GENETIC PREDICTORS IN ORO-FACIAL CLEFTS – AN OVERVIEW

Abhilash P R,
Professor, Department of Oral Pathology and Microbiology, Darshan Dental College, Udaipur, Rajasthan, India

DOI: http://dx.doi.org/10.24327/ijrsr.2020.1102.5090

ABSTRACT
Cleft lip or palate is a common congenital oro-facial anomaly posing a potential burden to patients and their families. More than 500 syndromes are described which are associated with CL/P resulting due to single gene mutations, chromosomopathies and terratogenic exposure. Non syndromic CL/P has no known etiology and hence genome studies are undertaken to elucidate the type of genes and their etiopathogenic roles. This review was done to extrapolate the various genes involved in CL/P cases so as to develop preventive measures in the future.

INTRODUCTION
Oro facial cleft is a common congenital defect identified at birth, which might refer to cleft lip with or without cleft palate or only cleft palate. A baby born with CL/P faces problems such as difficulty in feeding, speech problems, conductive hear loss and oral anomalies apart from the social and psychological issues. An accurate understanding of its etiology is imperative to determine its prognosis, treatment and prevention. Owing to its multifactorial origin, it requires a multidisciplinary approach to be managed comprising of paediatrician, cleft surgeon, ENT specialist, speech therapist, orthodontist, maxillofacial surgeon, psychologist and a geneticist.

Occurrence
The prevalence of cleft lip and palate is reported to be as 1 in 700 live births, though fluctuations might be observed due to varying ascertainment methods. Asia has the highest prevalence and Africa the lowest. CL cases occur mostly unilaterally (80-85%), and on the left side. CL/P exhibits a male predominance and with a severe intensity, while CP occurs mostly are females. It is also noted that the occurrence in females is higher when father is greater than 40 years.

Classification
CL/P cases are classified into Syndromic and Non-Syndromic. Nearly 70% of CLP cases and 50% of cleft palate cases are non-syndromic. The rest 30% have a Mendelian inheritance.

Syndromic CLP – They are associated with mutations in single genes and chromosomal abnormalities. Over 500 syndromes are reported with CL/P in the Online Mendelian Inheritance in Man Database (OMIM). Many cases of chromosomal trisomy 13, 18 and 21, partial deletions and chromosomal duplications are also associated. Literature reveals various genomic regions having loci, excessive or insufficient of which may result in CL/P.

Non-syndromic CL+P – It includes a broad clinical spectrum – a unilateral lip scar to bilateral cleft lip and cleft palate. It is a complex disorder, with unknown etiology.
Risk factors: Genetic and environmental factors are identified in dysregulating the complex molecular signalling pathways which play an important role in morphogenesis. Terratogenic risks such as maternal alcohol consumption, exposure to tobacco (either first hand or environmental smoke), chemicals like retinoic acid and folic antagonists are commonly identified. Bender et al and Dixon et al stressed the exposure of embryos to such factors in first trimester enhanced CL/P occurrence rate. Genes associated with CL/P

Interferon Regulatory factor 6 (IRF6) – It is situated in chromosome 1q32 and Majority of Van der Woude Syndrome (VWS) cases result due to the missense and nonsense mutations in IRF6. 80% of the pathogenic mutations are isolated in exons 3, 4, 7 and 9, though can occur in any region. IRF6 regulates keratinocyte differentiation, formation of oral periderm and palatal adhesion. IRF6 exerts its effects of mutations in embryonic development and also after birth, as children with VWS demonstrate an increased frequency of wound complications than children without following surgical intervention.

P63 - Mutations of heterozygous nature of p63 gene are associated with EEC syndrome, an autosomal dominant disorder. It exhibits an unusual phenomenon in that different parts of gene mutation influences cleft phenotype. Missense mutation of the conserved DNA binding domain area results in CLP while C-terminal mutations can result in CL or CP. No clefting or CP can be expressed with mutation at the N-terminal end.

PVRL1 - Mutations in the cell adhesion molecule PVRL1 is identified in CLP with ectodermal dysplasia (CLPED1). Cloning mapped the locus to 11q23 expressing itself in the developing face and plate. Nonsense homozygosity mutation W185X results in CLPED1, while unaffected population show high frequency of heterozygosity. Though CLPED1 occurrence though rare has a greater prevalence on Margarita Island (north of Venezuela). MSXI - Significant linkage disequilibrium was noted between CLP and CP with polymorphism in MSXI. A candidate gene based association study reported MSXI mutation in a Dutch family with tooth agenesis and CLP, demonstrating that a single gene and specifically a single mutation resulting in mixed clefting phenotype. Jezewski et al provided evidence for MSXI causation in CL/P was direct sequencing in a large cohort of various ethnic origin CL/P patients.

TBX22 – TBX22, a member of transcription factor gene family exhibits a high degree of penetrance and expresses itself as a X linked Mendelian inherited form of non-syndromic CP(CPX). Positional cloning identified the CPX locus as the gene encoding T – box. In addition to CP, patients also present with bifid or absent uvula and ankyloglossia. It is a significant diagnostic marker for CPX, and plays an important role in mesoderm specification. Point mutations include nonsense, splice site, frameshift and missense changes affect the highly conserved residues.

Transforming Growth Factor – alpha (TGFA) – TGFA gene was sequenced by Machida et al in NSCLP patients and observed five different mutations which proved to be the causative factor for oro-facial clefts. TGFA mutation combined along with environmental factor such as maternal smoking increases the risk of cleft palate by 6 – 8 times and of cleft lip with or without cleft palate by two times.

Transforming Growth Factor – beta (TGBF) - TGF-β is linked with non-syndromic CLP. TGF-β situated in chromosome 1q41 is involved in various biological activities associated with development. It induces palatal fusion and secondary palate development. An altered TGF-β signalling results in craniofacial deformities such as syndromic and non-syndromic cleft palate.

5,10 – Methylene tetrahydrofolate reductase (5,10 MTHFR) – catalyses the conversion of 5, 10 methylenetetrahydrofolate into 5 methyltetrahydrofolate in the folate metabolism pathway, which is important for neural tube formation and development. The MTHFR C677T Single - nucleotide polymorphism (SNP) poses a great risk for neural tube defects as it is heat liable. The presence of this genotype increases the risk of developing CLP by 4.6 times.

Special AT – rich sequence binding protein – 2 gene (SATB2) – This is a DNA binding protein situated in chromosome 2q32 – 33 and was isolated in cleft palate patients. It plays an important role in chromatin remodelling and transcriptional regulation. Expression analysis has confirmed the palatal involvement of the gene.

Midline 1 – Gene – Also referred to as RING finger protein gene located on chromosome Xp22. Mutations of this gene may result in cleft lip, laryngeal cleft, heart defects, hypospadias and corpus callosum agenesis.

Dihydrofolate Reductase Gene (DHFR) - is situated in chromosome 5q 11-q22 region. It plays a role in DNA synthesis, repair and methylation and mutation can result in CL with or without CP.

WNT9B Gene – Encodes the protein Wnt T- 9b playing a significant role in craniofacial development such as face morphogenesis. WNT gene malfunctioning can results in facial region defects, cleft lip and kidney morphogenesis.

FGFR1 – It results in mutations in as in case of autosomal recessive Kallmann syndrome. The mutation results in cleft lip and palate along with hypogonadotropic, hypogonadism and anosmia.

TTF -2 – Mutations of this forkhead genes has a craniofacial expression pattern, presenting as thyroid abnormalities and CL/P.

FOX C2 – Mutations of this genotype expresses as distichiasis, lymphoedema and cleft palate.

Acyl – CoA desaturase 4 (ACOD4) – Disruption of this gene expressed as CL in a single two generation family.

Future aspects

A lack of knowledge regarding gene networks and gene regulation expression resulted in the failure to point the precise molecular events leading to human CL/P. It is now know that several genes play a significant role in human craniofacial growth and development, which in turn can contribute to occurrence of non-syndromic CL/P.
understanding of these genes will provide us the necessary tools to study them and their genetic pathways. Information regarding the expression of genes can be determined by using expression profiling techniques and genome sequencing making the future quite optimistic.

CONCLUSION

CL/P is a complex group of disorders which requires family genetic evaluation by a trained group of geneticists so as to precisely define the diagnosis of the affected propositus, prognostic evaluation, indications for surgery, and, recurrence risk estimates for the individuals at risk. The precise clinical diagnosis of CL/P patients is significant for an accurate genetic counselling, patient management and decision for surgical intervention. Genomic technology advancement has lead for a better understanding of the genetic mechanisms resulting in CL/P which will be accomplished in the future.

References