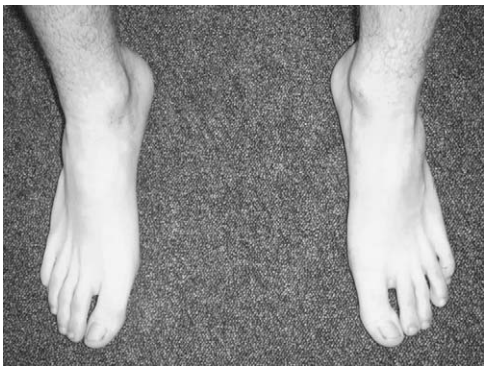
Fig. 3

Facial features showing broad forehead, downslanting palpebral fissures, long nasal tip and small chin.

special school since the age of 4 years. He still requires adult supervision for all his activities.

Our patient shows a number of musculoskeletal abnormalities. A postural scoliosis was noted at the age of 4 months, but it resolved by the age of 4 years. He also had marked ligamentous laxity of his joints, flat feet and a high arched palate. He then developed a progressive thoracic kyphosis in his early teenage years (Fig. 1). This is being treated conservatively with spinal braces. A diagnosis of Marfan syndrome was considered owing to his musculoskeletal abnormalities, tall stature and long, thin toes. His echocardiogram was reported to be normal and his developmental delay, learning difficulties and behavioural problems did not fit in with this diagnosis.

Fig. 4



Feet showing long, spidery thin toes with hypoplastic nails.

Investigations

Initial investigations at the age of 2 years included chromosome analysis and molecular genetic analysis for

Fragile X and Myotonic Dystrophy, all of which were normal. Telomere fluorescence in-situ hybridization analysis at the age of 7 years was also normal. The 3.8 Mb 17p11.2 'de-novo' duplication was first detected by segmental duplication array comparative genome hybridization (CGH) (confirmed by fluorescence in-situ hybridization) when the patient was 15 years old. The proximal breakpoint is between bacterial artificial chromosomes RP11-73L16 and RP11-148O23, and the distal breakpoint between RP11-793I24 and RP11-142H5 (Fig. 2).

Discussion

The 17p11.2 duplication found in our patient is the reciprocal of the deletion-causing Smith–Magenis syndrome. This duplication was not apparent on routine chromosome analysis and the diagnosis of PTLS was thus only made when an array CGH was performed. The syndrome arising from the duplication was first described by Potocki *et al.* (2000) and has recently been characterized and named the PTLS (Potocki *et al.*, 2007). There is a phenotypic overlap as well as diversity between the deletions–duplication syndromes of 17p11.2. Our patient shows a number of the characteristic features of PTLS including hypotonia and poor feeding in infancy, developmental delay, language delay and cognitive impairment. He also exhibits behavioural problems such as autistic traits and sleep abnormalities, which have been described in children with PTLS. He shows the same dysmorphic features including downslanting palpebral fissures, long philtrum and long nasal tip, noted in other individuals with PTLS (Fig. 3).

There have not been earlier case reports of PTLS showing musculoskeletal features of a connective tissue-like disorder such as tall stature, long spidery toes (Fig. 4), high arched palate, hyperextensible joints, flat feet and a marked progressive thoracic kyphosis. These features have not been reported in the Smith–Magenis syndrome either, although scoliosis has been frequently noted there. Scoliosis of more than 10° was also noted in three individuals in a study of 10 patients with PTLS (Potocki *et al.*, 2007). Interestingly, the authors also describe structural cardiovascular abnormalities, including a moderately dilated aortic root, in a subset of their patients, which could also represent another manifestation of a connective tissue disorder.

The human microfibril-associated glycoprotein gene, *MFAP4*, has been identified at 17p11.2 (Zhao *et al.*, 1995), and is a possible candidate in the causation of these features in our patient. Although the function of this gene is unknown, its structural features indicate that its fibrinogen-like domain may have transforming growth factor-β1 binding capacity. Dysregulation of transforming growth factor-β activation is known to contribute to the pathogenesis in Marfan syndrome (Neptune *et al.*, 2003). Hence, further studies need to be done to determine the role of *MFAP4* in the pathogenesis of this phenotype in PTLS.

At 16 years of age, our patient is the oldest patient reported with the relatively newly described PTLS and the onset of his thoracic kyphosis has been only since his early teens. This indicates that periodic examination of the spine is important in individuals affected with PTLS, particularly in older children and young adults. The combination of musculoskeletal features noted in our patient and aortic root dilatation reported by Potocki *et al.* (2007) suggests that 17p11.2 duplication must be considered as a diffential diagnosis for connective tissue disorders such as Marfan syndrome. This case report also emphasizes the fact that genome-wide analysis by array CGH in individuals with developmental delay, dysmorphic features and behavioural problems is helpful in detecting pathogenic submicroscopic chromosomal abnormalities that are not identified on routine karyotyping.

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