A Comprehensive Review of Craniofacial Dysmorphology

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ABSTRACT

The cranio-facial complex undergoes postnatal growth and remodeling, achieving its full potential during adolescence. The timing of facial development differs between males and females, with males achieving facial maturity between the ages of 12 and 14, and females achieving it roughly two years later. Neurofibromatosis type 1, hemifacial microsomia, Tracer Collins syndrome, Moebius syndrome, and other frequent craniofacial dysmorphologies are all examples of common craniofacial dysmorphologies. Despite the fact that this one had a lot of cranial-facial abnormalities, more rigorous reviews should be conducted.

Keywords: Craniofacial Dysmorphologies, Neurofibromatosis type 1**.**

Introduction

In comparison to other great apes as well as within our own species, the facial appreance of human beings & its related cranial and facial structures" has been significantly declared different from past various studies.[1] The evolution of human craniofacial structures, in comparison to the nearest living mutative family are mainly "chimpanzees and bonobos", has played a very important function in the evolution for human crainofacial struuctures. These changes have also potentially aided in adaptations related to bipedal locomotion, dietary habits, and speech articulation[2,3,4] "In accordance with the swift development of craniofacial characteristics, contemporary human craniums display diverse features compared to those of species who extinct hominins such as Homo erectus, archaic humans, and Neanderthals".[5] Conversely, It has been suggested that certain facial traits (such as nose shape) promote climate modification in human societies.[6] Because of its role in permitting biological adaptations, the human face is not only an important component of communication and social interactions but also a strong target of sexual selection.[7,8] As a result, the medical implications of craniofacial anomalies, which are among the most common congenital illnesses, are substantial, as are the social consequences for patients and their families. It is critical to understand the processes underlying human craniofacial variation in both health and sickness in order to create therapeutic strategies, treatment regimens, and reconstructive techniques for a wide variety of craniofacial abnormalities.

Embryology : Development Normal Anatomical Face

Throughout the embryonic stages, particularly between the third and eighth weeks of gestation, a complex process happens that culminates in the face.[9] Cranial neural crest cells (CNCCs), a transitory cell population that arises from the neural folds of the developing craniofacial plate, are the principal source of tissues for the craniofacial complex. After being characterized, cranial neural crest cells (CNCCs) migrate to the embryo's ventral half after undergoing an epithelial-to-mesenchymal transition. The aforementioned process ultimately leads to the formation of the craniofacial skeleton and connective tissue through the process of differentiation into cartilage, bones, and tendons.[10] In the initial phases of embryogenesis, there is a clear differentiation between the cranial neural crest cells (CNCs) responsible for generating the frontonasal prominence and those that populate the four pharyngeal arches. This event represents a significant division in the development of craniofacial tissues. The prominence located at the junction of the frontal and nasal bones, known as the fronto-nasal prominence, plays a crucial role in the morphogenesis of the forehead and nasal bones, particularly in the formation of the nasal bridge and dorsum. The paired maxillary and mandibular prominences are of embryonic origin and arise from the first branchial arch. These prominences remain distinct from each other because of the presence of the

stomodeum. The residual branchial arches are responsible for the development of structures outside of the craniofacial region. During the fifth week of embryonic development, the frontonasal prominence undergoes thickening on both sides, leading to the formation of nasal placodes that eventually give rise to the lateral and medial nasal prominences. The convergence of the mandibular prominences at the midline also influences the development of the jaw, chin, and lower lip. The process of merging the medial nasal prominences is followed by the merging of the maxillary prominences around seven weeks after conception, ultimately culminating in the development of the central anatomical components of the nose (columella) and the upper middle region of the lip (philtrum). When the lateral nasal prominences and the maxillary prominences come together, the sides and wings of the nose form. During the remaining weeks of pregnancy, the existing structures undergo a process of growth and development.[11]

The convergence of the mandibular prominences at the midline also influences the development of the jaw, chin, and lower lip. The process of merging the medial nasal prominences is followed by the merging of the maxillary prominences around seven weeks after conception, ultimately culminating in the development of the central anatomical components of the nose (columella) and the upper middle region of the lip (philtrum). When the lateral nasal prominences and the maxillary prominences come together, the sides and wings of the nose form. In the last stages of pregnancy, the structures that were already there grow and mature. This led to the discovery of three fundamental principles: (a) the importance of neural crest-specific cell-autonomous patterning; (b) the importance of neural ligands as embryo region-specific environmental cues for proper neural patterning; and (c) the observation that different combinations of the same neural crest patterns result in different craniofacial development. The generation of sequence-specific transcription factors through cell-autonomous and signaling-responsive pathways is a crucial method for achieving the desired patterning.[12]

"Several key signaling pathways that convey environmental signals to (CNCCs) and other types of craniofacial have been previously explored in detail in various studies". Listed are some of the few ones as follows: transforming growth factor beta (TGF-)[13], fibroblast growth factor (FGF)[14] , bone morphogenetic protein (BMP)[15], Sonic hedgehog (Shh)[16], wingless/Int-1[17], and TGF-β[18]. "naddition, studies done on birds had showed that species-specific feature for cranio -facial complex was mainy driven by the neural crest. Hence, (CNCCs) may be a major important factor for determining the craniofacial dysmorphology, despite their complex interactions presence between CNCCs and other cell types in the formation of craniofacial structures.[19]

"Various studies have shown that the craniofacial complex further leads to postnatal growth and remodeling, achieving its maximum potential during the period of adolescence".[20] There exists a discrepancy in the timing of facial development between males and females, with males achieving facial maturity at ages 12 to 14 and females reaching this milestone approximately two years later.[21] The process of remodeling is frequently influenced by the balance between osteogenesis, which involves the generation of new bones by osteoblasts, and osteoclastogenesis, which involves the breakdown of old bones by osteoclasts. Biomechanical stressors are partially responsible for the typical formation and dissolution processes.[22] While it is certain that various factors play a role in remodeling variation, the specific mechanisms through which they exert their influence remain largely ambiguous. "Recent studies have indicated the existence of skeletal stem cells in various regions of the body".[23,24]

Most Common Dysmorphology Of Craniofacial

A. Neurofibromatosis Type 1

"According to various past studies ,patients with NF1 often have a short mandible, maxilla, cranial base, and low facial height".[25,26] "Research done in 2012 by Visnapuu et al., concluded that around 20% of patients have an expanded mandibular canal".[27] In addition, according to many studies there was an increased length of the coronoid process, hypoplastic condyles, and zygomatic processes as well as increased frequency of the Class III molar relationship which can be observed in the posterior border of the mandibular ramus. On the basis of various studies conclusion, when the frequency of crainofacial dysmorphology (such as asymmetries and hypertelorisms) was compared between an NF1 reference group and the patients were with most severe NF1 phenotype (i.e., with type-1 NF1 deletions; see previous paragraph) which leads to be significantly lower frequencies of facial dysmorphology , then they observed that the entire NF1 reference group (6–8%) compared to the NF1 deletions (28%).[28]

B. Hemifacial Microsomia

"A study done on 2015 concluded that forty seven out of 51 patients (92%) present with uni- or bilateral (24/23) ear abnormalities that were associated with hearing loss".[29] Study done in 2014 where, HFM was present in 90% of the patients, which is consistent with its connection with facial nerve palsy (FNP). FNP may alter craniofacial growth asymmetry in addition to mandibular condyle hypoplasia and soft tissue asymmetry.[30] Among the most common craniofacial abnormalities of HFMin are hypoplasia of the zygomatic, mandibular, and maxillary bones, as well as hypoplasia of the facial muscles.[29] Upper eyelid colobomas are a rather common condition. Although most cases impact just one side, bi-lateral involvement has been seen. Patients with HM present an upward cant of the occlusal plane, a smaller occlusal plane, and a smaller occlusal plane.[31,32]

C. Treacher Collins Syndrome

"Not more recently ,Vincent et al. (2016) have demonstrated the incidence of all clinical features observed in TCS1 in 70 patients. These authors proved that the vast majority of the symptoms were: craniofacial and comprised downward-slanting palpebral fissures (in 100% of the patients); malar hypoplasia (in 99%); conductive deafness (in 91%); mandibular hypoplasia (in 87%); atresia of the external ear canal (in 72%); microtia (in 71%); coloboma of the l; andower eyelid (in 65%); facial asymmetry (in;53%), and projection of scalp hair onto the lateral cheek (in 48%)".[33] "In Vincent study, TCS1 patients were more likely to develop choanal stenosis or atresia (14%), as well as a research cleft palate (22%). It has also been reported that many children with TCS (of any form) have a narrow arched palate, maxillary hypoplasia, and a retrognathic jaw. Soft tissue hypoplasia is observed on the face.[33] " In various studies complex temporomandibular joint defects have been associated with anterior open bites of varying severity".[28] Some research has reported that many patients had cleft palate with or without cleft lip.[28]

D. Möbius Syndrome

"Studies have proved that sucking difficulties and excessive drooling are usually the first symptoms, followed by breathing difficulties".[34] Studies have also concluded in past that as children becomes older , his or her inability to regulate his or her facial muscles and eyes becomes more evident.[35,36] Other anomalies commonly associated with cleft lip and cleft palate include jaw abnormalities and orofacial dysmorphology have been illustrated in past studies.[28]

"Studies proved that MBS children are commonly born with chronic micrognathia and microstomia".[28] "Studies also concluded that around 30% of patients with this disorder have a cleft palate and their maxillae are usually tiny and arched upwards.[28]

E. Eec-Syndrome

EEC patients are more likely to have an orofacial cleft. Microcephaly, premaxillary protrusion, and midfacial, zygomatic, maxillary, and mandibular hypoplasia all occur in 1–5% of EEC patients. Studies have also proved that SNPs in a TP63 enhancer were linked to lip clefts with or without cleft palate (CL/P) in genome-wide meta-analyses of non-syndromic orofacial clefts.[28]

F. Kabuki Syndrome

"Many studies have concluded (KS) crainofacial charateristics which includes Microcephaly, a short columella, a broadened nose tip, arched eyebrows, long eyelashes, long palpebral fissures with eversion of lateral parts of the lower lids, and large protruding or cupped".[28] "Studies have concluded that almost half of all KS patients have a cleft palate, and those who do frequently have a highly arched palate as well. Open bites, unilateral posterior cross bites, and Angle class III malocclusions are all commonly seen".[28]

G. Kallmann Syndrome

A cleft palate has been reported in various past studies about one-fifth of KAL-1 patients. Patients with Kallmann had showed increased mandibular angulation in addition to severe mandibular and maxillary retrognathiain a lot of previous studies.[28]

H. Pierre Robin Sequence

According to previous studies conducted, it has been found that cleft palate is a prevalent condition among patients diagnosed with PRS, with a reported occurrence rate ranging from 75% to 100%. The mandibular morphology and location of patients with PRS exhibit variability based on the presence and characteristics of co-occurring disorders.When comparing patients with isolated Pierre Robin Sequence to healthy controls, it was observed that the ratio of ramus height to mandibular body and the gonial angle were both higher. Furthermore, it has been observed that individuals with nonsyndromic Pierre Robin Sequence exhibit elevated palatal and mandibular plane inclinations, in addition to a reduced cranial base and maxillary length. The absence of any indication regarding the manifestation of teenage catch-up development in the mandible may serve as a

preventive measure against mandibular micrognathia, as suggested by previous studies .[28]

I. Van Der Woude Syndrome

"The prevalence of clefts in VWS patients exhibits a broad range, as documented by various studies with reported rates ranging from 21% to 100%.[28] The maxillary height and sagittal length of patients with Velo-Cardio-Facial Syndrome (VWS) exhibit indications of insufficient growth. This phenomenon has been observed in previous studies, where a smaller angle between the nadir (ANB) and the bregma indicates a certain characteristic." The findings of previous studies did not support the aforementioned conclusions." According to past studies, individuals with Van der Woude syndrome (VWS) exhibit a reduced lower pharyngeal airway width in comparison to those without the syndromic type of orofacial clefting (OFC)".[28]

J. Coffin-Lowry Syndrome

Craniofacial anomalies exhibit a non-specific presentation in newborns with Claes-Jensen syndrome (CLS), and the distinctive facial features associated with the syndrome do not manifest until the child reaches two years of age. "The majority of affected males and some affected females exhibit typical craniofacial traits, including a broad forehead, hypertelorism, a flat nasal bridge, a downward slope of palpebral fissures, large and thick ears, and a wide mouth with lip ridges". Studies have concluded that posited that the aforementioned traits exhibit a decline in quality as individuals advance in age. The prevalence of high, narrow palates and malocclusions, such as open bites in the front, has been reported in previous studies.[28]

K. Opitz Gbbb Syndrome

"It has been clarily indicated with various past studies that a low-set ear position, a thin upper lip, a flat nasal bridge, and a prominent forehead with a widow's peak hairline are some of the craniofacial traits associated with this syndrome estimate that half of all people are born with a cleft lip and/or palate".[28]

L. Smith-Lemli-Opitz Syndrome

Previous studies have identified a range of craniofacial symptoms associated with this disorder, including microcephaly, bi-temporal constriction, ptosis, a short nose with anteverted nares, low-set and retroverted ears, ocular problems and hypertelorism, a small chin, and micrognathia.According to some, elevated levels of 7DHC are linked to additional clinical features such as cleft palate and bifid uvula. The occurrence of cleft palates was documented in 40–50% of patients, as reported by many studies in past. [28]

Publication	SNP	Gene	Effect
Paternoster et al., 2012	rs7559271	*PAX3*	Nasion–midendocanthion distance
Liu et al., 2012	rs4648379	*PRDM16*	Nose width and nose height
	rs168686344, rs12694574, rs974448	*PAX3*	Distance between eyeballs and nasion
	rs17447439	*TP63*	Distance between the eyeballs
	rs6555969	*C5orf50*	Nasion position
	rs805722	*COL17A1*	Distance between eyeballs and nasion
Adhikari et al., 2016	rs12644248	*DCHS2*	Columella inclination
	rs1852985	*RUNX2*	Nose bridge breadth
	rs17660804	*GLI3*	Nose wing breadth
	rs927833	*PAX1*	Nose wing breadth
	rs3827760	*EDAR*	Chin protrusion
Shaffer et al., 2016	rs6129564	*MAFB*	Cranial base width
	rs17106852	*PAX9*	Cranial base width
	rs17106852	*MIPOL1*	Cranial base width
	rs619686	*ALX3*	Intercanthal width
	rs11093404	*HDAC8*	Intercanthal width
	rs2424399	*PAX1*	Nasal width
Cole et al., 2016	rs79909949	*SCHIP1*	Centroid size
	rs12909111, rs12908400	*PDE8A*	Allometry

TABLE 1 : FACIAL MORPHOLOGY BY GWAS.[37]

Conclusion

The process of craniofacial morphogenesis is intricate and involves the regulation of signaling networks and gene expression patterns in a spatial and temporal manner. It commences with the production and migration of cranial neural crest cells and advances towards the development of facial prominences and their corresponding structures. The cranial-facial complex undergoes growth and alteration after birth,

achieving its maximal capability in adolescence. Males reach facial maturity at the age of 12–14, while females reach it two years later. This review included several crainofacial deformities; however, further in-depth reviews should be conducted**.**

Reference

1. Mitteroecker P, Gunz P, Bernhard M, Schaefer K, Bookstein FL. Comparison of cranial ontogenetic trajectories among great apes and humans. Journal of human evolution. 2004 Jun 1;46(6):679-98.
2. Katz DC, Grote MN, Weaver TD. Changes in human skull morphology across the agricultural transition are consistent with softer diets in preindustrial farming groups. Proceedings of the National Academy of Sciences. 2017 Aug 22;114(34):9050-5.
3. Neubauer S, Hublin JJ, Gunz P. The evolution of modern human brain shape. Science advances. 2018 Jan 24;4(1):eaao5961.
4. Lieberman P. The evolution of human speech: Its anatomical and neural bases. Current anthropology. 2007 Feb;48(1):39-66.
5. Barton RA, Venditti C. Rapid evolution of the cerebellum in humans and other great apes. Current Biology. 2014 Oct 20;24(20):2440-4.
6. Zaidi AA, Mattern BC, Claes P, McEcoy B, Hughes C, Shriver MD. Investigating the case of human nose shape and climate adaptation. PLoS genetics. 2017 Mar 16;13(3):e1006616.
7. Guo J, Tan J, Yang Y, Zhou H, Hu S, Hashan A, Bahaxar N, Xu S, Weaver TD, Jin L, Stoneking M. Variation and signatures of selection on the human face. Journal of human evolution. 2014 Oct 1;75:143-52.
8. Sheehan MJ, Nachman MW. Morphological and population genomic evidence that human faces have evolved to signal individual identity. Nature communications. 2014 Sep 16;5(1):4800.
9. Som PM, Naidich TP. Illustrated review of the embryology and development of the facial region, part 1: early face and lateral nasal cavities. American Journal of Neuroradiology. 2013 Dec 1;34(12):2233-40.
10. Cordero DR, Brugmann S, Chu Y, Bajpai R, Jame M, Helms JA. Cranial neural crest cells on the move: their roles in craniofacial development. American journal of medical genetics Part A. 2011 Feb;155(2):270-9.
11. Som PM, Streit A, Naidich TP. Illustrated review of the embryology and development of the facial region, part 3: an overview of the molecular interactions responsible for facial development. American Journal of Neuroradiology. 2014 Feb 1;35(2):223-9.
12. Naqvi S, Hoskens H, Wilke F, Weinberg SM, Shaffer JR, Walsh S, Shriver MD, Wysocka J, Claes P. Decoding the human face: Progress and challenges in understanding the genetics of craniofacial morphology. Annual review of genomics and human genetics. 2022 Aug 31;23:383-412.
13. Dudas M, Kaartinen V. TGF-B superfamily and mouse craniofacial development: Interplay of morphogenetic proteins and receptor signaling controls normal formation of the face. Current Topics on Developmental Biology. 2005 Mar 31;66:65-133.
14. Nie X, Luukko K, Kettunen P. FGF signalling in craniofacial development and developmental disorders. Oral diseases. 2006 Mar;12(2):102-11.
15. Graf D, Malik Z, Hayano S, Mishina Y. Common mechanisms in development and disease: BMP signaling in craniofacial development. Cytokine & growth factor reviews. 2016 Feb 1;27:129-39.
16. Dworkin S, Boglev Y, Owens H, Goldie SJ. The role of sonic hedgehog in craniofacial patterning, morphogenesis and cranial neural crest survival. Journal of developmental biology. 2016 Aug 3;4(3):24.
17. Reynolds K, Kumari P, Sepulveda Rincon L, Gu R, Ji Y, Kumar S, Zhou CJ. Wnt signaling in orofacial clefts: crosstalk, pathogenesis and models. Disease models & mechanisms. 2019 Feb 1;12(2):dmm037051.
18. Dudas M, Kaartinen V. 2005. Tgf-β superfamily and mouse craniofacial development: interplay of morphogenetic proteins and receptor signaling controls normal formation of the face. Curr. Top. Dev. Biol. 66:65–133**.**
19. Schneider RA. Neural crest and the origin of species-specific pattern. Genesis. 2018 Jun;56(6-7):e23219.
20. Som PM, Streit A, Naidich TP. Illustrated review of the embryology and development of the facial region, part 3: an overview of the molecular interactions responsible for facial development. American Journal of Neuroradiology. 2014 Feb 1;35(2):223-9.
21. Kau CH, Richmond S. Three-dimensional analysis of facial morphology surface changes in untreated children from 12 to 14 years of age. American Journal of Orthodontics and Dentofacial Orthopedics. 2008 Dec 1;134(6):751-60.
22. Enlow DH, Hans MG. Growth of the mandible. Essentials of facial growth. Philadelphia: WB Saunders. 1996:57-78.
23. Chan CK, Gulati GS, Sinha R, Tompkins JV, Lopez M, Carter AC, Ransom RC, Reinisch A, Wearda T, Murphy M, Brewer RE. Identification of the human skeletal stem cell. Cell. 2018 Sep 20;175(1):43-56.
24. Chan CK, Seo EY, Chen JY, Lo D, McArdle A, Sinha R, Tevlin R, Seita J, Vincent-Tompkins J, Wearda T, Lu WJ. Identification and specification of the mouse skeletal stem cell. Cell. 2015 Jan 15;160(1-2):285-98.
25. Heervä E, Peltonen S, Pirttiniemi P, Happonen RP, Visnapuu V, Peltonen J. Short mandible, maxilla and cranial base are common in patients with neurofibromatosis 1. European journal of oral sciences. 2011 Apr;119(2):121-7.
26. Cung W, Friedman LA, Khan NE, Romberg E, Gardner PJ, Bassim CW, Baldwin AM, Widemann BC, Stewart DR. Cephalometry in adults and children with neurofibromatosis type 1: Implications for the pathogenesis of sphenoid wing dysplasia and the "NF1 facies". European journal of medical genetics. 2015 Nov 1;58(11):584-90.
27. Visnapuu V, Peltonen S, Tammisalo T, Peltonen J, Happonen RP. Radiographic findings in the jaws of patients with neurofibromatosis 1. Journal of oral and maxillofacial surgery. 2012 Jun 1;70(6):1351-7.
28. Bartzela TN, Carels C, Maltha JC. Update on 13 syndromes affecting craniofacial and dental structures. Frontiers in physiology. 2017 Dec 14;8:1038.
29. Beleza-Meireles, A., Hart, R., Clayton-Smith, J., Oliveira, R., Reis, C. F., Venancio, M., et al. (2015). Oculo-auriculo-vertebral spectrum: clinical and molecular analysis of 51 patients. Eur. J. Med. Genet. 58, 455–465.
30. Choi J, Park SW, Kwon GY, Kim SH, Hur JA, Baek SH, Kim JC, Choi TH, Kim S. Influence of congenital facial nerve palsy on craniofacial growth in craniofacial microsomia. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2014 Nov 1;67(11):1488-95.
31. Shibazaki-Yorozuya R, Yamada A, Nagata S, Ueda K, Miller AJ, Maki K. Three-dimensional longitudinal changes in craniofacial growth in untreated hemifacial microsomia patients with cone-beam computed tomography. American

Journal of Orthodontics and Dentofacial Orthopedics. 2014 May 1;145(5):579-94.
32. Heike CL, Wallace E, Speltz ML, Siebold B, Werler MM, Hing AV, Birgfeld CB, Collett BR, Leroux BG, Luquetti DV. Characterizing facial features in individuals with craniofacial microsomia: a systematic approach for clinical research. Birth Defects Research Part A: Clinical and Molecular Teratology. 2016 Nov;106(11):915-26.
33. Vincent M, Geneviève D, Ostertag A, Marlin S, Lacombe D, Martin-Coignard D, Coubes C, David A, Lyonnet S, Vilain C, Dieux-Coeslier A. Treacher Collins syndrome: a clinical and molecular study based on a large series of patients. Genetics in Medicine. 2016 Jan;18(1):49-56.
34. Verzijl HT, van der Zwaag B, Cruysberg JR, Padberg GW. Möbius syndrome redefined: a syndrome of rhombencephalic maldevelopment. Neurology. 2003 Aug 12;61(3):327-33.
35. Zuker RM, Goldberg CS, Manktelow RT. Facial animation in children with Möbius syndrome after segmental gracilis muscle transplant. Plastic and reconstructive surgery. 2000 Jul 1;106(1):1-8.
36. Sjögreen L, Lohmander A, Kiliaridis S. Exploring quantitative methods for evaluation of lip function. Journal of Oral Rehabilitation. 2011 Jun;38(6):410-22.
37. Roosenboom J, Hens G, Mattern BC, Shriver MD, Claes P. Exploring the underlying genetics of craniofacial morphology through various sources of knowledge. BioMed research international. 2016 Oct;2016.