Fibrodyplasias ossificans Progressiva

aka Stone man syndrome
What is Fibrodysplasia ossificans progressiva (FOP)?

- Very Rare: 1 in 2 million people

**Symptoms**
- Muscle tissue and connective tissue gradually ossifies (organ transformation)
- Forms heterotopic and extra-skeletal bone
- Second Skeleton formed → constrained mobility

**Development**
- Genetic fault at birth
- Extra-skeletal bone formation begins in early childhood
- Malnutrition and Respiratory problems
- Trauma to the muscles → myositis → accelerated ossification
FOP effects
The Gene

- **Autosomal Dominant Condition but most often sporadic**
- **Mutations on the ACVR1 gene (activin A receptor, Type I)**
  - Cytogenetic Location: 2q23-q24
- **Gene type: protein coding**

**Biochemistry**
- ACVR1 provides instruction for bone morphogenetic protein (BMP) type I
- Mutation causes histidine to be substitute by arginine (point mutation)
- Changes shape of receptor \(\rightarrow\) disrupts inhibitor protein \(\rightarrow\) receptor constantly activated
Classical Diagnosis of FOP

- Biopsy performed
  - Excludes malignant lesion that indicates disease
  - Diagnosis rarely considered before biopsy
- Often, misinterpreted as fibromatosis or sarcoma at early stages
- S-100 antigen positivity in sections before differentiated osteochondral tissue
- By 2006, biopsies highly discouraged because it exacerbates the condition
- Consistent malformed big toe in children used as differential diagnosis tool
- Rapidly changing swellings on the head,
Treatment of FOP

- Unfortunately, no effective treatment yet
- With misdiagnoses, invasive surgical methods used to be used to remove extra bone
- Precautions can be taken:
  - trauma accelerates the progressive disease so caution should be taken
  - Avoid IM injections. Venipuncture, subcutaneous & intravenous meds
  - Intubation precautions: protect jaw and use anesthesia to unlock jaw and neck
  - Consultation for individual cases that progress at different rates
Novel Diagnostics

- FOP is misdiagnosed in 80% of patients and patients often see a total of 6 physicians before the disease is actually properly diagnosed.

- Gene Test: Prenatal Diagnosis
  - Using chorionic villus amniocentesis, periumbilical blood sampling, ultrasound, and fetoscopy.
  - Available in 3 clinics in the world.

- Targeted mutation analysis

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<td>Centogene GmbH The Rare Disease Company</td>
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<td>Rostock, Germany Christoph Ehlers; Prof Arndt Rolfs, MD; Prof Dr Jürgen Kohlhase, MD</td>
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Future for FOP

- Accurate diagnosis in neonatal stage is a step in itself
- Medications that relieve the symptoms are available
  - Target pain and inflammation
  - Corticosteroids during flare-ups
- Mast Cell inhibitors → tissue repair, wound healing
  - Accumulate and cause inflammation
  - Aminobiophosphonates + Rosiglitazone
    - Used to treat osteoporosis to stop bone remodeling
    - Anti-mast cell therapies
    - High doses worked in some cases
    - Anti-diabetic drug with high anti-inflammatory results
- Muscle Relaxants
- Bone Marrow Transplant
  - Bone marrow implicated in the targeting of ACVR1 gene and BMP receptor inhibitory RNA technology, monoclonal antibodies directed against ACVR1
Sources


