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Genetic component and oral clefting – an overview

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ABSTRACT

Cleft lip and palate is a congenital defect which arises from the interplay of multiple genetic and environmental factors. Dysmorphogenesis and abnormal growth is the most exciting of the challenges we face today as we strive to understand how environmental influences interact with and cause changes in the expression of the genetic factors governing the behavior of those cells which will give rise to the entire human body, and especially the face and palatal regions. The treatment of defective genes is very much a part of the current clinical agenda dealing with craniofacial defects. The basic scientist, the dysmorphologist, the clinician, and, importantly, those with natural or acquired craniofacial defects have gained significant advantage from the critical use of available information coming from classical and experimental studies of human morphogenesis. These advantages will continue to increase as laboratory scientists and clinician scholars move rapidly together into the world of molecular and gene biology. This article highlight the overview of genes that are possibly responsile for the formation of Cleft lip with or without cleft palate.

Keywords: oral clefting, overview, palate.

Introduction

Orofacial clefts represent a common class of congenital malformations and are a major public health concern. The worldwide prevalence of clefts has been estimated as approximately 1 in every 1000 newborns, a figure that is higher in certain ethnic groups[1]. Orofacial clefts can occur as part of complex malformation syndromes, or as an isolated anomaly, also called non-syndromic clefting. According to the National centre on Birth Defects and Developmental Disabilities (NCBDDD), birth defects affect about 1 in every 33 babies born in the United States each year[2]. They are the Leading cause of infant deaths, accounting for more than 20% of all infant deaths. Cleft lip with/without cleft palate (CL/P), collectively termed oral clefts, are the Second most commonly observed birth defects among newborns after congenital heart defect. Craniofacial development is one of the most complex and tightly controlled events during embryonic development. Disturbances during this period, which is critical for the formation of face (4-10 weeks for humans) may lead to orofacial clefts[3].

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Affected infants experience feeding difficulties during early weeks of life, resulting in nutrition problems and weight loss[4]. A study conducted in Swedish infants born between 1973 and 1992 showed that those affected with cleft lip and palate were lighter and shorter as compared with unaffected controls subjects[5]. Even after treatment affected individuals experience various health and psychosocial problems for e.g. higher risk for chronic otitis media, which may lead to conductive hearing loss[6]. Additionally, significantly increased lifetime mortality is associated with non-syndromic CL/P. A long-term follow-up study of 5331 Danish individuals with Non-syndromic cleft lip with/without cleft palate (NS CL/P) found a standardized mortality ratio of 1:4 for males and l:8 for females[7].Rare syndromes with oral clefts have distinct genetic causes where as the more common non-syndromic form of clefting has a multifactorial etiology with both genetic and environmental components, challenging the identification of underlying etiologies. Studying genetic factors involved in cleft lip and palate is vital to better understand its underlying etiologies and to improve the diagnosis, treatment, prognosis and eventually prevention, of this devastating birth defect.

Candidate genes

FOXE1

FOXE1 is a member of the forkhead/winged helix-domain transcription factor family, whose members are primarily involved in embryonic development. Targeted disruption of the mouse FOXEl gene results in cleft palate and thyroid malformation[8]. Loss-of-function mutations within its forkhead DNA-binding domain were shown as the cause of the Bamforth-Lazarus syndrome manifested by thyroid agenesis, choanal atresia, bifid epiglottis, spiky hair and cleft palate[9]. A meta- analysis of 13 genome-wide linkage studies showed a susceptibility gene on 9q22, in the vicinity of FOXEI also including other strong candidate genes. A recent mutation screening in NS CL/P cases detected missense mutations in two unrelated patients[10]. Subsequently, significant association between SNPs across FOXEI and NSCL/P has been detected in multiple populations; however no common coding variants have been identified, except a polymorphic polyalanine tract that shows no association with clefting. Efforts at identifying the causative variant(s) in the regulatory elements of FOXE1 are currently underway.

MSX1

Ablation of the murine muscle-segment Homeobox I (MSXI) gene resulted in a variety of craniofacial defects, including complete cleft of the secondary palate[11]. Subsequently, a nonsense mutation segregating with tooth agenesis and mixed clefting phenotype was found in an extended Dutch family suggesting that it also plays a role in human clefting[12]. Significant association between SNPs in MSX1 and NS CL/P and CPO was shown in different populations of diverse origin[13,14]. Direct sequencing of the MSX1 coding regions showed that mutations in MSXI could account for approximately 2% of NS CL/P cases[15]. However no common coding mutations have been identified. Mutation screening in two functionally characterized enhancer elements that drives MSX1 expression in the pharyngeal arch and facial ectoderm, revealed multiple very low-frequency variants at significantly conserved nucleotide positions, some of them only present in affected individuals.

SUMO1

SUMO1 gene is a 101 amino acid polypeptide involved in post-translational modification of a variety of proteins. SUMO1 haplo-insufficiency resulting from a balanced reciprocal translocation was found in a case with isolated unilateral cleft lip and palate. It is strongly expressed in the upper lip, primary palate and medial edge epithelium of the secondary palate in the mouse at E13.5 and SUMOl-deficient mice also have a cleft palate phenotype[16]. Ablation of the Eyal gene was shown to increase the incidence of cleft phenotype in mice in compound heterozygous state with SUMO1.

TBX22

Function impairing (nonsense, frame-shift, splice-site and missense) mutations in the T-box transcription factor gene TBX22 result in X-linked cleft of the secondary palate (CPX), usually associated with ankyloglossia or tongue-tie. Its expression was localized to the developing palatal shelves and the base of the tongue where the ankyloglossia is observed. A previous genome-wide linkage analysis in NS CL/P families identified a susceptibility locus in the TBX22 vicinity suggesting that the linkage signal may arise from this gene. In addition, mutations inTBX22 were also found in individuals with isolated CPO[17]. A recent study using an array of in-vitro functional assays demonstrated that TBX22 functions as a transcriptional repressor, and pathogenic missense mutations in the DNA-binding domain disrupt its DNA binding affinity and impairs its repression ability[18]. One interesting finding in this study was that regardless of the type and position of these missense mutations, they all compromised post-translational modification in SUMO1 gene translated protein.

GSTT1

The most well-established gene-environment interaction involved in human birth defects is the interaction between the null allele of glutathione S-transferase theta-l gene (GSTT1) and maternal smoking in orofacial clefting. GSTT1 is involved in the second phase of the detoxification pathway and it is highly expressed in embryonic craniofacial structures. In a case-control study, reported increased risk of orofacial clefting when mothers carry the GST77-null genotype and smoke cigarettes or when both mothers and infants carry the null genotype and mothers smoke. A recent comprehensive study on a well-defined, large-sample size from Iowa and Denmark identified significantly elevated risk for orofacial clefting in individuals with GSTT1-null genotype and whose mothers smoke during pregnancy ,whereas the association with either G5Tri-null allele or smoking was relatively less significant, demonstrating a clear gene-environment interaction[19].

TGFA

Significant interaction between the Taql site marker in the TGFA gene and smoking in isolated clefting was established[20]. The rare C2 allele of Taql site showed no association with clefting alone, however significantly increased risk of CPO among infants carrying the C2 allele was observed if the mother smoked during pregnancy suggesting potential gene-environment interaction[36].

Interferon Regulatory Factor 6 (IRF6)

IRF6 belongs to a family of transcription factors that share a highly conserved winged-helix DNA binding domain with a penta-tryptophan motif characteristic of IRF family. IRF6 consist of 467 amino acids encoded by a 4.3 kb transcript transcribed from 9 exons on the chromosomal arm 1q32. All IRF members bind to a consensus DNA-binding motif, called the Interferon stimulatory Response Element (ISRE), found mostly upstream of genes activated upon viral infection[21]. To date, nine members of this family of transcription factors have been described. All IRF members, except IRF6, have been implicated in interferon and immune response regulation, as evidenced by a series of knockout mouse studies[22]. However, the role of IRF6 in immune regulation is not yet known. IRF6 has also been shown to bind to consensus ISRE motif, although its in vivo targets have yet to be determined. IRF6 was shown to interact directly with mammary serine protease inhibitor (maspin), a tumor suppressor involved in highly metastatic forms of breast cancer, through its protein binding domain called IRF association domain (IAD or SMAD-IRF). Furthermore, a recent study demonstrated that IRF6, in collaboration with maspin, promotes mammary epithelial cell differentiation by facilitating entry into cell cycle arrest[23]. IRF6 is strongly expressed in the ectoderm covering developing facial primordia and in the medial edge epithelia of the secondary palatal shelves[24]. Human and murine IRF6 show high degree of evolutionary conservation. Mice deficient for both alleles of IRF6 develop abnormally thick skin with severe limb and craniofacial abnormalities, including cleft of the secondary palate[25]. However, mice heterozygous for the null allele show no apparent phenotype except occasional intraoral adhesions in only 4% of embryos. The thick skin in mutants has been shown to result from an excessive proliferation of the spinous layer and a failure of keratinocyte terminal differentiation, suggesting that IRF6 plays an important role in keratinocyte proliferation and differentiation. Lack of the outrnost cornified layer of the skin exposes the underlying hyper-proliferated and fusion-competent spinous layer which is thought to promote abnormal adhesions between adjoining tissues, particularly in the oral cavlty. The intra-oral adhesions in the knockout mice were observed between the epithelia covering the maxillary and mandibular prominences in the region of the molar tooth. Mice carrying the most common mutation (R84C) observed in PPS also develop hyper-proliferative skin and oral adhesions[26]. The inta-oral adhesions in these mice were detected between the epithelia covering the floor of the mouth and the ventral surface of the anterior tongue. Similarly, heterozygous embryos for the R84C mutation did not exhibit such adhesions. The clefting phenotypes observed in these mice seems to be caused by a failure of the palatal shelf elevation. These studies further suggest that the oral adhesions or compression of the oral cavity due to thickened skin prevent palatal shelf elevation resulting in the cleft of the secondary palate.
The significant overlap in the phenotype between VWS and NS CL/P, IRF6 was assessed as a potential candidate gene for NS CL/P. In 2005 Scapoli and others reported significant association between SNPs scattered over ~140 kb haplotype block encompassing IRF6 and NS CL/P in 1968 families from l0 distinct populations with an ancestry in Asia, Europe, and South America[27]. In particular, a non- synonymous variant that changes a highly conserved valine residue to isoleucine at amino position 274 (rs2235371,V274I), showed the most significant association in the entire dataset, the association in individuals of Asian and South American origin was particularly highly significant. Subsequently 5 additional studies independently replicated this association in additional populations from Europe and Asia[28,29].Based on the Scapoli et al. study, genetic variation in IRF6 has been estimated to be responsible for l2% of the genetic contribution to NS CL/P and tripled the recurrence risk in families with an affected child[34]. The associated allele of V274I is the evolutionarily conserved V allele which has a frequency of over 97% in European populations and ~99.5% in Africans, making this SNP an unlikely factor for disease susceptibility. Direct sequencing of 160 individuals with NS CL/P revealed no other coding or splice site variants. Therefore, the etiological variant(s) in IRF6 remained elusive[37].

Other Candidate Gene

In addition to these extensively studied genes and pathways that we reviewed here, preliminary evidence for a number of other genes exists supporting their role in NS CL/P. One recently identified gene associated with NS CL/P is CRISPLD2, with strong expression in

the fusing palatal shelves[30]. Ectopic expression of TBXl0 in transgenic mice results in cleft lip and palate and mutations in TBX10 were also detected in individuals with NS CL/P. Similarly, overexpression of the Sprouty2 gene causes stage-dependent craniofacial defects in transgenic mice. Mutations in human Sprouty 2 further delineates its role in cleft lip and palate[35]. Heterozygous mutations in p63 gene are responsible for the autosomal dominant ectrodactyly, ectodermal dysplasia with facial clefts (EEC)[31,32] . A de-novo missense mutation that disrupt a functional domain of p63 has recently been found in a NS CL/P patient[38].

Conclusion

Non-syndromic cleft lip with or without cleft palate (CL/P) is the most common craniofacial anomaly. The number of causative genetic loci is estimated to be between 2 to l4. One of the candidate gene contributing to CLIP, has been identified as IRF6. It was initially targeted for investigation after mutations were detected in the gene in patients with Van der Woude syndrome, an Autosomal dominant disorder characterized by cleft lip, cleft palate, and pits in the lower lip. Recent studies have suggested that DNA sequence variants associated with IRF6 are major contributors to non-syndromic CL/P in multiple human populations.

Future directions

The completion of the genome sequence has contributed to recent successes in identifying novel CL/P genes. The direct study of non-syndromic CL/P has previously been hampered due to the general lack of well-defined multiplex families with sufficient power to enable a genome-wide linkage study to provide a localization. The use of model organisms and in particular the mouse, has for some time been a rich source of information for craniofacial development. Transgenic and knockout technology has often, and sometimes quite unexpectedly, provided a long list of genes that confer an CL/P phenotype. The number and diversity of targeted genes that result in a cleft probably reflects why CL/P is one of the most common features seen in human birth defects. The use of mutant inbred strains to tease out causative genes and provide models is an exceptionally powerful tool. Nevertheless, the problem is to directly relate them to the complex human situation where genetic heterogeneity and varying environ- mental/socio-economic status is found.

Our general failure to pinpoint the precise molecular events that lead to human CL/P most likely stems from our lack of knowledge about the gene networks and regulation of gene expression during palatal development. Clearly we are now in a far better position to address this. We now have knowledge of several genes that play strong genetic roles in human craniofacial development and contribute to the incidence of non-syndromic CL/P. These genes will provide tools to study and elucidate the genetic pathways that they function in. This can be combined with a second powerful approach, using the latest generation of expression profiling techniques. In conjunction with the genome sequence and virtually a complete list of genes, detailed information about the genes that are expressed and those that are switched on or off at different stages of craniofacial development can be determined.

Recent examples of this are the ongoing studies of COGENE, where expression profiling using both microarray and SAGE technologies are being used to generate profiles of a variety of human orofacial structures between 4 and 8.5 weeks of development. Similarly, a recent study from Brown et al. used microarray analysis to look at expression profiles of mouse vertical, horizontal and fused (El3.5, 14.5 and 15.5) palatal shelves. An altemative approach has been reported by who performed a subtractive hybridization screen to enrich for E10.5 mouse embryonic branchial arches 1 - and 2-specific genes. The validity of this approach was demonstrated by identifying a variety of genes with established roles in craniofacial development in a random sampling.

There is now every reason to be optimistic about our future understanding of human CL/P whilst syndromic gene mutations may contribute no more than l0% to non- syndromic CL/P, these findings will lead to a better understanding of the gene pathways, interactions and novel candidates. For many, the benefits of precise diagnosis, accurate risk assessment and genetic counselling can be achieved. When integrated with tissue specific expression profiling and targeted developmental studies, the potential for treatments and preventative therapies may also become a reality.

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