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Exploring Sex-Specific Genetic Variants in Cleft Lip and/or Palate: A Literature Review

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ABSTRACT

Clefts of the lip and/or palate (CL/P) represent the most prevalent congenital anomalies in the oropharyngeal region, originating from defects in craniofacial fusion processes between the 5th and 12th weeks of embryonic development. The incidence of CL/P varies significantly across geographical regions, ethnic groups, and genders, with males exhibiting a higher prevalence of cleft lip and females more frequently affected by isolated cleft palate. Genetic studies have identified sex-specific variants that contribute to these differences, notably the MSX1 gene in males and GTF2A1L and LTBP1 genes in females. Environmental factors, including maternal smoking, alcohol consumption, and nutritional deficiencies, along with hormonal influences such as estrogen, play critical roles in the etiology of CL/P. Epigenetic mechanisms, particularly DNA methylation, also contribute to the phenotypic variability. Understanding the genetic and molecular mechanisms underlying CL/P is essential for early diagnosis and personalized treatment strategies. Prenatal genetic screening and counseling can mitigate risks and improve outcomes. Future research should prioritize large-scale genomic studies to elucidate the complex interactions between genetic and environmental factors in CL/P development, aiming for targeted and personalized therapeutic interventions.

KEYWORDS: cleft lip and/or palate (CL/P), craniofacial development, sex-specific genetic variants, MSX1 gene, GTF2A1L gene, LTBP1 gene, environmental factors, estrogen, DNA methylation, prenatal genetic screening

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INTRODUCTION

Clefts of lip and/or palate (CL/P) are the most common congenital anomalies affecting the oropharyngeal region. These anomalies are derived embryologically from defects in the primary fusion of craniofacial process which form the primary and secondary palate between the 5th and 12th weeks of development. The overall incidence of cleft lip and/or palate (CL/P) is estimated about 220.000 new cases per year or around 1.5 per 1000 live births, which varies widely across geographic areas, ethnicity, and the nature of the cleft. The studies reported of higher incidence among Asians around 0.82 – 4.04 per 1000 live births, intermediate in Caucasians (0.9 – 2.69 per 1000 live births), and found low in Africans around 0.18 – 1.67 per 1000 live births.[1,2]

A congenital cleft anomaly is defined as a congenital abnormal gap in the upper lip, alveolus, or palate. Orofacial clefts types generally distributed as cleft lip alone, cleft lip And palate, and isolated cleft palate. Cleft lip happens due to the failures of the frontonasal and maxillary processes fusion, resulting in a cleft of varying extent through the lip, alveolus, and nasal floors. A complete cleft indicates lack of connection between the alar base and the medial labial element, while an incomplete cleft does not extend through the nasal floor. The least common form of orofacial cleft is isolated cleft palate. This form affecting only 1 to 25 per 10.000 newborns or 33% of all oral clefts worldwide. The cleft palate develops from the deficiencies in neural crest cell migration in the craniofacial formation. The prevalence of cleft lip and/or palate (CL/P) shows differences between genders. Statistically cleft lips are more common in males than females with ratio 2:1, while the numbers of isolated clefts of palate is higher in females than males with ratio 1:2.[2]

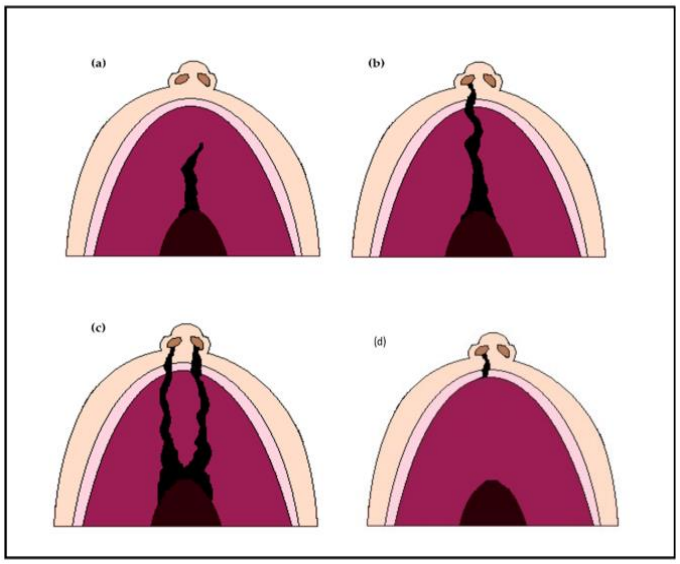

Figure 1. Types of orofacial clefts[3]; (a) incomplete cleft palate only; (b) Unilateral complete cleft lip and palate; (c) Bilateral complete cleft lip and palate; (d) Cleft lip only.

The difference in gender prevalence in orofacial cleft shows that males are more frequent to have a cleft lip while females have higher risk for cleft palate. The study about sex-specific genetic variants in cleft lip and/or palate (CL/P) still rare to found. Studies about sex-specific genetic variants will certainly help to improve the understanding of the molecular mechanism underlying the orofacial development. Improvement in antenatal genetic diagnosis allows early diagnosis and prevention of cleft lip and/or palate (CL/P) incidence, thus will help in personalizing the treatment based on the variants found.

Sex-specific genetic variants in cleft lip and/or palate (CL/P)

Studies have suggested that a major gene locus associates with the etiology of cleft lip and/or palate (CL/P). Research from Blanco and colleagues shows evidence in association between the MSX1 gene locus and cleft lip and/or palate (CL/P). Their study involving the Chilean population, the admixture of Native Amerindians with Spaniards, that has higher genetic susceptibility to cleft lip and/or palate (CL/P). The study presents the MSX1 allele frequencies divided by sex (male and female) in sample and controls. The MSX1 (HOX7) locus has a microsatellite sequence with four alleles. A test was performed to assess the differences in allele and genotype frequencies between the sample of cleft lip and/or palate (CL/P) patients versus the controls of non-clefts. It reveals that the allele in male sample shows significant differences from the male controls while no differences found in neither female sample nor control. The study concludes that the association of MSX1 locus with cleft lip and/or palate (CL/P) is sex-dependent, particularly in males. The results of this study suggest an enhanced risk of cleft lip and/or palate (CL/P) in males coexisting with genotypes carrying MSX1 locus.[4]

Other studies also proposed females are more frequently to have isolated cleft palate (CP) and hypothesized that female-specific genetic play a role in the occurrence of isolated cleft palate. A study performed a genome-wide association studies (GWAS) followed by a genome-wide gene-by-sex interaction analysis and identified 2 loci with significant interactions with isolated cleft palate: the general transcription factor IIA subunit 1 like (GTF2A1L) and the latent transforming growth factor beta-binding protein 1 (LTBP1) at 2p22.3 gene, both of the two loci were specific in females. The general transcription factor IIA subunit 1 like (GTF2A1L) locus are in the substantia nigra of the female brain and the latent transforming growth factor beta-binding protein 1 (LTBP1), said to have a part in the palatogenesis, in cultured fibroblast cells.

The latent transforming growth factor beta-binding protein 1 (LTBP1) is an extracellular matrix protein and a component of the large latent complex which binds to the second complex of associated proteins and mature transforming growth factor beta (TGF-β), regulating biological availability in the extracellular matrix. Disruption of the transforming growth factor beta (TGF-β) pathway leads to interruption in palatogenesis. In other words, variants in latent transforming growth factor beta-binding protein 1 (LTBP1) could cause dysregulation of the transforming growth factor beta (TGF-β) pathway resulted in cleft palate. Bi-allelic truncating variants in latent transforming growth factor beta-binding protein 1 (LTBP1) caused abnormalities in connective tissue leads to craniofacial dysmorphism, including high arched palates. latent transforming growth factor beta-binding protein 1 (LTBP1) disrupt the transforming growth factor beta (TGF-β) pathway by competing with glycoprotein A repetitions predominant (GARP) encoded by leucine rich repeat containing 32 (LRRC32), which plays a role in maturation, processing, and tethering of transforming growth factor beta (TGF-β) to the cell surface. Researchers have suggested variants in leucine rich repeat containing 32 (LRRC32) may cause imbalance in the process of palatogenesis, resulting in cleft palate.[5]

Orofacial cleft is widely accepted as a result from complex interplay between multiple genetic, environmental, and hormonal factors. Maternal exposures influence the risk of cleft lip and/or palate (CL/P), particularly cigarette smoking, alcohol consumption, folic acid and vitamins deficiencies. Studies have also found sex hormones such as estrogen have a role in cleft lip and/or palate (CL/P) pathogenesis.[6]

Folate plays a major role in one-carbon metabolism in the synthesis of nucleotides and amino acids in deoxyribonucleic acid (DNA) methylation, essential for consequent gene expression, hence it is important for the prevention of neural tube defects. Studies have shown that alcohol consumption inhibits retinoid acid production, which is required for cranial neural crest cell developmental and functioning including the

lip and palate, therefore increasing the susceptibility to cleft lip and/or palate. Alcohol intake reduces folate absorption, affecting the folate homeostasis by increasing folate excretion and causing inhibition of enzymes essentials for embryogenesis and early fetal development, such as methionine synthase (MTR) and methylene-tetra-hydro-folate reductase (MTHFR). Polymorphism in genes encoding the enzymes of the folate pathway might increase the susceptibility to cleft lip and/or palate (CL/P). Study found two common polymorphisms in the methylene-tetra-hydro-folate reductase (MTHFR) gene – 677C>T (rs1801133) and 1298A>C (rs1801131), and in addition, a polymorphism 2756A>G (rs1801394) in methionine synthase (MTR) gene, leads to the reduction of enzymes activity, resulting in the disruption of folate pathway.[7]

Recent studies also found a biological plausible association between estrogen hormones, ESRRG genes, and craniofacial malformation. Sex hormones are involved in some traits associated with sexual gene dimorphism, manifested in birth defects such as craniofacial malformation.[6]

Prevalence and types of cleft lip and/or palate (CL/P) in males versus females

A research by Desai and colleagues in Gujarat, India, shows that cleft deformities on male patients are higher that on female patients with 59% cleft deformities cases were male patients. The left-sided cleft lip and palate occurs most frequently (37,3%) both in males and females. Another study also concludes that males were affected more by cleft lip and/or palate while isolated cleft palate seen more frequent in females.[8]

The occurrence of cleft lip and/or palate (CL/P) has been linked to several environmental and dietary risk factors.[9,10] The risk factors include advanced maternal age, bad maternal history, consanguineous marriage, smoking, alcohol consumption, diabetes mellitus type I, deficiency of vitamins such as folic acid, and intrauterine irritation. Second-degree relatives than first degree. The correlation between consanguineous marriages has a link to the occurrence of cleft lip and it is a risk factor of cleft in craniofacial region. The family history of oral cleft either in paternal or maternal also has a strong correlation of these incidence. Smoking exposure during pregnancy and/or before pregnancy will increase the incidence of cleft palate and lip on baby. It includes the habit of chewing tobacco and/or smoking either by mother or father. Maternal history of abortion and miscarriage and also history of medications during pregnancy increase the occurrence of cleft lip and/or palate (CL/P). Several clinical syndromes like Down's, Pierre Robin's, and Van der Woude may be associated with cleft lip and/or palate (CL/P).

Mechanisms underlying sex-specific variations in cleft lip and/or palate (CL/P):

Craniofacial development is a coordinated formation process of the lip, palate, nose, and mouth. The formation occurs between the 4th and 12th gestational weeks of embryo development. In the fourth weeks, special neural crest cells originating from neuroectoderm migrate to the frontonasal and visceral arch regions, manifested in rise of the five facial structures or primordia, constitute of the maxilla-mandibular complex. Lip development normally occurs at the 4th and 8th week of gestation, where the maxillary prominences grow medially and fuse with the lateral nasal prominence, resulting in the lateral parts of the upper lip and cheeks. At the 5th week of gestation, the maxillary prominence grows medially and fuse with the medial nasal prominence bringing the nostrils closer. Alteration of this process caused by failure of the fusion between the maxillary prominence and nasal prominence in one side resulting in unilateral cleft lip while bilateral failure fusion resulting in bilateral cleft lip.[11]

The development of the palate starts at the 5th week continue until the 12th week with the 6th and 9th weeks become the most critical time. Two lateral palatine processes grow from the medial side to the maxillary prominence, lying vertically under the tongue. The two palatal shelves start to move to a horizontal position approaching each other when the tongue starts to move inferiorly. By 12th week, the palatal shelves fusses together with the nasal septum and hard palate. Failure of the elevation and fusion will result in cleft palate. Epithelial to mesenchymal transition, cell migration, and apoptosis work as the major mechanism of palate and shelf fusion. Large spectrum of signaling molecules and gene families are identified as mediators for cellular growth, proliferation, migration, and apoptosis. Mutations and variants of these genes resulted in severe orofacial development. Female palates close a week later that male, suggesting inheritance patterns for *cleft palate deformity are autosomal dominant and X-linked recessive*, a condition that appears more frequently in females. The condition results in females have twice the risk of inheriting a mutated X-chromosome that could manifested in cleft palate.[3,12]

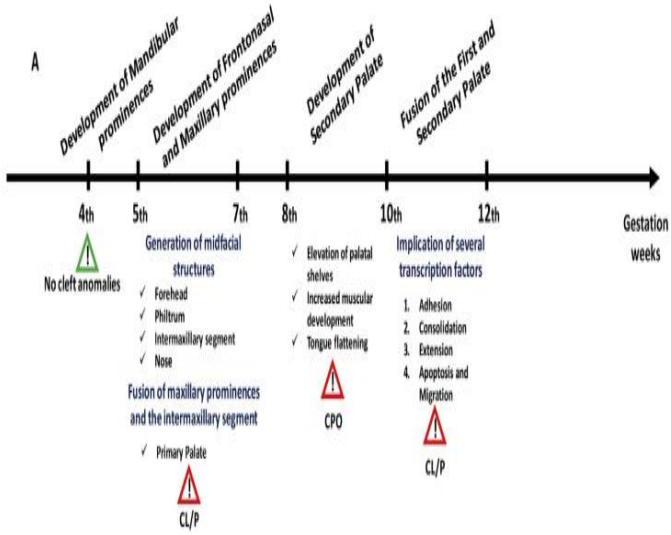

Figure 2. Lip and palate developmental process[10]

Multiple genes are suggested to increase the risk of cleft lip and/or palate (CL/P), including genes that encode growth factors such as transforming growth factor alpha (TGF-α) and

transforming growth factor beta 3 (TGF- β3), transcription factors such as MSX1 and genes involved in immune response (MSX1, IRF6). Past study shows IRF6 gene, found more frequently in the Asian population, may be a predisposed to cleft lip and/or palate (CL/P). variations in the gene account for 12% genetic contribution to cleft lip and/or palate (CL/P) and produce three times increased risk for families who has already had affected child.

Genome-wide associated study (GWAS) reported the 8q24 locus were a risk locus for cleft lip and/or palate (CL/P), mainly in the Caucasian populations. Dimorphism of the cysteine-rich secretory protein LCCL domain-containing 2 (CRISPLD2), a gene shown to be important for normal migration and differentiation of the neural crest cells during the formation of the palate, also results in disturbance of the palate formation. Other studies observed a rare variant of ventral anterior homeobox 1 (VAX1) and fibroblast growth factor receptor 2 (FGFR2) associated with sex-specific markers for the cleft lip and/or palate (CL/P), although it is still not clear how both genes contribute to sex differences in cleft lip and/or palate (CL/P). Researchers have been hypothesized the genes were involved in multiple-threshold multifactorial liability mainly in females.[13-15]

Research by Haaland and colleagues identified a significant association between genetic variants in estrogen-related receptor gamma (ESRRG) gene, estrogens –a group of steroi-based sex hormones involved in the developmental and physiological processes of cartilage proliferation and growth— and formation of the craniofacial complex. Signaling and dosage regulation of estrogen are regulated by estrogen receptors (ERs) and estrogen-related receptors (ESSRs), both share target genes ESRRG which encodes the nuclear receptor estrogen-related receptor gamma (ERRG or ERRγ). The ERRG / ERRγ is a sex-dependent negative regulator of postnatal bone formation. Researchers suggested that the difference in the male and female ratio of cleft lip and/or palate (CL/P) prevalence manifested from opposing sex steroid actions. Studies in animal shows either very high or very low dose of estrogens during embryonic development results in craniofacial skeletal development.[6]

Genome-wide association studies (GWAS) also identified around 40 genes risk variants for cleft lip and/or palate (CL/P) in European and Asian populations. There is a possibility that genetic risk variants may affects cleft lip and/or palate (CL/P) susceptibility through gene regulation pathways. New evidence shows that epigenetic mechanism, such as DNA methylation, have a role in the development of orofacial clefts by changes to gene expression.

A study by Howe and colleagues assessed a correlation in DNA methylation at the identified CpG sites or CG sites – regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide—from several different tissues (blood, lip, palate) and cleft subtypes. The study found a weak correlation between methylation in blood, lip, and palate tissue, mainly between blood and lip tissue, therefore suggested the DNA methylation may mediate genetic susceptibility to cleft lip and/or palate (CL/P). Their study found that liability to non-specific cleft lip and/or palate (nsCL/P) and variation in DNA methylation might be driven by the same genetic variant which was evident at VAX1 (10q25.3), LOC146880 (17q23.3) and NTN1 (17p13.1), suggesting that genetic variation at these loci may increase liability to nsCL/P by influencing DNA methylation.[16]

Clinical implications and future directions

Genetic predisposition and environmental factors play a great role in cleft lip and/or palate (CL/P) development. Clinicians have found that the higher prevalence of cleft lip and palate in male patients is linked to the MSX1 gene locus. Meanwhile, isolated cleft palate in female patients associates with the general transcription factor IIA subunit 1 like (GTF2A1L) and latent transforming growth factor beta-binding protein 1 (LTBP1) loci. These findings suggest the need for sex-specific approaches and personalized management strategies to be implemented as early as possible. Understanding these genetic factors prepares families with the risk ahead,[17] and calls for prenatal genetic screening and consultation to diagnose, to predict the severity, and to plan the treatment strategies. Families with risk factors should be educated about genetic risk despite the multifactorial etiology of cleft lip and/or palate (CL/P).

Large-scale genomic studies and functional analysis is important to elucidate the molecular mechanism behind sex-specific variations in cleft lip and/or palate (CL/P). Large-scale studies to identify relevant gene that influence sex-specific cleft lip and/or palate (CL/P) and its mechanism in the development of cleft lip and/or palate (CL/P) can help to develop targeted and personalized interventions.

CONCLUSION

Clefts of the lip and/or palate (CL/P) are among the most common congenital anomalies affecting the oropharyngeal region, resulting from defects in the craniofacial fusion processes during embryonic development. The incidence of CL/P varies widely by geography, ethnicity, and gender, with higher prevalence in males for cleft lip and in females for isolated cleft palate. Sex-specific genetic variants significantly contribute to these differences. Key genes such as MSX1 in males and GTF2A1L and LTBP1 in females have been identified as contributing to the development of CL/P.

Environmental factors, including maternal smoking, alcohol consumption, and nutritional deficiencies, alongside genetic predispositions, play critical roles in CL/P pathogenesis. Hormonal influences, particularly estrogen, further modulate the risk. Epigenetic mechanisms, like DNA methylation, also contribute to the variability in CL/P presentation.

Understanding the molecular mechanisms and genetic factors underlying CL/P is crucial for early diagnosis and personalized treatment approaches. Prenatal genetic screening and consultation can help manage risks and improve outcomes for affected families. Future research

should focus on large-scale genomic studies to uncover the complex interplay of genes and environmental factors in CL/P development, leading to targeted and personalized interventions.

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