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REVIEW

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Genetic etiology in mandibular prognathism: a scope review

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Abstract

Mandibular prognathism (MP) is a craniofacial disorder that can affect patients' appearance, characterized by a concave profile. MP can be influenced by genetic, epigenetic and environmental factors. However, the exact pathogenesis of MP remains unclear, presenting a complex clinical challenge. We gathered information on the potential etiology of MP from sources such as PubMed, ScienceDirect and Web of Science. As a result, MP is associated with 70 genes or factors, including *collagen type II alpha1 chain* (*COL2A1*), *insulin-like growth factor1* (*IGF1*), *matrilin-1* (*MATN1*), *Myosin 1H* (*MYO1H*) and *plexin A2* (*PLXNA2*). It is crucial to collect and summarize these findings to enhance our understanding of the molecular pathogenesis of both syndromic and nonsyndromic MP. Additionally, identifying gene-environment interactions and developmental mechanisms is essential in understanding the phenotypic diversity of MP. This study sheds light on the genetic etiology of MP, offering new evidence for prevention and future prospects of this condition.

Keywords

Mandibular prognathism; Genetic etiology; Clinical treatment

1. Introduction

Mandibular Prognathism (MP) is a facial deformity characterized by a concave profile, prognathic chin, anterior crossbite, and a mesial step relationship of the molars, leading to difficulties in mastication and pronunciation for patients.

It has been reported that the African (10–16.8%) and East Asian (8–40%) populations have a relatively high prevalence of MP [1]. The prevalence rate of MP is known to vary according to ethnicity, such as Mongoloid and Caucasians. This phenomenon demonstrates that ethnic background continues to be a crucial factor in terms of phenotype. In Ko *et al.*'s [2] study, correlation coefficients for MP incidence in parent-offspring and full siblings were found to be 0.2036 and 0.2003, respectively. The h2 of MP was estimated to be 21.5% after adjusting for sex and founder effects.

The harm caused by this deformity is primarily reflected in two aspects. Firstly, it can affect the physiological function of the stomatognathic system, leading to disorders in chewing, swallowing, articulation and temporomandibular dysfunction [3]. Secondly, the deformity can have a negative impact on the patients' mental health and social life due to its specific appearance [4].

In the context of 3-dimensional bone relationships, MP is described as increased mandibular bone growth in three planes. It is classified as a Class III skeletal pattern, with its main features easily observed on a lateral cephalometric radiograph. Li *et al.*'s [5] study focused on characterizing the phenotypic variations of Class III malocclusion within a community of Chinese individuals through a lateral cephalometric analysis. The analysis revealed four subtypes through cluster analysis (Table 1). The development of a more sophisticated classification system will aid in a more accurate understanding of the genetic etiology.

Currently, there are three treatment strategies available for MP, including growth modification, orthodontic camouflage therapy and surgical orthodontics [6]. Early orthopedic treatment often has limited efficacy in inhibiting MP, with 27–36% of patients still requiring orthognathic surgery as definitive treatment [7]. Orthognathic surgery combined with orthodontic procedures has been the mainstay of treatment for MP [8]. The most commonly used surgical procedures for treating MP include sagittal split ramus osteotomy (SSRO) and intraoral vertical ramus osteotomy (IVRO) [9]. A study by Li [9] revealed that the horizontal stability at B-point was superior in the IVRO group compared with the SSRO group in the correction of MP during the 2-year follow-up. Recently, a novel machine learning algorithm was utilized to assist in treatment decisions for adult patients with Class III malocclusion in borderline cases with 93% accuracy [10], highlighting the potential impact of artificial intelligence and machine learning in orthodontic diagnosis and treatment planning.

MP can manifest as a non-syndromic condition or as a phenotype of systemic diseases [11], such as Crouzon syndrome. This paper provides an overview of MP's etiology, with a particular emphasis on the impact of genetic components in both syndromic and nonsyndromic MP to promote interdisci-

TABLE 1. MP related subtypes.

Categories	Compositions
Subtype 1	Subjects with mild mandibular prognathism and a steep mandibular plane
Subtype 2	Subjects with a combination of prognathic mandibular growth and retrusive maxillary growth, with a flat or normal mandibular plane
Subtype 3	Individuals with severe mandibular prognathism and a normal mandibular plane
Subtype 4	Individuals with mild maxillary deficiency and severe mandibular prognathism, characterized by the lowest mandibular plane angle

Cluster analysis showed that there were 4 subtypes.

plinary interaction. Both genetic and environmental factors are believed to contribute to the development of this dentofacial deformity [11]. The complexity of etiology and unpredictable expression, as well as the wide spectrum of dentofacial variation present in individuals, explains why current treatments for MP target symptoms rather than etiology. The aim is to summarize the functional studies on the genetic etiology of MP and make progress towards effective treatment and prevention of this condition.

2. Materials and methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram is shown in Fig. 1. From 2004 to December 2024, we conducted a literature search on the potential genetic etiology of MP using PubMed, ScienceDirect and Web of Science. Two reviewers independently assessed and selected articles. In cases where discrepancies existed between the two reviewers and consensus could not be reached after discussion, a third reviewer intervened. Final decisions were made by all authors collectively. The study analyzed and summarized current perspectives on the incidence and epidemiology, clinical features, etiology, clinical treatment and future prospects of MP. The search terms used were “Malocclusion, Angle Class III”, “Hapsburg Jaw”, “Underbite”, “Prognathism, Mandibular”, “Habsburg Jaw”, “Angle Class III” as well as “Genetics”, “Genetic” and “Heredity”.

The following inclusion and exclusion criteria were considered for studies selection:

- Studies involving patients with MP or Class III malocclusion were included.
- Studies that mentioned genetic components.
- Recent studies performed from 2004 to the present.
- Studies written in English.
- Study type with original research or case report.
- Exclusion of studies unavailable of full text.
- Exclusion of animal studies.

3. Results

The etiology of MP is relatively complex, and studies have shown that it is the result of the combined action of environmental and genetic factors [12]. The advancement of genetic detection and analysis methods has facilitated the discovery of many genes and gene polymorphisms associated with MP [13]. The factors involved in MP are presented in Fig. 2.

Linkage analysis is an approach used by geneticists to identify genes or genetic variants that affect a particular trait. Kajii *et al*. [14] conducted whole-exome sequencing in a Japanese pedigree, implicating a rare non-synonymous single nucleotide variant (SNV) of *bestrophin 3* (*BEST3*) as a candidate for MP. In order to find susceptibility loci for MP, Saito *et al*. [15] conducted the first microsatellite-based genome-wide association studies (GWAS) with 240 patients with mandibular prognathism and 360 healthy individuals. They identified 6 loci (1p22.3, 1q32.2, 3q23, 6q23.2, 7q11.22 and 15q22.22) as susceptibility areas for MP, with candidate genes *synovial sarcoma X breakpoint 2 interacting protein* (*SSX2IP*), *plexin A2* (*PLXNA2*), *RAS p21 protein activator 2* (*RASA2*), *transcription factor 21* (*TCF21*), *calneuron 1* (*CALN1*) and *RAR related orphan receptor A* (*RORA*) respectively. Furthermore, subsequent studies have found that exogenous semaphorin-3A (sema3A) suppresses the expression of parathyroid hormone receptor 1 (PTH-R1) in human proliferative chondrocytes and suggested that sema3A may affect human chondrocytes via its receptor, plexin A2 [16].

Association studies can either focus on candidate genes or be genome-wide and hypothesis-free. Xiong *et al*. [17] conducted targeted sequencing on mutations in the *fibroblast growth factor* (*FGF*)/*fibroblast growth factor receptor* (*FGFR*) signaling pathway in 176 individuals with MP and 155 controls with Class I malocclusion. They discovered that variants within the FGF12 gene exhibited a significant association with MP. Jiang *et al*. [18] also identified that four single nucleotide polymorphisms (SNPs) in FGFR2 (rs2981578, rs1078806, rs11200014 and rs10736303) were linked to skeletal malocclusions.

In recent years, numerous genetic variants associated with MP have been reported, as presented in Table 2 (Ref. [14–17, 19–60]). As anticipated, it has been possible to ascertain that most of these genes are enriched in the signaling pathways that control and facilitate the growth of bone and cartilage. Specifically, these pathways include FGFR, wingless (WNT), hedgehog (HH) and the transforming growth factor beta (TGF-β) signaling pathway, which encompass the bone morphogenic proteins (BMPs) and activins [11].

3.1 Genetic variation associated with craniofacial bone development

Among the candidate genes mentioned above, several have been identified as being associated with bone formation. In a study by Perillo *et al*. [22] next-generation sequencing in a Caucasian population revealed *Rho GTPase activating*

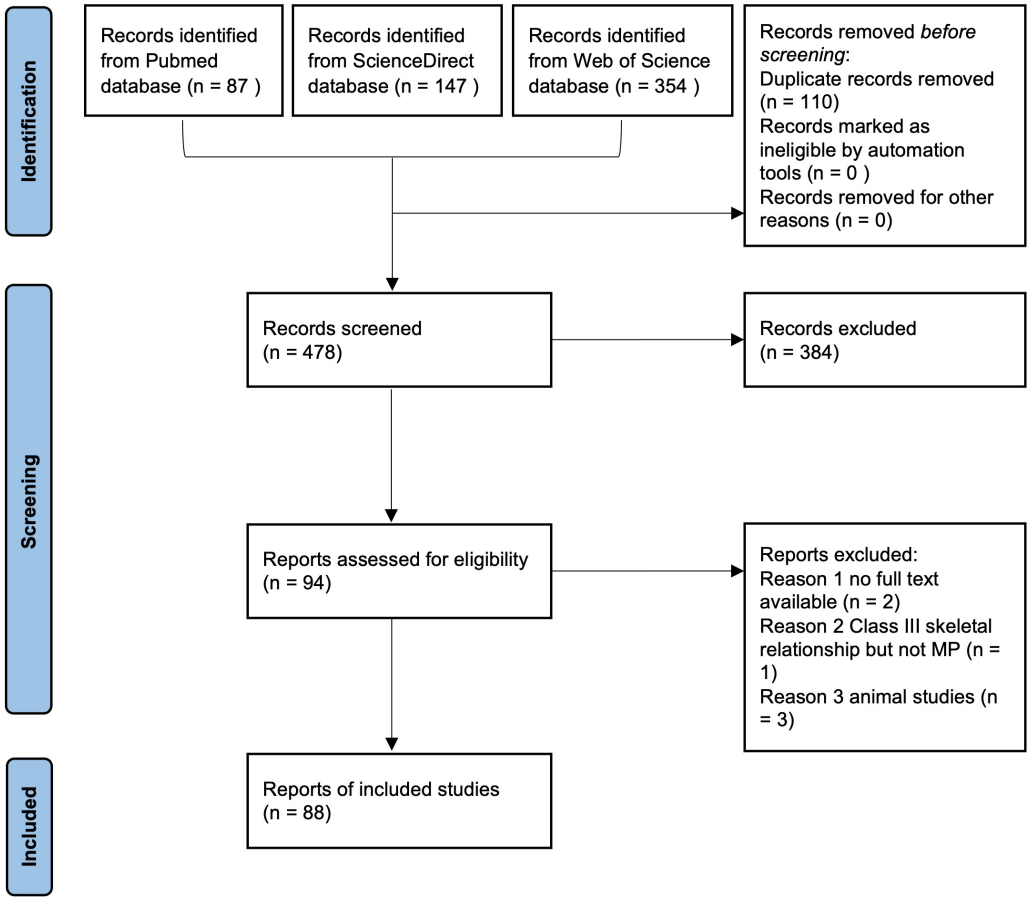

FIGURE 1. Flow diagram of the selection process of genetic etiology in MP. MP: Mandibular prognathism.

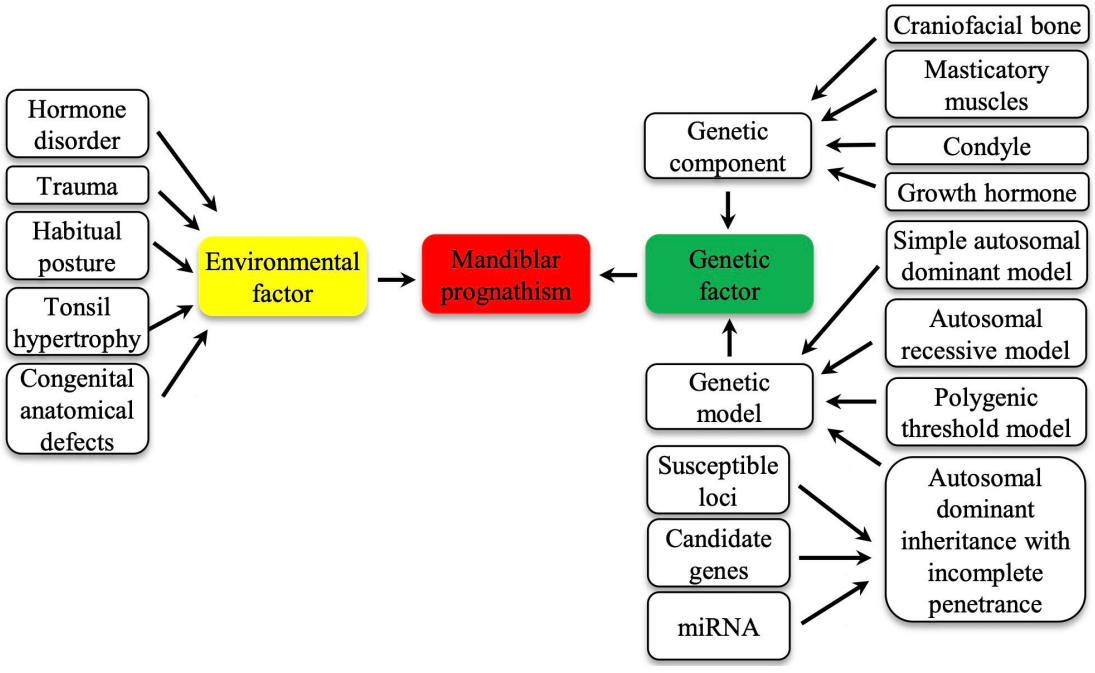

FIGURE 2. Factors involved in MP. Environmental factors, such as hormonal disorders, trauma, habitual postures, tonsil hypertrophy and congenital anatomical defects, can contribute to the development of MP. Similarly, genetic factors related to craniofacial bone, masticatory muscle, condyle, and growth hormone can also play a role. The interplay between these environmental and genetic factors influences the formation of MP. The black and white boxes represent different factors. The yellow box represents environmental factors, the green box represents various genetic factors, and the red box represents MP. The direction of the arrows indicates which contents of the boxes can be affected.

TABLE 2. MP related pathogenic genes or candidate genes.

Gene	OMIM	Phenotype
ADAMTS1	605174	2 single-nucleotide polymorphisms (rs2738, rs229038) of *a disintegrin and metalloproteinase with thrombospondin motifs 1* (*ADAMTS1*) were significantly associated with MP [19].
ADAMTSL1	609198	This is the first report that mutations in *a disintegrin and metalloproteinase with thrombospondin motifs like 1* (*ADAMTSL1*) are responsible for the pathogenesis of mandibular prognathism [20].
ADAMTS2	604539	Collectively, these data showed that *a disintegrin and metalloproteinase with thrombospondin motifs 2* (*ADAMTS2*) (c.3506G>T: p.G1169V) may confer susceptibility to risk of skeletal Class III malocclusion with maxillary deficiency [21].
ARHGAP21	609870	The Gly1121Ser variant in the *Rho GTPase activating protein 21* (*ARHGAP21*) gene was found to be shared by all MP individuals in the larger branch of the family with nearly complete penetrance. *ARHGAP21* protein strengthens cell-cell adhesions and may be regulated by bone morphogenetic factors, thus influencing mandibular growth [22].
BEST3	607337	Whole-exome sequencing implicates a rare non-synonymous single nucleotide variant (SNV) of *Bestrophin 3* (*BEST3*) as a candidate for mandibular prognathism in the Japanese pedigree [14].
C1orf167	619700	In study with the use of NGS on the largest reported number of families with MP, *chromosome 1 open reading frame 167* (*C1orf167*) was associated with familial MP in the eastern Mediterranean population [23].
CALN1	607176	*Calneuron 1* (*CALN1*) was suggested as candidate genes [15].
COL1A1	120150	Based on this study, we suggest that rs2249492 of *collagen type I alpha 1 chain* (*COL1A1*) plays an important role in Class III [24].
COL2A1	120140	Stickler syndrome; Kniest dysplasia
		An association between polymorphism in the *collagen type II alpha 1 chain* (*COL2A1*) gene and MP was observed. The results suggested that the *COL2A1* gene could be a new susceptibility gene for use in the study of genetic risk factors for MP [25].
DOCK1	601403	The present study identified a nonsynonymous variant of the *dedicator of cytokinesis 1* (*DOCK1*) gene as a candidate for temporomandibular disorders (TMD) and skeletal Class III malocclusion in affected individuals in the Iranian pedigree [26].
DUSP6	602748	Hypogonadotropic hypogonadism 19 with or without anosmia Transcriptional activation of *dual specificity phosphatase 6* (*DUSP6*) has been presumed to be regulated by *fibroblast growth factor* (*FGF*)/*fibroblast growth factor receptor* (*FGFR*) and mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases (ERK) signaling during fundamental processes at early stages of skeletal development. In this study, we identified *DUSP6*-rs2279574 as potential risk factors for MP using several web-based tools [16].
EP300	602700	With respect to rare variant analysis, variants within the *E1A binding protein p300* (*EP300*) gene showed an association with MP [27].
EPB41	130500	Elliptocytosis-1. An association between genetic polymorphisms in the *erythrocyte membrane protein band 4.1* (*EPB41*) gene and MP has been observed. Although the polymorphisms which may contribute to MP have not been determined, the results of our study suggest that the *EPB41* gene could confer susceptibility to MP [28].
ERLEC1	611229	Our results also showed that the proper level of *endoplasmic reticulum lectin 1* (*ERLEC1*) expression is crucial for proper osteogenic differentiation. The *ERLEC1* variant identified in this study is likely a causal mutation of Class III malocclusion [29].
EVC	604831	We further identified candidate genes of biologic interest for the locus using biologic approaches. This search revealed that human genes *EvC ciliary complex subunit 1* (*EVC*), *EvC ciliary complex subunit 2* (*EVC2*) are within this region [30].

TABLE 2. Continued.

Gene	OMIM	Phenotype
EVC2	607261	We further identified candidate genes of biologic interest for the locus using biologic approaches. This search revealed that human genes *EVC*, *EVC2* are within this region [30].
FBN3	608529	In this study, we identified *PLXNA2*-rs4844658, *DUSP6*-rs2279574 and *fibrillin 3* (*FBN3*)-rs33967815 as potential risk factors for MP using several web-based tools [16].
FGF12	601513	With respect to rare variant analysis, variants within the *fibroblast growth factor 12* (*FGF12*) gene showed significant association with MP ($p = 0.013$) [17].
FGF20	605558	With respect to rare variant analysis, variants within the *fibroblast growth factor 20* (*FGF20*) gene showed significant association with MP ($p = 0.022$) [17].
FGF23	605380	The p.A12D mutation may disrupt signal peptide function and inhibit secretory in *fibroblast growth factor 23* (*FGF23*). c.35C>A mutation in *FGF23* strongly associated with MP [31].
FGF3	164950	Genotypes ($p = 0.038$) and allele ($p = 0.037$) distributions for the *fibroblast growth factor 3* (*FGF3*) rs1893047 were significantly different according to the skeletal malocclusion. Carrying at least one G allele increased in more than two times the chance of presenting skeletal Class III malocclusion (OR = 2.21, 95% CI = 1.14–4.32; $p = 0.017$) [32].
FGFR1	136350	With respect to rare variant analysis, variants within the *fibroblast growth factor receptor 1* (*FGFR1*) gene showed significant association with MP ($p = 0.022$) [17].
FGFR2	176943	Crouzon syndrome: Both the patient and his mother have the appearance of craniofacial dysostosis, MP, ocular proptosis, short superior lip, scoliosis and thoracic deformity [33].
		Based on this study, we suggest that rs2249492 of *COL1A1* and rs2981582 of *fibroblast growth factor receptor 2* (*FGFR2*) play important roles in Class III [24].
FGFR3	134934	Crouzon syndrome with acanthosis nigricans (CAN): craniosynostosis syndrome, characterized by cloverleaf skull, hypertelorism, exophthalmos, external strabismus, parrot-beaked nose, short upper lip, hypoplastic maxilla and MP. The *fibroblast growth factor receptor 3* (*FGFR3*) Ala391Glu substitution was identified through molecular tests, confirming the diagnosis of CAN [34].
FOXO3A	602681	The results show significant differences of *forkhead box O3* (*FOXO3A*) between the 2 groups. In patients in Class III a downregulation for the genes of interest dominated [35].
GHR	600946	The present study supports *growth hormone receptor* (*GHR*) as a candidate gene associated with a Class III skeletal pattern in the Turkish population [36].
GLI2	165230	rs3738880 and rs2278741 in *GLI family zinc finger 2* (*GLI2*) seems to contribute to the genetic background for skeletal Class III [37].
HDAC4	605314	Independent sets of assays on a patient population show that expressions of both *histone deacetylase 4* (*HDAC4*) and *lysine acetyltransferase 6B* (*KAT6B*) are significantly greater in those with skeletal Class III malocclusion than in Class II malocclusion of the sagittal dimension [38].
HOXC	/	Candidate genes within the 12q23 region (ZLR = 2.93) include *insulin-like growth factor 1* (*IGF1*), *homeobox C* (*HOXC*) and *COL2A1* [25].
HSPG2	142461	The region 1p36 harbors positional candidate genes of interest, which include *heparan sulfate proteoglycan 2* (*HSPG2*), *matrilin 1*, *cartilage matrix protein* (*MATN1*) and *alkaline phosphatase* (*ALPL*). Recently, it has been reported that *HSPG2* is related to the formation of cartilage and to craniofacial abnormalities [39].
IGF1	147440	Candidate genes within the 12q23 region (ZLR = 2.93) include *IGF1*, *HOXC* and *COL2A1*. Chromosome 1 results (ZLR = 2.92) were similar to those reported previously in an Asian cohort with MP [25].
JAG1	601920	rs1051415 in an exonic region of *jagged canonical Notch ligand 1* (*JAG1*) was associated with MP [27].

TABLE 2. Continued.

Gene	OMIM	Phenotype
KAT6B	605580	In the total population, expressions of *HDAC4* ($p = 0.03$) and *KAT6B* ($p = 0.004$) were significantly greater in subjects with sagittal Class III than in Class II malocclusion [38].
LTBP2	602091	The authors detected a suggestive linkage for MP in a Han Chinese pedigree, the candidate functional genes are *transforming growth factor beta 3* (*TGFB3*) and *latent transforming growth factor beta binding protein 2* (*LTBP2*) [40].
MATN1	115437	The research found that single nucleotide polymorphism (SNP) in *matrilin 1* (*MATN1*) (rs1065755) positively correlated with MP [41].
MMP13	600108	Our search revealed a potential candidate on chromosome 11, *matrix metallopeptidase 13* (*MMP13*) or collagenase 3, but, based on the literature, we did not consider this a high-priority candidate gene [25].
MYH1	160730	The results show significant differences of *myosin heavy chain 8* (*MYH8*), *myosin heavy chain 1* (*MYH1*) and *FOXO3A* between the 2 groups. In patients in Class III a downregulation for the genes of interest dominated [35].
MYH8	160741	The results show significant differences of *MYH8*, *MYH1* and *FOXO3A* between the 2 groups. In patients in Class III a downregulation for the genes of interest dominated [35].
MYO1H	614636	The association between *myosin heavy chain 1* (*MYO1H*) and MP was found in Serbian patients with Class III malocclusion [42].
NBPF8	613998	In study with the use of NGS on the largest reported number of families with MP, *neuroblastoma breakpoint family, member 8* (*NBPF8*) was associated with familial MP in the eastern Mediterranean population [23].
NBPF9	613999	In study with the use of NGS on the largest reported number of families with MP, *neuroblastoma breakpoint family, member 9* (*NBPF9*) was associated with familial MP in the eastern Mediterranean population [23].
NCOR2	600848	With respect to rare variant analysis, variants within the EP300, *nuclear receptor corepressor 2* (*NCOR2*) and *presenilin 2* (*PSEN2*) gene showed an association with MP [27].
NOTCH3	600276	Six SNPs, including rs415929, rs520688 and rs423023 in an exonic region of *notch receptor 4* (*NOTCH4*); rs1044006 in an exonic region of *notch receptor 3* (*NOTCH3*); rs1051415 in an exonic region of *JAG1*; and rs75236173 in the 3′-untranslated region (3′-UTR) of *NUMB endocytic adaptor protein* (*NUMB*) were associated with MP [27].
NOTCH4	164951	Six SNPs, including rs415929, rs520688 and rs423023 in an exonic region of *NOTCH4*; rs1044006 in an exonic region of *NOTCH3*; rs1051415 in an exonic region of *JAG1*; and rs75236173 in the 3′-untranslated region (3′-UTR) of *NUMB* were associated with MP [27].
NUMB	603728	Six SNPs, including rs415929, rs520688 and rs423023 in an exonic region of *NOTCH4*; rs1044006 in an exonic region of *NOTCH3*; rs1051415 in an exonic region of *JAG1*; and rs75236173 in the 3′-untranslated region (3′-UTR) of *NUMB* were associated with MP [27].
PLXNA2	601054	In this study, we identified *plexin A2* (*PLXNA2*)-rs4844658, *DUSP6*-rs2279574 and *FBN3*-rs33967815 as potential risk factors for MP using several web-based tools [16].
PSEN2	600759	With respect to rare variant analysis, variants within the *EP300*, *NCOR2* and *PSEN2* gene showed an association with MP [27].
RASA2	601589	*RAS p21 protein activator 2* (*RASA2*) was suggested as candidate genes [15].
RORA	600825	*RAR related orphan receptor A* (*RORA*) was suggested as candidate genes [15].
SMAD6	602931	Significant associations at $p = 0.02$ were observed for SNPs rs3934908 (*SMAD family member 6* (*SMAD6*)) with prognathism (recessive model) [43].
SSX2IP	608690	*synovial sarcoma X breakpoint 2 interacting protein* (*SSX2IP*) was suggested as candidate genes [15].

TABLE 2. Continued.

Gene	OMIM	Phenotype
TBX5	601620	Skeletal Class III risk declined with SNPs in *T-box transcription factor 5* (*TBX5*) (OR = 0.5, p = 0.014) [44].
TCF21	603306	*transcription factor 21* (*TCF21*) was suggested as candidate genes [15].
TGFB3	190230	Within this interval, the candidate functional genes are *TGFB3* and *LTBP2*. In conclusion, the authors detected a suggestive linkage for mandibular prognathism in a Han Chinese pedigree [40].
WNT3A	606359	Significant associations at p = 0.02 were observed for SNPs rs708111 (*Wnt family member 3A* (*WNT3A*)) with skeletal class III (dominant model) [43].
Chromosome Xp22	302350	Nance-Horan syndrome (NHS) or X-linked cataract dental syndrome: it is characterized by ophthalmological, dental and facial anomalies. Individuals display facial dysmorphism, MP, congenital cataract and strabismus [45].
Deletion in 15q11-q13 chromosome	105830	Angelman syndrome (AS) is a neurodevelopmental disorder presented by jerky movement, speech delay and cognitive disability epilepsy as well as dysmorphic features. It occurs due to an expression deletion in 15q11-q13 chromosome. The case had abnormal behavior ataxia unusual laughing facial expression intellectual disability and MP [46].
PHOX2B	209880	Congenital central hypoventilation syndrome (CCHS): The *paired-like homeobox 2b* (*PHOX2B*) gene silent mutations can lead to structural and functional modification of their product providing to a group of children with Class III malocclusion similar features to those of CCHS (sleep apnea episodes and craniofacial malformations) [47].
DLX3	190320	Tricho-dento-osseous (TDO) syndrome: TDO-affected subjects showed a Class III skeletal pattern. Genetic studies have identified a 4-bp deletion in the *distal-less homeobox 3* (*DLX3*) gene that is associated with TDO [48].
GLI3	175700	Typical Greig cephalopolysyndactyly syndrome (GCPS): a patient with GCPS presenting polysyndactyly, frontal bossing, high forehead, skeletal Class III deformity due to maxillary retrognathism and MP. *GLI-Kruppel family member 3* (*GLI3*) is the only gene known to be associated with GCPS [49].
PTPN11	601321	Noonan Syndrome (NS): a high prevalance of orodental problems including high-arched palate, severe dental caries and gingivitis in patients with mutation-positive NS. Prognathism (maxillary or mandibular), macroglossia and gingival hyperplasia were also detected. The mutation in *protein tyrosine phosphatase nonreceptor 11* (*PTPN11*) gene, c.181G>A, p.D61N, may be associated with hypodontia in patients with NS [50].
SOST	269500	Sclerosteosis, a rare autosomal recessive genetic disorder caused by a mutation of the *sclerostin* (*SOST*) gene, manifests in the facial skeleton by gigantism, facial distortion, MP, cranial nerve palsy, and, in extreme cases, compression of the medulla oblongata [51].
RUNX2	119600	Cleidocranial dysplasia (CCD) is a rare congenital disorder characterized by anomalies in the development of the clavicles, craniofacial bones and skull. The disorder has been linked to mutations in the *runt-related transcription factor 2* (*RUNX2*) gene located on chromosome 6p21. MP and a high-arched palate were noted during the preanesthetic airway assessment [52].
SRCAP	136140	Floating-Harbor syndrome (FHS): It is caused by heterozygous mutations in the *Snf2-related CREBBP activator protein* (*SRCAP*) gene. In this case of a 14-year-old male with FHS was diagnosed with overbite, canine Class I and angle Class III, on both sides [53].

TABLE 2. Continued.

Gene	OMIM	Phenotype
PITX2	180500	Axenfeld-Rieger syndrome (ARS): they all presented systemic features, including maxillary hypoplasia, underbite, hypodontia, conical teeth. We further confirmed the possibility of development of ARS induced by this *paired-like homeodomain transcription factor 2* (*PITX2*) gene deficiency [54].
ANKH	123000	Craniometaphyseal dysplasia (CMD) is a rare genetically transmitted bone dysplasia characterized by alterations in the development of the craniofacial bones with abnormal remodeling of the metaphyses. The examination reveals prognathism, a Class III malocclusion. The final diagnosis of autosomal dominant CMD was confirmed by the molecular testing of the CMD gene (*ANKH inorganic pyrophosphate transport regulator* (*ANKH*)) [55].
SLC22A18	130650	Beckwith-Wiedemann Syndrome: malocclusion and MP caused by macroglossia (*solute carrier family 22* (*organic cation transporter*), *member 18* (*SLC22A18*)) [56].
NSD1	117550	Sotos syndrome is a genetic disorder characterized by distinct craniofacial features, overgrowth in childhood and impaired intellectual development, and caused by a heterozygous mutation in the *nuclear receptor binding SET domain protein 1* (*NSD1*) gene. These cases showed a skeletal mandibular protrusion [57, 58].
GPR101	300943	Acromegaly, a rare and slowly progressive disorder, usually results from a growth hormone (GH)-secreting pituitary adenoma. Patients were found to have a larger nose, thicker lips and MP (*G protein-coupled receptor 101* (*GPR101*)) [59].
Deletion in the *Twist*	101400	Classic features of Saethre-Chotzen syndrome (SCS) described in the literature include a prominent nasal bridge, eyelid ptosis, telorbitism, maxillary hypoplasia and MP [60]. Moreover, in some patients mental disability is observed, which may be connected with the size of the deletion in the *Twist* gene.

MP related pathogenic genes or candidate genes. We've included 70 different genes or factors that are known to have an effect.

protein 21 (*ARHGAP21*) as a potential candidate gene for MP. The *ARHGAP21* protein plays a role in enhancing cell-cell adhesion and may influence mandibular growth through its regulation by bone morphogenetic factors. A rare heterozygous variant was detected in the *endoplasmic reticulum lectin 1* (*ERLEC1*) gene, which was found to cosegregate with malformations within family members. Additionally, three other rare missense heterozygous variants were identified in 90 unrelated sporadic individuals. This study also demonstrated that *ERLEC1* is highly expressed in mouse mandibular osteoblasts and inhibits osteoblast proliferation [29].

3.2 Genetic variation related to masticatory muscle development

Milosevic *et al*. [42] found an association between the rs3825393 polymorphism of the *myosin IH* (*MYO1H*) gene and an increased risk for the MP phenotype. Class I myosins are classified as "unconventional" single-headed myosin monomers and are implicated in regulating membrane dynamics, intracellular vesicle transport, and inner ear auditory function. The association between *MYO1H* and MP suggests its involvement in musculoskeletal development, potentially affecting malocclusion and sagittal jaw deformities [61].

3.3 Genetic variation associated with condyle

Kantaputra *et al*. [20] performed whole-exome sequencing analysis in a Thai family and identified *ADAM metallopeptidase with thrombospondin type 1 motifs like 1* (*ADAMTSL1*) as a potential defect. This finding is significant as it represents the first report suggesting that mutations in *ADAMTSL1* may contribute to the pathogenesis of MP by impairing aggrecan cleavage in the condylar cartilage. *matrilin 1* has previously been implicated in mandibular positioning within the craniofacial skeleton or directly in the mandibular condylar cartilage. *matrilin 1* was identified as a risk factor for MP [41].

3.4 Genetic variation associated with growth hormone

The growth hormone (GH) is a polypeptide hormone that plays a crucial role in the growth and development of the craniofacial complex. A study conducted by Tunasoylu *et al*. [36] among Turkish populations identified the association between *growth hormone receptor* (*GHR*) gene and the Class III skeletal pattern. Another investigation by Park *et al*. [62], involving Korean subjects, demonstrated that the *GHR* was linked to the sagittal and vertical development of the mandible. Additionally, *GHR* SNPs may affect mandibular morphology differently based on gender.

3.5 Associated syndrome

Individuals with rare syndromes may exhibit MP. Crouzon syndrome is characterized by a series of craniofacial anomalies including MP [34]. The *fibroblast growth factor receptor 3* (*FGFR3*) Ala391Glu substitution was identified through molecular tests, confirming the diagnosis of Crouzon syndrome with acanthosis nigricans. Nance-Horan syndrome (NHS) is a multifactorial, congenital genetic condition also known as X-linked cataract dental syndrome with characteristic facial dysmorphism, such as MP [45]. Axenfeld-Rieger syndrome (ARS) is a rare autosomal dominant disorder. In the research of ARS pedigree [54], patients all exhibited systemic features, including maxillary hypoplasia and underbite. Cheng *et al*. [54] confirmed the possibility of development of ARS induced by *paired-like homeodomain transcription factor 2* (*PITX2*) gene deficiency. It was found that the predominant malocclusion in Down syndrome was Class III malocclusions [11]. According to Bierley *et al*.'s [63] study involving lateral cephalometric measurements, although Class III malocclusion is usually found in cases with Down syndrome, it doesn't seem to be related to MP. The need for further exploration of the underlying mechanisms of these syndromes associated with MP should be emphasized.

4. Conclusions and prospects

Recent investigations into the genetic etiology of MP have primarily focused on family linkage analysis and genome-wide association studies (GWAS). However, it is important to note that linkage analysis alone may not fully reveal the specific molecular mechanisms involved in MP. With the limitation of this paper, 70 genes or factors were summarized to be related to MP. Further reports are expected to be based on these results with the use of the newest molecular methods.

Additionally, the effectiveness of current genetic animal studies is limited by the lack of specialized animal models tailored for this condition. Therefore, further comprehensive research is needed to clarify the genetic basis of hereditary MP and develop standardized animal models that accurately reflect its phenotypic and genetic traits. Such efforts could significantly advance our understanding of the genetic and molecular factors contributing to MP and facilitate more targeted investigations into its pathogenesis.

In order to prevent MP in future generations, gene therapy and preimplantation genetic diagnosis (PGD) may be potential options. Gene therapy involves the use of recombinant nucleic acids to modify, repair, replace, add or delete genetic sequences in humans. This innovative therapeutic approach must be carefully assessed for safety and ethical concerns. On the other hand, PGD enables the detection of abnormal genetic features, such as chromosomal rearrangements or specific mutations, in early human embryos [64]. PGD could be beneficial for couples at high risk of passing on genetic mutations, including those associated with MP. Further research on the application of PGD in managing MP is crucial.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

FF, QL and SFL—designed the research study; wrote the manuscript. FF and QL—collected the data. FF—analyzed the data. YJX—provided help and advice on primary draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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