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Review Article

ACTN3 gene variations in various Ethnic populations and its association with Skeletal Malocclusion – A Literature Review

Ashwin Mathew George[1], Nagachandran K.S.[2], Sumathi Felicita.A[3], Vijayashree Priyadarshini. J[4], Anitha. P[5]

[1,2,3]Professor, Department of Orthodontics, Saveetha Dental College and Hospital.

[4]Associate Professor, [5]Research Scholar, Clinical Genetics Lab, Centre for Cellular and Molecular research, Saveetha Dental College and Hospital.

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Abstract: Genetic etiology of Skeletal Malocclusion has been explored extensively over recent years with the advent of advances in molecular technologies. Studies have reported that the masticatory muscles regulate skeletal development and few recent works of literature report that the muscle growth regulators influence the facial proportions in sagittal and vertical dimensions in Skeletal Class II malocclusion. This review is a humble attempt to highlight the role of one such muscle gene known as ACTN3 and its association with Skeletal Class II malocclusion.

Keywords: Genetics, ACTN3 gene, polymorphism, masseter muscle, facial height, malocclusion.

Address for Correspondence:

Nagachandran K.S., MDS

Professor, Department of Orthodontics,

Saveetha Dental College and Hospital,

Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University,

Chennai, TamilNadu, India

Email: orthodrnaga21@gmail.com

Phone: +91-9884152660

Introduction:

Malocclusion is a developmental condition influenced by genetic and environmental factors. The role of heredity on malocclusion is a much-discussed topic with multiple genetic factors exerting its influence on teeth, bones and musculature.[1] Although skeletal Class III malocclusion has proven to be commonly associated with genetic inheritance [2], the role of genetic factors influencing skeletal Class II malocclusions has also been reported in a few studies recently. Some of the genes that contribute to Skeletal Class II malocclusions include ACTN3, GHR, FGFR2, MSX1, MATN1, MYOH1, KAT6B, HDAC4, and AJUBA.[3] Among all the above-mentioned genes, recently more focus has been given to the ACTN3 gene variants which contribute to Skeletal Class II malocclusions in human subjects based on the Sagittal and Vertical dimensions resulting in variation in the facial height proportions caused due to transcription factors controlling muscle morphology.[4]

The present review was conducted to highlight the significance of the ACTN3 gene in human masticatory muscle development, especially the masseter muscle and its variations which plays a key role in determining facial height.

Masticatory Muscle Fibre types:

Human skeletal muscle is heterogeneous in nature and made up of two basic fibre types: Type I and Type II. Type II fibres are further divided into IIA and IIX based on the results of ATPase histochemical staining, where these fibres differ in terms of their maximum rate of shortening. Type I fibres display the slowest contractile properties while Type IIX display the fastest.[5] With respect to their histochemical properties, Type I fibres are high in oxidative enzymes but low in glycolytic enzymes, while Type IIX and IIA fibres with intermediate properties have high glycolytic activity and low oxidative activity. [6]

The multi-pennate intramuscular architecture of the masseter muscle fibre exhibits different biomechanical properties when compared to other skeletal muscles of the human body. This difference may be because embryologically, the masticatory muscles in the craniofacial region were derived from the neural crest cells that might have a characteristic fiber property which is deviant from the other skeletal muscle tissues.

Each muscle fibre is composed of long tubes (myofibrils) which in turn are composed of actin (thin) and myosin (thick filaments) whose arrangement is parallel to each other and contract when the thin filament slides past the thick filament. Actin filaments are stabilized by actin-binding proteins known as actinins (two main types- α-actinin 2 and α-actinin 3), which are related to dystrophin. [7]

Studies have revealed differences among existing musculature, with human jaw muscles containing a greater number of ATPase intermediate fibres and type IIC fibres than limb muscles. [8] Similarly, Type I fibres of the masseter muscle contain slow-acting myosin, whereas type II fibres contain fast-acting myosin, and this jaw closure muscle also contains neonatal myosin heavy chain (MHC) isoenzyme.

Sciote et al investigated the properties of human masseter muscle fibres in various sagittal, vertical malocclusions and proposed that both the types of fibres were closely related to variations in vertical facial growth rather than sagittal growth.[9]

Variation in size and tissue proportion of type II muscle fibres had a significant effect in the vertical malocclusion where deep bite individuals had different muscle fibre types in terms of fibre size and percent tissue occupancy. These muscle

fibre types might function differently to interact with growth factors to establish the craniofacial skeleton with various heights in the form of short or long face.

Thus, the importance of the muscle fibre types which contribute to the growth of skeletal structures especially the mandible during postnatal development in altering the vertical orientation of the face should be taken into consideration. Though the regulation of facial vertical growth is influenced by the genetic makeup of the individual, environmental factors such as masticatory forces, dietary habits, and chewing patterns might have a substantial effect in redirecting the direction of mandibular growth. Myosin, which comes in many isoforms, is primarily responsible for the masticatory muscles' ability to contract, especially the masseter muscle. These myosin heavy chains (MHC) proteins can undergo adaptive changes during development depending upon the functional requirement. Nevertheless, one should consider the fact that both genetic and epigenetic factors intermingle in the characterization of overall vertical facial growth, of which the role of "muscle genes" is emphasised in recent craniofacial research. Hence muscle genes might play a significant influence in determining the fibre types which interact with environmental conditions contributing to different facial types. Strong activity in the masseter muscle is linked to an anteriorly inclined, prognathic mandible with a tendency of a large open bite whereas weak activity in the masseter muscle is linked to a posteriorly inclined mandible with a tendency toward an anterior open bite. Histologic analysis of the masseter, temporal and medial pterygoid muscles, when compared with the lateral pterygoid (predominantly type I fibres) and digastric (predominantly type II fibres) have shown a more heterogenous fibre proportion indicating a significant difference between the fibres. The smaller Type II fibres might reflect an evolutionary change in masticatory habits in adaptation to soft food. High correlation between masseter muscle morphology, facial skeleton dimensions and bite force was seen in relation to their cross-sectional areas and facial heights.

Muscle growth regulators (Genes) and their influence on fibre properties:

The main factor to be considered is how genes influence the proportion of these muscle fibres. It is generally believed that the genomes of two randomly selected individuals show 99.5% similarity or contain 0.5% variation, this difference is known as “Polymorphism”. These differences arise because of gene changes such as short and variable number tandem repeats, deletion or insertion polymorphisms and Single Nucleotide Polymorphisms (SNP’s).

Skeletal muscle alpha-actinins are encoded by ACTN2 (all fibres) and ACTN3 (Type II fibres) genes. The protein component of the sarcomeric Z line is alpha actinins, which form a lattice structure that anchors thin filaments in skeletal muscle fibres and stabilises the muscle contractile apparatus.[10]

ACTN3 gene (Alpha-Actinin 3) encodes a gene located in Human Chromosome 11q13.2 whose size is about 16,940 bases (Fig 1) and is responsible for generation of increased force velocities. It contains two alleles: 577R, which is the normal functional version and 577X, which contains a sequence change preventing complete protein production. [11] This results in different proportion of Type I and Type II fibres in different individuals.[12] The R577X Polymorphism results in the absence of ACTN3, which leads to diminished fast contractile ability, enhanced endurance performance and reduced bone mass or density. This deficiency occurs in an estimated 1.5 billion people worldwide and results in reduced muscle strength and a shift towards a more efficient oxidative metabolism.

Alfred et al concluded in a meta-analysis study that the ACTN3 R577X RR genotype is predominantly found in Europeans but not related to athletic functionality in the general population.[13] Moreover, results from the published literature do not support the hypothesis that the X allele is beneficial to endurance athletic status. Similar studies by Vincent et al on its

association with fast glycolytic type IIx muscle fibres have reported that individuals with the RR genotype had a higher percentage surface and number of IIx fibres than those with the XX genotype.[14]

These data suggest that the prevalence of ACTN3 gene variations in different populations should be explored further.

Prevalence of ACTN3 Gene variations in populations:

From an evolutionary perspective, the mammalian ACTN3 gene appears to have descended from a gene duplication that occurred 310 million years ago, and the ACTN3 577X substitution occurred between 40,000 and 60,000 years ago, when modern humans migrated to Europe and Asia. In the recent past, demographic HapMap data reveals that the global latitudinal gradient might have influenced the differences in the frequency of ACTN3 577X genotype. [15]

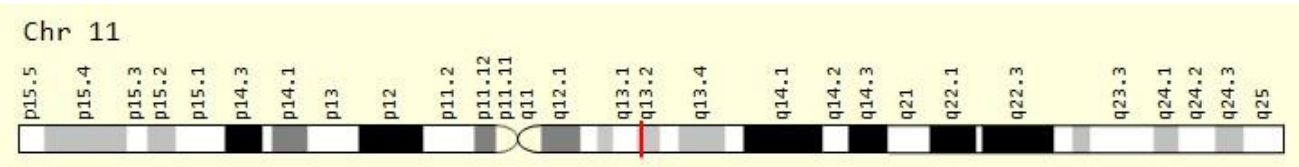
It has been demonstrated that ACTN3 (α-actinin–3) deficiency is common in the general population with the frequency of the alpha-actinin-3–deficient genotype being highest (25%) in the Asian population, 18% in Europeans and less than 1% in African Bantu populations. [16] Approximately 20% to 30% of the population has two mutant genes (X/X genotype), and individuals with one or two copies of the variant gene have no discernible effect. The ACTN3 577X mutated gene frequencies have been reported in different populations (Table 1).

Table 1: Frequencies of ACTN3 577X and 577R alleles in different populations

Population	Allele frequency of 577X	Allele frequency of 577R
Asian	0.50	0.50
Javanese	0.54	0.46
Asian-Americans	0.52	0.48
Native American	0.43	0.57
Hispanic	0.41	0.59
European White	0.42	0.58
North Indian	0.48	0.52
Iranian	0.44	0.56
Aboriginal Australian	0.29	0.71
African American	0.27	0.73
African	0.16	0.84
African Bantu	0.10	0.90

Courtesy: Prevalence of ACTN3 (the athlete gene) R577X polymorphism in Iranian population. [17]

Fig 1: Cytogenetic band of ACTN3 gene located in Chromosome 11q13.2



ACTN3 gene and its association with Skeletal Malocclusion:

ACTN3 gene and its single nucleotide polymorphism are of particular interest in skeletal muscle morphology and have been extensively studied in sports athletics. Several studies have shown the lower prevalence rate of ACTN3 XX gene in sprinters with the opposite seen in endurance athletes. Yang et al displayed a highly significant relationship between ACTN3 genotype and athletic performance by genotyping multiple athletes and controls from 14 sports. They reported elite sprint athletes to have a higher frequency of 577R allele, with the frequency differing in females where greater heterozygotes were found among sprint athletes.[16]

Researchers have focused on the role of the ACTN3 gene in the craniofacial region for its effect in determining the masticatory muscle especially masseter muscle fiber type and its consequence in the etiology of skeletal problems. Studies evaluating its genetic variations have been conducted in patients undergoing orthognathic corrections. [9] Results have shown that decreased fibre diameter was seen in association with open bite malocclusion and the opposite in deep bite malocclusion. Greater Type II fibre occupancy in the masseter muscle may have resulted in this outcome despite the smaller size of the fibre. Zebrick et al assessed the prevalence of two SNP's located at rs1815739and rs678397 (both being C-T transitions) in ACTN3 and reported ACTN3 577XX to be diminished in subjects with deep bite malocclusions, suggesting that muscle fibres variations can lead to differences in facial heights.[4]

RT-PCR (Reverse Transcription Polymerase Chain Reaction) studies have shown that ACTN2 levels remain unchanged in the 577XX genotype even when ACTN3 levels have reduced to miniscule volumes. These findings suggest that ACTN2 may not compensate for the absence of ACTN3 gene in the masseter. Significant differences in the SNPs have been studied between Class II skeletal problems and controls.

Kuchler et al conducted studies on bruxism in children and observed its association with genetic polymorphisms in the ACTN3 gene.[18] It has been reported that masticatory muscle contraction especially masseter muscle is involved in the manifestation of bruxism habit.[19] Studies have shown that the ACTN3 gene is only expressed in fast-acting glycolytic skeletal muscle fibres and its variations such as ACTN3 577X polymorphism have been associated with muscle endurance in humans. [20,21] It has been observed that the shape and size of the different muscles in the head and neck can profoundly influence the variation of the facial form. The masseter is the main muscle that can influence skeletal changes when compared to other muscles of the head and neck.

Killiardis et al, in an animal study compared the morphological changes of anterior deep and digastric muscles in 40 male albino rats divided into 3 groups by grouping the muscle fibers using their staining characteristics into 4 types, type I, type II (type IIA and type IIB), between these two types were the intermediate staining ones. [22] Final samples from both groups were dissected at the end of the experiment's 28-day duration and prepared for enzyme histochemistry. A small percentage of Type IIA fibres, large percentage of Type IIB was seen in the rats which followed a soft diet emphasizing the role of the functional demands on influencing muscle size and function.

Eriksson et al performed an extensive analysis of the medial pterygoid, masseter and temporalis muscle in young adults and found differing fibre types at different portions in relation to their functional demand. The fibre composition was also

different between regions with greater heterogenous distribution seen in the jaw-closing muscles reflecting evolutionary changes in the masticatory habits, such as adaptation to refined soft food. [23]

On calculating the mechanical advantage of the human temporalis and masseter, it was determined that patients with the short-face syndrome had greater bite force. Morphological differences between the short and long-face syndromes also result in an increased mechanical advantage for the adductor muscles of the short face patient, with the exception of a decreased temporalis mechanical advantage when ramus height is less. [24]
Cross-sectional dimensions of the masseter, medial pterygoid and anterior temporalis reported a reduction of 30%, 22% and 15% respectively in the vertical grower when compared to controls indicating the role of facial heights in muscle size and bite force. [25]

When the cross-sectional area, volume, width, thickness and length of contracted masseter using 3D-ultrasonography and correlation of these measurements are made with changes in facial morphology it was found a relevant negative correlation between volume and inclination of mandible including gonial angle and a significant positive correlation with ramus length and total posterior facial height suggesting that masseter muscle thickness can influence the growth pattern and posterior facial height.[26]

It has been hypothesized that ACTN3 gene polymorphism is associated with smaller diameters of fast-acting type II human masseter muscles and its metabolic function. [4] Hence further research on ACTN3 polymorphism in the Indian population might throw light on the probable genetic causation of Skeletal Class II malocclusion which is more prevalent in this population.

Conclusion:

ACTN3 gene variation has a major role in the human masticatory muscle pattern especially masseter muscle during its development as well as in its functions which might contribute to various facial growth patterns such as horizontal or vertical growers.

ACTN3 577XX polymorphism is disproportionately represented in skeletal class II malocclusions, implying a biological influence during bone growth and varying with influence in subjects with different vertical height growth patterns. Such genetic variations indicate the presence of muscle differences contributing to varying facial heights and can aid in the diagnosis of skeletal Class II malocclusions. Further studies correlating the genotypes with mRNA levels in analyzing the prevalence of different SNPs responsible for variation infacial morphology along with ACTN3 will confirm the effect of ACTN3 in influencing facial height morphology.

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Conflict of Interest:
The authors have no conflict of interests to declare.

References:

1) Sciote JJ, Raoul G, Ferri J, Close J, Horton MJ, Rowlerson A. Masseter function and skeletal malocclusion. Rev Stomatol Chir Maxillofac 2013;114:79-85.
2) Xue F, Wong RW, Rabie AB. Genes, genetics, and Class III malocclusion. Orthod Craniofac Res. 2010;13(2):69-74.
3) George AM, Felicita AS, Milling Tania SD, Priyadharsini JV. Systematic review on the genetic factors associated with skeletal Class II malocclusion. Indian J Dent Res. 2021;32(3):399-406.
4) Zebrick B, Teeramongkolgul T, Nicot R, Horton MJ, Raoul G, Ferri J, Sciote JJ. ACTN3 R577X genotypes associate with Class II and deep bite malocclusions. Am Orthod Dentofac Orthop 2014;146:603-611.
5) Bottinelli R, Reggiani C. Human skeletal muscle fibres: molecular and functional diversity. Prog Biophys Mol Biol. 2000;73(2-4):195-262.
6) Essén B, Jansson E, Henriksson J, Taylor AW, Saltin B- Essén B, Jansson E. Metabolic characteristics of fiber types in human skeletal muscle. Acta Physiol Scand. 1975;95(2):153-65.
7) Blanchard A, Ohanian V, Critchley D. The structure and function of alpha-actinin. J Muscle Res Cell Motil. 1989;10(4):280-9.
8) Hannam AG, McMillan AS. Internal organization in the human jaw muscles. Crit Rev Oral Biol Med. 1994;5(1):55-89.
9) Sciote JJ, Horton MJ, Rowlerson AM, Ferri J, Close JM, Raoul G. Human masseter muscle fiber type properties, skeletal malocclusions, and muscle growth factor expression. J Oral Maxillofac Surg. 2012;70(2):440-8.
10) Scott W, Stevens J, Binder-Macleod SA. Human skeletal muscle fiber type classifications. Phys Ther. 2001;81(11):1810-6.
11) Ahmetov II, Druzhevskaya AM, Lyubaeva EV, Popov DV, Vinogradova OL, Williams AG. The dependence of preferred competitive racing distance on muscle fibre type composition and ACTN3 genotype in speed skaters. Exp Physiol. 2011;96(12):1302-10.
12) Ahmetov II, Vinogradova OL, Williams AG. Gene polymorphisms and fiber-type composition of human skeletal muscle. Int J Sport Nutr Exerc Metab. 2012;22(4):292-303.
13) Alfred T, Ben-Shlomo Y, Cooper R, Hardy R, Cooper C, Deary IJ, Gunnell D, Harris SE, Kumari M, Martin RM, Moran CN, Pitsiladis YP, Ring SM, Sayer AA, Smith GD, Starr JM, Kuh D, Day IN; HALCyon study team. ACTN3 genotype, athletic status, and life course physical capability: meta-analysis of the published literature and findings from nine studies. Hum Mutat. 2011;32(9):1008-18.
14) Vincent B, De Bock K, Ramaekers M, Van den Eede E, Van Leemputte M, Hespel P, Thomis MA. ACTN3 (R577X) genotype is associated with fiber type distribution. Physiol Genomics. 2007;19;32(1):58-63.
15) Friedlander SM, Herrmann AL, Lowry DP, Mepham ER, Lek M, North KN, Organ CL. ACTN3 allele frequency in humans covaries with global latitudinal gradient. PLoS One. 2013;8(1):e52282.
16) Yang N, MacArthur DG, Gulbin JP, Hahn AG, Beggs AH, Easteal S, North K. ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet. 2003;73(3):627-31.
17) Fattahi Z, Najmabadi H. Prevalence of ACTN3 (the athlete gene) R577X polymorphism in Iranian population. Iran Red Crescent Med J. 2012;14(10):617-622

18) Calvano Küchler E, Arid J, Palinkas M, Ayumi Omori M, de Lara RM, Napolitano Gonçalves LM, Hallak Regalo SC, Paes Torres Mantovani C, Rezende Vieira A, Diaz-Serrano K. Genetic Polymorphisms in *ACTN3* Contribute to the Etiology of Bruxism in Children. J Clin Pediatr Dent. 2020;44(3):180-184
19) Beddis H, Pemberton M, Davies S. Sleep bruxism: an overview for clinicians. Br Dent J. 2018;28;225(6):497-501
20) Berman Y, North KN. A gene for speed: the emerging role of alpha-actinin-3 in muscle metabolism. Physiology (Bethesda). 2010 Aug;25(4):250-9.
21) Mills M, Yang N, Weinberger R, Vander Woude DL, Beggs AH, Easteal S, North K. Differential expression of the actin-binding proteins, alpha-actinin-2 and -3, in different species: implications for the evolution of functional redundancy. Hum Mol Genet. 2001;15;10(13):1335-46.
22) Kiliaridis S, Engström C, Thilander B. Histochemical analysis of masticatory muscle in the growing rat after prolonged alteration in the consistency of the diet. Arch Oral Biol. 1988;33(3):187-93.
23) Eriksson PO, Thornell LE. Histochemical and morphological muscle-fibre characteristics of the human masseter, the medial pterygoid and the temporal muscles. Arch Oral Biol. 1983;28(9):781-95.
24) Throckmorton GS, Finn RA, Bell WH. Biomechanics of differences in lower facial height. Am J Orthod. 1980;77(4):410-20.
25) Van Spronsen PH, Weijs WA, Valk J, Prahl-Andersen B, van Ginkel FC. A comparison of jaw muscle cross-sections of long-face and normal adults. J Dent Res. 1992;71(6):1279-85.
26) Benington PC, Gardener JE, Hunt NP. Masseter muscle volume measured using ultrasonography and its relationship with facial morphology. Eur J Orthod. 1999;21(6):659-

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