Genetic contributions to craniofacial growth: a review

A T Andriani¹, P K Zahra², E I Auerkari²
¹Orthodontic Residency Program, Faculty of Dentistry, University of Indonesia, Jakarta, Indonesia
²Department of Oral Biology, Faculty of Dentistry, University of Indonesia, Jakarta, Indonesia

corresponding author: ei_auerkari@yahoo.com

Abstract. The human head consist of numerous bones. The bones of the face are suspended from the anterior portion of the cranium. These bones are responsible for the face and head form. The facial surface is immediately recognizable and seen which has a close association to the skeletal and cartilaginous structures. The diversity in shape, relative size, and spatial arrangement (vertical, horizontal and depth) between the assorted facial features such as nose, eyes, lips, etc., make individual human face unique, respectively. In recent years, study of various number of genes that contribute to craniofacial growth continuous to evolve, while the impact of individual genes on normal craniofacial variation is few established. Genes such as Homeobox, Sonic Hedgehog, transcription factor and IHH take important roles in craniofacial growth. In the other hand, it is also known that the genetic disorder of these signalling pathways may result abnormalities in the growth or fusion of the craniofacial processes and numerous anomalies. Genes may therefore take part in the development of craniofacial complex. Furthermore, clinicians need to be knowledgeable the combination and interaction of genetic and environmental factors of growth potential to perform an appropriate diagnose and treatment planning. In this review, the function of various individual genes involved in growth of facial region are discussed.

1. Introduction

Growth and development are overtime changing process. Growth refers to the increases in size and number of cells. While development is defined as a maturation stage, differentiation, and acquisition of functionality [1,2]. Craniofacial growth involved many interactions between the hard and soft tissue that build up the skull, face, interactions of different bones. Information on an individual’s craniofacial anatomy and morphology can have certain importance in clinical applications: informing the specific models of patient, improving and diminishing the necessity for extensive surgical interventions of craniofacial anomalies or trauma, predicting or reconstructing the facial form of skeletal remains, and identifying the suspects from DNA. To date, it has been reported that inheritance has a significant role in the craniofacial anatomy and morphology.

On the other hand, if disturbances occur in the growth or fusion of the craniofacial processes, those may result in craniofacial anomalies. Whereas those are known to influence the development of craniofacial complex. This genetic situation results in cleft lip and palate, craniosynostosis, hemifacial microsomia, vascular malformation, hemangioma, deformational plagiocephaly accompanied by
different types of deformities and deficiencies in other parts of the body. Therefore, genetic factors are necessary to be considered when diagnosing the main cause of craniofacial anomalies. It is also important to conceive the interaction between genetic factors and environmental factors such as treatment that may affect facial growth [3]. The aim of this paper is to review what is studied about the genetics that affects facial growth.

2. Craniofacial anatomy
Skull is a complex structure, consist of 22 separates bones, 22 deciduous teeth and 32 permanent teeth. There are 2 components that make up the skull, the mandible and the cranium. The cranium is subdivided into neurocranium and viscerocranium. The sensory organs, which consist of olfactory, optic, and brain, are surrounded and protected by neurocranium. Frontal, parietal, occipital, sphenoid, and temporal bone are also covered by neurocranium. In the other hand, viscerocranium covered facial bones (mandible, maxilla, zygoma and nasal), palatal, pharyngeal, temporal and auditory bones [4,5]. Craniofacial complex is divided into three regions: (i) the neurocranium, which consists of calvaria and basicranium; (ii) the nasomaxillary complex; (iii) the mandible.

At human birth, skull consist of 5 major bones, two frontal bones, two parietal bones and the occipital bone. The bones are separated by suture as a growth zone, which consists of connective tissue. The suture has a flexible material that allows the skull and the brain to grow, and it will close gradually [6]. Cranial sutures have a main purpose is to allow the skull and the brain to grow and developed during fetal and infant life. Cranial sutures also absorb the load of mastication, and external forces load, and distortion of the skull during delivery [7].

![Figure 1. Craniofacial complex (Organ, 2013)](image)

The metopic suture, which separates the frontal bones, extends from the top of the head to the nasal bones. The sagittal suture separates the parietal bones. It extends from the head to the back of the head. The coronal suture separates the frontal bones from parietal bones, which extend from ear to ear. The lambdoid suture extends across the back of the head and separates the parietal bones and the occipital bone. The fontanelles are two soft spots where the sutures meet. On the posterior, there is a posterior fontanelle on the side of the frontal bone and parietal bone. On the anterior, there is anterior fontanelle, on the side of the occipital bone and the parietal bone. Fontanelles are made of strong membranes, and it will close within the first two years. The posterior fontanelle is the first to close, when the infant is two months old [8,9].
3. Growth mechanisms

The ossification and cranial bones growth happen in two ways: with ossification and growth of model cartilage, and ossification of endochondral with mesenchymal connective tissue and transformation and bones depositions on the surface of existing bones as well. Area of ossification joined into a large unit of bones. When intramembranous formed, bones are closed and there will be the development of suture. Growth of bone and adaptation can be developed because of bone separation on suture area and synchondroses. Premature fusion or any growth obstacle can induce an abnormal bone growth pattern that can cause cranial deformities[10,11].

Facial morphologies involved growth coordinates of facial height on the temporal and spatial sequence, that regulates by signaling pathway includes Wnt/β-catenin pathways, Fibroblast Growth Factor (FGF), Bone Morphogenetic Protein (BMP), and Growth Hormone Receptor (GHR)[12]. Soft tissue growth and facial changes must be understood as the effect of underlying bony changes. The face of a grown-up male tends to be more orthognathic[13]. The nose grows downward and forward, the commissure lips move down, and the upper lips lengthen. Growth of the nasal bone is complete at 10 years old, but the nasal cartilage and soft tissue continue to grow until the adolescent spurt. Female shows little profile change as they grow older. Their lips become thinner, with only minor changes at the nose and chin.

4. Growth pattern

Bone growth has two fundamental physiological processes, which are modeling and remodeling as well as Bash theories put forward. Modeling is defined as an opposition and resorption that occurs on the surface of the bone that changes size and shape of the bone. Remodeling occurs as reconstructions of bone by the turnover of Haversian system. According to Enlow's theories, changes in shape and size of the bone is the result of the basic principles: displacement, 'V-principle', cortical drift, relocation and remodeling[14].

The remodeling is a continuous process that preserves the bone proportions and shape throughout the growth period. When the deposition of the bone occurs, the bone will move to a fixed structure. These processes are known as drift. Appositional occurs on the surface, where the surface moves into the opposite direction of growth[15].

![Figure 2](example.com/figure2.png)

**Figure 2.** Enlow's "V" Principle. The earliest stage of development (A) grows through the "V" principle to the later stage (B) through deposition (+) and resorption (-) (Enlow, 2008)[14]
5. Genetic of craniofacial growth

Research In recent years, the study of the genetics and environmental factors affecting variations in human craniofacial morphology have been growing fast. This theory was introduced by Allan G. Brodie in 1940s, he said that craniofacial growth is controlled by genetics. Genes such as Homeobox, Sonic hedgehog, transcription factor and IHH have an important role in craniofacial development [17,18]. These genes belong to four families of growth factors. Growth factors are steroid hormone molecules or peptides that stimulate proliferation and differentiation and cellular growth. Mutation in genes of these signaling pathways may cause abnormalities in the growth or fusion of the facial processes [19].

In FGF family there are four major FGF receptors, but multiple variants exist. Each receptor can be activated by specific members of FGF family. The FGF signaling pathway is involved in stimulating cell proliferation, this substance is active in facial epithelium and mesenchyme. FGF and its receptors are also expressed during palatal formation. FGF signaling is also essential in tooth development. Mutation of this gene can cause craniosynostosis. This condition includes enlarging pulp chamber, hypo mineralized dentine, and non-curious exposure of the pulp leading to dental abscesses [20,21].

Figure 3. Diagram of the growth of the mandible. Black arrows are surface resorptive, and white arrows are depository (Enlow, 2008) [16]

Figure 4. Signaling molecules pathways [19]
Sonic Hedgehog is a member of the Hedgehog family associated with abnormal orofacial and tooth development. Because SHH is expressed at all stages of tooth development and plays an important role in the initiation of tooth formation, tooth size, and crown morphology, this gene is also expressed in the maxillary processes and ectoderm of the frontonasal during development. Excessive expression of SHH can cause midfacial widening with increased space between the eyes [22].

WNT signaling pathways activate intercellular signals that dictate a variety of cell activities. WNT family have a major role tooth initiation site of the oral epithelium, bone formation site of the maxilla and mandible, and in the mesenchyme of the elevating palatal shelves. Mutation of WNT3 will cause tetra-amelia. Tetra-amelia is a condition of lacking all four limbs and often have a cleft lip with or without cleft palate. Reduction of this gene during tooth initiation will cause the reduced size of the teeth [19].

Transforming Growth Factor beta (TGFβ) have a major role on all stages of tooth development. Activin signaling molecules and Bone Morphogenetic Protein (BMP) and are includes in this family. Mutation in TGFβ receptor genes (TGFβR2 or TGFβR3) is associated with a patient with aortic aneurism type syndrome, who also have craniosynostosis, bifid uvula, hypertelorism and cleft palate. The shape and the size of the face can be altered by adding Noggin as an inhibitor substance for BMP activation. Overexpression or inhibition of BMP signaling in embryos can cause cleft palate [23].

Table 1. Genes involved in growth and development of cartilage and bone.

| Genes | Functions |
|-------|-----------|
| **Cartilage** | |
| Master genes | |
| Type II collagen | Marker for chondroprogenitor cells |
| IIIA isoform | Marker for chondroprogenitor cells |
| Type IX collagen | Marker for chondroprogenitor cells |
| Aggrecan | Cartilage-specific proteoglycan |
| Regulatory genes | |
| Transcription factor 5 | |
| Smad9 | Signal chondrocyte differentiation |
| Growth factor/receptors | |
| Indian hedgehog (Ihh) | Stimulates chondrocyte proliferation and PTHR |
| Fibroblast growth factor receptors (FGFR2/FGFR3) | Stimulates chondrocyte proliferation and hypertrophy |
| Transforming growth factor receptors (TGFβR1/2) | Stimulates chondrocyte differentiation and hypertrophy |
| Bone morphogenetic protein receptors (BMP1/2/4/5) | Stimulates chondrocyte hypertrophy |
| Follistatin, bone-related proteins, receptors (FGFR2/FGFR3) | Stimulates chondrocyte proliferation |
| Retinoic acid receptors (RAR) | Stimulates chondrocyte hypertrophy |
| **Bone** | |
| Master genes | |
| Alkaline phosphatase | Potentiates Ca^2+ carrier, hydrolysis inhibitors of mineral deposition such as pyrophosphates |
| Type I collagen | Serves as scaffold of mineralization equipment |
| Bone sialoprotein | Neutrophil of mineralization |
| Osteopontin | Inhibit mineralization and promote bone resorption |
| Osteocalcin | Inhibit mineralization |
| **Osteonectin** | May mediate deposition of hydroxyapatite |
| Regulatory genes | |
| Transcription factor | |
| Cbfal, Runx2 | Essential for osteogenic commitment and differentiation |
| Oster1 | Essential for osteogenic differentiation |
| Twist | Essential for osteogenic differentiation |
| Msx2 | Inhibits osteoblast differentiation |
| Growth factor/receptors | |
| Fibroblast growth factor receptors (FGFR2/FGFR3) | Stimulates proliferation and differentiation |
| Transforming growth factor receptors (TGFβR1/2) | Stimulates proliferation and differentiation |
| Bone morphogenetic protein receptors (BMP1/2/4/5) | Inhibits Cbfal, Runx2 expression and stimulates differentiation |
| Insulin like growth factor (IGF) | Stimulates cell proliferation, differentiation and matrix production |
| Placental derived growth factor (PDGF) | Ligand for proliferation and recruit progenitor cells by stimulating chondrogenic induction |
6. Epigenetics of Craniofacial growth
Epigenetics occur as a result of natural and nurture factors. This study is about mitotically changes in gene expression which are not elucidated by changes to the DNA base-pair sequence [6]. The changes of the DNA sequence can be inherited to the next generation. These factors such as epigenome or epigenetic factors, carcinogenetic, stress, development, drugs, etc., are chemical modifications of DNA or specific amino acids on Histone protein around DNA. Epigenome has a main function as gene marker which gene should be activated and inactivated [24].

Epigenetic processes involve DNA methylation, histone modification, and chromatin remodeling, which by regulating transcription, can affect gene expression [6,25]. Those are closely relevant to craniofacial phenotypes due to the general importance of epigenetic in their particular role in neural crest development and gene regulation in embryonic development period [26].

To date, craniofacial epigenetic research has been widely focused on orofacial cleft cases. Prior epigenome-wide association studies (EWAS) have reported the relevance of DNA methylation in craniofacial development, in which there was a differential DNA methylation between cleft cases and controls and various orofacial cleft subtypes [27,28].

7. Anomalies
Variations in facial growth have been clinically associated with poor aesthetic self-image, malocclusion formation and the development of physical and/or functional deformities. Some of the craniofacial anomalies are deformational plagiocephaly, craniosynostosis, vascular malformation, cleft lip and palate, hemangioma, and hemifacial microsomia. Cleft lip and/or lip palate is a separation of the lip with or not palate or both. Cleft lip and palate are the most common congenital craniofacial anomalies seen at birth. A vascular malformation is a birthmark or growth present at birth, affects the aesthetic appearance. Craniosynostosis is a premature fusion of the skull sutures. This will affect brain and skull growth. Hemifacial microsomia is an underdeveloped tissue on one side of the face. Hemangioma is an abnormally growing blood vessel in the skin that present at birth. Deformation plagiocephaly is an abnormal shape of the head as the result of repeated pressure on the same area of the head.

8. Conclusion
Craniofacial growth is a continuous and complex process, which occurs by the connection of many different bones that build up the skull and many other tissues. Inheritance has a significant role in craniofacial growth. The understanding of the combination and interaction of genetic and environmental factors is important to decide the diagnose and treatment planning.

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