

CASE REPORT

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Interstitial 287 kb deletion of 4p16.3 including *FGFRL1* gene associated with language impairment and overgrowth

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Abstract

We report a male patient with developmental delay carrying an interstitial 4p16.3 deletion of 287 kb, disclosed by oligo array-CGH and inherited from his father with a similar but milder phenotype. This deletion is distal to the Wolf-Hirschhorn syndrome critical regions, but includes the *FGFRL1* gene proposed to be a plausible candidate for part of the craniofacial characteristics of Wolf-Hirschhorn syndrome patients. However, the proband lacks the typical facial appearance of the syndrome, but exhibits overgrowth, dysfunction of temporomandibular articulation and a bicuspid aortic valve. Given the pattern of expression of the *fibroblast growth factor receptor-like 1* and its involvement in bone and cartilage formation as well as in heart valve morphogenesis, we discuss the impact of its haploinsufficiency in the phenotype.

Keywords: 4p16.3 deletion, Developmental delay, *FGFRL1* gene, Language impairment, Cartilage formation

Background

Wolf-Hirschhorn syndrome (WHS; OMIM#194190) is a contiguous gene syndrome caused by deletion of the short arm of chromosome 4. There is a considerable variation in the phenotypic spectrum and a correlation between the size of the deletion and severity of the phenotype has been recognized [1]. Two Wolf-Hirschhorn critical regions, WHCR1 and WHCR2, have been identified within 4p16.3 [2,3]. Beyond this region, the loss of additional critical genes appears to be responsible for variable present features, the identification of patients with distal 4p deletions could help to identify for pathogenic genes that may be involved in components of the WHS phenotype.

Here we report a patient with a mild phenotype carrying an interstitial 287 kb deletion at 4p16.3, distal to the already described WHS critical regions, and encompassing

FGFRL1 gene proposed to be involved in the craniofacial characteristics. We discuss the involvement of this gene in the features displayed by the patient and compare with other patients reported with overlapping imbalances.

Case presentation

Clinical report

The 11-years-old male proband is the first child of unrelated parents. He was born at 38 weeks of gestation after uneventful pregnancy. His weight was 3900 g (90th percentile), length of 51 cm (50th percentile), and occipitofrontal circumference (OFC) of 36 cm (75th percentile). Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. He started to talk and walk independently at 2 years of age. It was noted to have difficulties in language skills, so he has been having language therapy since the age of 3. At 6 years he started to have pedo-psychiatric support. At the age of 11 years he was referred to genetics evaluation after diagnosis of bicuspid aortic valve in routine echocardiography. On physical examination, the patient showed overgrowth with a weight of 51,5 kg (95th percentile), height of 168 cm (>95th percentile), and OFC of 53,5 cm (50th-75th percentiles). Craniofacial findings included an asymmetric long face, with retrognathia, short philtrum

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(Figure 1a), high palate with misaligned teeth, dysfunction of temporomandibular articulation, long prominent nose and prominent ears (Figure 1b). The hands have long fingers (Figure 1c), the feet display bilateral sandal gap of the first toes with large halluces (Figure 1d). Because of the developmental delay and overgrowth, homocysteine levels were investigated but showed a normal result. Electroencephalogram was normal, but MRI of the brain revealed a slight diminish of the frontal lobe mainly on the right side. Although in orthopedic examination he didn't reveal any remarkable alterations, he has a postural kyphosis with sloping shoulders (Figure 1e) and asymmetric position of scapulas. He has a mild global cognitive impairment, but a more pronounced dysfunction in expressive language and articulation of speech.

His father has similar but milder phenotypic features and had strong learning difficulties at school, also with limitations in language articulation. He exhibits a tall stature, the facial appearance displays a slight asymmetry with a long prominent nose, short philtrum and retrognathia. Neither the patient nor his father have had seizures.

In the father's family there is a history of remarkable delay in his sister, brothers and nephews with learning difficulties. Unfortunately, it was not possible to evaluate any other of the affected family members.

The proband had already normal investigation results of conventional cytogenetics analysis, fragile-X syndrome testing and subtelomeric screening.

Methods

High-resolution comparative genomic hybridization (array-CGH) analysis was performed using Agilent SurePrint G3 Human Genome microarray 180 K (Agilent Technologies, Santa Clara, CA), an oligonucleotide microarray containing approximately 180,000 sixty-mer probes with a 17 kb average probe spacing, as described before [4]. In order to confirm the array-CGH result, MLPA (MRC Holland, Amsterdam, Netherlands) using the set of probes P373, was performed according to the manufacturers' instructions. The study of the parents was done with the same MLPA probemix.

Results

The oligo array-CGH showed an interstitial deletion at 4p16.3 spanning about 287 kb of genomic DNA from position 927,780 bp (clone A_16_P16565674) to 1,214,915 bp (clone A_16_P00907084) flanked by probe A_16_P00906727 (920,051 bp) and probe A_18_P23419088 (1,228,462 bp) according to UCSC Genome Browser (hg19; GRChBuild 37.1, February 2009) (Figure 2). The deleted segment contains 11 RefSeq genes, 7 genes are described in the OMIM database: *DGKQ* (#601207) a diacylglycerol kinase, *SLC26A1* (#610130) a sulfate anion transporter 1, *IDUA* (#252800) a alpha-L-iduronidase (associated to a lysosomal storage disease by homozygous or compound heterozygous mutation), *FGFRL1* (#605830) the fibroblast growth factor receptor-like 1, *RNF212* (#612041) a ring finger protein that plays a role in meiotic



Figure 1 Phenotypic characteristics of the patient at 14 years of age. (a) Asymmetric long face, with retrognathia and short philtrum, (b) long and prominent nose, large or prominent ears, (c) hands with long fingers, (d) bilateral sandal gap of the first toes with large halluces, (e) postural kyphosis with sloping shoulders.

In the work reported by Hammond *et al.* [12] a correlation between the genes involved in different deletions within 4p16.3 and the craniofacial phenotype is done. One of the patients was reported by Faravelli *et al.* [13], mother of the propositus, she carries a terminal deletion distal to both critical regions of WHS, but including *FGFRL1*, her facial features included hypertelorism, high nasal bridge, down-slanting of palpebral fissures and large protruding eyes, but our patient with a smaller deletion also harbouring *FGFRL1* doesn't display neither of these characteristics. South *et al.* [11] described two patients with 4p terminal deletions distal to WHS critical regions but including *FGFRL1* and a portion of *LETM1* in one of them (Figure 2), they didn't exhibit the typical facial features of the syndrome, but have prominent forehead, mild telecanthus and normal philtral length, in both it was observed growth delay and mild developmental delay. On the other hand the patient reported by Engbers *et al.* [5] with a 1.6 Mb deletion have typical facial signs of the WHS, this deletion includes *FGFRL1* but also other proximal genes that could be involved in the displayed phenotype (Figure 2). Our report supports the hypothesis that multiple genes are involved in the orchestration, not only of the facial phenotypic features but in the other malformations and cognitive skills observed in WHS patients in a contiguous manner. As it was confirmed in the study of Maas *et al.* [7], of a cohort of patients with different size deletions and genotype-phenotype correlation, several clinical features of WHS have considerable variable expressivity or penetrance, so it is difficult to pinpoint the genes involved in the more rare aspects of the WHS phenotype. The identification of distal 4p deletions covering about 0.4-0.5 Mb in individuals without a pathogenic phenotype suggests that monosomy of this region is likely benign [14,15]. But deletions extending to the 1.4 Mb region appear to be pathogenic (Figure 2), although with a mild phenotype [7,11,13] and no typical facial appearance of WHS. Deletions extending to 1.6 Mb can however display some overlapping features to the phenotype of WHS [5], suggesting the presence of other genes contributing to the displayed features.

Conclusions

The present report could help to unravel the phenotypic manifestations underlying the haploinsufficiency of the *FGFRL1* gene. Its involvement in the bone primordia formation and in heart morphogenesis has been described even in animal models [6]. However, the observation of a tall stature in the proband and his father is a specific finding of this report. A better characterization of patients with atypical and smaller interstitial deletions could contribute to the knowledge of the biological function of neighbouring genes out of the core critical regions of the WHS.

Consent

Written informed consent was obtained for publication of this paper and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EM drafted the manuscript and was involved in the interpretation of array-CGH results; FB provided the clinical data, the biological samples and revised the manuscript critically; JF and LMP carried out the microarray and molecular genetic studies; AM performed the cytogenetic studies; JBM was involved in array-CGH analysis and revised the manuscript critically; IMC coordinated the study, made substantial contribution to conception design and interpretation of data and revised the manuscript critically. All authors read and approved the final manuscript.

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