Fibrous Dysplasia Foundation
Patient and Family Meeting
New York City
2014

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National Institutes of Health
Bethesda, Maryland
Fibrous Dysplasia Foundation
Patient and Family Meeting

• Thank you
  – Charlie Harles, Dan Levine, Cindi Levin, Amanda Konradi, NYU, Dr. Gail Chorney, Ranit Shirky
  – All of the Doctors

• Meet with doctors
• Tight schedule
SYNDROME CHARACTERIZED BY OSTEITIS FIBROSA DISSEMINATA, AREAS OF PIGMENTATION AND ENDOCRINE DYSFUNCTION, WITH PRECOCIOUS PUBERTY IN FEMALES*

Report of Five Cases

BY FULLER ALBRIGHT, M.D., § ALLAN M. BUTLER, M.D., § AUBREY O. HAMPTON, M.D., § AND PATRICIA SMITH, M.D. §
1933 – 1937, 32 different names

“...perverted activity of the specific bone-forming mesenchyme.” Lichtenstein & Jaffe, 1943
What goes wrong in the bone?

Skeletal stem cell → Bone forming cell

Blood supporting cell → Cartilage forming cell

Stromal cell → Adipocyte

Maturation of the stem cell is blocked

Bianco...Robey, JCI 1998
FD results from multiplication of mutation-bearing skeletal stems cells

FD lesions are a mixture of mutant and normal cells
Mutation-bearing cells probably die off sooner

young patient

older patient

(Kuznetsov, JBMR, 2008)
McCune-Albright Syndrome - Definition

Any combination of two or more of these typical findings = MAS
These can occur in any combination
Marked variability in severity and treatment

- Café-au-lait
- Precocious puberty
- Fibrous dysplasia
- Hyperthyroid
- Gigantism/Acromegaly
- Cushings
- Rickets/Osteomalacia
- Others

Marked variability in severity and treatment
What causes FD?

- Disease caused by a mutation in a gene, \textit{GNAS}
- \textit{GNAS} is the code for the protein, \textit{G}_{\text{S} \alpha}
- Rare: $1/1,000,000$ – $1/100,000$
- No known “cause” for the mutation
- The mutation did not come from either parent
- The mutation will not be passed to your children

(Weinstein, NEJM, 1991)
$G_\text{S}\alpha$ is the “on and off switch” for many cells

- **Skin**: Café-au-lait
- **Ovary**: fibrous dysplasia
- **Bone**: precocious puberty
- **Thyroid**: hyperthyroidism
- **Pituitary**: growth hormone excess
How MAS Happens

Mutation occurs by chance

Mutation in the gene GNAS

*GNAS codes for the protein, Gsα*
How MAS Happens

Stem Cell

Mutation occurs by chance

Mutated cell proliferates

- Mutation is now in cells that will later give rise to different tissues: skin, bone, ovaries, etc.
How MAS Happens

Stem Cell

Mutation occurs by chance

Mutated cell proliferates

Mutated cells migrate & expands as embryo is formed
How MAS Happens

Stem Cell

Mutation occurs by chance

Mutated cell proliferates

Mutated cells migrate & expands as embryo is formed

Where and when the mutation occurs determines what your child will and won’t have
The “map” of affected tissues is drawn in utero.

- **Fibrous dysplasia**
- **Café-au-lait**
- **Precocious Pub.**
- **Thyroid**
- **Phosphate**
- **Growth hormone**
- **Cushings**

- **Age not visible yet**
- **Causess problems**
- **Can go away on its own**

By the age of 5 or so careful testing can identify all tissues that will ever be affected.
The *GNAS* gene is prone to mistakes (mutations) that lead to MAS.

There are no known environmental, ethnic, or geographic risk factors for the development of MAS. (It’s not your fault mom!)

So far, all cases of MAS are sporadic. The disease did not come from the parents and patients will not transmit it to their children.
How do you diagnose FD/MAS?

- Typical x-ray, + typical café-au-lait + prec. puberty
- Typical café-au-lait + typical x-ray
- Prec. puberty + typical x-ray
- Atypical café-au-lait + typical x-ray
- Typical x-ray, atypical location, + gene test
- Atypical x-ray, atypical location, “typical biopsy”
- Atypical x-ray, typical biopsy, + gene test
- Atypical x-ray, atypical biopsy, + gene test
- Atypical location and x-ray, no skin, no endo., no biopsy, no mutation testing
What bones are affected by FD?

(Kelly, OI, 2008)
Ages when and where FD appears

<table>
<thead>
<tr>
<th></th>
<th>% of disease present</th>
<th>Craniofacial</th>
<th>Extremity</th>
<th>Axial (spine, ribs, pelvis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>3.4*</td>
<td>13.7</td>
<td>15.5</td>
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Almost all clinically-significant bones disease is present by around age 5

Almost no clinically-significant new bone disease occurs after 5
When do fractures occur in FD

- fracture rate is highest in childhood
- fracture rate persists into adulthood
- marked variability between people
- variability is related to endocrine problems
- low blood phosphorus has the largest effect
FD of the spine

- FD of the spine is common (63%)
- scoliosis is common (40%)
- functional deficits are rare
- progression can be stopped by rods
Quality of life in adults with FD/MAS

* = p < 0.05 MAS vs US norms

Kelly, Bone, 2005
Quality of life in children with FD/MAS

* = p < 0.05 MAS vs US

Kelly, Bone, 2005
Acknowledgement of the work of……….

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In Memory of

Penelope Feuillan

Arabella Leet