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Updating Genetics Polymorphisms of Non-Syndromic Clefts Lip-Palates

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Abstract

Introduction: Non-Syndromic Clefts Lip-Palates (NSCLP/CP) are most common congenital malformation in the world, with very important psychic and social impact. Formation of NSCLP/CP arises from the interaction of environmental and genetic factors. This paper provides a review of recent progress in defining the genetic causes of NSCLP. **Methods:** A literature review was conducted on the Medline data by searching for the following keywords: genes, non-syndromic cleft lip-palate, and genetics of clefts lip-palates, until January 2018. **Results:** Various genes are identified in different population and country, with the study using case parent's trio. The aim of this study contributes to review relative gene which has been identify in non-syndromic cleft lip and palate, and to help to have a better understanding of the inheritance pattern of this pathology and the prevention of genetic disease. **Conclusion:** Although three major genes have been confirmed, the genetic research is necessary to provide an understanding of the pathophysiology of the clefts lip-palates.

Keywords

Cleft Lip, Cleft Palate, Cleft Lip and/or Cleft Palate, Non-Syndromic, Genetics

1. Introduction

The non-syndromic clefts lip-Palates or palates isolated (NSCLP/CP) are considered the most frequent congenital malformation in the world [1]. The prevalence of NSCLP/CP is estimated at 1/600 of births worldwide [2] with the birth prevalence varying based on geographic origin; it is higher in African population and lowest in Caucasians (1/500 vs. 1/2500 births, respectively) [1]. These differences appear to persist even after migration, suggesting that they are mediated by genetic, rather than environmental factors [3] [4]. Researchers are presently

working to identify the etiological variants in these novel loci for understanding developmental disorders that lead to NSCLP, and this knowledge should eventually result in improved prevention, treatment and prognosis.

The purpose of this literature review is to update the most frequently genes involved in the genesis of the NSCLP.

2. Material and Methods

A systematic literature search was conducted using electronic databases of the Medline data by searching for the following keywords: "cleft palate", "facial cleft", "Genetic", "cleft lip", and "non-syndromic". In addition, a combination of the following terms was also used: "Genetic cleft lip palate", "Genetic cleft lip palate" and "non-syndromic".

For the keyword: Genetics cleft lip palate, we found 1908 items (January 2018) speaking of location, size, and function of the genome responsible. Among these 1908 articles, only 30 articles speak about genetic complex of the NSCLP.

3. Results

In this review, we describe the genes and phenotypes associated, and identifying a genomic locus. These are described in detail below and summarized in Table 1.

4. Discussion

Craniofacial development is very complex with a wide range of genes involved, combined with the influence of environmental factors. Progress towards the

Table 1. Summarized genotypes of NSCLP/CP founded in literature review.

GENES	NAME	LOCUS	REFERENCES
CONFIRMES	IRF6	1q32-3q41	[5] [6] [7]
	VAX1	10q25	[8] [9]
	MYC	8q24	[6] [10]
	ABCA4	1p22.1	[10]
	MTHFR	1p36.312	[11] [12] [3]
	MSX1	4p16.2	[13] [14]
	TGFA	2p13	[15]
	GADD45G	9q22.2	[16]
UNDER STUDY	FOXE1	9q22.33	[17] [18]
	TMP1	15q22.2	[17]
	MAFB	20q12	[17] [19]
	SUMO1	2q33	[20] [21]
	PVRL1	11q23.3	[22] [23] [24]
	TGFB3	14q24	[25] [26]
	PDGFC	4q32	[27] [28]

definition of genetic variation underlying NSCLP using gene discovery techniques including wide linking genome mapping association and candidate gene approaches. The identification of key genes in the genesis of NSCLP/CP represents a major challenge. A recently published meta-analysis of the two broad GWAS (genome wide association study) studies on NSCLP identified six unknown regions of significant susceptibility [29]. This study increased the number of loci responsible for NSCLP/CP to twelve. Thus, we will treat in this sub-section the most frequently locus incriminated in the genesis of this malformation reported by Beaty *et al.* [29]. These include IRF6, MSX1, MHTFR and TFG A.

4.1. The Interferon Regulatory Factor 6 Encoding Gene (IRF6)

The Interferon Regulatory factor 6 (IRF6) gene is located on the long arm (q) of chromosome 1, between positions 32.3 and 41. Specifically, the IRF6 gene is found on base pairs 209, 785, 623 and base pairs 209, 806, 175 of chromosome 1. It is produce a protein playing an important role in early development. This protein is a transcription factor, which means that it attaches to specific regions of DNA control and helps control the activity of certain genes. The Interferon Regulatory factor 6 (IRF6) was the first founded factor involved in the two autosomal dominant syndromes in clefts lip-palate Vander Wood syndrome (VWS) and pterygium popliteal syndrome (PPS) [30]. This led to the hypothesis that IRF6 is likely to contribute to the etiology of CLP/CP, confirmed by the research of Zucchero *et al.*, involving several populations and subsequently resumed in both broad GWAS meta-analysis [31].

4.2. The Methylenetetrahydrofolate Reductase Gene (MHTFR)

Determining factors of genetic risk of NSCLP/CP has been the subject of numerous studies. It would then be possible that the variants of the genes involved in the pathway of folic acid metabolism could be associated with these risks. Among the genes involved in folic acid metabolism, is the MTHFR gene, and which has been most commonly associated with NSCLP/CP [32]. It produces an enzyme that catalyzes the methylation of the amino acid from homocysteine to methionine. Any defect on this route may result in methionine deficiency and an accumulation of homocysteine. In addition to the fundamental role of methionine as an important precursor in the methylation process of DNA and RNA, there is still the elevation of the serum homocysteine level in favor of teratogenicity during embryogenesis [33].

The coding gene for MTHFR is located at 1p36.312 and composed of 11 exons [34]. Several associations have been reported between the polymorphisms of the MTHFR gene and the risk of NSCLP/CP [35]. However, the results were contradictory, as is the case in a study by Han *et al.* [36]. It has been proved that the MTHFR gene would have a protective role rather than being a predisposing factor for NSCLP [36].

4.3. The Growth Foctor Alpha Encoding Gene (TGFA)

The gene encoding TFGA weighs 70 to 100 kilobases (kb), is located on the short arm of chromosome 2 (2p13) encoding a polypeptide of 50 amino acids [37]. This protein binds to the epidermal growth factor receptor (EGFR) and is located at the epithelium of the mouth during the closure of the palate [38].

An experimental study in the murine model without EGF [39] showed an increase in the incidence of CLP/CP. This study concluded that NSCLP/CP may have a genetic relationship with TGFA polymorphisms. On the other hand, Mann, Luetteke, *et al.* [40] reported that the mutant mice of the TGFA gene had damage to the skin, hair and eyes but not to the lip or palate. Case-control studies and triad cases in humans have reported contradictory results. Although several etiologic studies have emphasized that NSCLP/CP is associated with allelic variations of TGFA [41].

4.4. The Muscle Segment Homeobox 1 Gene (MSX1)

The MSX1 gene produces a protein that regulates the activity of other genes. The MSX1 gene belongs to a large family of homeobox genes that act at the onset of development to control craniofacial morphogenesis during tooth development.

The MSX1 gene corresponds to the locus 4p16.1 and extends over 4.05 kb. It contains two exons and one intron. MSX1 gene expression is associated with the D1 regulatory cycle, thus it inhibits cell differentiation. In homozygous transgenic animals, deficient in the MSX1 gene develop a cleft palate; show the failure of the development of the incisor as well as the stoppage of molar development [42]. In humans, the mutation of MSX1 showed an autosomal dominant form in dental agenesis [43]. Recently, a broad sequence analysis of MSX1 in 917 patients with CLP/CP identified mutations in 16 patients with a cleft lip with or without cleft palate or cleft palate alone, proving that this gene could be involved in both forms of cleft. The authors estimate that MSX1 mutations are responsible for only 2.2% in all NSCLP cases. A recent study has shown that the combined genetic study of rare variants of TGFA and MSX1 may increase the risk of cleft palate up to ten times, demonstrating the importance of gene-gene interactions in the etiology of NSCLP [44].

5. Conclusion

Understanding the genetic complex of NSCLP/CP allows for better preventive and clinical management by controlling risk factors and providing more accurate genetic counseling.

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