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International Journal of Orofacial and Health Sciences (IJOHS) is a peer reviewed biannual international journal dedicated to publish high quality of scientific research in the field of orofacial sciences, health sciences and interdisciplinary fields, including basic, applied and clinical research. The journal welcomes review articles, original research, case reports and letters to the editor. Areas that are covered include but are not limited to dental sciences, oral microbiology and immunology, oral maxillofacial and craniofacial surgery and imaging, dental stem cells and regenerative medicine, dental biomaterial, oral maxillofacial genetic and craniofacial deformities.

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Genetics of malocclusion: A review

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Abstract

Malocclusion is one of the most common craniofacial problems observed worldwide. Affected individuals suffer not only from aesthetic concerns but also from functional problems, such as with mastication and pronunciation. The prevalence of malocclusion in East Asians is higher than in other races. Reports have shown besides environmental factors, there is association between certain types of malocclusion with specific genes. Positive association of mandibular prognathism has been implicated to genes such as Matrilin-1; while mutation in DUSP6 has also been shown to contribute to the incidence of malocclusion. This review aimed to briefly discuss the involvement of other additional genes such as MYO1H and PAX9 in the incidence of malocclusion as observed from our local institution.

Keywords: malocclusion, genes

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Introduction

Malocclusion is one of the most common dental problems in mankind, together with dental caries, gingival disease and dental fluorosis (Dhar et al., 2007). A malocclusion is defined as an irregularity of the teeth or a mal-relationship of the dental arches beyond the range of what is accepted as normal (Walther et al., 1994). Malocclusion should not be considered as abnormal or pathological, instead as a variation of occlusion in a continuous multifactorial trait (Nishio et al., 2016).

Nonetheless, the condition of malocclusion may lead to distorted facial appearance, limited masticatory function, increased risk of dental trauma and compromise the quality of life (Claudino et al., 2013).

Classification of skeletal and dental malocclusion

The deviations from normal occlusion can be presented clinically from skeletal and/or dental. Skeletal discrepancy is caused by the distortion of the proper mandibular and/or maxillary growth during fetal development (Joshi et al., 2014). This can occur in any three plan of space:
anteroposterior, vertical and transverse (Alhammadi, 2019). Salzmann in 1950 was among the first to classify to the underlying skeletal structure into Class I, Class II (convex profile) and Class III (concave profile).

Dental malocclusion may be classified according to several classifications. One classification is by British Standard Institution (BSI, 1983) classifying the occlusion according to the incisor relationship, into Class I, Class II Division 1, Class II Division 2 and Class III. Class I incisor relationship is when the mandibular incisors edges occlude with or lie immediately below the cingulum plateau of the maxillary central incisors. Class II incisor relationship is subdivided into division 1 and division 2 according to the inclination of the upper incisors. Class II division 1 occurs when the maxillary central incisors are proclined (or with average inclination) with an increased overjet. Whereas, class II subdivision 2 happens when the maxillary central incisors are retroclined and the overjet can be minimum or maybe increased. Class III is when the mandibular incisors edges lie anterior to the cingulum plateau of the upper central incisors with the overjet reduced or reversed.

Angle classification used occlusal relationship of the first molar to classify type of malocclusion into three classes that are Class I, Class II and Class III (Weinberger, 1993). Class I molar relationship is characterized by normal mesio-distal relation of the jaws and dental arches, as indicated by the normal locking on eruption of the first permanent molars, at least in their mesio-distal relations, though one or more may be in buccal or lingual occlusion. Class II molar relationship can be explained by the molar relationship shows the buccal groove of the mandibular first molar distally positioned when in occlusion with the mesio-buccal cusp of the maxillary first molar.

On the other hand, Class III molar relationship is classified when the molar relationship shows the buccal groove of the mandibular first molar mesially positioned to the mesio-buccal cusp of the maxillary first molar when the teeth are in occlusion.

**Prevalence of malocclusion**

The prevalence of dental malocclusion in East Asians especially Class III is higher than in other races (Soh et al., 2005). This has been supported by a finding by Chu et al. (2007), which compared their study with those from surveys of young Caucasians, Africans and Asians. This study showed that the prevalence of Class I malocclusion in Chinese adults was higher than that in Caucasian adults (48% versus 23%), but was similar to that of Asian (48%) or African (50%) young adults. The prevalence of Class III malocclusion in Chinese and in Asian adults is higher than that in African adults (20% versus 14%). Although Class II malocclusion is less common in the Chinese young adults, a study using peer assessment rating index reported that Class II malocclusion being more severe than Class I or III malocclusion in young Asian males (Soh et al., 2005). While in the Northern part of Saudi Arabia, Class I malocclusion was dominant, followed by Class II and Class III, respectively (Alajlan et al., 2019).

Hardy et al. (2012) through his meta-analysis study reported that, Chinese from Hong Kong and Malaysian showed a relatively higher prevalence of Angle Class III malocclusion. In addition, Indian populations showed a relatively lower prevalence as compared to other races (Hardy et al., 2012). Our own demographic study showed that Class III
(according to BSI Incisor Classification) represents the majority of malocclusion cases observed in our local setting, whereby Malays constitute the highest number of orthodontic patients followed by Chinese and Indians (Ismail et al., 2017). The prevalence data indicated that the occurrence of different types of malocclusion varies according to geographical location.

**Genetics and malocclusion**

Aetiologically, skeletal malocclusions arise from skeletal disharmonies. Thus, it is essential to have a good understanding of the skeletal growth in general. In orthodontics, one of the most challenging aspects in treating patients is predicting their craniofacial growth patterns. In this respect, it is important to understand how genetic factors and their interactions with environmental factors affect facial growth in a particular individual.

Study of the aetiology of malocclusion is a complex subject since both genetic and environmental factors may affect craniofacial development (Mossey, 2014). Several studies have shown that there is a strong link of malocclusion especially skeletal malocclusion Class III or mandibular prognathism (MP), with both genetic as well as environmental factors (Jena et al., 2005; Chaturvedi et al., 2011; Hartsfield et al., 2012).

The relative genetic contribution to Class III malocclusion has been the subject of interest of many researchers. Some evidence has been found suggesting that genetic factors contribute to the malocclusion susceptibility. In a review article, Moreno et al. (2015) mentioned that association studies have found positive correlations for mandibular prognathism and genes \( \text{EPB41}, \text{SSX21P} \) and \( \text{PLXNA} \), located within the locus 1p22-p36, while genes \( \text{COL2A1}, \text{TGF\(_B\)3}, \) and \( \text{LTBP2} \) within the 12q13-q24 locus. \text{MATRILIN-1} is a cartilage matrix protein and its polymorphism has been shown to be associated with mandibular prognathism in Korean population (Jang et al., 2010). Genotyping results showed that the \text{Matrilin-1} polymorphism haplotype TGC had a pronounced risk effect for mandibular prognathism compared with controls which suggest that polymorphisms in \text{Matrilin-1} could be used as a marker for genetic susceptibility to mandibular prognathism.

The mutation in \text{DUSP6} has also been identified in cases of malocclusion and reinforces that the 12q22-q23 region is biologically relevant to craniofacial development and may be genetically linked to the Class III malocclusion (Nikopensius et al., 2013). Very recently, Nowrin et al. (2019) detected a missense mutation in EXON 3 of \text{DUSP6} gene in three members of a Malaysian Malay family with Class III malocclusion. This study further acknowledged the importance of \text{DUSP6} gene in skeletal functions (Nowrin et al., 2019).

With the advancement of dentofacial phenotyping and the availability of large-scale genomic data analysis, the fundamental aspect of genetic mechanism which underlies the developmental process of craniofacial complex is unravelled. Additionally, available genetic analysis such as linkage analysis, whole exome sequencing, polymorphism or mutational analysis has enabled genetic association study to be performed on malocclusion cases, hence broadened the knowledge on the involvement of certain genes with the incidence of malocclusion.
**Pax9 Genes**

Alterations in genes which are important during the process of craniofacial development have been associated with the incidence of craniofacial abnormalities. Paired Box 9 gene (PAX9 gene) located at chromosome 14 (locus 14q13.3) is a gene family which is responsible in tooth as well as skeletal development (Ghergie et al., 2013). Anne et al., (2015) claimed that PAX9 gene regulates cell proliferation, migration and determination in multiple neural crest-derived lineages, such as cardiac, sensory, and enteric neural crest, pigment cells, glia, craniofacial skeleton and teeth, or in organs developing in close relationship with the neural crest such as the thymus and parathyroids. PAX9 gene is a protein encoding gene that encodes the transcription factor that is important for craniofacial and dental development (Seo et al., 2013). Krivicka-Uzkurele et al., (2016) stated PAX9 gene is expressed in the developing facial processes and influence the formation of lower face. Kavitha et al., (2010) found that PAX9 gene has 4 exons which are highly conserved in human being. Mutated PAX9 gene is frequently associated with oligodontia or hypodontia as well as Class II/Division 2 malocclusion (Ghergie et al., 2013a). Animal studies conducted by Peter et al., (1998) and Nakatomi et al., (2010) found that mutated or absence of PAX9 gene shown poor development of skeletal and odontogenesis with lack of coronoid process formation. Peter et al., (1998) added this particular gene was highly expressed at the region of pharyngeal pouches, mesenchyme of nasal processes, maxillary and mandibular arches, as well as at the area of developing tooth buds hence supporting the importance of PAX9 in craniofacial, tooth and skeletal development.

Polymorphism in PAX9 gene; SNP marker rs8004560, has been suggested to have an association with Class II/Division 2 malocclusion with hypodontia except the third molar (Wall et al., 2009). Ghergie et al., (2013a) also found association between PAX9 SNP (rs8004560) with Class I malocclusion patients. We have performed sequencing analysis on patients with Class II skeletal base malocclusion for PAX9 SNP (rs8004560). However, no significant association of PAX9 SNP (rs8004560) with Class II skeletal base was observed from our local population (Saad et al., 2018). This might be due to small number of samples recruited in our study.

**Myo1H Genes**

Another gene which has been shown to be associated with malocclusion is MYO1H. MYO1H, located at 12q24.11 is a class 1 myosin that is in a different protein grouping than the myosin heavy chain isoforms found in the skeletal muscle sacromeres, which are the basis of fibre typing. Myosin is superfamily of motor proteins that involve in generating force and movement along actin filaments (Mooseker and Cheney, 1995). Class 1 myosin is necessary for cell motility; phagocytosis and vesicle transport (Rowlerson et al., 2005). Myosin heavy chain isoforms was revealed to be found in the masseter muscle via immunohistochemical staining and gene expression studies (Arun et al., 2016). Few studies suggest that muscle affect the skeletal growth during embryonic stage, postnatal stage, and homeostatic relationship in adult and aging process (Brotto, 2015). Therefore, genetic alteration in genes responsible for muscle function will also affect the skeletal growth. In a recent article, Sun et al. (2018) have shown that the expression of MYO1H orthologous genes were detected at mandibular jaw of zebrafish model, whereby jaw cartilage defects were demonstrated in the MYO1H knockdow
model. These developmental and functional studies strongly demonstrate the importance of MYO1H gene for proper jaw growth and development and its contribution towards the pathogenesis of mandibular prognathism and mandibular retrognathism in human (Arun et al., 2016; Sun et al., 2018).

Tassopoulou-Fishell et al. (2013) reported significant association between MYO1H SNP (rs10850110) with mandibular prognathism patients whom are mostly Caucasian. Ghergie et al. (2013b) also performed single nucleotide polymorphism analysis of MYO1H gene (rs10850110) on malocclusion Class I, II and III from Romanian population. Their study also detected association of MYO1H SNP (rs10850110) allele and genotypes with different malocclusion cases. Arun et al. (2016) studied genetic association by performing PCR-RFLP methods on three SNP markers of MYO1H on mandibular retrognathism cases. These markers include rs10850110, rs11611277 and rs3825393. The SNP rs3825393 showed a statistically significant association with mandibular retrognathism, while no association was detected in other two polymorphism markers with mandibular retrognathism (Arun et al., 2016). Due to these findings, we also initiated a preliminary analysis of MYO1H single nucleotide polymorphism of rs10850110 on mandibular prognathism cases, but no significant association was observed. Again, small sample size might contribute to this finding (Yahya et al., 2018). Thus, we are proposing for larger number of samples to be recruited for future genetic association study. In addition, the criteria for inclusion and exclusion to fulfil the exact classification of the malocclusion must be followed strictly.

To date, most of the genetic studies looking into the polymorphism of these genes with malocclusion have been done in other parts of the world. As far as we are aware, scanty data regarding dental malocclusion and its genetic analysis is available from our local population (Esa et al., 2001). Thus, we hope that the ongoing studies carried out in this institution could provide new scientific information for the betterment of the knowledge in the management and treatment of malocclusion in this population. This could attribute to clinicians and researcher in the field of craniofacial research.

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associated with different facial morphologies. 

American Journal of Orthodontics & Dentofacial Orthopedics, 127, 37-46


Wall, M. D. (2009). Association analysis of class II division 2 malocclusion and two genes linked to hypodontia (MSX1 and PAX9) (Doctoral Dissertation).


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