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Short communication

Dental developmental abnormalities in a patient with subtelomeric 7q36 deletion syndrome may confirm a novel role for the *SHH* gene ☆

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ABSTRACT

Studies in mice demonstrated that the *Shh* gene is crucial for normal development of both incisors and molars, causing a severe retardation in tooth growth, which leads to abnormal placement of the tooth in the jaw and disrupted tooth morphogenesis. In humans the *SHH* gene is located on chromosome 7q36. Defects in its protein or signaling pathway may cause holoprosencephaly spectrum, a disorder in which the developing forebrain fails to correctly separate into right and left hemispheres and that can be manifested in microforms such as single maxillary central incisor. A novel role for this gene in the developing human primary dentition was recently demonstrated. We report a 12-year old boy with a *de novo* 7q36.1-qter deletion characterized by high-resolution karyotyping, oligonucleotide aCGH and FISH. His phenotype includes intellectual disability, non-verbal communication, hypospadia, partial sacral agenesis and absence of coccyx, which are distinctive features of the syndrome and mainly correlated with the *MNX1*, *HTR5A* and *EN2* genes. No microforms of

Abbreviations: OFC, occipitofrontal circumference; BERA, brainstem evoked response audiometry; aCGH, array comparative genomic hybridization; CNV, copy number variation; FISH, fluorescence in situ hybridization; ASD, autism spectrum disorder

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holoprosencephaly spectrum were observed; but the patient had diastema and dental developmental abnormalities, such as conical, asymmetric and tapered inferior central incisors. The dental anomalies are reported herein for the first time in subtelomeric 7q36 deletion syndrome and may confirm clinically a novel role for the *SHH* gene in dental development.

Introduction

The classical phenotype of patients with terminal 7q deletions includes developmental delay, microcephaly, genital abnormalities in males, facial anomalies and intellectual disability. Deletions range in size and may extend from 7q32-qter to 7q36-qter. Comprehensive reviews summarized the clinical features of the previously reported patients with different 7q terminal deletions, mostly involving 7q32 (Frints et al., 1998; Lukusa et al., 2005). Nevertheless, only eight of these individuals had isolated 7q36-qter deletions.

In many patients the terminal 7q36 deletion was associated with microforms of holoprosencephaly, sacral agenesis and intellectual disability. The genes *SHH* (Sonic Hedgehog, MIM 600725), *MNX1* (Motor neuron and pancreas homeobox 1, MIM 142994), *HTR5A* (5-hydroxytryptamine receptor 5A, MIM 601305) and *EN2* (engrailed 2, MIM 131310) may be involved with the major clinical features of the syndrome (Cretolle et al., 2008; Dubourg et al., 2007; Millen et al., 1994; Rees et al., 1994). Since these genes are located at 7q36, a more accurate genotype–phenotype correlation would be possible with reports of additional patients who present as their sole rearrangement the deletion of this region.

In this study we report a 12-year old boy with partial sacral agenesis and absence of coccyx, intellectual disability, no signs of holoprosencephaly, diastema, dental developmental abnormalities and a *de novo* 7q36.1 deletion. The extension of the deletion was established by high-resolution karyotyping, oligonucleotide aCGH and FISH. In addition, we discuss his phenotype in relation to the putative genes located in the deleted region and we propose novel roles for the *SHH* gene related to diastema and dental developmental abnormalities such as conical, asymmetric and tapered inferior central incisors.

Materials and methods

This study was approved by the Research Ethics Committee of *Universidade Federal de Minas Gerais*. The written informed consent was undersigned by guardians.

Clinical report

A 12-year-old boy born to healthy unrelated parents is presented (Fig. 1). He has two older healthy brothers. The pregnancy and elective cesarean delivery were uneventful. At birth his weight was 3100 g (10–25th centile), length 49 cm (25th centile) and occipitofrontal circumference (OFC) 33 cm ($\leq$10th centile). He presented hypospadias and hipodysplasia was suspected, so he used double diapers until the age of seven months. Neonatal screening for PKU and hypothyroidism was normal.

Until 6 months he was a very quiet baby. His development was mildly delayed as he sat alone at 12 months and walked independently at 19 months of age. He spoke “mama” for a short time, and then his communication became only non-verbal and gestural.

He was evaluated by a geneticist at 12 months of age and presented weight 8720 g (10th centile), length 71.2 cm (10th centile), OFC 44.1 cm (5th centile), hypotonia, hand-flapping, thin and weak hair, hypospadias with urethral meatus opening in the glans penis and pubic hair. Hearing evaluation at 13 months revealed serous otitis and abnormal BERA with moderate to severe hipoacusia. Repeated evaluation with BERA nine months later was normal. He evolved also with mild hyperopia and astigmatism. Laboratory evaluation at this time showed normal biotinidase activity, blood amino acids, copper and ceruloplasmin, testosterone, 17-α-hydroxyprogesterone, androstenedione and complete blood count. His karyotype was reported as normal. At the age of 13 months, his bone age corresponded to