# The Roles of Genetic and Epigenetic Aspects in Mandibular Prognathism: A Review

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**Abstract.** Individuals with mandibular prognathism (MP) are characterized by a concave facial profile, and in severe cases, an extremely long face. These clinical characteristics mostly result from the extreme forward growth of the mandible, and are more prevalent in Asians than in Caucasians. MP is a multifactorial condition, with genetic, environment or their interaction (including epigenetics) as assumed etiological factors. As suggested by familial and ethnic traits, the genetic aspects are important, and MP has been found to have a relationship with numerous loci and genes. The present review aims to assess studies on the potential association of MP with the candidate genes of *MYO1H*, *RUNX2* and *MATN1*, and interactions between genes and environment. The results showed mechanisms of expression correlated genes developing MP. The interactions between these genes and others, or between the genes and the environment (epigenetics), have not been clearly demonstrated, except for the *RUNX2* gene that correlates with observed K(lysine) acetyltransferase 6B (KAT6B) and histone deacetylase 4 (HDAC4). In conclusion, the expression of *MYO1H*, *RUNX2*, and *MATN1* genes is indicated to play a vital role in genetic and epigenetic regulation to develop the phenotype of MP.

**Keywords:** Mandibular Prognathism · Genetic · Environment · Epigenetic · Etiology

## 1 Introduction

Over a century ago, the father of modern orthodontics, Edward Hartley Angle, set out three fundamental types of malocclusion: Class I, Class II, and Class III [1]. Class III malocclusion is described by the mesiobuccal cusp of maxillary first molar occludes mesial to the mesiobuccal groove of the mandibular first molar [2]. This classification, however, could not give the most effective information about the mechanisms of facial


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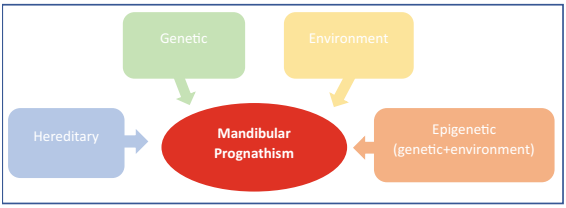


**Fig. 1.** Etiological factors of mandibular prognathism.

skeleton development. Thus, further information such as maxillomandibular relationship was also included [1, 3]. The results of further studies indicated that more than 60% of Class III malocclusions are derived from skeletal growth disharmony between the upper and lower jaw, and not from the first molar occlusion [4].

Several types of Class III malocclusion were further described by Charles Henry Tweed: pseudo Class III malocclusion with the underdeveloped maxilla and normal mandible, and skeletal Class III malocclusion with the underdeveloped maxilla and prognathic mandible [3]. The latter has been considered to be the most severe type of this skeletal disharmony, also recognized as mandibular prognathism (MP) [1].

Individuals with MP are characterized by a concave facial profile and in severe cases, adjunct with an extremely long face. These clinical characteristics mostly result from the extreme forward growth of the mandible [5, 6].

MP is a multifactorial condition. Genetics, environment, or their interaction (epigenetics) have been considered to be the etiological factors [2]. As suggested by familial traits and ethnic accretion, the genetic aspects must be important in the etiology of MP [7].

MP has been found to have a relationship with numerous loci and genes. The expression of some candidate genes is also indicated to play a vital role in epigenetic regulations to develop MP as a phenotype [8]. The compound results of earlier studies suggested that the causal genes of MP may be multiple and varied. Therefore, further review of the candidate genes is needed [9].

This paper aims to describe the association between MP and its etiological factors, focusing on the roles and interactions of associated genes, and interaction between genes and environment (epigenetics).

## 2 Etiological Factors

Mandibular prognathism is reported to be a multifactorial deformity. Numerous studies have implied that heredity plays a significant role in its development. However, various studies have also suggested strong influence for genetic and epigenetic, as well as environmental factors [6, 8]. Figure 1 illustrates the etiological factors of MP.

### 2.1 Heredity

The manifestation of familial ancestry of MP shows that genetic elements have a vital role in its etiology. Various studies have shown a substantially higher incidence of this phenotype in the affected individuals' relatives [1, 10].

The most-reported inheritance pattern of MP is autosomal-dominant. Several studies of Japanese families have indicated that if the father was affected, in the children the frequency of MP was about 31%. On the other hand, if the mother and both parents were affected, the frequency was around 18% and 40%, respectively [1] These figures were reinforced by one study that reported MP has the inheritance pattern of autosomal-dominant, with incomplete penetrance [8].

Even though a strong association is clear for familial inheritance of MP, the rate of developing this condition is similar (about 50%) in Asian individuals with a positive and negative family background. Thus, MP may depend on the genetic expressions, and the interaction between genes and environment may determine its severity [1, 11], [2].

### 2.2 Environment

Numerous environmental factors are associated with the development of MP, including congenital defects, endocrine disease, airway obstruction, habitual posture, and trauma. Cleft-lip-palate has been related to MP in terms of congenital anatomical defects. Pituitary adenoma, gigantism, and acromegaly, on the other hand, as kinds of endocrinal disease, have also been reported to have a contribution to the development of MP. Whereas enlarged tonsils that causing airway obstruction was suggested to be one of the environmental factors for the development of MP. Instrumental deliveries have been described as well to cause trauma on the lower jaw, resulting in this deformity [1, 6].

### 2.3 Genetics and Epigenetics

Three chromosomal loci of 6p21.1, 1p35.2 and 12q24.11 have shown reported association with MP [11]. The following candidate genes were suggested to be linked with MP; *MYO1H, RUNX2,* and *MATN1*. Also, the expression of *MYO1C, MYH3,* and *MYH8* is speculated to be implicated in the epigenetic regulation of the MP phenotype [8].

## 3 Associated Genes and Epigenetic Regulation

### 3.1 Associated Genes

As one of the most reported etiological factors of mandibular prognathism, genetics is expected to have a vital role in the development of this craniofacial deformity. Several candidate genes have been related to MP, such as *MYO1H*, *MATN1*, and *RUNX2*. Details of these genes and their function are described below, including their roles and mechanisms in developing MP [8, 9].

#### 3.1.1 MYO1H (Unconventional Myosin-1H Gene)

Myosins are called motor proteins that work together with actin filaments and couple hydrolysis of ATP to configurational changes resulting in the myosin movement and one actin filament corresponding within one and another [9, 12].

Myosin 1 proteins are the most copious and meticulously studied among the myosins. Myosin 1 proteins constitute of one or two heavy chains and several light chains. The

heavy chains are structured into three different territories by anatomy and function. Actin and ATP-binding sites in its globular head account for creating force [12, 13].

The *MYO1H* genes synthesizes the unconventional myosin 1H, a class 1 myosin that is a distinct protein unit from the other myosin isoforms with heavy chains [13]. Numerous diseases have been found associated with *MYO1H* including Central Hypoventilation Syndrome, several types of cancer, and also craniofacial deformities. Several studies have linked MP with *MYO1H* [9, 13]-[15].

Unconventional myosin 1H is a motor protein that has roles in vesicle transportation, auditory mechanotransduction, and intracellular movements [14]. One study also has suggested for it a vital role in phagocytosis and cell motility in humans [16]. Furthermore, these roles are associated with the alteration of skeletal muscle height through the nicotinic acetylcholine receptor signalling pathway [16].

The location of unconventional myosin 1H is in the human cytoskeleton, concentrating in the cytosol, plasma membrane, and nucleus. The *MYO1H* gene is mapped at the chromosomal locus 12q24.11, demonstrated by genomic sequence analysis [16]. It is 67.43 kbs, covers from 10982654 to 109893952, contains 30 exons, and its transcription produces 8 different mRNAs [17]. Various studies have identified several single nucleotide polymorphisms (SNPs) of *MYO1H* associated with MP. The G allele of SNP rs10850110, flanks the 5' end of the *MYO1H* gene is demonstrated to be related to an elevated risk of developing MP [15, 16]. The frequency of this SNP varies across ethnicity. The SNP rs3825393, C > T, p.Pro1001Leu, has also been demonstrated to be linked with skeletal maxillomandibular variations in horizontal dimensions [9]. These SNPs are single nucleotide missense mutations. However, the Pro1001Leu alteration in the protein by rs3825393 may not result in a loss of function [9].

*3.1.1.1. Mechanism of MYO1H in developing MP*

The assumed role of the *MYO1H* gene in developing MP suggests that muscle function could be more important than previously believed in modifyingg the developmental bone structures of the maxillomandibular complex [13].

It is thought that the expression of *MYO1H* as one of the motor proteins could change the proportion of fiber type (Type I and Type II) in the orocraniofacial complex muscle, with the greater composition of Type II fibers. This is suggested to create an alteration in muscle function and occupancy, leading to the changes in the mandibular dimensions. This is supported by the results of a study that demonstrated the differences in fiber composition of the masseter muscle in people with a mandibular deformity [18]. Additionally, the facial height might also be related to the different muscle proportions, and MP typically involves individuals with great facial height [19].

In contrast, one study found low expression of *MYO1H* gene in masseter muscle biopsies. This would suggest that the correlation between MP and *MYO1H* might not be related to the alteration of the fiber type in masseter muscle. Nevertheless, the study also reported changes in muscle fiber proportions that might be related to MP [16, 18].

### 3.1.2 MATN1 (Matrilin-1 Gene)

Matrilins form a family of four oligomeric, multidomain, noncollagenous proteins (and corresponding genes), from matrilin-1 to matrilin-4 (*MATN1 to MATN4*). Matrilin-1 is considered as the archetype of the family of matrilins [20].

Matrilin-1 was primarily indicated as *cartilage matrix protein*, as it is expressed in human cartilage. Throughout its connections with *CSPG* (chondroitin sulfate proteoglycan), it was initially recognized as an aggrecan-related protein. Using in vitro biomechanical assays, it was shown that matrilin-1 has direct interactions with collagen II and XI [20, 21].

The expression of *MATN1* has been found in numerous diseases and conditions, such as cancer, relapsing polychondritis, osteochondrodysplasias, and musculoskeletal deformities including MP [8, 10, 21, 22].

The *MATN1* gene encrypts a cartilage matrix protein that is included in the Von Willebrand Factor type A (VWA) family of proteins and it seems to have a significant role in skeletal development, particularly in the construction of filamentous networks inside the numerous tissues' extracellular matrices [23]. It is also reported that matrilin-1 is having a role in collagen fibrillogenesis [24].

As a component of cartilage extracellular matrix, matrilin-1 plays a vital part in upregulating the process of chondrogenesis [21]. An experimental study has verified that this protein is important in upholding and increasing chondrogenesis. However, this only happens when the process is initially promoted by TGF β 1 [8].

*MATN1* is primarily expressed in cartilaginous tissue of growing long bones [21]. It resides in the chromosomal locus 1p35.2, is 12 kbs in size and comprises 8 exons, and the mRNA size is around 1.5 kbs. The mRNA is foreseen to generate a monomer of 496 amino acids. It is projected that the mature protein has an unmodified molecular weight of 51344 [24].

It was shown in a case-control study that the increased risk of MP is associated with three non-synonymous missense single nucleotide polymorphisms (SNPs) contained in the *MATN1* gene; rs11499054 T > C, rs20566 G > A and rs1065755 C > T. Additionally, rs20566 G > A and rs20566-AA genotype were indicated as protective against the development of MP [21, 23].

*3.1.2.1. Mechanism of MATN1 in developing MP*

As noted above, the *MATN1* gene appears to play a role in the skeletal formation. Since mandibular form derives from bone growth and/or adjacent muscle function and growth, matrilin-1 could also be linked with the phenotype of MP. This implies that molecular pathways in the development of cartilage might be correlated with discrepancies in the mandibular sizes [23, 24].

With an important role in chondrogenesis, matrilin-1 might be related to endochondral ossification in the development of the human skeleton, including in the craniofacial complex. A study has shown that the synchondroses in the cranial base have a configuration of endochondral ossification comparable to the long bones' growth plates. With increasing expression of *MATN1*, the ossification in the mandible also increases, leading to the escalation of mandibular dimensions and size [24]. Also, for the period of growth, the mandible will have forward and downward displacement as the growth plate in the cartilage experiences endochondral ossification and growth in an upward direction. This zuggests that matrilin-1 might not only be linked with mandibular dimensions, but also with the mandibular position in the craniofacial structure [21].

### 3.1.3 RUNX2 (Runt-Related Transcription Factor 2 Gene)

The *RUNX* (Runt-related) gene family of transcription factors include three members, *RUNX1*, *RUNX2*, and *RUNX3*. They have a vital role in human body as the regulators of protein transcription, for instance, in the development of neural and hematopoietic systems, and also in bone and dental cell formation [25].

*RUNX2* is recognized as the main regulator of bone development. The ideal amount of *RUNX2* expression is required for normal bone development. A mutation, insufficiency, or hyperexpression of *RUNX2* could create some autosomal-dominant bone disorder, such as cleidocranial dysplasia and mandibular prognathism [26].

*RUNX2* is expressed in two different types of chondrocytes, prehypertrophic and hypertrophic ones. It is located in chromosome band 6p21.1 from 45,328,257 to 45,664,349 bp. It is constituted of eight exons and two promoters, PI and P2 that provide regulating function of *RUNX2* at the transcriptional level. The overall length of *RUNX2* is 227,766 nucleotides along with introns. The *RUNX2* gene produces two main isoforms, of which MASNS is transcribed from promoter P1 and MRIPV from P2. P1 contains 507 amino acids and P2 507 amino acids are constituted in the P2 isoforms [25, 27].

In bone cells, *RUNX2* works as an osteogenic differentiation factor. It interacts with several proteins resulting in the regulation (positive or negative) of its target genes upon numerous stimuli. Post-translantional modifications, for instance, acetylation, sumoylation, ubiquination, and phosphorylation regulate *RUNX2* activity at copious levels. Phosphorylation commands its operational collaborations with several other proteins in monitoring the differentiation of osteoblasts [26, 27].

The role of *RUNX2* single nucleotide polymorphism in MP is intriguing and still controversial. Some studies have suggested that rs6930053 A > G is associated with MP, while others have indicated this SNP to be also linked to the class II malocclusion [28, 29].

#### *3.1.3.1 Mechanism of RUNX2 in developing MP*

Looking at the location of *RUNX2* gene being expressed, the correlation between the *RUNX2* and mandibular prognathism is, therefore, can be suggested. The regulation of *RUNX2* has the main function of forming the axial and craniofacial skeleton. Its increased activity due to the alterations in the phosphorylation process has a direct effect on osteoblast differentiation [26, 27].

It is known that the activity of the *RUNX2* increases under mechanical loading. Therefore, the higher activity the *RUNX2* has within the mandibular chondrocytes, particularly in the condylar growth site, the higher the bone cell differentiation. This condition will promote the increased mandibular size and confers susceptibility to the phenotype of mandibular prognathism [28, 30].

It is also reported that the expression of the *RUNX2* gene in individuals with MP has a strong positive correlation with the occupancy of Type II fibers in the masseter muscle. This condition may modify the muscle function, contributing therefore to the alteration in mandibular size [18].

Table 1 summarizes the associated loci, genes, expressed proteins, and their significant variants related to mandibular prognathism in this review.

**Table 1.** Associated loci, genes, expressed proteins and their significant variants

| Loci | Genes | Proteins | Variants |
|---|---|---|---|
| 12q24.11 | MYO1H | Unconventional Myosin 1H | rs10850110, rs3825393 |
| 1p35.2 | MATN1 | Matrilin-1 | rs11499054, rs20566, rs1065755 |
| 6p21.1 | RUNX2 | Runt-related Transcription Factor-2 | rs6930053* |

* Still controversial

### 3.2 Epigenetic Regulation in MP

Several studies have reported that some changes in gene expression could be elaborated in the etiology of mandibular prognathism alongside the variations in the DNA sequence. DNA methylation and histone acetylation as epigenetic mechanisms control the transcription process in the sequence of nucleotide. This regulation is based on the activation and deactivation of particular genes [8, 31].

The power of masticatory muscles is recognized to influence the maxillomandibular development. Changes in the size and proportions of the orocraniofacial skeleton are also known to affect the masticatory muscles' tension. Various environmental factors, for instance, forces toward the mandible, might influence the epigenetic mechanisms regulating the expression of genes whose products will affect the growth of the mandible [8, 30].

One study has compared the amount of mRNA for types I, IIa, and IId/x *MYH7, MYH2,* and *MYH1* in the masseter muscle in individuals with prognathic and retrognathic mandible before and after surgery. The results suggested that in both groups, surgical improvement can create an epigenetic change indicating a shift from type I *MyHC* to type Iia [8].

Another study examined the change among pre- and post-surgery levels of mRNA for developmental types of *MyHC*, type 3 and type 8 in patients with mandibular prognathism and retrognathism. The analysis demonstrated that the expression of the *MYH8* gene in the mandibular prognathism group was twice as high as in the mandibular retrognathism one. However, the *MYH3* expression was not statistically different between the two groups [8].

*MYO1H*, *MATN1*, and *RUNX2* were reported to be associated with MP, involving the mechanisms in developing this deformity as described above. However, the interaction between those genes and others were not clearly demonstrated, except for *RUNX2*. Other various genes were reported to have interactions in developing the phenotype of MP, such as K(lysine) acetyltransferase 6B (*KAT6B)* and histone deacetylase 4 (*HDAC4)* genes whose correlations with *RUNX2* in the development of MP were reported in several studies. It is implied that these mechanisms frequently involve acetylation of lysin residues within the chromatin throughout acetyltransferases and deacetylases of the histones [8, 27].

A study carried out the assay on masseter muscle about the roles of *KAT6B* and *HDAC4* in encrypting histone-modifying enzymes in the etiology of skeletal malocclusions. The investigation showed that the expressions of *KAT6B* and *HDAC4* were substantially elevated in the groups of skeletal Class III and Class II malocclusions [31].

Further studies evaluated the roles of the expression of *MYO1C*, *KAT6B*, and *RUNX2* in developing malocclusions. The results showed that the quantity of the *KAT6B* mRNA was substantially greater in the skeletal Class III group compared to other groups. This report demonstrated the positive strong correlation between Type II fiber occupancy and the expression of *RUNX2* in all malocclusion groups, with the highest correlation in the mandibular prognathism group. The outcome was taken to suggest a nuclear isoform crucial function, and a connection between *KAT6B* and mandibular prognathism to be related to its activation of *RUNX2* osteogenic transcription factor that is crucial to skeletal growth and preservation [18, 26].

There was also one probable elucidation about how KAT6B affecting mandibular dimensions is the molecular interaction between KAT6B and RUNX2 as the transcription factor. The C-terminal domain in KAT6B is well known to be predicament to *RUNX2*, and the endogenous KAT6B is essential for the activation of *RUNX2*-dependent transcriptional function. The activation of *RUNX2* is also needed as the biomechanical stimulus of osteoblast gene expression. HDAC4 and KAT6B were linked to the differences in myosin gene expression and also to the growth modifications of the condyle and periosteal areas, therefore, they are considered to be fundamental epigenetic factors in the growth of orocraniofacial features [27].

There are strong correlations between mandibular prognathism and the expression of various genes, their interactions and the interactions between genes and the environment. MYO1H, MATN1, and RUNX2 genes were reported to have an association with mandibular prognathism. The expression of MYO1H gene could change the proportion of fiber type in the orocraniofacial complex muscles, with the greater composition of Type II fibers that lead to the longer mandibular dimensions. The increase of expression of *MATN1* gene, also proposed to lead the escalation of mandibular dimensions and size since the mandibular ossification increased and growth in an upward direction. *RUNX2* gene higher activity increased size of mandibular and has a strong positive correlation of the occupancy of Type II fibers in the masseter muscle that lead to an alteration in mandibular size as well. Other various genes reported to have interactions in developing mandibular prognathism, such as K(lysine) acetyltransferase 6B (KAT6B) and histone deacetylase 4 (HDAC4) genes whose correlation with RUNX2 considered as epigenetic factors.

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