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Mini Review

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Exploring the genetic factors affecting the craniofacial morphology of Egyptian ancestry

Mohamed ADEL[1,2], Lorri Ann MORFORD[1], James Kennedy HARTSFIELD, Jr[1], Yu HIKITA[2], Reina HATANAKA[3], Koutaro MAKI[2] and Tetsutaro YAMAGUCHI[3]

[1]Craniofacial Genetics Program, Division of Orthodontics, College of Dentistry, University of Kentucky, Kentucky, USA
[2]Department of Orthodontics, Showa University Dental Hospital, Tokyo, Japan
[3]Department of Orthodontics, Kanagawa Dental University Junior College, Kanagawa University, Kanagawa, Japan

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Abstract

The origin of the Egyptian race is a controversial subject and a variety of views have emerged from the theories proposed by Egyptologists based on their studies about ancient Egyptian history. In this review, we will discuss the unique craniofacial characteristics of modern Egyptians based on cephalometric images and compare these characteristics with those of populations that are believed to be the origin of the Egyptian race. Furthermore, we will discuss the effect of genetic variations in the growth hormone receptor (*GHR*) and fibroblast growth factor receptor 1 (*FGFR1*) genes on the craniofacial morphology of the Egyptian population and compare it with that of populations with other ancestries.

1. Genetics of craniofacial morphology

Populations comprised of individuals with different ethnic backgrounds tend to show variations in many measurable traits such as skin color, height, eye color, response to certain medications, and susceptibility to some diseases. Among these traits are craniofacial characteristics, which are considered to be one of the most unique and identifying features for each race. Studies of human facial growth and development confirm a strong link between genetics, patterning, and morphogenesis of facial traits[1]. Recent advances in digital imaging of the craniofacial complex in conjunction with highly reliable genotyping methods have allowed us to understand more about the genetic background of craniofacial morphology and why it could be considered an identifying aspect for each race[2]. Moreover, understanding how the genetic factors contribute to the pathogenesis of the various craniofacial abnormalities is necessary for early prevention and effective treatment modalities.

Genetic association studies have suggested a role for numerous gene variants in the generation of the observed craniofacial morphology diversity[3]. For example, a two-stage genome-wide association study involving 85 facial traits in 7,569 Korean subjects revealed associations between five novel genetic loci and the frontal contour of the face and the shape of the eye and nose[4]. Furthermore, Claes et al. (2014) found that a set of 20 genes had significant effects on normal facial variation using three-dimensional (3D) facial imaging in samples with mixed West African and European ancestry from three different geographical locations (namely Brazil, United States, and Cape Verde)[5].

In one of the largest genome-wide associated studies conducted using genomic DNA and 3D facial images obtained from 10,115 European subjects, 24 genetic loci were suggested to be associated with normal facial variation. Moreover, 10 of the discovered associations were confirmed in a follow up study of an additional 7,917 individuals from diverse ethnic backgrounds including specific groups from Europe, the United

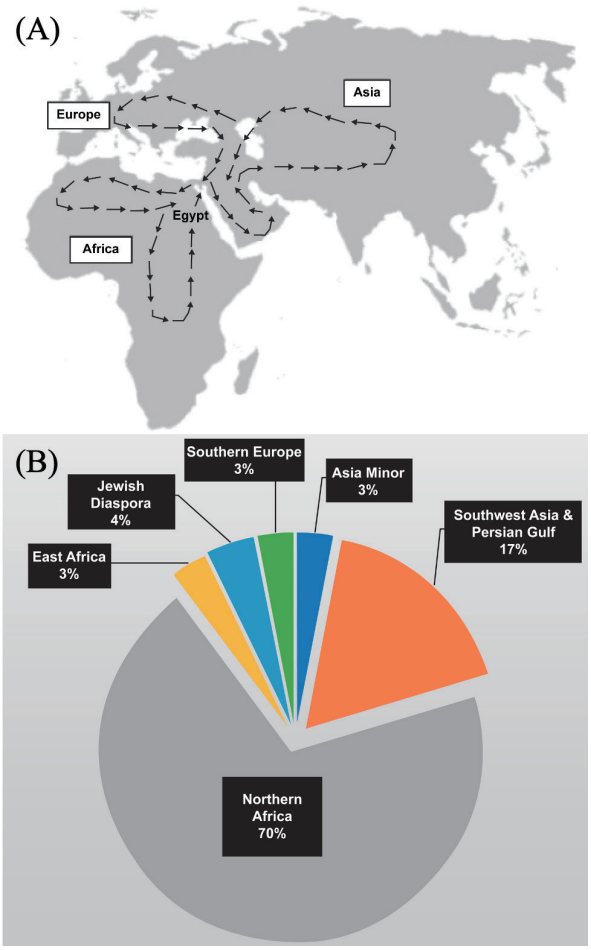

Figure 1. Movement of modern humans in and out of Africa, Europe, and Asia through Egypt.

States of America, Latin America, and Asia[6].

This review gives an overview of the specific craniofacial features of a sample of modern day Egyptians that can provide us with insights about the ancestral contributions to the Egyptian race. It also explores the role of the genetic factors in the craniofacial morphogenesis in the Egyptian population.

2. The origin of the Egyptian population

Where did the Egyptians come from? Where did they go? Are there still traces of ancestral DNA in today's Egyptians? The answers to these questions have long intrigued scientists from different disciplines. For almost 70 centuries, ancient Egypt was the leading civilization in the Mediterranean area. Like modern Egypt, the ancient counterpart was located in the center of the Nile Valley, in the Eastern Sahara, the largest desert in Africa. Climate changes in this region have likely played an essential role in shaping human migration and interaction throughout millennia. Because of its rich natural resources and strategic location on the crossroads of continents, ancient Egypt was a major gateway for the movement of humans in and out of Africa (Figure 1-A). Many monuments, objects, and artifacts have been recovered from different archeological sites and have been considered the main sources of information about ancient Egypt[7].

A central question for scholars of Egyptian civilization has concerned the origins of modern Egyptians. Discussions about what characterizes the ancient Egyptian race have been controversial as race includes both cultural and biological elements[8]. Different views were based on Egyptologists' theories founded by their studies on Egyptian history, religion, language, art, and architecture[7,8]. Previous reports on modern and ancient Egyptians indicated that they have specific common characteristics that are similar to those of Northeast

Africans, Mediterranean Asians, and Europeans[7,9,10].

The populations in Europe, Mediterranean Asia, South Asia, North Africa, and the African Horn are considered Caucasian in origin according to molecular biological and forensic evidence[11]. In 2005, the National Geographic Society in collaboration with scientists and universities from all over the world launched a genetic anthropological study called the Genographic Project. The aim was to study the pattern of human migration using collected DNA samples. The results revealed that the largest genetic component of modern-day native Egyptians is from North Africa (Figure 1-B)[12].

3. Biological and physical anthropology in the study of ancient civilizations

Human identification is one of the most intriguing subjects that confronts biological scientists. The use of biological (molecular) and physical (forensic) anthropology is crucial to support or disprove proposed theories regarding the origin of people of ancient civilizations[13]. Physical anthropology is defined as the comparative study of human evolution, classification, and variation through observation and measurement[14]. In the human skeleton, craniofacial morphology is considered one of the most reliable and valid indicators of ancestral phenotype that is inherited from one generation to the next. The presence or absence of certain unique anatomical cranial characteristics in some populations more than in others can be considered evidence of common ancestry[15]. Two-dimensional (2D) and 3D imaging techniques have been increasingly used as a tool for anthropological inquiry instead of the analysis of dry bones[16].

There is a strong relation between physical anthropology and molecular anthropology (population genetics, genomics, and/or proteomics) in the study of hypotheses about the origin of different races, historical population migrations, and phenotypic relations among different populations. Many studies have reported the use of ancient DNA samples to test various hypotheses about evolution and to deepen the knowledge about the genetics of different population and paleoecological changes[17,18]. The introduction of new DNA technologies, such as next-generation sequencing, has facilitated the recovery of DNA information from archeological and paleontological remains, allowing us to learn more about the genetic relationships between extinct organisms and their extant descendants[19].

The application of next-generation sequencing was limited to the analysis of archeological remains from the European continent initially, as the genetic material of such remains were well preserved due to the cold European climate. Recently, next-generation sequencing and in-silico approaches have allowed researchers to remains found further south in Southern Egypt, where the preservation conditions are usually not ideal due to extreme high temperatures and humidity[19,20]. For example, Schuenemann at al. (2017) studied ancient DNA obtained from three Egyptian mummies recovered from Middle Egypt in order to assess its authenticity and determine its relationship with the surrounding populations at the genetic level. They compared the ancient DNA with data obtained from modern Egyptians to test the previous hypotheses about the migration patterns and the admixture with other populations. Their analysis showed that compared with modern-day Egyptians, who recently received an additional sub-Saharan admixture, ancient Egyptians shared more ancestry with Eastern populations[17].

Importantly, when ancient intact DNA is not available, one can still retrieve historical data from the proteome (protein remains). Some studies have reported near complete proteome sequences of fossils from the heart of the African continent. Using these remarkable advanced techniques, substantial knowledge can be gained from the treasure of Egyptian mummies[11,15]. A pilot study was conducted on skin and muscle tissue samples taken from three 4,200-year-old Egyptian mummies, and proteomic analysis was performed to determine whether it would be possible to detect proteins in mummified skin and muscle tissue[21]. Indeed, large amounts of collagens and keratins were detected, as well as significant levels of various other proteins that indicated the presence of acute inflammation and systemic immune response. These results confirmed the possibility of identifying proteins from small-sized mummified skin and muscle samples that are over 4,000 years old[21]. Thus, the analysis of either the genome and/or the proteome found in remains may now allow the acquisition of a massive amount of information. By modeling different scenarios of population expansion and/or decline, and combining them with historical and physical anthropology, it is now possible to support or reject different hypotheses. This may result in new scenarios and hypotheses of origin and migration.

4. Craniofacial features of the Egyptian population

For over 80 years, the lateral cephalometric radio-

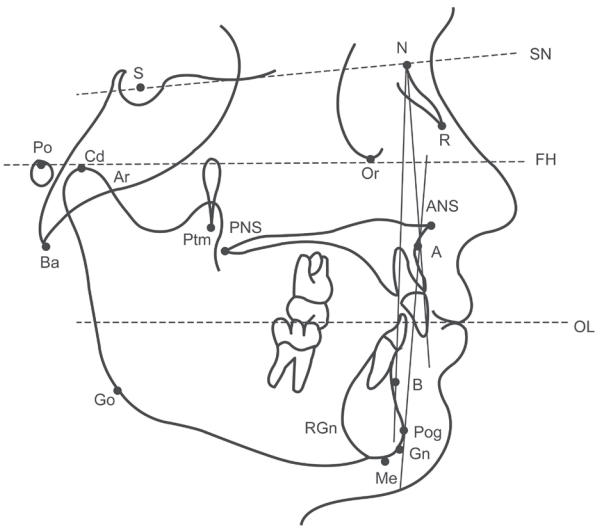

Figure 2. The facial characteristics of the Egyptians.
Or, orbitale; Cd, condylion; ANS, anterior nasal spine; PNS, posterior nasal spine; Ar, articular; Po, porion; Go, gonion; Me, menton; S, sella turcica; N, nasion; Ba, basion; Ptm, pterygomaxillary fissure; R, rhinion; A, point A; B, point B; Pog, pogonion; Gn, gnathion; RGn, retrognathion; FH, Frankfurt plane; OL, occlusal plane; SN, SN plane.

graph has been a standard tool to evaluate the morphological details of the craniofacial complex[22]. Forensic anthropologists can identify the ancestry of a skeleton by examining the morphology of its craniofacial complex. By taking some measurements of the skull vault (cavity) and face and comparing them with those of populations from different parts of the world, anthropologists are able to identify the individual's relationship to a population group[23,24]. In addition, craniofacial orthodontists and oral surgeons need baseline data on the craniofacial features of individuals from different geographic locations in order to provide more personalized treatment options.

Few studies have examined the craniofacial characteristics of Egyptians. One of these found that Egyptian males have a tendency towards a bimaxillary dental protrusion, and a shorter posterior face height compared to Iowa, USA Caucasian males, while Egyptian females have a more convex skeletal profile and a tendency towards greater mandibular dental protrusion than Iowa, USA Caucasian females[25]. Egyptians also possess a unique mandibular arch form when compared to Southern California Caucasians[26].

Cephalometric (Figure 2) norms from a sample of 300 adult male and female Egyptians were obtained and then compared with the published norms of other populations, i.e., Moroccan (North African), Anatolian Turkish (Mediterranean Asian), and Caucasian (European)[27], that may have common ancestors with Egyptians[7,9,10,12]. The results revealed that Egyptians have some facial characteristics that are similar among these groups, including a convex profile with a retrognathic mandible and a tendency towards a skeletal Class II malocclusion (particularly in females) (Table 1)[27-30].

5. Contribution of Fibroblast Growth Factor Receptor 1 (*FGFR1*) and Growth Hormone Receptor (*GHR*) gene variations to the craniofacial diversity observed in Egyptians

Factors affecting craniofacial morphology draws the attention of researchers from different fields, including maxillofacial and oral surgery, anthropology/evolutionary biology, developmental anatomy, genetics, and orthodontics. Craniofacial morphogenesis is the manifestation of complex genetic and environmental interactions[31]. The study of genetics is essential to understand such complex interactions and decipher the role of specific genetic variation in producing the final craniofacial phenotype[32]. Recently, many studies have confirmed the roles of the genes encoding *FGFR1* and *GHR* in the morphogenesis of various hard and soft

Table 1 Comparison of SNA, SNB, ANB, and facial profile amongst Egyptian, North African, Mediterranean Asian, and European samples; results indicate similar facial convexity (M Adel *et al*., 2016; Basciftci *et al*., 2004; Ousehal *et al*., 2012; Tecco & Festa, 2007).

Craniofacial measurements	Egyptians	North Africans	Mediterranean Asians	Europeans
SNA (°)	82.09	80.88	82.57	82.20
SNB (°)	77.90	77.90	79.90	78.20
ANB (°)	4.1	3.17	2.65	4.0
Facial profile	Convex	Convex	Convex	Convex

SNA, angle formed by Sella—Nasion—A-Point; SNB, angle formed by Sella—Nasion—B-Point; ANB, angle formed by A-Point—Nasion—B-Point.

tissue structures of the face[33-35].

5.1 Role of the *FGFR1* gene in craniofacial growth and development

One of the most important signaling pathways involved in craniofacial growth and development is that of fibroblast growth factors (FGFs) and fibroblast growth factor receptors (FGFRs)[36]. FGFs belong to a family of polypeptides that play an essential role in the mitogenic activity of mesenchymal, neuronal, and epithelial cells. FGFs are essential in cellular differentiation and also exert many functions in both adult and developing organisms by regulating several developmental processes[37,38]. The functions of FGFs are exerted through binding and activation of FGFRs that are encoded by four distinct genes (*FGFR1-FGFR4*)[36]. The binding of FGF proteins and to their receptors results in a chemical reaction that triggers a signaling cascade within the cell leading to cell survival, mitogenesis, or differentiation[38].

FGF-FGFR signaling is involved in the development of the axial and craniofacial skeleton. During the morphogenesis of the craniofacial skeleton, the FGF signaling pathway plays a crucial role in suture and synchondrosis regulation and in the development of the facial bones, cranial vault, and cranial base[36]. Accordingly, variation in genes encoding FGFs and FGFRs result in developmental disorders affecting the craniofacial region[39,40]. The identification of these genetic variants provides us with a better understanding of the role of FGF-FGFR signaling in normal craniofacial morphogenesis[41,42]. Many isolated and syndromic craniosynostoses such as Apert, Pfeiffer, and Crouzon syndromes, result from genetic variants of pathological significance in one or more of the FGFR genes, indicating a role of these genes in craniofacial morphogenesis[38,43,44]. Various studies found associations between variants in genes controlling the FGR-FGFR signaling pathway and craniofacial morphology (Table 2)[32,35,40,45-47].

The *FGFR1* gene is found on chromosome 8p11.1 and has 19 exons spanning 55 kb. FGFR1 is involved in FGR-FGFR signaling and controls numerous biological processes, including organogenesis, bone formation, and development[45,48]. During embryonic development, FGFR1 controls the differentiation of immature cells into bone cells[49]. It was also found that FGFR1 is highly expressed in the facial bones of the midface region during intramembranous ossification[50].

A mutation in the *FGFR1* immunoglobulin-like domains II-III linker region ($FGFR1^{P252R}$) results in Pfeiffer syndrome. This mutation alters the protein function, resulting in prolonged signaling, which in turn promotes the premature fusion of the sutures of the craniofacial complex[51]. The premature fusion of the sutures before the complete growth of the underlying structures disrupts the normal skull growth and impacts the shape of the head and midface[41,43,52]. In many genetic disorders, an obvious relation is observed between genetic variations and facial anomalies. Furthermore, genetic variants in genes associated with genetic disorders may play a role in normal facial variation[53].

5.2 Role of the *FGFR1* gene in the craniofacial variation of the Egyptian population

The craniofacial characteristics of Egyptians include features related to the midface[27], which was hypothesized to be associated with variation in the *FGFR1* gene. This was confirmed by a genetic association study

Table 2 Association studies between *FGFR* and *GHR* gene variations and craniofacial morphology

Study	Ethnicity	Gene	SNP	Associated traits
Coussens and van Daal (2005)	Caucasian, Asian, Australian Aboriginal, and African American populations	*FGFR1*	rs4647905 C>G (intronic variant)	Decreased Cephalic Index (CI) associated with the C-allele
Gómez-Valdés et al. (2013)	Mexican Native and two Mestizo Mexican populations	*FGFR1*	rs4647905 C>G (intronic variant)	Transversely narrow and elongated head (dolichocephalic face)
Adel et al. (2017)	Japanese (43 males/173 females) and Korean (132 males/95 females)	*FGFR1*	rs13317 T>C (3'-UTR variant); rs6996321 G>A (intronic variant)	Small face, midfacial retrusion, protruded forehead, and relatively wide orbit and cheek area
Xiong et al. (2017)	Chinese (79 males/97 females with mandibular prognathism individuals and 60 males/95females with class I malocclusion)	*FGFR1*	rs13317 T>C (3'-UTR variant)	Association with mandibular prognathism
da Fontoura et al. (2015)	Caucasians (USA; 53 Skeletal Class I; 128 Skeletal Class II, and 88 Skeletal Class III patients)	*FGFR2*	rs11200014 G>A (intronic variant)	Increased risk of Skeletal Class II versus Skeletal Class I malocclusion
da Fontoura et al. (2015)	Caucasians (USA; 53 Skeletal Class I; 128 Skeletal Class II, and 88 Skeletal Class III patients)	*FGFR2*	rs2162540 T>C (intronic variant); rs11200014 G>A (intronic variant)	Increased risk of Skeletal Class II or III versus Skeletal Class I malocclusion
Jiang et al. (2019)	Chinese (895 Orthodontic patients)	*FGFR2*	rs2162540 T>C (intronic variant)	Associated with Skeletal Class II malocclusion
Jiang et al. (2019)	Chinese (895 Orthodontic patients)	*FGFR2*	rs2162540 T>C (intronic variant); rs2981578 C>T (intronic variant); rs1078806 A>G (intronic variant); rs11200014 G>A (intronic variant); rs10736303 G>A (intronic variant)	Associated with Skeletal Class III malocclusion
Yamaguchi et al. (2001)	Japanese (50 males / 50 females)	*GHR*	rs6184 C>A (Pro561Thr)	Increased mandibular ramus height (Co-Go) rs6184-C (vs CA)
Tomoyasu et al. (2009)	Japanese (50 males / 117 females)	*GHR*	rs6182 G>T (Cys422Thr)*; rs6184 C>A (Pro561Thr)*	Increased mandibular ramus height (Co-Go); rs6182-GG (vs GT) or rs6184-CC (vs CA)
Sasaki et al. (2009)	Japanese	*GHR*	rs6184 C>A (Pro561Thr)	Mandibular growth
Zhou et al. (2005)	Han Chinese (145 individuals)	*GHR*	rs6180 C>A (Leu526Ile)	Mandibular ramus height (S-Go, Co-Go, and Ar-Go)
Kang et al. (2009)	Korean (100 men and 59 women; ages 18 to 58 years)	*GHR*	rs6182 G>T (Cys422Thr),	Increased mandibular ramus height (Co-Go) rs6182-GG (vs GT) or rs6184-CC (vs CA);
			rs6184 C>A (Pro561Thr),	Increased mandibular ramus height (Co-Go)
			Exon-3-deleted (d3)/full length (fl)-GHR haplotype	No copies of the d3/*fl-GHR* haplotype-4 (vs 1 copy of the d3/*fl-GHR* haplotype-4)
Bayram et al. (2014)	Turkish (99 individuals with Class I / 99 individuals with severe Class III)	*GHR*	rs6184 C>A (Pro561Thr)	Increased mandibular length (Co-Gn) rs6184-CA (vs CC); Increased lower face height (ANS-Me) rs6184-CA (vs CC)
Nakawaki et al. (2017)	Japanese	*GHR*	rs6180 C>A (Leu526Ile)	Distance between the left and right coronoid processes
Adel et al. (2017)	Egyptian (92males and 99 females ages 18 to 55 years)	*GHR*	rs6180 C>A (Leu526Ile)	No correlation between rs6180 and measures of mandibular form

SNP, single nucleotide polymorphism; *FGFR*, fibroblast growth factor receptor; GHR, growth hormone receptor; 3' untranslated region (UTR) variant; Co-Go, Condylion to Gonion; S-Go, Sella to Gonion; Ar-Go, Articulare to Gonion; Co-Gn, Condylion to Gnathion; ANS-Me, Anterior Nasal Spine to Menton; **SNPs are in complete Linkage Disequilibrium (|D'|=1, r^2=1)

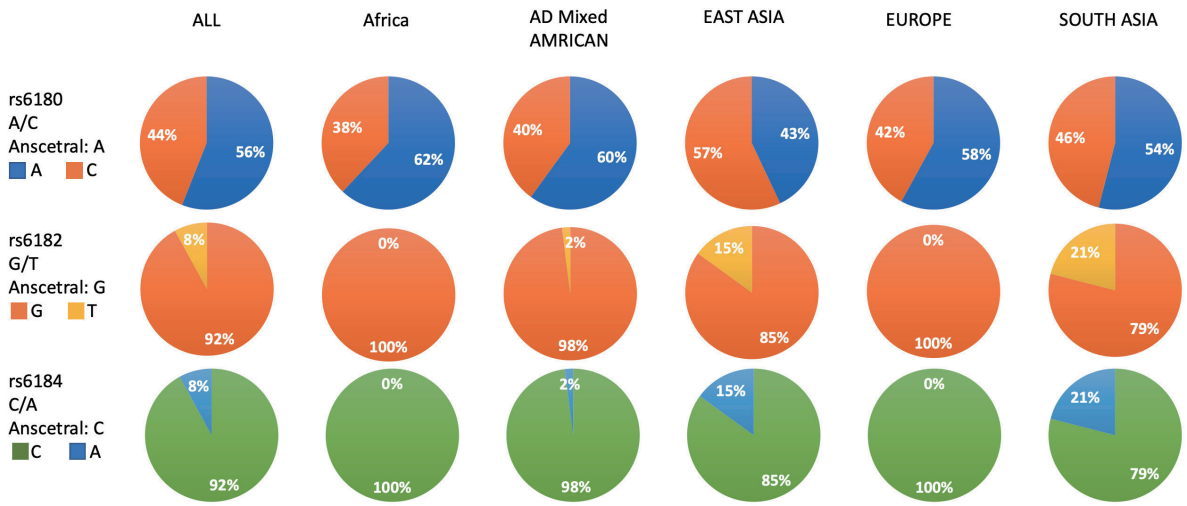

Figure 3. The allele frequency of the rs6180, rs6184, and rs6182 variants of the *GHR* gene in different populations with different ethnic backgrounds (www.internationalgenome.org).

that found the common (reference) allele of the *FGFR1* gene variant rs13317 to be associated with decreased depth of the orbits (Orbitale) to the Nasion as projected by a vertical line through the Nasion tangent to the Frankfort Horizontal plane[54]. This confirmed the genotype-phenotype association in East Asian (Japanese and Korean) subjects[35], indicating that common *FGFR* gene polymorphisms may play a role in the morphogenesis of the craniofacial morphology, particularly that of the upper midface region[54].

5.3 Role of the *GHR* gene in craniofacial growth and development

Growth hormone (GH) and insulin-like growth factor 1 (IGF1) are essential for normal growth and development. Somatotrophs in the anterior pituitary are the cells responsible for GH secretion. GH acts on tissues either directly via specific GHRs or indirectly via the production of IGF1, which mediates most of the anabolic effects of GH[55]. A functional variation in the GHR can result in a variation or inability to produce IGF1[56]. In addition to the important roles GHR and IGF1 play in longitudinal bone growth, skeletal maturation, bone mass gain, and maintenance[55,57], they also affect facial growth and morphology[58,59].

GH insensitivity (Laron syndrome) and incomplete GH insensitivity, which causes idiopathic short stature, are examples of conditions associated with *GHR* variants of pathological and developmental significance[60,61]. Children with Laron syndrome grow at a subnormal rate and present a uniform type of growth delay, along with pleiotropic effect on their facial morphology[56,62,63].

5.4 Role of the *GHR* gene in the craniofacial variation of the Egyptian population

Many studies confirm the relationship between variants in the *GHR* gene and craniofacial morphology in multiple populations, and discovered SNPs (rs6180, rs6184, and rs6182) correlated to mandibular morphology (Table 2)[33,34,64-68]. To confirm these findings, the association between the *GHR* variants rs6180 and rs6184 and mandibular measurements obtained from lateral and posteroanterior cephalograms of 191 Egyptian adults was analyzed[69]. rs6182 was not examined as it was found to be in strong linkage disequilibrium with rs6180 in populations found in the International HapMap Project (hapmap.ncbi.nlm.nih.gov). The minor allele frequency (MAF) of the rs6184 variant was very low in the Egyptian sample (1.5%), hence it was also excluded from the analysis. The results showed no significant association between the rs6180 variant and the mandibular morphology measurements of the examined Egyptian subjects. Although there have been associations found between the rs6180, rs6184, and rs6182 SNPs and mandibular morphology in Asian samples, variations in mandibular morphology in the Egyptian population are unlikely to be associated with these particular GHR variants.

There are racial/ethnic differences in frequencies of the examined *GHR* variants[70] (e.g., the MAF of rs6184

is 15-21% in East and South Asians, but 0% in African and European samples, Figure 3), which may contribute to the inconsistency in the result with the previous studies. Different *GHR* variants in different linkage disequilibrium blocks might be responsible for the variation in mandibular morphology in Egyptians. The lack of association and difference in MAF may reflect the finding that the genetic background of Egyptians is approximately three percent Asian[12]. Therefore, further investigation is needed to identify the genetic factors that affect the morphogenesis of the mandible in the Egyptian population.

6. Conclusion

Craniofacial features are considered one of the most unique features of populations with different ethnic backgrounds. The Egyptians present facial features close to those of Northeast Africans, Mediterranean Asians, and Europeans, all of them sharing Caucasian ancestry. This was further confirmed by the results of the DNA analysis conducted through the Genographic Project. Based on analysis of *FGFR1* and *GHR* gene variants we suggest that Egyptians share more facial features and associated DNA variants with Caucasian groups than with East and South Asian groups, supporting the premise that Egyptian genetic ancestry is closer to Caucasian than Asian. Identifying the genetic factors that contribute to specific craniofacial features may facilitate more personalized treatment of craniofacial abnormalities and could increase the potential for more predictable treatment outcomes. This conclusion is limited by the small number of DNA variants for which there is data for the different groups, and the use of 2D cephalograms to evaluate the craniofacial morphology of the examined subjects. Future association studies with more DNA variants using recent and more standardized 3D imaging techniques, such as cone-beam computed tomography imaging, may allow for more accurate evaluations of the variations in craniofacial morphology.

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Conflict of interest statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Johannsdottir B, Thorarinsson F, Thordarson A, Magnusson TE: Heritability of craniofacial characteristics between parents and offspring estimated from lateral cephalograms. *Am. J. Orthod. Dentofac. Orthop*. **127**(2): 200-207, 2005.
2. Weinberg SM, Cornell R, Leslie EJ: Craniofacial genetics: Where have we been and where are we going? *PLoS Genet*. **14**(6):e1007438, 2018.
3. Roosenboom J, Hens G, Mattern BC, Shriver MD, Claes P: Exploring the Underlying Genetics of Craniofacial Morphology through Various Sources of Knowledge. *Biomed Res Int*. 2016.
4. Cha S, Lim JE, Park AY *et al*.: Identification of five novel genetic loci related to facial morphology by genome-wide association studies. *BMC Genomics*. **19**(1): 1-17, 2018.
5. Claes P, Liberton DK, Daniels K *et al*.: Modeling 3D facial shape from DNA. *PLoS Genet*. **10**(3): e1004224, 2014.
6. Xiong Z, Dankova G, Howe LJ *et al*.: Novel genetic loci affecting facial shape variation in humans. *Elife*. E49898, 2019.
7. Brace CL, Tracer DP, Yaroch LA, Robb J, Brandt K, Nelson AR: Clines and clusters versus "race:" a test in ancient Egypt and the case of a death on the Nile. *Am. J. Phys. Anthropol*. **36**(S17): 1-31, 1993.
8. Sanders ER: The Hamitic hyopthesis; its origin and functions in time perspecive. *J. Afr. Hist*. **10**(4): 521-532, 1969.
9. Bosch E, Calafell F, Perez-Lezaun A, Comas D, Mateu E, Bertranpetit J: Population history of North Africa: evidence from classical genetic markers. *Hum Biol*. 295-311, 1997.
10. Poloni ES, Semino O, Passarino G *et al*.: Human genetic affinities for Y-chromosome P49a, f/TaqI haplotypes show strong correspondence with linguistics. *Am. J. Hum. Genet*. **61**(5): 1015-1035, 1997.
11. Coon CS. The races of Europe. Greenwood Pub Group, pp. 393-401, 1972.
12. National Geographic Reference Populations – Geno 2.0 Next Generation https://genographic.nationalgeographic.com/reference-populations-next-gen/; 2020.
13. Ousley S, Jantz R, Freid D: Understanding race and human variation: why forensic anthropologists are good at identifying race. *Am. J. Phys. Anthropol*. **139**(1): 68-76, 2009.
14. Dirkmaat DC, Cabo LL, Ousley SD, Symes SA: New perspectives in forensic anthropology. *Am. J. Phys. Anthropol*. **137**(S47): 33-52, 2008.
15. Snow CC, Hartman S, Giles E, Young FA: Sex and race determination of crania by calipers and computer: a test of the Giles and Elliot discriminant functions in 52 forensic science cases. *J. Forensic Sci*. **24**(2): 448-460, 1979.
16. Garvin HM, Stock MK: The Utility of Advanced Imaging in Forensic Anthropology. *Acad. Forensic Pathol*. **6**(3): 499-516, 2016.

17. Schuenemann VJ, Peltzer A, Welte B *et al*.: Ancient Egyptian mummy genomes suggest an increase of Sub-Saharan African ancestry in post-Roman periods. *Nat. Commun*. **8**(1): 11-11, 2017.
18. Pääbo S, Poinar H, Serre D *et al*.: Genetic analyses from ancient DNA. *Annu Rev Genet*. **38**(1): 645-679, 2004.
19. Rizzi E, Lari M, Gigli E, De Bellis G, Caramelli D: Ancient DNA studies: new perspectives on old samples. *Genet. Sel. Evol*. **44**(1): 1-19, 2012.
20. Linderholm A: Ancient DNA: the next generation–chapter and verse. *Biol. J. Linn. Soc*. **117**(1): 150-160, 2016.
21. Jones J, Mirzaei M, Ravishankar P *et al*.: Identification of proteins from 4200-year-old skin and muscle tissue biopsies from ancient Egyptian mummies of the first intermediate period shows evidence of acute inflammation and severe immune response. *Philos. Trans. R. Soc*. **374**(2079): 20150373, 2016.
22. Miyazato E, Yamaguchi K, Fukase H, Ishida H, Kimura R: Comparative analysis of facial morphology between Okinawa Islanders and mainland Japanese using three-dimensional images. *Am. J. Hum. Biol*. **26**(4): 538-548, 2014.
23. Alcalde RE, Jinno T, Pogrel MA, Matsumura T: Cephalometric norms in Japanese adults. *J Oral Maxillofac Surg*. **56**(2): 129-134, 1998.
24. Nanda R, Nanda RS: Cephalometric study of the dentofacial complex of North Indians. *Angle Orthod*. **39**(1): 22-28, 1969.
25. Bishara SE, Abdalla EM, Hoppens BJ: Cephalometric comparisons of dentofacial parameters between Egyptian and North American adolescents. *Am. J. Orthod. Dentofac. Orthop*. **97**(5): 413-421, 1990.
26. Bayome M, Sameshima GT, Kim Y, Nojima K, Baek S-H, Kook Y-A: Comparison of arch forms between Egyptian and North American white populations. *Am. J. Orthod. Dentofac. Orthop*. **139**(3): e245-e252, 2011.
27. Adel M, Yamaguchi T, Nadim M *et al*.: Evaluation of the craniofacial morphology of Egyptian adults undergoing orthodontic treatment. *Dentistry*. **6**(379): 2161-1122, 2016.
28. Basciftci FA, Uysal T, Buyukerkmen A: Craniofacial structure of Anatolian Turkish adults with normal occlusions and well-balanced faces. *Am. J. Orthod. Dentofac. Orthop*. **125**(3): 366-372, 2004.
29. Ousehal L, Lazrak L, Chafii A: Cephalometric norms for a Moroccan population. *Int. Orthod*. **10**(1): 122-134, 2012.
30. Tecco S, Festa F: Cervical spine curvature and craniofacial morphology in an adult Caucasian group: a multiple regression analysis. *Eur. J. Orthod*. **29**(2): 204-209, 2007.
31. Keita S, Boyce AJ: Genetics, Egypt, and History: Interpreting Geographical Patterns of Y Chromosome Variation 1. *Hist. Afr.* **32**: 221-246, 2005.
32. Gómez-Valdés JA, Hünemeier T, Contini V *et al*.: Fibroblast growth factor receptor 1 (FGFR1) variants and craniofacial variation in Amerindians and related populations. *Am. J. Hum. Biol*. **25**(1): 12-19, 2013.
33. Nakawaki T, Yamaguchi T, Isa M *et al*.: Growth hormone receptor gene variant and three-dimensional mandibular morphology. *Angle Orthod*. **87**(1): 68-73, 2017.
34. Yamaguchi T, Maki K, Shibasaki Y: Growth hormone receptor gene variant and mandibular height in the normal Japanese population. *Am. J. Orthod. Dentofac. Orthop*. **119**(6): 650-653, 2001.
35. Adel M, Yamaguchi T, Tomita D *et al*.: Contribution of FGFR1 variants to craniofacial variations in East Asians. *PLoS One*. **12**(1), e0170645, 2017.
36. Du X, Xie Y, Xian CJ, Chen L: Role of FGFs/FGFRs in skeletal development and bone regeneration. *J. Cell. Physiol*. **227**(12): 3731-3743, 2012.
37. Francis-West P, Ladher R, Barlow A, Graveson A: Signalling interactions during facial development. *Mech. Dev*. **75**(1-2): 3-28, 1998.
38. Teven CM, Farina EM, Rivas J, Reid RR: Fibroblast growth factor (FGF) signaling in development and skeletal diseases. *Genes Dis*. **1**(2): 199-213, 2014.
39. Manocha S, Farokhnia N, Khosropanah S, Bertol JW, Santiago J, Fakhouri WD: Systematic review of hormonal and genetic factors involved in the nonsyndromic disorders of the lower jaw. *Dev. Dyn*. **248**(2): 162-172, 2019.
40. Xiong X, Li S, Cai Y, Chen F: Targeted sequencing in FGF/FGFR genes and association analysis of variants for mandibular prognathism. *Medicine*. **96**(25), 2017.
41. Ornitz DM, Marie PJ: FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev*. **16**(12): 1446-1465, 2002.
42. Dorey K, Amaya E: FGF signalling: diverse roles during early vertebrate embryogenesis. *Development*. **137**(22): 3731-3742, 2010.
43. Cunningham ML, Seto ML, Ratisoontorn C, Heike C, Hing A: Syndromic craniosynostosis: from history to hydrogen bonds. *Orthod Craniofac Res*. **10**(2): 67-81, 2007.
44. Hao Y, Tang S, Yuan Y, Liu R, Chen Q: Roles of FGF8 subfamily in embryogenesis and oral-maxillofacial diseases. *Int. J. Oncol*. **54**(3): 797-806, 2019.
45. Coussens AK, Van Daal A: Linkage disequilibrium analysis identifies an FGFR1 haplotype-tag SNP associated with normal variation in craniofacial shape. *Genomics*. **85**(5): 563-573, 2005.
46. da Fontoura CG, Miller S, Wehby G *et al*.: Candidate gene analyses of skeletal variation in malocclusion. *J Dent Res*. **94**(7): 913-920, 2015.
47. Jiang Q, Mei L, Zou Y *et al*.: Genetic Polymorphisms in FGFR2 Underlie Skeletal Malocclusion. *J Dent Res*. **98**(12): 1340-1347, 2019.
48. Wanaka A, Johnson Jr EM, Milbrand J: Localization of FGF receptor mRNA in the adult rat central nervous system by in situ hybridization. *Neuron*. **5**(3): 267-281, 1990.
49. Jacob AL, Smith C, Partanen J, Ornitz DM: Fibroblast growth factor receptor 1 signaling in the osteo-chondrogenic cell lineage regulates sequential steps of osteoblast maturation. *Dev. Biol*. **296**(2): 315-328, 2006.
50. Rice D, Rice R, Thesleff I: Fgfr mRNA isoforms in craniofacial bone development. *Bone*. **33**(1): 14-27, 2003.
51. Chen L, Deng C-X: Roles of FGF signaling in skeletal development and human genetic diseases. *Front Biosci*. **10**(1): 961-976, 2005.
52. Britto JA, Evans RD, Hayward RD, Jones BM: From genotype to phenotype: the differential expression of FGF, FGFR, and TGFbeta genes characterizes human cranioskel-

etal development and reflects clinical presentation in FGFR syndromes. *Plast. Reconstr. Surg*. **108**(7): 2026-2039, 2001.
53. Boehringer S, Van Der Lijn F, Liu F *et al*.: Genetic determination of human facial morphology: links between cleft-lips and normal variation. *Eur. J. Hum. Genet*. **19**(11): 1192-1197, 2011.
54. Adel M, Yamaguchi T, Tomita D *et al*.: Association between the FGFR1 rs13317 single nucleotide polymorphism and orbitale-nasion depth based on cephalometric images. *J. Hum. Genet*. **63**(8): 901-909, 2018.
55. Giustina A, Mazziotti G, Canalis E: Growth hormone, insulin-like growth factors, and the skeleton. *Endocr. Rev*. **29**(5): 535-559, 2008.
56. Laron Z: Laron Syndrome (Primary Growth Hormone Resistance or Insensitivity): The Personal Experience 1958–2003. *J. Clin. Endocrinol. Metab*. **89**(3): 1031-1044, 2004.
57. Litsas G: Growth hormone and craniofacial tissues. An update. *Open Dent J*. **9**: 1, 2015.
58. Preda SA, Albulescu D-M, Mitroi M-R *et al*.: Craniofacial morphology aspects in children with isolated growth hormone deficiency-a cephalometric study. *Rom J Morphol Embryol*. **60**(2): 653-658, 2019.
59. 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 Orthod*. **18**(1): 1-8, 2017.
60. Butler MG, Roberts J, Hayes J, Tan X, Manzardo AM: Growth hormone receptor (GHR) gene polymorphism and Prader–Willi syndrome.American. *J. Med. Genet*. **161**(7): 1647-1653, 2013.
61. Goddard AD, Covello R, Luoh S-M *et al*.: Mutations of the growth hormone receptor in children with idiopathic short stature. *N. Engl. J. Med*. **333**(17): 1093-1098, 1995.
62. Pedicelli S, Peschiaroli E, Violi E, Cianfarani S: Controversies in the definition and treatment of idiopathic short stature (ISS). *J Clin Res Pediatr Endocrinol*. **1**(3): 105, 2009.
63. Laron Z, Lilos P, Klinger B: Growth curves for Laron syndrome. *Arch. Dis. Childh*. **68**(6): 768-770, 1993.
64. Tomoyasu Y, Yamaguchi T, Tajima A, Nakajima T, Inoue I, Maki K: Further evidence for an association between mandibular height and the growth hormone receptor gene in a Japanese population. *Am. J. Orthod. Dentofac. Orthop*. **136**(4): 536-541, 2009.
65. Sasaki Y, Satoh K, Hayasaki H, Fukumoto S, Fujiwara T, Nonaka K: The P561T polymorphism of the growth hormone receptor gene has an inhibitory effect on mandibular growth in young children. *Eur. J. Orthod*. **31**(5): 536-541, 2009.
66. Zhou J, Lu Y, Gao X *et al*.: The growth hormone receptor gene is associated with mandibular height in a Chinese population. *J Dent Res*. **84**(11): 1052-1056, 2005.
67. Kang EH, Yamaguchi T, Tajima A *et al*.: Association of the growth hormone receptor gene polymorphisms with mandibular height in a Korean population. *Arch. Oral Biol*. **54**(6): 556-562, 2009.
68. Bayram S, Basciftci FA, Kurar E: Relationship between P561T and C422F polymorphisms in growth hormone receptor gene and mandibular prognathism. *Angle Orthod*. **84**(5): 803-809, 2014.
69. Adel M, Yamaguchi T, Tomita D *et al*.: Association of Growth Hormone Receptor Gene Variants with Mandibular Form in an Egyptian Population. *Showa Igakkai Zasshi*. **29**(2): 173-180, 2017.
70. Huang T, Shu Y, Cai Y-D: Genetic differences among ethnic groups. *BMC Genom*. **16**(1): 1-10, 2015.