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Original Article

Association between myosin 1H polymorphisms and skeletal–facial profile in Taiwanese patients with mandibular prognathism

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KEYWORDS
Mandibular prognathism;
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Abstract *Background/purpose:* Mandibular prognathism (MP; skeletal Class III malocclusion) results from complex genetic and environmental interactions. However, genetic variants related to craniofacial morphology in Taiwanese individuals remain underexplored. This study examined the association between single nucleotide polymorphisms (SNPs) in the myosin 1H

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MYO1H gene;
Genetic polymorphisms;
Single nucleotide polymorphisms

(MYO1H) gene and cephalometric parameters of MP in a Taiwanese population.
Materials and methods: Blood samples and lateral cephalograms were collected from 185 Taiwanese participants. Based on the ANB angle, subjects were classified into an Class III group (ANB $<0°$) and a NON-Class III group (ANB $\geq 0°$). MYO1H SNPs (rs3825393, rs7319591, rs10850110) were genotyped using quantitative real-time polymerase chain reaction. Associations between genotype distributions and skeletal classification were analyzed using Pearson's chi-square test.
Results: The MYO1H rs10850110(G > A) polymorphism was significantly associated with MP. Individuals with the GA genotype showed a lower risk of MP than those with the GG genotype (odds ratio [OR] 0.43, $P = 0.01$). Under dominant and recessive models, the GA + AA group had approximately a 50 % lower risk than the GG group (OR = 0.50, $P = 0.04$). Cephalometric data indicated that GG carriers exhibited significantly larger SNB angles and more negative ANB and Wits appraisal values compared with GA carriers.
Conclusion: The MYO1H rs10850110(G > A) polymorphism is significantly associated with MP in Taiwanese individuals, with the GA genotype showing a protective effect. These findings support the role of MYO1H in mandibular growth regulation and suggest potential population-specific genetic variation.

Introduction

Craniofacial skeletal development is a complex process affected by both intrinsic growth potential and surrounding tissues and external factors. Skeletal development processes follow a specific pattern and growth trajectory. Furthermore, certain parts of craniofacial bones are affected by brain growth, and their growth patterns reflect these functional influences. Craniofacial tissues include the nasal cavity, oral cavity, nasopharyngeal airway, facial muscles, and masticatory muscles. Overall, craniofacial bones typically grow downward and forward, accompanied by lateral expansion.[1,2] Among all craniofacial structures, the mandible is the last to complete growth but demonstrates the greatest postnatal growth potential. Mandibular development is influenced by the cranial base and midfacial bones; however, unlike the maxilla, it lacks sutural connections to adjacent bones, making it the only movable bone of the craniofacial skeleton.[1,2]

Although mandibular growth is largely determined by genetic inheritance, it can be modified by environmental factors, such as mouth breathing, abnormal tongue posture, and improper lip positioning. Imbalances between maxillary and mandibular growth contribute to a range of malocclusions.[3] Clinically, Class III malocclusion is characterized by forward positioning of the lower molars relative to the upper molars. This condition may result from abnormal occlusion or functional interferences that shift the mandible anteriorly. Patients with MP often present with Class III malocclusion in which the mandible is positioned forward relative to the maxilla, producing a pronounced anterior crossbite and mandibular protrusion. The myosin IH (MYO1H) gene, located on chromosome 12q24.11, contributes to cell motility, phagocytosis, and vesicle transport. Scholars[4–9] have hypothesized that MYO1H promotes actin filament binding and microfilament motor activity, thereby contributing to actin filament organization. Recent studies[4–9] have reported that MYO1H affects craniofacial muscle strength and, consequently, jawbone morphology. Thus, MYO1H may play a role in the development of skeletal malocclusion and in shaping specific craniofacial characteristics.

Several studies[10–12] have examined MYO1H polymorphisms in relation to skeletal Class III malocclusion across different populations, but the findings remain inconsistent. Some reported that the G allele of rs10850110 increases the risk of mandibular prognathism, whereas others observed no association or even a protective role of the A allele. These discrepancies may reflect ethnic differences and motivated us to investigate this SNP in a Taiwanese population. MYO1H encodes a class I myosin involved in actin-based motility and craniofacial muscle activity, which may influence mandibular growth. The rs10850110 (G > A) variant, located in a regulatory region of MYO1H, may affect transcriptional control or splicing efficiency.

To date, MYO1H variants in Taiwanese patients with skeletal Class III malocclusion have not been investigated in any genomic study. We therefore identified MYO1H variants associated with MP and established a database of related single nucleotide polymorphisms (SNPs) in the Taiwanese population.

Materials and methods

Sample and data collection

Patients were recruited from the Departments of Oral and Maxillofacial Surgery and Orthodontics at Kaohsiung Medical University Hospital. Lateral cephalometric radiographs were obtained with a Pax-400C imaging system (Vatech A/

S, Hwaseong-si, Gyeonggi-do, South Korea). During imaging, patients were positioned with their head in a natural posture and maximum intercuspation. Anatomical landmarks definitions are as followings (Fig. 1): S (Sella): The center of the sella turcica; N (Nasion): The junction of the nasal and frontal bones; Ba (Basion):Most inferior point on the anterior margin of the foramen magnum; Point A: The most concave point of the anterior maxilla; Point B: The most concave point of the mandibular symphysis; AO: Perpendicular line drawn from Point A onto the occlusal plane; BO: Perpendicular line drawn from Point B onto the occlusal plane; ANS (Anterior nasal spine): Tip of median sharp bony process of the palatine bone; PNS (Posterior nasal spine): Tip of posterior spine of the palatine bone; Ar (Articulare): Intersection of inferior contour of the posterior cranial base and posterior contour of the ramus; Co (Condylion): Most posterior and superior point on the condylar head; Gn (Gnathion): Most antero-inferior point on the mandibular symphysis; Me (Menton): Lowest point on the bony outline of the mandibular symphysis; Go (Gonion): Most lateral-external point at the junction of the horizontal and ascending ramus of the mandible.

The ANB angle was determined on the basis of three anatomical landmarks: the nasion (junction of the nasal and frontal bones), point A, and point B. The skeletal Class III group (MP group) included Taiwanese patients with an ANB angle of $<0^{\circ}$, no systemic disease, no developmental abnormalities of the craniofacial skeleton, and no history of facial or dental trauma. The Non-Class III group (control group) consisted of patients without MP who had an ANB angle of $\geq 0^{\circ}$. Accordingly, 185 Taiwanese patients were enrolled in this study. For cephalometric analysis, the following distance were measured Ar-Go, Go-Me, Co-A, Co-Gn, ANS-PNS, S–N, S–Ba, S–Ar, ANS-Me, Wits appraisal value (AO-BO, the distance between points A and B along the occlusal plane), posterior facial height (PFH, S-Go) anterior facial height (AFH, N–Me) and PFH/AFH ratio. This study was approved by the Institutional Review Board of Kaohsiung Medical University Chung-Ho Memorial Hospital (IRB No. KMUHIRB-G(I)-20220009).

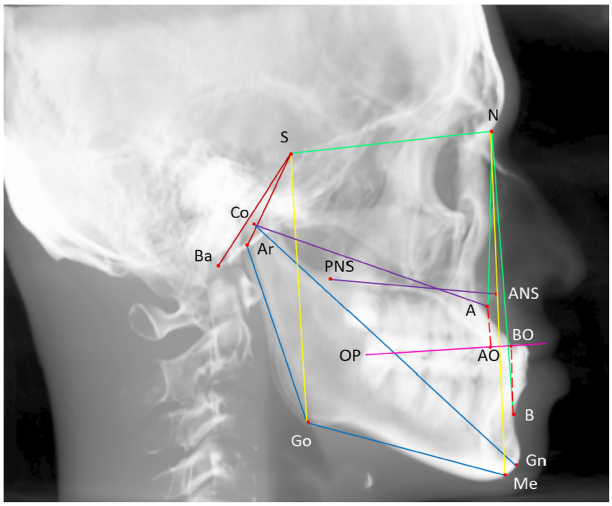

Figure 1 Cephalometric landmarks: Sella (S), Nasion (N), Basion (Ba), Anterior nasal spine (ANS), Posterior nasal spine (PNS), Point A, Point B, Gnathion (Gn), Menton (Me), Gonion (Go), Ar(Articulare) and Condylion (Co). AO and BO represent the perpendicular projections of Points A and B onto the occlusal plane, respectively. The following cephalometric values were measured: (1) angles (degree): SNA, SNB, and ANB (2) distances (mm): Ar-Go, Go-Me, Co-A, Co-Gn, ANS-PNS, S–N, S–Ba, S–Ar, ANS-Me, Wits appraisal value, S-Go (posterior facial height, PFH), and N–Me (anterior facial height, AFH).

Genomic DNA collection and isolation

Peripheral venous blood samples (10 mL) were obtained from each participant at the blood collection counter of the Department of Laboratory Medicine with a purple-cap ethylenediaminetetraacetic acid (EDTA) anticoagulant tube (BD Vacutainer K2E [EDTA])10 mL (Becton, Dickinson and Company, Broken Bow, NE, USA). Samples were centrifuged to separate the plasma, buffy coat, and red blood cells. Plasma was aliquoted into cryogenic tubes and stored at −80 °C. Genomic DNA was extracted from whole blood with a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) and dissolved in Tris–EDTA buffer (10 mM Tris, 1 mM EDTA, pH 7.8). OD260 absorbance was measured to assess DNA concentration and quality. The DNA samples were stored at −80 °C until use. Genetic polymorphism analysis was performed using an ABI StepOne Real-Time PCR System and TaqMan Assay chemistry system.

Gene selection and genotype assay of targeted SNPs

Three SNPs in the MYO1H gene (rs3825393, rs73195991, rs10850110) were selected as potential markers associated with MP. These SNPs were chosen on the basis of genotype and minor allele frequencies ($P > 0.1$) reported for the Han Chinese population within the International Genome Sample Resource database (1000 Genomes Project). For SNP genotyping, customized quantitative real-time PCR (qPCR) assays with dual fluorescent-labeled probe were performed at Topgen Biotechnology (Topgen Biotech, Kaohsiung, Taiwan). Each qPCR reaction used 20 ng genomic DNA and was performed with 2 × AceGT Genotyping Master Mix (Topgen Biotech). A ViiA 7 Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) was employed for amplification under the following cycling conditions: initial denaturation at 95 °C for 5 min, followed by 40 cycles at 95 °C for 3 s and 60 °C for 40 s. Data were collected before the PCR read at 60 °C for 30 s and after the PCR read at 60 °C. Genotypes were determined using allelic discrimination analysis conducted in ViiA 7 Software v1.3. (Thermo Fisher Scientific, Waltham, MA, USA).

Statistical analysis

All statistical analyses were performed in SPSS version 23 (IBM Corp., Armonk, NY, USA). The association between genotype frequency and skeletal pattern in 185 participants was investigated. The participants were divided into two groups on the basis of ANB angle. A Hardy–Weinberg equilibrium (HWE) was assessed for each SNP, and normal data distribution was confirmed using a Shapiro–Wilk test. Parametric analytical methods were employed.

Demographic, cephalometric, and genetic variables were analyzed. Comparisons of categorical data were made using Pearson's chi-square test and Fisher's exact test. Odds ratios (ORs) for associations of genes with MP were calculated. One-way ANOVA and independent-sample t tests was used to compare cephalometric parameters across genotypes. A P value < 0.05 was considered statistical significant.

Results

Demographic and cephalometric characteristics of study sample

The study included 185 participants (81 men, 104 women; Table 1). The Non-Class III (control group) without MP included 94 individuals (40 men, 54 women; mean age 30.66 $\pm$ 10.45 years). The Class III group (MP group) included 91 individuals (41 men, 50 women; mean age 27.53 $\pm$ 5.66 years). The SNA angle did not differ significantly between groups (Class III group: 81.42° $\pm$ 3.84°; Non-Class III group: 81.18° $\pm$ 3.85°). The SNB and ANB angles differed significantly between groups ($P < 0.001$; Class III group: SNB85.01° $\pm$ 4.70° and ANB −3.74° $\pm$ 3.50° (ANB); Non-Class III group: SNB 77.25° $\pm$ 3.98° and ANB 3.96° $\pm$ 2.41°).

Correlation between genotype and MP

Fig. 2 represents the output file of allele discrimination software plot and multicomponent plot of MYO1H rs3825393, rs7315991, and rs10850110. The three selected SNPs (Table 2, Tables 3, and Table 4) on the MYO1H gene (rs3925393, rs7315991, and rs10850110) were all in Hardy–Weinberg equilibrium ($P > 0.05$), which indicates that allele and genotype frequencies remain constant across generations in the absence of evolutionary influences. As indicated in Table 2, genetic analysis of the MYO1H rs3825393 (C > T) polymorphism in the Class III group revealed the CC, CT, and TT genotypes in 19 (20.9 %), 48 (52.7 %), and 24 (26.4 %) individuals, respectively. The C and T alleles were observed in 86 (47.3 %) and 96 (52.7 %) individuals, respectively. Among the non-Class III group, 22

Table 1 Descriptive and cephalometric characteristics of Class III group and Non-Class III group.

Variables	Class III group (n = 91)	Non-Class III group (n = 94)	*P*-value
Male/Female	41/50	40/54	0.64
Age, year	27.53 $\pm$ 5.66	30.66 $\pm$ 10.45	0.72
SNA (degree)	81.42 $\pm$ 3.83	81.18 $\pm$ 3.85	0.68
SNB (degree)	85.01 $\pm$ 4.69	77.25 $\pm$ 3.98	<0.001*
ANB (degree)	−3.74 $\pm$ 3.50	3.96 $\pm$ 2.40	<0.001*

*: Significant: $P < 0.05$.

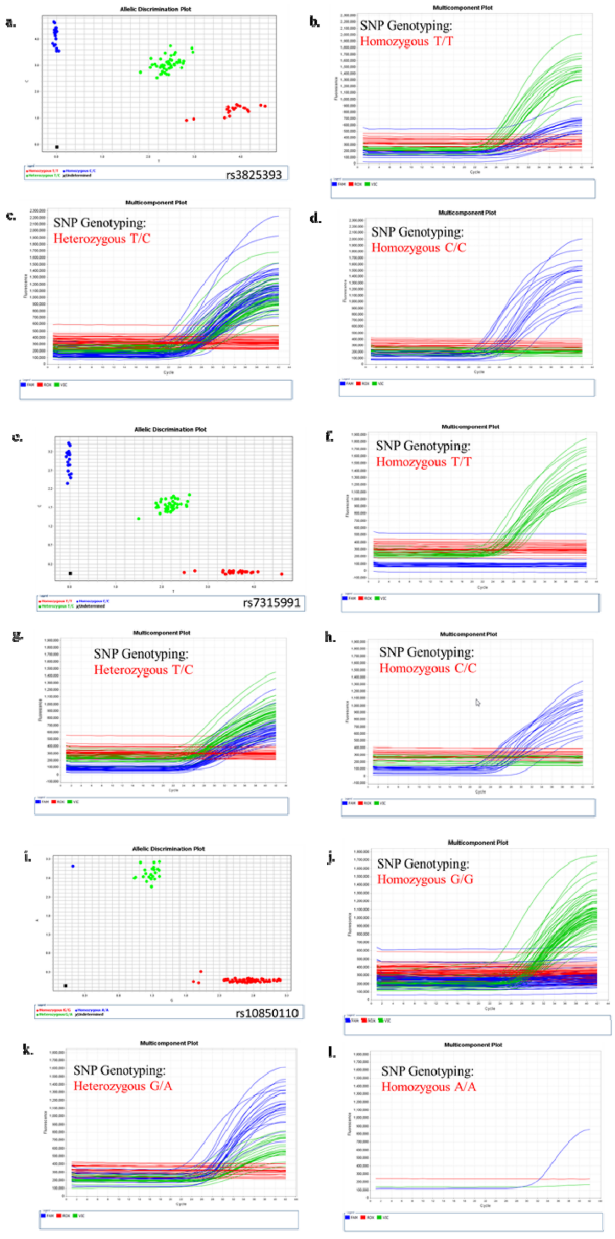

Figure 2 The output file of allele discrimination software plot and multicomponent plot of MYO1H rs3825393(a–d), rs7315991(e–h) rs10850110(i–l), and. (a) Allelic discrimination plot, (b) The TT genotyping subjects (carrying the T allele only) (homozygote), (c) The TC genotyping subjects (carrying the T and C allele) (heterozygote), (d) The CC genotyping subjects (carrying the C allele only) (homozygote), (e) Allelic discrimination plot, (f) The TT genotyping subjects (carrying the T allele only) (homozygote), (g) The TC genotyping subjects (carrying the T and C allele) (heterozygote), (h) The CC genotyping subjects (carrying the C allele only) (homozygote), (i) Allelic discrimination plot, (j) The GG genotyping subjects (carrying the G allele only) (homozygote), (k) The GA genotyping subjects (carrying the G and A allele) (heterozygote), (l) The AA genotyping subjects (carrying the A allele only) (homozygote).

Table 2 Genotype and allele Frequencies of myosin IH (MYO1H) gene (rs3825393) in Class III and Non-Class III group.

MYO1H	Class III group	Non-Class III group	OR	*P*-value
rs3825393 (C > T)	(n = 91)	(n = 94)	(95 % CI)	
Genotype frequency				
CC	19 (20.9)	22 (23.4)	1	
CT	48 (52.7)	53 (56.4)	1.05 (0.51–2.17)	0.89
TT	24 (26.4)	19 (20.2)	1.46 (0.62–3.46)	0.38
CC vs. CT + TT	19 (20.9)/72 (79.1)	22 (23.4)/72 (76.6)	1.16 (0.58–2.32)	0.67
CC + CT vs. TT	67 (73.6)/24 (26.4)	75 (79.8)/19 (20.2)	1.41(0.71–2.81)	0.32
CC + TT vs. CT	43 (47.3)/48 (52.7)	41 (43.6)/53 (56.4)	0.86 (0.48–1.54)	0.61
Allele frequency				
C	86 (47.3)	97 (51.6)	1	
T	96 (52.7)	91 (48.4)	1.19 (0.79–1.79)	0.40
HWE (X^2/*P* value)	0.31/0.57	1.55/0.21		

Hardy–Weinberg equilibrium (chi-square/*P* value): HWE (X^2/*P* value).
Data are presented as n (%). Pearson chi-square or Fisher exact test.
*: Significant: $P < 0.05$.

Table 3 Genotype and allele Frequencies of myosin IH (MYO1H) gene (rs7315991) in Class III and Non-Class III group.

MYO1H	Class III group	Non-Class III group	OR	*P*-value
rs7315991 (T > C)	(n = 91)	(n = 94)	(95 % CI)	
Genotype frequency				
TT	28 (30.8)	21 (22.3)	1	
TC	42 (46.2)	51 (54.3)	0.62 (0.31–1.24)	0.17
CC	21 (23.0)	22 (23.4)	0.72 (0.31–1.63)	0.42
TT vs. TC + CC	28 (30.8)/63 (79.2)	21 (22.3)/73 (77.7)	0.65 (0.34–1.25)	0.19
TT + TC vs. CC	70 (77.0)/21 (23.0)	72 (76.6)/22 (23.4)	0.98 (0.5–1.94)	0.94
TT + CC vs. TC	49 (53.8)/42 (46.2)	43 (45.7)/51 (54.3)	0.72 (0.41–1.29)	0.27
Allele frequency				
T	98 (53.8)	93 (49.4)	1	
C	84 (46.2)	95 (53.6)	0.84 (0.56–1.26)	0.39
HWE (X^2/*P* value)	0.46/0.49	1.58/0.4		

Hardy–Weinberg equilibrium (chi-square/*P* value): HWE (X^2/*P* value).
Data are presented as n (%). Pearson chi-square or Fisher exact test.
*: Significant: $P < 0.05$.

(23.4 %), 53 (56.4 %), and 19 (20.2 %) individuals carried the CC, CT, and TT genotypes, respectively. The C and T alleles were observed in 97 (51.6 %) and 91 (48.4 %) individuals, respectively. The CC genotype group was used as the reference group for the OR analysis between individuals with and without MP with different genotypes. Participants with the CT genotype were 1.05 times more likely to develop MP than those with the CC genotype. Participants with the TT genotype were even more likely to develop MP than those with the CC genotype. However, both trends were nonsignificant ($P = 0.89$ and 0.38, respectively). For rs3825393 (Table 5), PFH/AFH ratio was 0.64 ± 0.06 (CC), 0.66 ± 0.05 (CT), and 0.68 ± 0.06 (TT), showing a significant difference ($P = 0.01$). Post hoc analyses indicated significant differences in PFH/AFH ratio between CC and TT genotypes.

Regarding the MYO1H rs7315991 (T > C) polymorphism (Table 3), in the Class III group, 28 (30.8 %), 42 (46.2 %), and 21 (23.0 %) individuals had the TT, TC, and CC SNPs, respectively. The T and C alleles were observed in 98 (53.8 %) and 96 (46.2 %) individuals, respectively. In the Non-Class III group, the corresponding genotype distribution was TT, TC, and CC in 21 (22.3 %), 52 (54.3 %), and 22 (23.4 %) individuals, respectively. The C and T alleles were observed in 93 (49.4 %) and 95 (53.6 %) individuals, respectively. With the TT genotype as the reference group, the TC genotype demonstrated a nonsignificant protective effect against MP (OR: 0.62, $P = 0.17$, 95 % CI = 0.31–1.24). For rs7315991 (Table 5), PFH/AFH ratio was 0.66 ± 0.05 (TT), 0.64 ± 0.05 (TC), and 0.67 ± 0.06 (CC), showing a significant difference. The PFH/AFH ratio of TT and CC genotypes were significant greater than TC genotype.

Regarding the MYO1H rs10850110 (G > A) polymorphism (Table 4), 136 (73.5 %), 45 (24.3 %), and 4 (2.2 %) participants had the GG, GA, and AA SNPs, respectively. When

Table 4 Genotype and allele Frequencies of myosin IH (MYO1H) gene (rs10850110) in Class III and Non-Class III group.

MYO1H	Class III Group	Non-Class III Group	OR	*P*-value
rs10850110 (G > A)	(n = 91)	(n = 94)	(95 % CI)	
Genotype frequency				
GG	73 (80.2)	63 (67.0)	1	
GA	15 (16.5)	30 (31.9)	0.43 (0.21−0.87)	0.01*
AA	3 (3.3)	1 (1.1)	2.59 (0.26−25.52)	0.39
GG vs. GA + AA	73 (80.2)/18 (19.8)	63 (67.0)/31 (33.0)	0.5 (0.26−0.98)	0.04*
GG + GAvs.AA	88 (96.7)/3 (3.3)	93 (98.9)/1 (1.1)	3.17 (0.32−31.05)	0.29
GG + AAvs. GA	76 (83.5)/15 (16.5)	64 (68.1)/30 (31.9)	0.42 (0.21−0.85)	0.01*
Allele frequency				
G	161 (88.5)	156 (83.0)	1	
A	21 (11.5)	32 (17.0)	0.64 (0.36−1.17)	0.13
HWE (X^2/*P* value)	3.37/0.06	1.58/0.2		

Hardy−Weinberg equilibrium (chi-square/*P* value): HWE (X^2/*P* value).
Data are presented as n (%). Pearson chi-square or Fisher exact test.
*: Significant: $P < 0.05$.

Table 5 Association between SNP rs3825393 and rs10850110 genotypes and cephalometric parameters (only statistically significant differences presented).

		Mean	SD	*P* value	Significant
rs10850110(G > A)					
SNB (°)	GG (n = 136)	81.46	5.77	0.04*	GG > GA
	GA (n = 45)	79.46	5.65		
ANB (°)	GG (n = 136)	−0.31	4.85	0.02*	GA > GG
	GA (n = 45)	1.68	4.70		
Wits (mm)	GG (n = 136)	−6.28	6.82	0.03*	GA > GG
	GA (n = 45)	−3.97	6.02		
PFH/AFH (ratio)	GG (n = 136)	0.66	0.06	0.08	
	GA (n = 45)	0.65	0.05		
rs7315991(T > C)					
PFH/AFH (ratio)	TT (n = 49)	0.66	0.05	0.04*	TT > TC
	TC (n = 93)	0.64	0.05	0.02*	CC > TC
	CC (n = 43)	0.67	0.06		
rs3825393(C > T)					
PFH/AFH (ratio)	CC (n = 41)	0.64	0.06	0.01*	TT > CC
	CT (n = 101)	0.66	0.05		
	TT (n = 43)	0.68	0.06		

*: Statistically significant, $P < 0.05$.
Note: The rs10850110 (AA) genotype group (n = 4) was excluded from the statistical analysis due to insufficient sample size.

dominant and recessive models were analyzed, GG and GA + AA were identified in 136 (73.5 %) and 49 (26.5 %) individuals, respectively. Similarly, GG + GA was observed in 181 individuals (97.8 %), compared with AA in 4 individuals (2.2 %). The G and A alleles were observed in 317 (85.7 %) and 53 (14.3 %) individuals, respectively. In the Class III group, the GG, GA, and AA genotypes were observed in 73 (80.2 %), 15 (16.5 %), and 3 (3.3 %) individuals, respectively. In the Non-Class III group, the GG, GA, and AA genotypes were identified in 63 (67 %), 30 (31.9 %), and 1 (1.1 %) individuals, respectively. With the GG genotype as the reference group, the GA genotype demonstrated a protective effect against MP (OR: 0.43, $P = 0.01$, 95 % CI = 0.21−0.87). We obtained similar results in our analysis of dominant and recessive genetic models. Individuals in the GA + AA group were half as likely as those in the GG group to develop MP (OR: 0.50, $P = 0.04$, 95 % CI = 0.26−0.98). Likewise, individuals in the GG + GA group were less likely than those in the AA group to develop MP (OR: 0.42, $P = 0.01$, 95 % CI = 0.21−0.85), providing further evidence of a protective effect.

In Table 5, the rs10850110 (AA) genotype group (n = 4) was excluded from the statistical analysis due to insufficient sample size. Independent-sample t-tests revealed that the SNB angle of the GG genotype group (n =136; 81.46°) was significantly greater than that of the GA genotype group (n = 45; 79.46°). The ANB angle of the GA genotype group (1.68°) was significantly greater than that

of the GG genotype group (−0.31°). Moreover, the Wits appraisal of the GA genotype group (−3.97 mm) was significantly higher than that of the GG genotype group (−6.28 mm). The PFH/AFH ratio of GA and GG genotypes were not significantly different (P = 0.08).

Discussion

Malocclusion arises from a complex interplay of genetic and environmental factors, including local conditions and external influences. Disturbances in tooth eruption, such as delayed eruption or premature loss of primary teeth, are common causes of malocclusion. Occlusal discrepancies, such as excessive overjet (marked by pronounced protrusion of the maxillary incisors) and reverse overjet (caused by mandibular advancement), also play a role. Irregularities in tooth morphology, including supernumerary, congenitally missing, or undersized teeth, can further contribute to spacing and alignment problems. Parafunctional habits, such as thumb sucking, prolonged pacifier use, and tongue thrusting, are well-documented etiological factors that may induce both dental and skeletal malocclusions. Similarly, mouth breathing can influence jaw growth and facial development, often narrowing the arch form and compromising occlusion. Although these environmental factors are influential, genetic inheritance remains a critical determinant of malocclusion, particularly in individuals with skeletal discrepancies, which may predispose them to more severe malocclusions.[13]

Selçuk et al.[14] reported high MYO1H expression in the central nervous system, particularly in the forebrain, midbrain, and lower medulla. MYO1H is a protein-coding gene that is broadly expressed throughout the reticular formation of the lower medulla and within the motor neurons of the facial and vagal nerves, especially in regions essential for respiratory control. MYO1H variants have been associated with congenital central hypoventilation syndrome (CCHS),[15] a disorder characterized by impaired autonomic regulation of breathing that causes shallow respiration. Todd et al.[16] further demonstrated distinctive craniofacial morphology in individuals with CCHS, marked by a shorter and flatter facial profile with reduced forehead slope and a box-shaped appearance due to decreased vertical facial height relative to facial width. This phenotype is characterized by considerably reduced upper facial height, increased nasal tip projection, a decreased nasolabial angle, and shortened upper lip height, all of which contribute to the unique facial features observed in affected individuals.

Among the three MYO1H SNPs we analyzed, only rs10850110 (G > A) was significantly associated with MP. Patients with the GA genotype had less than half the risk of developing a MP profile than those with the GG genotype (OR: 0.43, $P = 0.01$, 95 % CI: 0.21–0.87). Similar findings were observed in specific inheritance models, including the dominant model (GG vs. GA + AA, OR: 0.50, $P = 0.04$, 95 % CI: 0.26–0.98) and the overdominant model (GG + GA vs. AA, OR: 0.41, $P = 0.01$, 95 % CI: 0.21–0.85). These results suggest that the GA genotype may serve as a genetic protective factor against MP.

Atteeri et al.[10] also examined the MYO1H rs10850110 (G > A) polymorphism among patients in India, reporting similar results to those we obtained. They observed that the G allele was overrepresented in patients with MP relative to the A allele ($p < 0.0001$). This finding indicates that the G allele may be a risk factor for MP in Indian patients. In our study, within the MP group, 73 (80.2 %), 15 (16.5 %), and 3 (3.3 %) individuals had the GG, GA, and AA genotypes, respectively. In the control group, 63 (67.0 %), 30 (31.9 %), and 1 (1.1 %) individuals had the GG, GA, and AA genotypes, respectively. In our sample of Taiwanese patients, the genotype distribution followed the pattern GG > GA > AA. By contrast, Atteeri et al.[10] reported a distribution pattern of GG, AA, and GA genotypes in 16 (53.3 %), 11 (36.7 %), and 3 (10 %) individuals in their Class III malocclusion group, respectively. In their Class I group, the observed distribution was GG, AA, and GA in 19 (63.3 %), 9 (30 %), and 2 (6.7 %) individuals, respectively. Thus, distributions in both groups followed the pattern GG > AA > GA. These differences indicate potential population-based genetic variations in MYO1H rs10850110 (G > A) distribution.

In a 2020 study, Dalaie et al.[11] examined the rs10850110 and rs11611277 polymorphisms of the MYO1H gene in 64 Iranian patients with MP who were seeking orthognathic surgery and 60 patients with skeletal Class I as controls. The Class I group was characterized by an ANB angle of 2°–4° and a Wits appraisal of 0–2 mm, whereas the Class III group had an SNB angle greater than 2°. In the MP group, two individuals (3.1 %) had the rs10850110 polymorphism (G > A), and in the control group, four individuals (6.7 %) had the AA genotype ($P = 0.680$). Similarly, for the rs11611277 polymorphism (C > A), 1.6 % of individuals in the MP group and 5 % of individuals in the control group had the variant ($P = 0.602$). Our genotype distribution was consistent with those observed by Dalaie et al.,[11] following the distribution pattern GG > GA > AA. However, their statistical analysis revealed no significant difference in the frequency of either polymorphism between the patient and control groups, indicating that these variants may not be strongly associated with MP in Iranian patients.

Tassopoulou-Fishell et al.[12] conducted a study involving 44 patients with MP and 35 candidates for orthognathic surgery in Pittsburgh, United States. The researchers sought to replicate their findings by analyzing 33 SNPs across eight candidate regions in a homogeneous sample set. The G allele of rs10850110 was significantly overrepresented in patients with MP ($P = 0.03$), aligning with the pattern we observed in our sample. However, the difference in frequency between the G and A alleles was not significant in our study (P = 0.13). Additionally, the genotype distribution in both studies followed the pattern GG > GA > AA. Stricter clinical definitions may increase homogeneity and support further research on genetic susceptibility to malocclusions.

Guillianne et al.[17] examined the MYO1H gene rs10850110 polymorphism in relation to the skeletal profile in 50 Indonesian patients with MP, 50 with Class II malocclusion, and 50 with Class I malocclusion. DNA samples were collected from the nail clippings and hair follicles of patients in the MP group, and buccal swabs and blood cells were used for the Class I and II skeletal malocclusion groups. The genotype distribution was GG > GA > AA in the Class I and II groups and GA > GG > AA in the MP group. In the Class II group, the GA and GG genotypes accounted for

34 % and 66 % of patients, respectively. The distribution was reversed in the MP group, with GG and GA genotypes observed in 34 % and 66 % of patients, respectively. Notably, no participant in any group had the AA genotype. The OR for the Class II group was 1.145, indicating that the G allele posed a 1.145 times higher risk of Class II malocclusion than the A allele; this lower frequency implies a protective effect. Conversely, in the MP group, the A allele had a 2.1 times higher risk than the G allele, suggesting the A allele is a risk factor for MP in Indonesian patients. By contrast, our findings suggest that the A allele is a protective factor that reduces rather than increases the risk of MP. These findings further reinforce the malocclusion- and population-based genetic variations in MYO1H gene polymorphisms. Our results indicate that the MYO1H rs10850110 (G > A) polymorphism may contribute to MP in Taiwanese patients.

Cruz et al.[18] investigated the MYO1H rs10850110 (G > A) variant in a Brazilian population. Their results revealed a significantly higher risk of MP in participants with the G versus A allele (OR: 7.44, 95 % CI: 4.02−13.77, $P < 0.001$). By contrast, in our study, individuals with the GA genotype had a significantly lower risk of MP than individuals with the GG genotype (OR: 0.43, $P = 0.01$, 95 % CI: 0.21−0.87), implying a protective effect. This finding further supports the role of MYO1H in mandibular growth regulation and MP development and highlights possible population-specific genetic variations.

Our cephalometric analysis revealed a significant correlation between the PFH/AFH ratio and the MYO1H rs3825393 (C > T) polymorphism. The PFH/AFH ratio is an essential cephalometric measurement in orthodontics and craniofacial analysis, and it assesses the vertical proportions of the face. Clinically, a higher PFH/AFH ratio suggests a short facial height structure, often associated with brachyfacial (short-faced) and deep bite individuals. In comparison, a lower PFH/AFH ratio indicates increased lower facial height, commonly seen in dolichofacial (long-faced) and open-bite individuals. In our study of the MYO1H rs3825393 (C > T) polymorphism, participants with the TT genotype (0.68 ± 0.06) exhibited a higher PFH/AFH ratio compared to those with the CC genotype (0.64 ± 0.06). Sun et al.[7] investigated the genetic polymorphisms associated with hereditary MP within the Chinese population. Their findings indicated that the MYO1H rs3825393 polymorphism was associated with a nonsynonymous common variant (rs3825393, C > T). The C allele was connected to an increased risk of MP, which was characterized by higher SNB values, lower ANB values, and greater mandibular length, suggesting a potential genetic influence on mandibular growth and skeletal Class III development. In contrast, our findings showed no significant differences in SNB and ANB angles or Wits appraisal distance but presented a statistically significant difference in the PFH/AFH ratio.

De Fontoura et al.[4] conducted a genetic study involving 269 individuals in the United States, categorizing them into Class I (n = 53), Class II (n = 128), and Class III (n = 88) based on cephalometric parameters, such as the ANB angle, overjet, and Wits appraisal. Saliva samples were collected for genetic analysis, focusing on the MYO1H rs11066446 and rs7315991 polymorphisms. Their results revealed a significant difference for rs11066446 between the Class II and Class III groups, while rs7315991 showed no significant association among the three groups. Our results correspond with those of De Fontoura et al.,[4] further confirming that rs7315991 does not show a significant difference between Class III and Non-Class III groups.

For rs10850110 (G > A), along with an analysis of craniofacial measurements, indicated a correlation between the SNB and ANB angles. The higher SNB and negative ANB values indicate a more protrusive (forward-positioned) mandible, which is a characteristic feature of skeletal Class III relationship. Our results coincide with those of Cruz et al.,[18] who investigated the MYO1H rs10850110 (G > A) variant in a Brazilian population. Their results indicated that participants with the G allele had a significantly higher risk of developing skeletal Class III with MP compared to those with the A allele (OR = 7.44, 95 % CI = 4.02−13.77, $P < 0.001$). Furthermore, their principal component analysis (PCA) revealed that higher scores in principal component 1 (PC1) correlated with anteroposterior discrepancies, particularly in mandibular dimensions, encompassing both mandible position and length. The MYO1H rs10850110 polymorphism demonstrated a statistically significant association with PC1. In contrast, our findings indicated that individuals with the GA genotype had a lower risk of developing skeletal Class III relation compared to those with the GG genotype, with an odds ratio (OR) of 0.43, suggesting a protective effect and was statistically significant. Overall, the findings strengthen the evidence that MYO1H contributes to mandibular growth control and the etiology of Class III malocclusion, suggesting that genetic variations may differ among populations.

This study had several limitations. The small number of participants carrying the AA genotype of rs10850110 reduced statistical power and warranted cautious interpretation. In addition, inclusion of both skeletal Class I and Class II individuals in the non-Class III group might have introduced heterogeneity. Future studies with larger samples and strictly skeletal-normal controls are needed to confirm these findings and clarify whether rs10850110 is also associated with Class II malocclusion.

In conclusion, The MYO1H rs10850110 (G > A) polymorphism is associated with MP in our sample of Taiwanese patients. Individuals carrying the GA genotype have a 43 % reduced risk of this malocclusion compared with those carrying the GG genotype. Under dominant and recessive genetic models, individuals in the GA + AA group were 50 % less likely than those in the GG group to develop MP. Additionally, craniofacial measurements indicated that individuals with the GG genotype had significantly larger SNB, negative ANB and Wits appraisal values compared to those with the GA genotype.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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