Insights into McCune-Albright Syndrome: A Complex, Rare Disease with Individual Presentations

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NIH National Institute of Dental and Craniofacial Research

Pediatric Endocrinology Nursing Society
National Conference
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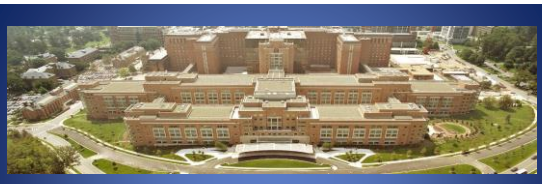
Conflict of Interest Disclosure

Lori Guthrie and Jamie Streit

NIDCR receives research funds from Amgen Inc. and QED Therapeutics for studies involving McCune-Albright Syndrome and other disorders.

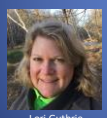


The National Institutes of Health (NIH) is the nation's largest hospital devoted entirely to clinical research.

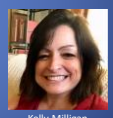
We are located in Bethesda, Maryland,
just a few miles north of Washington, DC.

NIDCR – National Institute of Dental and Craniofacial Research

We are Research Nurse Specialists who coordinate research studies for children and adults with rare bone and endocrine conditions, one of which is McCune-Albright Syndrome (MAS).


Lori Guthrie


Jamie Streit


Kelly Milligan

We work on a team that is comprised of:

- Adult and Pediatric Endocrinologists
- Endocrine Fellows
- Dental/Craniofacial Surgeon
- Research Nurses
- Lab Manager
- Students

Objectives

1. Name the gene mutation associated with McCune-Albright Syndrome.
2. List the three body systems most commonly affected by McCune-Albright Syndrome.
3. Discuss the current medical treatments used to manage McCune-Albright Syndrome.
4. Identify three psychosocial aspects related to the challenges of living with McCune-Albright Syndrome.
5. Discussion/Questions.

MAS Natural History Research Study at NIH

- Prospective Cohort Study – detailed phenotyping to define spectrum and natural history
- Largest cohort of MAS patients in the world, >289 on-site
- Range from <1 to 102 years of age
- Current study: 1998 to present
  Prior studies: mid 1980s - 1998

Comprehensive NIH Clinical Evaluation

- History and Physical Exam
- Serum and Urine Endocrine Markers
- Skeletal X-rays
- Rehabilitation Medicine

- Ophthalmology
- Audiology
- Otolaryngology
- Bone scan

Mon Tues Wed Thur Fri

- Thyroid Ultrasound
  Gonad Ultrasound
- CT Skull
- Dental
- MRI Pancreas

- Clinical Photography
- Quality of Life Questionnaires
- Wrap Up Meeting

Additional Testing as Needed:
- Gynecology
- Pain and Palliative Care
- Serial Blood Tests:
  - 3 hour OGTT
  - 12 hour Growth Hormone Sampling (overnight)
  - 1 hour ACTH
- Kidney Ultrasound
- MRI Pituitary
- MRI Brain
- MRI Face/Sinus/ENT
- Pulmonary Function Tests
- Echocardiogram
- Neuropsychiatric Testing
- Overnight Sleep Study
- Mental Health Interview

McCune-Albright Syndrome
first descriptions

SOCIETY FOR PEDIATRIC RESEARCH

Annual Meeting, May 5, 1936

OSTEITIS FIBROSA CYSTICA; THE CASE OF A NINE YEAR OLD GIRL WHO ALSO EXHIBITS PRECOCIOUS PUBERTY, MULTIPLE PIGMENTATION OF THE SKIN AND HYPERTHYROIDISM. DR. D. J. MCCUNE, New York.

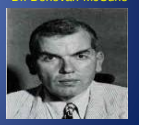
Dr. Donovan McCune

The New England Journal of Medicine

APRIL 29, 1937

SYNDROME CHARACTERIZED BY OSTEITIS FIBROSA DISSEMINATA, AREAS OF PIGMENTATION AND ENDOCRINE DYSFUNCTION, WITH PRECOCIOUS PUBERTY IN FEMALES*

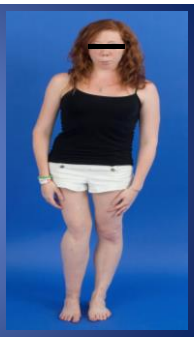
Report of Five Cases



Dr. Fuller Albright

What is McCune-Albright Syndrome?

- Rare genetic disorder
- Affects 1 in 100,000 to 1 in 1,000,000 people worldwide
- No known "cause" for the mutation
- The mutation did not come from either parent and will not be passed to their children



MAS Differential Diagnosis

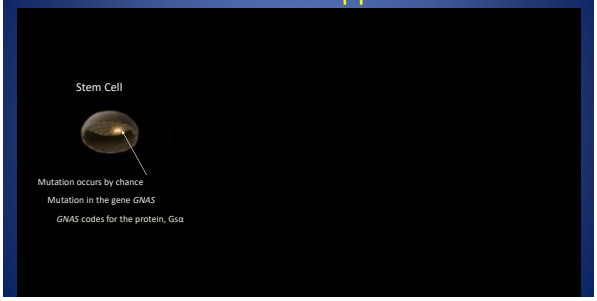
These depend on presentation and may include:

- Neurofibromatosis
- Osteofibrous dysplasia
- Non-ossifying fibromas
- Idiopathic central precocious puberty
- Milder forms of osteogenesis imperfecta
- Ovarian neoplasm

MAS Gene Mutation

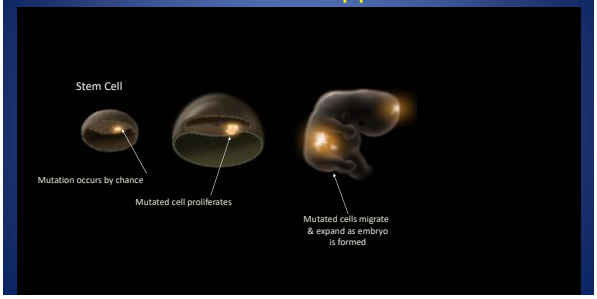
- *GNAS* (guanine nucleotide binding protein, alpha stimulating activity polypeptide 1)
- Spontaneous mutation: long arm (q) arm of chromosome 20 at position 13.3
- Mutates cells within variously affected tissues
- Highly variable presentations – depends on specific tissues involved and extent of involvement

How MAS Happens

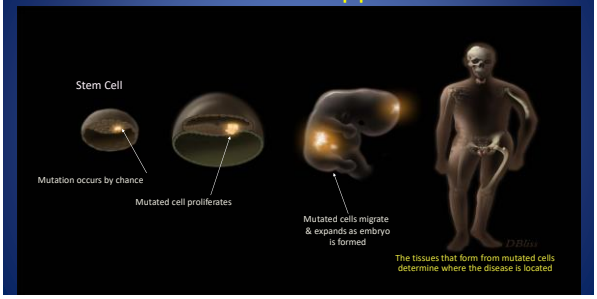


How MAS Happens

How MAS Happens



How MAS Happens

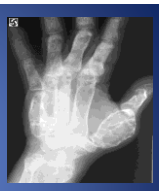


$G_s\alpha$ is the "on and off switch" for many cells

Skin	Ovary	Bone	Thyroid	Pituitary
café-au-lait macules	precocious puberty	fibrous dysplasia	hyperthyroidism	growth hormone excess

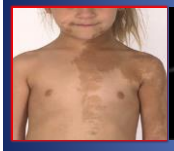
In MAS, the hormone receptor get stuck in the "on" position

Diagnosis

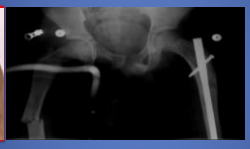


- Diagnosis most often occurs in early childhood
- May be diagnosed:
  - at birth - presence of café-au-lait macules
  - early childhood - development of precocious puberty, bone fractures, or bone deformities
  - adulthood - incidental finding on imaging
  - The name: McCune-Albright Syndrome versus fibrous dysplasia

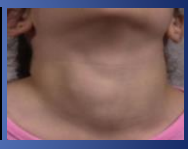
Clinical Manifestations in MAS



Skin – ectoderm



Bone – mesoderm

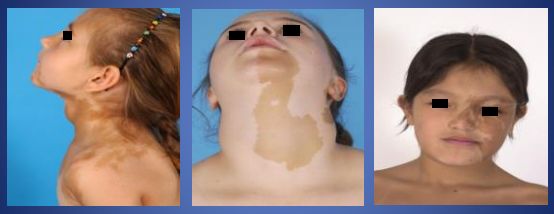


Endocrine- endoderm

Skin – café-au-lait macules

- Light brown patches of skin, often present at birth
- Irregular edges are often compared to a map of the coast of Maine
- Not specific for MAS - 10% of healthy population have café-au-lait macules

Spectrum of café-au-lait macules

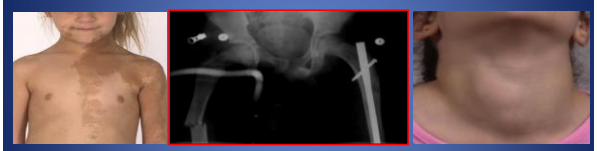


- first sign of MAS
- coast of Maine appearance

Spectrum of café-au-lait macules

- Often starts or ends near the midline
- *NO* correlation with location or extent of bone disease

Clinical Manifestations in MAS



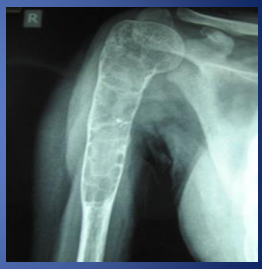
Skin – ectoderm

Bone – mesoderm

endocrine- endoderm

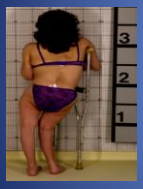
Fibrous Dysplasia (FD)

- Abnormal scar-like (fibrous) tissue in bones. "Ground glass" appearance
- Monostotic – affecting one bone
- Polyostotic – affecting multiple bones
- No medical treatments known to alter the course of FD
- Surgery - correct deformity and repair fractures
- Physical therapy and occupational therapy - optimize mobility and function



Fibrous Dysplasia

Deformity, Pain, Limp, Fractures, Disability



Wind-swept deformity

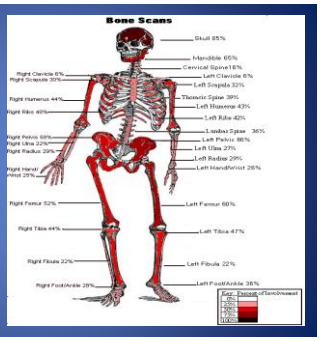
Shepherd's crook deformity

Leg length discrepancy

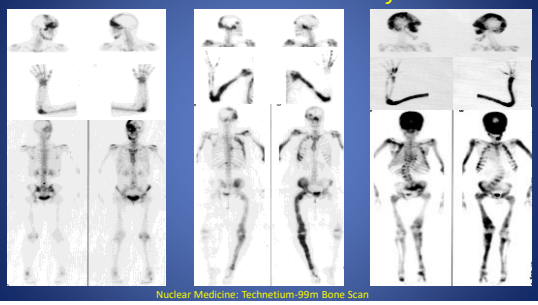
Fibrous Dysplasia

Virtually any bone in the body may be affected.

Most common are:
– facial and skull bones
– pelvis
– femur
– tibia
– humerus
– ribs
– small bones in hands and feet

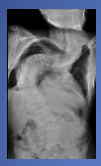


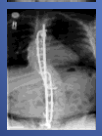
FD – variations in severity



Nuclear Medicine: Technetium-99m Bone Scan

FD in the spine: scoliosis



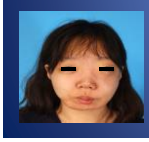


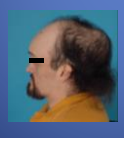
- Scoliosis occurs at sites of FD
- Scoliosis is more common with leg length discrepancy
- Worsens with untreated endocrine disorders, especially hyperthyroidism and hypophosphatemia
- Progression can be stopped by rods

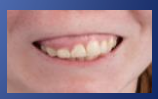
FD - Craniofacial

In the craniofacial area (bones of the skull and face) most complications are related to FD expansion.

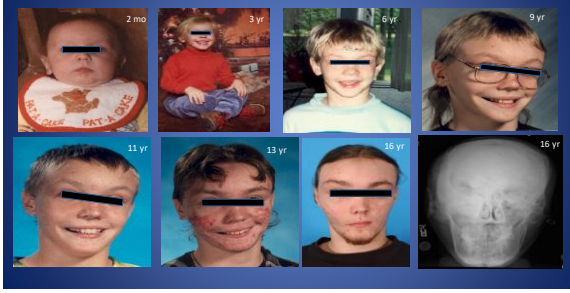
This may lead to facial asymmetry, and very rarely, loss of vision and hearing.





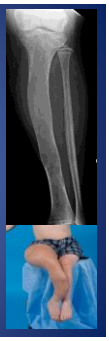


Craniofacial fibrous dysplasia: progression

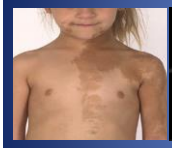


Fibrous Dysplasia and Pain

- Common; can occur in any FD location
- Pain may be due to the expansion in the FD bone, fracture or hypophosphatemia
- Treatment:
  - Prevention: strength training, range of motion, correction of leg length discrepancies (orthotics, shoe lifts)
  - Over the counter medications (such as acetaminophen, ibuprofen, and naproxen) - mild to moderate pain
  - Pain specialist to guide pharmacologic (narcotics for acute issues - fractures or surgery) and non-pharmacologic therapies (massage, acupuncture)
  - Intravenous bisphosphonates (such as pamidronate or zoledronic acid) – ONJ link



Clinical Manifestations in MAS



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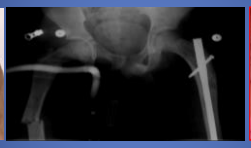
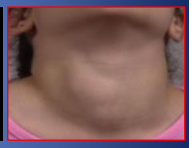


Bone – mesoderm

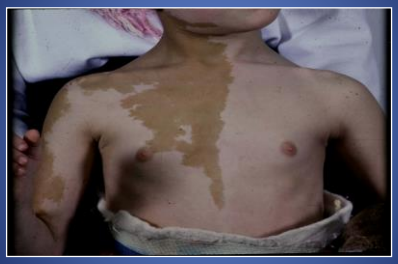


Endocrine- endoderm

McCune-Albright Syndrome

Café-au-lait

Fibrous Dysplasia



Precocious Puberty

Growth Hormone Excess

Hyperthyroid

Neonatal Cushing Syndrome

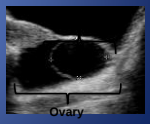
Phosphate Wasting

Peripheral Precocious Puberty in Girls

arises from early activation of ovaries

- Breast development
- Vaginal bleeding
- Recurrent ovarian cysts
- Increased growth velocity
- Bone age advancement
- Reduced final adult height

- Some teens/women have menstrual irregularities
- Women with MAS are often able to become pregnant and have healthy children



Ovary

Pelvic Ultrasound

Peripheral Precocious Puberty in Boys

arises from early activation of testicles

- Less common in boys, than girls
- Increased growth velocity
- Bone age advancement
- Reduced final adult height
- Pubic and axillary hair
- Increased growth of testicles/penis
- Early sexual behavior/aggression
- Leydig or Sertoli cell hyperplasia on testicular ultrasound

PP: 20 yo, 4 feet, 11 inch

Precocious Puberty - Treatment

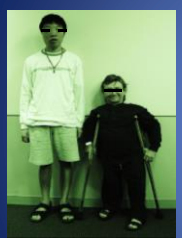
Peripheral Precocious Puberty:

- Girls – letrozole (blocks action of estrogen)
- Boys – combination of letrozole and spironolactone (blocks action of testosterone)

Central Precocious Puberty:

- When a child who was previously well-controlled on peripheral precocious puberty meds, presents with signs of "breakthrough" puberty (pituitary gland turns on too early)
- Leuprolide is added (suppresses the pituitary gland)

Growth Hormone (GH) Excess

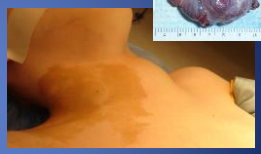


Gigantism due to GH excess

Short stature due to precocious puberty

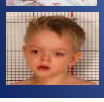
- Production of high levels of growth hormone from the pituitary gland
- Main symptoms - accelerated growth rate and FD expansion
- If untreated, GH excess leads to higher risk of vision and/or hearing loss in patients with skull disease
- Treatments:
  - Octreotide is a drug that prevents the release of growth hormone from the pituitary
  - Pegvisomant is a medication that blocks the action of growth hormone on its receptor
  - Pituitary surgery or radiation - used rarely

Hyperthyroid



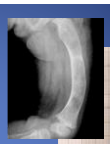
- Production of excess thyroid hormone, resulting in hyperthyroidism
- Other thyroid abnormalities: goiter, cysts, and nodules
- Very slight increased risk of thyroid cancer
- Treatment:
  - Methimazole - drug that blocks thyroid hormone production
  - Most patients with MAS and hyperthyroidism will eventually have a thyroidectomy, and will then need standard thyroid hormone replacement
- Some patients may regrow thyroid tissue after thyroid removed

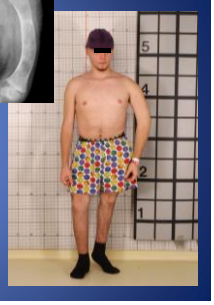
Neonatal Cushing Syndrome



- Excess cortisol production, a rare complication
- Presents during infancy or the first few years of toddlerhood
- Symptoms vary: low birth weight and abnormal weight gain, especially in the face and trunk
- Can become severely ill, and is sometimes fatal
- In a few cases in MAS, neonatal Cushing has resolved on its own
- Treatment: depends on age of the child and severity of illness
  - Drugs that block cortisol production
  - Surgery to remove the adrenal glands

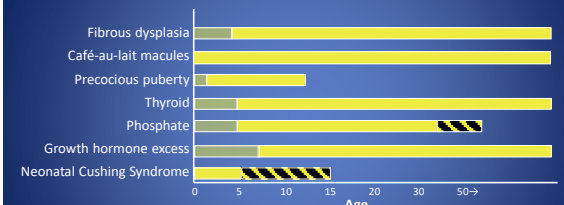
Phosphate Wasting





- Hypophosphatemia: low levels of phosphorus in the blood
- Causes bone pain, muscles weakness, increased fractures, rickets
- Occurs when fibrous dysplasia bones produce excess amounts of **FGF23**, a hormone which causes the kidneys to lose phosphorus in the urine
- Treatment: a combination of oral phosphate supplements and vitamin D

"Map" of Tissues is established in utero and manifests at an early age



subclinical
clinically evident
spontaneous resolution possible

-> Complete staging after age 5 allows for determination of affected *and unaffected* tissues

NIH MAS cohort

Findings	Prevalence (%)
Fibrous dysplasia	99
Café-au-lait macules	89
Gonads/precocious puberty	
male	77
female	78
Thyroid	69
Phosphate wasting	48
requiring treatment	17
Growth hormone excess	18
Neonatal Cushing Syndrome	7

NIH Collaborative Research Related to MAS

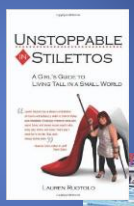
- **Pancreatic**
  - collaboration with Johns Hopkins University
  - prospective research, part of NIH natural study, to determine incidence of pancreatic neoplasm (intraductal papillary mucinous neoplasm - IPMN) in high risk subjects of the NIH MAS population
- **Dental**
  - collaboration with University of Pennsylvania
  - retrospective study to determine dental/orthodontic outcomes in NIH MAS population
- **Sleep/Psychiatric/Neuropsychological**
  - collaboration with NIMH to determine incidences of sleep, psychiatric, and neuropsychological differences in the NIH MAS population
- **Novel Therapies**
  - denosumab drug trials (for bone pain)

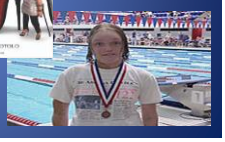
Psychosocial Considerations Related to MAS

- Impaired physical function +/- physical limitations
  - Low risk activities to avoid fracture/injuries to bone (modified PE/Gym; encourage activities such as swimming, recreational dance)
  - Adaptations if necessary - cane, crutches, wheelchair, orthotics, shoe lifts, etc.

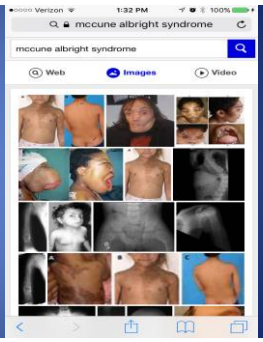

Psychosocial Considerations - continued

- Self esteem/mental health impact
  - QOL: MAS perception verses parents' perception
  - Recommend counseling for specific concerns – coping with physical signs of early puberty, teasing/bullying, life transitions (ie high school to college, long-term relationships, adaptations to work, etc.)
- Knowledge deficit related to disease process
  - Education
  - Support groups - Magic Foundation, Fibrous Dysplasia Foundation



When parents search the internet for "McCune-Albright Syndrome," what do they see?



Resources for Patients and Families

The MAGIC Foundation®

"Children have a short time to grow and a lifetime to live with the results" ©

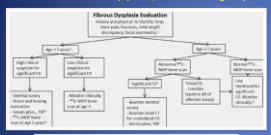
http://www.magicfoundation.org/www

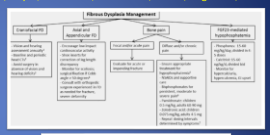
Fibrous Dysplasia FOUNDATION

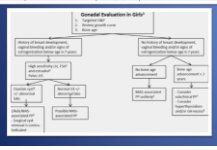
http://fibrousdysplasia.org/

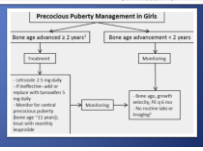
Resources for Clinicians

GeneReviews: Fibrous Dysplasia/McCune-Albright Syndrome, Boyce, Florenzano, F de Castro, Collins, August 16, 2018









Selected References

1. Boyce AM, Florenzano P, de Castro LP, Collins MT. Fibrous Dysplasia/McCune-Albright Syndrome. 2018 August 16. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.
2. Brillante B, Guthrie L. "McCune-Albright Syndrome," in *Advanced Practice in Endocrinology Nursing* (Springer International Publishing, Springer Nature Switzerland AG, 2019).
3. Brillante B, Guthrie L, Van Ryzin C. McCune-Albright Syndrome: an overview of clinical features. Journal of Pediatric Nursing. 2015; 30(5): 815-817.
4. Boyce AM, Brewer C, DeKlotz TR, Zalewski CK, King KA, Collins MT, Kim HJ. Association of hearing loss and otologic outcomes with fibrous dysplasia. JAMA Otolaryngol Head Neck Surg. 2018;144:102–7.
5. Boyce AM, Chong WH, Shawker TH, Pinto PA, Linehan WM, Bhattacharyya N, Merino MJ, Singer FR, Collins MT. Characterization and management of testicular pathology in McCune-Albright syndrome. J Clin Endocrinol Metab. 2012a;97:E1782–90.
6. Boyce AM, Glover M, Kelly MH, Brillante BA, Butman JA, Fitzgibbon EJ, Brewer CC, Zalewski CK, Cutler Peck CM, Kim HJ, Collins MT. Optic neuropathy in McCune-Albright syndrome: effects of early diagnosis and treatment of growth hormone excess. J Clin Endocrinol Metab. 2013;98:E126–34.
7. Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab. 2010;95:1508–15.
8. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. 2012. Orphanet J Rare Dis.
9. Estrada A, Boyce AM, Brillante BA, Guthrie LC, Gafni RI, Collins MT. Long-term outcomes of letrozole treatment for precocious puberty in girls with McCune-Albright syndrome. Eur J Endocrinol. 2016;175:477–83.
10. Lee JS, FitzGibbon EJ, Chen YR, Kim HJ, Lustig LR, Akintoye SO, Collins MT, Kaban LB. Clinical guidelines for the management of craniofacial fibrous dysplasia. Orphanet J Rare Dis. 2012;7 Suppl 1:S2.
11. Stanton RP, Ippolito E, Springfield D, Lindaman L, Wientroub S, Leet A. The surgical management of fibrous dysplasia of bone. Orphanet J Rare Dis. 2012;7 Suppl 1:S1.
12. Tessaris D, Corrias A, Matarazzo P, De Sanctis L, Wasniewska M, Messina MF, Vigone MC, Lala R. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Horm Res Paediatr. 2012a;78:151–7.

Questions?