Brief communication

Gene involvement in cleft lip and palate (CLP) patients

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Abstract:
It is supposed that the most frequent birth defect worldwide is clefts of the lip and/or palate (CL+-P). The frequency is non-syndromic where CL+-P happens in segregation of additional phenotypes; and syndromic clefts are referred when one or more additional features are involved. The etiologies of CL+-P is multifaceted and occupy both major and minor genetic influences with changeable relations from environmental factors. This study extends the involvement of various genes, which are responsible for both syndromic and non syndromic CL+-P patients.

Key words: *gene; syndrome; non syndrome; cleft lip and palate*

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Cleft lip and/or palate(CL+-P) is one of the most frequent congenital anomalies are affecting 1 in every 500 to 1000 births worldwide [1].The frequency are non-syndromic where CL+-P occurs in segregation of other phenotypes. And syndrmic clefts are referred when one or more additional features are involved. CL+-P has a major clinical contact requiring surgical, dental, orthodontic, speech, hearing and psychological treatments or therapies throughout childhood. The etiologies of CL+-P is multifaceted and occupy both major and minor genetic influences with erratic connections from environmental factors. Although many studies have been done to find the genetic pattern of this malformation, there is still no precise answer. It is indispensible to highlight the gene involvement in CL+-P patients according to literature survey.

Carinci et al. [2] reviewed the genes and available loci in the literature whose participation in the beginning of non syndromic orofacial cleft (OFC) have more sound scientific proof. It is established from several genetic studies on human populations have that CL+-P and cleft palate isolated (CPI) have different genetic backgrounds and, therefore, environmental factors probably disclose only these malformations. OFC from 1 to 10 have been accredited in CL+-P several loci. The first locus, OFC1, has been charted to chromosome 6p24. Other CL+-P loci have been charted to 2p13 (OFC2), 19q13.2 (OFC3) and 4q (OFC4). OFC5—8 are acknowledged by mutations in the MSX1, IRF6, PVRL1, and TP73L gene. OFC9 maps to 13q33.1-q34, whereas OFC10 is related with the SUMO1 gene. In cleft inception, MTHFR, TGF-b3, and RARA play a role in additionally. At present TBX22 is also identified in CPI.

On chromosome 6, inside the region 6p24.3, studied using YACs proved the existence of a major dominant gene referred to as OFC1, placed closely to HGP22 and AP2 genes involved in the morphogenesis of human face. In some populations the association of CL+-P with mutations of the TGFA gene located on chromosome 2p13 (locus OFC2) was strongly proved [3].

A similar study about gene involvement in CL+-P revealed that the risk factor of CL+-P were associated with TGFA, TGFB2, TGFB3, MSX1, MTHFR BCL3 & RARA [4].

Kohli and Kohli [5] discussed the etiology of CL+-P

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Table 1: Gene involvement in CLP patient, literature survey.

Author & year	Type of cleft	Susceptible loci/locus	Chromosomic location	Mutation identified	Association
Carinci et al. (2)	NS CL+-P	OFC1	6p24-p23	Occur	
		OFC2	2p13		Found
		OFC3	19q13.2		Found
		OFC4	4q21-q31		Found
		OFC5/MSX1	4q16	Occur	
		OFC6/IRF6	1q32.3-q41	Occur	
		OFC7/PVRL1	11q23.3	Occur	
		OFC8/TP73L	3q28	Occur	
		OFC9	13q33.1-q34		
		OFC10/SUMOL	2q33		
		MTHFR	1q36	Occur	
		TGFB3	14q24		Found
		RARA	17q21.1		Found
	CPI		2q32	Occur	
	CPX	TBX22	X 49.0	Occur	
Tudose and Bara (3)	CL+-P	OFC1	6p24.3		
		OFC2-TGFA	2p13	Occur	Found
Rajion and Alwi (4)	CL+-P	TGFA	2p13	Occur	Found
		TGFB2	1q41		Not found
		TGFB3	14q24	Occur	Found
		MSX1	4q25	Occur	Found
		MTHFR	1q36	Occur	Found
		BCL3	19q13.2		
		RARA	17q21-q24		Found
Kohli and Kohli (5)	S CLP	TBX22	Xq21	Occur	
		PVRL1	11q23	Occur	Found
		IRF6	1q32	Occur	
	NS CLP	TGFA	2p13		Found
		MSX1	4p26	Occur	Found
		MTHFR	1p36		Found
		TGFB3	14q24		Found
		SATB2	2q32	Occur	
		ACOD4	4q21	Occur	
		CLPTM1	19q13	Occur	
			6p23	Occur	
Chevrier et al. (6)	NS CLP	MTHFR			
Jugessur et al. (7)	CP	TGFB3	14q24		Not found
		MSX1	4p16		Found
		TGFA	2p13		Found
	CL+-P	TGFB3	14q24		Little asso--ciation found
		MSX1	4p13		Little asso--ciation found
		TGFA	2p13		Little asso--ciation found
Marcano et al. (8)	CPX	TBX22		Occur	
Braybrook et al. (9)	CPX	TBX22	Xq21	Occur	
Gorski et al. (10)	CPX	DXYS1	Xq21.3	Not occur	
		PGK1	Xq13	Occur	
Singh et al. (11)	NS CLP	TGFB3 rs2300607	14q24	occur	

from recent data and conducted a search of the MEDLINE database (Entrez Pub Med) from 1986 to 2010. They established that several genes responsible for syndromic CL+-P. Three of them are T-box-transcription factor-22 (TBX22), poliovirus receptor-like-1 (PVRL1), and interferon regulatory factor-6 (IRF6)—were responsible for causing cleft palate X-linked (CPX), CL+-P ectodermal dysplasia syndrome, Van der Woude and popliteal pterygium syndromes, correspondingly they were also implicated in non syndromic CL+-P.

An investigation of the role of maternal folate intake was done by Chevrier et al. [6]. Their assessment was about diet or vitamin supplementation and found CL+-P and CPI was on risk because of methylenetetrahydrofolate reductase gene (MTHFR) polymorphism and their interaction.

262 case-parent triads from a population-based study of OFC in Norway were selected and analyzed TGFA, TGFB3, and MSX1 which were responsible for OFC or not.. 174 triads of CL+/-P cases and 88 triads of CPI cases were taken for examination. A little participation was observed of any of these genes with CL+-P and the robust association was a 1.7-fold risk with two copies of the TGFB3-CA variant. Among CPO cases, there was a 3-fold risk with two copies of the TGFA TaqI A2 allele, and no increase with one copy. Among children homozygous for the MSX1-CA A4 allele, TGFA genotype was even stronger raising the possibility of interface between these two genes [7].

TBX22 was scrutinized with a large number of CL+-P patients with no pre-selection for legacy or ankyloglossia which was a familiar feature of CPX. Mutations in CPX families and united phenotype/genotype analysis of the familial cases have been observed by Marcano et al. [8]. Cleft palate and ankyloglossia together were commonly shown by males but CPO and/ or ankyloglossia were shown by families which indicating that defects are distinct parts of the phenotypic spectrum. It can be apprised that for cleft palate, a significant risk factor is TBX22.

Distinctive mutation is occurred in CPX by T-box-containing transcription factor TBX22 [9]. According to their explanation, in early human development, TBX22 is noticed in the palatal shelves and is highest prior to elevation to a horizontal position above the tongue. In case of CPX patients mRNA was also identified in the frenulum area of the base of the tongue which is communicated with ankyglossia. However, they completed their study with the CPX phenotype, TBX22 is completely reliable gene factor.

In a study also executed DNA marker linkage of a large British Columbia (B.C.) Native family with CPX found DXYS12 and DXS17 was responsible gene for CPX which were located to theXq21.3-q22 region [10].

TGFB3 rs2300607 (IVSI+ 5321) gene is associated with non syndromic CL+-P and may be a good screening marker for non syndromic CL+-P [11].

In a study assessing various factors affecting degree of malocclusion as favorable and unfavorable dental arch relationship of Japanese unilateral CLP patients revealed, clefts patients tend to develop unfavorable dental arch relationship not only as an effect of primary surgery but also due to a genetic influence of family history of class III [12].

The results of literature survey of involvement of gene in CLP patients are shown in Table 1.

In all-purpose, the genetic cause of CL+-P is still controversial because of genetic intricacy of clefting. Consequences from earlier studies support the presence of heterogeneity among populations and the presence of multiple genes concerned in the etiology of CL+-P. Furthermore, current scientific advances in gene manipulation promises a motivating time ahead for CL+-P research.

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