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REVIEW ARTICLE

Cranial suture biology and dental development: genetic and clinical perspectives

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Premature fusion of the calvarial bones at the sutures, or craniosynostosis (CS), is a relatively common birth defect (1:2000–3000) frequently associated with limb deformity. Patients with CS may present oral defects, such as cleft soft palate, hypodontia, hyperdontia, and delayed tooth eruption, but also unusual associations of major dental anomalies such as taurodontism, microdontia, multiple dens invaginatus, and dentin dysplasia. The list of genes that are involved in CS includes those coding for the different fibroblast growth factor receptors and a ligand of ephrin receptors, but also genes encoding transcription factors, such as *MSX2* and *TWIST*. Most of these genes are equally involved in odontogenesis, providing a pausible explanation for clinical associations of CS with dental agenesis or tooth malformations. On the basis of the present knowledge on genes and transcription factors that are involved in craniofacial morphogenesis, and from dental clinics of CS syndromes, the molecular mechanisms that control suture formation and suture closure are expected to play key roles in patterning events and development of teeth. The purpose of this article is to review and merge the recent advances in the field of suture research at the genetic and cellular levels with those of tooth development, and to apply them to the dental clinics of CS syndromes. These new perspectives and future challenges in the field of both dental clinics and molecular genetics, more in particular the identification of possible candidate genes involved in both CS and dental defects, are discussed.
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Keywords: suture biology; craniosynostosis; odontogenesis; fibroblast growth factor; bone morphogenetic protein; transcription factors

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Introduction

Craniofacial and dental anomalies often have a genetic background. Recent advances in molecular genetics have revealed a genetic explanation for numerous conditions and have provided a deeper insight into the genetic processes that control morphogenesis of the skull and teeth. A variety of oral anomalies are considered specific to a number of disorders, including congenital anomalies, such as orofacial clefting and calvarial synostosis, but also to some metabolic disorders, such as hyperthyroidism or mucopolysaccharoidoses. Although the molecular mechanisms that regulate patterning and development of teeth are yet incompletely understood, in a large number of these disorders it is most likely that anomalies in, e.g. tooth number form and structure may result from, or may be influenced by the gene mutation that is causal to the disease. Knowledge of the genes and the possible effects of its mutations may contribute to a better understanding of the complex clinical phenotype. More in particular, linking the temporospatial expression and the biochemical function(s) of the gene(s) during growth and development of the face and the mouth is pivotal in understanding the molecular background of the conditions that we meet and treat at centers for craniofacial anomalies.

The purpose of this review was to provide an overview of the recent advances in molecular biology of calvarial suture formation and odontogenesis. While many of the studies have focused on animal models, recent reports show that sutures and teeth share a number of signaling pathways during cytodifferentiation in humans. This information will briefly be tested against a number of unreported clinical cases with craniosynostosis (CS; premature fusion of the calvarial sutures) and unusual oral findings. These new perspectives and future challenges on the interface between dental clinics and molecular genetics, more in particular the identification of possible candidate genes involved in both CS and dental defects, are discussed.

Development and growth of the cranial bones

The vertebrate skull is formed from two embryonic tissues, i.e. neural crest and mesoderm. The distinct contributions of each tissue to the skull and other craniofacial structures have only recently been elucidated in mammalian embryos, by using conditional knockout mice (1, 2) These studies have defined the pattern of cranial neural crest cell migration and demonstrated a relationship between the neural crest–mesoderm tissue boundaries and the position of sutures in the craniofacial skeleton. This information is essential to understand the origin of the cranial bones and sutures.

Development of the craniofacial region is directly related to the formation of the underlying central nervous system. In mammalian embryos, neural crest cells from the forebrain and midbrain become the nasal processes, palate, and mesenchyme of the first pharyngeal pouch. This mesenchyme forms the maxilla, mandible, incus, and malleus. The neural crest cells of the anterior hindbrain migrate and differentiate to become the mesenchyme of the second pharyngeal pouch, stapes, and facial cartilages. The bones of the skull develop directly from mesenchyme (intramembranous ossification) produced by neural crest cells from the trigeminal crest, which migrate to the frontonasal and first branchial arch regions (3). The cranial sutures are the primary sites of bone formation during skull growth. Development and maintenance of the cranial sutures is dependent on tissue interactions, especially those with the underlying dura mater. Tissue interactions are required during formation of the sutures in the embryo, and later for maintenance of functional bone growth centers resistant to premature obliteration during growth of the skull (4). Co-ordinate growth of the brain and skull is achieved through a series of interactions between the developing brain, the growing bones of the skull, and the sutures that unite the bones. These processes couple the expansion of the brain to the growth of the bony plates at the sutures (5).

Suture biology and pathogenesis of craniosynostosis

Three of the calvarial sutures, i.e. the sagittal, metopic, and lambdoid sutures, are formed by the narrowing of membranous gaps between bones that are initially widely separated (Fig. 1). They develop in a first step by proliferation of cells at the periphery of the extending bone fields: the osteogenic front (6). Osteogenic fronts approximate each other either in the same plane (end-to-end suture) or overlapping, forming a beveled structure (7, 8). End-to-end sutures, such as the sagittal and metopic sutures, are formed in the midline. By contrast, sutures away from the midline, such as the coronal and lambdoid sutures, are of the overlapping, beveled type. In normal conditions, complete fusion of the cranial bones usually does not occur until adulthood. Premature fusion (synostosis) of the skull bones (craniosynostosis) can result in an abnormally shaped head and can impair brain growth. Decreased growth along the sagittal suture axis (as a consequence of early suture closure) is compensated by increased growth in the fronto-occipital direction (resulting in a scaphocephalic skull); decreased growth along the coronal suture axis is compensated by increased growth in the parieto-parietal or cranio-caudal direction (resulting in, respectively, a brachycephalic or turricephalic skull) (3).

The fate and form of sutures correlate with the embryological origin of the interacting tissues. Recent studies using transgenic mice (1–3) have revealed the likely embryonic origin of the calvarial bones and dura mater. The metopic and sagittal sutures are located between bones from the same embryonic origin: neural crest for the metopic suture and mesodermal for the sagittal suture. The coronal sutures are situated between bones of distinct embryonic tissues, the frontal and parietal bones (4). Thus, the origin of the opposed bones could play a role in determining suture type and related molecular pathways involved in suture development. A summary of the genes that play a role in the developing calvarial suture is displayed in Table 1. Most of these genes are expressed in the three major tissues/structures that make up the calvarial suture, i.e. the two approaching osteogenic fronts, the surrounding sutural mesenchyme, and the dura (9). Studying the temporospatial expression pattern of these genes allows us to determine precisely the stage at which these genes are expressed during osteoblast differentiation in suture development. It may also give us some insights in the interactions between them.

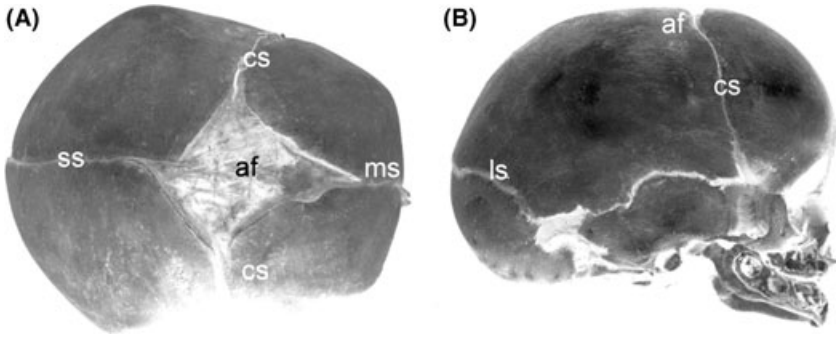

Figure 1 Sutures of the human skull bones, vertex (A) and lateral (B) views: *af* anterior fontanel, *cs* coronal suture, *ls* lambdoid suture, *ms* metopic suture, *ss* sagittal suture..

Table 1 Master genes expressed in developing calvarial suture

Gene	*Osteogenic front*	*Sutural mesenchyme*	*Dura*	*References*
Bmp2/Bmp4/Bmp7	+		+	(9)
Fgf1			+	(4)
Fgf2	+	+	+	(76), (89)
Fgfr1/Fgfr3	+			(77), (91)
Fgfr2(IIIb)	+			(77), (4)
Msx2	+	+	+	(67), (9)
Cbfa1/Runx2	+	+		(90), (89)
Twist		+		(76)

Insights into the molecular basis of suture formation have largely come from identification of mutations in genes responsible for different CS syndromes. CS has different causes and is genetically heterogeneous. It is often associated with additional birth defects, such as hearing loss or limb malformations. The overall frequency of CS is estimated at 1 to 2000–3000 live births. Primary or isolated CS includes single-, or multiple-suture synostosis, i.e. coronal synostosis, or coronal and sagittal synostosis. In secondary CS, a known disorder results in the synostosis. Conditions with secondary CS also include a number of teratogens that are associated with occasional cases of CS (Table 2) (10). During the last decades, a number of environmental risk factors for CS have been documented (11), and identification of genes involved in CS syndromes has revealed important insights into the key molecules and their specific roles in calvarial suture biology. The list of genes, which is currently growing at a good pace, includes those coding for the different fibroblast growth factor receptors, *FGFR1*, *FGFR2*, and *FGFR3*, which are cell membrane receptor kinases binding to their principal ligands, fibroblast growth factors (Fgf). Also genes, such as *MSX2* and *TWIST*, encoding transcription factors, and *EFBN1*, coding for a tyrosine kinase ligand of ephrin receptors, may cause syndromic CS (12) (Table 3). Recent observations in normal and transgenic mice suggest the possible involvement of other candidate genes in human CS, underlining the great genetic heterogeneity of the condition.

Signaling pathways involved in suture biology and dental development

The development and patterning of vertebrate organs and tissues is controlled by a number of regulatory genes (or master genes) that share similar molecular networks. The majority of these genes are associated with the signaling pathways transmitting interactions between cells and tissues. They include genes encoding the actual signals as well as their receptors, mediators of signaling in the cytoplasm, and transcription factors that regulate gene expression in the nucleus. The Fgfs, bone morphogenetic proteins (Bmps), sonic hedgehog (Shh), and wingless (Wnt) protein families and their transcription factors (Msx1, Msx2, Twist, Axin 2, and Runx2/Cfba1) have been identified as key players in the epithelial–mesenchymal signaling networks driving the development of the cranial–oral–facial tissues, including teeth and sutures (13). Failure of one of these signaling proteins can result in disruption of several signaling loops, and, depending on the molecule and its timing of required expression, may produce anomalies in different craniofacial structures.

Fibroblast growth factors

Fibroblast growth factor signaling plays a critical role in craniofacial and dental development. Fgf signaling is inductive for neural crest formation (14–16), and later on during development, Fgf signaling is present in both the epithelia and mesenchyme where it mediates the epithelial–mesenchymal interaction. The Fgfs (Fgf3, -8, -9, -10, -15, and -17) are expressed in restricted domains in the cranium and the facial primordia (17, 18), with, e.g. Fgf8 being particularly important in both early craniofacial and dental patterning and growth (13, 19).

Table 2 Conditions with secondary or occasional craniosynostosis[a]

Type	*Condition*	*Oral/dental characteristics*[b]
Metabolic disorders	Hyperthyroidism	Enamel defects, small teeth
	Rickets (various forms)	Enlarged pulp chambers, enamel and dentin defects
Mucopolysaccharoidoses	Hurler syndrome	Abnormal tooth form, delayed eruption, odontogenic cysts
	Morquio syndrome	Enamel and dentin defects
	β-Glucuronidase deficiency	Broad alveolar ridges
	Mucolipidosis type III	Mandibular prognatism
Hematological disorders	Thalassemia	Enamel defects, discoloration
	Sickle cell anemia	Enamel and dentin defects, delayed eruption
	Polycythemia vera	None
	Congenital hemolytic icterus	Enamel defects, discoloration (primary dentition)
Teratogens	Diphenylhydantoin, retinoids, valproate, aminopterin, fluconazole, cyclophosphamide	Oligodontia, abnormal tooth form, microdontia, enamel and dentin defects, discoloration
Malformations	Holoprosencephaly	Single upper central incisor
	Microcephaly	None
	Encephalocele	None
Iatrogenic disorders	Hydrocephalus with shunt	None

[a]Adapted after Cohen and McLean (10).
[b]Occurring with variable incidence and expression.

Table 3 Genes involved in craniosynostosis (CS) syndromes

Gene	*Syndrome*	*Main characteristics*	*OMIM entry*[a]
Fgfr1	Pfeiffer	Broad first fingers, hypertelorism	101600
Fgfr2	Apert	Fusion of digits, midface hypoplasia	101200
	Crouzon	Midface hypoplasia, ocular proptosis	123500
	Pfeiffer	Broad first fingers, hypertelorism	101600
	Beare-Stevenson	Midface hypoplasia, corrugated skin	123790
	Jackson-Weiss	Midface hypoplasia, foot anomalies	123150
	Craniofacial-skeletal-dermatological dysplasia	Broad thumbs/toes, severe scoliosis, acanthosis nigricans	–
Fgfr3	Crouzon	Midface hypoplasia, ocular proptosis, acanthosis nigricans	134934[b]
	Muenke CS	Digital defects, hearing loss, mental delay	602849
Msx2	Boston-type CS	Cloverleaf skull, hyperopia	604757
Twist	Saethre-Chotzen	Syndactyly	101400
EFNB1	Craniofrontonasal syndrome	Hypertelorism, digital defects	304110

[a]Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/Omim (last accessed January 2007).
[b]Allelic variant 0.0011.

Loss of Fgf8 function in the ectoderm of the first branchial arch results in an almost complete loss of the derived skeletal structures (20) and agenesis of both the mandibular and maxillary molars (21, 22).

In the developing craniofacial skeleton, Fgf signaling is present in both endochondral and intramembraneous bones and regulates their development and growth (9, 23, 24). Fgfr1, Fgfr2 and Fgfr3, three Fgf receptor isoforms, are broadly expressed in the facial primordia (17, 25), and play important roles in advancing skeletogenesis by regulating osteoblast (12, 26–29) and chondroblast (12, 30–32) differentiation. Mutations in *FGFR1*, -2, and -3, the genes encoding the respective receptors, have been described as causing both syndromic and non-syndromic forms of CS (Table 3). The majority of these are mis-sense mutations, with a smaller number of in-frame insertions and deletions (25). The same mutation in a different gene but at a similar position can cause a similar but phenotypically distinct phenotype. For instance, ProArg substitution (position 252/253) in the linker region between the second and third immunoglobulin-like loops can cause Pfeiffer syndrome in *FGFR1*, Apert syndrome in *FGFR2*, and Muenke CS in *FGFR3*. Furthermore, there is evidence that the same syndrome may be caused by mutations in different genes (33, 34). These mutations are gain-of-function mutations resulting in reduced ligand dissociation, increased affinity for Fgf ligands and/or ectopic expression of Fgf isoforms, leading to increased calvarial cell differentiation and bone matrix formation (12, 25, 35, 37, 38).

Fibroblast growth factors are also mitogenic to dental tissues except for the enamel knot, which lacks receptor expression (36). Failure of Fgfs [Fgf4, -8, -9, and -20 in the epithelium (39) and Fgf3, -7, and -10 in the mesenchyme (36)] and their respective receptors required as targets or in feedback mechanisms during early tooth development, may result in dental agenesis (13, 40). The Fgf signal also directs the growth and folding of the dental epithelium; transgenic mice lacking functional Fgfr2b isoforms do not develop teeth beyond the bud stage and show mild hypodontia (41). Furthermore, Fgf signal induces expression of Msx2 and Runx2 in the dental mesenchyme during the early developing stage, which is critical for tooth formation (42).

Bone morphogenetic proteins

The Bmp family represents another important family of signaling molecules that are active in a broad range of developmental processes, including mesoderm induction, odontogenesis, limb development, and skeletal patterning (18, 43–46). In those processes, the Bmp signaling pathway interacts with Fgf, Shh, and Wnt signaling pathways and regulates the expression of several critical transcription factors, such as Runx2/Cbfa1, Msx1, and Msx2 (47–50). Although no mutations in the genes encoding the different Bmp isoforms have yet been found in human CS, it has been suggested that Bmp signaling is crucial in suture formation of the human bones. Both Bmp2 and Bmp4 are present in the osteogenic fronts of cranial sutures (51), and high expression of Bmp2 was observed in the mesenchyme during palatal fusion (18). Deficiency of Bmp signaling in mouse neural crest cells shows multiple defects in craniofacial skeleton, such as cleft palate and a hypotrophic mandible (52). Bmp signaling was also found to induce and upregulate the expression of homeobox gene *DLX5* (53), a critical factor for the development of both the craniofacial skeleton (54, 55) and teeth (13, 56).

From early tooth initiation to crown morphogenesis, the Bmp/Msx signaling loop mediates reciprocal interactions between the epithelium and the mesenchyme (57). Failure of Bmps [Bmp2, -4, and -7 in the epithelium and Bmp2–Bmp7 in the mesenchyme (58)], and their respective receptors required as targets or in feedback mechanisms during early tooth development, may result in dental agenesis (13, 40).

Muscle segment homeobox-containing (Msx) transcription factors

Msx1 and Msx2 are transcription factors expressed in overlapping patterns at multiple sites of tissue interactions during vertebrate development (59). In particular, they have been associated with epithelial–mesenchymal interactions during craniofacial/dental development, as targets of Bmp and Fgf signaling (60).

For instance, Bmp2 and Bmp4 induce the upregulation of Msx gene expression in tooth explants as well as in rhombomeres (44, 61, 62), and several Fgfs induce the expression of Msx1 in dental mesenchyme (39). Msx1 and Msx2 have also been associated with the differentiation of neural crest-derived intramembraneous bones in the skull (63).

Three different loss-of-function mutations in the *MSX2* gene have been reported to cause CS, resulting in decreased parietal ossification (64). These are in contrast to the gain-of-function mutation for Boston-type CS, which is caused by a mis-sense mutation Pro148His (substitution of histidine for proline at amino acid position 7 of the homeodomain), resulting in an increased sutural ossification (65). *msx2*-deficient mice exhibit defective proliferation of osteoprogenitors in the developing calvaria and have defects of skull ossification and persistent interparietal foramina (66). Transgenic mice overexpressing the *MSX2* mutation appear to have different phenotypes depending on which promotor is used, varying from precocious bone formation with accelerated suture closure (67) to craniofacial defects with aplasia of the interparietal bone (68).

Msx1 and Msx2 also determine the position and shape of teeth (so-called field model, linking patterning of tooth type to spatial expression of homeobox genes in the dental mesenchyme). Mutations in *MSX1* (42, 60, 62, 69) and *MSX2* (66) in mice may produce moderate to severe hypodontia in association with defects of ectodermal organ formation (e.g. hair, nails, and sweat glands). In humans, about seven different *MSX1* mutations have been identified, resulting in autosomal dominant hypodontia (70, 71) with or without orofacial clefting (72, 73), or in association with small and conical teeth (Witkop syndrome) (74). No specific oral anomalies have yet been documented in human *MSX2* mutation.

Twist transcription factor

Twist is a helix–loop–helix transcription factor that plays a role in cranial neural tube morphogenesis (75). Twist is expressed very early as a negative regulator of osteoblast differentiation and its expression decreases with maturity, i.e. Twist is expressed by osteoprogenitors but not by mature osteoblasts (76, 77). Fgf2/Fgf4 and Twist exhibit overlapping expression patterns, both being intensively expressed in the mid-sutural mesenchyme between the calvarial bones (76) and in the mesenchyme during early tooth initiation (79). It was shown recently that Twist is one of the integrating parts of the Shh, Fgf, Bmp, and Msx2 signaling pathways mediating a number of common effects at the cellular level during development of, e.g. the cranial structures (78), limbs (80), the palate, and teeth (79).

Mutations in the *TWIST* gene cause Saethre–Chotzen syndrome (75, 81, 82), resulting from a loss-of-function mechanism (76). In contrast to *FGFR* and *MSX2* mutations, these are mostly deletions or nonsense mutations. Twist knockout mice die before osteogenesis has started, with a failure of the cranial neural folds to fuse and defects in the head mesenchyme (83). Experimental animal studies further support the idea that Fgf signaling may lie both up- and downstream of Twist (9, 76, 77, 81, 84).

Other transcription factors and receptor ligands

Other candidate genes for human CS are *AXIN1*, *AXIN2*, and *RUNX2*. Axin1 and its homologue Axin2 (also known as conductin or Axil) are negative regulators of the canonical Wnt pathway that suppress signal transduction by promoting degradation of β-catenin. The Wnt signaling pathway is one of the major pathways regulating cell differentiation and proliferation (85, 86), which is required from early tooth germ formation throughout tooth development. Targeted disruption of Axin2, which is expressed in the osteogenic fronts and periosteum of developing sutures, in mice induces malformations of skull structures resembling CS in humans (87). Recently, a nonsense mutation in *AXIN2* (Arg656Stop) was found to cause familial oligodontia and colorectal cancer in a Finnish family, and a frameshift mutation (1994–1995insG) in the same gene was identified in a single case with severe dental agenesis (88). These findings provide strong evidence for the importance of Wnt signaling for the development of teeth in humans.

Runx2 (previously known as Cbfa1 or Aml3), a key transcription factor in osteoblast differentiation, was recently shown to be a powerful mediator of the expression of Bmp2 in response to Fgf stimulation in cranial bone development in mice (89). In previous animal studies, Runx2 expression was observed in the critical area of cranial suture closure in parietal bones, osteogenic fronts, and sutural mesenchyme (90, 91). Recently, it was demonstrated that Runx2 mediates the function of Fgf during tooth morphogenesis (58), in several instances resulting in arrested development of all tooth primordia at the cap/bell stage (92). In humans, heterozygous *RUNX2* mutations are causing cleidocranial dysplasia, occasionally presenting with supernumerary teeth (88, 89, 93, 94).

Ephrin-b1 is a tyrosine kinase ligand for ephrin receptors that is crucial to the epithelial–mesenchymal interactions that regulate both cranial/oral morphogenesis. Over 20 mutations causing craniofrontonasal syndrome have been described in *EFNB1*, the gene encoding ephrin-b1. This is an X-linked disorder whose main clinical manifestations include coronal CS, frontonasal dysplasia and digital defects (95).

Dental clinics of sydromic and non-syndromic craniosynostosis

Little has been reported on oral features of patients with CS. A characteristic trapezoidal-shaped mouth and byzantine-arch shaped palate has been designated as a general trait of Apert syndrome (96). Additional oral anomalies of this condition, which is caused by mutations in *FGFR2*, include clefting of the soft palate or bifid uvula (75% of cases), severely delayed and ectopic eruption of teeth (96–98), severe malocclusion with mandibular overjet and crowding of teeth (96, 97, 99). Severe midface

hypoplasia with Angle Class III malocclusion and a narrow maxillary arch have been reported in Crouzon syndrome (100). Multiple natal teeth have been found in a single instance with Pfeiffer syndrome (mutation in either *FGFR1* or *FGFR2*) (101). Features indicative of abnormal tooth development and/or morphogenesis include shovel-shaped incisors in Apert syndrome (96), whereas broad teeth with bulbous crowns, thin and narrow tapering roots, and diffuse pulp stones in all posterior teeth have been reported in a single case of Saethre–Chotzen syndrome (mutation in *TWIST*) (102).

From our clinical experience, however, it is clear that also other dental anomalies may present in patients with syndromic or non-syndromic CS. We report here agenesis of a lower permanent central incisor, moderate talon cusps of the upper permanent central incisors, and moderate taurodontism (hypodont type) of the permanent molars in a Caucasian girl with Apert syndrome (Fig. 2). Unilateral CS was seen in association with agenesis of all lower permanent incisors, microdontia, and taurodontism of both dentitions, odontoma-like malformation of the upper permanent central incisors,

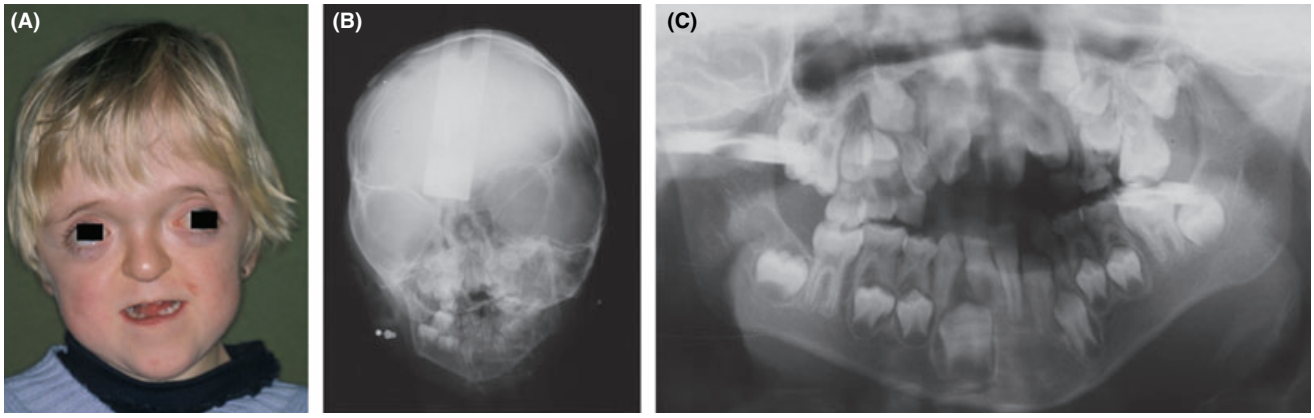

Figure 2 (A) Caucasian girl with Apert syndrome. (B) Decreased growth in the plane of the coronal sutures is compensated for by an increased growth in skull breadth (antero–posterior cephalograph). (C) Panoramic radiograph displaying a novel and unusual association of dental features, i.e. agenesis of a lower permanent incisor, moderate talon cusps of the upper permanent incisors, and moderate taurodontism of the permanent molars.

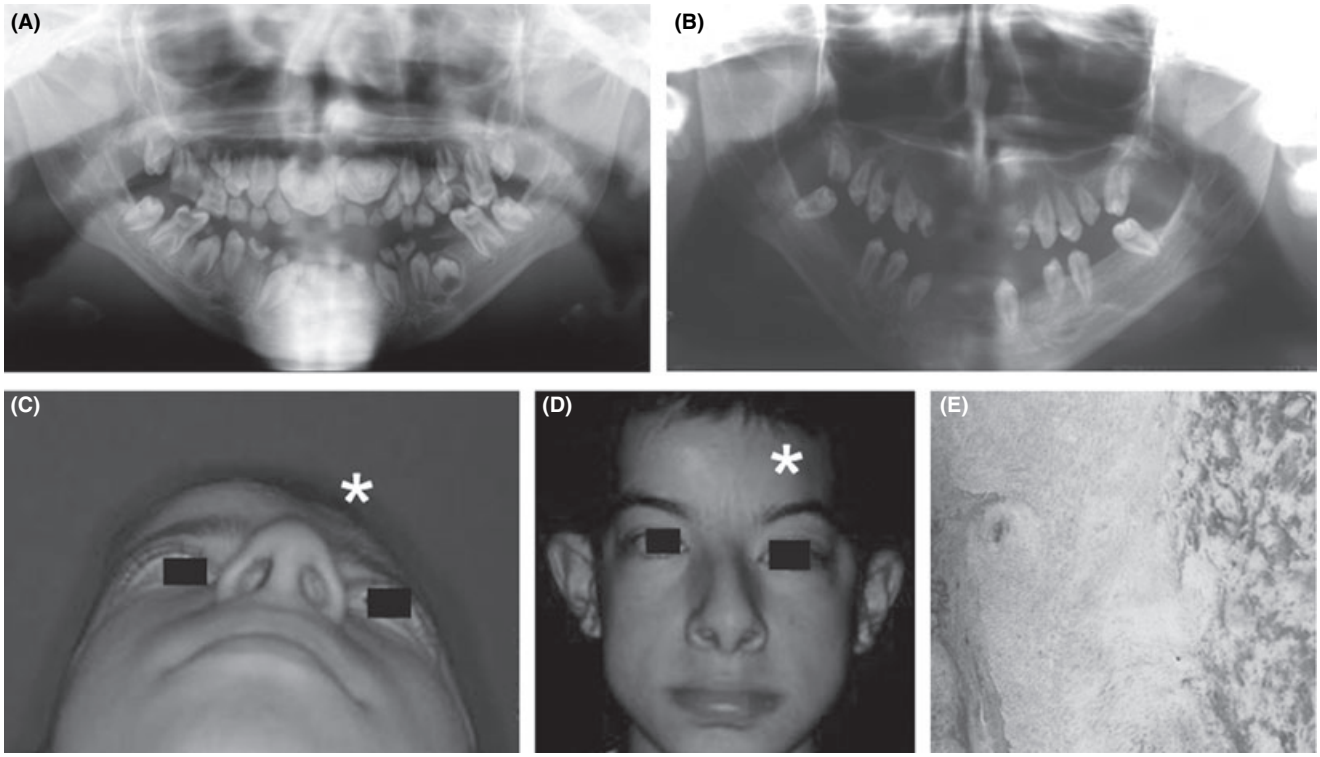

Figure 3 (A, B) Panoramic radiographs of a boy with undiagnosed unilateral (*) craniosynostosis (C, D) in association with agenesis of the lower permanent incisors, microdontia and taurodontism of both dentitions, odontoma-like malformation of the upper central incisors, and multiple dens invaginatus. (E) Histologic appearances of circumpulpal dentin showing abnormal organization and structure of dentinal tubules (dentin dysplasia). 100 ×.

multiple dens invaginatus, and dentin dysplasia in a Turkish boy of consanguineous parents (Fig. 3A–C). Taurodontism, microdontia, and dental agenesis, either occurring combined or as a solitary oral trait, have been reported in a large number of syndromic and non-syndromic conditions, and have been accorded important diagnostic weight (103). Although a genetic analysis is still ongoing, the present findings strongly suggest that the genes and transcription factors that cause CS may also play key roles in the development and morphogenesis of the teeth. Further advances in the molecular research of tooth/suture development and future establishment of novel genotype–phenotype correlations may contribute to understanding the complex interaction between these genes and their related pathways.

Conclusion

The list of genes that are involved in CS includes those coding for *FGFR1*, *FGFR2*, and *FGFR3* or a specific ligand of ephrin receptors (*EFBN1*), but also genes encoding transcription factors, such as *MSX2* and *TWIST*. Most of these genes are also involved in odontogenesis, explaining the occurrence of tooth anomalies in many of the CS syndromes. Further analyses of genotype–phenotype correlations in patients with syndromal CS will give us more insight into the developmental role of the *MSX2*, *FGFR*s, and *TWIST* genes. However, more genes involved in regulating both suture maintenance and closure as well as tooth development are expected to be unraveled in the near future. The identification of these new genes will add to our understanding of human development disorders in the craniofacial region.

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