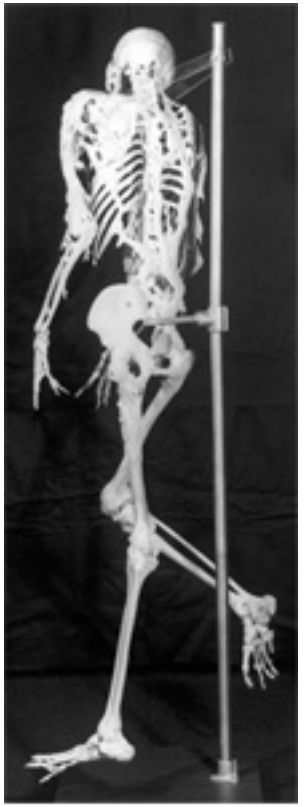
Fibrodysplasia ossificans Progressiva

aka Stone man syndrome

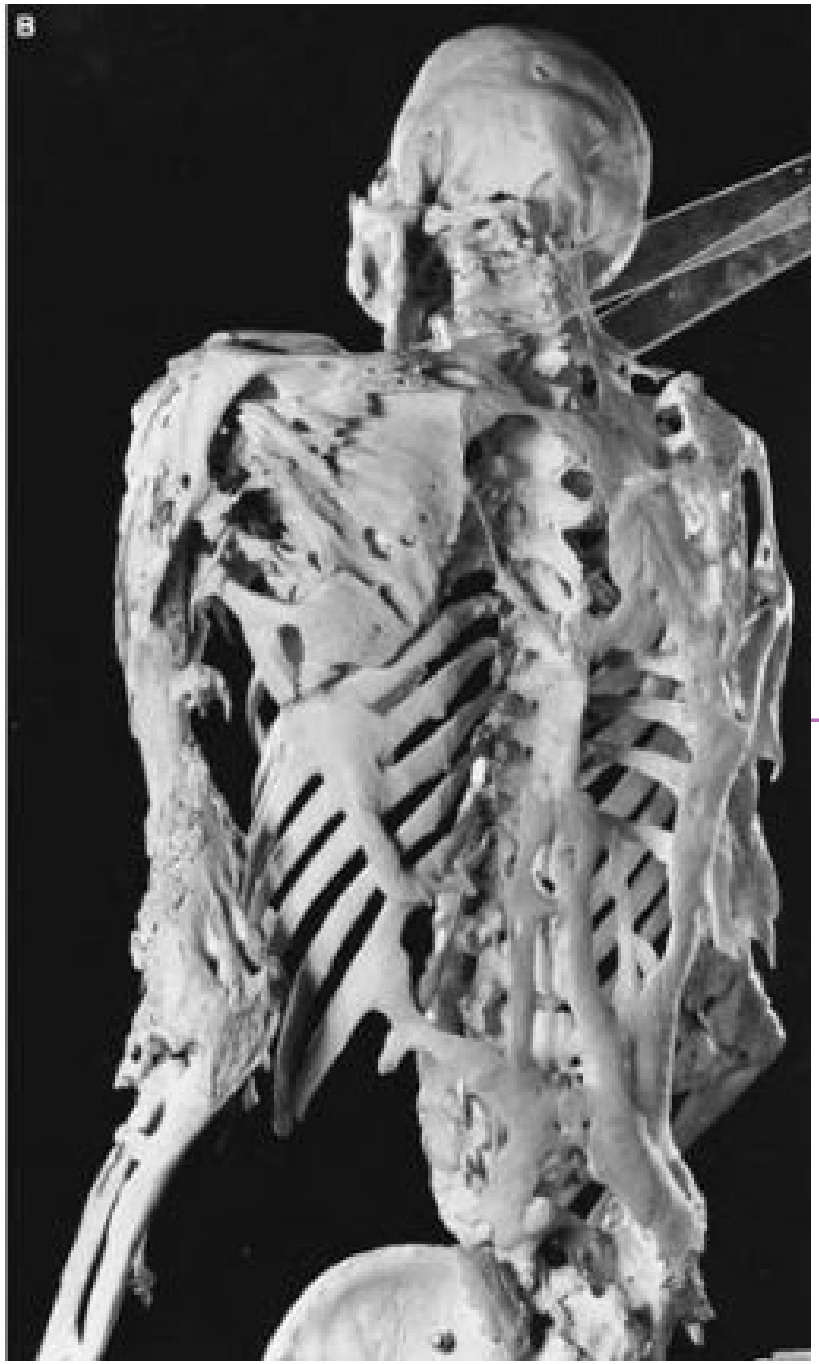
What is Fibrodysplasia ossificans progressiva (FOP)?

- 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

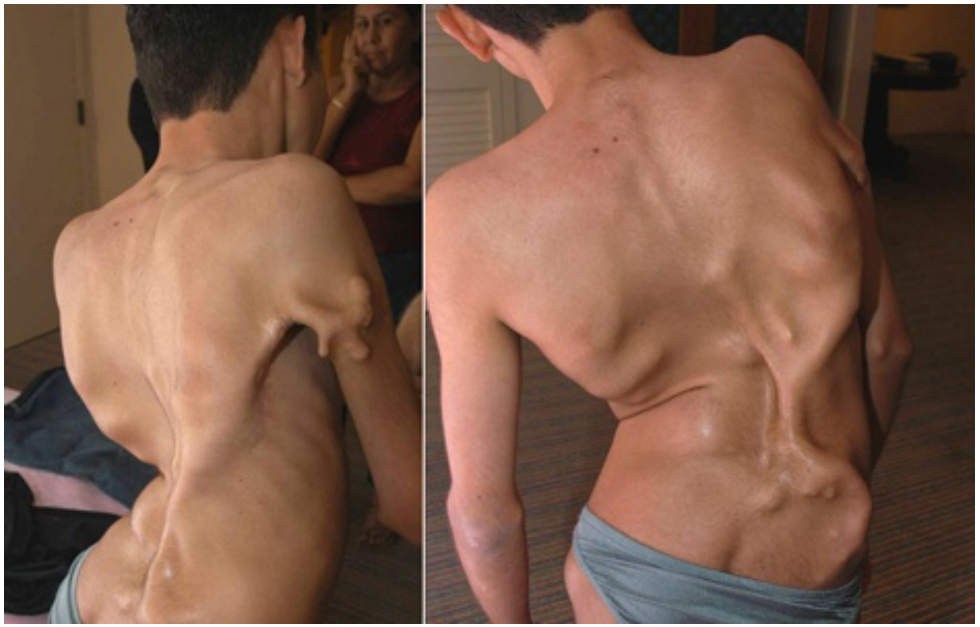


Skeleton of Harry Eastlack, who had FOP. Connective tissue on the back has turned into bone.

Courtesy of Muller Museum, College of Physicians of Philadelphia.

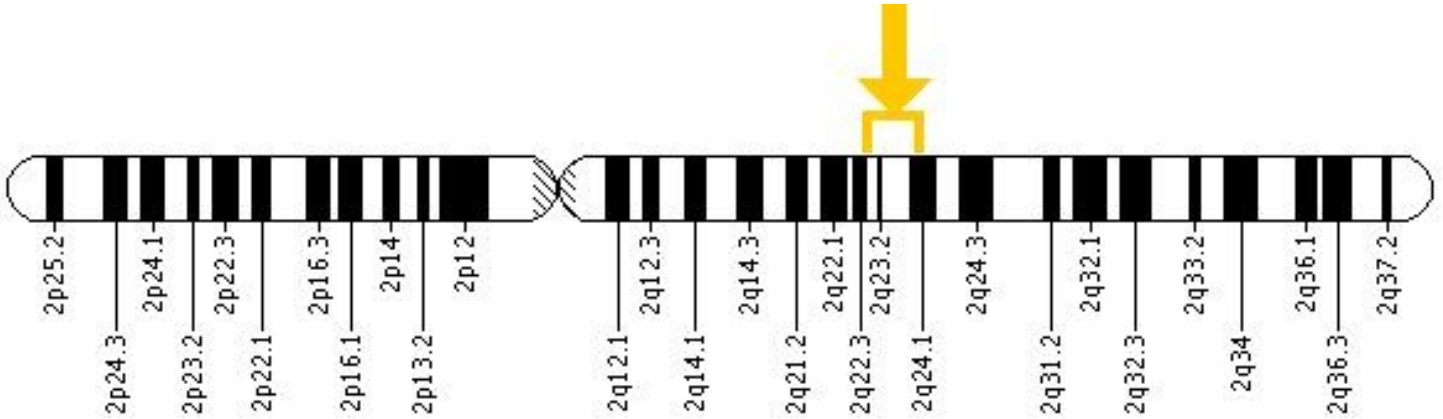


FOP effects



The Gene

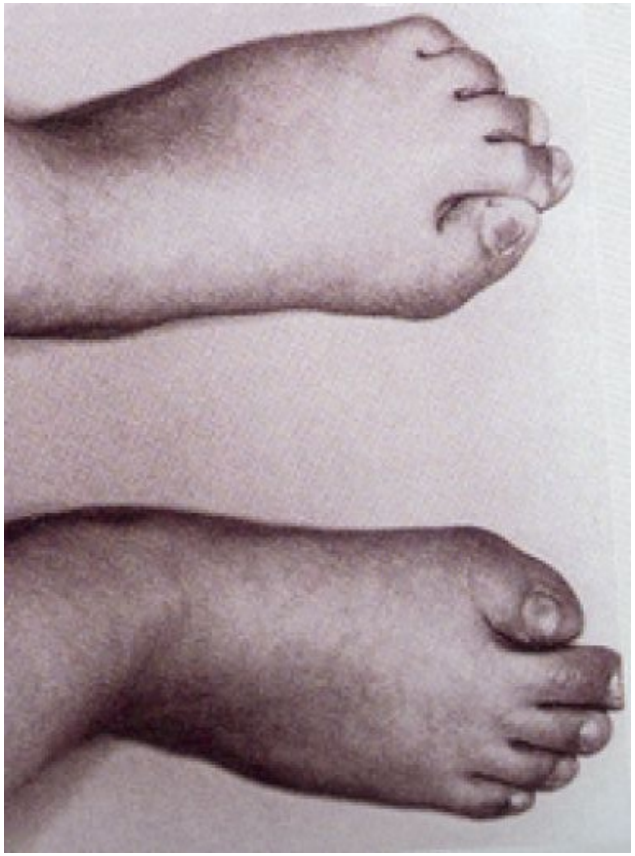
- Autosomal Dominant Condition but most often sporadic
- Mutations on the ACVR1 gene (activin A receptor, Type I)
  - Cytogenetic Location: 2q23-q24
  - 732,373



- 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 → disrupts inhibitor protein → receptor constantly

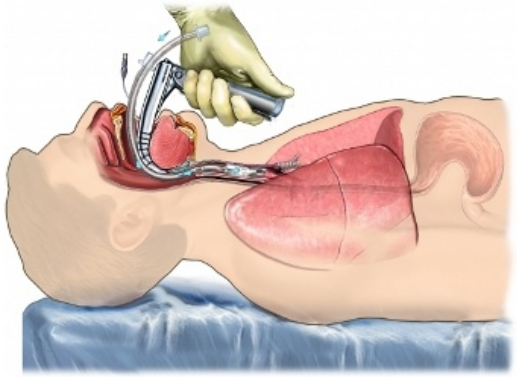
Classical Diagnosis of FOP

- 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



dividua

at diff

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

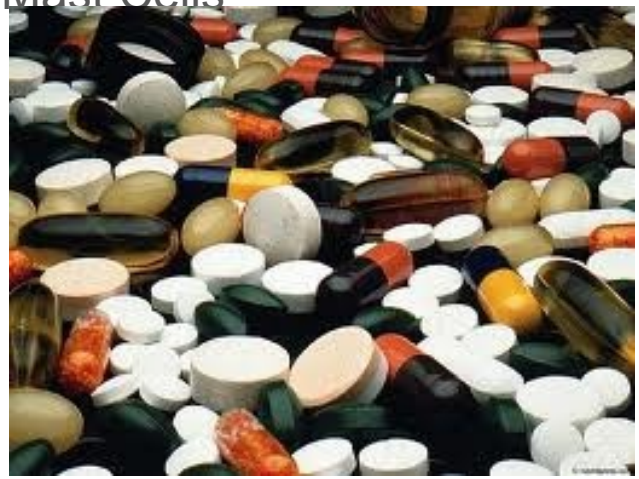
Laboratories offering clinical testing:	Sequence analysis of the entire coding region	Targeted mutation analysis	Prenatal diagnosis
Centogene GmbH The Rare Disease Company Rostock, Germany Christoph Ehlers; Prof Arndt Rolfs, MD; Prof Dr Jürgen Kohlhase, MD	•		•
Genomic Systems (Sistemas Genomicos SL) Medical Genetics Unit Paterna, Comunidad Valenciana, Spain Dr Sonia Santillán, MD, PhD; Dra Celia Buades, PhD; Diego Cantalapiedra, BSc, MSc; Dra Lucia Pérez, PhD, BSc; Marian Lazaro, MSc; Dr Alejandro Romera, PhD	•	•	•
University of Pennsylvania School of Medicine Genetic Diagnostic Laboratory Philadelphia, PA Arupa Ganguly, PhD		•	•

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
  - High doses worked in some cases
  - Anti-diabetic drug with high anti-inflammatory results
- Muscle Relaxants
- Bone Marrow Transplant

New drugs are developing to inhibit the action of Mast Cells

- Anti-mast cell therapies



Sources

- "Fibrodysplasia Ossificans Treatment & Management.". N.p., n.d. Web. 03 Oct. 2012. <http://emedicine.medscape.com/article/1112501-treatment>
- "Result Filters." National Center for Biotechnology Information. U.S. National Library of Medicine, n.d. Web. 03 Oct. 2012. <http://www.ncbi.nlm.nih.gov/pubmed/21755739>.
- "Fibrodysplasia Ossificans Progressiva (FOP) - OrthoInfo - AAOS." N.p., n.d. Web. 03 Oct. 2012. <http://orthoinfo.aaos.org/topic.cfm?topic=A00431>.
- Genetics Home Reference. N.p., n.d. Web. 03 Oct. 2012. http ://ghr.nlm.nih.gov/
- The International Fibrodysplasia ossificans progressiva association. N.p., n.d. Web. 04 Oct. 2012. <http://www.ifopa.org/

- OMIM Entry - # 135100 - FIBRODYSPLASIA OSSIFICANS PROGRESSIVA; FOP. N.p., n.d. Web. 03 Oct. 2012. <http://www.omim.org/entry/135100?search=number:(102576 OR 135100)>.
- "MedlinePlus. N.p., n.d. Web. 03 Oct. 2012. http://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=medlineplus
- "Fibrodysplasia Ossificans Progressiva." UCSF Benioff Children's Hospital. N.p., n.d. Web. 03 Oct. 2012. <http://www.ucsfbenioffchildrens.org/conditions/fibrodysplasia_ossificans_progressiva/index.html>.
- NIH Office of Rare Diseases Research (ORDR) - Error." NIH Office of Rare Diseases Research (ORDR) - Error. N.p., n.d. Web. 03 Oct. 2012. <http://rarediseases.info.nih.gov/GARD/Disease.aspx?PageID=4