Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/aob

Novel *MSX1* mutation in a family with autosomal-dominant hypodontia of second premolars and third molars

Adrianna Mostowska [a,*], *Barbara Biedziak* [a,b], *Pawel P. Jagodzinski* [a]

[a] *Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poznan, Poland*
[b] *Private Dental Clinic, Poznan, Poland*

ARTICLE INFO

Article history:
Accepted 7 January 2012

Keywords:
MSX1
PAX9
Mutation
Hypodontia
Second premolars

ABSTRACT

Objective: Tooth agenesis is the most common developmental anomaly of the human dentition, with aetiology involving both genetic and environmental factors. The aim of the study was to search for casual mutations underlying hypodontia in a family with agenesis of the second premolars and third molars.

Design: Direct sequencing of the coding regions including exon–intron boundaries of the *MSX1* and *PAX9* genes was performed in all affected family members.

Results: Novel heterozygous mutation segregating in an autosomal dominant model was identified in the *MSX1* gene. This c.T671C transition leads to a substitution of leucine by proline at position 224, which is the penultimate amino acid residue of the highly conserved homeodomain. None of the control subjects (600 chromosomes) were carriers of this novel, probably damaging to protein function, mutation.

Conclusions: Our results demonstrate for the first time that *MSX1* might play a substantial role in familial cases of hypodontia involving only second premolars and third molars. The novel c.T671C mutation might be the etiological variant of the *MSX1* gene responsible for the lack of permanent teeth in the tested family.

1. Introduction

Congenital agenesis of one or more permanent teeth, hypodontia (OMIM #106600), is the most common developmental dental anomaly. *It occurs* in both *sporadic* and *familial forms*, *and* can be classified as either non-syndromic (isolated) or syndromic based on the presence of other inherited abnormalities.[1] The incidence of hypodontia, excluding the lack of the third molars, varies from 1.6 to 9.6% depending on ethnic background.[2,3] The most frequently missing teeth are the third molars, which are absent in around 20% of the population, followed by the mandibular second premolars and maxillary lateral incisors.[4] Oligodontia, the absence of six or more permanent teeth (excluding third molars), is a considerably less frequent condition affecting approximately 0.14% of the worldwide population.[2] Familial tooth agenesis may have either an autosomal dominant, autosomal recessive or X-linked inheritance.[5]

The aetiology of tooth agenesis is complex and both genetic and environmental factors are considered as possible causative agents.[3,6] It is now well established that mutations and polymorphisms in the *MSX1*, *PAX9*, *AXIN2* and *EDA* genes are associated with hypodontia.[7–10] However, their nucleotide variants can still explain only a small part of the total genetic contribution to the risk of this dental anomaly. Recently, it has been shown that nucleotide variants of *TGFα*, *IRF6*, *FGFR1*, *WNT10* and *CHDH* may also influence the pathogenesis of this

* *Corresponding author at*: Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, 6 Swiecickiego St., 60-781 Poznan, Poland. Tel.: +48 618546513; fax: +48 618546510.
E-mail address: amostowska@wp.pl (A. Mostowska).
0003–9969/$ – see front matter
doi:10.1016/j.archoralbio.2012.01.003

dental anomaly.[11–14] Moreover, epistatic interaction that may affect the risk of hypodontia has been observed between the *CHDH* and *PLD2* genes belonging to the folate and choline pathways.[13]

To date, the majority of the mutations responsible for tooth agenesis have been identified in *MSX1* (OMIM *142983) and *PAX9* (OMIM *167416), which are genes encoding transcription factors that play a crucial role during odontogenesis.[3,15] Studies in animal models have revealed that *Msx1* and *Pax9* knockout mice exhibit an arrest in tooth development at the bud stage and have other craniofacial abnormalities, including cleft palate.[16,17] In these mutant animals, the dental mesenchymal expression of Bmp4, an effector molecule involved in the induction of a transient signalling centre within dental epithelium (enamel knot), is markedly downregulated.[18,19] Further studies have shown that a key function of the signalling pathway involving Msx1 and Pax9 is the maintenance and regulation of mesenchymal Bmp4, which is critical for the progress of tooth morphogenesis from the bud stage to the cap stage.[20,21] Pax9 interacts with Msx1 at both the gene and protein levels, and this interaction enhances the ability of Pax9 to transactivate Msx1 and Bmp4 expression.[20,22]

Most of the *MSX1* and *PAX9* mutations responsible for hypodontia in humans are located in the highly conserved sequences of these genes that encode DNA binding domains (homeobox and paired box sequence, respectively). It has been shown that the *MSX1* mutations are associated with hypodontia that predominantly affects second premolars and third molars, whilst mutations in *PAX9* lead to agenesis of most molars, which can sometimes be combined with the absence of other teeth, including second premolars.[15,23] Therefore, the aim of the present study was to screen for mutations in the *MSX1* and *PAX9* genes in a family with autosomal-dominant hypodontia of second premolars and third molars.

2. Materials and methods

2.1. *Patient and control samples*

A girl aged 17 years 9 months was referred for orthodontic treatment to the Private Dental Clinic in Poznan. A pedigree construction of her family was made by clinical examinations and interviews, and the diagnosis of hypodontia was verified by panoramic dental radiographs. Peripheral blood samples were taken from all available family members (5 affected and 8 unaffected) and 300 unrelated healthy individuals who were not affected with tooth agenesis and other craniofacial abnormalities (control group). The study was approved by

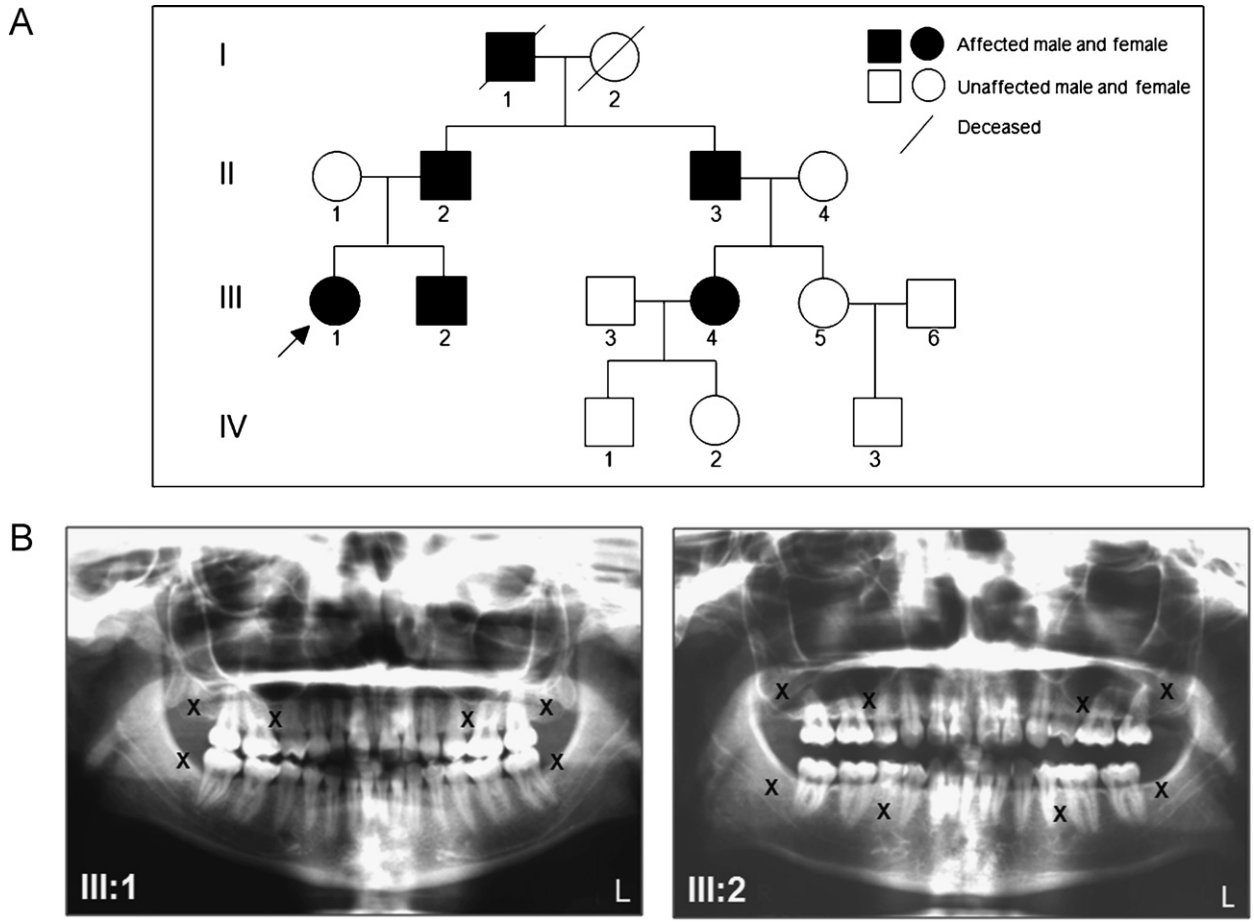

Fig. 1 – (A) Pedigree of the studied family with autosomal-dominant hypodontia of second premolars and third molars. (B) Panoramic radiographs of the proband (III:1) and her affected brother (III:2). Missing teeth are indicated with x; L, left.