

# Extraskkeletal manifestations of fibrous dysplasia

FIBROUSDYSPLASIAFOUNDATION'S  
PATIENTANDFAMILYCONFERENCE2017

Michael T. Collins, MD

Chief Section on Skeletal Disorders and Mineral Homeostasis,  
National Institute of Dental and Craniofacial Research  
National Institutes of Health

# Extraskkeletal manifestations of fibrous dysplasia

- **Phosphate**
- **Pancreas**
- **Cancer**
- **Brain**

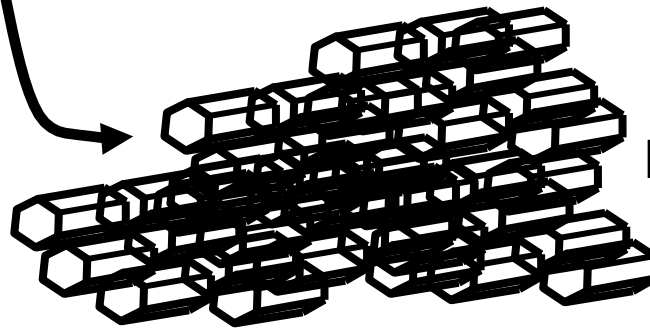
# Why do we care about Phosphate?

**Phosphate** →



← **Calcium**

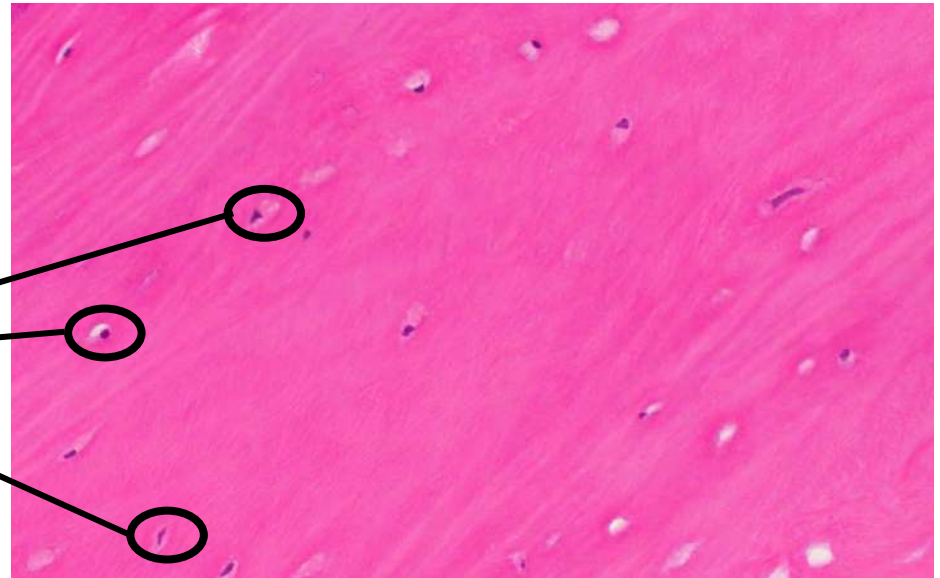
mineralization; the hard stuff the makes up bone



hydroxyapatite

bone is mostly hard stuff

with a few cells



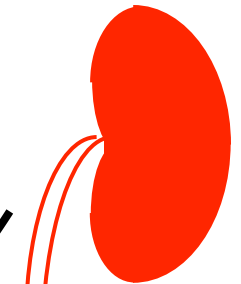
# FD overproduces FGF23

FGF23 made by FD, acts at the kidney to regulate blood phosphate and active vitamin D levels




**fibroblast growth factor 23**

**kidney**

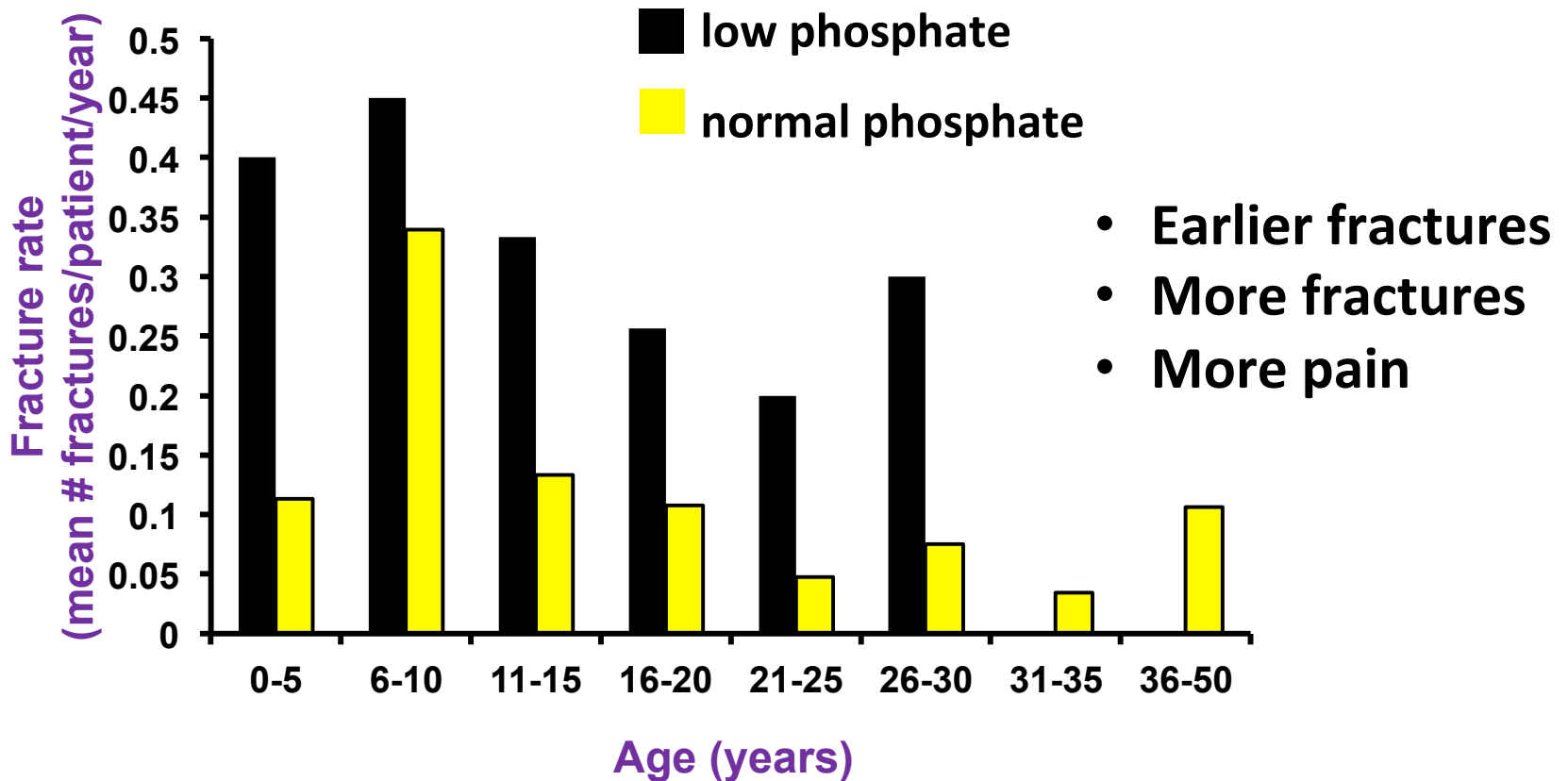


↓ **blood phosphate**

↓ **blood active vitamin D (1,25-D)**

  
urinary  
phosphate

# What are the effects of too much FGF23 on FD ?



- the more FD, the more FGF23
- probably need  $>1/2$  if the skeleton to be FD to get  $\uparrow$  FGF23

# Treatment of low phosphate

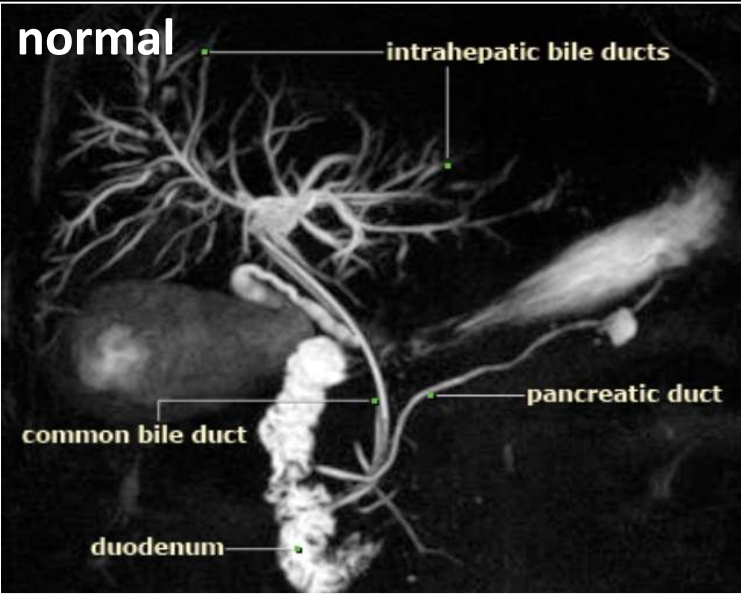
- **Oral phosphate + active vitamin D**
  - 3-5 times per day
  - diarrhea common
  - risk of kidney stones
- **May go get better/go away with time**
- **New drugs on the horizon**

# Pancreas in FD/MAS

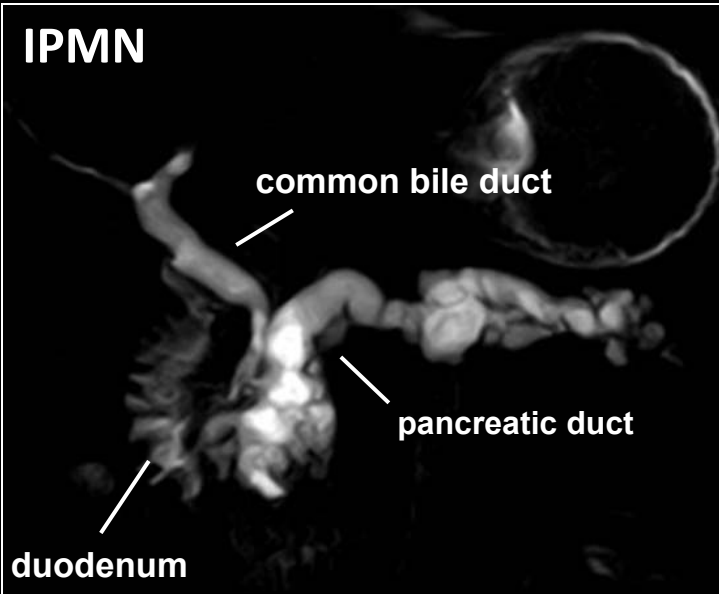
- **Some patients reported a history of pancreatitis**
- **We and a group in Paris began looking at the pancreas in MAS**
- **We found IPMNs (intraductal papillary mucinous neoplasms)**
  - **IPMNs are benign cyst-like lesions seen fairly commonly**
  - **may be a “precancerous” lesion**

# IPMNs - MRCP

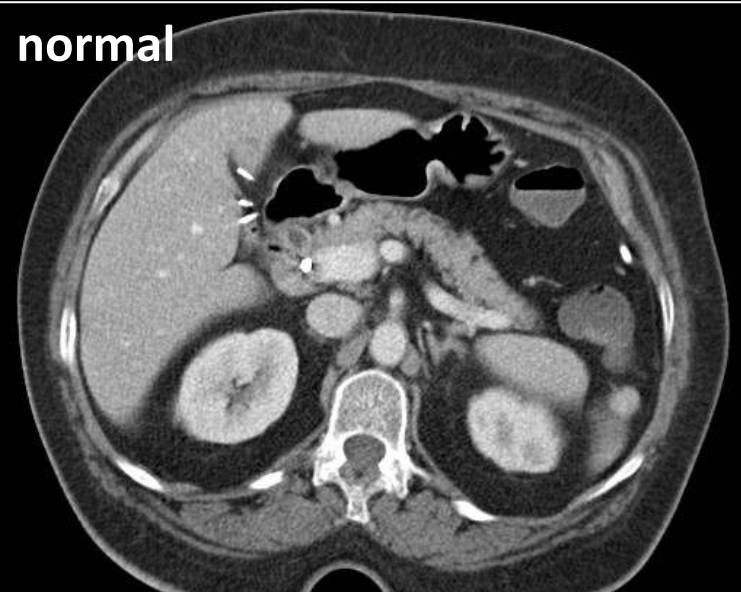
normal



IPMN



normal

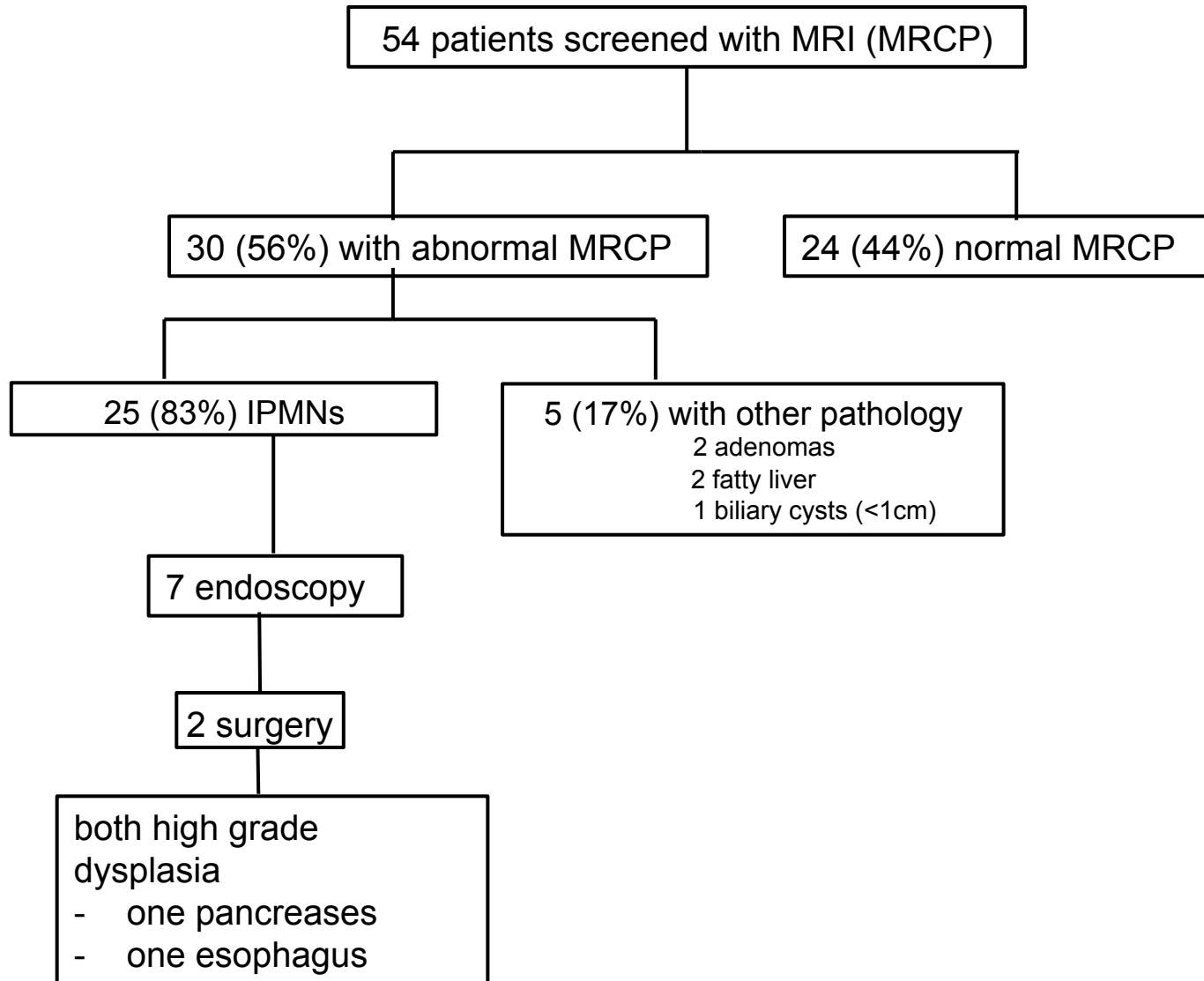


IPMN





# Pancreatic disease in MAS



# Recommendations: Pancreas in FD/MAS

- Baseline screening with MRCP
- If negative – you're done
- If abnormal → referral to a center with experience in complicated pancreas disease
- This is an evolving story...

# Cancer in MAS

- The gene mutation that causes FD/MAS,  $G\alpha_s$ , is a weak “oncogene” (a gene mutation that promotes tumor growth); the *gsp* oncogene
- It is NOT sufficient to cause cancer
- Cancer only occurs after several to dozens of mutations occur in a cell/tissue

# Cancers that have been seen in association with FD/MAS

- Bone
  - An increase noted following a period when FD was treated with high dose, radiation
- Thyroid
  - Only 2 cases reported ever
- Testicular
  - Only one case reported
- Pancreas
  - 2 cases reported
- Breast

# Breast Cancer in MAS

- Study of breast cancer in 2 large groups of women with FD/MAS
  - Leiden University Medical Center, Netherlands (134 women)
  - NIH (121 women)
- 15 cases of breast cancer identified
- 3.4-3.9-fold increase compared to the general population

# Breast Cancer in MAS

- Average age 41 years (range 27-54)
- *GNAS* mutation found in only 4/9 cancers
- Risk factors:
  - Precocious puberty
  - FD in the thorax (chest region)

# Breast Cancer in MAS

- Treatment: surgery, chemo, radiation
- 100% survival, 0 metastases
  - average 8.5 years follow-up, range 2-15
- Conclusions:
  - Women with MAS may be at increased risk of breast cancer
  - Compared to the general population, occurred at a younger age, less aggressive, with excellent long-term outcomes
  - Recommend: regular self-exams, and screening mammograms starting at age 40

# FD/MAS and the brain

- $G\alpha_s$  is found throughout the brain
- Mice with mutant  $G\alpha_s$  (*gsp*) expressed in certain regions of the brain have abnormal behavior
- In the NIH patients we have observed abnormal behavior/functioning in <10% of the patients
- Area of active research – more work needed...



# Thank you: to the patients, families, and co-workers



## Former Trainees

Elizabeth Hart  
Azar Khosravi  
Claudia Dumitrescu  
Penny Andreopoulou  
William H. Chong  
Tarek Metwally  
Jason Berglund

## NIH Clinical Center

Janice Lee  
Edmund FitzGibbon  
Scott Paul  
Jeffrey Kim  
Janice Lee  
Clara Chen

## DuPont Institute

Robert Stanton

Mary Scott Ramnitz  
Diana Ovejero  
Beth Brillante  
Diala El-Maouche  
Alison Boyce  
Andrea Estrada  
Andrea Burke  
Lori Guthrie  
Nisan Bhattacharyya  
Luis Fernandez de Castro  
Sri Tella  
Pablo Florenzano  
Rachel Gafni



Penny Feuillan



Arabella Leet



Paolo Bianco

**National Institute of Dental & Craniofacial Research  
Fibrous Dysplasia Foundation**

**International Consortium of FD Investigators**  
(US, UK, Netherlands, France, Italy, Chile)

