



## Review Article

## Association between growth hormone receptor gene polymorphism and craniofacial morphology – A review

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## ABSTRACT

Craniofacial development is a sophisticated process which has multiple genetic and epigenetic factors involved. Disturbance in the developmental process can cause morphologic and functional defects, which may also affect the psychological health of the individual. It is imperative for orthodontists to have a thorough knowledge about the growth of the face in general and of the maxilla and mandible in particular, to help modify growth and treat the skeletal malocclusions. Multiple genes have been implicated in the growth of the craniofacial complex, growth hormone receptor gene (GHR) being one of them. Growth hormone plays an important role in the post-natal development of an organism, both skeletal and soft tissue growth. Mutation of its receptor will affect the expression of the gene, and in turn influence the growth. Studies have shown that polymorphisms in the GHR gene receptors affect the morphology of the maxillomandibular skeleton. This article is a review about the polymorphisms of the GHR gene which affect the facial skeletal pattern.

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## 1. Introduction

The development of the face is a complex process, prone to increased disturbance due to the involvement of multiple genetic and environmental factors.<sup>1,2</sup> Defects in the development of the mandible and/or the maxilla can lead to various problems like malalignment of the teeth, functional disturbance, sleep apnea, and airway obstruction.<sup>3</sup> This may also affect the psychosocial health of the individual.<sup>4</sup>

Skeletal malocclusion may have varied presentation with micrognathia (small maxilla or mandible) being the common characteristic feature, affecting 1/1500 live births.<sup>3,5</sup> Though inheritance of vertical dimensions is higher than anteroposterior dimensions, sagittal discrepancies show familial inheritance.<sup>6</sup> They are caused by multiple factors including genetic and environmental influences.

About 150 genes/loci have been found to be associated with various craniofacial conditions, some of which include

MATN1, EPB41, growth hormone receptor, COL2A1, COL1A1, MYO1H, DUSP6, ARHGAP21, ADAMTS1, FGF23, FGFR2.<sup>2,5-9</sup>

Studies have shown that Skeletal Class III malocclusion maybe inherited in families in an autosomal dominant pattern and can also be caused by mutations in multiple genes.<sup>10</sup> Studies by Yamaguchi et al,<sup>11</sup> Cruz et al,<sup>12</sup> Xue et al,<sup>13</sup> Ikuno et al,<sup>14</sup> Liu et al,<sup>9</sup> Saito et al<sup>8</sup> show polymorphisms in multiple genes in Class III individuals including HSPG2, matrilin 1, MATN1, ALPL, HOX3, IGF, COL2A1, EPB41, MYO1H, DU,6,19,11SP6, GHR, PLXNA2, SSX2IP genes. They were mapped to various loci in chromosomes 1, 3, 6,11,12,19, etc. almost all mutations affected the mandibular size including mandibular ramus height, and body length.

Few studies on skeletal Class II malocclusion propose a genetic etiology for Class II Division 2 type. But there are no genome wide association studies (GWAS) to support this.<sup>10</sup>

Growth of an organism is regulated by growth factors and hormones. Growth hormone plays a major role in postnatal development of the organism both soft tissue and skeletal

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growth.<sup>15–18</sup> Studies have shown that hypersecretion of growth hormone causes gigantism and acromegaly, and hypo secretion causes dwarfism. It promotes postnatal longitudinal growth, and regulates lipid, carbohydrate, and also the immune system by regulating lymphocyte function and its function is facilitated by the Growth Hormone receptor<sup>16</sup>

Any mutation in the receptor will affect the expression of the hormone. This review aims to describe the relationship between growth hormone receptor gene polymorphism and craniofacial morphology.

## 2. Growth hormone and its receptor

Growth hormone (GH), a peptide, is synthesized and secreted by the somatotrophs (acidophilic cells) in the anterior pituitary gland. Its secretion is regulated by the growth hormone releasing hormone (GHRH) and somatostatin (hypothalamic hormones). GHRH binds to receptors on somatotrophs, which increases intracellular cAMP, which in turn causes secretion of GH. GH acts on liver, muscle, bone, and adipose tissue and other target tissues, and increases serum concentration of IGF-1. This has a growth promotion effect.<sup>1</sup>

Skeletal growth occurs by either membranous or endochondral ossification or both. GH and somatomedin have been shown to influence chondrocyte proliferation, and also has mitogenic effect and causes cellular differentiation and proliferation.<sup>16,19</sup>

GH also effects soft tissue proliferation and influences the differentiation and proliferation of myoblasts. GH/IGF-1 (growth hormone/insulin like growth factor) axis is an important physiological regulatory mechanism for post-natal skeletal muscle development.<sup>16,19</sup> GH has both direct and indirect effect on skeletal growth and development.

Growth hormone exerts its effects by Growth Hormone Receptors (GHR), which is a member of a large class of receptors known as the class 1 cytokine receptor superfamily.

Godowski et al<sup>20</sup> reported that the growth hormone receptor gene (GHR) has 9 exons that encode the receptor and several additional exons in the 5-prime untranslated region. The coding exons span at least 87 kilo base of chromosome 5. Exon 2 encodes the signal peptide, exons 3 through 7 encode the extracellular domain, exon 8 encodes the transmembrane domain, and exon 9 and part of exon 10 encode the intracellular domain

The receptors are present in various tissues like liver, muscle, adipose, mammary glands, bone, kidney, embryonic stem cells, etc. GH can cross blood brain barrier, and with increasing age, there is decrease in the binding of the hormone with receptors in brain. Receptors are also present in immune tissues like B-cell, T cells, lymphocytes and monocytes.

GHR is membrane bound, and has an extracellular region, a transmembrane domain, and an intracellular region. There is also a soluble, extracellular growth hormone binding protein (GHBP), present in the serum of humans. In humans, it is produced by limited proteolysis of GHR molecule and is found in liver, muscle and fat tissues. Studies show that 60% of circulating GH is bound to GHBP which acts as a reservoir of GH, maintaining its serum levels, even when its secretion is low. It thus increases the half-life of GH.

Single site in the human genome contains the sequence for GHR. It is present in the proximal short arm of chromosome 5 in region p13.1-p12.

Importance of GHR was first reported when “knockout” mice were created (mice with mutated GHR/GHBP gene) through homologous recombination. Portions of exon 4 and introns 4/5 were replaced with neoresistant gene. Homozygous mice showed post-natal growth retardation and dwarfism. They grew to only half the size of non-transgenic mice, and did not show any GHRs or GHBPs. They also had decreased IGF-1 levels and increased GH levels in serum. Heterozygous mice were slightly smaller than the non-transgenic mice, and showed decreased GHR, GHBPs and IGF-1 levels.<sup>16</sup>

## 3. GHR gene expression

Various factors like development, nutrition, and hormones seem to control the GHR gene expression.<sup>16</sup> Animal studies show that when chronic GH treatment was given to hypophysectomized sheep and rat, there was increased binding in hepatic tissues. And when no treatment was given there were reduced GHRs. Acute GH treatment in rats showed that there was an increase in the receptors initially, which then decreased to its normal level after a few hours. In humans, GHBP when given in a particular concentration, increased GHR mRNA, beyond which the level of GHR mRNA decreased.

Fasting and undernutrition causes GH resistance. There is increased levels of circulating GH and decreased IGF-1 levels. Glucose also has been shown play an important role –there is decreased GHR in the presence of GH, if glucose is removed form culture media.

## 4. A ssoiation between GHR gene and craniofacial morphology

Several studies have been done, in various ethnic populations, to assess the relationship between GHR gene and maxillomandibular parameters. Significant associations have been found between the gene and mandibular length/ramus length. Maxillary measurements did not show any significant association.

Study by Yamaguchi et al,<sup>21</sup> in 2001 evaluated the association between P561T SNP of the GHR gene and

craniofacial morphology. The sample consisted of 50 Japanese men and 50 Japanese women who were either volunteers or patients from dental hospitals. Whole blood was collected for DNA extraction and PCR. Lateral cephalograms were taken for each participant and 5 linear craniofacial measurements were used for analysis. Body height was also recorded for each participant. Results showed that there was a significant correlation of mandibular ramus length (Co-Go), and the ratio of Co-Go to height to P561T variant. It was concluded that normal Japanese population with P561T had a decreased mandibular ramus length.

Zhou et al,<sup>22</sup> in 2005 studied the relationship between GHR gene polymorphisms and mandibular morphology in two major Han Chinese population. The first population consisted of 95 volunteers from among University students and the second population consisted of 50 patients from Beijing stomatology Hospital with either short or long mandibular ramus height. Peripheral blood leukocytes were used to extract genomic DNA and craniofacial measurements were made from standardized lateral cephalograms. Four SNPs of GHR gene were selected – G168G, C422F, I526L and P561T. Significant correlation was found between I526L and mandibular ramus height. Individuals with genotype CC had increased ramus lengths compared to those with genotype AC or AA, in the first population. Haplotype analysis in the second population, reinforced the association between I526L and ramus length.

Kang et al,<sup>23</sup> in 2009 conducted a study in Korean Population – 100 men and 59 women who were either volunteers from the Pusan area or patients at dental hospitals. Among the participants, 87 had Class I, 44 Class II and 28 Class III skeletal pattern. Maxillomandibular and cranial measurements were made from standardized lateral cephalograms. DNA samples of 24 Han Chinese, 24 African-Americans, 24 European-Americans, and 24 Hispanics, were collected from the Coriell Cell Repository and were used as references for allelic frequencies of GHR polymorphism assessed in this study.

Genomic DNA, extracted from buccal swab, was used to obtain two common isoforms of GHR - full length (fl-GHR) and lacking extracellular domain (d3-GHR) which was coded by exon 3, and also for genotypes C422F, S473S, P477T, and I561T of GHR in exon 10. Cranial base length, overall mandibular length, mandibular corpus length, mandibular ramus height and maxillary length were measured from the lateral cephalograms. Association was found between P561T and C422F SNPs and mandibular ramus height. d3/fl-GHR polymorphism was found to have diverse frequency in different populations.

Association between SNP in GHR gene and mandibular growth in early childhood was studied by Sasaki et al,<sup>24</sup> in 2009. The sample consisted of 16 male and 17 female children between the ages 3-12 years, with mandibular

protrusion, and 14 normal male and 13 normal female children with Class I occlusion between the ages 3-13 years. Subjects who had maxillary protrusion were excluded. For DNA extraction, sample was collected from buccal swabs. Wild type and heterozygous mutation of P561T was determined. 101 lateral cephalograms from 24 subjects with mandibular protrusion and 17 normal subjects were analyzed. Remaining subjects were excluded due to lack of radiograph. Ramus length, mandibular body length, mandibular length, maxillary length and angular measurement of Ar-Go-Mn were measured. There was no statistically significant result in the difference between frequency of P561T variants between normal subjects and patients with mandibular protrusion. But when compared with Japanese norms of mandibular parameters from previous studies, linear mandibular measurements were found to be smaller in subjects with heterozygous mutation than in normal or wild types.

Tomoyasu et al,<sup>25</sup> in 2009 carried out a study to evaluate the association between 5 SNPs of GHR and craniofacial parameters. 167 Japanese subjects were included in the study which comprised of 50 men and 117 women. Genomic DNA was obtained from buccal swabs of all participants. Lateral cephalogram was used for craniofacial measurements. DNA samples were obtained from the Coriell Cell Repository for 24 Han Chinese, 24 African Americans, 24 European Americans and 24 Hispanics, to compare the allelic frequencies of the SNPs. 5 SNPs were evaluated – C422F, S473S, P477T, I526L and P561T. Body height, maxillary length, overall mandibular length, mandibular corpus length, mandibular ramus height, and cranial base length were measured. Significant association was found between P561T and C422F variants and mandibular ramus height. Those with genotype GG of C422F and CC of P561T had greater mandibular height than those with genotypes GT and CA. Sample collected from subjects of other ethnicities showed that they have different frequencies in exon 10 of GHR when compared to those of Japanese.

A study was conducted in Turkish population, by Bayram et al,<sup>26</sup> in 2014. The subjects comprised of 99 Class III patients with mandibular prognathism who were planned to undergo or had already undergone orthognathic surgery, and 99 patients with normal occlusion. Peripheral blood leukocytes were used for DNA extraction and P561T and C422F variants of GHR gene were obtained. Cranial and maxillomandibular parameters were measured from standardized lateral cephalograms. The two population did not show any difference in the frequency of P561T and C422F variants. Effective mandibular length and lower facial height were found to be associated with P561T. Correlation was also found between body height and all mandibular measurements, being highest with effective mandibular length. Subjects with longer mandible and

**Table 1:**

Study	Study population	Sample for dna	SnP	Genotype	Phenotype
Yamaguchi, 2001	Japanese, 50 male, 50 female	Blood	P561T		Decreased Ramus height
Zhou, 2005	145 Han Chinese	Blood	I526L	CC	Increased Ramus length
Tomoyasu, 2009	Japanese, 50 men, 170 women	Buccal swab	P561T C422F	CC GG	Increased Ramus height Increased Ramus height
Sasaki, 2009	Japanese, 16 male, 17 female children with mandibular protrusion, 14 male, 13 female normal children	Buccal swab	P561T		Decreased mandibular growth
Kang, 2009	Korean, 100 men, 59 women - 87 Class I, 44 Class II, 28 Class III	Buccal swab	P561T C422F		Associated with Ramus height
Bayram, 2014	Turkish, 99 Class III, 99 Class I	Blood	P561T	CA	Increased mandibular length, Increased lower facial height
Arroyave, 2017	Columbian, 306 Class I, II, III	Saliva	P561T	CA	Decreased ANB Increased mandibular body length Class III

SNP – Single Nucleotide Polymorphism

longer lower facial height had genotype CA than those who had genotype CC.

Arroyave et al,<sup>27</sup> in 2017 carried out a study in Columbian population. 306 subjects participated in the study between the ages of 15 and 53 years, who had attained completion stage of the cervical vertebral maturation. Saliva sample and lateral cephalogram were obtained for each participant. The participants were classified into Class I, Class II and Class III skeletal facial profile based on lateral cephalometric parameters. Various linear and angular measurements were recorded. DNA extraction was done from the saliva, and genotypes of P561T and I526L SNPs were identified. Rs6184 polymorphism was found to have a significant association with skeletal facial profile. Individuals with Genotype CA of P561T had Class III profile. Regardless of the diagnosis group, all individuals with this genotype had significantly larger mandibular body length and mandibular length, and smaller ANB angle. No significant relation was found between I526L and the skeletal facial profiles of the participants.

Summary of these studies is presented in Table 1

## 5. Conclusion

Successful treatment of any malocclusion is dependent on the appropriate diagnosis of the etiology. Recent advances in diagnosis and genetics have paved a path for better understanding the problem in a holistic manner which can improve the probability of achieving all treatment goals.

Growth hormone is one of the major factors in general and craniofacial growth. Identifying any mutation or polymorphism in the growth hormone receptor gene will aid

in timely interception of skeletal dentofacial deformities.

## 6. Abbreviations

GH - Growth hormone, GHR – Growth hormone receptor, GHRH – Growth hormone releasing hormone, IGF 1 – Insulin like growth factor 1, GHBP – Growth hormone binding protein, SNP Single nucleotide polymorphism.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

## References

1. Wilkie AOM, Morriss-Kay GM. Genetics of craniofacial development and malformation. *Nat Rev Genet.* 2001;2(6):458–68.
2. Tomaszewska A, Kopczynski P, Fliieger R. Genetic basis of mandibular prognathism. *Arch Biomed Sci.* 2013;1(2):16–9.
3. Joshi N, Hamdan AM, Fakhouri WD. Skeletal malocclusion: a developmental disorder with a life-long morbidity. *J Clin Med Res.* 2014;6(6):399.
4. Garg K, Tripathi T, Rai P, Sharma N, Kanase A. Prospective evaluation of psychosocial impact after one year of orthodontic treatment using PIDAQ adapted for indian population. *Journal of clinical;*11(8):ZC44.
5. Doraczynska-Kowalik A, Nelke KH, Pawlak W, Sasiadek MM, Gerber H. Genetic Factors Involved in Mandibular Prognathism. *J Craniofac Surg.* 2017;28(5):e422–31.
6. Cakan DG, Ulkur F, Taner TU. The genetic basis of facial skeletal characteristics and its relation with orthodontics. *Eur J Dent.* 2012;6:340.
7. Uribe LMM, Miller SF. Genetics of the dentofacial variation in human malocclusion. *Orthod Craniofac Res.* 2015;18:91–9.

8. Saito F, Kajii TS, Oka A, Ikuno K, Iida J. Genome-wide association study for mandibular prognathism using microsatellite and pooled DNA method. *Am J Orthod Dentofac Orthoped.* 2017;152(3):382–8.
9. Liu H, Wu C, Lin J, Shao J, Chen Q, Luo E, et al. Genetic etiology in nonsyndromic mandibular prognathism. *J Craniofac Surg.* 2017;28(1):161–9.
10. Hartsfield JK, Jacob GJ, Morford LA. Heredity, genetics and orthodontics: How much has this research really helped? *Semin Orthodont.* 2017;23(4):336–47.
11. Yamaguchi T, Park SB, Narita A, Maki K, Inoue I. Genome-wide Linkage Analysis of Mandibular Prognathism in Korean and Japanese Patients. *J Dent Res.* 2005;84(3):255–9.
12. Cruz CV, Mattos CT, Maia JC, Granjeiro JM, Reis MF, Mucha JN, et al. Genetic polymorphisms underlying the skeletal Class III phenotype. *American Journal of Orthodontics and Dentofacial Orthopedics.* 2017;151(4):700–707.
13. Xue F, Wong RWK, Rabie ABM. Genes, genetics, and Class III malocclusion. *Orthod Craniofac Res.* 2010;13(2):69–74.
14. Ikuno K, Kajii TS, Oka A, Inoko H, Ishikawa H, Iida J, et al. Microsatellite genome-wide association study for mandibular prognathism. *Am J Orthod Dentofac Orthoped.* 2014;145(6):757–62.
15. Piwien-Pilipuk G, Huo JS, Schwartz J. Growth Hormone Signal Transduction. *J Pediatr Endocrinol Metab.* 2002;15(6):771–86.
16. Kopchick JJ, Andry JM. Growth Hormone (GH), GH Receptor, and Signal Transduction. *Mol Genet Metab.* 2000;71:293–314.
17. Lupu F, Terwilliger JD, Lee K, Segre GV, Efstratiadis A. Roles of Growth Hormone and Insulin-like Growth Factor 1 in Mouse Postnatal Growth. *Dev Biol.* 2001;229:141–62.
18. Davidopoulou S, Chatzigianni A. Craniofacial morphology and dental maturity in children with reduced somatic growth of different aetiology and the effect of growth hormone treatment. *Prog Orthodont.* 2017;18(1):1–8.
19. Crenshawl P, Murray JD, Pomp D. The epigenetic influence of growth hormone on skeletal development. *Growth, Dev Aging.* 1993;57:163–82.
20. Godowski PJ, Leung DW, Meacham LR, Galgani JP, Hellmiss R, Keret R, et al. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. *Proce National Acad Sci.* 1989;86(20):8083–7.
21. Yamaguchi T, Maki K, Shibasaki Y. Growth hormone receptor gene variant and mandibular height in the normal Japanese population. *Am J Orthodont Dentofac Orthop.* 2001;119(6):650–3.
22. Zhou J, Lu Y, Gao XH, Chen YC, Lu JJ, Bai YX, et al. The Growth Hormone Receptor Gene is Associated with Mandibular Height in a Chinese Population. *J Dent Res.* 2005;84(11):1052–6.
23. Kang EH, Yamaguchi T, Tajima A, Nakajima T, Tomoyasu Y, Watanabe M, et al. Association of the growth hormone receptor gene polymorphisms with mandibular height in a Korean population. *Arch Oral Biol.* 2009;54(6):556–62.
24. Sasaki Y, Satoh K, Hayasaki H, Fukumoto S, Fujiwara T, Nonaka K, et al. The P561T polymorphism of the growth hormone receptor gene has an inhibitory effect on mandibular growth in young children. *Eur J Orthod.* 2009;31(5):536–41.
25. Tomoyasu Y, Yamaguchi T, Tajima A, Nakajima T, Inoue I, Maki K, et al. Further evidence for an association between mandibular height and the growth hormone receptor gene in a Japanese population. *Am J Orthod Dentofac Orthoped.* 2009;136(4):536–41.
26. Bayram S, Basciftci FA, Kurar E. Relationship between P561T and C422F polymorphisms in growth hormone receptor gene and mandibular prognathism. *Angle Orthod.* 2014;84(5):803–9.
27. Tobón-Arroyave SI, Jiménez-Arbeláez GA, Alvarado-Gómez VA, Isaza-Guzmán DM, Flórez-Moreno GA, Pérez-Cano MI, et al. Association analysis between rs6184 and rs6180 polymorphisms of growth hormone receptor gene regarding skeletal-facial profile in a Colombian population. *Eur J Orthod.* 2018;40(4):378–86.

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