

Frontofacionasal Dysplasia- A Review

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Abstract-

The complex anatomy of the skull and face arises from the requirement to support multiple sensory and structural functions. During embryonic development, the diverse component elements of the neuro- and viscerocranium must be generated independently and subsequently united in a manner that sustains and promotes the growth of the brain and sensory organs, while achieving a level of structural integrity necessary for the individual to become a free-living organism. While each of these individual craniofacial components is essential, the cranial and facial midline lies at a structural nexus that unites these disparately derived elements, fusing them into a whole. Defects of the craniofacial midline can have a profound impact on both form and function, manifesting in a diverse array of phenotypes and clinical entities that can be broadly defined as Frontofacionasal dysplasias (FNDs). Recent advances in the identification of the genetic basis of FNDs along with the analysis of developmental mechanisms impacted by these mutations have dramatically altered our understanding of this complex group of

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Introduction

The rationale for association of the specific features defining Frontofacionasal Dysplasia is based on the developmental origin of the Craniofacial midline. A brief introduction to the early stages of craniofacial development illustrates the common origins of the structures impacted in Frontofacionasal Dysplasia and aids in understanding why certain phenotypes occur together. The mid and upper face is constructed from 3 major tissue blocks: The paired maxillary processes which produce the upper Jaw, cheek bones, and lateral nasal structures, plus the Fronto nasal process (FNP) which produces the midline tissue including the frontal bones, nasal bridge and nasal tip, and which are responsible for uniting the bilateral maxillary arch-derived structures (Fig.1). The maxillary and fronto nasal processes are composed of an outer covering of ectoderm overlaying a small but highly proliferative neural crest derived mesenchyme responsible for the construction of the facial skeleton. However, while the maxillary process is enclosed on the prospective oral surface by an endodermally derived epithelium, FNP forms in direct contact with the anterior neural tube that will form the telencephalon and eventually the forebrain. Thus, FNP is subject to direct influence from the developing forebrain neuroepithelium, and this influence has profound implications for growth and patterning of the midface.

Developmental Origins

The neural crest is a highly migratory and invasive population of mesenchymal cells derived from the lateral margins of the epithelial neural plate following a process known as epithelial to mesenchymal transformation [12,13,18]. The neural crest cells that contribute to FNP originate in the prospective caudal forebrain and rostral midbrain neural plate prior to cranial neural tube closure and migrate between the basal surface of the neural plate and overlying ectoderm. During this migratory phase, the frontonasal neural crest cells spread as a sheet-like population, passing over the prospective telencephalon and eye to take up residence in the most rostral aspect of the neural tube [9]. As the telencephalon expands, this population becomes predominantly restricted to the prospective frontonasal region of the developing face. The frontonasal neural crest cells are initially restricted in number as they exit the neural plate and must expand through rapid proliferation. Expansion begins during migration, but the neural crest cells encounter major mitogenic influences upon reaching their destinations within the frontonasal region and nasal processes. The frontonasal neural crest cells are initially restricted in number as they exit the neural plate and must expand through rapid proliferation. Expansion begins during migration, but the neural crest cells encounter major mitogenic influences upon reaching their destinations within the frontonasal region and nasal processes. The coordinated expression of Shh, Bmp4, and Fgf8 plays a profound role in establishing growth and patterning of the facial primordia, and disruption of this coordination results in FNP defects and facial clefting [4,5,8]. The expression domains of Fgf8 and Shh in the frontonasal ectoderm form a signaling centre known as the frontonasal ectodermal zone that dictates the morphogenetic outcome of FNP development [5,7,8]. Bmp signaling, and Bmp4 in particular, is also a key factor in patterning and outgrowth of FNP [1,2,16]. In addition to promoting the growth of FNP, Blockade of Bmp signaling results in down regulation of Shh in FNP [4] and compromises the Ability of Shh to induce its own expression [8]. Similarly, Fgf signalling from the nasal pits is required for normal proliferation of FNP mesenchyme, and blocking this signalling also results in facial clefts [14]. The efficacy of these patterning systems requires tightly regulated spatial and temporal gene expression, and the distribution of these factors serve as markers of the individual facial primordia enabling a fine scale analysis of developmental defects. The patterning influence of the frontonasal ectodermal zone has been best characterized in the chicken embryo, where disruption of the tightly regulated distribution of FGF8 and SHH results in failure of midface outgrowth [5,7]. However, a similar signalling system has been demonstrated in mouse embryos, suggesting that the regulation of mid- and upper facial patterning by this SHH/FGF8 mechanism is broadly utilized [6]. The individual facial processes expand and elongate as the mesenchymal populations proliferate and eventually adjacent processes make contact between opposing epithelial surfaces. The fusion process is best characterized in the formation of the secondary palate where individual epithelial cells make an initial contact through extension of cell surface protrusions known as filopodia [15]. Following this initial contact, opposing epithelial surfaces make direct contact, forming a transient bi-epithelial seam which is itself removed through a combination of programmed cell death and conversion of epithelial cells into mesenchyme via epithelial to mesenchymal transformation [10,11,17]. Following successful fusion, the previously separate mesenchymal populations become united as a single continuous population. The neural crest cells responsible for the production of skeletal elements within the mid and upper face generate both bone and cartilage through direct transition from a multipotent mesenchymal state into terminally differentiated cell types [3]. The differentiation of neural crest-derived progenitors within the unified facial processes subsequently results in formation of a continuous facial skeleton. It is important to note that fusion of the facial processes precedes osteogenic differentiation of neural crest-derived progenitor cells. This implies that overt clefting and facial hypoplasia of otherwise intact skeletal elements may arise from defects in temporally separable developmental events. The challenge may therefore be to determine if these defects in different individuals are attributable to the same or independent genetic or environmental insults.

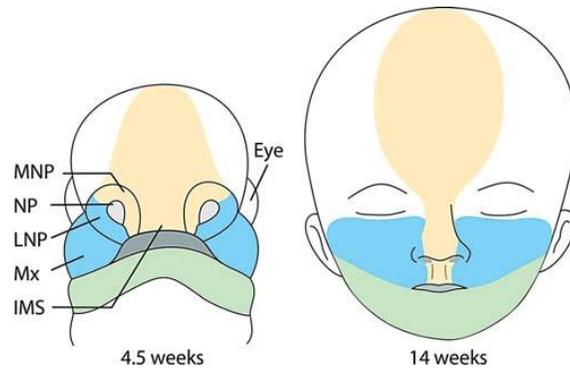


Fig.1 Embryological origins of the frontonasal process

The paired maxillary processes (blue) and FNP (yellow) have begun development by the end of the first month of gestation (Fig.2). Under normal circumstances, FNP has fused with the maxillary primordial by the end of the first trimester to form the midfacial structures. IMS = Intermaxillary segment; LNP = lateral nasal process; MNP = medial nasal process; Mx = maxillary process; NP = nasal pit.

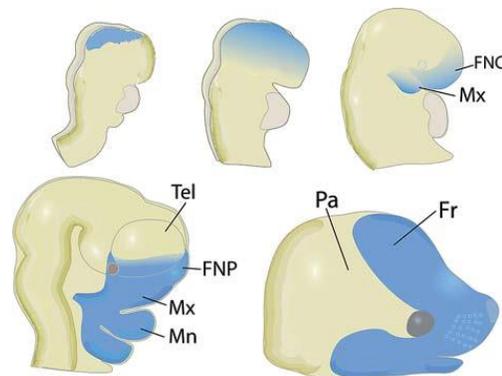


Fig.2 Origin and distribution of the frontonasal neural crest cells.

The frontonasal neural crest cell population (blue) emerges from the lateral margin of the neural folds prior to neural tube formation. B, C FNCs then migrate ventrally over the anterior neural folds (B) eventually reaching the frontonasal region of the neural tube soon after fusion of the neural folds (C). D FNCs are subsequently restricted to the prospective frontonasal region as the telencephalic vesicles rapidly expand. E The expansion of FNCs results in outgrowth of the midface and formation of the frontal bone over the forebrain. FNC = Frontonasal neural crest cell; FNP = frontonasal process; Fr = frontal bone; Mn = mandibular process; Mx = maxillary process; Pa = parietal bone; Tel = telencephalon ^[19,20].

Discussion

Frontofacionasal dysplasia is a rare genetic disorder that is apparent at birth (congenital). The disorder is primarily characterized by malformations of the head and facial (craniofacial) area and eye (ocular) defects. Craniofacial malformations may include an unusually short, broad head (brachycephaly); incomplete closure of the roof of the

mouth (cleft palate); an abnormal groove in the upper lip (cleft lip); and underdevelopment (hypoplasia) of the nose with malformation of the nostrils (Fig.3). Affected infants may also have abnormal narrowing of the folds (palpebral fissures) between the upper and lower eyelids (blepharophimosis) and an unusually increased distance between the eyes (ocular hypertelorism). Additional eye abnormalities may include partial absence of tissue (coloboma) from the upper eyelids or the colored regions of the eyes (irides) and an inability to completely close the eyes (lagophthalmos). The signs and symptoms of frontofacionasal dysplasia are highly variable. Frontofacionasal dysplasia appears to be inherited as an autosomal recessive trait. Faces of one of two sibs with bi-lateral facial clefts, blepharophimosis, lagophthalmos, telecanthus, S-shaped palpebral fissures, and eyelid coloboma[19].



Fig.3 Fronto-facio-nasal dysplasia.

Signs and symptoms

Infants with frontofacionasal dysplasia typically have distinctive malformations of certain bones forming the skull as well as additional facial, nasal, and eye (ocular) defects. For example, the disorder may be associated with premature closure of the fibrous joints (sutures) between particular bones of the skull (craniosynostosis), causing the head to appear unusually short and broad (brachycephaly). In addition, there may be early conversion of fibrous tissue into bone (early ossification) within the base of the skull (sphenoid bone), and some of the air-filled cavities (i.e., paranasal ethmoidal sinuses) within certain bones around the nose may be abnormally large. Underdevelopment of the middle portion of the face (midface hypoplasia) also occurs. Affected infants may also have additional, associated skull defects, such as underdevelopment (hypoplasia) of part of the bone forming the front of the skull (frontal bone) and an abnormal opening (congenital cleft) within the frontal bone (cranium bifidum). In some infants with a congenital cleft of the skull, there may be protrusion of a portion of the brain and its surrounding membranes (meninges) through the skull defect (encephalocele). However, in others, there may be no associated abnormality of the brain or meninges (cranium bifidum occultum).

Causes

Frontofacionasal dysplasia appears to be inherited as an autosomal recessive trait. Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. Recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and, therefore, have an affected child is 25 percent with each pregnancy. The risk to have a child who is a carrier like the parents is 50 percent with each pregnancy. The chance for a child to receive normal genes

from both parents and be genetically normal for that particular trait is 25 percent. The risk is the same for males and females.

The parents of some individuals with frontofacionasal dysplasia have been closely related by blood (consanguineous). In recessive disorders, if both parents carry the same gene for the same disease trait, there is an increased risk that their children may inherit the two genes necessary for development of the disease.

Affected Populations

Since the disorder was originally described in 1981 (T.R. Gollop) in a brother and sister, fewer than 10 cases of Frontofacionasal dysplasia have been reported in the medical literature. The two siblings as well as the third individual reported with the disorder are of Brazilian descent.

Conclusion

FND is a diverse collection of conditions sharing key Features affecting the frontal cranial and midfacial skeleton. Ironically, while the core features of expanded skull Vault and epicanthal distance combine to produce a relative increase in craniofacial volume, the underlying Mechanisms driving the aberrant development of these Structures are centered on loss and reduction of skeletal Precursors and their derivatives. This phenomenon highlights the central role of the cranial and facial midline in Uniting the complex architecture of the craniofacial skeleton. The FND spectrum disorders are fundamentally defects of cranial neural crest development and can therefore be considered as neurocristopathies. However, the Diverse presentations of FND involve a range of other developmental systems, and in these respects, animal models have been invaluable in understanding the complex Roles of specific FND genes in the development of FNP And other comorbid tissues. The implications for the majority of FND yet to be defined molecularly are unclear but highlight the need to be open to unexpected scenarios in the continuing search for the causes of craniofacial dysmorphology

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