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Original Article

Association between Mandibular Prognathism and Matrilin-1, Bone Morphogenic Protein, Tyr67Asn, Homeobox Protein Hox-A2, Rho-GTPase Activating Protein, and Myosin 1H Genes in the Indian Population

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Abstract

Introduction: Mandibular prognathism (MP) patients present with aesthetic concerns and functional issues, including difficulties in mastication and pronunciation. Studies revealed that mandibular prognathism had definitive Mendelian inheritance patterns. This study aimed to ascertain distinct genetic markers associated with mandibular prognathism in individuals of Indian descent, focusing on exploring the prevalent genetic variations associated with certain genes. This study sought to identify the association of the following gene markers with mandibular prognathism: 1) *Matrilin-1* (*MATN1*) (rs1065755), 2) Bone morphogenic protein 3 (*BMP-3*) (Tyr67Asn), 3) Homeobox protein hox-A2 (*HOXA2*) (Val327Ile), 4) Rho-GTPase activating protein (*ARHGAP 21*) (Gly1121Ser), 5) Myosin 1H (*MYO1H*) (rs10850110)

Materials and methods: Forty subjects (age group 18–30 years) were chosen based on their clinical examination, study model, and lateral cephalogram. Ten subjects had normal skeletal jaw-base relationships, and 30 had prognathic mandibles (skeletal class III jaw-base relationships). Two milliliters of blood were taken from each person. The genes, as mentioned above, associated with mandibular prognathism were studied.

To assess the association between genetic markers and mandibular prognathism, the following statistical tests were used: an unpaired *t*-test was used to compare the mean values of continuous variables between the normal and prognathic groups; a chi-square test was used to evaluate the association between genetic markers and the jaw-base relationship; and an odds ratio was used to assess the strength of association between genetic markers and the prognathic mandible. Statistical analyses were conducted using SPSS software.

Results: Out of five single nucleotide polymorphisms (SNP) selected in the study, namely rs10850110, rs1065755, rs111419738, rs143043350, and rs74764079, three SNPs—rs111419738, rs143043350, and rs74764079—did not show differences in the genotypes among the study and control samples. Thus, this indicates that these three SNPs may be related to mutations seen in MP in other populations but do not exhibit any association with the people covered in this study. The other two SNPs, rs10850110 and rs1065755, showed variant genotypes in control and study samples.

Conclusions: Our research found that rs10850110 and rs1065755 positively correlated with mandibular prognathism. Further studies are needed to see the association between these two restriction sites in MP subjects.

Keywords

candidate gene, class III malocclusion, genetic variant, mandible, prognathism, Matrilin-1

INTRODUCTION

Progenism, or mandibular prognathism (MP), is a craniofacial developmental condition. It is characterized by irregularities in the size, shape, and location of the individual bones. The anomaly is characterized by an excessive lower jaw protrusion that frequently coexists with insufficient upper jaw growth, causing problems with dental alignment. Complete mesial occlusion, a unique reverse overjet of the incisors, and two-sided buccal occlusion are their outward signs.[1] The usual facial profile caused by mandibular prognathism often prompts patients to seek orthodontic therapy, sometimes in conjunction with surgery. Early phenotypic observances are possible, and the phenotype becomes increasingly apparent with growth.[2]

The prevalence of MP differs based on ethnic background. The prevalence of mandibular prognathism varies among different populations. In Asian people, such as Chinese, Japanese, and Koreans, the prevalence ranges from 8% to 40%.[3] Sub-Saharan African individuals also exhibit a higher prevalence, ranging from 3% to 8%.[4] In contrast, individuals of European ethnicity are not frequently affected, with a prevalence ranging from 0.48% to 4%.[5-9] Environmental factors associated with MP include low oxygen levels, exposure to ionizing radiation, inadequate nutrition, metabolic and hormonal issues during pregnancy, and enlarged tonsils.[10]

The inheritance patterns of mandibular prognathism (MP) are diverse and have been suggested to include recessive[14,15], autosomal dominant[16,17], dominant with partial penetrance[11-13], and variable expressivity and penetrance, with variations observed among different ethnic groups[16]. Additionally, a polygenic threshold model has been proposed.[8] The precise contribution of genetic and environmental factors to the development of MP [2] is a subject that requires further clarification and study.

Genetic markers are genes or DNA codes that have a known place on a chromosome and can be used to tell people or species apart. Variations in the genetic locus may come from mutations or other changes. Some genetic markers are short DNA sequences, like the region surrounding a single nucleotide polymorphism with a single base-pair alteration, or an extensive DNA sequence, like a minisatellite. Genetic markers can help identify the genetic source of an inherited disease, such as a gene mutation that causes a defective protein. It is well known that DNA strands close together on a chromosome inherit genetic material. This feature allows the establishment of a marker to specify the inheritance pattern of a poorly localized gene. Numerous research studies have discovered a connection between the presence and incidence of mandibular prognathism and genetic markers, including *Matrilin-1*, bone morphogenic protein 3 (*BMP3*), homeobox protein hox-A2 (*HOXA2*), Rho-GTPase activating protein (*ARHGAP 21*), and *Myosin 1H* (*MYO1H*).

This case-control study aims to identify common genetic variations linked to specific genes and investigate their ties to the risk for MP.

MATERIALS AND METHODS

Forty people between the ages of 18 and 30 from the Bharati Vidyapeeth Dental College and Hospital in Pune and the Xcelris Laboratories in Ahmedabad participated in the study. The institution's Research Ethics Review Board approved the study. The case-control study had 30 MP patients (20 men and 10 women between the ages of 18 and 30; mean age was 24.73±3.10 years) and 10 healthy people with normal occlusion (2 men and 8 women between the ages of 18 and 30; mean age was 23.4±4.09 years) **(Table 1)**. Informed consent was obtained from all patients. All study participants had lateral cephalograms done with the same machine (PLANMECA [PM 2002]). A single author drew all of the lateral cephalograms. The lateral cephalograms of MP patients and the control group were analyzed using the

Table 1. Socio-demographic characteristics of the sample population

		Study Group n=30	Control group n=10	P value
Age, yrs		24.73±3.10	23.4±4.09	0.451*, not significant
Sex	Male	20 (66.6 %)	2 (20%)	0.047#, significant
	Female	10 (33.3 %)	8 (80%)	
Total		30 (100%)	10 (100%)	

* using unpaired t-test; # using chi-square test; $p>0.05$ – not significant; $p<0.05$ – significant; $p<0.001$ – highly significant

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Legan-Burstone analysis, focusing on the following points as well as jaw length:

- ANB: point A-nasion-point B angle,
- SNA: sella-nasion-point A angle, and
- SNB: sella-nasion-point B angle.

"Sella" refers to the midpoint of the sella turcica (a saddle-shaped depression in the sphenoid bone of the human skull), "nasion" is the midpoint of the frontonasal suture, "point A" is the deepest point on the anterior contour of the maxillary alveolar process, and "point B" is the deepest point on the anterior contour of the mandibular alveolar process.

Legan and Burstone's study showed that people in the control group had normal mandibular length and normal ANB (2±2 degrees), normal SNA (82±2 degrees), and normal SNB (80±2 degrees) angles. The study did not include patients with craniofacial conditions, such as cleft lip and palate, endocrine problems, tooth, number, morphology, eruption problems, face asymmetries, and cases with retrognathic maxilla.

For the genotyping of samples, 2 mL of venous blood was collected from the antecubital area of the arm, and DNA was extracted from each sample (Xcelgen blood DNA isolation kit by Xcelris Laboratory, Ahmedabad). We used synthetic primer sets to amplify extracted DNA in the PCR procedures for five different restriction sites:

1. Primers for the restriction site-containing area 10850110
   Forward TGTAAAACGACGGCCAGTGTGGTGGTATCTCATTGTGG
   Reverse CAGGAAACAGCTATGACCTCTAAAGCCAGGAGTTGGAGAC
2. Primers for the restriction site-containing area 1065755
   Forward TGTAAAACGACGGCCAGTAATATCCGGAGAGCACTGAG
   Reverse CAGGAAACAGCTATGACCGCTTCCAGTACAGGAAGTCACT
3. Primers for the restriction site-containing area: 74764079
   Forward TGTAAAACGACGGCCAGTAGAGAGACCGAAGCCACCTTT
   Reverse CAGGAAACAGCTATGACCAACTGGGCTTACAGGAGATG
4. Primers for the restriction site-containing area 143043350
   Forward TGTAAAACGACGGCCAGTGAAACTGGGTCAGGGAATCACT
   Reverse CAGGAAACAGCTATGACCTTTGAGCAAGCCCTTAGCGT
5. Primers for the restriction site-containing area 111419738
   Forward TGTAAAACGACGGCCAGTATGACTTGAGGAAATCCGGTGG
   Reverse CAGGAAACAGCTATGACCCGAGGATTCAGGTCCTATCA

The ABI 3730xl at Xcelris Laboratory sequenced all PCR products. ExoSAP (USB) purified the amplicons, and an ABI 3730xl Genetic Analyzer from Applied Biosystems in the US sequenced them. For sequencing, Big Dye Terminator v. 3.1 was employed. The sample's allele presence or absence was marked YES or NO, and the data was collected in percentage. The MP case and control allele frequencies were compared for distribution. In PCR, we employed synthetic primer sets to amplify isolated DNA.

To assess the association between genetic markers and mandibular prognathism, the following statistical tests were used: 1. An unpaired *t*-test was used to compare the mean values of continuous variables between the normal and prognathic groups; 2. A chi-square test was used to evaluate the association between genetic markers and jaw base relationships; and 3. An odds ratio test was used to assess the strength of association between genetic markers and prognathic mandible. Statistical analyses were conducted using SPSS software.

RESULTS

Differences in age between the two groups were not statistically significant. Still, they showed significant variations between both groups as regards the gender of the participants, indicated by a p-value of 0.047 in **Table 1**. **Table 2** depicts the mean values for SNA, SNB, and ANB angles, Wits appraisal, and overjet measurement performed between cases and controls. Comparison for each parameter separately amongst cases exhibited a highly significant difference between subjects and controls. **Table 3** shows the association of presence of various parameters between study group and control group. The odds ratio of 1.45 signifies that the individuals with SNP at rs10850110 were at 1.45 times higher risk of developing mandibular prognathism than those without mutation. The odds ratio of 2 signifies that the individuals with SNP at rs1065755 were at 2 times higher risk of developing mandibular prognathism than those without mutation. The distribution of SNP at rs111419738, rs143043350, rs74764079 among cases and controls were inconclusive due to absence of mutation. **Table 4** compares DNA modifications at two regions (rs10850110 and rs1065755) in MP subjects and controls. The presence of both mutation types in cases is 20%, while in controls, it is 0%. Single mutation types exist in 26.6% of patients and 40% of rules. The absence of both mutations is seen in 53.3% of subjects and 60% of controls, indicating protection against developing MP. **Table 5** depicts the genotype distribution in five restriction sites among cases and controls. In restriction site 10850110, the genotypes GA and AG were associated with a significantly increased risk of MP while the GG genotype was associated

with a decreased risk of MP. Percentage of samples showing GA and AG genotypes in the study group were 20% and 6.7%, respectively. In restriction site 1065755, the genotypes TC and TT were associated with a significantly increased risk of MP while the CC genotype was associated with a decreased risk of MP. Percentages of samples showing TC and TT genotypes in the study group were 26.7% and 6.7%, respectively. The three SNPs rs111419738, rs143043350, and rs74764079 did not show any differences in the genotypes among study and control samples. **Table 6** compares study and control group alleles per marker. MP individuals had an over-presented G allele at restriction site 10850110 (p=0.78). MP participants had an over-presented C allele at restriction site 1065755 (p=0.47).

Table 2. Comparison of SNA, SNB, ANB angles, Wits appraisal and overjet measurement between study group and control group, respectively

	Groups	N	Mean	Std. deviation	Unpaired t-test	p-value
SNA⁺	Study group	30	81.6	1.5	−0.289	0.776
	Control group	10	81.8	0.44		
SNB⁺	Study group	30	86.1	2.13	5.324	< 0.001**
	Control group	10	80.8	0.83		
ANB⁺	Study group	30	−4.5	1.37	−9.210	< 0.001**
	Control group	10	1.4	0.54		
WITS	Study group	30	9.0	5.17	−4.240	< 0.001**
	Control group	10	1.0	0.0		
OVERJET	Study group	30	−2.76	1.14	−9.428	<0.001**
	Control group	10	2.2	0.27		

* p<0.05 – significant difference; ** p<0.001 – highly significant difference; ⁺ANB: point A-nasion-point B angle; SNA: sella-nasion-point A angle; SNB: sella-nasion-point B angle

Table 3. Association of the presence of various parameters between study group and control group

		Study group n (%)	Control group n (%)	Odds Ratio (95% CI)	p-value
rs10850110 *Myosin 1H*	Present	8 (26.66 %)	2 (20%)	1.45	0.766, not significant
	Absent	22 (73.34%)	8 (80%)		
rs1065755 *Matrilin 1*	Present	10 (33.33 %)	2 (20%)	2	0.573, not significant
	Absent	20 (66.67 %)	8 (80%)		
rs111419738 *Rho-GTPase*	Present	0 (0 %)	0 (0 %)	-------	-------
	Absent	30 (100 %)	10 (100 %)		
rs143043350 *Homeobox 2*	Present	0 (0 %)	0 (0 %)	-------	-------
	Absent	30 (100 %)	10 (100 %)		
rs74764079 *BMP3*	Present	0 (0 %)	0 (0 %)	-------	-------
	Absent	30 (100 %)	10 (100 %)		

Table 4. Comparison of mutation at DNA region of primer 1 (rs10850110) and primer 2 (rs1065755) among study group and control group as a risk indicator

Risk	Study group	Control group	Odds Ratio	p-value*
High risk	6 (20 %)	0 (0%)		
Moderate risk	8 (26.6 %)	4 (40%)	2.43	0.038, significant
No risk	16 (53.3 %)	6 (60%)		
Total	30 (100%)	10 (100%)		

* chi-square test

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Table 5. Comparison of each genotype per marker in study group and control group, respectively

Marker	Genotype	Study group	Control group	Chi-square	Marker
rs10850110 *Myosin 1H*	GA	6 (20 %)	2 (20%)	0.356	*p*=0.837, no significant difference
	AG	2 (6.7 %)	0 (0%)		
	GG	22 (73.3%)	8 (80%)		
	Total	30 (100%)	10 (100%)		
rs1065755 *Matrilin-1*	CC	20 (66.7%)	8 (80%)	0.495	*p*=0.781, no significant difference
	TC	8 (26.7%)	2 (20%)		
	CT	0 (0%)	0 (0%)		
	TT	2 (6.7%)	0 (0%)		
	Total	30 (100%)	10 (100%)		
rs111419738 *Rho-GTPase*	CC	30 (100%)	10 (100%)	0.0	*p*=1.0, no significant difference
	Total	30 (100%)	10 (100%)		
rs143043350 *Homeobox 2*	C	30 (100%)	10 (100%)	0.0	*p*=1.0, no significant difference
	Total	30 (100%)	10 (100%)		
rs74764079 *BMP3*	T	30 (100%)	10 (100%)	0.0	*p*=1.0, no significant difference
	Total	30 (100%)	10 (100%)		

Table 6. Comparison of each allele per marker in study group and control group, respectively

Marker	Allele	Study group	Control group	Chi-square test	p-value
rs10850110 *Myosin 1H*	A	8 (13.3%)	2 (10%)	0.076	0.783, No significant difference
	G	52 (86.7%)	18 (90%)		
	Total	60 (100%)	20 (100%)		
rs1065755 *Matrilin-1*	C	48 (80%)	18 (90%)	0.519	0.471, No significant difference
	T	12 (20%)	2 (10%)		
	Total	60 (100%)	20 (100%)		
rs111419738 *Rho-GTPase*	C	60	20	---	---
	Total	60 (100%)	20 (100%)		
rs143043350 *Homeobox 2*	C	60	20	---	---
	Total	60 (100%)	20 (100%)		
rs74764079 *BMP3*	T	60	20	---	---
	Total	60 (100%)	20 (100%)		

DISCUSSION

Treating patients with MP [18] is challenging for orthodontists as it aims to improve facial aesthetics and address functional problems. Existing dental issues and attempts to hide disproportionate jaw bases limit treatment possibilities for these patients. Early orthodontic treatment patients may need surgery after growth.[18] Identifying class III MP patients earlier may assist orthodontists in planning future orthodontic care.[18] Identifying the mutation in the candidate gene responsible for the development of MP will help determine environmental factors leading to the prognathic phenotype and decide the scope of early treatment and prediction of the prognosis.

The non-collagenous chondrocytes secrete cartilage protein *Matrilin-1*. [19] TMJ condyle chondrocytes express *Matrilin-1* like the long bones.[20] *Matrilin-1* is crucial for synoviocyte chondrogenic development.[21] Newborn

mice's long bones, skull, and nasal septum bones contain *Matrilin-1*.[22] *Matrilin-1* knockout mice display abnormal type II collagen fibrillogenesis and fibrous organization.[23] Korean and Japanese studies found various backbone proteins on chromosome 1p36, including *Matrilin-1*. [21] No significant difference in rs1065755 SNP distribution between cases and controls was found (p=0.575). Individuals with the rs1065755 SNP often had a higher risk of MP than those without the mutation.

Our findings contradict Jang et al.[24] They compared the genotype distribution of MP and controls at three restriction sites in the Korean *Matrilin-1* gene to determine how mutation affects MP. They examined restriction sites rs20566, rs1149045, and rs1065755. The frequency of SNP at rs20566 and rs1065755 in patients was substantially more significant than that in controls. Restricting area 1065755 genes TC and TT also increased the MP risk. In contrast, the CC genotype lowered the MP risk.[24] The study by Lavi et al. demonstrated that the 354 T >C (rs20566) polymorphism in the exon 5 region of the *MATN1* gene, specifically the CC genotype, is a significant risk factor for class III skeletal malocclusion with mandibular prognathism in the Deutero-Malay population.[25]

Our investigation found no significant difference in SNP distribution at rs10850110 between patients and controls (p=0.766). The study group had 26.66% mutant samples compared to 20% in the control group. The study group had 73.34% mutation-free samples, while the control group had 80%. People with SNP at rs10850110 had a 1.45-fold increased risk of MP than those without mutation. Tassopoulou et al.[26] examined MP *MYO1H* genetic variation. Atteri et al. found a significant association between the rs10850110 polymorphism in the *MYO1H* gene and an increased risk of mandibular prognathism in a local population, with the G allele notably overrepresented in MP cases compared to the A allele.[27] Contrarily, Dalaie et al. reported no significant correlation between the rs10850110 and rs11611277 polymorphisms of the *MYO1H* gene and MP in the Iranian population.[28] However, they noted a lower frequency of these polymorphisms in the patient group, suggesting a potential association with mandibular retrognathism that warrants further investigation with a larger sample size. Milosevic et al. aimed to examine the association between *MATN1*, *MYO1H*, and *BMP-4* gene polymorphisms and MP in the Serbian population. Among 110 participants, only the *MYO1H* polymorphism showed a significant difference, with heterozygous carriers of the T allele having nearly a 3-fold increased risk of developing MP. No associations were found for *MATN1* and *BMP-4* polymorphisms, suggesting that *MYO1H* gene polymorphisms may be risk modulators for MP in Serbian patients.[29]

We examined allele frequency at 1p22.2 and found that the G allele was more common in MP cases than in controls (p=0.54). The genotypes GA and AG at restriction site 10850110 increased the MP risk, while GG significantly reduced it. The research samples had genotypes of GA and AG at frequencies of 20% and 6.7%, respectively. Our MP investigation found no statistically significant G allele at 1p22.2 frequency (p=0.78).

The study found no significant differences in rs111419738 SNP distribution between patients or controls and no changes in rs143043350 SNP distribution between patients and controls. Mutations in cases and controls did not cause the SNP at rs143043350. A unique Val327Ile variant was found in the *HOXA2* mutation[30], but MP lacked this variant. No Tyr67Asn variant in MP's *BMP3* gene was found, highlighting the need for further research on MP genetics in India. Not having enough sample size to verify statistical significance was one of our research limitations.

CONCLUSION

The study found no significant difference between cases and controls in the SNP distribution of the rs10850110 locus. However, the GA and AG genotypes were associated with MP risk, while the GG genotype was associated with MP. The rs1065755 locus had no significant difference between cases and controls, with TC and TT genotypes associated with MP risk. The study also found a positive association between mandibular protrusion and rs10850110 and rs1065755, but further research is needed to understand their interaction.

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Competing Interests

The authors have declared that no competing interests exist.

Author contributions

Anish Doke: carried out the research project; *Anand Sabane*: conceptualization; *Amol Patil*: conceptualization, observation, and writing; *Jayesh Rahalkar*: provided patients and data; *Tulsi Subramaniam*: writing and observation; *Monali Nikalje*: writing and observation.

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Связь между нижнечелюстным прогнатизмом и генами матрилина-1, костного морфогенетического белка, Tyr67Asn, Homeobox Protein Hox-A2, белка, активирующего Rho-GTPase, и миозина 1H в индийской популяции

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Резюме

Введение: Пациенты с прогнатизмом нижней челюсти (ПНЧ) сталкиваются с эстетическими проблемами и функциональными проблемами, включая трудности с жеванием и произношением. Исследования показали, что прогнатизм нижней челюсти имеет определённые менделевские модели наследования. Целью этого исследования было установление отдельных генетических маркеров, связанных с прогнатизмом нижней челюсти у лиц индийского происхождения, с упором на изучение распространённых генетических вариаций, связанных с определёнными генами. В этом исследовании была предпринята попытка выявить связь следующих генных маркеров с прогнатизмом нижней челюсти: 1) Matrilin-1 (MATN1) (rs1065755), 2) Bone morphogenic protein 3 (BMP-3) (Tyr67Asn), 3) Homeobox protein hox-A2 (HOXA2) (Val327Ile), 4) Rho-GTPase activating protein (ARHGAP 21) (Gly1121Ser), 5) Myosin 1H (MYO1H) (rs10850110).

Материалы и методы: Сорок субъектов (возрастная группа 18–30 лет) были выбраны на основе их клинического обследования, модели исследования и боковой цефалограммы. Десять субъектов имели нормальные скелетные соотношения челюстей и основания, а 30 имели прогнатические нижние челюсти (скелетные соотношения челюстей и основания III класса). У каждого человека было взято два миллилитра крови. Были изучены гены, как упоминалось выше, связанные с прогнатизмом нижней челюсти.

Для оценки связи между генетическими маркерами и прогнатизмом нижней челюсти использовались следующие статистические тесты: непарный t-тест использовался для сравнения средних значений непрерывных переменных между нормальной и прогнатической группами; тест хи-квадрат использовался для оценки связи между генетическими маркерами и соотношением челюсти и основания; и отношение шансов использовалось для оценки силы связи между генетическими маркерами и прогнатизмом нижней челюсти. Статистический анализ проводился с использованием программного обеспечения SPSS.

Результаты: Из пяти однонуклеотидных полиморфизмов (ОНП), выбранных в исследовании, а именно rs10850110, rs1065755, rs111419738, rs143043350 и rs74764079, три ОНП — rs111419738, rs143043350 и rs74764079 — не показали различий в генотипах среди исследуемых и контрольных образцов. Таким образом, это указывает на то, что эти три ОНП могут быть связаны с мутациями, наблюдаемыми при ПНЧ в других популяциях, но не показывают никакой связи с людьми, охваченными этим исследованием. Другие два ОНП, rs10850110 и rs1065755, показали вариантные генотипы в контрольных и исследуемых образцах.

Заключение: Наше исследование показало, что rs10850110 и rs1065755 положительно коррелируют с прогнатизмом нижней челюсти. Необходимы дальнейшие исследования, чтобы увидеть связь между этими двумя сайтами рестрикции у субъектов с ПНЧ.

Ключевые слова

ген-кандидат, класс III аномалии прикуса, генетический вариант, нижняя челюсть, прогнатизм, Matrilin-1

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