DOI: 10.1111/j.1365-263X.2008.00915.x

Deletion of *PAX9* and oligodontia: a third family and review of the literature

ANDREA GUALA[1], VITTORIO FALCO,[2] GUIDO BREEDVELD,[3] PAOLA DE FILIPPI[4] & CESARE DANESINO[4]

[1]SOC Pediatria, Ospedale Castelli, Verbania, Italy, [2]SOS Odontoiatria, Ospedale S. Andrea, Vercelli, Italy, [3]Clinical Genetics, Erasmus University, Rotterdam, The Netherlands, and [4]Genetica Medica, Università di Pavia and Fondazione IRCCS S. Matteo, Pavia, Italy

International Journal of Paediatric Dentistry 2008; 18: 441–445

Objective. This study was conducted to report a family affected by benign hereditary chorea in which a large deletion including *TTF1*, *PAX9*, and other genes was identified and results in oligodontia.
Methods. Clinical and radiological studies of the two affected members (mother and daughter) were used to describe the oligodontia present in both of them.
Results. The missing teeth in both patients are described in detail, and these data are compared with the dental anomalies observed in the only two other families with deletions of *PAX9* and with the data available for 12 previously reported families carrying different types of *PAX9* mutations.
Conclusions. There is a clinical relevance for recognizing such families, and offering available therapies since childhood is stressed. Some genotype–phenotype correlations between *PAX9* mutations and dental anomalies can be drawn.

Introduction

The gene *PAX9* codes for a paired domain-containing transcription factor relevant for the development of dentition in mammals. It has been associated with selective agenesis of teeth mainly involving the posterior teeth both in humans and mice, and even a specific polymorphism (Ala240Pro) has been interpreted as advantageous and related to missing third molars[1].

A total of 13 families with multiple members affected with oligodontia and one sporadic case have been reported in association with mutations or deletions of *PAX9*.

We report a new family with a complete deletion of *PAX9* and oligodontia, and review the literature.

Case report

Family M was seen for genetic counselling because of benign hereditary chorea (BHC).

Correspondence to:
Cesare Danesino, Genetica Medica, Università di Pavia, via Forlanini 14, 27100 Pavia, Italy. E-mail: cidi@unipv.it

The proposita, a 10-year-old girl, was diagnosed with BHC, and the same disorder was present in her mother, but not in maternal grandparents. The family was initially reported by Guala *et al.*[2], and subsequently a 1.2 mb deletion causing the loss of five genes (*MBIP*, *TTF1*, *NKX2*, *PAX9*, and *SLC25A21*) was identified by Breedveld *et al.*[3] (case IT1) in the girl and her mother. The family became available again for follow-up only in 2005, and was then investigated for the presence of oligodontia.

The proposita (case 1), when she was 16 years old, showed class III malocclusion, bilateral cross-bite, and right posterior open bite. Primary teeth 54, 62, 64, 65, 71, 85 were still present, whereas permanent agenesis of teeth involved 18, 17, 16, 15, 12, 24, 25, 26, 27, 28, 31, 37, 38, 47, 48; an abnormal shape of 14 and 22 was observed, and 46 was retained (Fig. 1). Choreic movements are still present, unrelieved by any therapy, and occasional increase of TSH is also observed (5.4 μU/mL, nv: 0.4–4, FT3 and FT4 within normal limits, normal values).

Her mother (case 2) showed deep bite; agenesis of 18, 17, 16, 24, 26, 27, 28, 31, 36, 37, 44, 46, 47; primary teeth 65, 71 were still

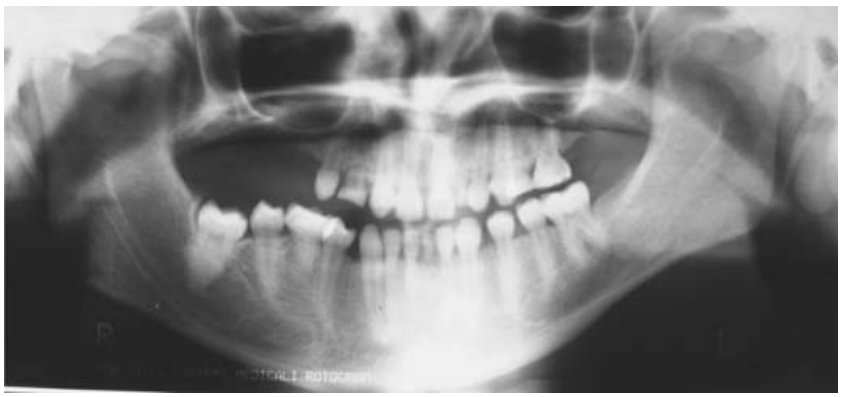

Fig. 1. Panoramic radiography of case 1, with multiple agenesis of teeth and persistence of some primary teeth.

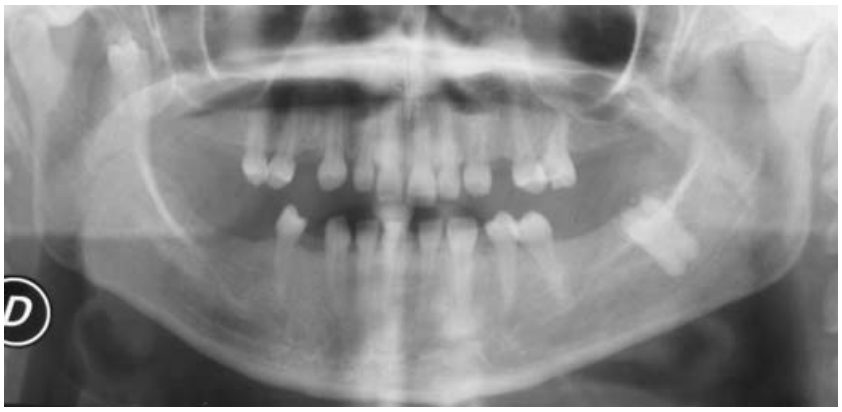

Fig. 2. Panoramic radiography of case 2, with multiple agenesis of teeth and persistence of some primary teeth.

present, whereas 48 was ectopic, and 38 was retained (Fig. 2). Choreic movements are still present, unrelieved by any therapy, and TSH was found elevated any time checked (11.1 μU/mL, nv: 0.4–4, with FT3 and FT4 within normal limits, May 2003; confirmed in May 2005).

Neither patient showed dysmorphic features or abnormalities in sweat glands, hair, or nails. Maternal grandparents of the proposita are not carrier of the deletion reported, and do not show either choreic movements or oligodontia.

Discussion

Dental size, number, and morphology show wide variations in humans. Anomalies of tooth formation are frequently observed for instance in ectodermal dysplasia[4]. Agenesis of a single tooth is a common trait, which can be observed in up to 20% of the population. More complex patterns of agenesis of teeth are much rarer, and their aetiology is largely unknown, but at least three genes are associated to non-syndromic forms (*AXIN2*, *MSX1*, and *PAX9*)[1,5].

Oligodontia is referred to as agenesis of six or more permanent teeth, and Stockton *et al*. in 2000 first reported in a large family that this trait was caused by mutations in the *PAX9* gene. Agenesis of teeth mainly involved permanent teeth, and molars were much more frequently absent than incisors.

Including our family, a total of 15 families[6–17], and a sporadic case[18] have since been reported in whom different kinds of mutations in *PAX9* caused agenesis of teeth.

Complete deletions of *PAX9* were observed in three families[3,9,16], with a total of seven patients (four men). In the family reported by Das *et al*.[9] and in our cases, the agenesis of permanent teeth is quite similar mainly in the upper arch with consistent loss of molars (Fig. 3a). In younger members of both families also, anomalies of primary teeth are present; in our family is peculiar the persistence of some primary teeth, whereas the patient by

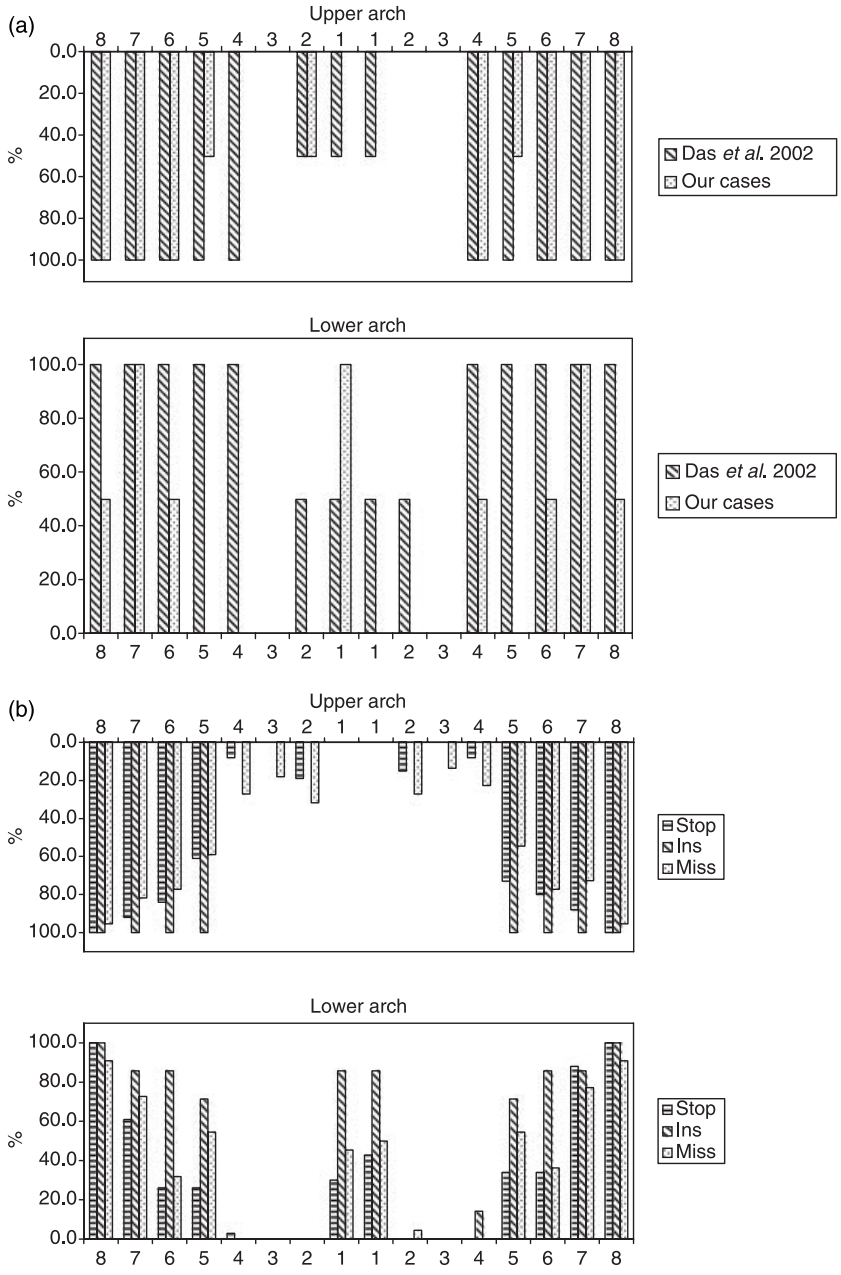

Fig. 3. (a,b) Summary of the distribution of agenesis of teeth including all members of the families with oligodontia and *PAX9* mutations included in the text. Stop refers to stop codons; del to partial or total deletions of the gene; ins to insertions; miss to missense mutations.

Das *et al.*[9] is still too young (7 years) to evaluate this point. In the family reported by Devos *et al.*[16], the only available information is the presence of 'hypodontia'.

A summary of the distribution of agenesis of teeth including all members of the reported families for other types of mutations is entered in Fig. 3b: stop mutations were observed in four families[6–8,17], with a total of 26 affected subjects (12 men); insertions were observed in two families (family Den8 in Das *et al.*[10] and Mostowska *et al.*[14]) with a total of seven cases (three men); missense mutations were observed in six families (Den3 and Den9 in Das *et al.*[10] and various authors[11–13,15]), and in a single patient[18] for a total of 22 cases (11 men).

The teeth in the upper arch are consistently more severely affected than those in the lower arch, with the exception of 13 and 14 (inferior medial right and inferior medial left incisors) frequently absent regardless the mutation type present in the families.

Overall, molars are consistently absent in the upper arch in families presenting with stop mutations, insertions, and deletions, and slightly

less involved in families carrying missense mutations. In the lower arch, molars are in general less involved and teeth 16-26-36-46 in particular are frequently present.

Canines are usually conserved in both the upper and lower arch, and the only reported losses are for three of ten patients in three families carrying missense mutations (Den9 in Das *et al.*[10] and various authors[11,12]).

In the two families with insertions (Den8 in Das *et al.*[10] and Mostowska *et al.*[14]), teeth 14-13-12-11; 21-22-23-24 are never absent in the upper arch, whereas in the lower arch 31 and 41 are frequently absent.

Intrafamilial variations are usually present, as observed also in the recent report by Hansen *et al.*[17], but less consistent than interfamilial variations.

The phenotype resulting from different *PAX9* mutations seems to be more severe for deletions than in missense mutations. In families with deletions, the resulting haploinsufficiency of *PAX9* may act through the down-regulation of *MSX1*[19], whereas the precise mechanism of action of missense mutations is not yet fully elucidated[15].

Finally, our family fits the contiguous gene deletion model described by Devos *et al.*[16] in the only other family reported with a similar large deletion including *PAX9* and *TTF1*.

The comparison of different types of oligodontia, for instance involving mainly incisors, as well as the accurate recording of associated (and apparently unrelated) clinical signs, as hypothyroidism in our family, will enable the identification of other genes relevant for dental development.

What this paper adds

- The pattern of teeth agenesis associated with mutations in the *PAX9* gene, as derived from the study of a new family and from review of the literature.
- The information that in some families presenting with teeth agenesis, a more complex phenotype can be observed.

Why this paper is important to paediatric dentists

- The knowledge of the genotype–phenotype correlation between *PAX9* mutations and teeth agenesis is relevant for genetic counselling, for a more comprehensive evaluation of the patient, and for forecasting appropriate management of the dental abnormalities especially in children.

Acknowledgements

We wish to thank Dr Peter Heutink (Erasmus University, Rotterdam) for molecular work in defining the deletion and for critical reading of manuscript.

References

1 Pereira TV, Salzano FM, Mostowska A, *et al*. Natural selection and molecular evolution in primate *PAX9* gene, a major determinant of tooth development. *Proc Natl Acad Sci USA* 2006; **103**: 5676–5681.
2 Guala A, Nocita G, Di Maria E, *et al*. Benign hereditary chorea: a rare cause of disability. *Ital J Pediatr* 2001; **27**: 150–152.
3 Breedveld GJ, van Dongen JW, Danesino C, *et al*. Mutations in TITF-1 are associated with benign hereditary chorea. *Hum Mol Genet* 2002; **11**: 971–979.
4 Lexner MO, Bardow A, Hertz JM, Nielsen LA, Kreiborg S. Anomalies of tooth formation in hypohidrotic ectodermal dysplasia. *Int J Paediatr Dent* 2007; **17**: 10–18.
5 Seifi M, Kazemi B, Golkar P. The role of *MSX1* in tooth agenesis in Iranians. *Int J Paediatr Dent* 2007; **17**: 254–258.
6 Stockton DW, Das P, Goldenberg M, D'Souza RN, Patel PI. Mutation of *PAX9* is associated with oligodontia. *Nat Genet* 2001; **24**: 18–19.
7 Nieminen P, Arte S, Tanner D, *et al*. Identification of a nonsense mutation in the *PAX9* gene in molar oligodontia. *Eur J Hum Genet* 2001; **9**: 743–746.
8 Frazier-Bowers SA, Guo DC, Cavender A, *et al*. A novel mutation in human *PAX9* causes molar oligodontia. *J Dent Res* 2002; **81**: 129–133.
9 Das P, Stockton DW, Bauer C, *et al*. Haploinsufficiency of *PAX9* is associated with autosomal dominant hypodontia. *Hum Genet* 2002; **110**: 371–376.
10 Das P, Hai M, Elcock C, *et al*. Novel missense mutations and a 288-bp exonic insertion in *PAX9* in families with autosomal dominant hypodontia. *Am J Med Genet A* 2003; **118**: 35–42.
11 Lammi L, Halonen K, Pirinen S, Thesleff I, Arte S, Nieminen P. A missense mutation in *PAX9* in a family with distinct phenotype of oligodontia. *Eur J Hum Genet* 2003; **11**: 866–871.
12 Jumlongras D, Lin JY, Chapra A, *et al*. A novel missense mutation in the paired domain of *PAX9* causes non-syndromic oligodontia. *Hum Genet* 2004; **114**: 242–249.
13 Klein ML, Nieminen P, Lammi L, Niebuhr E, Kreiborg S. Novel mutation of the initiation codon of *PAX9* causes oligodontia. *J Dent Res* 2005; **84**: 43–47.
14 Mostowska A, Biedziak B, Trzeciak WH. A novel mutation in *PAX9* causes familial form of molar oligodontia. *Eur J Hum Genet* 2006; **14**: 173–179.
15 Kapadia H, Frazier-Bowers S, Ogawa T, D'Souza RN. Molecular characterization of a novel *PAX9* missense mutation causing posterior tooth agenesis. *Eur J Hum Genet* 2006; **14**: 403–409.

16 Devos D, Vuillaume I, De Becdelievre A, *et al*. New syndromic form of benign hereditary chorea is associated with a deletion of *TITF-1* and *PAX-9* contiguous genes. *Mov Disord* 2006; **21**: 2237–2240.
17 Hansen L, Kreiborg S, Jarlov H, Niebuhr E, Eiberg H. A novel nonsense mutation in *PAX9* is associated with marked variability in number of missing teeth. *Eur J Oral Sci* 2007; **115**: 330–333.
18 Mostowska A, Kobielak A, Biedziak B, Trzeciak WH. Novel mutation in the paired box sequence of *PAX9* gene in a sporadic form of oligodontia. *Eur J Oral Sci* 2003; **111**: 272–276.
19 Peters H, Neubuser A, Kratochwil K, Balling R. *PAX9*-deficient mice lack pharyngeal pouch derivatives and teeth and exhibit craniofacial and limb abnormalities. *Genes Dev* 1998; **17**: 2735–2747.