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Genetic Aspects of Cleft Lip and Palate – A Review

Ravi Teja Chitturi[1]*, Baddam Venkat Ramana Reddy[2], Kattapagari Kiran Kumar[3], Poosarala Chandrashekar[4], Kantheti Lalith Prakash Chandra[4] and Gontu Sridhar Reddy[4]

[1]*Senior Lecturer, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India*
[2]*Professor and HOD, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India*
[3]*Professor, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India*
[4]*Reader, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India*

Abstract

Craniofacial abnormalities especially Cleft Lip and Palate (CLP) are considered to be one of the most commonly occurring birth defects in humans. CLP is considered to be a very important disorder to be understood because of the the complications it produces in an infant. Recent advances in molecular techniques has given a good insight into the various changes that occur at a genetic level, thus shedding some light on the pathogenesis of CLP. This review aims to give the reader an uptodate information regrading various genes that are involved in oro facial clefting especially CLP.

Keywords: Cleft lip and palate; Craniofacial abnormalities

Introduction

Craniofacial abnormalities are considered to be one of the most commonly occurring birth defects in humans. The statistics reveal that in the United States of America (USA), 2651 babies are born with a Cleft Palate (CP) and 4,437 babies are born with a Cleft Lip (CL) with or without a cleft palate [1]. As far as the statistics in India is concerned, there is an estimated birth of 24.5 million babies per year and the prevalence of Cleft Lip and Palate (CLP) is recorded somewhere between 27,000 and 33,000 per year. An important fact to be considered is that the records in India are highly unreliable to give an exact statistics. This is because of several reasons such lack of infrastructure and poor access to health care centers to people below the poverty line [2]. All that being said, it is still very important to understand CLP at a genetic level because these clefts cause considerable disfigurement which results in complications in speech, feeding, hearing and psychological development [3]. To understand the genetic basis of clefting, it is very important to understand the abnormality clinically. CLP may occur clinically in two forms: syndromic and non syndromic. Association with two or more malformations with CLP is termed syndromic and occurrence of isolate CLP is termed non-syndromic [4].

Our main interest is the occurrence of the non-syndromic CLP because the knowledge regarding its remains relatively poor. This is due to the fact that there exists a complex and diverse mechanism in embryogenesis at a molecular level and also due to undeniable fact that there are various environmental and genetic factors involved [5]. Over the years advances in molecular biology and techniques has brought numerous insights regarding the genetics of CLP and this review aims in highlighting the various genes involved in the complex orchestration of events that lead to CLP.

Embryonic Development

To understand the complex genetic mechanisms underlying cleft lip and palate a brief review of the development of face is discussed. In the fourth week of intrauterine life development of face begins when the facial primordium is formed when the neural crest cells migrate from the dorsal area of the anterior neural tube. After this, the maxillary and nasal prominences are formed and begin to fuse in the sixth and seventh weeks of intrauterine life. This results in the formation of the inter-maxillary segment and also the filtrum and primary palate along with the lateral parts of the upper lip. The secondary plate is also formed from the neural crest cells which grow out as palatal shelves from the maxillary prominences [6]. Studies done on mouse models have revealed that *Gli2, Gli3, Tgfb2* and *Hoxa2* are responsible for migration and differentiation of neural crest cells and disturbances in them are responsible for CLP [7,8].

The formation of the palatal shelves involves proliferation of the mesenchymal cells and elevation of them is due the intrinsic forces developed due to the Extracellular Matrix (ECM). Genes such as *Msx1* and *Lhx8* are found to be involved in mesenchymal proliferation and knock out models in mouse results in CP due to insufficient mesenchyme [9,10]. The elevation of the palatal shelves is an interesting process that occurs due to increased turgidity through input of water which results as a result of increased hyaluronan. *Pax9* seems to be one of the genes responsible for this process [11,12].

Several ECM molecules and growth factors are required for signalling facial primordia identity, differentiation of epithelial cells and remodeling of the palatal shelves. Sonic hedgehog (*Shh*) plays a crucial role in induction of the formation of the facial primordia. Later bone morphogenic proteins (Bmp) such as *Bmp 2* and *Bmp 4* are required to form the epithelium and mesenchyme of the palatal shelves. *Msx1* homeobox gene is required for the expression of the aforementioned genes during development of the facial primordium and the palatal shelves [13,14].

Nixon et al., who have been extensively working in this field have made some important contributions to the literature such as the role of some growth factors. They found that Epidermal Growth Factor (EGF) and Transforming Growth Factor α (TGF-α) play a very important role in the biosynthesis of ECM in the palatal shelves and mesenchyme [15]. Epithelial-mesenchymal signaling plays a very important role I

***Corresponding author:** Ravi Teja Chitturi, Senior Lecturer, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India-522509, Tel: +91 – 9676767387; E-mail: dr.raviteja@gmail.com

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the development of the face. Proteins such as collagen IX play a critical role in the epithelial mesenchymal interactions whereas, transcription factors such as the Distal-Less (*Dlx*), *Hox*, *Gli* and *T-box* families which are regulated by *Shh, Bmps and Fgf* have a great part in maxillary and mandibular specification [16,17]. Furthermore role of TGF-β is very interesting in the formation of the palate, especially during elevation of palatal shelves and fusion. TGF-β 1 and 2 seem to accelerate this function whereas TGF-β 3 is found to have inhibitory roles and these growth factors seem to be controlled by the *Smad* signaling network [18].

Genetics of Syndromic and Non-Syndromic CLP

Isolated CLP i.e., without any association of any other syndrome are quite common accounting to about 75% of all the CLP reported (syndromic and non-syndromic) [19]. Mutations in various genes have been found to result in both syndromic and non – syndromic CLP. Some of them described in the literature are mutations in genes such as *Msx1*, *Foxe1, Gli2, Jag2, Lhx8, Satb2, Ryk1* and others [20,21]. Also a wide number of chromosomes have been implicated and thus making CLP heterogenic. Chromosomes 1q, 2p, 4q, 6p, 14q, 19q and Xq have been found to be associated with CLP [22]. The genes that are have been found to have association with CLP have been described.

Interferon regulatory factor 6 (IRF6); 1q32.3–q41

Association of IRF 6 is not limited to non syndromic CLP but also with syndromes such as popliteal ptreygium and van der woude syndrome [23]. A Meta analysis by Marazita et al., has proved that mutation in IRF 6 gene increases the risk of the fetus to have isolated CLP [22]. All these investigations resulted in assessing the role of IRF 6 in development of palate. It was found to have to interaction with TGF-β during the fusion of the medial palatal shelves and also seems to have a role in interacting with the *Smad* proteins which transducer TGF-β signals [24,25].

Methylenetetrahydrofolate reductase (MTHFR); 1p36.3

The role of MTHFR in non syndromic CLP has been very skeptical mainly due to lack of enough studies to prove its role in CLP. It was in late 1990's that first association between this gene and CLP was found [26]. Since then various authors have reported in isolated studies, although a thumping evidence of its association is not present till date. After the discovery of its association, determining the role of MTHFR has found interest of researchers. Viera et al., found it to be important for the conversion of homocystine to methionine. And methionine has found to have a role in closure of the neural tube [20].

Transforming growth factor alpha (TGF-α-); 2p13

TGF-α is found to have only a modifying effect on clefting rather than being a direct cause for oro facial clefting. The functional association has been ascribed to the fact that TGF-α is similar to Epidermal Growth Factor (EGF) and has similar effect on the cells of the bone marrow which is considered to be mitogenic and responsible for differentiation of osteoblasts. Thus, as per the work of Carter et al., it has been shown that TGF–α does not seem to have a direct role in CLP [27,28].

Msh homeobox - MSX1; 4p16.3–p16.1

As mentioned earlier Msx proteins play a critical role in epithelial-mesenchymal tissue interactions during craniofacial development. In animal models it has been found that Msx 1 plays a role in development of various bones of the craniofacial region including the palate. The occurrence of CP in Msx 1 deficient mice has been attributed to the fact that it plays a role in formation of palatal mesenchyme [29,30].

Endothelin 1 - EDN1; 6p24.1

Endothelin 1, a peptide is potent vasoconstrictor that is produced by the vascular endothelial cells. They also have a role in central nervous system in the neurons and glial cells. The chief function of EDN 1 is considered to be the maintenance of the vascular tone. There are few studies that have showed the mutant EDN 1 genes can result in isolated CP [31].

Forkhead box E1 - FOXE1; 9q22

FOXE1 is a gene that is associated with congenital hypothyroidism and thyroid agenesis. Although the form of CLP associated with the above mentioned conditions is seen predominantly in mutant FOXE 1 mice, a second phenotype has been found where there is occurrence of isolated CL and P or CLP [32].

Transforming growth factor - beta 3 (TGF-β3); 14q24

TGF–β occurs in five isoforms that is not related in anyway to TGF–α. The investigation regarding role of TGF-β in CLP ages far back in the literature. It is considered to be key mediator for cell to cell interaction during development. Use and human models have indicated that TGF-β null models produce CLP and the reason most probably could be due to impaired adhesion of the opposing medial epithelial edges of the palatal shelves and elimination of medial epithelial seam [33,34].

Jagged- 2 Protein precursor (JAG2); 14q32

Jagged 2 protein is found to be associated with craniofacial development. It has shown its expression throughout the oral epithelium. It activates *Notch 1* during differentiation of the oral periderm. Mutant mice studies have shown that this protein is required for both elevation and fusion of the palatal shelves.

Poliovirus receptor-related 2 mediator (PVRL2); 19q13.2

Margarita Island clefting syndrome along with CLP is said to be associated with mutation of PVRL 2 gene. PVRL2 is a glycoprotein (transmembrane) in the poliovirus receptor family. This is one gene that has been long associated with syndromic CLP [35].

T-box 22 T-box transcription factor (TBX22); Xq21.1

T-box genes encode numerous transcription factors that are involved in the regulating various developmental processes and is believed to play a major role in palatogenesis [28]. Most of the studies till date reveal that a mutation in TBX 22 results in CP and ankyloglossia, though there are studies that indicate mutation of TBX 22 can result in CP alone [30].

Reseant Advances

Recently few more genes have been found to have an important role in CLP such as *MAFB, ABCA4, PAX7* and *VAX* [36]. Interestingly some of these genes seem to be involved predominantly in the Asian population and these genes have been found to be implicated in the fusion of the palatal shelves during development [37]. Over the last few years advances in the field of genomics has considerably improved the status of knowledge regarding genetic basis of CLP. The genome-wide studies which includes analyses of copy number variation (CNV), genome-wide association and linkage and exome sequencing (ES) have helped us to provide more accurate information for unraveling the

genetic causes of diseases including orofacial clefts and especially CLP [38]. Such studies along with genetic analysis have identfied the role *Wnt* signalling in CLP. Various researchers have begun to understand the role of *Wnt* signalling in craniofacial development especially the development of palate [39]. Various splice variants of *Wnt* family have been studied and it has been found in initial studies that *Wnt3* is involved in the pathogenesis of CLP [40]. Another important association between *Wnt* signalling and oro facial clefting that has been recently found is with oral squamous cell carcinoma (OSCC). Research has shown that *Wnt11* that is associated with oro facial clefting also seems to have a potetial risk of developing OSCC if mutated [41]. Thus additonal studies in relation to this family is of prime importance to understand its role in developmental biology and pathogenesis of CLP.

Conclusion

The purpose of any review is to correlate it with the clinical importance. CLP represents a major health problem throughout the world especially in India due to the socio economic status of the majority of the population. The variety of problems associated with CLP include speaking, feeding, hearing and social integration. It is very important to assess the environmental and genetic risk factor for primary prevention. Though various genes have been implicated in CLP as described in this article, numerous signalling mechanisms during palatogenesis have to be elucidated to identify potential mutant genes responsible for oro-facial clefting and CLP. He need of the hour is a complete genome analysis to evaluate the various intricate mechanisms in oro-facial clefting. Large number of samples across the globe has to examined to understand the various environmental and genetic risk factor involved with CLP and thus providing information to serve the mankind.

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