Cleft Lip/Palate, Short Stature, and Developmental Delay in a Boy with a 5.6-Mb Interstitial Deletion Involving 10p15.3p14

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Key Words

10p15 deletion · Array-CGH · Cleft lip/palate · DiGeorge syndrome 2

Abstract

The chromosome interval 10p15.3p14 harbors about a dozen genes. This region has been implicated in a few well-known human phenotypes, namely HDR syndrome (hypoparathyroidism, sensorineural deafness, and renal dysplasia) and DGS2 (DiGeorge syndrome 2), but a number of variable phenotypes have also been reported. Cleft lip/palate seems to be a very unusual finding within the clinical spectrum of patients with this deletion. Here, we report a male child born with short stature, cleft lip/palate, and feeding problems who was found to have a 5.6-Mb deletion at 10p15.3p14.

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Patients with 10p15.3p14 deletions can present with clinical findings including hypoparathyroidism, heart defects, immunodeficiency, deafness, renal malformations, neurocognitive alterations, motor delay, hypoto-

nia, seizures, and craniofacial dysmorphism among other less frequent findings [Verri et al., 2004; Lindstrand et al., 2010; DeScipio et al., 2012]. Usually, more distally located deletions are associated with HDR syndrome (hypoparathyroidism, sensorineural deafness, and renal dysplasia), while more proximally located deletions are associated with DiGeorge syndrome 2 (DGS2) [Lichtner et al., 2000; Van Esch et al., 2000; Melis et al., 2012]. However, none of these phenotypes is associated with cleft lip/palate in the clinical spectrum. Among facial findings, cleft lip/palate has seldom been reported. Here, we describe a male patient presenting with bilateral cleft lip/palate, delayed psychomotor development, and feeding problems who was found to have a deletion involving 10p15.3p14 without the classical findings of either DGS2 or HDR.

Materials and Methods

Case Report

A male patient (fig. 1) was referred to the Hospital for Rehabilitation of Craniofacial Anomalies, USP at the age of 3 months for assessment and management of cleft lip/palate. He was the

Fig. 1. Facial appearance of the patient.

first child of a healthy and unrelated couple. The pregnancy was unremarkable with no exposure to known teratogens, and there was no relevant family history. Delivery was at 34 weeks of gestation by cesarean section; birth weight was 1,400 g (<3rd centile), length was 39 cm (<3rd centile), and OFC was 27 cm (<3rd centile). He cried immediately at birth, Apgar scores at 1 and 5 min were 8 and 9, respectively, and a bilateral cleft lip/palate was noticed. Neonatal heel prick sample test results were unremarkable. He remained at the hospital due to feeding problems during the first month of life. Since the age of 3 months, he has been fed through a nasogastric feeding tube but with no satisfactory weight gain. At the age of 8 months, his weight was 4,250 g (<3rd centile), his length was 58.5 cm (<3rd centile), and his OFC was 38.5 cm (<3rd centile). Neuropsychological development was delayed; he had normal cervical control and was able to roll over, but he could not sit without support. Further examinations showed mild prominence of the metopic suture, telecanthus, upslanted palpebral fissures, epicanthus inversus, a broad and low nasal root, and bilateral cleft lip/palate. Upper and lower limbs, the spine, and the cardiovascular system were normal, and results of blood laboratory tests were also in the normal range. A BERA test was recently performed and turned out unremarkable. Also, kidney ultrasound was performed at the age of 12 months and did not show any anomalies.

Fig. 2. **A** Array-CGH profile of the 5.6-Mb interstitial deletion at the short arm of chromosome 10. **B** DGS2-deleted region and the 10p15.3p14 deletion in the present case (red bars). The green line indicates the deletion of the GATA3 gene in both deleted regions.

Cytogenetics

Chromosomal analyses were performed on peripheral blood samples using conventional GTG-banding techniques at the 550-band level.

Array Comparative Genomic Hybridization

Array comparative genomic hybridization (array-CGH) using the whole genome Cytosure™, ISCA V2 array 4×180K (Oxford Gene Technology, UK) was performed according to the manufacturer's instructions. Scanned images of the arrays were processed

and analyzed using Feature Extraction software and Genomic Workbench software (Agilent Technologies) with the statistical algorithm ADM-2 and a sensitivity threshold of 6.0. We applied a 'loop design' in our hybridizations as previously described [Allemeersch et al., 2009], resulting in 2 reverse labeling hybridizations per sample. To be recognized by the software, alterations had to encompass at least 3 consecutive probes with aberrant log₂ values, and those not detected in both dye-swap experiments of the same sample were excluded from the analysis.

Table 1. Genes contained in the 10p15.3p14 deletion

Gene	Function
<i>PFKP</i>	Phosphofructokinase, key regulatory enzyme in glycolysis
<i>KLF6</i>	Kruppel-like factor 6, transcription factor, tumor suppressor
<i>AKR1C2</i>	Encodes a member of the aldo/keto reductase superfamily which consists of more than 40 known enzymes and proteins. These enzymes catalyze the conversion of aldehydes and ketones to their corresponding alcohols by utilizing NADH and/or NADPH as cofactors.
<i>CALML5</i> and <i>CALML3</i>	Calcium-binding proteins (calmodulin family)
<i>UNC3</i>	Urocortin 3, endogenous ligand for corticotropin-releasing factor type 3 receptor
<i>ASB13</i>	Ankyrin repeat and SOCS box containing 13
<i>GDI2</i>	GDP dissociation inhibitor 2
<i>FBXO18</i>	F-box protein family. The F-box proteins constitute one of the 4 subunits of ubiquitin protein ligase complex called SCFs which function in phosphorylation-dependent ubiquitination.
<i>IL15RA</i>	Interleukin 15 receptor alpha, cytokine receptor; enhances cell proliferation and expression of apoptosis inhibitor BCL2L1/BCL2-XL
<i>IL2R</i>	Interleukin receptor 2, T cell growth factor receptor; confers lower immune responsiveness and predisposes to type 1 diabetes
<i>RBM17</i>	RNA binding motif protein 17. The encoded protein is part of the spliceosome complex and functions in the second catalytic step of mRNA splicing.
<i>PFKFB3</i>	Synthesis and degradation of fructose 2,6-bisphosphate
<i>PRKCQ</i>	Protein kinase C (PKC) is a family of serine- and threonine-specific protein kinases. Each member of the PKC family has a specific expression profile and is believed to play a distinct role.
<i>SFMBT2</i>	Transcriptional repressor of HOXB13 gene. HOXB13 is a transcription factor that belongs to the homeobox gene family. Genes of this family are highly conserved among vertebrates and essential for vertebrate embryonic development.
<i>ITIH5</i> , <i>ITIH2</i>	The inter-alpha-trypsin inhibitors (ITI) are a family of structurally related plasma serine protease inhibitors involved in extracellular matrix stabilization and in prevention of tumor metastasis.
<i>ATP5C1</i>	Participates in the cellular response to DNA damage
<i>TAF3</i>	TAFs contribute to promoter recognition and selectivity and act as antiapoptotic factors. TAF3 can interact with several other transcription factors to control gene expression.
<i>GATA3</i>	Encodes a protein which belongs to the GATA family of transcription factors, is an important regulator of T cell development, and plays an important role in endothelial cell biology. Defects in this gene are the cause of hypoparathyroidism with sensorineural deafness and renal dysplasia.

Genes in bold indicate possible contributors to the clinical phenotype.

Results and Discussion

Conventional cytogenetic analysis revealed a normal 46,XY karyotype for both the patient and his father, and the mother had a normal 46,XX karyotype. Array-CGH results of the patient showed a 5.6-Mb interstitial deletion at 10p15.3p14, spanning from position 2,834,518 to 8,485,795 bp (HG19) and encompassing several genes (fig. 2). Array-CGH of the parents was normal, indicating that it is a de novo deletion.

Chromosome 10p deletions have been described in approximately 60 patients with 2 main phenotypes: HDR and DGS2 syndromes [Lindstrand et al., 2010]. The first condition is associated with haploinsufficiency of the *GATA3* gene [Van Esch et al., 2000] and the latter with partial monosomy 10p within the DGS2 region [Monaco et al., 1991; Melis et al., 2012]; however, phenotypic heterogeneity has also been noted in several instances [Tremblay et al., 2011; DeScipio et al., 2012].

In the present report, array-CGH analysis revealed a 5.6-Mb deletion at 10p15.3p14, encompassing several genes, including *GATA3* (table 1). Patients with *GATA3* haploinsufficiency usually present with hypoparathyroidism, heart defects, deafness, and renal malformations, while patients with partial monosomy 10p within the DGS2 region present with hypocalcemia, cardiovascular malformations, immunodeficiency, and facial dysmorphism, symptoms which are similar to those found in patients with 22q11.2 microdeletions. Our patient did not present with the usual findings of these conditions, although he did show growth retardation and developmental delay which have both been reported in patients with 10p15 deletions [Grunnarsson et al., 2009; Christopoulou et al., 2012].

Haploinsufficiency in 3 other genes (*UNC3*, *IL15RA*, *AKRIC2*) due to the deletion may contribute to these clinical manifestations. The *UNC3* gene, the endogenous ligand for corticotropin-releasing factor type 3 receptor, is expressed in many tissues of the brain, including the hypothalamus, and is associated with mental retardation [Lindstrand et al., 2010]. The interleukin gene family (*IL15RA*) has neurological functions and is associated with synaptic transmission in the CNS, suggesting an involvement during embryogenesis [Kurowska et al., 2002]. The aldo-keto reductase family 1, member C2 gene (*AKRIC2*) is related to 46,XY sex reversal and obesity, hyperphagia, and developmental delay; however, its effective function during development is poorly known.

Poor weight gain and feeding difficulties have been reported in patients with 10p deletions and, similarly to our

patient, one patient showed no signs of hearing loss, renal dysplasia, or hypoparathyroidism [Lindstrand et al., 2010]. Cleft lip/palate was reported in 2 patients who had an involvement of chromosome 10p [Gottlieb et al., 1998; Lindstrand et al., 2010]. However, the phenotype observed in our patient is different from those previously reported in patients with 10p deletions.

Comparing the phenotype of our patient with the literature, he does not show any typical signs of the HDR and/or DGS2 syndromes, besides the developmental delay. The HDR syndrome is an autosomal dominant disorder, and all affected patients have hearing loss, while the other trait is more variable.

In summary, our patient presented with growth retardation, developmental delay, and cleft lip/palate which have been seldom reported in patients with 10p15 deletions. Despite this uncommon phenotype/genotype correlation, further investigations should be performed in order to clarify the role of the genes involved in relation to the phenotype presented by this patient.

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