

A Review on Candidate Genes or Loci and Their Importance in Non-Syndromic Cleft Lip and Cleft Palate

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Abstract

Non-syndromic orofacial malformations do not manifest any symptoms. Various signaling pathways are important in lip and palate development, but the specific genes in these pathways that play a role in causing oral clefts in humans remain unknown. Orofacial clefts are related to 14q chromosome with its associated candidate genes like *ISGF3G* at 14q11.2, *JAG2* at 14q32, *PAX9* at 14q13.3, *TGFB3* at 14q24.3 and *BMP4* at 14q22. Previous studies excluded the pathways linked to candidate genes and their role in formation of orofacial clefts. Linkage pathways of specific genes involved in formation of orofacial malformations are not well established in humans due to different varieties of approach. More studies need to be established in understanding the pathways linked to candidate genes involved in orofacial malformations.

Keywords Orofacial malformations; Cleft lip; Chromosome; Candidate genes; Segregation analysis

Introduction

Non-syndromic cleft lip with or without palate is a malformation disease. It does not show any symptoms of abnormal condition like abnormal physical appearance or psychological disorder. Candidate genes are located in a particular chromosome region suspected of being involved in the disease and contributing to a complex phenotype, based on understanding of biochemical function of gene or phenotypic mutations associated with that gene [1,2]. The etiology of oral clefts have been well known and 14q chromosome contains several oral cleft candidate genes such as *ISGF3G* at 14q11.2, *JAG2* at 14q32, *PAX9* at 14q13.3, *TGFB3* at 14q24.3 and *BMP4* at 14q22.2. DNA samples derived from cleft lip and palate subjects are probable and effective methods for identifying the candidate genes with their loci in genetic mapping [3].

Transforming Growth Factor-Alpha (TGFA)

Transforming growth factors (TGFA) are family growth factors and the gene of *TGFA* is located at chromosome 2p13 [4]. *TGFA* plays a significant role in the regulation of palate development. Previous genetic literatures stated the significant association between transforming growth factor alpha (*TGFA*) and CL/P [5,6].

Transforming Growth Factor-Beta 2 (TGFB2)

TGFB2 is one of the genes of conserved TGFB super-gene family and is located at chromosome 1q41 [7]. It is involved in palatogenesis along with other TGFB family isoforms. The expression of *TGFB2* can be observed in mesenchymal cells adjacent to medial edge epithelium and regulates mesenchymal cell proliferation and extracellular matrix synthesis of palate along with *TGF1* whereas *TGFB3* orchestrates fusion of the palatal seam [8,9].

Transforming Growth Factor-Beta 3 (TGFB3)

TGFB3 is associated with non-syndromic CL/P in humans and is located at chromosome14q24. This gene is 23 kb in size and contains seven exons. There are mixed reports regarding the role of this gene in relation to incidence of CLP [10].

Proto-Oncogene BCL3

Dominant mutation in *BCL 3* results in increased binding to the transcription factor and lead to inhibition of the expression of genes important to growth in the developing mesenchyme. Growth failure in mesenchyme cells leads to cleft palate formation.

Methylenetetrahydrofolate Reductase (MTHFR)

Methylenetetrahydrofolate reductase (*MTHFR*) located in chromosome 1q36 are and plays a crucial role in folic acid metabolism [11]. The size of this gene is about 19 kb and contains 5 exons. The common folate-related polymorphism associated with thermo-labile form of *MTHFR* is significantly more frequent in CL/P and higher mutation frequency of *MTHFR* in mothers of children with CL/P was noted [12,13].

Retinoic Acid Receptors (RARA)

A region on chromosome 11 associated with CLP in animal model is homologous to 17q21-q24 in humans and marked by retinoic acid receptor-a (RARA). It has association with CLP in some populations and supported the case for CLP locus linked to RARA in humans [6]. Citation: Janaki CS, Lokanadham S (2018) A Review on Candidate Genes or Loci and Their Importance in Non-Syndromic Cleft Lip and Cleft Palate. J Genet DNA Res 2: 1000107.

Interferon Regulatory Factor (IRF6)

IRF6 (Interferon Regulatory Factor 6) is a Protein Coding gene. This 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. The encoded protein may be a transcriptional activator. Mutations in this gene are also associated with non-syndromic orofacial cleft type 6. An important contributor of cleft lip and palate, but the functional variant leading to the defect has not yet been identified [14].

PAX9

The *PAX9* (paired box gene 9) at 14a 12-q13, encodes a transcription factor containing the DNA-binding paired domain. Mouse *PAX 9* is extensively expressed in the neural-crest-derived mesenchyme of the palatal shelves and tooth. *PAX9* Knock-out mice presented with secondary cleft palate, tooth agenesis, and other abnormalities [15]. *PAX 9* mutations in human are reported to cause hypodontia involving molars that are frequently accompanied by CL/P [16].

Current Concepts in Genetics of Non Syndromic Cleft Lip/Palate

The study of non-syndromic clefting in humans has been complicated by its inheritance patterns. Segregation analysis suggests a mixed model with elements of Mendelian (both autosomal recessive and dominant) inheritance with variable contributions of reduce penetrance, sex differences, and environmental overlays in different studies [17-19]. Attempting gene identification for such a complex disorders can be problematic [20]. Parametric linkage – based analysis is used when sufficient families are available on whom the linkage parameters of penetrance, gene frequency and inheritance pattern have been specified by prior segregation analysis. One can also use nonparametric approaches such as sib-pair or affected-pedigree – member strategies. Finally, the use of candidate gene – based association techniques can succeed, if high Quality candidate genes are available [21].

Key Candidate Genes for Non-syndromic Oral Clefts

The worldwide estimates of CLP and CP only vary by ethnicity and geographic region [22]. Research suggests that multiple genes are involved in oral cleft etiology. The most recent estimates suggest that anywhere from 3 to 14 genes contribute to cleft lip and palate [23]. There are various signaling pathways that are important in lip and palate development, but the specific genes in these pathways that play a role in causing oral clefts in humans remain unknown[19]. There have been consistent findings of an association with non-syndromic oral clefts for only one gene, interferon regulator factor 6 (IRF6); however, this gene does not account for the majority of the genetic contribution to non-syndromic oral clefts, and more genes remain to be identified. Studies using a variety of approaches have produced inconclusive or conflicting results, possibly because of inadequate power and population diversity [24]. Statistical evidence of interactions between IRF6 (transcription factor), IRF6 and TGFA has been reported [14]. The identification of interactive genes will be a crucial step toward providing relevant clinical information to families inquiring about risks for having a baby with cleft lip and palate.

Exclusion of Candidate Genes in Non-syndromic Orofacial Clefts

Despite of the many candidate genes investigated, only the *IRF6* gene has shown a convincing degree of consistency across studies and was considered to be responsible for 12%-18% of non-syndromic CL/CLP/CP cases [25]. These results were replicated in different populations, confirming the role of the *IRF6* gene in CL/CLP/CP formation in different ethnic groups [26]. Mutation screening of more than 20 non-syndromic clefts candidate genes showed that only 2%-6% of all screened individuals have mutations in genes including *FOXE1*, *GL12*, *JAG2*, *LHX8*, *MSX1*, *MSX2*, *SATB2*, *SKI*, *SPRY2*, *TBX10* [27,13].

Conclusion

Many studies excluded the pathways linked to candidate genes in non-syndromic orofacial malformations in humans. The complete linkage pathways of specific genes involved in formation of orofacial malformations are not well established in humans due to different varieties of approach in understanding the role of genetics in orofacial clefts. There are some candidate genes which were excluded in formation of orofacial clefts, but still the mutations of *PAX9*, *IRF6*, *MSX1* and *TGFA* and *B* series and other associated candidate genes have significant role in orofacial malformations.

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