Genes Contributing in Cleft Lip and Cleft Palate: A Literature Review

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Abstract

Failure of the palatal shelves with the primary palate or with each other results in cleft palate, with varying degrees of disability. Orofacial clefts are common birth defects of complex etiology involving the interplay of genetic predisposition and environmental exposures. Both genetic and environmental factors playing an important and influential role. Ethnic and sex differences in the prevalence of orofacial clefting provide further support of a genetic component to these disorders. The researches in genetics subject have shown several genes that cause orofacial cleft, it can be the single gene disorder or alteration of the chromosome.

Keywords: Cleft palate, cleft lip, genetic, gene, chromosome.


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Introduction

Orofacial clefts represents a large proportion of birth defects and have a multifactorial cause with the worldwide frequency is 1 in 700 live births.¹,² There are many possible etiologies including single-gene disorders, chromosome aberrations, exposure to teratogens, and sporadic conditions of unknown cause.² Both genetic and environmental factors playing an important and influential role. Primary evidence for a genetic role has been available for some years; the sibling risk for cleft lip and palate is approximately 30 times higher than that for the normal population prevalence.³

Orofacial clefts can be subdivided into those that affect the lip and palate and those that impact the palate only.¹ Approximately 30% of all clefts are associated with one of more than 400 described syndromes, while the remaining 70% are isolated defects.⁴ The clinical manifestations of these defects are diverse, ranging from isolated clefts of the lip to complete bilateral clefts of the lip, alveolus and palate.³ Children with cleft lip and palate can face problems during feeding, show speech and hearing difficulties, and to varying degrees suffer from disturbances in the normal facial and dental development.⁴ Children with these disorders require surgical intervention, starting from the first year of their life and potentially for many years afterwards, plus also requiring nutritional, dental, speech, medical, and behavioral follow-up assistance.¹

The disorder has a complex inheritance pattern with no clear mode of inheritance and reduced penetrance, with a positive family history for clefting in approximately one third of patients. To date, 13 genome-wide scans for non syndromic cleft lip with or without cleft palate (NSCL/P) have been carried out; a meta-analysis has been performed on the 6 published and 7 ongoing genome scans, revealing multiple loci. Many mouse mutants with isolated clefts have also been described where the specific gene has been identified. These genes have also contributed to the set of candidates that have been considered for genetic studies.¹ This literature review is about alteration of some genes that cause orofacial cleft.

LITERATURE REVIEW

Etiology of Cleft

Oral-facial clefts are common birth defects of complex etiology involving the interplay of genetic predisposition and environmental exposures.⁵ Most orofacial clefts are caused by the interaction between genetic and environmental factors. Genetic factors create susceptibility for clefts, and when environmental...
factors interact with a genetically susceptible genotype, a cleft develops during an early stage of development. The study of cleft lip and palate is further complicated by the fact that a combination of genetic and environmental factors contributes to its etiology.

Most orofacial clefts are believed to be nonsyndromic, with the rarer syndromic cases resulting from factors such as chromosomal abnormalities, characterized Mendelian single-gene syndromes and teratogenic effects. The high rates of familial occurrences, recurrence risks, and elevated concordance rates in monozygotic twins provide evidence for a strong genetic component in NSCL/P. The disorder has a complex inheritance pattern with no clear mode of inheritance, with a positive family history for clefting in approximately one third of patients. Defects of growth factors of their receptors have been shown to cause isolated (non-syndromic) or syndromic oral clefts in humans. For the development of the head a group of cells with stem cell properties, called cranial neural crest (CNC) cells, are of particular importance. These cells delaminate from the lateral ridges of the neural plate (which will form the neural tube) and then emigrate towards the developing branchial arches. The proliferation of the CNC cells is responsible for the budding of tissues around the future oral cavity. Continuous neural crest stem cell proliferation leads to the formation of a single frontonasal process and of pairs of maxillary and mandibular processes. As development advances, all these processes join and fuse giving rise to the completed face. Thereafter, in both the maxillary and mandibular processes teeth will form.

Orofacial and dental disorders result when mutations in the sequence of either a gene or a group of genes cause alterations to the expression or function of the encoded protein(s). Gene mutations, but also environmental factors, can affect the expression of genes or interfere with the normal function of their protein products.

Mutations in single genes and chromosomal abnormalities are the most common mechanisms underlying syndromic cleft lip with or without palate. The Online Mendelian Inheritance in Man database (OMIM) describes more than 500 syndromes with cleft lip with or without palate as part of the phenotype. Furthermore, several cases of trisomy of chromosomes 13, 18, and 21 associated with cleft lip with or without palate were described, as well as partial deletions and duplications of other chromosomes. These findings suggest that there may be several genomic regions containing loci which, in excess or in insufficiency, may lead to cleft lip with or without palate.

Cleft lip with or without palate can be caused by both exogenous and genetic factors. However, the precise etiology and pathogenesis remain obscure. Some environmental factors are known to cause cleft lip and/or palate, including steroids, anticonvulsants, retinoids, and rubella virus. Although many teratogenic substances have been discovered, the incidence of cleft lip/or palate has not decreased significantly. Maternal cigarette smoking leading to embryonic hypoxia, has been associated with an increased incidence of non-syndromic cleft lip and palate, and also nutritional status of pregnant mothers.

**Prevalence of Cleft**

Occurrence estimates range between 1/300 and 1/2500 births for cleft lip and palate and approximately 1/500 births for cleft palate only. Ethnic and sex differences in the prevalence of orofacial clefting provide further support of a genetic component to these disorders. It is well established that there is substantial population to population variation in the rates of orofacial clefting at birth on the basis of geographic origin, with Asian populations having the highest prevalence of clefting at birth (1/500 births) and African populations having the lowest (1/2500 births), with Caucasians being intermediate (1/1000 births). The cleft lip with or without cleft palate is more common, affecting 1-2 in 1000 births and presenting considerable differences in prevalence, with Native Americans and Asians showing the highest rate and Africans the lowest. The cleft palate only phenotype is less common, with a prevalence of approximately one in 1500-2000 births in most ethnic backgrounds.

**Cleft Classification**

Oro-facial clefts can be further classified as non-syndromic (isolated) or syndromic, based on the presence of other structural anomalies. It is generally accepted that cleft lip with or without cleft palate and cleft palate only are genetically distinct phenotypes. Broadly speaking, approximately 70% of cleft lip with or without cleft palate cases are non-syndromic, occurring as an
isolated condition unassociated with any other recognizable anomalies, while the remaining 30% of syndromic cases are present in association with deficits or stuctural abnormalities occurring outside the region of the cleft.\(^3\)

With all clinically recognizable syndromes, cases of syndromic cleft lip and palate or cleft palate can be broadly subdivided into:\(^1\):

1. Those that occur as part of a characterized Mendelian disorder (resulting from a single gene defect)
2. Those arising from structural abnormalities of the chromosomes, syndromes associated with known teratogens
3. Those whose causation remains obscure and are therefore currently uncharacterized.

**Syndromic CLP**

Single gene disorder are the result of specific gene mutations on the autosomes or sex chromosomes and are inherited following Mendelian rules (autosomal dominant or recessive and X-linked dominant or recessive, respectively) with varying levels of penetrance and expressivity. Cytogenesis, or the study of chromosomal abnormalities, has revealed a wide range of physical chromosomal alterations, including variaions in both number and structur, which can cause perturbarions of gene function and congenital malformations.\(^3\) One of the most common human autosomal dominant disorders associated with cleft lip and palate is van der Woude syndrome (VWS), which contributes to around 1-2 % of syndromic cleft lip and palate cases. VWS is a single gene disorder with an autosomal dominant pattern of inheritance. This condition is associated with highly characteristic pitting of the lower lip mucosa and cleft lip and palate, fistulae on the lower lip, and hypodontia. Kondo et al. showed that missense and nonsense mutations in interferon regulatory factor 6 (IRF6) were responsible for the majority of VWS cases.\(^3,7\)

**Syndromic Cleft Palate (CP)\(^3\)**

X-linked CP (CPX) is a rare semi-dominant X-linked disorder characterized by CP and ankyloglossia. The causative gene was originally localized to chromosome Xq21, but recently Braybrook et al succeeded in pinpointing a variety of mutations in the TBX22 gene in individuals from a number of separate families, as being responsible for CPX. TBX22 is also expressed in the developing palate and potential target genes for this transcription factor have been shown to include members of the fibroblast growth factor and TGFβ families, which are known to encode signalling molecules heavily implicated in early craniofacial development. TBX22 is the first gene to be identified for a major CP syndrome and is particularly significant in view of the fact that targeted disruption of Tbx1 in the mouse results in a wide range of developmental anomalies which encompass almost all of the common features of the DiGeorge/ velocardiofacial syndromes. These syndromes, which arise as manifestations of deletions in chromosome 22q11, are taught to be caused by a failure in function or migration of neural crest cells and predominantly affect derivatives of the third and fourth branchial arches and their associated pharyngeal pouches, but affected individuals can also have CP.

**Non-syndromic clefting\(^3\)**

The first report of such analysis suggested possible linkage between cleft lip and palate (CLP) and the blood clotting factor XIII gene (F13A) on chromosome 6p. Linkage has been reported for CLP to endothelin-1 (ET1), which encodes a vasactive peptide expressed in vascular endothelial cells. ET1 is involved in the regulation of blood pressure. They exhibit craniofacial defects including a marked reduction in tongue size, microagnathia and cleft palate (CP) in mice. A more recent GWAS in families with multiple cases of non-syndromic CLP concluded that no single major CLP locus exists and a multifactorial model was the most likely explanation of the genetic component of this disorder.

**Genes Contributing in Cleft**

1. **Transforming Growth Factor (TGF)**
   a. **Transforming Growth Factor Beta 2 (TGFβ2)**

The Transforming Growth Factor Beta (TGFβ) family of growth factors plays multiple and critical roles during all stages of tooth development.\(^4\) TGFβ2 is a member of the highly conserved TGFβ super-gene family and located at chromosome 1q41. TGFβ2 is involved in palatogenesis along with other TGFβ family isoforms. Inactivation of a TGFβ receptor gene (TGFβ2) in mouse neural crest cells resulted in cleft palate and abnormalities in the formation of the cranium.\(^8\)
b. TGFβ3

TGFβ3 is one of the strongest candidate gene for cleft lip and palate in humans. TGFβ3 has a broad spectrum of biological activities and is known to induce palatal fusion especially secondary palatal development. Inactivation of the TGFβ3 gene in mice results in bilateral cleft of the secondary palate due to the non-fusion of the palatal shelf processes. TGFβ3 is located at chromosome 14q24. The role of TGFβ3 in clefts has emerged from animal studies which indicate that TGFβ3 play a crucial role in secondary palate development. In humans, TGFβ3 is associated with non-syndromic CL/P in different populations.  

c. Transforming growth factor-alpha (TGFα)

The gene is located at chromosome 2p13. TGFα have been shown to be present in the regulation of palate development and are present at high levels in the MEE of palatal shelves. Previous genetic studies have demonstrated a significant association between transforming growth factor-alpha(TGFα) and CL/P. In contrast, Lidral et al. and Passos-Bueno et al. showed no association between TGFA with CL/P in non-Caucasian population.  

2. Interferon Regulatory Factor 6 (IRF6) Gene

Disease-causing mutations in the IRF 6 gene have been identified in Van der Woude syndrome, a single-gene Mendelian disorder that includes presentation of a cleft lip or cleft palate phenotype, this gene maps to 1q32. Van der Woude syndrome is the most common syndromic form of oral clefts and has an autosomal dominant inheritance pattern. Mutations in the interferon regulatory factor 6 (IRF6) gene are responsible for approximately 70% of VWS case, while the other 30% of cases have unknown cases.  

IRF6 is strongly expressed in the ectoderm covering the developing facial primordia. Mice deficient for both Irf6 alleles develop abnormally thick skin with severe limb and craniofacial abnormalities, including cleft of the secondary palate. The lack of a normally stratified epidermis in Irf6-null mice, due to a defect in keratinocyte proliferation and differentiation, confirms an important role for Irf6 in epidermal development. Significant associations between IRG6 and NSCL/P have been reported in multiple populations. In a follow-up study, a common etiologic variant (rs642961) in a highly conserved IRF6 enhance element was responsible for 18% of cleft lip occurrence in Northern European populations (Rahimov et al., 2008). IRF6 and TGFA gene belong to transcription factors and growth factors respectively. IRF6 contains a helix-turn-helix DNA-binding motif and is thought to play an important role in NSCL/P as mutations have been identified in this gene in Van der Woude syndrome, which is a dominant disorder sharing some symptoms with NSCL/P. There were a SNPs loci found being overtransmitted in the study of Zuccher and colleagues, rs2235375. Scapoli et al obtained strong evidence that linkage disequilibrium existed between rs2235375 and NSCL/P in an Italian population. However the same evidence was not found between rs2235375 and NScl/P in the current research. Since the etiology of NSCL/P is complex, the different results might be due to ethnic and/or environment variances between the Chinese population and Italian population, or the small sample size. In a larger context this study provides evidence of the IRF6 gene contributing to the formation of NSCL/P in southeast China. This study attempts to screen IRG6 among cleft families with at least two affected members and also single cases with CLO that have been classified as nonsyndromic.  

3. Axis Inhibition Protein 2 (AXIN2) Gene

WNT signaling has been implicated in regulation of diverse developmental events, as well as in aberrations of cell homeostasis that may lead to cancer. Experiments in mice have also shown that SHH and WNT signals are necessary for normal tooth development. It is thought that integrated networks of signaling pathways are the key regulators of tooth morphogenesis.  

Members of the WNT gene family have been associated with clefts in humans and mice. The AXIN2 (axis inhibition protein 2) gene is a negative regulator of the WNT pathway due to its role in the degradation of β-catenin. Mutations in AXIN2 have been associated with increased susceptibility to cancer and in some cases have been detected segregating together with familial tooth agenesis. The mutations of AXIN2 are
responsible for the severe oligodontia of the patients, showing that AXIN2 function is essential for the development of dentition in humans. Letra, et al. found Axin2 and Irf6 proteins co-localizing particularly in the developing secondary palate, nasal, oral, and eye epithelial.

4. Poliovirus Receptor-Related 1 (PVRL1) Gene

Poliovirus receptor related gene 1 (PVRL1) which is located on chromosome 11 was shown to have a significant association with non-syndromic CL/P in northern Venezuela. Rare mutations in sporadic cases and a statistically significant association between a common coding variant (G361V) in PVRL1 and NS CL/P were found in multiple population.

5. Cysteine-rich secretory protein containing LCCL domain 2 (CRISPLD2) Gene

CRISPLD 2 (cysteine-rich secretory protein containing LCCL domain 2) gene is located on chromosome 16q24.1 and has been recently associated with nonsyndromic CL/P in US Caucasian and Hispanic populations. Moreover, the authors detected CRISPLD2 expression in the mandible, palate, and nasopharynx regions during craniofacial development at E13.5-E17.5 and have suggested CRISPLD2 as a novel candidate gene for the etiology of NSCL(P).

6. Forkhead Box E1 (FOXE1) Gene

FOXE1 is a member of the forkhead/winged helix domain transcription factor family whose members are primarily involved in embryonic development. Targeted disruption of mouse Foxe1 results in cleft palate and thyroid malformation. Loss-of-function mutations within its forkhead DNA-binding domain cause Bamforth-Lazarus syndrome, which is characterized by thyroid agenesis, choanal atresia, bifid epiglottis, spiky hair, and cleft palate (Clifton-Bligh et al., 1998; Castanet et al., 2002). Subsequently, significant associations were reported between FOXE1 and NS CL/P in multiple populations, although no common coding variants were identified.

7. Murine Muscle-segment Homeobox 1/Msh Homeobox 1 (MSX1) Gene

MSX1 encodes a transcription factor and also demonstrates a regionally restricted expression pattern in the developing murine craniofacial complex, including the palate. Mice lacking Msx1 function exhibit a variety of craniofacial defects including clefting of the secondary palate, complete arrest of tooth development at the bud stage and anomalies of several facial bones. A heterozygous MSX1 nonsense mutation has recently been identified in a three-generation Dutch family exhibiting various combinations of CLP, CP, and selective tooth agenesis. Significant linkage disequilibrium has also been found between CLP and neutral polymorphisms within MSX1 and TGFβ.

8. Sonic Hedgehog (SHH) Gene

Sonic hedgehog (SHH) is the main member of the Hedgehog family which is associated with abnormal orofacial and tooth development. SHH is expressed in the ectoderm of the frontonasal and maxillary processes during development. In humans, mutations of SHH result in holoprosencephaly, demonstrating the crucial role of this growth factor in the development of the face. In the chick model, the transient loss of SHH signalling results in midfacial clefts analogous to the human cleft lip/palate.

9. Methylenetetrahydrofolate Reductase (MTHFR) Gene

Methylenetetrahydrofolate reductase (MTHFR) maps on chromosome 1q36 is a key enzyme in folic acid metabolism. Previous studies in non-syndromic CL/P, the MTHFR C77T genotype in the mother conferred an increased risk of CL/P in their offspring. Similarly Carinci et al. demonstrated a significantly higher mutation frequency of MTHFR in mothers of children with CL/P. Thus, the important of peri-conceptional folate intake were emphasized in these studies and its deficiencies could lead to CL/P.

10. MMPs

During embryonic development, the process of morphogenesis is accompanied by changes in the composition of the extracellular matrix that further allow for cell migration and differentiation, cell-cell interactions, and tissue resorption. Matrix metalloproteinases (MMPs) are a family of proteolytic enyzmes that are known to play an important role in these processes because of their ability to collectively degrade all components of the ECM. Previous studies have
suggested MMPS as potential candidate genes for CL/P based on expression patterns and the roles they play in modelling craniofacial tissues during early embryogenesis. Furthermore, they may be implicated in cleft lip/ palate. The MMP family is composed of 23 enzymes that share significant sequence homologies. It is divided into five classes: collagenases, gelatinases, stromelysins, membrane-type MMPS, and others, including a few of the most recently identified MMPS.

MMP-3 shows the most extensive distribution of all MMPS during palatal shelf morphogenesis. MMP-3 has been detected in vivo subjacent to the MEE following contact of the palatal shelves and has been demonstrated to play a role in epithelial-mesenchymal transformation (EMT). Induction of its exression results in cleavage of cadherin, loss of the epithelial phenotype and subsequent stable conversion of epithelio into mesenchyme. Constantly high levels of active MMP-3 were observed during the latter stages of palatogenesis and may represent an important stimulus for EMT.

11. Dihydrofolate reductase (DHFR) Gene

The role of folate in risk reduction of orofacial clefts has been supported by several studies. Folic acid is a water soluble B-vitamin that plays a crucial role in embryonic development. In fact, it is essential for DNA stability maintenance, being involved in DNA synthesis, repair, and methylation. Alterations involving genes responsible for each step of the folate pathway can lead to aberrations in organogenesis that result in congenital malformations such as neural tube defects or oral clefts.

Alteration of folate metabolism appears to modify the risk of at least two congenital malformations: neural tube defects (NTDs) and orofacial clefts (OFC). These embryogenesis anomalies occur almost at the same time of development and both involve the embryo midline structures. This study is a family-based-association study to test if DHFR polymorphisms could influence the risk of NS-CL/P.

12. Fibroblast Growth Factor (FGF) Gene

Genes in the fibroblast growth factor (FGF) signaling pathway are excellent candidate genes for NSCL/P. This study tested markers in 10 FGF and FGF receptor (FGFR) genes for their potential role in controlling risk to NSCL/P using 297 case-parent trios from the populations. Wang H, et al. collected peripheral blood and all subjects were classified as having an isolated, nonsyndromic iCL(P). Single nucleotide polymorphisms (SNPs) were selected in 10 FGF/FGFR genes (including FGFBP1, FGF2, FGF10, FGF18, FGFR1, FGFR2, FGF19, FGF4, FGFR3, and FGFR9). 111 markers in 10FGF/FGFR genes using 297 case-parent trios collected from an international study, SNPs in seven of these genes gave some evidence of linkage and association with unobserved casual variants for iCL(P). Genes in the FGF/FGFR pathway are considered good candidates for iCL(P) because they play important roles in craniofacial development and several of them (FGFR1, FGFR2, and FGFR10) control Mendelian malformation syndromes that can include oral clefts as a hallmark feature. Mammalian fibroblast growth factors (FGFs) (FGF1-FGFI0 and FGF16-FGF23) control multiple developmental processes including craniofacial and palatal development. The biological activities of FGFs are conveted by seven principal FGF receptor tyrosine kinases encoded by four distinct genes (FGFR1-FGFR4).

It has been revealed that coordinated epithelial-mesenchymal interactions are essential during the initial stages of palate development and require an FGF signaling network, which mediates the epithelial-mesenchymal interaction involving in the development of palate and upper lip. In addition, several lines of studies on animal models point to the involvement of FGF-FGFR signaling in the pathogenesis of oral clefting.

13. Gremlin-1 (GREM1)

GREM1 plays a specific role not only in the development of the lip, but also during formation of the soft palate. Analyses of Grem1-deficient mouse models have shown that during embryogenesis Gremlin1 function is crucial for limb development and kidney formation. However, complete loss of Gremlin1 function causes no obvious craniofacial defects. GREM1 acts as a secreted antagonist of various members of the bone morphogenetic protein (BMP) family, which has been shown to play a critical role in both lip and palate development.
14. Special AT-rich sequence-binding protein 2 (SATB2)

The role of SATB2 in craniofacial development has been discussed widely. Strong expression of SATB2 was detected during palatal shelves development with maximum expression in the mesenchyme underlying the medial edge epithelia. Strong evidence emerged from multiple unrelated reports including several patients who had deletion at 2q32-33, a patient who had a translocation with a breakpoint site in the SATB2 gene and another who had SATB2 mutation. The Satb2 is the first cell-type-specific transcription factor that specifically binds nuclear matrix attachment regions (MARs) and is involved in transcriptional regulation and chromatin remodelling. It plays an important role in tooth and craniofacial development.

15. Midline-1 Gene (MID1)25

MID1 is a gene that is responsible for Opitz Syndrome (OS), a congenital disorder affecting primarily midline structures. In fact, OS patients exhibit facial anomalies, such as cleft lip and palate, hypertelorism, and also laryngo–tracheo–esophageal, cardiac, and genitourinary defects. MID1 encodes a protein belonging to the TRIM/RBCC family (TRIM/ RBCC: proteins having a tripartite motif composed of a RING domain, one or two B-box motifs and a coiled-coil region).

Mutations in the MID1 gene have been found in OS-affected individuals and suggest that a loss-of-function mechanism is the basis of OS pathogenesis. The specific cellular function of the MID1 protein product, and its role in the pathogenesis of the disease and its possible involvement in causing NSCLP, are still to be determined.

16. WNT9B26

The wingless-type MMTV integration site family (Wnt) signaling pathway plays an important role in craniofacial development. Wnt signaling genes are conserved among species and are essential to the development of several processes, including face morphogenesis. Studies using animal models have revealed that these genes are expressed in the midface of mice and chickens and that Wnt signaling plays an important role in various aspects of craniofacial development in many species.

Loss of function of WNT genes is associated with defects in the facial region, incomplete penetrance of cleft lip, and defects in kidney morphogenesis in homozygous mice mutants.

17. Paired Box 9 Gene (PAX9)27

Animal models demonstrated that FGFs interact with Pax9 during craniofacial development. Fgf3 expression is strongly affected by combined reduction of Pax9 and Msx1 gene dosages and interestingly our study provides statistical evidence that oral clefts can be the result of FG3 and PAX9 interaction.

Treatment of Cleft

Patients with orofacial clefts require surgical, nutritional, dental, speech, medical and behavioral interventions and impose a substantial emotional and economic burden on the society. Identification of the molecular players and unravelling of the genetic pathways that dictate palatogenesis and lip formation could offer new and exciting possibilities for the prevention and therapy of cleft lip and palate. Stem cell therapy is another future possibility of correcting cleft lip and palate before birth. During the formation of orocafacial structures (5 to 12 weeks of pregnancy) the immature immune system of the foetus allows the introduction of stem cells free of the genetic abnormality. The transplantation and enfragement of suitable stem cells could in principle result in the correction of the malformation. Stem cell technology combined with tissue engineering could also provide solutions for improvements in the treatment of oral clefts in children.

When surgically correcting oral clefts, the surgeon frequently faces the problem of tissue shortage. Currently, intense research is under way for the isolation of suitable stem cells from amniotic fluid and adult tissues, including the dental pulp, which could be potentially used to treat orofacial abnormalities. Such programmed cells can be seeded on suitably engineered scaffolds to regenerate an appropriate craniofacial tissue of the desired shape and dimensions.

Conclusions

1. Oral-facial clefts are common birth defects and the etiology is complex, involving the genetic factor and environmental exposures.
2. There are many genes that had considered to be the etiology of orofacial clefts.

3. Orofacial cleft case still needs more GWAS to identify the genes that contributes this defect.

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Declaration of Interest
The authors report no conflict of interest.

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