

REVIEW ARTICLE

Genetics of malocclusion: A review

Khairani Idah Mokhtar^{1*}, Noraini Abu Bakar², Aisyah Hanani Bt Md Ali @ Tahir³

¹*Department of Fundamental Dental and Medical Sciences, Kulliyah of Dentistry, IIUM Kuantan Campus.*

²*Department of Orthodontics, Kulliyah of Dentistry, IIUM Kuantan Campus,*

³*Department of Biomedical Science, Kulliyah of Allied Health Sciences, IIUM Kuantan Campus.*

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

*Corresponding Author

Email address: drkhairani@iium.edu.my

Tel: +6013-927 8779

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 (Alhammedi, 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 *EPB41*, *SSX21P*

and *PLXNA*, located within the locus 1p22-p36, while genes *COL2A1*, *TGFB3*, and *LTBP2* within the 12q13-q24 locus. *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 *Matrilin-1* polymorphism haplotype TGC had a pronounced risk effect for mandibular prognathism compared with controls which suggest that polymorphisms in *Matrilin-1* could be used as a marker for genetic susceptibility to mandibular prognathism.

The mutation in *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 *DUSP6* gene in three members of a Malaysian Malay family with Class III malocclusion. This study further acknowledged the importance of *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* knockdown

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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