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Review Article

Genomic expression in non syndromic cleft lip and palate patients: A review

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ABSTRACT

Cleft lip and palate are common congenital anomalies with significant medical, psychological, social, and economic ramifications, affecting one in seven hundred live births. Genetic causes of non syndromic cleft lip and/or palate (NSCLP) include chromosomal rearrangements, genetic susceptibility to teratogenic exposures, and complex genetic contributions of multiple genes.

Development of the orofacial clefts in an individual will depend on the interaction of several moderately effecting genes with environmental factors. Several candidate genes have been genotyped in different population types, using case parent trio or case control design; also genes have been sequenced and SNPs have been reported. Quantitative and molecular analysis have shown linkage and association studies to be more relevant. Recent literature search shows genome wide association studies using microarray. The aim of this paper was to review the approaches to identify genes associated with NSCLP and to analyze their differential expressions.

Although no major gene has been confirmed, a lot of research is ongoing to provide an understanding of the pathophysiology of the orofacial clefts.

Cleft lip and palate are common congenital anomalies with significant medical, psychological, social, and economic ramifications, affecting one in seven hundred live births.[1] Its incidence varies according to race, gender and cleft type, being more common among Indian and Oriental populations (2.3 per thousand total clefts) and least common among Afro-Caribbean groups (0.6 per thousand total clefts).[2] NSCLP is a common congenital anomaly with incidence ranging from 1 in 300 to 1 in 2500 live births.[3–5] A child is therefore born with a cleft somewhere in the world approximately two and a half minutes. In India, cleft lip/palate occurs in nearly 1 in 500 live births; majority of which are not surgically corrected.[6] The number may be much more than expected as most of the births in rural areas are not reported.

As oral clefts are believed to be of multifactorial etiology, both genetic predisposition and environmental influences, such as age, sex, race; smoking, alcohol, caffeine, benzodiazepines, corticosteroids; as well as other occupational exposures, may play a role. The maxillary, medial nasal, and lateral nasal prominences through a complicated process of epithelial bridging, programmed cell death, and subepithelial-mesenchymal penetration lead to a defect of epithelial

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fusion involving many possible genetic loci or intracellular signaling pathways.

Segregation analyses demonstrate that genetic factors are important in the pathogenesis of NSCLP. Genetic causes of cleft include chromosomal rearrangements, genetic susceptibility to teratogenic exposures, and complex genetic contributions of multiple genes. Literature provides an overview of genetic approaches to identify disease genes for genetically complex birth defects.[7] Several genes that have a combined role in up to 20% of all clefts have been identified. Ongoing human genome-wide linkage studies have identified a major gene on chromosome 9, positive in multiple racial groups.[8] Population-based candidate-gene studies identify genes involved in the etiology where family-based linkage studies are compromised by lack of access to affected members, low penetrance, and/or genetic heterogeneity.

The aim of this paper is to review the approaches to identify genes associated with NSCLP and to analyze their differential expressions.

1. Review of literature

Literature was searched for key words " genes, genetic, cleft, cleft lip, cleft palate" to include articles published on various genetic studies conducted on cleft lip, palate genomics. The search yielded 850 relevant articles that had information on gene location, size and function and thus we finally, collected 134 references on the genes in relation with NSCLP. Online Mendelian Inheritance in Man catalog was found to list more than 400 single-gene causes of NSCLP.

2. Candidate genes

2.1. *MSX1 & TGFβ*

Muscle segment homeobox 1, (MSX1) is also known as homeobox 7, homeobox protein MSX-1, HOX7, HYD1, MSH homeobox homolog 1, MSH Homeo Box Homolog 1 (Drosophila) Gene, MSX1_Human, OFC5. The MSX1 gene provides instructions for making a protein that regulates the activity of other genes and acts during early development to control the program of craniofacial morphogenesis during development of teeth and craniofacial skeleton.

Mutations in MSX1 have been observed to contribute in NSCLP.[9–13] Human MSX1 gene maps to 4p16.1 locus and spans 4.05 kb. It contains two exons and an intron. MSX1 gene expression is associated with cyclin D1 up-regulation, thus inhibits cellular differentiation by regulating cell cycle.[9,14]

Transforming growth factor-beta 3 (TGFβ3) gene encodes a member of the TGF-beta family of proteins, secreted during embryogenesis and cell differentiation. A number of studies suggest show the role of TGFβ3 gene to be related to NSCLP.[5,15,16]

The TGFβ family is particularly involved in palate development and all isoforms 1, 2 and 3 are expressed during this process. Studies on TGF family genes suggest that their function in the embryonic palate is mediated through the smad signaling system.[17] TGFβ3 is expressed initially in the epithelial component of the vertical shelves. Later, it is also expressed in the horizontal shelves, but expression becomes undetected once the epithelial seam disrupts. TGFβ1 expression is limited to the horizontal shelves but like TGFβ3, switches off soon after epithelial seam disruption while TGFβ1, 2 accelerate palatal shelf fusion.[18–20]

MSX1gene and TGF family gene show mutations and may contribute to NSCLP.[21] Candidate genes TGFA, MSX1, and TGFβ3 in Vietnamese population have demonstrated transmission distortion for alleles of MSX1 for the whole population and identified two missense mutations including one (P147Q) in approximately 2% of the population.[21] Case-parent trio and case–control studies on the MSX1 gene in NSCLP from Korea showed results consistent with other studies in the US and Chile in determining the risk of CLP.[22] Transmission disequilibrium test analysis for MSX1 and TGFβ3 in South American children showed evidence of association with MSX1. With likelihood ratio test analysis, "cleft lip only" showed association with MSX1 and "cleft palate only" with TGFβ3.[23] In an association study between MSX1 polymorphism and NSCLP from Operation Smile Colombia, four alleles from MSX1 microsatellite sequence were analyzed. Significant statistical difference was found between patients who carried allele 3 and CLP. Allele 4 (heterozygous and homozygous form) was the most frequent in CLP (74%) patients and controls (82%).[24] This relationship, when studied by polymerase chain reaction (PCR) and denaturing polyacrylamide gel electrophoresis (PAGE), the allele CA4 frequency in CLP and cleft palate only group was significantly higher than that of controls.[25]

Candidate gene approaches have identified important roles for MSX1 and genes in the Fibroblast growth factor (FGF) family.[26,27] Evaluation of association data for four candidate genes using a population from Philippines, however, showed no evidence for association with previously reported allelic variants of transforming growth factor-beta 2 (TGFβ2), homeobox 7 (MSX1), or transforming growth factor-alpha (TGFA), or with the new TGFβ3 variant.[28] Linkage analysis performed in five affected pups to study evidence for linkage between the trait and TGFβ3 or MSX1 excluded TGFβ3 and MSX1 as candidate genes.[29]

Fiquet and colleagues studied the implication and role of angiogenesis-related genes in the etiology of CL/P and found that these genes participate in several biological activities and their implication might not be always related to angiogenesis defects.[30]

2.2. *IRF6*

Interferon regulatory factor-6 (IRF6) gene encodes a member of the interferon regulatory transcription factor (IRF) family. Family members share a highly-conserved N-terminal helix-turn-helix DNA-binding domain and a less conserved C-terminal protein-binding domain. Mutations in this gene can cause X-linked CLP, ectodermal dysplasia, Van der Woude's and popliteal pterygium syndromes.[31] This gene is found to play important role in palate formation. Candidate gene approaches have identified important roles for IRF6 and genes in the FGF family.[27] Single nucleotide polymorphism (SNPs) in and around IRF6, when tested for association with NSCLP in Honduran