A review of genetics of nasal development and morphological variation

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Abstract

The nose is central in the determination of facial esthetics. The variations in its structural characteristics greatly influence the ultimate dentoskeletal positioning at the end of an orthodontic therapy. A careful insight into its developmental etiology will greatly aid the health care professional in identifying patient's real concern about the facial appearance. This in turn will aid in the fabrication of a better treatment plan regarding the end placement goals for the teeth and jaws in all the three dimensions of space. However, this important structure is often missed as a part of the diagnostic and treatment planning regime owing to the lack of meticulous understanding of its developmental etiology by the orthodontists. The development of the nose in the embryo occurs in pre skeletal and skeletal phases by a well-coordinated and regulated interaction of multiple signaling cascades with the crucial importance of each factor in the entire mechanism. The five key factors, which control frontonasal development are sonic hedgehog (SHH), fibroblast growth factors (FGF), transforming growth factor β (TGFβ), wingless (WNT) proteins, and bone morphogenetic protein (BMP). The recent evidence suggests the association of various nasal dimensions and their related syndromes with multiple genes. The revelation of nasal genetic makeup in totality will aid in ascertaining the direction of growth, which will govern our orthodontic treatment results and will also act as a harbinger for potential genetic editing and tissue engineering. This article describes at length the morphological and genetic aspect of nasal growth and development in light of the gender and racial variability along with the emphasis on the importance of knowing these nasal features with regard to diagnosis and treatment planning in orthodontics.

Keywords: Craniofacial, development, frontonasal, genetics, neural crest cell, nose

Introduction

Nasal morphology has a great bearing on the facial appearance of an individual. An eye-tracking analysis of observers asked to identify a male or female face has shown gaze concentration around the nasal base.[1] The importance of the nose in facial esthetics was first emphasized by Jones,[2] whereas Meerdink

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et al. found a high correlation between nasal attractiveness and facial esthetics.[3] Further, its importance can be elucidated from the fact that rhinoplasty is a commonly performed procedure to improve facial esthetics.[4] Moreover, the nasal region was found to be more reliable in the detection of asymmetry as compared to mouth or eyes.[5] The orientation of the nasal ridge greatly affects the perception of symmetry owing to its location at the facial center of gravity.[6] Thus off-centered nose tip may lead to disparity in the size of either side of the face and may be mistaken for facial asymmetry. The nose is proximal to tissues affected by the orthodontic treatment, and hence nasal dimensions, growth, and development should be considered while making the treatment plan. Therefore, when studying facial esthetics,

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it is essential to understand growth, form, and function of the nose and the role of genes in defining nasal morphology. This is highly important in the cases of craniofacial syndromes where nasal form may show significant deviations and may limit the scope of orthodontic treatment unless surgical corrections are planned. The primary care physicians must have a thorough understanding of these facts concerning the facial appearance of the patients to direct appropriate treatment measures. Thus, the current paper describes the genetic basis affecting the various aspects of nasal morphology at length along with the clinical relevance of various anatomical variations in nasal morphology.

Data selection

We retrieved pertinent literature on the genetics of the development of the nose and its morphological variation, selected references and internet services using PubMed and Google scholar databases. We conducted comprehensive literature search using keywords, "craniofacial development;" "frontonasal development", "nose and genetic variation" and "facial morphology and genes."

Clinical and research consequences

A.   Morphological aspects of nasal development

i). Nasal growth, form, and function

- **1. Nasal Growth-** The nasal growth is central to the growth and development of the entire face. The nasal septum acts as a growth site producing maxillary pull, which directs facial growth in forward and downward direction causing sevenfold increase in vertical length between 10th and 40th weeks post conception. The nasal cavity and nasal septum continue to be the prime determinant of facial growth pattern even post natally by acting as functional matrices.

At birth, the nasal cavity floor lies between orbits and gradually positions below them by the age of 6 years.[7] The nasal growth ceases by the age of 16 years in girls and 18 years in boys.[8] The nasal length increases at the rate of 1.5 mm per year.[9]

The deficient growth and development of the nose and associated maxillary hypoplasia is seen in Binder's syndrome [Table 1]. The maxillary development remains deficient in the absence of nasal septal cartilaginous growth.

- **2. Nasal form and function**. The nasal profile varies with varying skeletal transverse, sagittal, and vertical facial dimensions. Orthodontic treatment involving expansion, facemask therapy, extraction, growth modification, and orthognathic surgery impact nasal appearance.[10]

One of the major functions of the nasal cavity is the conditioning of the upper respiratory tract before passing it to the lower respiratory tract.[11] Thus, variations in the shape of the nose across populations may be attributed to acclimatization to prevailing climatic conditions.[11] The nasal obstruction affects

the development and further growth of dentofacial complex. The correlation of form and function of the nose is well reflected in mouth breathers where the inadequate use of the empty space of the nasal cavity by mouth breathing causes long narrow face and high palatal vault.[7]

ii). Racial and gender variation

Racial and gender differences were observed in the nasal index (width of the nasal aperture/height of the nasal aperture).[12,13] The distance between nasal alare was found to be higher in West African, South and East Asian races as compared to European races.[12]

3-D observations have revealed the protuberance of the nose as the largest anatomical sexual dimorphism in the human face[14] with nasal dimensions being higher in males.[15] Ideal nasal form has a dorsum which is straight, along with the presence of supratip break formed by cartilages above the nasal tip.[16] Enlow *et al.* observed straight to convex nose in males and straight to concave nose in females.[17] Thus, racial and gender variations in nose are important considerations for plastic surgeons while planning for rhinoplasty and also for forensic investigations.[13]

B. The genetic basis of development of the nose

With the great advancements at the molecular level, the role of genes is evident in determining the embryonic plan of the craniofacial development. Unlike genetic mutations that are alterations in DNA sequence, epigenetic alterations are changes in gene expression while both are heritable.[18]

The development of the nose is a multistep process involving cross talk among multiple signaling cascades, epithelial mesenchymal interactions, which regulate neural crest development, frontonasal process outgrowth, patterning, and skeletal differentiation. Overall, 173 genes are expressed in frontonasal prominence. There is an upregulation of 64 genes in the 4th week, 26 genes in the 5th week in frontonasal prominence, 36 genes in the 6th week in medial nasal prominence, and 45 genes in lateral nasal prominence.[19]

The nasal cartilaginous capsule is derived from neural crest cells. The development of nose occurs in 2 phases:

1) The pre skeletal phase, which consists of the formation of mesenchymal swellings encompassing external nasal placodes,
2) The skeletal phase comprising chondrocranial phase, which establishes cartilaginous scaffolding and ossification phase involving an ingression of cellular constituents followed by the coalescence of skeletal components.[20]

1.   Pre skeletal phase

The five key factors, which control frontonasal development through cell proliferation and differentiation are sonic hedgehog (SHH), fibroblast growth factors (FGF), transforming growth factor β (TGFβ), wingless (WNT) proteins, and bone morphogenetic protein (BMP)[21] [Figure 1]. Neural crest cells contributing to frontonasal process originate from the caudal

Table 1: Syndromes having nasal deformities and the associated genes

Syndrome	Gene	Chromosome	Nasal deformity
Apert syndrome (OMIM #101200)	FGFR2	10q25-10q26	Short broad nose, depressed nasal bridge, deviated nasal septum,[57] choanal stenosis and saddle nose with bulbous tip.[58]
Crouzon syndrome (OMIM #123500)	FGFR2	10q25-10q26	Parrot beak appearance of the nose due to frontal shortening of the dorsum of the nose,[59] narrow anterior nares and nasal septal deviation.[58]
Pfeiffer syndrome (OMIM #101600)	FGFR1, FGFR2	8p11.2-p12 (FGFR1),10q (FGFR2)	Beaked[58] and small nose with low nasal bridge.
Hutchinson Gilford progeria syndrome (OMIM #176670)	LMNA (LMNA encodes laminins A and C, which are the main components of intermediate filamentous lamina, function as a structural support, and are essential for DNA replication and mRNA transcription.)	1q22	Thin nasal skin, convex nasal profile,[59] and beaked nose.
Treacher Collins syndrome (OMIM #154500)	TCOF1	5q31.3-33.3	Nasal deformity leads to compromised respiration.[59]
Waardenburg syndrome (OMIM #193500)	PAX3	2q36.1	Increased distance between medial canthi of the eyes and broad nasal ridges.[60]
Craniofacial-deafness hand syndrome (OMIM #122880)	PAX3	2q35	Short nose and hypoplasia of nasal bones.[61]
Fraser syndrome (OMIM #219000, OMIM #617666, OMIM #617667)	FRAS1,FREM2,GRIP1 (present in basement membrane and have role in epithelial mesenchymal interaction)	4q21 (FRAS1) 13q13 (FREM2) 12q14 (GRIP1)	Broad nose with midline groove, a depressed nasal bridge, hypoplastic nares with colobomas, choanal stenosis, and a beaklike appearance.[62]
Cleidocranial dysplasia (OMIM #119600)	RUNX2	6p21	Depressed nasal bridge and hypoplastic nasal bone.
Axenfeld Reiger syndrome (OMIM #602482)	PITX2, FOXC4	4q25 (PITX2), 6p25 (FOXC4)	Broad flat nasal root.[59]
Goltz syndrome (OMIM #305600)	PORCN	Xp11.23	Asymmetrical ala nasi.[59]
Otofaciocervical syndrome (OMIM #615560)	PAX1	20p11	Sunken nasal root and excessive narrowing.[63]
Greig cephalopolysyndactyly syndrome (OMIM #175700)	GLI3	7p13	Broad nose.[64]
Binder syndrome	*	*	Hypoplasia of the anterior nasal spine, a short columella, an obtuse nasofrontal angle, flat nasal bridge, abnormal nasal bone position and nasal mucosa atrophy.
Holoprosencephaly type 3	SHH	7q36	Flat nose and single nares (cebocephaly).[65]
Rubinstein Taybi syndrome (OMIM #180849)	CREBBP	16p13.3	Beaked nose and deviated nasal septum.[59]
Orofacial digital syndrome I (OMIM #311200)	OFD1	Xp22.2	Aplasia of alar cartilage and broadened nasal bridge/root.[59]
Cornelia de Lange syndrome (OMIM #300882)	HDAC8	Xq21.2-q21.3	Depressed nasal bridge and bulbous nose tip.[66]
Alagille syndrome (OMIM #118450)	JAGGED1, NOTCH2	20p12 (JAGGED1) 1p13 (NOTCH2)	Straight nose with bulbous tip and depressed nasal bridge.[67]
Opitz syndrome (OMIM #614140)	SPECC1L (interaction with actin cytoskeleton and microtubules and has a role in migration and adhesion of facial processes) MID1 (microtubule associated protein and responsible for microtubule dynamics)	22q11.23 (SPECC1L) Xp22 (MID1)	Broad nasal bridge, anteverted nares and hypertelorism.[68]
Burn-Mckeown syndrome (OMIM #608572)	TXNL4A	18q23	Prominent nose with high nasal bridge.[69]

Contd...

| Syndrome	Gene	Chromosome	Nasal deformity
		Table 1: Contd...	
Saethre-Chotzen syndrome (OMIM #101400)	TWIST1	7p21	Beaked nose with deviated nasal septum and broad depressed nasal bridge.[58]
Muenke syndrome (OMIM #602849)	FGFR3	4p16.3	Choanal stenosis and saddle nose with bulbous tip.[58]
Stickler syndrome (OMIM # 108300)	COL2A1	12q13.11	Depressed nasal bridge.[58]
Shprintzen syndrome (OMIM #192430)	TBX1	22q11.2	Nose is prominent, with a broad nasal dorsum and narrow alar base.[58]

* not identified in the literature
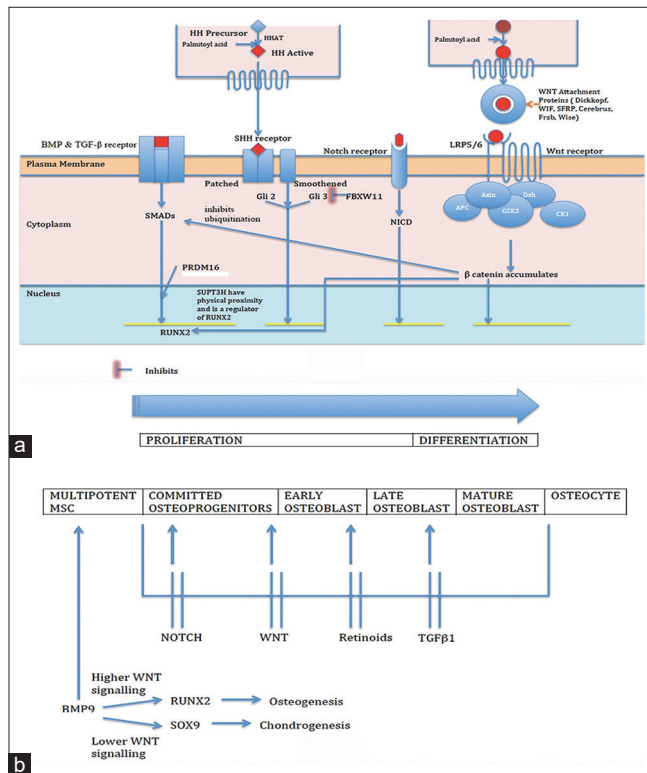
Figure 1: Cell signaling in frontonasal development. (a) Depicted are TGFβ, BMP, SHH, NOTCH, and WNT signaling cascades in osteoblastogenesis. (b) Signaling pathways at various stages of osteoblastic differentiation of mesenchymal stem cells
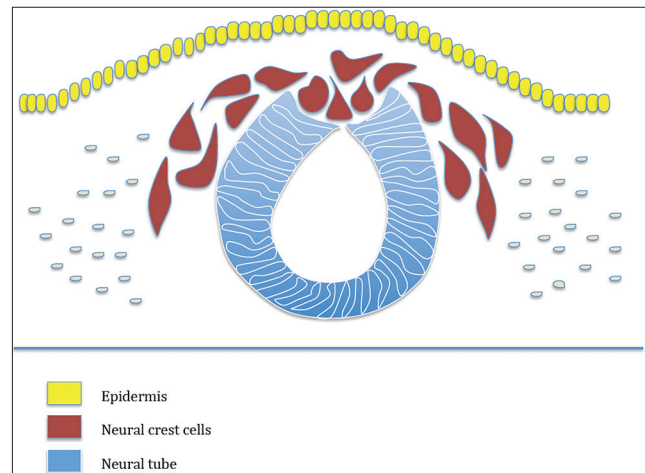

Figure 2: Neural crest cells contributing to frontonasal process originate from the crest of the neuroectoderm under BMP signaling and undergo an epithelial-to-mesenchymal transition on WNT stimulation

FGF8 and SHH are expressed in neuroepithelium and ectoderm of the frontonasal process creating a frontonasal ectodermal zone (FEZ) with an expression boundary between them. FGF8 is essential for early FEZ activity[24] and later was down regulated for the growth of frontonasal process. Retinoic acid (RA) synthesized in the frontonasal process (FNP) ectoderm expresses in neural crest cells through RA receptors. RA dependent signal from neural crest mesenchyme maintains the expression of FGF8 and SHH. FGF8 and SHH, in turn, maintains neural crest mesenchyme to initiate FNP outgrowth [Figure 3].

At the 5th week of intrauterine life (IU), FNP develops medial and lateral nasal prominences on the both sides from mesoderm bordering the nasal placodes arising from surface ectoderm.[25] In the 6th week, nasal placodes invaginate into paraxial mesoderm to form the nasal pits under signaling by WNT production from the facial epithelium.[26] The SHH is expressed in the ectoderm of early medial nasal process and later its expression extends to the base of the nasal pit.[27]

The internal nose develops by theexpansion of nasal cavity with the atrophy of existing tissues and the formation of mesenchymal structures. The nasal pits deepen and lead to the formation of nasal sac by posterior fusion at the end of the 6th week. The oronasal membrane separates the nasal sac from the oral cavity and ruptures in the 7th week forming an opening with the oral

forebrain and the rostral midbrain neural plate under BMP signaling in the gastrula stage and migrate over prospective telencephalon to reach the most rostral aspect of the neural tube[22] [Figure 2]. The initiation of WNT1 expression causes epithelial to mesenchymal transition (EMT) of crest cells and the expansion of telencephalon restricts these neural crest cell population to the frontonasal region of developing face. WNT signaling triggers FGF8 expression in facial ectoderm, which aids in maintaining the survival of cells in facial ectoderm as well as mesenchyme in the course of establishment of facial primordia.[23]

Initially, FGF8 expression is present in cephalic ectoderm that will cover the frontonasal process. The expression of SHH is initiated with the migration of neural crest cells in cephalic ectoderm, which restricts FGF8 expression to nasal pits.[24] The
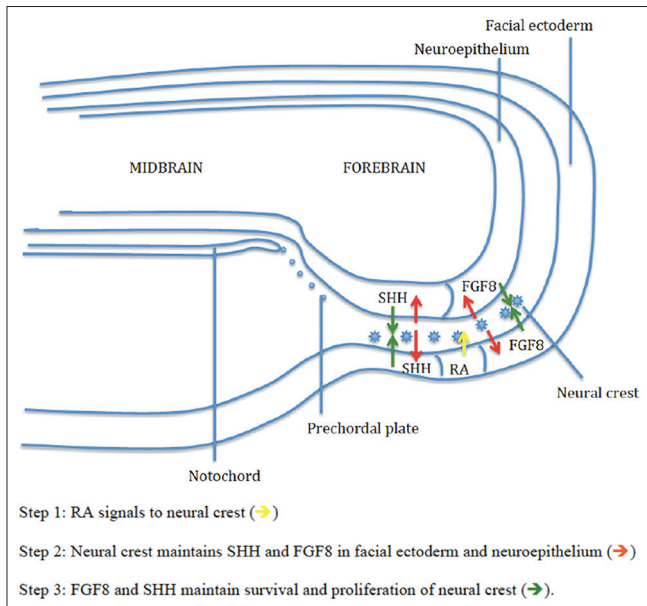
Figure 3: Signalling interactions in the initiation of the frontonasal process outgrowth. FGF8, Fibroblast growth factor 8; RA, retinoic acid; SHH, Sonic hedgehog

cavity. The primary palate lies as floor of the primary nasal fossa. The definitive choanae arise with the formation of the secondary palate, at the junction of definitive nasal cavity and pharynx.[26]

2. Skeletal Phase
The skeletal phase begins with the condensation of mesenchymal stem cells from neural crest mesoderm and sex-determining region Y (SRY)-box 9 (*SOX9*) and muscle segment homeobox (msh) homeobox 2 (*MSX2*) genes are upregulated.[28] The nasal cartilaginous frame is formed of ventral mesethmoid cartilage and dorsal ectethmoid cartilage. Mesethmoid comprises nasal septum and vomer, whereas ectethmoid forms olfactory system, lamina cribrosa, crista-galli apophysis, crura, and chonchae. Mesethmoid determines proximodistal nasal dimensions and ectethmoid decides nasal bridge location and size.[29] These cartilaginous structures either undergo endochondral ossification or get resorbed. SOX9 directly activates type-II collagen promoter and also upregulates BMP4, which induces chondrogenesis. SOX9 also activates the promoters of cartilage markers aggrecan and type X collagen, whereas MSX2 represses SOX9 mediated chondrogenesis.[28]

With the degeneration of oronasal membrane at the 6.5 weeks, cartilaginous nasal capsule becomes distinct. Nasal bridge forms by frontal prominence while the crest and nasal tip forms by coalescence of medial nasal prominences. The alae of the nose and the paired lateral crura of alar cartilages develop from lateral nasal prominences.[26,29] Three paired chondrification centers form lateral nasal cartilages.

At the 5th week, nasal septum arises from frontal prominence and grows in an antero-posterior direction to join tectoseptal mesenchymal expansion and finally palatine processes

resulting in two nasal chambers. The nasal septum comprises a plate of ethmovomerine cartilage having high BMP receptor type IB (BMPRIB) expression.[30] At the 8th week, bony nasal septum forms over cartilaginous capsule by two ossification centers, one on each side of the middle line. The postero-superior segment of this cartilage ossifies into the perpendicular plate of ethmoid; antero-inferior part remains as septal cartilage, while vomer ossifies in the membranus covering of its postero-inferior portion. Mesenchymal stem cells undergo osteogenic differentiation upon induction by BMP9 and these committed osteoprogenitors are subjected to further osteogenic differentiation by TGFβ.[31] BMP can also induce core binding factor alpha 1 (*CBFA1*)/runt-related transcription factor 2 (*RUNX2)* gene, which is a marker of osteogenesis. RUNX2 is prerequisite for osteoblastic differentiation and hence bone and cartilage formation.[32]

Orthodenticle homeobox 2 (*OTX2*) gene (14q21-22) is expressed in the neural crest cells of frontonasal region and its mutations affect the development of lateral nasal wall and nasal epithelium.[33] At 9-10 weeks, cartilages of superior, middle, and inferior conchae having high expression of BMPRIB and BMPRII[30] arise from cartilaginous nasal capsule. This is initiated by the appearance of furrows, six in number that are separated by ridges resembling ethmoturbinals. The uncinate process remains after the regression of first ethmoturbinal process. The second ethmoturbinal gives rise to middle turbinate, and the third forms the superior turbinate. The fourth and fifth processes fuse to form supreme turbinate. The middle meatus and hiatus semilunaris develop from first primary furrow, superior meatus from second, and supreme meatus from third. At 13-14 weeks, the bone of maxilla replaces the lateral cartilaginous capsule to form the lateral wall of the middle meatus. At 15-16 weeks, all the three nasal turbinates are completely formed. At 17-18 weeks, ossification of cartilaginous turbinates start.[34] Lateral nasal walls extend diverticula into maxillary, frontal, ethmoid, and sphenoid bones to form paranasal sinuses. Each nasal bone is ossified from a single center, which arises in the membrane covering the cartilaginous nasal capsule at the initiation of third fetal month.

Ossification increases until puberty with outer nasal cartilages and some vomeronasal organ associated structures remaining as cartilages thereafter. It may be due to non responsiveness of FNP to WNT signaling while lateral nasal prominence is WNT positive.[35]

C. Correlation of nasal morphology and genetic basis of nasal development
The genotype along with epigenetic and environmental factors determines the phenotype of the organism, but the genotype is established prior to the characterization of phenotype. The nasal features like nose width, height, and prominence have a strong genetic component.[36] Nasal morphological dimensions have been represented in Figure 4. Loss of Aristaless like homeobox genes (*ALX1*, *ALX3*, and *ALX4*) has been observed to cause frontonasal dysplasia in humans. *ALX1* greatly affects the early
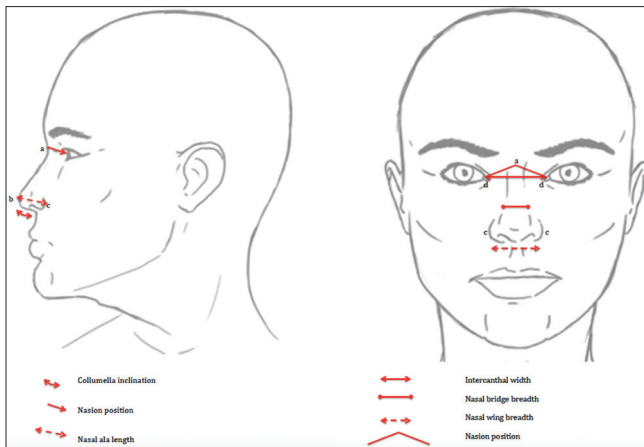
Figure 4: Nasal dimensions with identified genetic associations. a, Nasion; b, Ala; c, Endocanthion; d, Nasal tip

phase of chondrocyte development.[37] Bifid nose and hypertelorism occurs due to disruption in the fusion of frontal and medial nasal prominences as seen in *ALX3* and *ALX4* loss-of-function mutant phenotypes. Hypertelorism is a prominent feature of frontonasal dysplasia and may be due to disruptions of the Hedgehog signaling pathway. *ALX* genes are expressed in frontonasal mesenchyme and are thought to increase *SHH* activity.[38]

1. Nasal ala length

Nasal ala length has a strong association with rs4648379, an intronic variant in PR domain containing 16 (*PRDM16*) gene at 1p36.23-p33 and rs1982862 of calcium voltage-gated channel auxiliary subunit alpha2 delta3 (*CACNA2D3*) gene at 3p14.3.[39] *PRDM16* is associated with orofacial development and its transcripts were found in the nasal septum.[40] Nasal ala length was also observed to be associated with rs8007643 at 14q11.2, a region containing many genes of craniofacial development.[39] Among these, zinc finger protein 219 (*ZNF219*) encodes a transcription factor, which along with SOX9 is essential for chondrogenesis,[41] and chromodomain helicase DNA binding protein 8 (*CHD8*) is associated with autism spectrum disorder including a broad nose. *SOX9 (*17q24.3) and cancer susceptibility 17 genes (*CASC17*), which are 1Mb from each other have both been observed to influence the nasal shape.[42] In mice, Bbfc (Babyface) mutation of *Sox9* gene and *Sofa* ("short face") mutation of phosphoribosylformylglycinamidine synthase (*Pfas*) gene resulted in the short nose as it leads to decreased purine availability for the transcription of genetic expression.[43] Moreover, mutations in mice type 2 collagen (*Col2a1*), Src homology 3 (SH3), and PX domains 2B *(Sh3pxd2b)*, (*Fgfr3*) and phosphate regulating endopeptidase homolog X-linked (*Phex*) genes have also been found to cause shortened nose.[44] The DEAD (Asp-Glu-Ala-Asp) box polypeptide 10 gene (*Ddx 10*) in mice which encodes a DEAD box containing ATP-dependent RNA/DNA helicase caused short/split nose and DEAD-box helicase 10 gene (*DDX10*) mutation in humans has been observed to cause pear-shaped nose.[45]

2. Intercanthal width

An intronic single nucleotide polymorphism (SNP) (rs17447439) of tumor protein p63 (TP63) on chromosome 3q28, is

linked to distance between the eyeballs.[46] SNP rs619686 of glutathione S-transferase mu 2 (*GSTM2*) gene at 1p13.3 and rs11093404 at chromosome Xq13.2 near histone deacetylase 8 gene (*HDAC8*) were associated with intercanthal width.[39] SNPs (rs16863422, rs12694574, rs974448, and rs7559271) at paired box3 (*PAX3*) in chromosome 2q35 and SNP rs805722 in collagen alpha-1 (XVII) chain (*COL17A1*) on chromosome 10q24.3 were found to be associated with the position of nasion relative to the eyeballs.[46] *PAX3* is expressed in neural tube portion, which forms neural crest and is also observed in migrating neural crest cells. Thus, *PAX3* might have a role in epithelial mesenchymal transformation.[47] SNP rs2289266 in the intron of the *PAX3* was found to be associated with the transverse nasal prominence angle. *PAX3* gene mutations are linked to Waardenburg syndrome, which shows prominent, broad nasal root and a round or square nose tip. Variants rs12041465, rs12076700, rs74884233, rs6741412, rs10496971, and rs59037879 located in the introns of *LIM Homeobox 8* (*LHX8*), *Lamin A* gene (*LMNA*), and *Rotatin* gene (*RTTN*), Family with Sequence Similarity 49 Member A gene (*FAM49A*), Testis Expressed 41 gene (*TEX41*), and Zinc Finger E-Box Binding Homeobox 1 (*ZEB1*) respectively were associated with transverse nasal prominence angle. *LHX8* is involved in patterning and differentiation of various types of tissues. Its mutations causes secondary palate clefts in mice. *LMNA* protein is a component of inner nuclear membrane, which forms framework for the nuclear envelope and also interacts with chromatin to disrupt mitosis and induces premature senescence of the cell. *RTTN* gene maintains normal ciliary structure and controls left-right organ specification, axial rotation, and notochord development. The *FAM49A* protein might interact with microRNA (miRNA) molecules during pre implantation. *ZEB1* is a transcriptional repressor. SNPs rs892457 and rs892458 located in the long non coding RNA (lncRNA) gene *AC073218*.1, were associated with the transverse nasal prominence angle. SNP rs2357442, located in the Long Interspersed Nuclear Element 1 (*LINE-1*) retrotransposon sequence was also associated with the transverse nasal prominence angle. It comprises approximately 21% of the human genome and modulate the expression of neighbouring genes.[48] Mice with shortened COL11A2 mRNA (the second alpha chain of type XI fibrillar collagen) display shorter and dimpled nasal bones.[47]

SNP rs6555969 near *C5orf50* (chromosome 5 open reading frame 50) at 5q35.1 is associated with nasion position.[46] *C5orf50* encodes a transmembrane protein, which affects *FBXW11* (F-box and WD repeat domain containing 11) expression, a gene linked to SHH signaling [Figure 1]. *C5orf50* mutations have been observed in holoprosencephaly involving defects in midface and forebrain.[49]

3. Columella and nasal bridge breadth

SNP rs12644248 at 4q31 in *DCHS2* (Dachsous cadherin-related 2 gene) affects the columella inclination. rs2045323 is located at the evolutionary conserved zone in *DCHS2-SFRP2* (Secreted Frizzled- related protein2) intergenic region, and it was found

to have a strong association with nose protrusion and nose tip angle.[50] DCHS2 is a calcium dependent cell adhesion protein, which was found to be involved in regulatory network influencing cartilage differentiation in craniofacial development. This regulation also involves *SOX9*, mutations of which were linked to craniofacial defects.[50] The allele C of single nucleotide polymorphism (SNP) rs2193054 (*SOX9*) was associated with protrusion of the nose than the alternate allele. The T allele of SNP rs2206437 (*DHX35*) was associated with wider and lower nose than allele A.[51] *SFRP2* is expressed in osteoblast and has WNT inhibiting effect because of structural homology to frizzled receptor.[52] *SUPT3H* affects nasal root and lateral parts of the nasal bridge but spares nasal tip.[42] *SUPT3H* promoter can modulate *RUNX2*-P1 activity via direct association.[53] RUNX2 mutation was also observed in cleidocranial dysplasia and has role in differentiation of osteoblasts, chondrocytes, mesenchymal stem cells, and bone development.[54] *KCTD15* (potassium channel tetramerization domain containing 15) at 19q13.11 affects nasal tip and its mutation has been observed to cause reduced snout length in mice.[42]

4. Nasal wing breadth

Nose wing breadth is associated with SNP rs4648379 of *PRDM16* gene, rs17640804 at 7p13 containing *GLI3* (GLI family zinc finger 3) gene, rs927833 and rs2424399 at 20p11 containing *PAX1* gene.[39,50] GLI3 regulates SHH signaling, involved in chondrocyte differentiation.[55] PAX1 is expressed in facial primordial mesenchyme during late facial development, which may have a role in epithelial mesenchymal interaction and affects chondrocyte differentiation.[56] Variant rs79867447 and Intronic SNP rs58733120 of Eyes Absent Homolog 1 and 2 (*EYA1* and *EYA2*) gene was associated with the nose width and nasal index. The *EYA* encoded protein acts as histone phosphatase, which controls transcription during organogenesis. Missense mutation rs37369 in the Alanine-Glyoxylate Aminotransferase 2 gene (*AGXT2*) was associated with nose width, nasal index, and transverse nasal prominence angle. SNP rs1482795, located in the RNA gene *RP11-494M8.4* was associated with the nose width and nasal index. SNP rs7311798, located in the lncRNA gene *RP11-408B11.2* was associated with the nasal index.[48]

D. Gene identification in syndromes associated with nasal deformities

Genes associated with various syndromes having nasal deformities has been elaborated in Table 1.

Future prospects

The understanding of these genetic associations has led to the emergence of two strategies as future solutions to craniofacial reconstructive challenges. Pre natally, bacterial based type II clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system will serve as a genomic editing tool to target desired location of genes, resulting in the incorporation of novel DNA fragments into the target site. Post natally, gene therapy for tissue regeneration can

transform cells at the site of injury into induced-pluripotent stem cells, which will enhance their ability to differentiate towards their tissue of origin and aid in craniofacial reconstruction.

The presence of morphological variations despite unaltered gene sequence on a large scale might be explained by the study of proteins as they change with the turning on or off of genes in response to environmental changes. Moreover, the science of proteomics will facilitate identification of new biomarkers, which will enhance an understanding into phenotypic variations.

Application of genetic screening in orthodontics

Future progress in identifying the role of genes in the development of face and nose would change the face of orthodontic practice. Decision to implement a particular orthodontic intervention will be guided by the alteration of the dentofacial region in concordance to the future nasal shape changes predicted through genetic screening. Instead of making an educated guess about patient's future growth, orthodontists might employ software to make genetic growth prediction based on variation in genome sequencing. Moreover, the spatial and temporal control of any gene expression in orthodontically relevant tissues can now be done.

Conclusion

Nasal dimensions have not yet drawn attention and gained appropriate consideration by orthodontists. Ascertaining the genotype should be accompanied by appreciable association with phenotypic characteristics, which entail prospective research to predict the treatment outcomes. Patients having variations in genetic constitution respond differently to the same intervention. The complex interactions of genetic factors govern orthodontic and dentofacial orthopedic treatment outcome.

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Conflicts of interest

There are no conflicts of interest.

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