An Overview of Nicolaides-Baraitser Syndrome (NCBRS)

Dr. Resham Ejaz

Medical Genetics PGY3

July 11th 2015

Supervised by Dr. David Chitayat

Objectives

- To describe and define Nicolaides-Baraitser syndrome (NCBRS)
- To explain the genetics and known underlying biology
- To review the variable clinical manifestations of NCBRS
- To present the evolution of features in NCBRS
- To discuss directions for future research

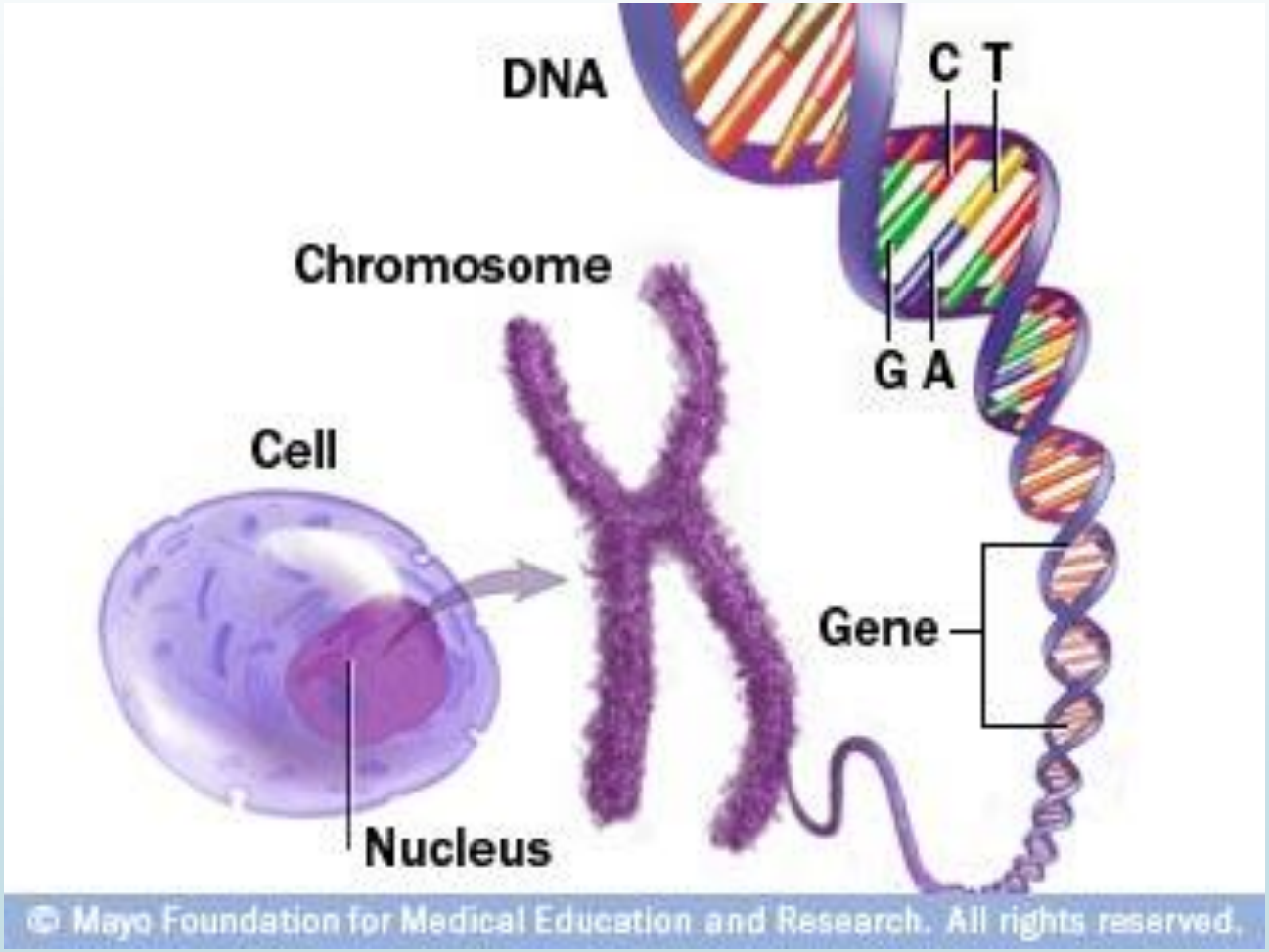
What is NCBRS?

- Rare genetic disorder encompassing developmental delay, sparse hair, seizures, short stature, characteristic facial features and prominent interphalangeal joints
- About 60 reported cases in literature, with more unreported individuals being diagnosed
- Syndrome: constellation of findings that occur more often together than expected and are a result of the same underlying reason

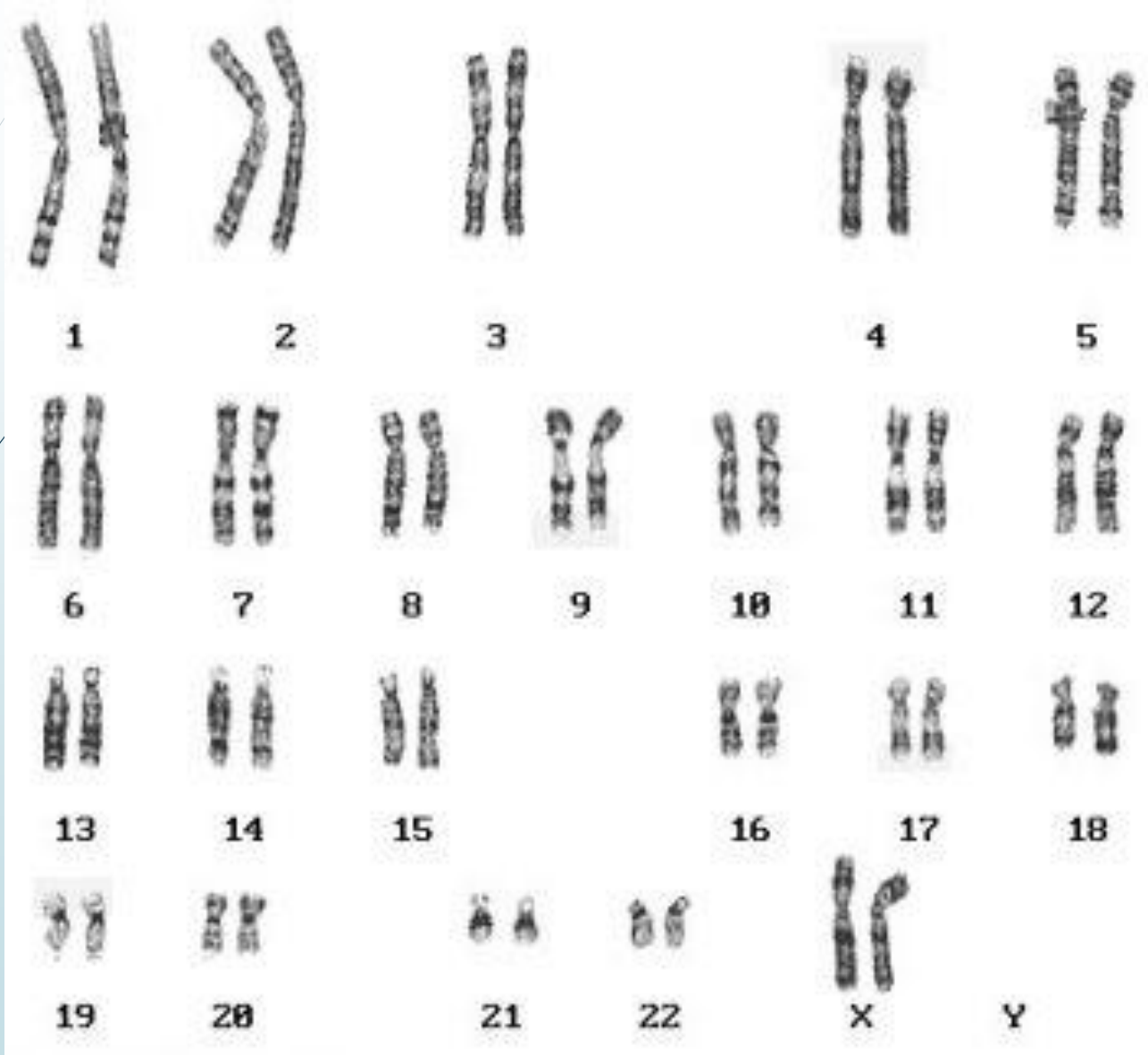
- Affects individuals of all ethnicities
- Affects both males and females, slighter higher proportion reported males
- Median age of reported individuals is 10 years
- Average paternal age is 32.9 years and average maternal age is 30.1 years

Why does it happen?

- Has been shown to be due to heterozygous missense mutations in the SMARCA2 gene

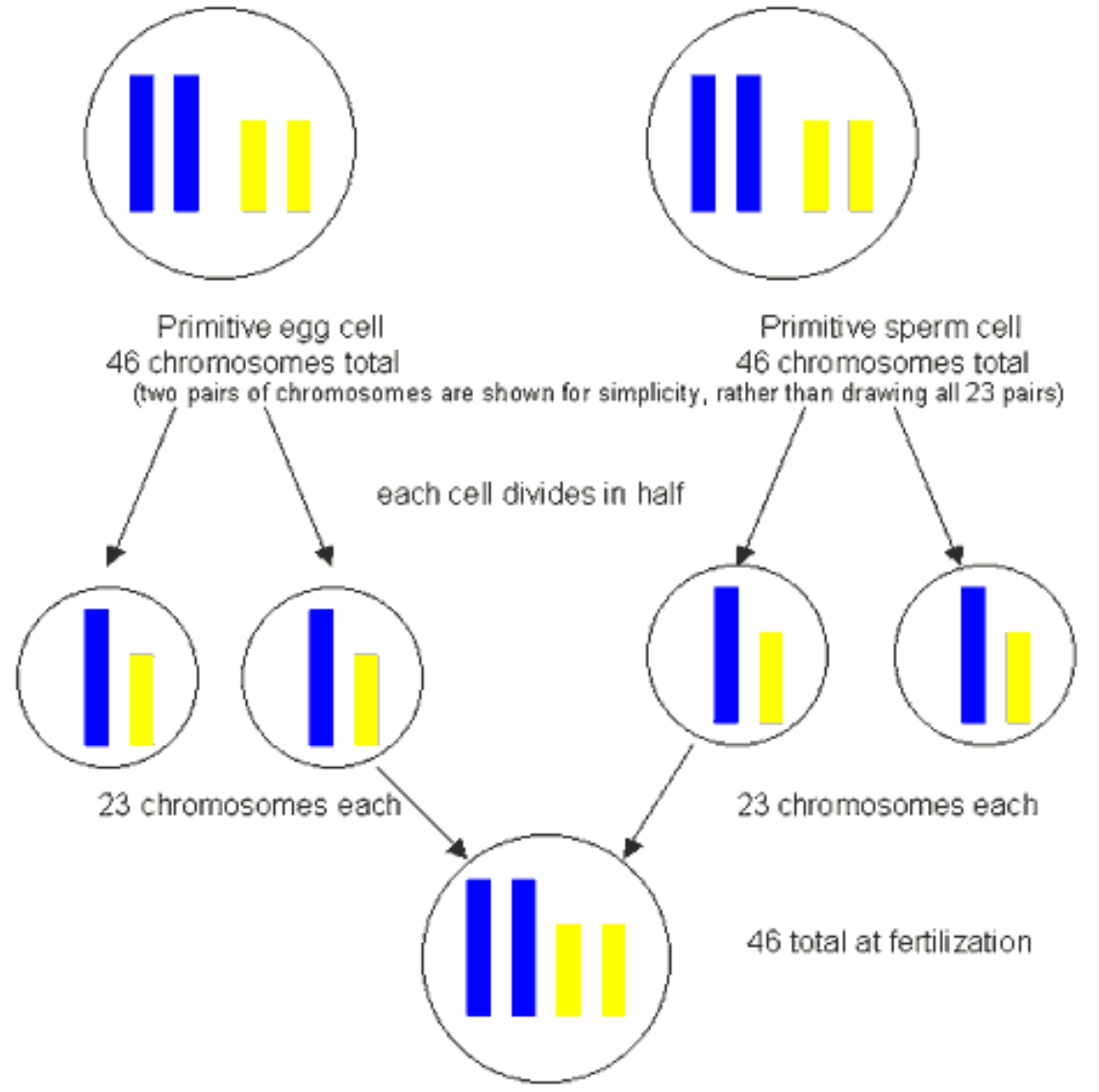


The human chromosomes



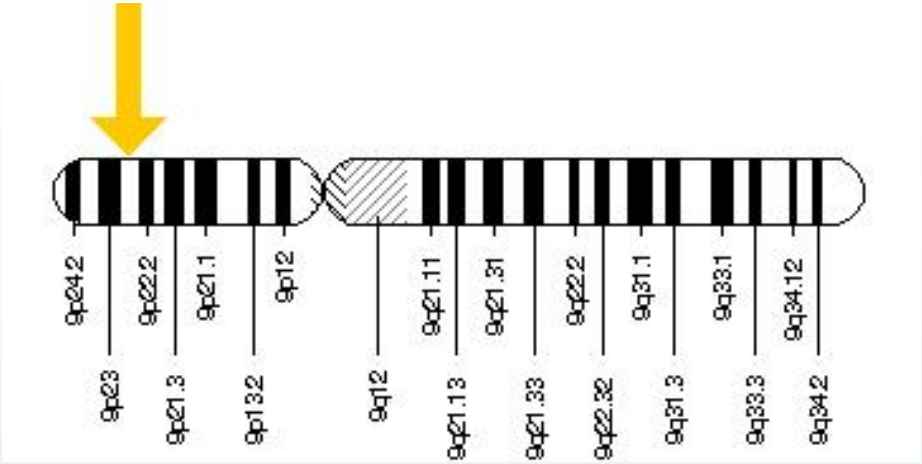
Genetic Education, Murdoch Children's Medical Research Institute

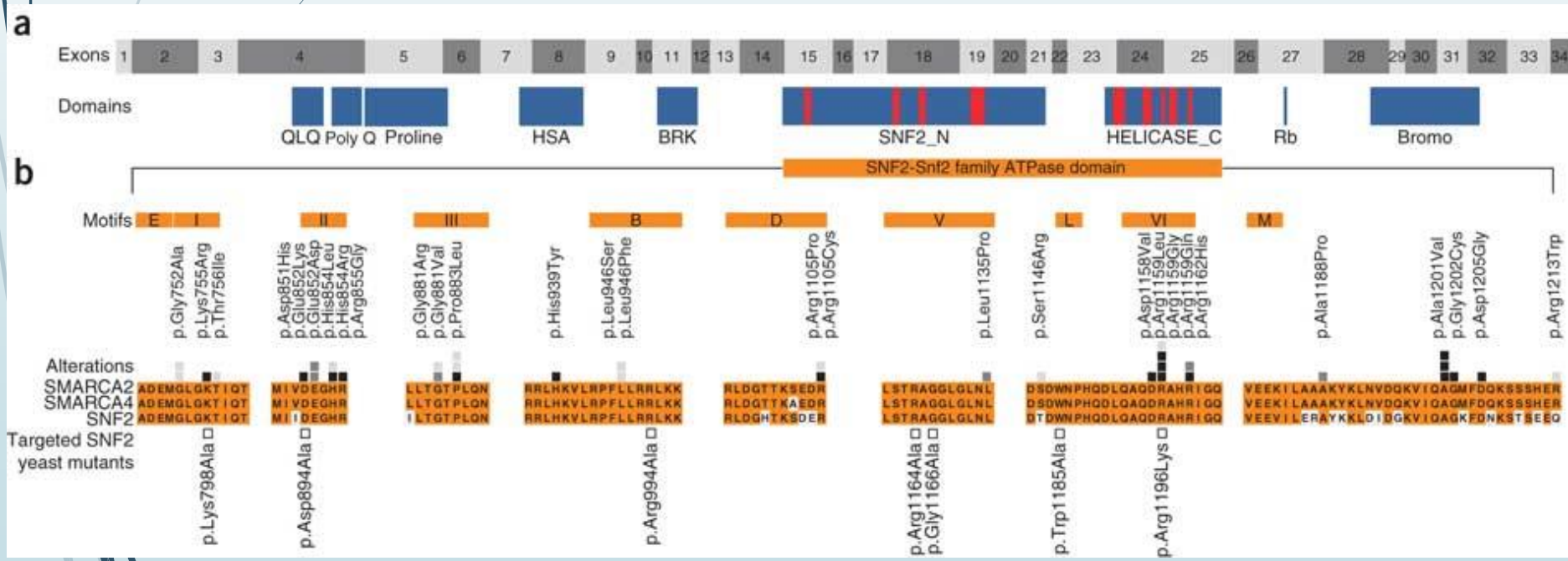
How do changes happen?



http://www.chw.org/medical-care/genetics-and-genomics-program/medical-genetics/chromosome-abnormalities/how-chromosome-abnormalities-happen/

The SMARCA2 gene





http://ghr.nlm.nih.gov/gene/SMARCA2

Van Houdt JKJ et al. 2012. Heterozygous missense mutations in SMARCA2 cause Nicolaides-Baraitser syndrome. Nat Genet

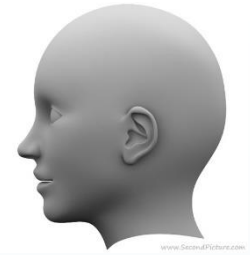
What does SMARCA2 do?

- Involved in remodeling of the chromosomes to allow for gene expression
- Help activate genes that may otherwise be turned off
- Plays an important role in neural development

Clinical Presentation of NCBRS

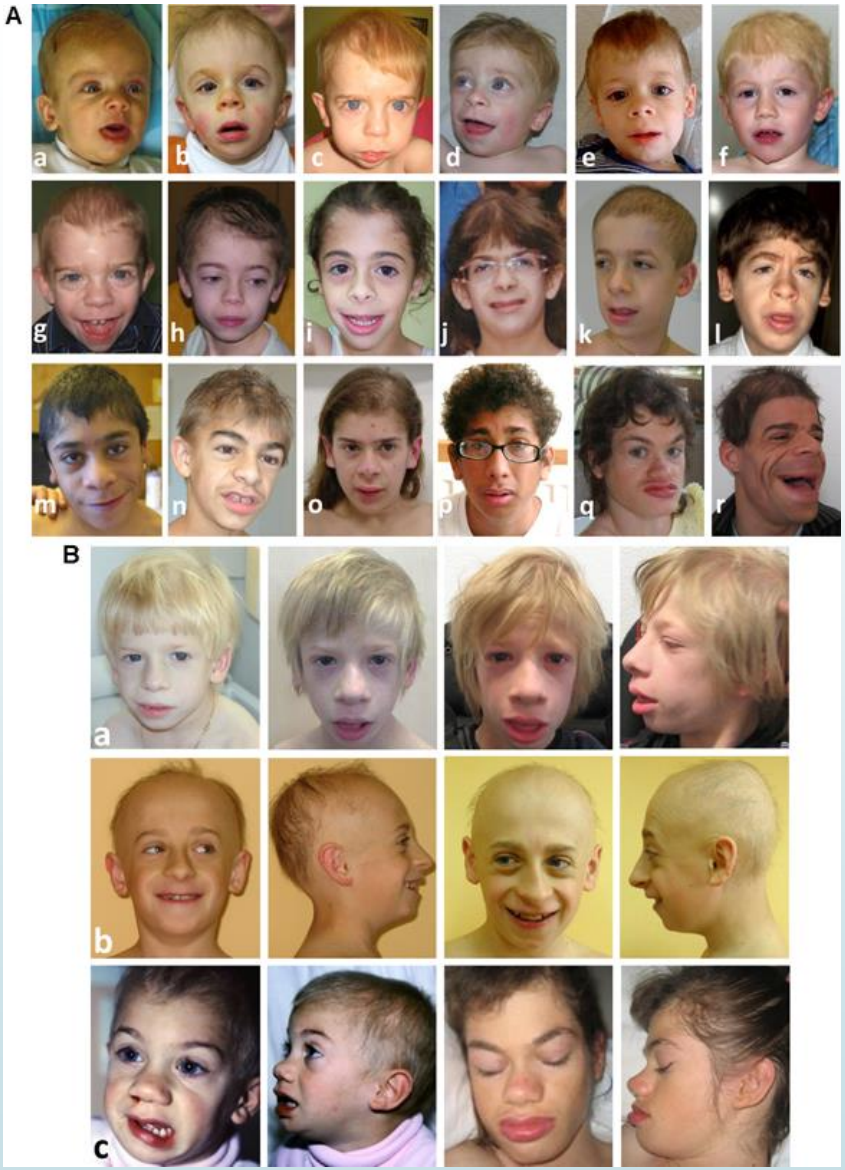
- First reported in 1993 by Paediatrician Dr. Nicolaides and Clinical Geneticist Dr. Baraitser
- 16 year old girl noted to have intellectual disability, sparse hair, prominent lower lip, seizures, short fingers with particular bone changes
- Next confirmed report in 2003, with many other emerging after, helping broaden the known features of NCBRS
- Cohort of 61 patients described by Sousa et al (2014)

1) Head and Face



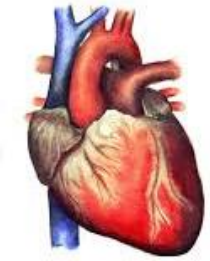
- Sparse scalp hair, can be variable from mild in babies to more sparse in adults
- Hair grown on other parts of body preserved
- Characteristic facial features can be subtle and become progressively more pronounced with age
- Features include a triangular face, thick nares, thick and everted lower lip, possible increased wrinkling of skin, broad jaw with age

Facial features in Nicolaides–Baraitser syndrome



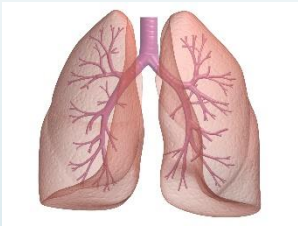
American Journal of Medical Genetics Part C: Seminars in Medical Genetics
Volume 166, Issue 3, pages 302-314, 28 AUG 2014 DOI: 10.1002/ajmg.c.31409
http://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31409/full#ajmgc31409-fig-0001

2) Heart



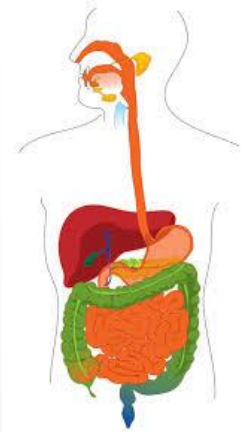
- Heart defects are not a common feature of NCBRS
- 6 out of 61 patients by Sousa et al (2014) had cardiac abnormalities, the majority of which were mild

3) Lungs



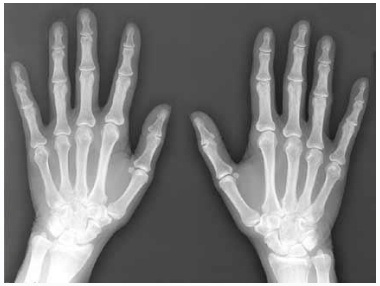
- Easy choking can lead to aspiration risk
- Rare a chest wall deformity can be present
- No specific lung malformation noted thus far

4) Gastrointestinal tract



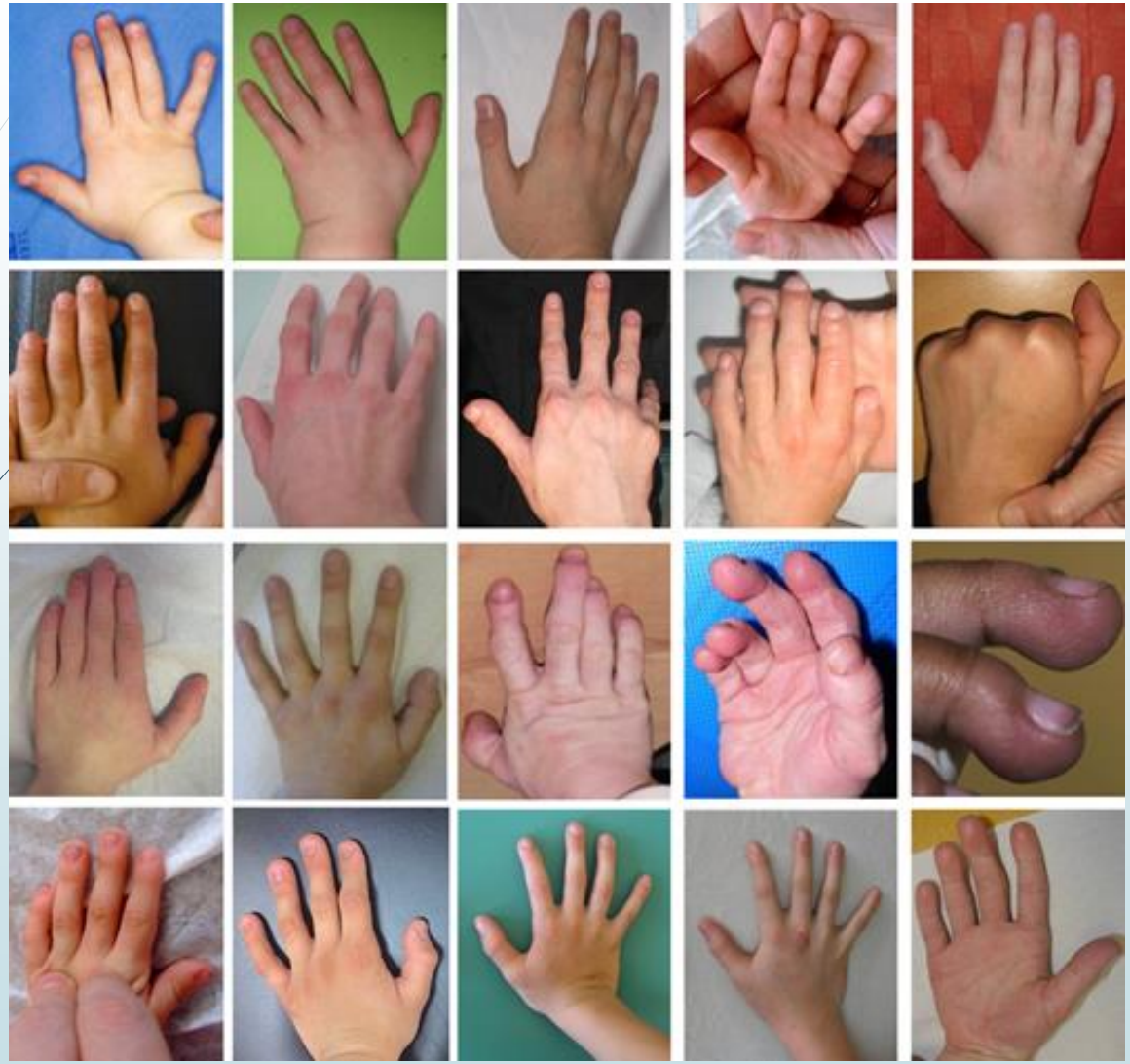
- Feeding difficulties are common (nearly 50 %)
- Often do not require enteral tube but documented case of non-permanent G-tube feeds
- Food texture preferences are common, such as pureed
- Chewing difficulties noted
- Inguinal or umbilical hernia noted in 45%, could require surgery

5) Skeletal system



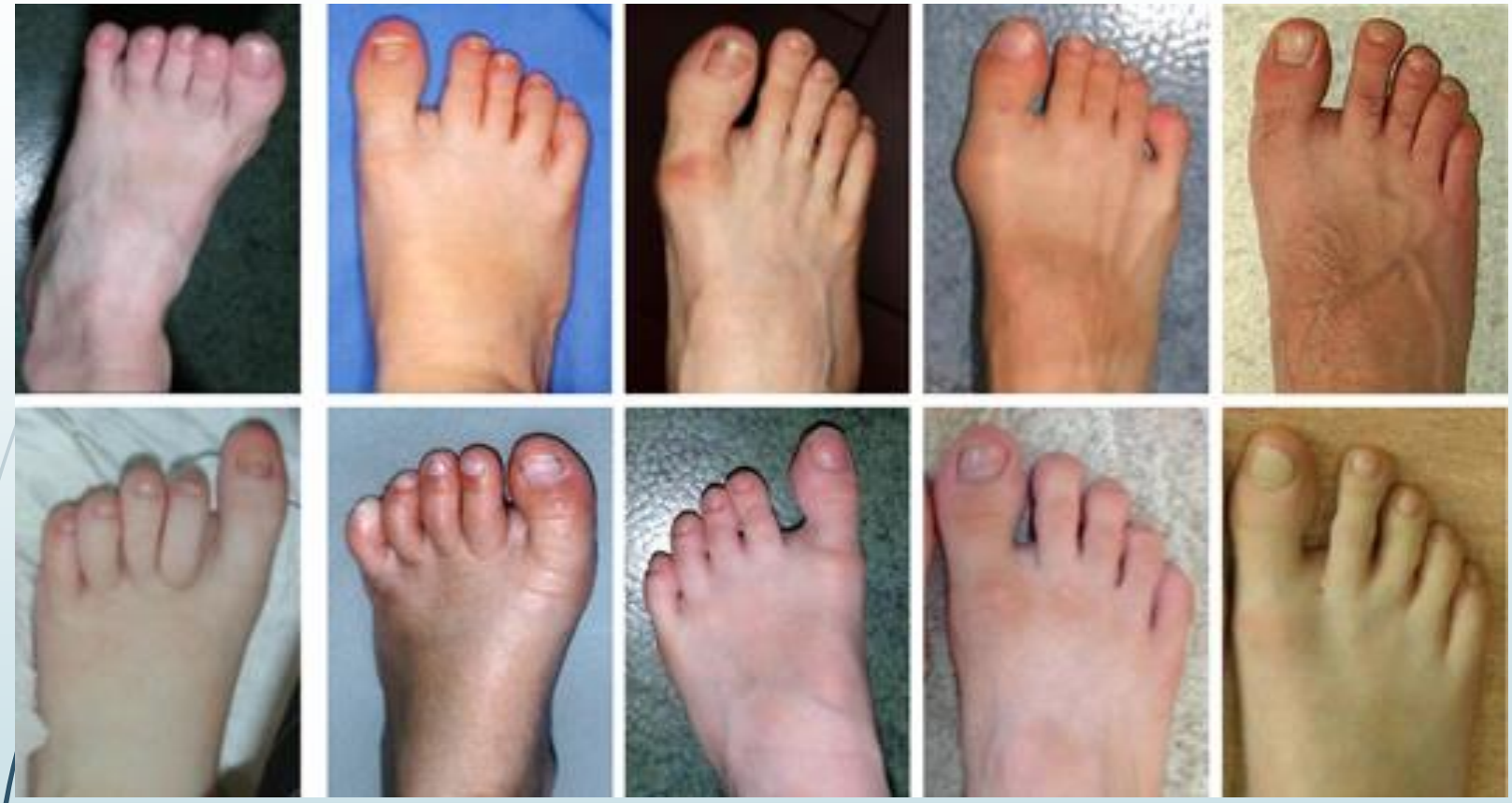
- Broadening of the distal phalanges develops over years
- Interphalangeal joints become more prominent and are a key clinical feature
- Fingers may be shorter than average
- Arthritis is not present at a young age
- Scoliosis (curvature of back) was seen in 17/60 patients
- Hip dislocation is less common – 4/45 patients

Hands in Nicolaides-Baraitser syndrome



American Journal of Medical Genetics Part C: Seminars in Medical Genetics
Volume 166, Issue 3, pages 302-314, 28 AUG 2014 DOI: 10.1002/ajmg.c.31409
http://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31409/full#ajmgc31409-fig-0002

Feet in Nicolaides–Baraitser syndrome



American Journal of Medical Genetics Part C: Seminars in Medical Genetics
Volume 166, Issue 3, pages 302-314, 28 AUG 2014 DOI: 10.1002/ajmg.c.31409
http://onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31409/full#ajmgc31409-fig-0003

6) Growth

- One-third of NCBRS individuals are small at birth
- Short stature emerges in half of patients
- Microcephaly is common and increases with age
- Many patients are smaller than average for weight
- Swallowing and food preferences can contribute to poor weight gain

7) Development

- Development is an important concern for families and can often be the first trigger for medical assessment
- Degree of intellectual disability varies, reported numbers are mild (18%), moderate (36.1%), and severe (45.9%)
- Currently trying to see if gene mutation can predict expected delay
- Speech can also range from absent (30%), limited, to conversational
- Speech decline may be related to seizure onset

- Seizures → type of seizure can vary, occurring in two-thirds of individuals
- Average age of onset 1.5-2 years
- Can be difficult to control and require multiple medications but can also resolve

- Behavioural changes → autism like behaviours and aggression have been noted
- Autism like behaviours can be seen in childhood
- Aggression or self-harm may emerge in adolescence

Summary of key features

NCBRS features	Reported patients
Small for gestational age	33.3%
Pre & post-natal microcephaly	23% pre, 65% post
Short stature	53.5%
Sparse hair	96.7%
Seizures	63.9%
Intellectual disability	Mild 18%, moderate 36%, severe 46 %
Interphalangeal joint prominence	84.7%
Speech delay	31.7% absent speech, 21.4% with speech decline
Behavioural changes	19 patients, hyperactivty, aggression
Hypospadias	2.8%,1 patient
Cryptorchidism	58.8%
Scoliosis	28.3%

Variability in clinical manifestations in NCBRS. Reported patients from Sousa et al., 2014.

Diagnosis

- Rule out similar conditions, such as Coffin-Siris syndrome (has fifth finger underdevelopment)
- Blood test to sequence the SMARCA2 gene (looks for spelling mistakes)
- If new mutation is found, can check to see if parents carry the same mutation
- Sometimes, can incidentally diagnose NCBRS by checking all of the genes in the genome through exome test

Management

Requires multidisciplinary approach to ensure medical needs addressed

1) Support for development (Speech language pathology, occupational therapy)

2) Seizure control (Neurology)

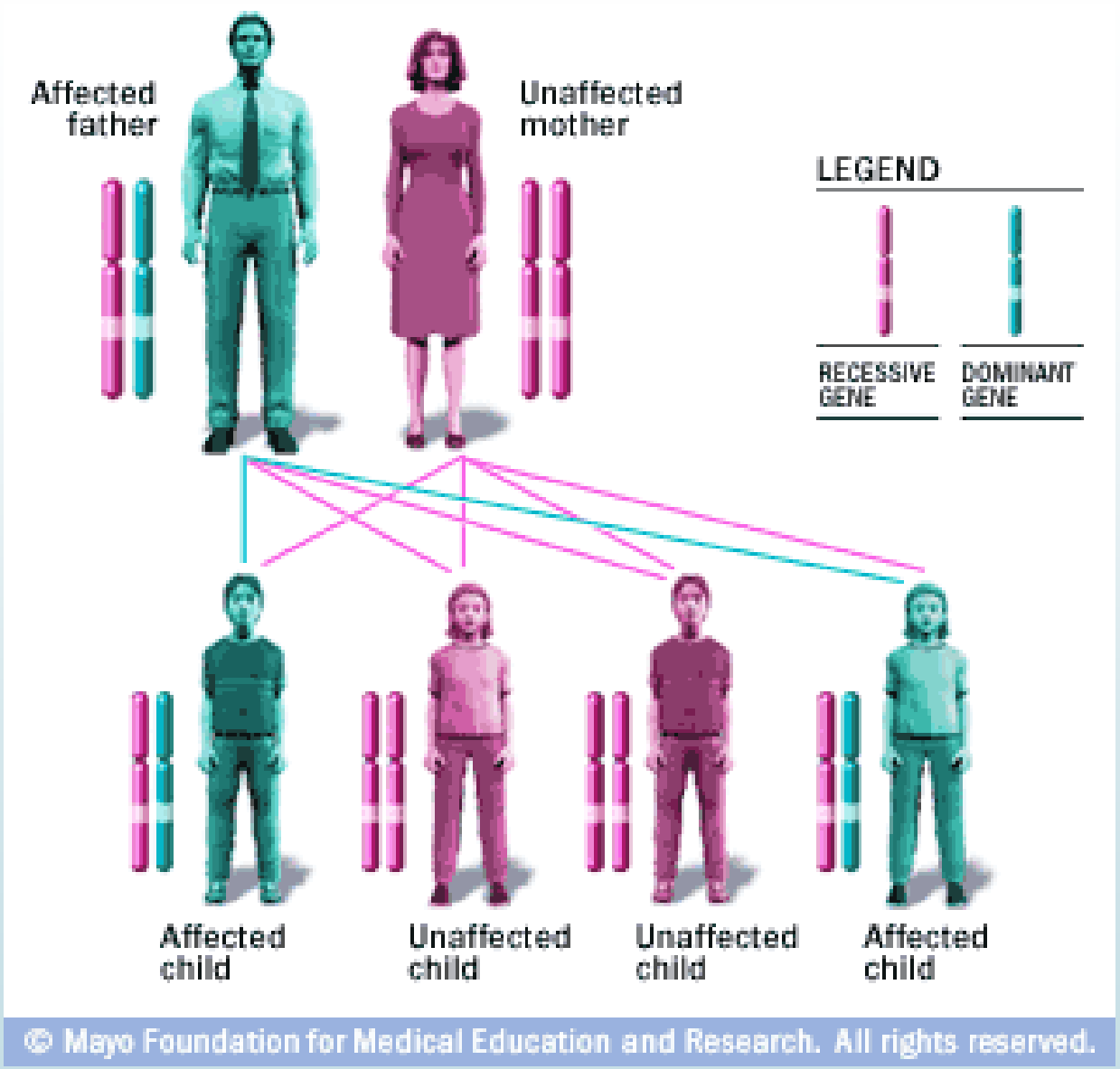
3) Strategies for behavioural modifications (Developmental Pediatrics)

4) Weight monitoring and optimize nutrition (General Pediatrics)

Chance of recurrence

- 1) In other family members:
- Low likelihood of having a another affected child if parents are not found to be carriers
- Thus far, all mutations have been new events in the affected individuals
- We cannot rule out germ-line mosaicism so a small likelihood is always quoted

- 2) <u>In offspring of affected individual:</u>
- No present reported cases of offspring to affected individuals
- Reproductive tracts in intact and reported women reach menses at average ~ 15 years age
- If SMARCA2 mutation found, 50% chance of passing on the gene with the mutation and 50% chance of passing the normally functioning gene

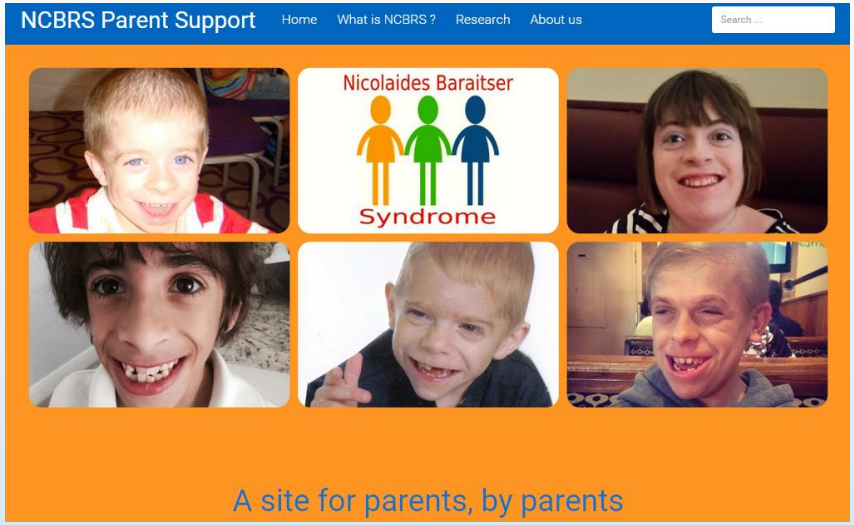


Future Directions

- Relationship of mutation type to predicted presentation of NCBRS
- Relationship to seizure onset or persistence to speech development
- Better understanding of SMARCA2 function to look toward developing targeted therapies

Resources

- www.ncbrs.com For parents, by parents



- Research Article: Phenotype and genotype in Nicolaides–Baraitser syndrome

  by Sergio B. Sousa, Raoul C. Hennekam, 2014. In the American Journal of Medical Genetics

  (data referred to in this presentation)

Thank you!

Questions?