Journal of Current Medical Research and Opinion
Received 22-09-2021 | Revised 08-10-2021 | Accepted 10-10-2021 | Published Online 12-10-2021

DOI: https://doi.org/10.52845/CMRO/2021/4-10-1
CMRO 04 (10), 1030–1034 (2021)

ISSN (O) 2589-8779 | (P) 2589-8760

ORIGINAL RESEARCH

GENES — The Key Culprit In Orofacial Clefting

Dr. Gurmeet Kaur[1] | Dr. Serat Virk[2] | Dr Karan Gera[3] | Shubhkarman Virk[4] | Dr. Varun Suri[5]

[1]BDS MDS (Orthodomtics) Smile and Profile Dental Centre Karnal

[2]BDS Smile and Profile Dental Centre Karnal

[3]Intern PGIMS

[4]BDS 2yr student Himachal Institute of Dental Sciences, Himachal

[5]Reader

Abstract
Cleft lip with or without cleft palate is the most common facial birth defect and it is caused by a complex interaction between genetic and environmental factors. Although the gene identification process for orofacial clefting in humans is in the early stages, the pace is rapidly accelerating. Recently, several genes have been identified that have a combined role in up to 20% of all clefts. Ongoing human genome-wide linkage studies have identified regions in the genome that likely contain genes that when mutated cause orofacial clefting, including a major gene on chromosome 9 that is positive in multiple racial groups. Currently, efforts are focused to identify which genes are mutated in these regions. The ultimate goal of these studies is to provide knowledge for more accurate risk counseling and the development of preventive therapies.
Keywords: Cleft Lip, Cleft Palate, Genes, Candidate Gene, Mutation

1 | INTRODUCTION

In humans, orofacial clefts are common congenital anomalies with a prevalence of 1 to 2 per 1000 live births. They can be separated into two different phenotypes: (1) cleft lip with or without cleft palate (CL/P); and (2) cleft palate only (CPO). Orofacial clefts can be further classified as nonsyndromic (isolated) or syndromic based on the presence of other anomalies. Approximately 30% of CL/P and 50% of CPO patients have one of more than 400 described syndromes. (1–4) The focus of this review having CPO.

The approach in this situation involves scanning of the human genome to look for the shared region between affected members within a family. This can be readily accomplished by using approximately 400 DNA markers. The sharing is statistically evaluated under the assumption that each child has a 50:50

Supplementary information The online version of this article (https://doi.org/10.52845/CMRO/2021/4-10-1) contains supplementary material, which is available to authorized users.

chance of inheriting a specific chromosome carrying the mutated or normal copy of the gene, since the genome consists of pairs of chromosomes and only one is transferred from a given parent to an offspring. The statistical output of these genetic tests is usually the LOD score, which is the log10 of the odds that a trait (disease) and DNA marker are linked versus the odds that they are not linked, assuming a 50:50 chance for each individual.

2 | SYNDROMIC FORMS OF CLP

Syndromic forms of CL/P often have simple Mendelian inheritance patterns and are thus more suitable for conventional genetic mapping strategies. (7)

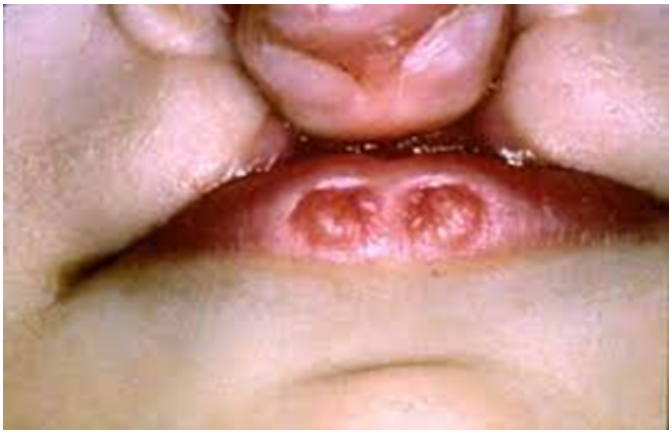

FIGURE 1: Cleftlip and cleft palate in an infant with van der Woude syndrome showing raisedpits of lower lip

Van der Woude Syndrome

Van der Woude syndrome (VWS) is an autosomal dominant form of orofacial clefting with an estimated prevalence of 1 per 34,000 live births (8) . VWS has a variety of features that distinguish it from nonsyndromic CL/ P, including the presence of lower lip pits Figure 2 hypodontia, and either CL/P or CPO. Furthermore, the penetrance is very high, approximately 97%. The disease gene was localized by linkage mapping to a large region on the long arm of chromosome 1, 1q32-q41. (9) Monozygotic twins, one with VWS and the other normal, were sequenced and a mutation discovered in the interferon regulatory factor 6 (IRF6) gene. (10)

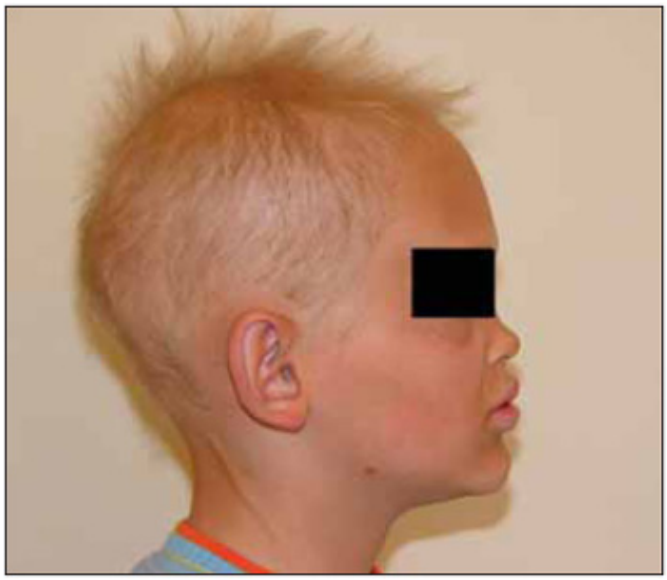

FIGURE 2: Notethe sparse scalp hair and eye brows with cleft lip

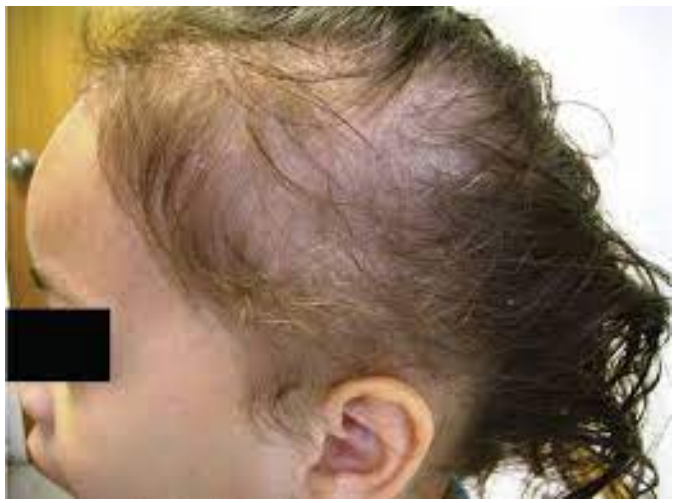

FIGURE 3: Thin,curly, sparse scalp hair on posterior scalp.

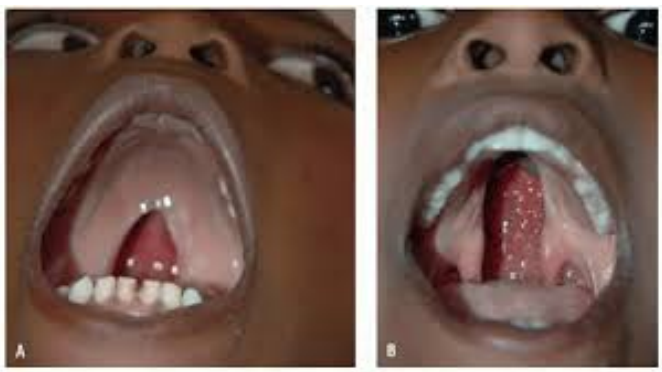

FIGURE 4: Partialcleft of secondary palate

CL/P Ectodermal Dysplasia Syndrome

CL/P ectodermal dysplasia (CLPED1) syndrome is characterized by cleft lip, cleft palate, partial syndactyly of the fingers and toes, dental anomalies, and sparse hair. (11) It is a rare autosomal recessive trait. However, there is a very high prevalence on Margarita Island, suggesting a founder effect in the small and relatively isolated population. Mutations were identified in the poliovirus receptor-like 1 (PVRL1) gene. (12) Similar to IRF6, the PVRL1 gene name is misleading, suggesting an infectious function rather than an important facial developmental gene. (13)

X-Linked Cleft Palate and Ankyloglossia

Cleft palate occurring with ankyloglossia (CPX) has been reported segregating in an X-linked recessive pattern. CPX was the first orofacial cleft syndrome mapped, with linkage being identified to a large region on the long arm of chromosome X. (14) Recently, the causal gene was identified as TBX22,25 which is expressed in the palatal shelves and tongue during development. (15, 16)[15,16] X -linked diseases are interesting since males have one X chromosome and females two X chromosomes. If a male inherits a mutated TBX22, it is highly likely that he will have the disease since this is the only copy of the TBX22 gene.

Genetics of Nonsyndromic CL/P

Nonsyndromic CL/P is an example of a genetically complex trait. The majority of affected patients have no positive family history and the evaluation of inheritance patterns in the familial cases has not revealed a simple Mendelian mode of inheritance. It is also clear that there is reduced penetrance. However, there is solid evidence that CL/P is a genetic trait, since there is a 40-fold risk for CL/P among first degree relatives of an affected individual and there is greater concordance in identical (monozygotic) compared with fraternal (dizygotic) twins. However, the concordance rate in monozygotic twins is only 40% to 60%, suggesting the influence of environmental factors is also important.

Human studies have used both association and linkage analyses to evaluate the role of candidate genes in the etiology of CL/P.

3 | CANDIDATE GENES

Initial efforts to identify genes for nonsyndromic CL/P relied on candidate gene approaches.5,35 Genes at 1q32 (IRF6), 2p13 (TGFA), 4p16 (MSX1), 6p23 to 25, 14q24 (TGFB3), 17q21(RARA) and 19q13 (BCL3, TGFB1) have the most supporting data (Table 1).

The VWS Gene, IRF6, Is Associated with Nonsyndromic CL/P

Estimates suggest that genetic variation in IRF6 contributes to 12% of CL/P and triples the recurrence risk in some families. These results have been replicated in additional populations, although the specific mutations have not yet been identified. This discovery constitutes one of the most exciting discoveries so far in the field of isolated CL/P.

MSX1

MSX1 is a DNA binding transcription factor that when inactivated in mice results in cleft palate and tooth agenesis.40 This finding greatly aided the identification of an MSX1 mutation in a family with hereditary tooth agenesis that was recruited by an orthodontic resident who subsequently received the Milo Herman award. At the same time, another study revealed that DNA variations in MSX1 were associated with CL/P.[5]

Transforming Growth Factor Beta 3 (TGFB3)

Studies of TGFB3 further underscore the importance of animal studies because the observation of cleft palate in mice missing TGFB3 led to the discovery of associations with CL/P in humans.[5]

19q13.1 (BCL3, CLPTM1, PVRL2, TGFB1)

Several studies have found linkage or association with candidate genes on the long arm of chromosome 19.[5] Furthermore, a chromosomal anomaly involving this region was found in a family with CL/P.

Syndromic Orofacial Clefts Provide Important Clues

TABLE 1: Selectedcandidate Genes with positive evidencefor a role in Non syndromic Cleft Lip orPalate

Candidate Region	Candidate gene	Link-age	Associa-tion	Animal model	Choromosomal Anomaly	Cleft syndrome
1p 36	MTHFR,SKI, PAX7		X	X	X	
1q 32	IRF6	X	X	X	X	X
2p 13	TGFA	X	X			
4p16	MSX1		X	X	X	X
6p23 to 25	TFAP2A,OFCC1	X	X	X	X	
14q24	TGFB3 BMP4 PAX9	X	X	X		
17q12-21	RARA Clf1	X	X	X		
19q13	BCL3, CLPTM1, PVRL2 TGFB1	X	X		X	

In addition to the IRF6 and PVRL1 examples of syndromic genes playing a role in nonsyndromic clefting, efforts are under way to determine whether variants in other cleft syndrome genes have similar roles. Mutations and deletions in the FGFR1 gene account for 10% of Kallman syndrome patients.

4 | GENE-ENVIRONMENT INTERACTIONS

Epidemiologic studies have revealed an increased risk for CL/P with alcohol and smoking exposure during pregnancy. Furthermore, studies suggest periconceptional folate or multivitamin supplementation has a protective effect against CL/P. However, not all mothers who drink or smoke have children with CL/P; nor do all mothers taking multivitamins have normal children. Thus it is likely that certain genes that interact with these environmental factors and genetic variation within these genes affect the risk for CL/P. It is plausible that a fetus may have a low risk for CL/P due to its genes, but that this risk increases due to maternal environmental exposures and her genetic ability to detoxify exposures. Genetic variation has been identified in a variety of genes involved in the detoxification of agents found in tobacco smoke including common deletions of the glutathione S-transferase theta 1-1 (GSTT1) and glutathione S-transferase mu 1 (GSTM1) genes.

5 | SUMMARY

In general, the gene identification process for CL/P is still in the early stages, especially compared with other common diseases. However, the candidate gene approaches have identified variations that are associated with up to 25% of patients with CL/P. Furthermore, genomewide linkage scans have identified the location of several genes, including the previously unknown locus on chromosome 9. Future studies will determine how these genes interact with each other and the environment to develop models for improved genetic counseling and public health policies.

Conflict of interest: None
Acknowledgement: None
Funding received: Nil

REFERENCES

1. Gabriel SB, Schaffner SF, Nguyen H, et al: The structure of haplotype blocks in the human genome. Science 296: 2225-2229, 2002 ;.
2. Marazita ML, Mooney MP: Current concepts in the embryology and genetics of cleft lip and cleft palate. Clin Plast Surg 31:125-140, 2004;.

3. Vanderas AP: Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. Cleft Palate J 24:216-225, 1987 ;.

4. Murray JC: Face facts: genes, environment, and clefts. Am J Hum Genet 57:227-232, 1995 ;.

5. Cohen MM: Syndromes with cleft lip and cleft palate. Cleft Palate J 15:306-328, 1978 ;.

6. Shprintzen RJ, Siegel VL, Amato J, et al: Anomalies associated with cleft lip, cleft palate, or both. Am J Med Genet 20: 585-595, 1985 ;.

7. Gorlin RJ: Syndromes of the head and neck. New York, Oxford University Press, 1990 ;.

8. Rintala AE, Ranta R: Lower lip sinuses: I. Epidemiology, microforms and transverse sulci. Br J Plast Surg 34:26-30, 1981 ;.

9. Murray JC, Nishimura DY, Buetow KH, et al: Linkage of an autosomal dominant clefting syndrome (Van der Woude) to loci on chromosome 1q. Am J Hum Genet 46:486-491, 1990 ;.

10. Kondo S, Schutte BC, Richardson RJ, et al: Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet 32:285-289, 2002 ;.

11. Zlotogora J: Syndactyly, ectodermal dysplasia, and cleft lip/palate. J Med Genet 31:957-959, 1994 ;.

12. Suzuki K, Hu D, Bustos T, et al: Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. Nat Genet 25:427-430, 2000 ;.

13. Subramanian RP, Dunn JE, Geraghty RJ: The nectin- I [alpha] transmembrane domain, but not the cytoplasmic tail, influences cell fusion induced by HSV-1 glycoproteins. Virology 339:176-191, 2005 ;.

14. Moore GE, Ivens A, Chambers J, et al: Linkage of an X-chromosome cleft palate gene. Nature 326:91- 92, 1987;.

15. Braybrook C, Lisgo S, Doudney K, et al: Craniofacial expression of human and murine TBX22 correlates with the cleft palate and ankyloglossia phenotype observed in CPX patients. Hum Mol Genet 11:2793-2804, 2002 ;.

16. Bush JO, Lan Y, Maltby KM, et al: Isolation and developmental expression analysis of Tbx22, the mouse homolog of the human X-linked cleft-palate gene. Dev Dyn 225:322-326, 2002;.

How to cite this article: Kaur, G., Virk, S., Gera, K., Virk, S., & Suri, V. (2021). GENES — THE KEY CULPRIT IN OROFACIAL CLEFTING . Journal of Current Medical Research and Opinion, 4(10), 1030 −1034. https://doi.org/10.52845/CMRO/2021/4-10-1