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Original article

The association of polymorphisms in *BMP2/MYO1H* and skeletal Class II div.1 maxillary and mandibular dimensions. A preliminary 'report

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ABSTRACT

Introduction: The genetic impact directly or indirectly predefines maxillofacial dimensions, potentially leading to an inappropriate relationship of the jaws and subsequently skeletal malocclusion. Previous studies focused mainly on genetic polymorphisms and class III malocclusion. This study was set out to investigate the association between genetic polymorphisms in two genes *BMP2* (rs235768) and *MYO1H* (rs11066446) with Class II division 1 malocclusion, skeletal variation in vertical plane, and maxillary and mandibular jaws length.

Subjects and methods: Sixty patients classified as Skeletal Class I (n = 30) and Class II division 1 (n = 30) were recruited. DNA was extracted from saliva and analyzed by Sanger sequencing. Lateral cephalometric radiographs were measured for the anterio-posterior relationship of maxillary and mandibular arch using digital tracing. Hardy-Weinberg equilibrium analysis of genotype frequencies was performed using Chi-square test to compare genotype distribution among groups and multiple logistic regression analysis adjusted by gender was also performed.

Results: The rs235768 polymorphism in *BMP2* was associated with hypodivergent face, increased maxillary length, and decreased mandibular length. Meanwhile, the rs11066446 polymorphism in *MYO1H* was associated with decreased mandibular length. New polymorphism was identified in *MYO1H* (rs10850090) in association with decreased mandibular length.

Conclusion: A potential association between polymorpisms in *BMP2* rs235768 and *MOY1H* rs11066446 and rs10850090 and Class II division 1 skeletal malocclusion related phenotypes exists, however, the degree of it has to be further investigated and yet to be discovered.

1. Introduction

Craniofacial complex development including mandibular and maxillary arches, involves delicate timely migrations and interactions of various types of cell populations, as well as highly coordinated patterns of cell differentiation and growth pattern (Kouskoura et al., 2011). The etiology of skeletal malocclusions is influenced by genetic factors that are expressed in different dimensions including vertical, anterioposterior, and horizontal interrelationships of the dental arches (Šidlauskas et al., 2016; Doraczynska-Kowalik et al., 2017). Evidence from twin and family genetic-based studies has proved that genetic factors are involved in the etiology of skeletal malocclusions (Manfredi et al., 1997; Da Fontoura, et al., 2015). Different human genes may directly or indirectly increase or decrease arch dimensions, resulting in an inappropriate relationship of the jaws leading to facial balance distortion (Šidlauskas et al., 2016).

Genes required for cartilage developement, bone metabolism and skeletogenesis are potential candidates for skeletal malocclusions. Among these candidate genes, members of the Transforming growth factor β (TGF-β) superfamily, the *BMP* genes (bone morphogenetic protein), around 20 *BMP* family members have been identified and characterised, are known to play an important role in craniofacial development, proliferation, and differentiation (Kamiya and Mishina, 2011). BMPs can activate multiple kinase

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pathways like PI3 kinase and MAPK along with SMAD proteins (SMADs regulate the transcription of TGF-β superfamily genes) (Kishigami and Mishina, 2005). There is a direct involvement of *BMP2* (OMIM *112261) in bone biology, and in the regulation of craniofacial growth and dental structures (Ali and Brazil, 2014). Different studies found a strong correlation between ontogenesis and *BMP2* along with *BMP4* which involved in differentiation of cells during skeletogenesis (Bandyopadhyay et al., 2006). A recent study found that the single-nucleotide polymorphisms (SNPs) in *BMP2* could be involved in the etiology of vertical and sagittal malocclusions (Küchler et al., 2021). Jankovska *et al,* reported BMP2/4 expression in both maxillary and mandibular arch in patients with Cl.II and Cl.III malocclusion (Jankovska et al., 2017).

The myosin IH gene (*MYO1H,* OMIM *614636), located on chromosome 12 at 12q24.11, encodes the unconventional myosin IH which is involved in cell motility, vesicle transport and phagocytosis (Rowlerson et al., 2005). Evidence from a previous research has suggested that orofacial musculature affect craniofacial morphology (Mew, 1986). Thus, genetic alteration that affects the muscles could affect the skeletal growth (Moss, 1997). Previous studies have linked polymorphisms in *MYO1H* with mandibular discrepancy in Class III malocclusion (Da Fontoura et al., 2015; Wise et al., 2000; Sun et al., 2018; Atteeri et al., 2021).

In additin, SNPs in certain genes have been associated with various types of malocclusions. Previous studies focused mainly on genetic polymorphisms and class III malocclusion with limited knowledge on SNPs and class II division 1 maloclclusion (Yahya et al., 2007). As the aforementioned genes have been reported to be associated with craniofacial bone and cartilage formation; thus we hypothesize that they could offer a genetic contribution with Class II division 1 malocclusion. Hence, the aims of the present study were to investigate the association of SNPs in *BMP2* and *MYO1H* with Class II malocclusion, skeletal variation in vertical plane, and maxillary and mandibular dimensions.

2. Subjects and methods

2.1. | *Subjects*

The protocol of the study was approved by the Human Ethics Committee of the College of Dentistry-University of Baghdad (reference number: 258421) and complied with the Declaration of Helsinki. All participants gave informed consents before participating in the study.

The statement of checklist from the Strengthening the Reporting of Genetic Association study (STREGA) was followed (Little et al., 2009). Genomic DNA was extracted from salivary samples, additionally pre-treatment lateral cephalometric X-rays were evaluated for eligibility.

Out of 256 clinically assessed individuals, a total of 60 subjects (Arabic ethnic background) were included in this study following clinical examination and cephalometric analysis and they were distributed into two group: 30 patients presenting with Class I occlusion (18 male and 12 female) and 30 patients had Class II division 1 malocclusion (13 male and 17 female). Subjects with underlying hereditary syndromes such as cleft lip and palate, growth disturbances, and congenital disorders were excluded from the study.

2.2. | *Phenotype assessments*

Pre-treatment lateral cephalometric radiographs were utilized for phenotyping assessment of all subjects. The lateral cephalograms were imported into Dolphin Imaging software (Dolphin Imaging version 11.95 premium, Chatsworth, CA, USA) for digitization and further investigation. The measurements were conducted by one examiner trained by a specialist orthodontist (ASH). Intra-examiner reproducibility was assessed in which 10 randomly selected radiographs were examined twice (the second time was after one month). Kappa test was used to validate the reliability and a value of 0.62 was reported, indicating a strong re-producibility of the data.

Tracing landmarks and reference planes consisted of eight anatomical hard tissue points (point A, point B, Nasion (N), Sella (S), Gnathion (Gn), Menton (Me), Gonion (Go) and Condylion (Co), three angular measurements (SNA, SNB, ANB) and four linear measurements (Sella-Gonion (S-Go), Nasion-Menton (N-Me), Condylion-Gnathion (Co-Gn) and Condylion-A point (Co-A)). Steiner's SNA, SNB and ANB angles were used to determine sagittal skeletal jaw relationship (type of malocclusion). Therefore, the sample was classified according to the ANB angle as class I (2°-4°), class II (>4°) malocclusion. In addition, Jaraback ratio was calculated to determine vertical skeletal discrepancy using the following measurement; proportion between the posterior facial height (S-Go) and the anterior facial height (N-Me) was calculated. The face is hyperdivergent face was concluded if the ratio was 59% or less, hypodivergent if the ratio was 65% or more, and normal face when the proportion is between 60 and 64%. Finally, maxillary and mandibular lengths were calculated using (Co-A) and (Co-Gn) planes respectively. Reference points, lines and normal value of angles were measured according to McNamara, Jarabak and Steiner (Stiener, 1953; McNamara, 1981; Jarabak, 1985).

2.3. | *Genotype assessments*

Salivary DNA was used for genotyping analysis. The genomic DNA extraction was performed using the ReliaPrep™ Blood gDNA Miniprep System (Promega, WI, USA) according to the manufacturer's instructions. The quality of DNA was determined by agarose gel electrophoresis and sent for Sanger sequencing at Macrogen (Seoul, Korea) using an ABI3730XL, automated DNA sequencer.

Two SNPs, rs235768 (A > T) in *BMP2* and rs11066446 (C > G) in *MYO1H* were Sanger sequenced, having previously identified with diseases or development dysfunction in bone and/or cartilage of the craniofacial region (Da Fontoura et al., 2015). The validated primers used for the selected SNPs were supplied by Macrogen, Korea (supplementary Table S2). The Geneious software was used for the analysis of data through forward and reverse reading and determined sequence variation between samples of specific gene.

2.4. | *Statistical analysis*

The statistical analysis was performed using Graphpad Prism version 8 (Graphpad Software Inc.,La Jolla, CA). Alleles and genotypes of gene SNPs were presented as numbers and percentage of frequencies. Chi-squared test was performed to estimate Hardy-Weinberg equilibrium analysis of genotype frequencies among groups was performed using Chi-square test to compare genotype distribution among groups. Multiple logistic regression analysis was also performed adjusted by gender as a co-variants, to assess the posssible effect of this factor on the measurement with odd ratios and confidence interval. Alpha was set as *significant at p value ≤ 0.05 and ** significant at p value ≤ 0.01 to ensure broad inclusion of possible determinants.

3. Results

The mean age of Class I malocclusion group was 21.8 years (SD: 2.23) while, the mean age of the Cl.II div.1 malocclusion group was 23.26 years (SD: 2.67). The characteristics of the studied population are presented in Table 1.

3.1. Genotype-phenotype associations

The distribution of genotype for each SNP according to each phenotype is demonstrated in Table 2. SNP rs235768 in *BMP2* was significantly higher in subjects with decreased anterior facial high (hypodivergent face) especially in those who carry the TT genotype (25/64%, $p \leq 0.0001$) (Fig. 1A). Moreover, the same SNP was significantly higher in subjects with decreased mandibular anterior-posterior length (17/59%, $p \leq 0013$) and increased maxillary anterio-posterior length (8/80%, $p \leq 0015$) especially those who carry TT genotype.

The rs11066446 in *MYO1H* was significantly associated with decreased mandibular antero-posterior length of subjects with the CG genotype (16/55%, $p \leq 0.0001$) (Fig. 1B). Interestingly, three more SNPs were identified during Sanger sequencing comprising rs73190701, rs74915028, and rs10850090. None of them showed significant association with any phenotypes except the rs10850090 in which a significant association was identified with the decreased mandibular anterio-posterior length with the AG genotype (16/55%, $p \leq 0.0001$) as seen in Table 2.

A logistic regression analysis was performed using gender as a co-variable (Table 3). The results revealed a significant association between SNP in *BMP2* (rs235768) in subjects who carry the TT genotype and hypodivergent face ($p \leq 0.0001$, OR = 391.0, CI 95% = 14.7788–10344.582). Similarly, subjects who carry the AT genotype showed the significant association ($p \leq 0.0001$, OR = 60.6364, CI 95% = 3.0287–1213.993). The same SNP (rs235768) with the AT genotype was significantly higher in cases with decreased mandibular anterior-posterior length ($p \leq 0013$, OR = 2.400, CI 95% = 0.5304–10.11). The TT genotype was significantly higher in cases with increased maxillary anterior-posterior length ($p \leq 0015$, OR = 41.2857, CI 95% = 1.8377–927.5461). SNPs in *MYO1H* (rs11066446) was significantly associated with decreased mandibular anterior-posterior length in subjects who carry the CG genotype ($p \leq 0.0001$, OR = 52.4118, 2.7666–992.9210) and GG genotype ($p \leq 0.0001$, OR = 729.00, CI 95% = 13.4603–39482.2443). Interestingly, rs10850090 in *MYO1H* was significantly associated with decreased mandibular anterior-posterior length in subjects who carry the AG genotype (p=<0.0001, OR = 52.4118, CI 95%= 2.7666 to 992.9210) and GG genotype ($p \leq 0.0001$, OR = 729.00, CI 95% = 13.4603–39482.2443).

Table 1
Population characteristic for each phenotype.

Phenotypes	N (%)
Class I MalocclusionAge: Mean (SD) Male/Female	30 (50)21.8 (2.23)18 (60) / 12 (40)
Class II Division 1 MalocclusionAge: Mean (SD) Male/Female	30 (50)23.26 (2.67)13 (43.3) /17 (56.7)
Vertical dimension	
Normal face	17 (28.33) [12Cl.I/5Cl.II]
Hyperdivergent	4 (6.66) [1Cl.I/3Cl.II]
Hypodivergent	39 (65) [18Cl.I/21Cl.II]
Maxillary-mandibular anterio-posterior measurement	
Normal	21 (35) [15Cl.I/6Cl.II]
Decreased mandibular length	29 (48.3) [10Cl.I/19Cl.II]
Increased maxillary length	10 (16.7) [3Cl.I/ 7Cl.II]

4. Discussion

Various observational and *in vitro* studies reported that normal post-natal growth and development of craniofacial structures require the coordination of different mechanisms and precise timing of migration of specific cells along with coordination of tissue differentiation and interaction of different molecules (Kouskoura et al., 2011; Pallares et al., 2015; Rodrigues et al., 2020). The development of maxilla and mandible is a complex and dynamic process influenced by genetic and environmental factors. The environmental factors include pressures from surrounding muscles and soft tissues, mastication forces, and habits such as thumb sucking, and nail biting. Several genes and signaling pathways including homeobox genes, fibroblast growth factors, transforming growth factors, and bone morphogenetic proteins influence the pattern of the developing jaws (Cobourne and Sharpe, 2003). Genetic predisposition of maxilla/mandible phenotypes have been associated with multiple risk loci. Mandibular prognathism has been associated with loci in genes such as growth hormone receptor gene (GHR) (Bayram et al., 2014), collagen type II alpha-1 (COL2A1) (Xue et al., 2014), and fibroblast growth factor 12 (FGF12), FGF20, and FGFR1 (Xiong et al., 2017). Maxillary hypoplasia correlates with variants in DUSP6 related to FGF signaling (Li et al, 2007) and mandibular hypoplasia with the SNP in Noggin (Gutierrez et al., 2010). A recent systematic review and meta-analysis has showed that class III malocclusion is associated with the variants in GHR (rs2973015,rs6184, rs2973015), MYO1H (rs10850110), BMP3 (rs1390319), SNAI3(rs4287555), FGF7(rs372127537), and FGF10 (rs593307) across the studies (Dehesa-Santos et al., 2021). Previously, studies have evaluated the association of maxillary or mandibular discrepancy and different genes as well as face morphology (Liu et al., 2017; Cunha et al., 2019). Genetic-based studies focused mainly on mandibular prognathism and skeletal class III malocclusion (Xue et al., 2010; Nowrin et al., 2019). Recently, more studies focused on craniofacial phenotypes including other types of malocclusions as well as sagittal and vertical discrepancies (Küchler et al., 2018; Küchler et al., 2021). Due to the lack of sufficient data, the present study aimed to investigate the association between SNPs in the *BMP2* and *MYO1H* gene in Class II division 1 malocclusion and sagittal and vertical craniofacial phenotypes in each jaw. Moreover, to the best of our knowledge this is the first genetic study that mainly involved subjects who presented with skeletal class II division 1 due to mandibular deficiency. We decided to evaluate SNPs in these specific genes because of their role in bone and cartilage growth and development and skeletal muscle maturation and construction (Gershater et al., 2021).

In mice, *Bmp2* regulates the development of Meckel's cartilage in the mandible (Wang et al., 2013). Alteration in the *BMP* signal leads to craniofacial development abnormality. The heterozygous *Bmp2* mutant mice developed the neural tube defects at E9.5 while the homozygous null mutants died at embryonic stage (Castranio and Mishina, 2009). In humans, the defects in the craniofacial region including cleft palate and mandibular reterognathism are associated with *BMP2* haploinsufficiency (Sahoo et al., 2011). Recently, a study on *BMP2* (rs235768) has reported that the missense *BMP2* variant (Argenine > Serine) is involved in decreased mandibular length and craniofacial development including tooth agenesis (Küchler et al., 2021). Other studies reported an association between the *BMP2* rs235768 with orofacial cleft (Kiranahayu et al., 2020). Our data identified the same association between *BMP2* rs235768 and mandibular retrognathism, decreased anterior facial height (hyodivergent face), decreased mandibular, and increased maxillary anterio-posterior length. Interestingly, a previous study reported that *BMP2* is expressed not only in the mandibular process but also in the maxillary process (Bennett

Table 2
Genotype distribution of each SNP according to each phenotype in sagittal and vertical patterns and maxillary-mandibular dimensions.

Gene and SNP		Phenotypes	Genotypes n (%)			*p* value
			AA	AT	TT	
BMP2 rs235768	Sagittal relation	Class I	8 (26.7%)	12 (40%)	10 (33.3%)	Ref.
		Class II Div.1	3 (10%)	9 (30%)	18 (60%)	0.0722
	Vertical relation	Normal face	11 (63%)	5 (33%)	1(4%)	Ref.
		Hyperdivergent face	0 (0%)	2 (50%)	2 (50%)	0.060
		Hypodivergent face	0 (0%)	14 (36%)	25 (64%)	≤0.0001 **
	Maxillary-Mandibular length	Normal	8 (38%)	10 (48%)	3 (14%)	Ref.
		Decreased mandibular	3 (10%)	9 (31%)	17 (59%)	0.0013 **
		Increased maxillary	0 (0%)	2 (20%)	8 (80%)	0.0015 **
MYO1H rs11066446	Sagittal relation		CC	CG	GG	
		Class I	12 (40%)	12 (40%)	6 (20%)	Ref
		Class II Div.1	10 (33%)	13 (44%)	7 (23%)	0.631
	Vertical relation	Normal face	9 (53%)	4 (23.5%)	4 (23.5%)	Ref
		Hyperdivergent face	0 (0%)	0 (0%)	4 (100%)	0.7195
		Hypodivergent face	14 (35.9%)	20 (51.3%)	5 (12.8%)	0.783
	Maxillary-Mandibular length	Normal	13 (62%)	8 (38%)	0 (0%)	Ref
		Decreased mandibular	0 (0%)	16 (55%)	13 (45%)	≤0.0001 **
		Increased maxillary	10 (100%)	0 (0%)	0 (20%)	0.9020
MYO1H rs74915028	Sagittal relation		TT	TG	GG	
		Class I	29 (97%)	1 (3%)	0 (0%)	Ref
		Class II Div.1	27 (90%)	3(10%)	0 (0%)	0.9722
	Vertical relation	Normal face	17 (100%)	0 (0%)	0 (0%)	Ref
		Hyperdivergent face	4 (100%)	0 (0%)	0 (0%)	0.511
		Hypodivergent face	35 (90%)	4 (10%)	0 (0%)	0.170
	Maxillary-Mandibular length	Normal	21 (100%)	0 (0%)	0 (0%)	Ref.
		Decreased mandibular	26 (93%)	3 (7%)	0 (0%)	0.128
		Increased maxillary	9 (100%)	1 (0%)	0 (0%)	0.140
MYO1H rs73190701	Sagittal relation		CC	CG	GG	
		Class I	30 (100%)	0 (0%)	0 (0%)	Ref.
		Class II Div.1	30 (100%)	0 (0%)	0 (0%)	1
	Vertical relation	Normal face	17 (100%)	0 (0%)	0 (0%)	Ref.
		Hyperdivergent face	4 (100%)	0 (0%)	0 (0%)	0.511
		Hypodivergent face	34 (87%)	5 (13%)	0 (0%)	0.1219
	Maxillary-Mandibular length	Normal	20 (95%)	1 (5%)	0 (0%)	Ref
		Decreased mandibular	27 (93%)	2 (7%)	0 (0%)	0.884
		Increased maxillary	9 (90%)	1 (10%)	0 (0%)	0.705
MYO1H rs10850090	Sagittal relation		AA	AG	GG	
		Class I	12 (40%)	12 (40%)	6 (20%)	Ref.
		Class II Div.1	10 (33%)	13 (44%)	7 (23%)	0.631
	Vertical relation	Normal face	9 (53%)	4 (23.5%)	4 (23.5%)	Ref.
		Hyperdivergent face	0 (0%)	0 (0%)	4 (100%)	0.719
		Hypodivergent face	13 (334%)	21 (53.8%)	5 (12.8%)	0.856
	Maxillary-Mandibular length	Normal	13 (62%)	8 (38%)	0 (0%)	Ref.
		Decreased mandibular	0 (0%)	16 (55%)	13 (45%)	≤0.0001 **
		Increased maxillary	9 (90%)	1 (10%)	0 (0%)	0.107

et al., 1995), which may explain the association of the rs235768 and increased anterior-posterior length of the maxillary arch. Multiple logistic regression analysis showed the TT genotype was overexpressed in hypodivergent face, the AT genotype was significantly associated with decreased mandibular anterioposterior length and the TT genotype was more common in patients with increased maxillary anterioposterior length. Collectively, an increased maxillary length and decreased mandibular length are common phenotypes in patients with Class II division 1 malocclusion, suggesting that the rs235768 is associated with Class II division 1 malocclusion.

A previous research has pointed out the significant effect of muscles on facial bones (Saccomanno et al., 2012). The effect of muscle translates on areas of bone insertion as the mechanical forces and results in modification of skeletal structures. The genetic variations that effect composition or the properties of muscles could change the skeletal configuration (Klingenberg et al., 2004). Genetic polymorphisms that directly affect the muscle would also indirectly affect the adjoining skeletal areas according to the functional matrix hypothesis in which skeletal growth is linked to its underlying muscular matrix (Moss, 1997). The composition of muscle fibers is highly influenced by genetic factors. Different variations of myosin heavy chain isoforms are found in the masseter muscle of humans and the most common isoform observed in humans is Type-I myosin heavy chain isoform (Berg et al., 2001). The *MYO1H* plays an important role in intracellular transport (Cruz et al., 2017). The variants in *MYO1H* have been linked with mandibular prognathism (Tassopoulou-Fishell et al., 2012). The *MYO1H* is expressed in the mandibular jaw and correlated with mandibular growth and chondrocytes proliferation (Sun et al., 2018).

MYO1H was previously identified to be associated with mandibular prognathism or mandibular retrognathism (Yahya et al., 2007; Arun et al., 2016). Previous researches mainly focused on Class III malocclusion. Yahya *et al.*, reported the association of *MYO1H* rs10850110 and mandibular prognathism in the Malaysian population (Yahya et al., 2007). Conversely, Dalaie *et al.*, reported in the Iranian population a non-significant correlation between *MYO1H* rs10850110 and skeletal class III due to mandibular prognathism (Dalaie et al., 2020) and the same finding was

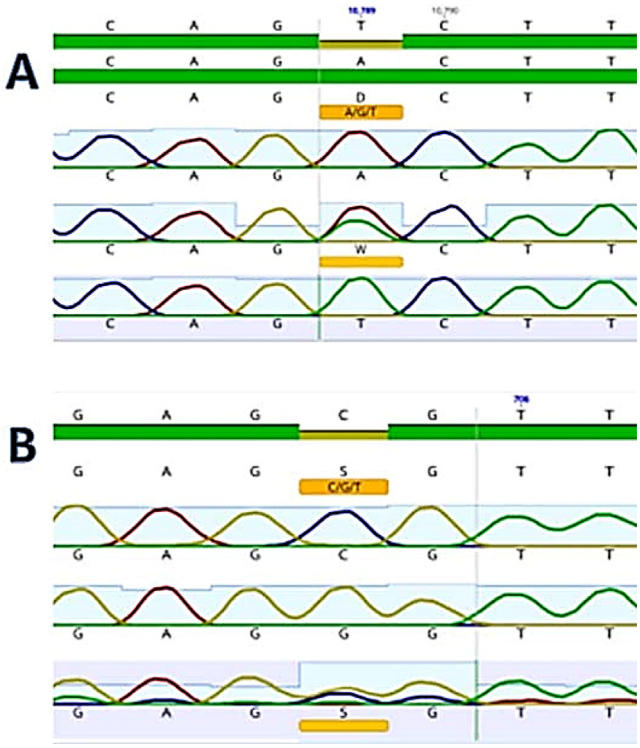

Fig. 1. Chromatograms of SNPs taken from Cl.I and Cl.II div.1 groups. (A) Analysis of rs235768 SNP of the *BMP2* gene. Single "A" peak indicative of A homozygous allele. Single "T" peak indicative of a T homozygous allele. Presence of the "A" and "T" peak indicative of A/T heterozygous allele. (B) Analysis of rs11066446 SNP of the *MYO1H* gene. Single "C" peak indicative of a C homozygous allele. Single "G" peak indicative of a G homozygous allele. Presence of the "C" and "G" peak indicative of C/G heterozygous allele.

reported in the Brazilian population by Cunha (Cunha et al., 2019). Moreover, *MYO1H* was selected as a candidate gene for further functional investigations for its role in mandibular growth. The present study investigated the rs11066446 in *MYO1H* and identified an association between the rs11066446 and decreased mandibular length, however, no association was found with Class II malocclusion and vertical relation. Multiple logistic regression analysis showed that GG genotype was more common in the patients with decreased mandibular length. Similarly, Da Fontoura et al identified the same SNP in American patients who had maxilla-mandibular discrepancies ranging from extremely convex profile and Class II skeletal malocclusion to concave profile and Class III skeletal malocclusion (Da Fontoura et al., 2015). These findings suggest that the rs11066446 in *MYO1H* could be considered as a contributory candidate SNP for a decrease in mandibular anterior-posterior dimension in patients with skeletal Class II division 1 malocclusion.

Interestingly, three more SNPs were also identified in *MYO1H* comprising rs73190701, rs74915028 and rs10850090. None of them showed a significant association with any phenotypes except the rs10850090 which was significantly associated with decreased mandibular length. Multiple logistic regression analysis identified that the GG genotype was more common in patients with decresaed mandibular anterio-posterior length, suggesting a possible association of the rs10850090 and Class II malocclusion. However, no previous publication is available to support our findings.

An important limitation of our study was the sample size, as a sufficient sample size is crucial to explore the possible association between the newly identified SNPs and certain phenotypes. Nevertheless, this study is an initial study showing a significant association between the *BMP2* (rs235768) and *MYO1H* (rs11066446) and the targeted phenotypes. We also identified the new *MYO1H* rs10850090 associated with decreased mandibular length. Therefore, future studies including larger cohorts and various population profile are required to confirm our findings as well as test the newly identified SNPs.

5. Conclusions

The genetic polymorphisms in *BMP2* and *MYO1H* are associated with Class II division1 malocclusion especially in patients with decreased anterioposterior mandibular length. Further studies including larger sample size are necessary to validate these findings.

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Author contributions

ASH and MA contributed to investigation, data interpretation, drafted and critically revised the manuscript. TP analyzed the data and critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

Institutional review board statement

The Human Ethics Committee of the College of Dentistry-University of Baghdad approved this study (project number: 258421, reference number 258 in 20-3-2021), All the participants were consented before participating in the study.

Table 3
Multiple logistic regression analysis with SNPs and phenotypes associated with genotype distribution.

Phenotype	Genes	SNPs	Reference	Genotype	Odds Ratio (CI 95%)	*p* value
Hypodivergent face	***BMP2***	**rs235768**	AA	TT	391.0 (14.7788–10344.582)60.6364	0.0001**
				AT	(3.0287–1213.993)	≤0.0001**
Decreased mandibular anterio-posterior length				TT	15.11 (2.563–70.05)2.400	0.2789
				AT	(0.5304–10.11)	0.0013 **
Increased maxillary anterio-posterior length				TT	41.2857 (1.8377–927.5461)	0.0015 **
Decreased mandibular anterio-posterior length	***MYO1H***	**rs11066446**	CC	CG	52.4118 (2.7666–992.9210)	≤0.0001 **
				GG	729.00 (13.4603–39482.2443)	≤0.0001 **
		rs10850090	AA	AG	52.4118 (2.7666–992.9210)	≤0.0001 **
				GG	729.00 (13.4603–39482.2443)	≤0.0001 **

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2022.103405.

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