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GENETIC EFFECT AND PREVALENCE OF CLASS III MALOCCLUSION IN DIFFERENT POPULATION: AN OVERVIEW

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ABSTRACT

The prime aim of this review is to highlight the genetic effect and prevalence of class III malocclusion in different population. A literature search was conducted. Evidence from previous studies also established that class III malocclusion is strongly influenced by the genetic factors. May be class III malocclusion had developed by polygenic or monogenic mode of inheritance. But the environmental factors also responsible for this trait. Class III malocclusion has been the topic of intension and eager to many researchers. Researchers concluded that diverse combinations of skeletal and dental rudiments are drawn in to produce class III malocclusion. Genome wide linkage scan technology can detect several chromosomal regions, responsible for the mandibular prognathism. However, very few genome wide family based linkage study have been done for the determination of the mandibular prognathism. This article motivated on understanding the genetic influence and the prevalence of class III malocclusion in different population.

KEYWORDS: Class III malocclusion, genetic influence, Prevalence, genetic factor, Genome wide linkage scan technology.

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INTRODUCTION

Class III malocclusion is skeletally characterized by an overgrowth of the mandible (mandibular prognathism), an undergrowth of the maxilla (maxillary deficiency), or a combination of both[1]. The prevalence of Class III malocclusion has been described between 1%[2, 3] to over 10%[4], depending on ethnic background[2], sex[4, 5] and age[6]. It has been reported that approximately 75% of Class III cases in male Caucasians have a skeletal origin and are a result of mandibular prognathism or macrognathia[7]. The prevalence of Class III malocclusion among Caucasian people ranges from 0.48% to 4%[2]. But compare to Caucasian people the prevalence of class III malocclusion higher in Japanese population. It rises as high as 10%[8]. Diagnosis and treatment of class III malocclusion are chocked up with contradiction in the type, timing and duration of treatment. To know the exact aetiology of any dentofacial characteristics genetic evaluation is mandatory. The effects of genetic association in orthodontic treatment are poorly understood. Although there has been extensive literature concerning genetic basis of the dentofacial abnormalities and malocclusions, data provided by these studies were quite sparse[9]. Furthermore, surveys dealing with genetics constituted only the 0.5% of the total in orthodontic journals since 1980's[10]. To date, many investigations have focused largely on treatment modalities and outcomes, with little being accomplished toward an understanding of the aetiology of class III phenotype and potential relationship between the genetic components or how genetic factors may influence the response to treatment[11]. In this review, genetic effect and prevalence of class III malocclusion in different population will be highlighted.

MATERIALS AND METHODS

In view of cephalometric analysis, the importance of genetic association with class III and the prevalence of class III malocclusion in different population, a search in literature were conducted. The electronic databases searched included Medline-PUBMED, Science Direct, and ISI Web of Knowledge search engines with defined key word combinations (Table 1). No language limit was applied. Original research articles, case report and reviews of the literature were selected. In addition, a comprehensive search was performed by hand searching of relevant references and textbooks. Need to add Table 1.

Table 1
Electronic database searched and combinations of key words.

Electronic Database Searched	• NCBI databases PubMed PubMed Central PubMed Health • Medpilot Medline Catalogue ZB MED Catalogue Medicine Health. Excerpta Medical Database (EMBASE) • Web of Science • SciSearch • Science Direct • Research gate • Google Scholar
Key words for search	Class III malocclusion + Genetic effect Class III malocclusion + Prevalence Class III malocclusion + Orthodontics

DISCUSSION

Class III malocclusion has been the topic of intension and eager to many researchers. Diverse combinations of skeletal and dental rudiments are drawn in to produce class III malocclusion[1]. However some author attributed that the reason of this phenotype is overdeveloped ramus[12]. The aetiology of class III malocclusion is an interesting subject and there is still much to be clarify and understood.

Prevalence of class III malocclusion (Table 2)

Several studies have documented the prevalence of Angle Class III malocclusion[3, 4, 7]. Nevertheless, different population has different equation. Multiple studies have stated that Asian races have a higher prevalence of Angle class III malocclusion than other races[2, 13-18]. Emrich and colleagues[2] observed 10,133 Caucasian children 6-8 years old and 13,475 children 12-14 years old and found that 1% of both grouped had class III malocclusion. Altemas[19] reviewed 3,289 Negroes between the ages of 12 and 16 and reported class III malocclusion present in 5% of those examined. Emrich and associates[2] also found that 3 % of the Negroes surveyed at the age of 12 to 14 years and 2% of the Negroes surveyed the age 6-8 years had class III malocclusion. Another article established that 4% of 137 Swedish persons 21 years of age had Class III malocclusions[20]..Lew *et al.,* [13]surveyed 1,050 Chinese school children of age between 12 to 14 years old to assess both qualitatively and quantitatively certain occlusal features. The population was found to have a high incidence of Class III malocclusions compared with Caucasians. Similarly 1,601 school going children including 16 different primary schools in Tanzania age 12 to 16 years old were observed and found among them only 2% of children showed class III malocclusion[21]. Dacosta[22] also found 2% of class III malocclusion surveying 1,028 school children in Northern Nigeria. The prevalence of malocclusion was investigated in 245 children from a pastoral community in Kenya. Among them 5% of class III malocclusion was found[23]. Woon *et al.,*[16] surveyed the occlusal relation between three ethnic races Chinese, Malay and Indian in Malaysia. He found significant higher prevalence of Class III occlusion among the Chinese and Malays as compared to the Indians. One of the Indian studies showed that among 3,164 samples (Age 6-15 years) only 1.3% showed class III malocclusion[24]. Where in other population the prevalence of class III malocclusion found 1-5%, in Chinese and Korean population it increases 9.4 to 19%[25, 26].

Table 2
Prevalence of class III malocclusion in different population

Author	Total number of study	Age(years)	Prevalence rate (%)	Race/ Population
Emrich*et al.*[2]	10,133	6-8	1	Caucasian
	13,475	12-14	1	Caucasian
Altemas[18]	3,289	12-16	5	Negro
Emrich*et al.*[2]	1,476	12-14	3	Negro
	903	6-8	2	Negro
Seipel[19]	137	21	4	Swedish
	474	13	2.7	Swedish
Lew *et al.*[12]	1,050	12-14	12.6	Chinese
Mtaya*et al.*[20]	1,601	12-16	2	Tanzania
Dacosta[21]	1,028	11-18	2	Northern Nigeria
Guaba*et al.*[23]	3,164	6-15	1.3	India

Genetic effect and Class III malocclusion

Human gene

In living organism, the molecular element of heredity is called gene. It is accepted by the scientific community that these genes are stretches of deoxyribonucleic acid and ribonucleic acid (RNA) that code for the body proteins. Human bodies consist of billion cells. Most of the cells comprise a nucleus with its nuclear membrane. The nucleus contains the

hereditary information stored in the form of deoxyribonucleic acid (DNA). The gene is defined as "a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions, and or other functional sequence regions"[27].

Mutation of gene

A mutation may be demarcated as any change in the genetic make-up of a cell, an organism or a population of cells. Random interaction with the surroundings or because of the normal cellular function natural mutations usually takes place. To maintain the double helix structure of DNA there are two base pairs (guanine-cytosine and adenine-thymine) play an important role. If changes follow in single base nucleotide with another nucleotide of the genetic material, then it is called point mutation. It is also called as ''single nucleotide polymorphism'' (SNP). Point mutation can be fixed naturally but sometimes cannot. Then it can be transferred through generation to generation by inheritance. Commonly by transitioning, comprising the substitution of an adenine – thymine (A –T) pair with a guanine – cytosine (G – C) pair or vice versa[28]. Point mutation or SNPs occur through the human genome is predicted at every 3-1 kilobases (kb), whereas other types of genetic mutations result from insertions or deletions[29].

Genetic polymorphism

After genetic mutation the most common fact is genetic polymorphism. Genetic polymorphism is the result of gene mutations. But it also can occur by the result of external agents such as viruses. But if the association of the virus is due to any form of disease then it is termed as a mutation[30]. A particular fragment of DNA is not necessarily identical in different people. If a genetic change follows in more than one percent of the population it's called a polymorphism[31]. Once different alleles of a certain gene co-exist in the human population, they are referred to as genetic polymorphisms[32]. Alleles are different arrangements (polymorphisms) of a gene that can reside in a specific chromosomal site (locus). Two or more alleles for a certain locus may exist in nature throughout evolution, but could develop at any time. As an example if a polymorphic locus is bi-allelic, the rarer allele (R-allele) must follow with an occurrence >1% in the population, and the most common normal variant (N-allele) among them follows with < 99% incidence in the population[28].

Effects of genetic polymorphism on disease

Multiple genes and their polymorphisms may all have a small overall influence and virtual risk to disease severity and susceptibility. Complex diseases are typically polygenic[33]. Study of any disease is usually constructed the analysis of genetic polymorphism[34]. Due to genetic polymorphisms, there are alterations in distinctive and adaptive immunity that may regulate the diseases outcome.

Genetic polymorphism and Class III malocclusion

Evidence from previous studies also established that class III malocclusion is strongly influenced by the genetic factors[1, 8]. May be class III malocclusion had developed by polygenic or monogenic mode of inheritance. But the environmental factors also responsible for this trait. Few works has been done to evaluate the quantitative role of heredity in the aetiology of this condition. Suzuki[35] surveyed 1,362 family members from 243 Japanese families, observed that the families who have history of mandibular prognathism, 34.3% of the family member exhibited the trait. Whereas the families without the history of mandibular prognathism still 7.5% exhibited the trait. Litton *et al.*,[36] examined the families of probands with class III malocclusion followed by Angle and found that about 13% of the siblings of probands exhibited the trait which suggesting a strong genetic influence in class III malocclusion. And this study indicates the transmission is polygenic mode of inheritance. Saunders *et al.*,[37] studied the similarities in craniofacial dimensions between members of 147 families. By calculating Standard product moment and intraclass correlation coefficients were compared parents with offspring and siblings with siblings. The results show a high level of meaningful co-relations between first-degree relatives which are compatible with a

polygenic theory of inheritance. Schulze and Weise[38] also mentioned that in case of mandibular prognathism the polygenic mode of inheritance is the transmission medium by studying monozygotic and dizygotic twins. However, a number of study have reported that the genetic transmission is follows the monogenic or Mendelian pattern of inheritancei.e Cruz *et al*.,[39] studied with 2,562 members from 55 families and conclude that a major gene influences the expression mandibular prognathism with clear signs of Mendelian inheritance. The large European noble family studies with 409 members from 13 families conclude that mandibular prognathism is determined by a single autosomal dominant gene[40]. El-Gheriani *et al.,*[41] also came to a same conclusion after analysing the families in Libya with mandibular prognathism that the inheritance is in the monogenic method.

Different loci and genes responsible for class III malocclusion (Table 3)

Now genomewide linkage scan technology can detect several chromosomal regions which is/are responsible for the mandibular prognathism. But very few genomewide family based linkage study have been done to determine the specific gene or genes for mandibular prognathism. Yamaguchi *et al.,*[42] identified three chromosomal loci 1p36, 6q25 and 19p13.2 which are susceptible for mandibular prognathism. This study is done on fifty Japanese and forty Korean sibling-pairs. Using permutation of datasets, the Monte-Carlo approximation of Fisher's exact test done for estimating the different allelic frequency between these Korean and Japanese population. In the linkage region of chromosome 1, D1S2864, D1S234 and D1S2333 allelic frequency of microsatellite markers found in Korean and Japanese probands (33 each)[43]. Japanese population showed linkage in chromosome 9 and 10 and Korean siblings pair showed linkage chromosome in 4. Though commonly linkage pattern is similar between Korean and Japanese population, these differences may occur due to genetic heterogeneity. But in the Monte-Carlo approximation of Fisher's exact test there is no statistical significance.So it can be say that same etiological background exists for mandibular prognathism in these two populations.

Five loci (1p22.1, 3q26.2, 11q22, 12q13.13 and 12q23) are found in Colombian families for class III malocclusion as a suggestive of linkage in another study. Candidate genes within the 12q23 region include IGF1, HOXC and COL2A1. For influencing body size IGF1 plays an important role in both human and mice. HOX counts as a centric gene in vertebrate craniofacial development. And type II collagen cartilage encoded by COL2A1 gene[11]. EPB41 and MATN1 are found as plausible genes for the mandibular prognathism on chromosomal locus 1p36 respectively Chinese and Korean population[44, 45].

After investigating 211 case and 224 control EPB41 showed the strongest risk of significant association in case of mandibular prognathism. The study stated that, EPB41 gene counts as an important fundamental element of the membrane skeleton of erythrocyte that's made a crucial contribution to the fundamental integrity of the centrosome and mitotic spindle and plays a title role in cell division[46-48].

Link between the mandibular prognathism and single-nucleotide polymorphisms (SNPs) in Matrilin1 among 164 mandibular prognathism patients and 132 controls with normal occlusion explored three sequence variants (-158 T>C, 7987 G>A, 8572 C>T). Comparing with control 158T, 7987G, and 8572C alleles had a marked hazardous effect for mandibular prognathism. This study proposed that for mandibular prognathism polymorphisms in Matrilin 1 can be used as an indicator[45].

A susceptible locus was invented on chromosome 14q24.3-31.2 in Han Chinese population where the candidate genes are TGFB3 and LTBP2[49]. Transforming growth factor beta (TGF-β) superfamily contains TGFB3 gene. There are three forms of TGF-β having the same construction and in vitro biological activities. They are TGF-β1, TGF-β2 and TGF-β3[50].Formation of growth factors and differentiation of bone tissue TGF-β considered being the vital growth factor. Participation in the growth of oral cleft patients in central European origin[51] and association of mineral maturation matrix[52]. TGFB3 plays an important role.

LTBP2 also playing a functional role in elastic fibres. It disturbs the extracellular matrix homeostasis[53]. LTBP2 also established the contribution in the process of chondrogenic differentiation in vitro study[54]. These advised that may be there is relation of TGF-β superfamily and LTBP2 in mandibular prognathism. Recently Nikopensius *et al.,*[1] performed whole exone sequencing on five siblings from Estonian family who are affected by class III malocclusion. This study showed that in 12q22-q23 region DUSP6 gene implicated the mandibular growth. Two different studies found that 12q23 chromosomal locus is more susceptible for class III malocclusion. Recent studies of craniofacial growth have reported that several genes that encode specific growth factors or other signalling molecules, including Indian hedgehog homolog (IHH), insulin like growth factor-1 (IGF1), and vascular endothelial growth factor (VEGF), and variations in their levels of expression have an important role in the aetiology of Class III malocclusion[43]. IGF1 is located at the 12q23 linkage region and represents an excellent candidate gene of biological interest because the GH/GHR/IGF1 system has an essential role in skeletal growth and normal bone metabolism[55]. In addition, other growth factors, including EGF, HGF, NGF, and PDGF, can activate ERKs during development and in adult tissues and induce the transcription of other members of the DUSP6 family, which could compensate for the lack of DUSP6 in knockout models. However, although various growth factors are capable of inducing dusp6, there could exist a specific, preferential relationship between FGF and DUSP6 at the level of transcription[56]. Alternatively, FGF/FGFR signalling could regulate the access of transcription factors to promoter regions of dusp6 by specific epigenetic mechanisms and modifications of the chromatin, as reported previously for some other genes[57]. Evidence from population studies has demonstrated that Class III malocclusion is influenced strongly by genetic factors, and multiple environmental factors have been shown to affect mandibular growth. If there is any skeletal class III among family history there is more chance to develop adverse arch relation like maxillary undergrowth or mandibular over growth[58]. According to the previous studies as the prevalence rate of class III malocclusion is high in Asian race, linkage study and genetic determination will be helpful to find out the exact aetiology of the class III malocclusion.

Table 3
Susceptible loci/ locus found in different population

Author	Susceptible loci/ locus	Candidate gene	Race/ Population
Yamaguchi *etal.*[39]	1p36, 6q25, 19p13.2		Korean and Japanese
Frazier-Bowers *et al.*[11]	1p22.1, 3q26.2, 11q22, 12q13.13, 12q23	IGF1, HOXC and COL2A1 on 12q23	Colobian
Xue*et al.*[41]	1p36	EPB41	Chinese
Jang *et al.*[42]	1p36	MATN1	Korian
Li *et al.*[46]	14q24.3-31.2	TGFB3 and LTBP2	Han Chinese
Nikopensius*et al.*[1]	12q22-q23	DUSP6	Estonian

CONCLUSION

From this study, it can be concluded that genetic analysis is an important tool in clinical Orthodontics. The etiological diversity is the main complicating factor for treatment and diagnosis in class III malocclusion. Living in a nano era, the technique like linkage analysis is possible to identify the causative genes responsible for this phenotype. But it still need time to be better accepted by dentists and explore the advantages.

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