Review

Genetic etiology of cleft lip and cleft palate

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Abstract: Genetic studies in humans have demonstrated that Cleft lip with or without cleft palate (CL/P) have a diverse genetic background and probably environmental factors influencing these malformations. CL/P is one of the most common congenital birth defects in the craniofacial region with complex etiology involving multiple genetic factors, environmental factors and gene-environment interaction. Children born with these defects suffer from various difficulties such as difficulty in speech, hearing, feeding and other psychosocial problems, and their rehabilitation involves a multidisciplinary approach. The article describes the brief introduction of CL/P, epidemiology and general concepts, etiological factors, and the genes implicated in the etiology of nonsyndromic CL/P (NSCL/P) as suggested by different human genetic studies, animal models, and other expression studies.

Keywords: cleft lip; cleft palate; genetics; candidate genes; molecular biology; mutations; genome-wide association study

1. Introduction

Cleft lip with or without cleft palate (CL/P) is one of the most common congenital birth defects in the craniofacial region [1]. The etiology is polygenic and multifactorial, involving various genetic and environmental factors [2–4]. Children born with these defects may suffer from difficulty in speech, hearing, feeding and other psychosocial problems, and their rehabilitation involves a multidisciplinary approach [5]. In 2008, the World Health Organization (WHO) has recognized that birth defects cause
significant infant mortality and childhood morbidity and have included CL/P in their global burden of disease (GBD) initiative [6].

2. Epidemiology and general concepts

The epidemiological data reveal that the prevalence of Cleft lip with or without cleft palate (CL/P) ranges from 1 in 700 to 1000 live births worldwide. It is highest among Asians and American Indians (1:500), average rates in Caucasians (1:1000) and lowest in Africans (1:2500) [7–10]. The incidence of cleft lip and palate varies according to geographical location, ethnicity, race, gender and socioeconomic status [11–14].

Higher prevalence of clefts has been observed in individuals who live in rural areas and lower socioeconomic status [15–17]. The influence of socioeconomic status on the prevalence of orofacial clefts has not been conclusively determined [3,18]. Possible explanations for this geographic variation and socioeconomic statuses include environmental factors such as nutrition, access to the excellent health care system and lifestyle risk factors such as alcohol, smoking.

Several studies have suggested consanguinity is a risk factor for nonsyndromic cleft lip with or without cleft palate (NSCL/P) [19,20], whereas systematic reviews and meta-analyses reported that there is almost twice the risk of a child with NSCL/P being born if parental consanguinity exists [21].

The incidence of clefts in India is around 1:800 to 1:1000 and three infants are born with some type of cleft every hour [22]. Indian Council of Medical Research (ICMR) task force project revealed that 15% of CL/P cases had a familial association of cleft whereas, 85% of cases did not reveal any positive familial history [23]. A 13year retrospective study from a cleft center suggested consanguinity is a risk factor for NSCL/P in Indian population [24].

In India, majority of these defects are not surgically corrected because of lack of awareness among parents of child born with a cleft have no access to counseling on the care, affordability and availability of experts to provide the quality treatment. Evidence showed the association of MSX1 [25], IRF6 [26] gene with NSCL/P whereas, CRISPLD2 gene did not show any association with clefts in Indian population [27].

Cleft lip with or without cleft palate (CL/P) can be classified into syndromic and nonsyndromic. Most studies suggest that about 70% of the CL/P cases are nonsyndromic and occur as isolated cases without any other physical abnormalities, whereas 30% of are syndromic which are associated with some other developmental anomalies[28–30]. The syndromic cases are significant in number and can be subdivided into chromosomal syndromes, Mendelian disorders, teratogens (e.g. phenytoin or alcohol) and uncategorized syndromes [31,32].

The frequency of occurrence of cleft lip and cleft palate differs with regard to gender and side of clefting. Cleft lip is more common in males at a 2:1 male to female ratio, whereas a cleft palate is more common in females with a ratio of 1:2 male to female [7,33]. Approximately 90% of clefts are unilateral [34]. Among unilateral cases of CL/P, left-sided clefts are common (66%) than right-sided clefts at a 2:1 ratio of left- to right-sided clefts [35]. Figure 1 shows the prevalence of cleft lip and cleft palate.
Figure 1. Prevalence of Cleft Lip and Palate (CLP).

The epidemiological studies have reported, adult patients with CL/P may suffer from various difficulties such as esthetics, difficulty in speech, hearing, and psychosocial problems. These individuals may have episodes of depression, low self-esteem and low emotional development even after achieving satisfactory cosmetic, functional, and speech therapy. Many adults will reach a point at which they refuse take the final stages of dental and other surgical treatment. All these problems associated life-long impact on the quality of life of the CL/P patients [36,37].

3. Etiology of cleft lip with or without cleft palate (CL/P)

Although the precise etiology of CL/P is unknown, the complex embryogenesis of the lip and palate make these tissues vulnerable to a variety of potential interferences during a critical stage of development. The etiology is believed to be complex and multifactorial, involving various genetic factors, environmental factors and gene-environment interactions.
3.1. Genetic causes

Evidence for a genetic etiology has been available for many years. Scientific literature shows the heritability of NSCL/P (70%), evidence from twin studies and segregation analysis further confirmed the genetic role in the etiology of CL/P [38,39]. The risk of CL/P is more when a positive family history exists, and an affected parent has a 3% to 5% risk of having an affected child, when one child is affected, parents have a 40% chance of having another affected child [2].

3.2. Environmental causes

Several epidemiological studies showed an increased prevalence of CL/P in patients whose mothers were exposed to smoking, alcohol consumption (binge levels), antiepileptic medications, Corticosteroids, nutritional deficiencies (folic acid) and infectious diseases during pregnancy may adversely affect the intrauterine environment during embryogenesis [7,40]. These environmental factors found to increase the risk of NSCL/P. Recently, maternal illnesses such as hyperthermia, parental occupations, diabetes mellitus and obesity [41] have been identified as risk factors.

The preventive effects of maternal folic acid supplementation on NSCL/P are commonly reported, but the evidence remains generally inconsistent. Van Rooij et al. reported a 74% reduction in CL/P risk with using the folic acid supplements in addition to a high folate diet [42] and Wilcox et al. reported a 39% decrease in CL/P risk with using folic acid but no preventive effects were observed for cleft palate only (CPO) cases [43].

The deficiency of enzymes arylamine N-acetyltransferases (NAT1 and NAT2), glutathione S-transferase (GST), and Cytochrome P450 (CYP1A1) may cause greater risk of CL/P if the individuals were exposed to smoking byproducts during pregnancy. These enzymes play an important role in the detoxification and secretion of smoking byproducts and Cytochrome P450 (CYP1A1) is related to the bioactivation of chemicals such as dioxin in cigarette smoke. The increased risk resulting from exposure to maternal smoking during the periconceptual period raises the possibility that deficiencies in detoxification pathways and genes in certain interactions as a cause of NSCL/P [44].

A study reported that homozygous deletions of S-glutathione transferase M1 (GSTM1) and S-glutathione transferase T1 (GSTT1) in mother genome increased the risk of NSCL/P. However, correlation between smoking status, GSTM1/GSTT1 genotypes and risk of CL/P was not very significant [45]. A population-based case-control and family triad study in Norway showed association between a NAT2 gene and isolated cleft lip in case-triads [40] and, there was no association found between TGFA gene and smoking in the etiology CL/P in Indian population [46].

Maternal alcohol intake (binge levels) in short periods of time will increase risk of CL/P has been supported by association with variation in the alcohol dehydrogenase (ADH1C) gene, because the ADH1C involved in the metabolic pathways of many alcohols. Several studies showed an increased risk of nonsyndromic CL/P in women who reported drinking alcohol during the first trimester, compared with women who did not. The mutation of ADH1C gene has suggested its role in the etiology of NSCL/P [47,48].
3.3. *Gene-environment (GxE) interaction*

Cleft lip and palate is a complex disorder involving the multiple genes and environmental factors. It is essential to consider gene-environment interaction as it helps for a better understanding of the pathogenesis of the disease and analyzing both susceptible and non-susceptible individuals [49]. Several Studies identified gene-environment interactions of maternal smoking, maternal alcohol consumption and folic acid deficiency as a causative factor for NSCL/P [50,51].

Maternal smoking and folic acid intake are the two important factors that appear to modify genetic risks for cleft lip and palate. Studies have found gene-environment interactions between smoking and variants in transforming growth factors (TGF), muscle segment homeobox (MSX) and retinoic acid receptor genes [52]. Two polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene C677T and A1298C have been shown to decrease MTHFR activity and the C677T polymorphism also decreases circulating folate and increases homocysteine levels and associated with an increased risk of NSCL/P in Asian populations [53]. The observation that drinking high doses of alcohol in short periods of time will increase risk of CL/P has been supported by association with variation in the alcohol dehydrogenase (ADH1C) gene [47]. Genetic variants in TGFA, TGFB3 and MSX1 genes have been investigated for interactions with environmental risk factors such as smoking, alcohol consumption [54].

3.4. *Genetic etiology of CL/P*

A variety of genetic approaches have been used to identify genes and loci contributing to CL/P which includes animal models expression studies, genomic rearrangements and copy number variants, linkage studies, candidate gene-based association studies, candidate gene sequencing and genome-wide association (GWA) studies [4,55].

In the recent genomic era, advances in genetics and molecular biology techniques have explored the genetic basis of development of these craniofacial defects, and several genes and loci associated with CL/P have been discovered. This article provides an overview of the genes implicated in the etiology of Nonsyndromic CL/P (NSCL/P) as suggested by different human genetic studies, animal models, and other expression studies. Table 1 demonstrates the list of genes involved in the etiology of Nonsyndromic CL/P.
### Table 1. Genes involved in the etiology of Nonsyndromic CL/P.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal location</th>
<th>OMIM</th>
<th>Evidence</th>
<th>References</th>
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<td>188825</td>
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</table>

Notes: *GWAS: Genome-wide association studies, L: Linkage, M: Mutations, LD: Linkage disequilibrium.

### 4. Overview of genes involved in the etiology of Nonsyndromic CL/P

#### 4.1. The interferon regulatory factor-6 (IRF6)

The Interferon regulatory factor-6 (IRF6) is one of the most important and consistent gene implicated in the etiology of CLP and belongs to a family of transcription factors that share a highly
conserved helix-turn-helix DNA-binding domain. It is located on the ‘q’ arm of chromosome 1, between positions 32.3 and 41. Van der Woude’s syndrome (VDWS) is the most common form of syndromic CL/P and is characterized by CL/P, isolated CP, pits or mucous cysts on the lower lip, and hypodontia and accounts for 2% of all CL/P cases [56]. Popliteal pterygium syndrome (PPS) has all the features of VDWS plus popliteal pterygium, toe/fingers abnormality, syndactyly, and genital abnormalities. Mutation in the IRF6 causes these two autosomal dominant syndromes in CL/P [57], thereby confirming a common genetic etiology in both syndromes.

Evidence of IRF6 causing CLP/CP, has been confirmed in several populations by the research of Zucchero et al. (2004), Blanton et al. (2005), Jugessur et al. (2008), Huang et al. (2009) and subsequently in GWAS meta-analysis [58–62]. A Genome-wide association (GWA) study consisting of NSCL/P case-parent trios from different populations showed four SNPs of IRF6 having strong genome-wide significance with orofacial clefting [63]. Other studies also reported the substantial contribution of IRF6 in the etiology of nonsyndromic CL/P [25,64].

4.2. MSH homeobox 1 (MSX1)

Muscle segment homeobox 1 (MSX1) regulates and stimulates the appropriate protein required dedifferentiation process. It is also known as homeobox protein MSX-1/ HOX7/MSH Homeo Box Homolog 1 (Drosophila) gene. Human MSX1 gene located at 4p16.1 spans around 4.05 kb and consists of two exons and one intron. MSX1 gene has a role in cyclin D1 up-regulation; thus, it inhibits cell differentiation. It plays a vital role during the development of teeth and craniofacial structures.

In homozygous transgenic mice models, nonfunctioning Msx1 gene showed cleft palate and facial and dental abnormalities [65]. In humans, a nonsense mutation of MSX1 resulted in autosomal dominant tooth agenesis, cleft lip and cleft palate, isolated cleft palate in a Dutch family, suggesting MSX1 involvement in human clefting [66,67]. Several studies in different populations and a meta-analysis have reported the MSX1 gene as a causative factor in NSCL/P [68–71].

4.3. Transforming growth factor alpha (TGFA)

Transforming Growth Factor Alpha gene encodes a growth factor that binds the epidermal growth factor receptor, which activates a signaling pathway for cell proliferation, differentiation and development, so this gene has been studied extensively in the family of growth factors. TGFA plays an important role in the development of palate and present in the medial edge epithelium of palatal shelves. Several studies have demonstrated a significant association between transforming growth factor-alpha (TGFA) and CL/P [72]. A study showed infants with TGFA genotype whose mothers did not use multivitamins containing folic acid periconceptionally are at a higher risk of being born with CL/P [73]. A meta-analysis and other studies showed inconclusive data and failure of association between TGFA with CL/P due to genetic heterogeneity [74,75]. A combined case-parent trios and case-control study suggested gene to gene interaction between TGFA and IRF6 influences the risk of developing cleft lip with/without cleft palate [76]. Recently, two meta-analyses confirmed the TGFA Taq 1 polymorphism may be associated with the risk of CL/P [77,78].
4.4. **Bone morphogenetic protein 4 (BMP4)**

BMP4 is a member of the BMP family and transforming growth factor beta (TGFβ) superfamily of secretory signaling molecules that play crucial roles during cartilage and bone formation, tooth development and facial development. It is located on chromosome 14q22.2, consists of 5 exons and spans about 7 kb. Mutations in this gene are associated with orofacial cleft and microphthalmia in humans. A study reported BMP4 mutation in a child caused cleft lip and palate [79]. Several studies have suggested the risk of nonsyndromic oral clefts may be influenced by variation in the BMP4 gene [80,81]. Two different meta-analyses also confirmed the association of BMP4 gene SNP (rs17563) with NSCL/P [82,83].

4.5. **Paired box protein Pax-7 (PAX7)**

Paired box 7 is a member of the paired box (PAX) family, encode for specific DNA binding transcription factors and located at 1p36.13. It contains a paired box domain, an octapeptide, and a paired-type homeodomain. The Functions of PAX7 includes Neural crest development, fetal development, expressed in palatal shelves of the maxilla, Meckel’s cartilage, Nasal cavity and Myogenesis. Animal studies showed that mutant mice have a malformation of the maxilla and thus confirming its role in craniofacial development [84].

In humans, a case-parent trio study of PAX7 associated with NSCL/P in four populations (76 from Maryland, 146 from Taiwan, 35 from Singapore, and 40 from Korea) where they assessed the maternal transmission effects of PAX7 genes and they concluded that these genes might influence the risk of CL/P [85], a meta-analysis [86], genome-wide association studies [87,88] and other studies suggested a role of PAX7 in the etiology of NSCL/P [89,90].

4.6. **Runt-related transcription factor 2 (RUNX2)**

RUNX2 is a member of the RUNX family of transcription factors and encodes a nuclear protein with a Runt DNA-binding domain which is essential for osteoblastic differentiation and skeletal morphogenesis. In humans and mice study showed, the RUNX2 act as a transcriptional regulator for bone formation and tooth development. Mutations in the RUNX2 gene cause a rare autosomal dominant disorder cleidocranial dysplasia, characterized by skeletal defects, supernumerary teeth, and delayed tooth eruption, clefts of the palate or submucous palate [91–93]. A case-parent trio design consists of four populations (Maryland, Taiwan, Singapore, and Korea) were genotyped for 24 single nucleotide polymorphisms (SNPs) of RUNX2 gene, among that three SNPs showed significant excess maternal transmission suggesting RUNX2 may influence the risk of NSCL/P through imprinting effects [94]. Evidence of gene-environment interaction of the RUNX2 gene in a Chinese case-parent trio design showed maternal over-transmission RUNX2 markers and suggested it may influence the susceptibility to NSCL/P through interacting with environmental tobacco smoke [95].

4.7. **Small ubiquitin-like modifier 1 (SUMO1)**

SUMO1 is a protein coding gene involved in various cellular processes, such as nuclear transport, transcriptional regulation, apoptosis, and protein stability. In Mouse model, haploinsufficiency of
Sumo1 gene resulted in cleft palate [96]. In humans, genetic associations between NSCL/P and SUMO1 variants have been reported in different populations [97,98]. A meta-analysis provided empirical evidence of 4 single-nucleotide polymorphisms (SNPs) in the SUMO1 gene contribute to the risk of nonsyndromic cleft lip with or without palate [99].

4.8. Ventral anterior homeobox 1 (VAX1)

Ventral anterior homeobox1 is a transcriptional regulator containing a DNA binding homeobox domain. Genes of this family are involved in the regulation of body development and morphogenesis. The homeobox sequences of mouse and human VAX1 are identical. It is expressed in various craniofacial structures, and its deficiency causes cleft palate [100]. A homozygous missense mutation of vax1 was expressed in an Egyptian child from a consanguineous family with bilateral microphthalmia, bilateral CLP, and corpus callosum agenesis [101]. GWAS using case-parent triads from different populations two rare missense mutations in VAX1 replicated previous GWAS findings for markers in VAX1 in the Asian and Saudi population, and identified rare variants of VAX1 that may contribute to the etiology of CL(P) [102–104].

4.9. Forkhead box E1 (FOXE1)

The FOXE1 belongs to a forkhead box (FOX) /winged helix-domain transcription factor family involved in embryogenesis and located at 9q22.33. A mouse model study showed thyroid agenesis, cleft palate [105] similar to previously reported [106]. Mutations within the FOXE1 gene in two siblings resulted in congenital hypothyroidism, athyroidal and Cleft Palate [107]. Genome-wide association studies (GWAS) and meta-analyses also reported the significant association between FOXE1 and nonsyndromic CL/P in different populations [108,109].

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

CRISPLD2 gene located on chromosome 16q24.1 contains 15 exons and extends about 110 kb. In mouse embryos, Crispld2 expressed in nasopharynx, mandible, nasal cartilage, palate, and tooth development [110,111]. Three SNPs of CRISPLD2 in a northern Chinese population [112,113] and Next-generation sequencing of eighteen SNPs of CRISPLD2 confirmed genetic polymorphism with an increased risk of NSCL/P in a Chinese Xinjiang Uyghur population [114], in contrast, three SNPs rs1546124, rs4783099, and rs16974880 of CRISPLD2 gene did not show any association with clefts in Indian population [27].

4.11. The methylenetetrahydrofolate reductase gene (MTHFR)

Methylenetetrahydrofolate reductase (MTHFR) located on 1q36 and is a major enzyme of folic acid metabolism. Mutations in this gene are associated with methylenetetrahydrofolate reductase deficiency [115]. Several associations have been reported between the polymorphisms of the MTHFR gene and the risk of NSCL/P [116–118]. A systematic review and meta-analysis reported the association of MTHFR polymorphism of SNP (rs1801133) as a risk factor for NSCL/P [119]. A Next-generation
A sequencing study identified the mutation (c.G586A, p.G196S) in the MTHFR gene as a possible cause of NSCL/P [120].

4.12. **Wingless-type MMTV integration site family, member 9B (WNT9B)**

WNT9B is a member of the WNT gene family that encodes extracellular signaling proteins. These genes are required for body axis patterning, cell fate specification, cell proliferation and cell migration during embryonic development. WNT9B directly regulates facial development and expressed in the facial ectoderm at critical stages of midfacial morphogenesis [121]. WNT9B mRNA is expressed in maxillary, medial nasal, and lateral nasal ectoderm. During lip fusion, WNT9B is expressed in the epithelial seam between the fusing medial and lateral nasal processes [122,123]. It also signal through the canonical Wnt signaling pathway to regulate midfacial development and lip fusion and are therefore candidategene for an etiological role in NSCL/P [124,125].

Several studies have reported the involvement of WNT9B gene in the families of NSCL/P [126–129]. A miRNA study confirmed the role of miR-497-5p and miR-655-3p in the etiology of CL/P by inhibiting cell proliferation during lip fusion [130].

4.13. **Myosin heavy chain 9 (MYH9)**

Myosin heavy chain 9 (MYH9) is located on chromosome 22q13.1 and encodes myosin IIA heavy chain, which participates in a number of cellular functional activities, including the maintenance of cell shape, cytokinesis, migration, and adhesion [131]. It has been reported that polymorphisms of MYH9 are associated with a variety of diseases, including MYH9–related diseases (MYH9-RD), macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss and deafness, and cleft lip and palate [132]. During palatal morphogenesis, MYH9 is abundantly expressed in midline epithelial seam (MES) of palatal shelves before fusion suggesting its role during palate development and contribute to NSCL/P [133].

Several studies have reported the MYH9 role in the etiology of NSCL/P [134–136]. Further, a next-generation sequencing study consisted of 103 cases of nonsyndromicorofacial clefts and 100 normal controls in the Taiwanese population [137] and a case-control study also confirmed MYH9 association with NSCL/P [138].

4.14. **Other candidate genes**

A variety of genetic approaches have identified several genes and loci contributing to etiology of NSCL/P. Candidate genes located on different chromosomes involved in the etiology of NSCL/P is shown in Figure 2.

Advances in molecular and cellular biology techniques have led the way to the discovery of multiple genes involved in the etiology of NSCL/P. A multicenter association study identified various genes significantly associated with NSCL/P, including MSX1, SPRY1, MSX2, PRSS35, TFAP2A, SHH, VAX1, TBX10, WNT11, PAX9, BMP4, JAG2, AXIN2, DVL2, KIF7, and TCBE3, a Stepwise regression analysis revealed that out of 16 genes, 11 genes contributed to 15.5% of the etiology of NSCL/P in a Brazilian population [139]. Different genome-wide association studies have reported
multiple candidate genes such as IRF6, MSX1, SPRY1, SPRY2, CHD7, GABRB3, NOG, NTN1, MMP16, KRT18, DICER1, RAD54B, CREBBP, GADD45G, TFAP2A, VAX1, GSC, PTCH1, MYC, TAF1B, MAFB, OFCC1, ARHGAP29, WNT9B, FGFR1, FGFI0 [140,141] although 26 genes were studied, only 14 genes were associated with clefts in Chinese population. A Microarray hybridization analysis reported COL11A1, TERT, MIR4457, CLPTM1, ESR1, GLI3, OFD1, TBX1, PHF8 and FLNA, POMGNT2, WHSC1, GRM5, ALX1, PAX9, DLK1, FOXC2-FOXl1, MAU2, IRF6, MYCN, VAX1, MAFB [142] association in the etiology of NSCL/P in Chinese population, among these genes, only 14 genes were identified in the pathogenesis of NSCL/P and this evidence suggest that, genetic heterogeneity between the sub-phenotypes of NSCL/P and among different populations.

![Diagram of candidate genes located on different chromosomes involved in the etiology of Nonsyndromic CL/P](Diagram.png)

**Figure 2.** Candidate genes located on different chromosomes involved in the etiology of Nonsyndromic CL/P; individual chromosomes have been marked by using a colour scheme in which each gene has been labelled to their parent chromosome by the corresponding colours.

The etiology of cleft lip and palate is polygenic and multifactorial, model of inheritance can be influenced by several factors, such as gender of the affected individual, severity of the orofacial cleft, and number of affected relatives. Results from previous studies support the presence of heterogeneity among populations and the presence of multiple genes involved in the etiology of CL/P. Due to genetic heterogeneity associated with NSCL/P, a family with several affected individuals can actually represent the segregation of a single-gene disorder, which would not be promptly recognized based solely on
clinical evaluation. The recurrence risk among families with one first-degree affected relative may vary depending on the population and the identification of other individuals with CL/P in the family should be always interpreted with caution [143,144].

Significant knowledge of the genetic etiology and risk factors of CL/P has already been gained and is being used to reduce the overall health burden of these defects. Identification of specific genetic and environmental causes of CL/P could enable major changes in genetic counseling, improved programs for personalized medicine applications and aid in taking effective preventive measures. With the advances in genomic technology, understanding of the genetic mechanisms leading to CL/P will be achieved in the upcoming years and this will allow more accurate methods of genetic screening, identification high risk individuals and families, and improved prenatal diagnosis.

5. Conclusion

Genetic studies in humans have demonstrated that Cleft lip with or without cleft palate (CL/P) have a diverse genetic background and probably environmental factors influencing these malformations. Several studies have suggested genetic factors play an important role in the etiology of CL/P and by understanding the relative contribution of these candidate genes could be integrated into a genetic test for the weighed risk of CL/P.

Conflict of interest

All authors declare no conflicts of interest in this paper.

Web Resources:


References


