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Review Article

Genetics of Cleft Lip and Palate – Is it still patchy?

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Abstract

Clefts of the lip and/or palate (CL/P) are immediately recognizable disruptions of normal facial structure. Approximately 1 in 700 children born have a cleft lip or a cleft palate or both with a lifetime cost of treatment estimated at $200,000. CLP and CP individuals may experience difficulties in feeding, speaking, hearing and social integration. Recent successes in genome-wide linkage and association studies have identified novel loci that are significantly associated with CLP. In larger cohorts of people with CL/P, approximately 20% have other relatives with CL/P, and an increased prevalence is observed among first and second degree relatives. Many syndromes with phenotypes that include CL/P are now known. In some of the CL/P syndromes, the genes involved have been identified and the list is constantly increasing, primarily due to improved sequencing facilities. Genetics of NSCLP has been investigated by various studies such as Familial and Segregational Analysis, Twin Studies, Linkage Analysis, Association studies. There is overlapping of genes determining syndromic and non¬syndromic forms of CL /P. Greater efforts are necessary in order to have a complete picture of the main factors involved in lip and palate malformation.

INTRODUCTION

Cleft lip (*cheiloschisis*) and cleft palate (*palatoschisis*), which can also occur together as cleft lip and palate, are variations of a type of clefting congenital deformity caused by abnormal facial development during gestation. Clefts of the Lip and/or Palate (CLP) are immediately recognizable disruptions of normal facial structure. It is the non-fusion of the body's natural structures that form before birth. Orofacial clefts, notably Cleft Lip (CL) and Cleft Palate (CP), are the most common craniofacial birth defects in humans and represent a substantial personal and societal burden. Approximately 1 in 700 children born have a cleft lip or a cleft palate or both with a lifetime cost of treatment estimated at $200,000 [1,2]. In decades past, the condition was sometimes referred to as harelip, based on the similarity to the cleft in the lip of a hare, but that term is now generally considered to be offensive.

Clefts involving the Lip and/or Palate (CLP) or isolated Clefts of the Palate (CP) are a significant congenital anomaly, requiring complex long-term treatment and having lifelong implications for those individuals unfortunate enough to be affected. They represent a complex phenotype and reflect a breakdown in the normal mechanisms involved during early embryological development of the face [3].

CLP does cause considerable morbidity to affected children and imposes a substantial financial risk for families with a concomitant societal burden [2]. CLP and CP individuals may experience difficulties in feeding, speaking, hearing and social integration. This can be corrected by varying degrees of surgery (multiple craniofacial and dental surgeries), speech & hearing therapy and psychosocial intervention.

Recent successes in genome-wide linkage and association studies have identified novel loci that are significantly associated with CLP. Researchers are currently striving to identify the etiologic variants at these novel loci to understand the developmental disturbances leading to CLP [4-8]. This knowledge should eventually result in improved prevention, treatment and prognosis for individuals with these conditions.

This review article was planned to understand the etiologies of clefting and ultimately summarising the ways of prevention, treatment and prognosis for individuals affected by orofacial clefting.

Genetic regulation of the development of the clefts

The palate is formed by the fusion of one median palatine process (primary palate) and two lateral palatine processes. The median palatine process is formed by the fusion of right and left medial nasal processes. The fused medial nasal processes form median part of upper lip, the part of upper jaw (which carries four incisors) and the primary palate.

The two lateral palatine processes are formed by shelf-like outgrowths from the maxillary processes in the 6th week of development. The growth of shelf-like process depends upon the interaction between ectoderm and mesenchyme. The following important genes play important role in the development of the palate. The Sonic Hedgehog (SHH), Bone Morphogenetic Proteins (BMP), Fibroblast Growth Factors (FGF) and members

of the Transforming Growth Factor β (TGF β) gene super family determine the formation of the palate [9]. Over 300 syndromes are known to have clefting of the lip or palate as an associated feature. Isolated cleft lip with or without cleft palate belongs to a group of relatively common multifactorial congenital defects [10].

Etiology of clefts

The etiology of CL/P is complex and thought to involve genetic influences with variable interactions from environmental factors. The etiological factors of cleft lip and cleft palate can be grouped as under:

A. Nongenetic: This includes various environmental (teratogenic) risk factors which may cause CL/P.

B. Genetic: Genetic causes include:

Syndromic: Here the cleft is associated with other malformations. Usually, it is due to a single gene (monogenic or Mendelian) disorder. The clefting may also occur due to other chromosomal abnormalities due to multiple gene involvement.

Nonsyndromic: Here the cleft is mostly an isolated feature and occurs in the vast majority of individuals having a cleft-lip or palate (up to 70% cases). In this form of cleft neither a recognized pattern of malformation nor a known cause for the disorder can be identified.

Besides the genetic factors, environmental factors also play a very important role in the etiology of CL/P. Warkany et al (1943) found a higher incidence of congenital malformations, including cleft palate in the off springs of female rats deprived of riboflavin. Despite of so many researches on environmental factors and their influence on CL/P, no single environmental factor has been identified as posing a major risk for CL/P.

Antileptic medication, alcohol intake and smoking have been shown to aggravate the risk of CL/P and lead to other to other malformations in humans. However, alcohol intake, anti-epileptic medication, and smoking during pregnancy have all been shown to increase the risk of CL/P and other malformations in humans [11-13]. Only weak or ambiguous results have been found for folic acid and other nutrients, maternal disease and stress during pregnancy, chemical exposures and corticosteroids [14].

ROLE OF GENETICS IN CLEFT LIP AND PALATE

Various epidemiological observations have laid the foundations of the role of genetics in the etiology of cleft lip and palate. In larger cohorts of people with CL/P, approximately 20% have other relatives with CL/P, and an increased prevalence is observed among first and second degree relatives [15]. Monozygotic twins (60%) have considerable higher concordance rate than dizygotic twins and siblings (5-10%) [15-17]. Syndromic CL/P cases also indicate a genetic aetiology, because more than 400 known syndromes include orofacial clefting, and many of these follow classic Mendelian inheritance patterns.

Clefts does not have simple monogenic basis because of the segregation patterns which do not fit the classical Mendelian inheritance patterns. Segregation analyses point to polygenic or multifactorial inheritance, with each locus only providing a minor contribution to the risk [17,18]. Segregation analysis of CL/P in multiplex families has estimated that the most likely number of involved loci is between 2 and 14 [19]. Polygenic inheritance specifically complicates the unravelling of the etiology of CL/P. Factors like environmental, maternal genotypes also play a very important role in complicating the dissection of the complex Condition (CL/P) [20-22]. Genetic research in complex diseases, such as CL/P, has experienced some successes recently, and the hope that unravelling this frequent and partly disabling malformation may in fact offer improvement to patients with CL/P in the future, spurs the continuing investigation of the genetic aetiology in CL/P.

Syndromic forms of cleft lip and palate

Many syndromes with phenotypes that include CL/P are now known. A search in OMIM - Online Mendelian Inheritance in Man (as of February 2014) revealed 365 and 667 hits searching for “cleft palate” and “cleft lip” respectively. In some of the CL/P syndromes, the genes involved have been identified and the list is constantly increasing, primarily due to improved sequencing facilities [23] (Table 1).

Non-Syndromic forms of cleft lip and palate

The majority of orofacial cleft cases lack additional features and are categorized as “non syndromic,” that is, 70% of all CL/P cases and 50% of all CPO cases.[24] Cleft lip with or without cleft palate is a common birth defect found in more than 200 recognizable syndromes, but more often as an isolated birth defect, called Nonsyndromic Cleft Lip with or without cleft Palate (NSCLP) [24]. NSCLP occurs in 1/1,000 Caucasian live births with males affected twice as frequently as females. A similar birth prevalence of NSCLP has been reported in the Hispanic population but is less frequent among African-American live births. NSCLP affects approximately 4,000 newborns /year in the U.S. and has a significant impact on the health care of these children. Although many studies have reported the prevalence of CL/P, those that have distinguished CLP from CL observed that CLP is twice as common as CL [25]. While surgical techniques have improved facial repair, NSCLP is associated with medical and social consequences.

The nonsyndromic clefting is said to be polygenic in nature. It is produced out of interaction between a number of genes; each producing a small effect that add up together to create the clefting. In other words, a cleft occurs when, the total genetic liability of an individual reaches a certain minimal level termed the threshold. It should be noted that every individual carries some genes that predisposes cleft formation but if the liability due to these genes is less than the threshold or the critical levels, no cleft results.

NSCLP is also said to be a complex multifactorial trait with interactions between genetic and environmental factors playing an important role in its causation. As the etiology of NSCLP is complex, many reports in the literature are contradictory [26].

Genetics of NSCLP has been investigated by various studies such as Familial and Segregational Analysis, Twin Studies, Linkage Analysis, Association studies.

Familial and Segregational Analysis have indicated towards a multifactorial mode of inheritance while others are of opinion

Table 1: Syndromic forms of cleft lip and palate.

Syndrome	Gene *name (symbol)*	*Location on chromosome*	*Inheritance*
Waardenburg syndrome, type IIA	Microphthalmia-associated transcription factor(M ITF)	3p14.1-12.3	AD
DiGeorge syndrome	DiGeorge syndrome chromosome region (CATCH22)	22g11	AD
Treacher-Collins mandibulofacial dysostosis	Treacle (TCOF1)	5q32 -q33.1	AD
Van der Woude syndrome	Interferon regulatory factor 6 (IFRF 6)	1q32-q41	AD
CLP-ectodermal dysplasia synderome	Poliovirus receptor related –1 (PVRL1)	11q23.3	AR
Ectrodactyly, ectodermal dysplasia orofacial cleft syndrome (EEC)	p63	3q27	AD
Zollinger syndrome-3	Peroxisomal membrane protein-3 (PXMP3)	8q21.1	AD
Diastrophic dysplasia	Diastrophic dysplasia sulfate transporter (DTDST)	5q32-q33.1	AR
Gorlin syndrome (Basal cell nevus syndrome)	Patched (PTCH)	9q22.3	AD
Waardenburg syndrome, type I	Paired box homeotic gene-3 (PAX3)	2q35	AD
Simpson dysmorphia syndrome	Glypican-3 (GPC3)	Xq26	X-linked
Phenylketonuria	Phenylalanine hydroxylase (PAH)	12q24.1	AR
Holoprosencephaly, type 3	Sonic hedgehog (SHH)	7q36	AD
Retinoblastoma	Retinoblastoma (RB1)	13q14.1-q14.2	AD
Crouzon craniofacial dysostosis (including Apert and Pfeiffer syndromes)	Fibroblast growth factor receptor-2 (FGFR2)	10q26	AD
Stickler syndrome, type II	Collagen type XI, alpha-2 chain (COL11A2)	6p21.3	AD

Besides the above mentioned syndromes, mutations in genes MSX, TBX 22 are also one of the etiological factors of syndromic clefting.

Table 2: Possible genes whose mutation may result in the nonsyndromic clefting.

Name of the candidate gene	Symbol	Ch. Location
Transforming growth factor-alpha	(TG FA)	2p13
Transforming growth factor-133	(TGF133)	14q24
Methylene tetra-hydrofolate Reductase	MTHFR	1p36.3
Blood clotting factor XIII gene	F 13A	6p24-25
Endothelin-1 gene	ET1	6p24
Proto-oncogene BCL3	BCL3	19q13.2
Retinoic acid receptor alpha gene	RARA	17 (t15/17)
MSX-1	MSX-1	4q25

that the inheritance has a mixture of monogenic and multifactorial patterns.

Twin Studies has shown the concordance rate in monozygotic twins is approximately 25 to 45% as opposed to 3-6% in dizygotic twins [15-17]. On the other hand, lack of complete concordance was also found similar to any other multifactorial trait. This suggested involvement not only of genetic but also of environmental factors in the causation of nonsyndromic clefting.

Linkage analysis studies are based on the co-segregation of genetic loci with disease and can be performed in large, multiplex families or in pairs of affected relatives. To date, 13 genome wide linkage scans have been performed for NSCLP. Analysis of breakpoints in patients with balanced rearrangements has identified CLPTM1, SATB2, SUMO1, and FGFR1 as candidate genes for CL/P, and implicated 9q and 17q as potential risk loci [27]. Association studies are based on two approaches, i.e. candidate gene approach and genome wide association studies which are reported for nonsyndromic clefting. Association studies have identified many genes for the clefting (Table 2).

CONCLUSION

One may say that genetic analysis of CL/P is quite confusing as mutation screening of specific candidate genes, association studies and even genome-wide scans have largely failed to reveal the exact molecular basis of human clefting. There is also overlapping of genes determining syndromic and nonsyndromic forms of CL /P. Greater efforts are necessary in order to have a

complete picture of the main factors involved in lip and palate malformation. These elements will permit us to better understand and better treat patients affected by clefting.

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