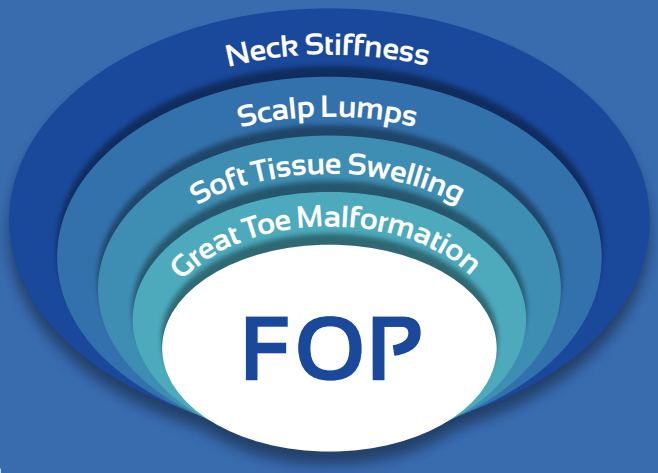
What is FOP? ~1 PER MILLION INDIVIDUALS Approximate **Prevalence**

Fibrodysplasia Ossificans Progressiva (FOP) is a rare, severely debilitating congenital myopathy characterized by a hallmark great toe malformation, painful and recurrent episodes of soft tissue swelling (flare-ups), and heterotopic bone formation in muscle, tendons, and ligaments. In FOP, disability is cumulative and increases the risk of a shortened lifespan.

Clinical Features



Early Signs & Symptoms

At birth, nearly all individuals with FOP have a hallmark bilateral toe malformation in which the great toe is shortened and bent inwards resembling a bunion. In infancy, additional symptoms may appear including:

1) **Neck stiffness that causes difficulty crawling**
2) **Scalp lumps that appear and disappear rapidly, migrate, or change shape**
3) **Painful, soft-tissue swellings (flare-ups) on the neck, chest, or back**

Disease Progression

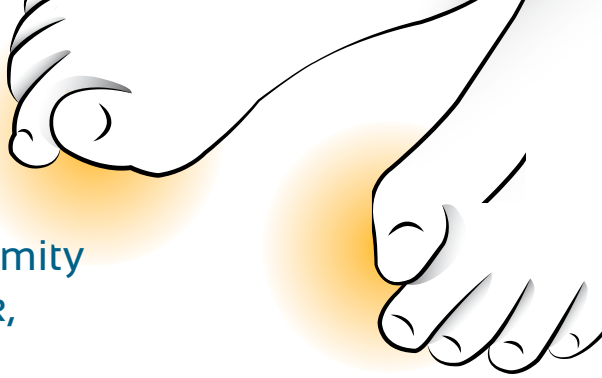
Beginning in early childhood, most affected children experience episodic, painful inflammatory flare-ups that result in heterotopic bone in muscle, tendons and ligaments. Flare-ups can occur spontaneously or following trauma including minor soft tissue injury, muscular stretching, over-exertion and fatigue, intramuscular immunizations, mandibular blocks for dental work, falls, and influenza-like illnesses.

FOP is progressive with most affected individuals confined to a wheelchair by the third decade of life. Bone formation in the jaw area can cause difficulty with speech and eating, potentially leading to severe malnutrition. Bone formation around the rib cage restricts expansion of the lungs and diaphragm and can cause respiratory compromise. Death often results from complications of thoracic insufficiency syndrome with an estimated median lifespan of 56 years old.

clementia

Know the Signs:

Shortened great toes with hallux valgus deformity
"Tumor-like" soft tissue swellings on the neck, shoulders, or back



Less Common Features

Other skeletal anomalies associated with FOP include short malformed thumbs (brachydactyly), curvature of a digit (clinodactyly), short broad femoral necks, and proximal medial tibial osteochondromas. Hearing loss occurs in many individuals with FOP. A small percentage of affected individuals have less common symptoms including but not limited to: milder (or more severe) toe/thumb malformations, neurological manifestations, eye conditions, or sparse hair.

Genetics

FOP is an autosomal dominant condition with complete penetrance and variable expressivity. About 95% of cases of FOP are not inherited but instead caused by de novo mutations in the ACVR1 gene. The remaining 5% are inherited.

To date, only a small number of mutations associated with FOP have been described in the ACVR1 gene. The most common mutation, R206H (c.617G>A; ARG206HIS), is present in approximately 97% of individuals with FOP.

Diagnosis

Failure to associate the hallmark toe malformation with early signs and symptoms of FOP often results in misdiagnoses. Common misdiagnoses include aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma.

Common diagnostic and medical procedures, such as biopsies, intramuscular injections and surgery, can provoke flare-ups and subsequent debilitating heterotopic ossification.

ACVR1 gene testing for FOP can confirm a clinical diagnosis and is commercially available. Genetic confirmation performed prior to heterotopic ossification can prevent any harm caused by unnecessary interventions.

Treatment

Only palliative treatment for FOP flare-up associated symptoms exists at this time. Guidelines for symptomatic flare-up management can be found at the International Fibrodysplasia Ossificans Progressiva Association website (www.IFOPA.org). Clementia Pharmaceuticals is investigating a potential treatment for FOP (www.clementiapharma.com/clinical-trials).

[1] Connor, J. M., Evans, D. A. P. (1982). Fibrodysplasia ossificans progressiva: the clinical features and natural history of 34 patients. J. Bone Joint Surg. 64: 76-83.

[2] Kaplan F.S. et al. (2009). Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat. 30:379–90. doi: 10.1002/humu.20868.

[3] Kaplan, F.S. et al. (2010). Early Mortality and Cardiorespiratory Failure in Patients with Fibrodysplasia Ossificans Progressiva. The Journal of Bone and Joint Surgery. American Volume, 92(3), 686–691. doi:10.2106/JBJS.I.00705.

[4] Kaplan, F.S. et al. (2008). Fibrodysplasia ossificans progressiva. Best Practice & Research. Clinical Rheumatology, 22(1), 191–205. doi:10.1016/j.berh.2007.11.007

[5] Melton, Christin. (2015). Fibrodysplasia Ossificans Progressiva: Before You Biopsy, Look at the Toes. Retrieved 2015 June 5, from http://www.raredr.com/articles/Fibrodysplasia-Ossificans-Progressiva-Look-Toes.