

The Craniofacial Phenotype of Fibrodysplasia Ossificans Progressiva

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Abstract

Patients with fibrodysplasia ossificans progressiva (FOP) develop a craniofacial phenotype characterized most notably by mandibular hypoplasia. Other less well-defined features of FOP include involvement of the joints, muscles, and associated fascia of the head and neck. Although absent at birth, the craniofacial phenotype generally emerges during the second decade of life. The craniofacial features of FOP may provide important insight into underlying molecular signaling pathways involved in the pathogenesis of the disease.

Key Words: Fibrodysplasia ossificans progressiva (FOP); craniofacial; BMP4.

The Facial Phenotype of Fibrodysplasia Ossificans Progressiva

Minor physical features of a genetic condition can provide powerful and important clues to the underlying pathways responsible for the condition. Anyone who has ever attended a fibrodysplasia ossificans progressiva (FOP) event knows that there are remarkable facial similarities between unrelated individuals who have FOP. To date, there have been no studies on the facial features or craniofacial phenotype of FOP. However, anecdotal observations have been made by physicians and patients regarding the similarities of facial features in adults with FOP. The most prominent anecdotal facial feature

noted in many patients with FOP is mandibular hypoplasia associated with a maxillary overbite, which seems to be present by the second decade of life regardless of whether or not there is ankylosis of the temporomandibular joint (TMJ).

Congenital Malformations and Degenerative Changes in the Craniofacial Skeleton in FOP

Although much clinical attention in FOP centers on malformations of the great toes and on progressive heterotopic ossification of the trunk and limbs, FOP also affects the postnatal development of the craniofacial structures, resulting in morphological changes in the head, neck, and face (1–3). In 1982, Renton et al. described an unusual appearance of the mandibular condyles in patients with FOP and noted the presence of broad, flat, malformed mandibular condyles in association with posterior osteophytes (4). A case report by Chichareon et al. described an

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associated osteochondroma of the coronoid process of the mandible in a patient who had FOP (5). Interestingly, many patients with FOP have abnormalities in mastication even before the onset of heterotopic bone formation that affects the jaw (4).

The Cranio-Cervical Skeleton in FOP

Abnormalities of the cervical spine, first described by Connor and Smith in 1982 (6), are well-noted in patients who have FOP. A more recent and comprehensive survey on the cervical spine in patients with FOP showed posterior fusion of the cervical vertebrae between C2 and C7 in a pattern that was remarkably similar to the cervical spine of mice who had homozygous deletions of the gene encoding Noggin, a secreted bone morphogenetic protein (BMP) antagonist (7).

One of the earliest and most overlooked clinical manifestations of FOP is evanescent soft-tissue swelling of the scalp, often mistaken for a cephalohematoma and commonly present in the first month of life. Where available for review, magnetic resonance imaging studies clearly indicate that the swelling is not a hematoma at all, but rather a large soft-tissue lesion involving the galea aponeurotica. The swelling appears suddenly, may wax and wane rapidly, and often leaves behind sheets of new bone in the area of the galea. This heterotopic bone may fuse with bone of the underlying skull and may be incorporated into the growth of the skull. There have been no reported cases of galeal involvement leading to craniosynostoses in patients who have FOP.

Additional involvement of the aponeuroses, fascia, and soft-tissue structures of the craniofacial region include flare-ups of the nuchal ligament and the cervical fascia. These soft tissues may ossify in early childhood and may lead to severe limitation in neck movement (1–3). In addition to malformations of the TMJs and facet joints of the cervical spine, malformations have also been noted in the ossicles of the ear with secondary hearing abnormalities noted in many FOP patients (8) (Table 1).

FOP Flare-Ups Involving the Muscles of the Craniofacial Region

FOP flare-ups commonly involve muscles of the craniofacial region. FOP flare-ups of the sternoclei-

Table 1
Factors Contributing to Craniofacial Involvement in Fibrodysplasia Ossificans Progressiva

Structures	Congenital malformations	Disease flare-ups and heterotopic ossification
<i>Bones</i>		
Temporal	+	
Mandible	+	
Ossicles of ear	+	
Cervical vertebra	+	
<i>Joints</i>		
Facet joints (C-spine)	+	
Temporomandibular	+	
<i>Muscles</i>		
Temporalis		+
Frontalis		+
Masseter		+
Buccinator		+
Ptyrygoids		+
Myohyoid		+
Omohyoid		+
Sternocleidomastoid		+
<i>Aponeuroses/Fascia/Ligaments</i>		
Galea aponeurotica		+
Nuchal ligament		+
Cervical fascia		+

domastoid muscles can often be mistaken for mumps or cervical adenopathy. The combination of congenital malformations of the cervical vertebra along with the FOP flare-ups involving the cervical fascia, nuchal ligaments, and sternocleidomastoid muscles frequently lead to permanent ankylosis the neck (1–3) (see Table 1).

Among the most feared lesions in FOP are those that involve the muscles of mastication. In a worldwide survey of the FOP community, 24% of patients had an immediate FOP flare-up with subsequent ankylosis of the jaw following a mandibular block for dental work. Such procedures involve the injection of a local anesthetic into the pterygoid muscle in order to block the mandibular branch of the trigeminal nerve (9).

FOP flare-ups in the submandibular region are also quite common and involve the myohyoid and omohyoid muscles. Submandibular swelling in patients with FOP can be a medical emergency and

requires intensive precautionary measures to avoid catastrophic clinical deterioration. These measures include avoidance of lesional manipulation, airway monitoring, aspiration precautions, and glucocorticoid therapy. Submandibular swelling with subsequent heterotopic ossification is a recognized and variable feature of FOP and can contribute to the facial phenotype (10).

Mandibular Development in FOP

In addition to congenital malformations, secondary degenerative changes, and disease-related flare-ups of the craniofacial region, patients with FOP have disturbances in the growth of the mandible (4). Regardless of whether or not the TMJ has ankylosed or whether there has been involvement of the submandibular region, many patients with FOP develop mandibular hypoplasia and a maxillary overbite by the time of skeletal maturity. The profiles of many young adults with FOP clearly demonstrate the disproportionate growth between the maxilla and the mandible.

BMPs and Mandibular Development

Recent studies have shown that the BMP4 signaling pathway, a dysregulated pathway in the cells of patients with FOP, plays an essential role in the growth of the mandible, skull, and in the formation of the inner ear (11–15). In an animal model of mandibular hypoplasia, elevated BMP4 activity downregulated the expression of fibroblast growth factor (FGF)-8, an important survival factor for cells populating the mandibular bud leading to decreased cell survival during mandibular outgrowth (15). Likewise, embryos lacking BMP antagonists (and thus having increased BMP4 activity) exhibited strong reduction in FGF-8 expression in the pharyngeal ectoderm and increased cell death in the mandibular bud.

BMP4 also promotes chondrocyte proliferation and hypertrophy in the endochondral cranial base and BMP4 gene expression is an important factor at the putative site of fusion in the midfacial region (13). In addition, BMP4 antagonists disrupt the development of the inner ear and may play a role in the development of the ossicles of the ear (12). Thus, in addition to its effects on mandibular growth and

development, the BMP4 signaling pathway may have other wide-ranging effects on the prenatal and postnatal development of the craniofacial skeleton. Whether or not these morphological changes are relevant to the mandibular abnormalities seen in patients with FOP is unknown. However, the BMP4- and FGF-8-signaling pathways and their role in mandibular growth and development warrant further attention in the context of FOP.

Discussion

Widespread anecdotal evidence within the FOP community suggests the presence of a prominent facial phenotype in many adults with FOP. This phenotype is characterized most notably by mandibular hypoplasia and a maxillary overbite. Other subtle facial features of FOP that are directly related to prenatal and postnatal involvement of the craniofacial skeleton and soft tissue structures may also contribute to the phenotypic similarity in facial morphology noted in patients with FOP (*see* Table 1). However, knowledge can fundamentally bias what one sees, and a rigorous anthropometric and photogrammetric approach to craniofacial features of FOP would be extremely useful in further characterizing craniofacial phenotype of the condition. Craniofacial anthropometry and three-dimensional analysis of facial morphometry has proven useful in quantifying and analyzing craniofacial phenotypes that exist in myriad craniofacial disorders (16–18). Such an analysis is planned for future FOP gatherings and symposia.

In summary, there is strong anecdotal evidence of a facial phenotype of FOP characterized by mandibular hypoplasia, and a maxillary overbite, and possibly including other more subtle features involving a wide range of aponeuroses, fasciae, muscles, bones, joints, and growth plates of the craniofacial region (*see* Table 1). Many of these noted abnormalities are secondary to FOP flare-ups involving the craniofacial structures and some may result from growth disturbances involving the bones of the head and face. Dysregulation of the BMP4-signaling pathway occurs in cells from patients with FOP, and the BMP4-signaling pathway and developmental pathways interacting with the BMP4-signaling pathway likely play important roles in the emergent craniofacial phenotype of FOP.

References

1. Connor JM, Evans DAP. 1982 Fibrodysplasia ossificans progressiva (FOP). The clinical features and natural history of 34 patients. *J Bone Joint Surg Br* 64:76–83.
2. Cohen RB, Hahn GV, Tabas J, et al. 1993 The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am* 75:215–219.
3. Kaplan FS, Shore EM, Connor JM. 2002 Fibrodysplasia ossificans progressiva. In: Royce PM, Steinmann B, eds. *Connective Tissue and Its Heritable Disorders: Molecular, Genetic, and Medical Aspects*, 2nd Ed. Wiley-Liss; John Wiley & Sons., New York, pp. 827–840.
4. Renton P, Parkin SR, Stamp TCB. 1982 Abnormal temporomandibular joints in fibrodysplasia ossificans progressiva. *Br J Oral Surg* 20:31–38.
5. Chichareon V, Arporkaeklong P, Donsakul N. 1999 Fibrodysplasia ossificans progressiva and associated osteochondroma of the coronoid process in a child. *Plastic Reconstructive Surg* 103:1238–1243.
6. Connor JM, Smith R. 1982 The cervical spine in fibrodysplasia ossificans progressiva (FOP). *Br J Radiol* 55:492–496.
7. Schaffer AA, Kaplan FS, Tracy MR, et al. 2005 Developmental anomalies of the cervical spine in patients with fibrodysplasia ossificans progressiva are distinctly different from those in patients with Klippel-Feil syndrome: clues from the BMP signaling pathway. *Spine* 30:1379–1385.
8. Levy CE, Lash AT, Janoff HB, Kaplan FS. 1999 Conductive hearing loss in individuals with fibrodysplasia ossificans progressive. *Am J Audiol* 8:29–33.
9. Luchetti W, Cohen RB, Hahn GV, et al. 1996 Severe restriction in jaw movement after route injection of local anesthetic in patients who have fibrodysplasia ossificans progressiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81:21–25.
10. Janoff HB, Zasloff MA, Kaplan FS. 1996 Submandibular swelling in patients with fibrodysplasia ossificans progressiva. *Otolaryngol Head Neck Surg* 114:599–604.
11. Dudas M, Sridurongrit S, Nagy A, Okazaki K, Kaartinen V. 2004 Craniofacial defects in mice lacking BMP Type I receptor Alk2 in neural crest cells. *Mechanisms Dev* 121:173–182.
12. Gerlach LM, Hutson MR, Germiller JA, Nguyen-Luu D, Victor JC, Barald KF. 2000 Addition of the BMP4 antagonist, noggin, disrupts avian inner ear development. *Development* 127:45–54.
13. Gong SG, Guo C. 2003 BMP4 gene is expressed at the putative site of fusion in the midfacial region. *Differentiation* 71:228–236.
14. Shum L, Wang X, Kane AA, Nuckolls GH. 2003 BMP4 promotes chondrocyte proliferation and hypertrophy in the endochondral cranial base. *Int J Dev Biol* 47:423–431.
15. Stottman RW, Anderson RM, Klingensmith J. 2001 The BMP antagonists chordin and noggin have essential but redundant role in mouse mandibular outgrowth. *Dev Biol* 240:457–473.
16. Hammond P, Hutton TJ, Allanson JE, et al. 2004 3D Analysis of facial morphometry. *Am J Med Genetics* 126A:339–348.
17. Ward RE, Jamison PL, Allanson JE. 2000 Quantitative approach to identifying abnormal variation in the human face exemplified by a study of 278 individuals with five craniofacial syndromes. *Am J Med Genet* 91:8–17.
18. Ward RE, Jamison PL, Farkas LG. 1998 Craniofacial variability index: a simple measure of normal and abnormal variation in the head and face. *Am J Med Genet* 80:232–240.