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Role of *MSX1* Gene Mutation as Predictive Factor in Cleft Palate/Lip-A Mini Review on Facial Skeletal Malformations

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Introduction

Syndromic cases of cleft lip/palate are associated with genes like *MSX1* and PAX9 in formation of cleft lip/palate discussed in previous studies [1]. In knockout humans and mice, the phenotypic abnormalities are manifested due to MSX gene mediated inductive interactions. *MSX1*, IRF6 PVRL1, and TBX22 causes syndromic oral clefts as a single gene defect have been identified [2,3]. These are good candidate genes for some instances of nonsyndromic Cleft lip/palate and CPO because it has been shown that reduced activity of the proteins they encode can affect oral development [4,5]. *MSX1* is a *homeobox* gene under non-clustered category plays significant role in clefting in humans. Five variants of *MSX1* mutation were found as responsible for cleft palate forming. They were: A34G, G110G, P147Q, M37L and G267A. The *MSX1* gene critical for the normal development of the teeth and other structures in the mouth. *MSX1* and MSX2 expressed with Bmp-4 in mesenchymal cells that condense around tooth buds. Patterning of incisors, canine sand premolars and craniofacial development. The mutations within *MSX1* may also lead to rare congenital defects such as Wiktop syndrome and Wolf-Hirschhorn syndrome [6,7]. Studies in knockout mice and humans indicate that defects in the genes *MSX1* and PAX9 are possible causes of Non-syndromic cleft lip/palate associated with hypodontia [8]. Studies on animal research related to cellular and molecular morphogenesis of face are involved in genetic complexities in variant genes like *MSX1* SHH, FGF10, SHOX2 and BMP4 were stated in the previous studies [8-10].

Role of *MSX1* Gene Mutation in Formation of Cleft Lip/Palate

MSX1 and MSX2 are the members of MSX gene family and are strongly expressed in the mesenchyme of the developing facial component derived from neural crest cells and plays major role in specification of face and skull development [10]. The regulation, expression and functional analysis of MSX genes have major predictive relevance to craniofacial development in humans and mice. *MSX1* plays major role in formation of secondary lip/palate indicating mutations of *MSX1* gene significantly enhancing the isolated cleft palate/lip. 2% of non-syndromic clefts in humans are due to mutations in *MSX1* gene. The interaction between genes showed influence on formation of cleft palate is higher indicating significant role in 20% cleft palate/lip cases [11]. *MSX1* gene contribution in formation of cleft palate, isolated tooth agenesis and tooth agenesis was reported in previous studies [12,13]. Mutations of *MSX1* gene and its rare variants stated in individuals with hereditary tooth agenesis and cleft lip/palate [14-16]. Previous literature stated that secondary palatal cleft and developmental failure of tooth noted in a mouse due to lack of *MSX1* gene [17]. Children are more affected with cleft palate associated with tooth agenesis when compared with normal population [18,19]. Severity of cleft palate/lip markedly increased with hypodontia and is more significant in children. It has been proposed that mutations of *MSX1* gene alone could contribute to as many as 2% of total cleft lip and palate [5,20]. The mutation of *MSX1* P147Q was first reported in a Vietnamese population and this mutation was thought to have arisen from a founder individual Vietnamese families. The mutation was later found in two Filipino families. The frequency of the *MSX1* P147Q mutation was as high as 8% in Thai people in a study suggested that *MSX1* P147Q mutation is not pathogenic [20]. Perhaps the most interesting case related to the *MSX1* P147 Q saga is that of one Vietnamese child who was born with a sporadic cleft lip and palate carried two *MSX1*. Mutation of *MSX1* is associated with hypodontia and cleft palate/lip. Cleft lip/palate and tooth agenesis was observed due to a nonsense mutation in exon 1 of *MSX1* gene in chromosome 4p in a Dutch family [2]. The mouse *homeobox* gene *MSX1* is expressed only in the anterior palatal mesenchymal cells and the loss of *MSX1* function in mice results in a complete cleft palate rather than only an anterior cleft, indicating the importance of anterior palate development in palate fusion [17,21,22]. Furthermore, the cleft palate caused by *MSX1* inactivation can be rescued by trans-expression of the BMP4 gene [21,22]. Interestingly, *in vitro* explant culture showed that only the anterior, but not the posterior, palatal mesenchymal cells can proliferate in response to the addition of BMP [21,22]. The expression of PAX9 is restricted to the posterior region during palate development and disruption of this gene in mice results in cleft palate [22,23]. Statistical evidence of gene interaction leading to clefts has been reported for *MSX1* (a transcription repressor) and TGFβ3 (involved in cell differentiation) and for *MSX1* and RGFA (a growth factors) [13,24]. In both studies the evidence of interaction was related to carrying two copies of the *MSX1* risk allele. Cleft lip/palate and tooth agenesis outside the cleft region cases were associated with the variants of *MSX1*gene [12].

Future perspectives and Conclusion

The genetic factor is thought to play a crucial role in 20% of cases of clefts. The *MSX1* and TGFβ3 genes are found to be the genes most strongly related to cleft anomalies. The expression of an antisense RNA which is partial complimentary to the protein coding sense RNA due to bidirectional transcription plays significant role in regulation of *MSX1*gene expression in developmental sites [25]. Antisense RNA has been associated with various processes, such as RNA interference, imprinting and transcription inhibition. In contrast, hypomorphic MSX 1 allele has ability to reduce the activity of antisense RNA to inhibit its function as a transcriptional suppressor. Another hypomorphic allele in a different gene TGFA or TGFB3 could decrease the ability of those

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genes to promote growth or cell differentiation. Alone, the hypomorphic allele does not lead to disease, even if two copies of the same are present. However, if hypomorphic allele in more than one gene occur in the same individual, the reduced *MSX1* function (by the individual carrying two copies of the hypomorphic alleles) combined with the reduced TGF A (or TGFB3) may lead to cleft lip and palate. Recent studies suggest that *MSX1* causative mutations for tooth agenesis may not be sufficient to cause oral clefts. Few researchers stating in contrast with *MSX1* gene as predictive factor influencing clefts and also claim that *MSX1* might not be an etiologic factor responsible for orofacial clefting. To conclude; *MSX1* and other associated genes plays predictive role in formation of cleft palate/lip when it occurs in parallel with the PAX9 gene mutation. The diagnostic techniques in the field of molecular genetics make it possible to identify relevant morphogenesis or genetic markers in facial malformations due to MSX gene family to be evaluated in clear due to its clinical importance.

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