First reported more than 250 years ago by Patin who describe it as “turning into wood” (1), Fibrodysplasia (Myositis) Ossificans Progressiva (FOP) is a rare autosomal dominant disorder (approximately 1 in 1.6 million worldwide) marked by post-natal progressive heterotrophic ossification (HO) of soft tissue including tendons, ligaments, fascia and muscle (1). Despite all the great advances in science and technology over the past two centuries, little is known about the genetics and molecular biology of the disease and as such, definitive treatment remains just out of grasp. Ultimately, scientists hope to cure this debilitating and horrific disease.

DIAGNOSIS AND PHENOTYPE

More than 95% of children with FOP are born with a characteristic congenitally malformed big toe (1). This malformation, along with the onset of HO is sufficient for the diagnosis of FOP (1). The average age of onset of HO is five years (range between birth and twenty five years), with 80% of patients having some HO by the seventh year (2). By the age of 15, 95% of patients have severely restricted mobility of the upper limbs (2). Although easy to detect clinically, misdiagnosis is common and delayed diagnosis is common (1). Possible differential diagnoses include: isolated congenital malformations, brachidactyly, juvenile bunions, sarcoma, lymphoma, desmoid tumor, and aggressive juvenile fibromatosis (1).

The heterotrophic ossification is immediately preceded by painful swellings as a result of lymphocytic infiltration into skeletal muscle (3). The skeletal muscle soon dies and is replaced by highly vascular fibro-proliferative tissue that matures into ossicles of heterotropic bone with marrow spaces (1). The maturation of the bone is via the normal endochondral pathway; the timing and location of such formation is abnormal (3).

Early HO is usually seen in the axial, dorsal, cranial, and proximal portions of the body (1). The first sites of HO are often the neck, spine and shoulder girdle (2). In fact, stiffness of the neck is usually an early symptom and a sign of impending HO (1). Swellings of the neck and back are more bulbous in morphology as compared to those of the appendicular skeleton, and are often misdiagnosed as cancer (1). Later, the HO can spread to all areas of the body resulting in ankylosis of all major joints thereby restricting all major movement. Interestingly, the tongue, diaphragm, extra-ocular muscles, all smooth muscle, and cardiac muscle remain unaffected by the disease (1).

Swelling and the eventual HO of the tempero-mandibular joint and the submandibular region can prove acutely life-threatening as it could compromise the airway and/or lead to difficulty swallowing (1). Importantly, the progression of HO is highly variable and flare-ups of HO can be instigated by certain events. Of note, falls, soft-tissue injuries, surgical trauma, mandibular blocks, intramuscular immunizations and the influenza virus has all been shown to induce HO in people with FOP (1).

Other abnormalities, although not definitive for diagnostic purposes, are commonly seen in FOP. Perhaps most notably, more than 50% of patients born with FOP have congenitally malformed thumbs (1). In addition, more than 50% of patients develop hearing loss during childhood or adolescence usually as a result of middle ear ossification (1). Tall
cervical vertebral bodies, fusion of C2-C7, short broad femoral necks, and proximal medial tibial osteochondromas are also common skeletal abnormalities. Other, less common features include baldness, and menstrual abnormalities (1).

**OCCURANCE**

FOP is a very rare heritable disorder, with a current frequency of 1/ 1.6 million, which occurs sporadically, affecting a single individual, in a family with no previous history of it. It affects males and females equally, and has been reported in all racial and ethnic backgrounds (1).

**GENETIC TRANSMISSION**

In the past, because of its rarity, the gene that causes this disorder was difficult to discover and was believed to be caused by mutation of a single locus, and not multiple genes (4). However, recent data has linked the disorder to the mutation of a gene for a receptor called ACVR1 in the bone morphogenetic protein-signaling pathway (5).

Individuals with FOP have low reproductive fitness, thus making it difficult to study the inheritance pattern; however, of the eight families that passed on the disorder, the inheritance pattern appeared to be autosomal-dominant (4). Although there is no real evidence of non-penetrance in FOP, a case has shown that it is possible that individuals can be silent carriers of the mutated gene (4).

Furthermore, a case has suggested gonadal mosaicism, which is a proven cause of recurrence in siblings of other autosomal-dominant disorders or nonpenetration of the mutated gene in one of the parents (4). Other studies, particularly focused on monozygotic twins, have shown that congenital toe malformations that are associated with FOP were identical for each pair of the twin, however, the progression and severity of the disease varied- thus suggesting that FOP may be influenced by genetic determinants during the prenatal time-frame and by post-natal environmental factors, such as those that cause cellular or tissue trauma (4).

**RISK INHERETANCE**

As in any genetically inherited disorder, any child with a parent that has FOP has a 50% chance of getting it; and some studies have suggested that increased risk factor of occurrence may occur with increased paternal age (4). Currently, there are no prenatal diagnostic tools that are available to detect FOP (4).

**GENETIC LINKAGE ANALYSIS**

A genome-wide linkage analysis used four small, mutigenerational families, and linked the FOP phenotype to markers in a region of 4q-27-31; and several candidate genes were identified within the chromosome 4q-27-31 linkage interval (6). The coding regions within these candidate genes were examined for the FOP mutations in patients, however, mutations that correlate with the disorder were not identified (4). The small number of families with FOP limited the linkage study; however one of the major limitations was accurate identification of affected and unaffected individuals, because of a varied range in expression, age of onset, and severity (4).

Preliminary results, of a more recent linkage analysis study that focuses on four families with unambiguous features of FOP, show that the chromosome 4 region is less likely the region containing the gene believed to cause FOP. Instead, a locus on chromosome 2 appears to have a consistent linkage of FOP in all of the families recently studied (4).
IDENTIFICATION OF CANDIDATE GENES

Because there are few families available for linkage analysis and positional cloning, a new candidate gene approach has been used to find the gene and understand its cellular effects using genetic and molecular approaches. Studies of Bone Morphogenic Protein (BMP), inducers of heterotrophic bone formation, have found that the BMP-signaling pathway is misregulated in the FOP (4). In addition, BMP antagonists are possible candidates for the cause of misregulation of the pathway (4). For example, the antagonist noggin gene has been found to be under expressed in FOP; however genetic linkage studies and extensive DNA sequence analyses did not link the noggin gene with FOP (4).

In a brief communication recently published this past spring, scientists have definitively linked the disease to chromosome 2q23-24 by linkage analysis, and identified a mutation in the ACVR1 domain found in all affected individuals examined (5). Obviously further research must be done in this area.

BIOCHEMISTRY

There are several underlying biochemical reasons for the horrific presentation associated with FOP that are obviously intimately related with the genetics of this disorder. Namely, there appears to be a regulatory pathway that malfunctions and results in the excess bone deposition associated with the disorder. Importantly, there are two sets of pathways that can unleash the biochemical response, one that it is associated with development, and one that is associated with trauma (7). Both pathways have a common source, namely a defect in Bone Morphogenic Protein Receptor (BMPRIA). In the developmental path, without the presence of trauma, preformed heterodimers are formed at the cell surface; in contrast, with the trauma-associated pathway, homodimers of the receptor, after binding with ligand, actually form tetramers (7).

At this point the pathways diverge. In the developmental pathway of FOP that results in congenital malformations such as those associated with the big toe, various proteins known as SMADs (specifically SMAD 1, 5 and 8) cause increased signaling when the receptor complexes are internalized, resulting in the congenitally malformed toes (7). However, in the inflammatory pathway (which can result for example when there is injury to an individual suffering from FOP), p38 MAPK is thought to be responsible for the excess bone deposition (7). Namely, it causes increased signaling with ligand binding, which in conjunction of the internationalization of receptor complexes, results in the greatly upregulated ossification associated with this condition and the difficulty of treatment options (7).

CONCLUSION

As can be imagined, this disease presents enormous difficulties in terms of quality of life, as treatment is at this point inadequate to relieve most of the symptoms. At present there are several treatments used in the hopes of alleviated the debilitating symptoms (8). As there is a pathway associated with inflammation due to injury, every attempt is made to limit the potential of the child hurting himself, this includes everything from worrying about vaccines to injury while playing to dental procedures which can result in lock jaw if the appropriate precautionary measures are not taken (8). Special precautions surrounding illnesses such as the flu need to be taken as these can also trigger an inflammatory episode resulting in aberrant bone deposition (8).

In addition to these precautionary measures, bone marrow transplants and high doses of corticosteroids have been able to improve patient quality of life; other anti-inflammatory agents such as cyclo-oxygenase 2 inhibitors and NSAIDs have become increasingly used (8). Aminobisphosphonates, molecules that regulate the modeling of bone, have also been used to
help step FOP-associated bone deposition (8). In addition, as bone deposition is highly
dependent on vascularization, anti-angiogenic agents (using a similar rational used in cancer,
namely to starve the tumor) can also be used to cut blood supply to the new bone, thereby
preventing growth (8).

Even with all of these treatments, one can imagine that the quality of life of
individuals suffering from the illness can be characterized as poor. Routine activities such as
visits to the dentist, getting the cold at school, and the potential for over-reaction on the part
of the body to traumas such as bumping yourself when playing at school can have dire
consequences on the patient. As joints harden over time, mobility is lost leading to
increasing dependence on others. The illness is progressive and patients tend to lose mobility
by the age of 30 and die by the age of 40. However, there is hope that the current treatments
in conjunction with ongoing research maybe able to relieve patients of the debilitating effects
of this illness.

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