EPIDEMIOLOGY AND GENETIC ASPECT OF NON-SYNDROMIC MANDIBULAR PROGNATHISM: A LITERATURE REVIEW

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Abstract
Mandibular prognathism is a Class III skeletal base manifestation in which the lower jaw overgrows with or without the upper jaw undergrowing, causing the lower jaw to appear more prominent than the latter. This manifestation results in an unattractive facial profile, misaligned bite, and hampered speech. Several reports suggested that the prevalence rate of mandibular prognathism varies depending on the demographic, and its primary aetiology is genetics. This literature review summarises the prevalence rate of mandibular prognathism in various populations, its inheritance pattern in different pedigree groups, and the loci and candidate genes involved in non-syndromic mandibular prognathism. Most studies show no relationship between gender and phenotypic prevalence, with Caucasians having the lowest prevalence of mandibular prognathism and East Asians having the greatest. The inheritance pattern of mandibular prognathism is diverse, with the most typical inheritance pattern being the dominant trait with incomplete penetrance. Genetic findings from many documented reports suggest that there may be more than a single gene that causes mandibular prognathism. Through genome-wide linkage analyses, several possible chromosomal loci and various candidate genes have been discovered, particularly in patients from the Chinese (FGF12, ADAMTS1, TGFB3, LTBP2, and COL2A1), Japanese (PLXNA2 and SSX2IP), and Korean (Matrilin-1) populations. It was discovered that the majority of the locus variations and candidate genes were expressed during the development of the mandible, which may cause mandibular prognathism.

Keywords: Mandibular Prognathism, Prevalence, Genetics, Gene, Class III Skeletal Pattern

Introduction

A jaw discrepancy condition known as mandibular prognathism (OMIM:176700; Online Mendelian Inheritance of Man, http://omim.org/entry/176700) is a part of Class III skeletal base manifestations. It can occur solely because of an overgrown mandible, undergrown maxilla, or a combination of both (1), giving the mandible a more prominent appearance than the maxilla and the front teeth with reverse overjet (2). According to OMIM, mandibular prognathism can manifest as either a non-syndromic condition or a systemic disorder such as Apert syndrome and Crouzon syndrome (3). Most of the time, early childhood does not reveal any abnormalities. Mandibular prognathism development emerges gradually, accelerates during puberty, and fully manifests once the body fully develops (4). Uncertainty exists concerning the perceived contributions of genetic and environmental factors to the aetiology of non-syndromic mandibular prognathism (5, 6). Nevertheless, there is an agreement that genetics play a part in determining the presence of mandibular prognathism, even though the genetic models are different (5).

The unattractive facial profile caused by mandibular prognathism may lower patients' social self-confidence and may result in severe psychological impairment. In addition, the bite between the lower and upper anterior teeth cannot be established, leading to low

masticatory efficiency (7). In turn, digestive issues and a weakened nutritional state may follow. Speech articulation problems could also result from the upper and lower jaw's uneven bite (8). The condition often results in a more expensive treatment, such as combined orthodontics and orthognathic surgery. Numerous recent studies have focused on understanding the genetic elements contributing to malocclusion and how these genetic factors may affect individual responses to orthodontic therapy (9). This article reviews the prevalence of mandibular prognathism in many groups, various theories of mandibular prognathism inheritance, probable chromosomal sites, and candidate genes that cause mandibular prognathism in diverse ethnic backgrounds.

Epidemiology of mandibular prognathism

The prevalence of mandibular prognathism varies relative to the population (10). Different ethnic backgrounds result in different affected ratios and mandibular prognathism prevalence (11). According to a meta-analysis study, populations from South East Asia, including Chinese and Malaysians, have the highest prevalence rate of Class III malocclusion, ranging between 12.58% and 26.6%. However, in the Malaysian population, the prevalence skyrocketed mainly because of the dental origin of the malocclusion. It is unknown whether there is an influence from the skeletal features, as it was not reported in the study. The prevalence of mandibular prognathism in Middle Eastern populations ranges between 9.48% and 11.38%, whereas an average prevalence rate of 4.88% was found in the European population.

Meanwhile, the Indian population had a prevalence rate of 1.19%, whereas African groups ranged from 1.22% to 19.72% (12). It was also claimed in other studies that mandibular prognathism is significantly more common among East Asians, with 10% of the Japanese population (13) and 2.1% to 10% in the Chinese group (3). On the other hand, the Caucasian population was said to have the lowest prevalence of mandibular prognathism, ranging from 0.48% to 4.3% (3).

There is no conclusive correlation between gender and mandibular prognathism prevalence, as evident by the equal numbers of affected males and females found in the Eastern Mediterranean population study (14). Other studies also reported no gender difference in the number of affected males and females (15, 16). However, a demographic assessment in Brazil found that Brazilian women had a higher likelihood of having mandibular prognathism than Brazilian men (1).

Genetic aspect of mandibular prognathism

The diversity in malocclusion expression may be explained by how hereditary and environmental factors interact (17). Although there might be many different environmental influences, Class III malocclusion is believed to develop due to inherited Class III skeletal components (11). In addition, numerous genetic hypotheses have identified and explained familial aggregation of mandibular prognathism related to Class III skeletal base (5). However, these genetic analyses show distinct locations, candidate genes, and inheritance patterns for mandibular prognathism, indicating that there may be a unique mutation of non-syndromic mandibular prognathism in each different population.

Inheritance pattern

The mandibular prognathism inheritance pattern is heterogeneous, and reported findings point to a polygenic transmission model, autosomal dominant inheritance, autosomal recessive inheritance, or dominant inheritance with partial penetrance (10).

Monogenic inheritance, which follows the Mendelian inheritance pattern, is brought on by a single altered gene (9). Numerous studies supported the monogenic hypothesis of mandibular prognathism inheritance. Two studies conducted segregation analyses of mandibular prognathism, which involved Libyan and Brazilian populations (1, 5). A study on the Libyan population found that autosomal dominant was the most sparing (5). In contrast, a study on the Brazilian group discovered that 65.3% of the pedigrees showed that the mandibular prognathism's primary mode of inheritance was autosomal dominant with incomplete penetrance (1). This was further reinforced by studies on Chinese Han and Hispanic pedigrees, which indicate that autosomal dominant with incomplete penetrance is the most probable pattern of inheritance (17, 18). In a study of a community in the Eastern Mediterranean, 51 family pedigrees showed that autosomal dominant inheritance was prevalent in most cases (14). An autosomal dominant form of mandibular prognathism inheritance was also found in two studies on the Chinese population that used a visual analysis of the pedigree (3, 10).

The inheritance of a phenotypic trait that may be linked to two or more susceptibility genes and their relationship with the environment is known as a polygenic or multifactorial inheritance (9). For example, research on the Korean population reveals that the inherited susceptibility of mandibular prognathism among Korean Class III patients was not mainly due to Mendelian transmission of major genes but rather the accumulation of minor effects from numerous different genes and the influence of environmental factors (11). Additionally, research on the Brazilian population reveals that 7.3% of the families have sporadic cases, which may be caused by phenocopies, for example, exposure to the environment, singular growth disorders, drug consumption, or other modes of inheritance like autosomal recessive or new dominant mutations (1).

Susceptible loci and candidate genes

It had been discovered that many potential genes and chromosomal loci were susceptible to mandibular prognathism. However, because of the variable outcomes of these studies in various ethnic groups, there may be multiple mandibular prognathism-causing genes. Moreover, the molecular process regulating jaw development is not entirely understood (8).

A genome-wide examination of 90 affected patients from the Japanese and Korean populations, including 40 Korean and 50 Japanese sibling pairs, revealed possible associations between the disorder and chromosomes 1p36, 6q25, and 19p13.2. Skeletal-system-related genes like alkaline phosphatase from the liver, bone, and kidney, heparan sulphate proteoglycan 2 (perlecan), and Matrilin-1 (cartilage matrix protein) are some positional candidate genes in the 1p36 locus that are of interest. These candidate genes were suggested to be involved in the development of the bone that may lead to mandibular prognathism (19). A genome-wide association study on a Japanese cohort revealed two loci, 1q32.2 and 1p22.3, as possible mandibular prognathism susceptibility regions, and the candidate genes SSX2IP and PLXNA2 were proposed. They hypothesised that SSX2IP controls the activity of synovial tissue in the temporomandibular joint (TMJ), which may cause mandibular prognathism, while PLXNA2 may cause excessive growth of the mandibular bone (20). In a different Japanese group, microsatellites were used in another genome-wide association study that identified six mandibular prognathism loci (1p22.3, 1q32.2, 3q23, 6q23.2, 7q11.22, and 15q22.22) as well as the candidate genes SSX2IP, PLXNA2, RASA2, TCF21, CALN1, and RORA. The locus 1p22.3 was supported by previous linkage analysis on Japanese patients, while the other five loci are new loci. In a different Japanese group, microsatellites were used in another genome-wide association study that identified six mandibular prognathism loci (1p22.3, 1q32.2, 3q23, 6q23.2, 7q11.22, and 15q22.22) as well as the candidate genes SSX2IP, PLXNA2, RASA2, TCF21, CALN1, and RORA. The locus 1p22.3 was supported by previous linkage analysis on Japanese patients, while the other five loci are new loci (21). A whole exome sequencing study in Japanese pedigree suggests a rare non-synonymous single-nucleotide variant (SNV) of the BEST3 gene as a candidate for mandibular prognathism (13).

Another research on the Korean population found that the associated Matrilin-1 polymorphism haplotype TGC (ht4;158T, 7987G, and 8572C alleles) has a significant risk effect for mandibular prognathism, suggesting that Matrilin-1 polymorphisms could serve as a marker for genetic susceptibility to mandibular prognathism. Matrilin-1 is a non-collagenous protein released by chondrocytes and is primarily expressed in cartilage (22). In addition, matrilin-1 can be released by chondrocytes in the TMJ condyle, notably in arthritic articular mandibular cartilage (23).

Several new susceptible loci and novel mutations were associated with mandibular prognathism in Chinese populations. One study reported that variant rs79176051 within the fibroblast growth factor (FGF) 12 gene, variant rs13317 in FGFR1, and variant rs149242678 in FGF7 were associated with mandibular prognathism. A previously unreported single nucleotide polymorphism (SNP), rs14924267 in FGF7, is significantly related to increased facial height. The craniomaxillofacial skeleton, muscle, palate, tooth, and submandibular salivary gland all contain FGFR1, which has a wide range of functions during craniofacial morphogenesis. In a recent study, variants in FGF12 were revealed to affect cleft lip significantly (24). In addition, another research found that FGF23 has a novel heterozygous mutation. The susceptibility locus of 12pter-p12.3 contains the FGF23 c.35C>A, which is strongly associated with the mandibular prognathism phenotype. It was predicted that the FGF23 c.35C>A mutation could cause a substitution of Asp for Ala in codon 12 (p.A12D) of the FGF23 protein. The mutation in p.A12D may interfere with the function of the signal peptide and inhibit secretory in FGF23 (3). Another study found that regions on chromosome 12 are biologically relevant to craniofacial development and suggests that locus 12q13 might be associated with mandibular prognathism and COL2A1 as the candidate gene. Another research suggests the ADAMTS1 gene (c. 742I>T) has a single-nucleotide missense mutation and is strongly related to mandibular prognathism. However, prior genome-wide association analyses did not identify this gene (8).

A single SNP analysis in the Chinese Han population indicated that the SNP rs1793953 in the COL2A1 gene showed a possible association with mandibular prognathism. The COL2A1 gene on chromosome 12q13 plays a vital role in cartilage formation (6). Furthermore, another genome-wide linkage analysis of the Chinese Han population identifies TGFB3 and LTBP2 as potential functional genes that are likely to be involved in the development of the craniofacial region and may be connected to mandibular prognathism (17).

Additionally, Genno et al. (14) reported that the genetic analysis of their samples from the East Mediterranean did not match any previously known genes associated with mandibular prognathism. Instead, they reported three unique genes (C1orf167, NBPF8, NBPF9) on chromosome 1 that may be related to mandibular growth and prognathism. Five loci; 1p22.1, 3q26.2, 11q11, 12q13.13, and 12q23, on four chromosomes and three genes; IGF1, HOXC, and COL2A1 on loci (11q22, 12q13.13, and 12q23) respectively were identified as candidate genes in a non-parametric linkage study of a Hispanic population (18). In the meantime, a rare variant (Gly1121Ser) in the ARHGAP21 gene was shared by every mandibular prognathism person in the broader family division in the Caucasian population with nearly complete penetrance (25). Cell-cell adhesions are

improved by the ARHGAP21 protein and may be controlled by bone morphogenetic elements, which may affect the growth of the mandible (25). All susceptible loci and candidate genes are listed in Table 1.

Table 1: Susceptible loci and candidate genes causing MP in the different affected populations.

Susceptible loci and candidate genes that cause MP	Affected population
Chromosomes 1p36, 6q25, and 19p13.	Korean and Japanese sibling pairs
Matrilin-1 polymorphism haplotype TGC (ht4;158T, 7987G, and 8572C alleles)	Korean
Six susceptible loci; 1p22.3, 1q32.2, 3q23, 6q23.2, 7q11.22, and 15q22.22	Japanese
Two loci; 1q32.2 and 1p22.3	
Candidate genes SSX2IP, PLXNA2, RASA2, TCF21, CALN1, and RORA	
A rare non-synonymous single-nucleotide variant (SNV) of the BEST3 gene	
Variant rs79176051 within the FGF12, variant rs13317 in FGFR1, and variant rs149242678 in FGF7	Chinese
Mutation of p.A12D in FGF23	
Locus 12q13 in Chromosome 12	
Candidate gene COL2A1	
A single-nucleotide missense mutation in the ADAMTS1 gene (c. 742I>T)	
SNP rs1793953 in the COL2A1 on chromosome 12q13	Chinese Han
TGFB3 and LTBP2 as potential functional genes	
Three unique genes (C1orf167, NBPF8, NBPF9) on chromosome 1	East Mediterranean
Five loci (1p22.1, 3q26.2, 11q11, 12q13.13, and 12q23) and three candidate genes (IGF1, HOXC, and COL2A1)	Hispanic
A rare variant (Gly1121Ser) in the ARHGAP21 gene	Caucasian

Conclusion

Mandibular prognathism has been concluded to result from diverse genetic and environmental factors. Some of the aetiology might influence the regulation of mandibular growth during the developmental phase. The unattractive facial profile brought on by mandibular prognathism may cause patients to feel less confident in social situations and may even result in severe psychological impairment.

Unravelling the underlying mechanism of genetic mutation in a specific targeted population will help researchers and clinicians to justify the need for treatment, either by modifying the growth using chin-cup therapy in very young patients or by planning for orthognathic surgery once the growth has stopped. Furthermore, it is essential to comprehend the genetics causing dentofacial diversity in patients with malocclusion to create preventive measures and reduce treatment modalities. Thus, it will be vital to conduct an additional study on this subject in the future, focusing on the related functions of the mutated genes and identifying the unique biomarkers associated with mandibular prognathism.

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References

1. Cruz RM, Krieger H, Ferreira R, Mah J, Hartsfield Jr J, Oliveira S. Major gene and multifactorial inheritance of mandibular prognathism. Am J Med Genet Part A. Wiley Online Library; 2008; 146(1):71–7.
2. Vuuren C van. A review of the literature on the prevalence of Class III malocclusion and the mandibular prognathic growth hypotheses. Aust Orthod J. 1991; 12(1):23.
3. Chen F, Li Q, Gu M, Li X, Yu J, Zhang YB. Identification of a mutation in FGF23 involved in mandibular prognathism. Sci Rep. Nature Publishing Group; 2015; 5.

4. Morrill LR, Baumrind S, Miller D. Surgical correction of mandibular prognathism: I. A cephalometric report. Am J Orthod. Elsevier; 1974; 65(5):503–18.
5. El-Gheriani AA, Maher BS, El-Gheriani AS, Sciote JJ, Abu-Shahba FA, Al-Azemi R, *et al.* Segregation analysis of mandibular prognathism in Libya. J Dent Res. SAGE Publications; 2003; 82(7):523–7.
6. Xue F, Rabie ABM, Luo G. Analysis of the association of COL 2 A 1 and IGF-1 with mandibular prognathism in a C hinese population. Orthod Craniofac Res. Wiley Online Library; 2014; 17(3):144–9.
7. English JD, Buschang PH, Throckmorton GS. Does malocclusion affect masticatory performance? Angle Orthod. 2002; 72(1):21–7.
8. Guan X, Song Y, Ott J, Zhang Y, Li C, Xin T, *et al.* The ADAMTS1 gene is associated with familial mandibular prognathism. J Dent Res. SAGE Publications Sage CA: Los Angeles, CA; 2015; 94(9):1196–201.
9. Xue F, Wong RWK, Rabie ABM. Genes, genetics, and Class III malocclusion. Orthod Craniofac Res. Wiley Online Library; 2010; 13(2):69–74.
10. Li Q, Zhang F, Li X, Chen F. Genome scan for locus involved in mandibular prognathism in pedigrees from China. PLoS One. Public Library of Science San Francisco, USA; 2010; 5(9):e12678.
11. Ko JM, Suh YJ, Hong J, Paeng JY, Baek SH, Kim YH. Segregation analysis of mandibular prognathism in Korean orthognathic surgery patients and their families. Angle Orthod. 2013; 83(6):1027–35.
12. Hardy DK, Cubas YP, Orellana MF. Prevalence of angle class III malocclusion: A systematic review and meta-analysis. Open J Epidemiol. 2012; 02(04):75–82.
13. Kajii TS, Oka A, Saito F, Mitsui J, Iida J. Whole-exome sequencing in a Japanese pedigree implicates a rare non-synonymous single-nucleotide variant in BEST3 as a candidate for mandibular prognathism. Bone. Elsevier Inc.; 2019; 122:193–8.
14. Genno PG, Nemer GM, Zein Eddine SB, Macari AT, Ghafari JG. Three novel genes tied to mandibular prognathism in eastern Mediterranean families. Am J Orthod Dentofac Orthop. Mosby Inc.; 2019; 156(1):104-112.e3.
15. Litton SF, Ackermann L V., Isaacson RJ, Shapiro BL. A genetic study of class III malocclusion. Am J Orthod. 1970; 58(6):565–77.
16. Li Q, Li X, Zhang F, Chen F. The identification of a novel locus for mandibular prognathism in the Han Chinese population. J Dent Res. SAGE Publications Sage CA: Los Angeles, CA; 2011; 90(1):53–7.
17. Uribe LMM, Vela KC, Kummet C, Dawson D V., Southard TE, Moreno Uribe LM, *et al.* Phenotypic diversity in white adults with moderate to severe Class III malocclusion. Am J Orthod Dentofac Orthop. Elsevier; 2013; 144(1):32–42.
18. Frazier-Bowers S, Rincon-Rodriguez R, Zhou J, Alexander K, Lange E. Evidence of linkage in a Hispanic cohort with a class III dentofacial phenotype. J Dent Res. 2009; 88(1):56–60.
19. Yamaguchi T, Park SB, Narita A, Maki K, Inoue I. Genome-wide linkage analysis of mandibular prognathism in Korean and Japanese patients. J Dent Res. SAGE Publications; 2005; 84(3):255–9.
20. Ikuno K, Kajii TS, Oka A, Inoko H, Ishikawa H, Iida J. Microsatellite genome-wide association study for mandibular prognathism. Am J Orthod Dentofac Orthop. Mosby Inc.; 2014; 145(6):757–62.
21. Saito F, Kajii TS, Oka A, Ikuno K, Iida J. Genome-wide association study for mandibular prognathism using microsatellite and pooled DNA method. Am J Orthod Dentofac Orthop. Mosby Inc.; 2017; 152(3):382–8.
22. Jang J, Park EK, Ryoo HM, Shin HI, Kim TH, Jang JS, *et al.* Polymorphisms in the Matrilin-1 gene and risk of mandibular prognathism in Koreans. J Dent Res. SAGE Publications Sage CA: Los Angeles, CA; 2010; 89(11):1203–7.
23. Ohno S, Murakami K, Tanimoto K, Sugiyama H, Makihira S, Shibata T, *et al.* Immunohistochemical study of matrilin-1 in arthritic articular cartilage of the mandibular condyle. J Oral Pathol Med. Wiley Online Library; 2003; 32(4):237–42.
24. Xiong X, Li S, Cai Y, Chen F. Targeted sequencing in FGF/FGFR genes and association analysis of variants for mandibular prognathism. Medicine (Baltimore). Wolters Kluwer Health; 2017; 96(25).
25. Perillo L, Monsurrò A, Bonci E, Torella A, Mutarelli M, Nigro V. Genetic association of ARHGAP21 gene variant with mandibular prognathism. J Dent Res. SAGE Publications Sage CA: Los Angeles, CA; 2015; 94(4):569–76.