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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A B S T R A C T

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 antero-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 polymorphisms in BMP2 rs235768 and MYO1H 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.

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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, anterio-posterior, and horizontal interrelationalships 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 development, 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...
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 (Bandopadhyay 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 (Mrowlson et al., 2005). Evidence from a previous research has suggested that orofacial musculature affect craniofacial morphology (Mrow, 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 addition, 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 malocclusion (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 groups: 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-productibility 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 possible 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 < 0.0001) (Fig. 1A). Moreover, the same SNP was significantly higher in subjects with decreased mandibular anterior-posterior length (17/59%, p ≤ 0.0013) and increased maxillary antero-posterior length (8/80%, p ≤ 0.0015) especially those who carry TT genotype.

The rs11066446 in MYO1H was significantly associated with decreased mandibular antero-posterior length of subjects with the AG genotype (16/55%, p < 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 antero-posterior length with the AG genotype (16/55%, p < 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 AT genotype and hypodivergent face (p < 0.0001, OR = 391.0, 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 ≤ 0.0013, OR = 2.400, CI 95% = 0.5304–10.11). The TT genotype was significantly associated with decreased mandibular anterior-posterior length of subjects with the decreased mandibular antero-posterior length of subjects with the CT genotype (16/55%, p < 0.0001) (Table 3). The results revealed a significant association (p = 0.0001, OR = 60.6364, CI 95% = 3.0287–1213.993). The same SNP showed the significant association (p ≤ 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 ≤ 0.0013, OR = 2.400, CI 95% = 0.5304–10.11). The TT genotype was significantly higher in cases with increased maxillary anterio-posterior length (p = 0.0001, 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 AG genotype (p < 0.0001, OR = 52.4118, CI 95% = 2.7666 to 992.9210) and GG genotype (p ≤ 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 ≤ 0.0001, OR = 729.00, CI 95% = 13.4603–39482.2443).

### Table 1

| Phenotypes | N (%) |
|------------|-------|
| Class I MalocclusionAge: Mean |       |
| (SD) |       |
| Male/Female |       |
| Class II Division 1 MalocclusionAge: Mean |       |
| (SD) |       |
| Male/Female |       |
| Vertical dimension |       |
| Normal face |       |
| Hyperdivergent |       |
| Hypodivergent |       |
| Maxillary-mandibular antero-posterior measurement |       |
| Normal |       |
| Decreased mandibular length |       |
| Increased maxillary length |       |
Table 2
Genotype distribution of each SNP according to each phenotype in sagittal and vertical patterns and maxillary-mandibular dimensions.

| Gene and SNP | Genotypes n [%] | p value |
|-------------|-----------------|---------|
| **BMP2 rs235768** | | |
| Sagittal relation | | |
| Class I | 8 (26.7%) | 12 (40%) | 10 (33.3%) |
| Class II Div.1 | 3 (10%) | 9 (30%) | 2 (66%) |
| Vertical relation | | |
| Normal face | 11 (63%) | 5 (33%) | 1 (4%) |
| Hyperdivergent face | 0 (0%) | 2 (50%) | 2 (50%) |
| Hypodivergent face | 0 (0%) | 14 (36%) | 25 (64%) |
| Maxillary-Mandibular length | | |
| Normal | 8 (38%) | 10 (48%) | 3 (14%) |
| Decreased mandibular | 3 (10%) | 9 (31%) | 17 (59%) |
| Increased maxillary | 0 (0%) | 2 (20%) | 8 (80%) |
| **MYO1H rs11066446** | | |
| Sagittal relation | | |
| Class I | 12 (40%) | 12 (40%) | 6 (20%) |
| Class II Div.1 | 10 (33%) | 13 (44%) | 7 (23%) |
| Vertical relation | | |
| Normal face | 9 (33%) | 4 (23.5%) | 4 (23.5%) |
| Hyperdivergent face | 0 (0%) | 0 (0%) | 4 (100%) |
| Hypodivergent face | 14 (35.0%) | 20 (51.3%) | 5 (12.8%) |
| Maxillary-Mandibular length | | |
| Normal | 13 (62%) | 8 (38%) | 0 (0%) |
| Decreased mandibular | 0 (0%) | 16 (55%) | 13 (45%) |
| Increased maxillary | 10 (100%) | 0 (0%) | 20 (20%) |
| **MYO1H rs74915028** | | |
| Sagittal relation | | |
| Class I | 29 (97%) | 3 (1%) | 0 (0%) |
| Class II Div.1 | 27 (90%) | 3 (10%) | 0 (0%) |
| Vertical relation | | |
| Normal face | 17 (100%) | 0 (0%) | 0 (0%) |
| Hyperdivergent face | 4 (100%) | 0 (0%) | 0 (0%) |
| Hypodivergent face | 35 (90%) | 4 (10%) | 0 (0%) |
| Maxillary-Mandibular length | | |
| Normal | 21 (100%) | 0 (0%) | 0 (0%) |
| Decreased mandibular | 26 (93%) | 3 (7%) | 0 (0%) |
| Increased maxillary | 9 (100%) | 1 (0%) | 0 (0%) |
| **MYO1H rs73190701** | | |
| Sagittal relation | | |
| Class I | 30 (100%) | 0 (0%) | 0 (0%) |
| Class II Div.1 | 30 (100%) | 0 (0%) | 0 (0%) |
| Vertical relation | | |
| Normal face | 17 (100%) | 0 (0%) | 0 (0%) |
| Hyperdivergent face | 4 (100%) | 0 (0%) | 0 (0%) |
| Hypodivergent face | 34 (87%) | 5 (13%) | 0 (0%) |
| Maxillary-Mandibular length | | |
| Normal | 20 (95%) | 1 (5%) | 0 (0%) |
| Decreased mandibular | 27 (93%) | 2 (7%) | 0 (0%) |
| Increased maxillary | 9 (90%) | 1 (10%) | 0 (0%) |
| **MYO1H rs10850090** | | |
| Sagittal relation | | |
| Class I | 12 (40%) | 12 (40%) | 6 (20%) |
| Class II Div.1 | 10 (33%) | 13 (44%) | 7 (23%) |
| Vertical relation | | |
| Normal face | 9 (33%) | 4 (23.5%) | 4 (23.5%) |
| Hyperdivergent face | 0 (0%) | 0 (0%) | 4 (100%) |
| Hypodivergent face | 13 (33%) | 21 (53.8%) | 5 (12.8%) |
| Maxillary-Mandibular length | | |
| Normal | 13 (62%) | 8 (38%) | 0 (0%) |
| Decreased mandibular | 0 (0%) | 16 (55%) | 13 (45%) |
| Increased maxillary | 9 (90%) | 1 (10%) | 0 (0%) |
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 the GG genotype was more common in the patients with decreased mandibular length. 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 decreased mandibular antero-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.

Table 3

| Phenotype                              | Genes | SNPs     | Reference | Genotype | Odds Ratio (CI 95%) | p value  |
|----------------------------------------|-------|----------|-----------|----------|---------------------|----------|
| Hypodivergent face                     | BMP2  | rs235768 | AA        | TT       | 391.0 (14.7788–10344.58260.6364) | 0.0001** |
|                                        |       |          |           | AT       | (3.0287–1213.993)   | ≤0.0001**|
| Decreased mandibular antero-posterior length |       |          |           | TT       | 15.11 (2.563–70.05) | 0.2789   |
|                                        |       |          |           | AT       | (0.5304–10.11)      | 0.0013** |
| Increased maxillary antero-posterior length | MYO1H | rs11066446 | CC       | TT       | 41.2857 (1.8377–927.5461) | 0.0015** |
| Decreased mandibular antero-posterior length | MYO1H | rs10850090 | AA       | CG       | 52.4118 (2.7666–992.9210) | ≤0.0001** |
|                                        |       |          |           | GC       | 729.00 (13.4603–39482.2443) | ≤0.0001**|
|                                        |       |          |           | GG       | 729.00 (13.4603–39482.2443) | ≤0.0001**|

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Fig. 1. Chromatograms of SNPs taken from CI and CI div. I 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.

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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.
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.sbi.2022.103405.

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