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Role of ARHGAP29 Gene in Orofacial Clefting : A Systematic Review

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ABSTRACT

The Gene ARHGAP 29 , has long been considered as a candidate gene for Orofacial clefting. There has been considerable interest in finding the human studies that are involved in ARHGAP 29 gene. A need for a systematic review of literature was felt . The search bases Pubmeb , Cochrane and science direct were chosen and with the inclusion criteria of the study , three studies were shortlisted . The studies found a link between the ARHGAP29 gene and Orofacial clefting .

Keywords: ARHGAP29 gene, Systematic review, Orofacial clefting.

INTRODUCTION

Orofacial clefting has since time immemorial affected humans . It affects the individual 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 .

The search for eitiology 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 .

ARHGAP29 gene

ARHGAP29 gene is found on the chromosome 1p22 that forms the Rho GTPase activating protein (GAP) 29,[3] this protein mediates the cyclical regulation of smaller GTP(binding) proteins such as RhoA.[4]

Function

The gene ARHGAP29 is found in the developing face and may also act downstream of IRF6 gene in craniofacial development[3]

Structure

The Gene ARHGAP29 contains a total of four domains including a coiled-coil region, this is known to interact with the Rap2,[6] the C1 domain, GTPase domain , the Rho , and a small C-terminal region that interacts with PTPL1.[4]

Clinical Significance

The 1p22 locus having the ARHGAP29 was long associated with nonsydromic cleft lip/palate clefting a by genome wide association[7] and meta-analysis.[8] A follow-up study[5] identified rare coding variants that included a nonsense and subsequently a frameshift variant in patients with nonsydromic cleft lip/palate. The gene ARHGAP29's primary role in craniofacial development was found after an adjacent ABCA4 gene lacked functional or expression data to support it as the main etiologic gene responsible for nonsydromic cleft lip/palate, even though earlier the SNPs in the ABCA4 gene were associated with nonsyndromic cleft lip/palate.

To test the null hypothesis

The ARHGAP 29 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 Direct association of the ARHGAP29 gene mutation to orofacial clefting Human subjects with Cleft

RESULTS

Pub med direct gave 22 , Science direct 6 and Cochrane 0 articles. Further using the inclusion criteria , 3 articles were selected

DISCUSSION

The Role of ARHGap 29 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 ARHGAP29 gene . In all the 3 studies have implicated a direct relation to orofacial clefting . These studies have covered a broad research database spanning three major databases . Venkatesh Babu Gurramkonda et all[9] in a sample of 173 cases and 176 controls of nonsyndromic cleft lip and palate patients , could not find single nucleotide polymorphisms (SNP) located at chromosomal region 1p22, further the authors concluded that there was no link to south Indian non syndromic cleft lip & palate . Elizebeth J Leslie et all[10] in a study done on 182 individuals from the US and Phillipines affected with Nonsyndromic cleft lip & palate found that the gene *ARHGAP29* revealed eight potentially deleterious variants in cases including a frameshift and a nonsense variant. Deepak Chandrasekharan and Arvind ramanathan[11] reported a nonsense mutation in exon 1 of ARHGAP29 that caused substitution of lysine to stop codon at codon position 32 in a subject with nonsyndromic cleft lip with cleft palate among 60 patient samples . The reports of ARHGAP 29 gene in orofacial clefting is rare but has been reported from populations around the world .

CONCLUSION

The ARHGAP 29 gene , has been implicated in the formation of orofacial clefting . Several human studies have shown mutations in different populations .

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