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Role of IRF6 Gene in Orofacial Clefting : A Systematic Review

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ABSTRACT

The search for the genetic etiology of non syndromic clefting has been pursued for some time now . Amongst the probable genes that could be involved in NSCLP , the IRF6 gene has shown to be linked .With a lot of studies that have implicated the IRF6 gene to NSCLP ,there was a need to have a systematic review of the literature available and to find the association of IRF6 gene to NSCLP . The review was designed to search the common scientific search bases, Pubmeb , Cochrane and Science direct were chosen. Pub med direct displayed 27 , Science direct 50 and Cochrane 0 articles .Further using the specific inclusion criterias comprising a, a direct association of the IRF6 gene mutation to non syndromic orofacial clefting b, human subjects with Non Syndromic Orofacial Clefting , 3 articles were selected . The selected studies found a strong link between the IRF6 gene and Non syndromic Orofacial clefting , reported from different populations around the world.

Keywords: IRF6 gene, Non syndromic clefting, Literature review.

INTRODUCTION

Orofacial clefting has since time immemorial affected humans . It affects the patient in many ways ,which includes the phycological and physical aspects . The Incidence of orofacial clefts in India has been reported to be around 1:500[2] . Orofacial clefts range from an isolated cleft around the face to a bilateral cleft lip and palate of the affected individual . The severe facial deformation associated with the clefting ,renders the affected individuals with a psychological set back . Some developing and underdeveloped countries suffer from a deficiency of sufficient health care for the patients with clefting . In countries like India where the cleft care does not reach the rural population , the severity of the psychological and physical effects can be felt .

Organogenesis occurs between 25th to 28th days of IU life of a human being . Any disruption which includes environmental , nutritional or development to the the developing fetus will result in a malformation .The Anomalies that result on this disruption are classified according to the organs that are affected .[9]

Congenital anomalies are divided into three types a*) Disruptions:* A rare anomaly related to breakdown of the original normal foetal developmental process, e.g. craniofacial cleft resulting from amniotic bands. *b) Deformations:* These occur secondary to mechanical forces leading to anomalies of a lesser degree when compared to disruption, e.g. club foot, cleft palate, Pierre Robin sequence etc. *c) Malformations*: A morphologic defect in an organ from

an intrinsically abnormal developmental process, e.g. polydactyly, congenital heart anomalies, cleft lip etc.[9]

The search for aetiology of orofacial clefting has been a topic of contemporary research for quite sometime now . While the two forms of orofacial clefting , the syndromic and non syndromic clefting have been under research for a while now. The interest generated in non syndromic clefting has increased relatively more , as it involves an apparently healthy individual with orofacial clefting and without any other systemic condition .

In 1969 Carter proposed a model (MF/T)[1] multifactorial clefting inheritance ,where he stated that non syndromic clefting was caused by the additive effects of minor abnormal genes and environmental factors .

IRF6 gene

The IRF6 gene is found on the chromosome 1:209.79-29.81 in the humans and chromosome 1:193.15-193.17 Mb in the mouse[3].

Function

The IRF6 gene is responsible for the development of the interferon regulatory transcription factor (IRF) family[3].

Significance

A mutation in the IRF6 gene can lead to the autosomal dominant van der woude syndrome (VWS) . The VWS syndrome comprises of cleft lip and palate features and lip fistulas . IRF6 gene has also been known to be associated with non syndromic cleft lip and palate . A study by Birnbaum and colleagues in 2009 has shown that IRF6 is responsible for NS cleft lip and palate . The Geneva cleft consortium study , confirmed findings that the IRF6 gene is responsible for clefting . Most studies on the gene have been conducted on mice . There was a strong need to look at the literature on the human studies which linked the IRF6 gene to non syndromic clefting[4].

To test the null hypothesis

The IRF6 gene mutation is responsible for orofacial clefting.

METHODOLOGY

Three search bases, Pubmed, Science direct and Cochrane were searched using the key words.

The Inclusion criteria used in the study was :
a, A Direct association of the IRF6 gene mutation to non syndromic orofacial clefting
b, Human subjects with Non Syndromic Orofacial Clefting

RESULTS

Pub med direct gave 27, Science direct 50 and Cochrane 0 articles.

Further using the inclusion criteria, 3 articles were selected.

DISCUSSION

Nonsyndromic cleft lip with or without cleft palate (CL/P [MIM 119530]) and cleft palate only (CPO [MIM 119540]) although common are genetically dissimilar .Several studies have shown that a significant percentage of patients with CLP and CPo have a family history of orofacial clefting and that a simple mendelian model of inheritance may not be sufficient to explain the mode of inheritance[8].

CL/P can be classified as syndromic and nonsyndromic, respectively. Both forms of CL/P are characterized by a strong genetic component. Syndromic forms are in many cases due to chromosomal aberrations or monogenic diseases. Among these, the Van der Woude syndrome, caused by mutation of the IRF6 gene, represents the commonest form of syndromic CL/P, accounting for about 2% of all cases. On the other hand, nonsyndromic CL/P is a multifactorial disease derived by the interaction between genetic and environmental factors. In recent years, great efforts have been made to identify the genes involved in the susceptibility to nonsyndromic CL/P and to disclose their relationship with specific environmental risk factors, to get information about the pathogenic mechanism leading to the malformation[8].

The Role of IRF6 gene in Human orofacial clefting has been a topic of debate for sometime now, the present systematic review was designed to research if there were any human studies that implicated orofacial clefting to the IRF6 gene .

The Present Systematic review which covered 77 articles from 3 common scientific search bases and included ,3 studies which have implicated a direct relation to Non syndromic orofacial clefting .

Khandenwal KD[5] *et al* in a sample of 1072 cases found 3 missense mutations ,they performed targeted multiplex sequencing using molecular inversion probes (MIPs) in 1,072 OFC patients, 67 TA patients, and 706 controls. They also identified 3 potentially pathogenic de novo mutations in OFC patients. In addition, 3 rare missense variants were identified, for which pathogenicity could not unequivocally be shown, as all variants were either inherited from an unaffected parent or the parental DNA was not available. Retrospective investigation of the patients with these variants revealed the presence of lip pits in one of the patients with a de novo mutation suggesting a Van der Woude syndrome (VWS) phenotype, whereas, in other patients, no lip pits were identified.

Leslie *et al*[6] screened 1521 trios with presumed non-syndromic OFCs to determine the frequency of causal IRF6 mutations. The authors identified seven likely causal IRF6 mutations, although a posteriori review identified two misdiagnosed VWS families based on the presence of lip pits. They found no evidence for association between rare IRF6 polymorphisms and non-syndromic OFCs. They combined their results with other similar studies (totaling 2472 families) and concluded that causal IRF6 mutations are found in 0.24-0.44% of apparently non-syndromic OFC families. The authors suggested that clinical mutation screening for IRF6 be considered for certain family patterns such as families with mixed types of OFCs and/or autosomal dominant transmission.

Iman Salahshourifar[7] *et al* studied 39 individuals, including 16 patients with CLO and 23 patients with a family history of cleft, were examined for *IRF6* mutations . Seven variants, including five known (c.-75-4 A>; G, c.-73T>; C, c.459G>; T 5, c.820G>; A, and c.1060 + 37C>; T) and two novel (c.-75-23G>; C and c.1380G>; T), were found. Both novel variants were inherited from non-affected parents and they did not find them, in the 120 control chromosomes. The silico analysis revealed that both c.1380G>; T and c.-75-23G>; C variants may disrupt a putative exonic splicing enhancer and intronic splicing binding site for SC35, respectively.

Taken together, the presence of deleterious *IRF6* variants in patients with non-syndromic oral clefts could be most likely an evidence for VWS. While, *IRF6* variants could, at best, contribute to clefting as part of a complex inheritance pattern, with both additional genes and environmental factors having a role.

The studies involving IRF6 gene , have shown to have a strong link to non syndromic orofacial clefting apart from the VWS . Therefore it is suggested that further studies on IRF6 in most of the NSCLP affected population should be undertaken to ascertain the genetic eitiology of NSCLP .

CONCLUSION

The IRF6 gene , has long been implicated in the formation of orofacial clefting , through animal studies and human studies . Although its role in the syndromic orofacial clefting was established , there was a need to review the role of the gene in NSCLP . The systematic review of literature has shown its link in different populations affected with NSCLP .

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