UNITY * STRENGTH * HOPE
JUNE 24-26 • EAGLEWOOD RESORT, ILLINOIS • 2016
RETT SYNDROME, MECP2 DUPLICATION, CDKL5 DISORDER, FOXG1 DISORDER
FAMILY CONFERENCE

Nothing replaces the experience
of meeting face-to-face
Genetics 101: What do MECP2, CDKL5 and FOXG1 have to do with one another?
June 24, 2016
Eaglewood Resort, IL
GOALS FOR TODAY’S TALK

- Introduction to MECP2, CDKL5 and FOXG1
- Basic review of genetics
- Genetic Counseling Issues
- Understanding mutation reports
- Your questions?
Timeline Connecting MECP2, CDKL5 and FOXG1

• 1966 Rett syndrome described by Dr. Rett
• 1983 Hagberg’s seminal article in English
• 1993 Rett variants (atypical forms) described
• 1999 MECP2 associated with Rett syndrome
• 2005 CDKL5 associated with early seizure variant of Rett
• 2005 MECP2 duplications reported
• 2008 FOXG1 associated with congenital variant of Rett
Rett-Like Conditions

- CDKL5 – X-linked, early onset seizures
- FOXG1 – 14q12, microcephaly, abnormal corpus callosum, “congenital form”
- TCF4 (Pitt-Hopkins syndrome) – 18q21.2, typical facial features, breathing abnormalities
- MEF2C – 5q14.3
- IQSEC2 – Xp11.2
- WDR45 – Xp11.23
Next Generation Sequencing (Massively Parallel Sequencing)

• Rapid sequencing of large amounts of DNA code, less expensively
• Large gene panel tests
  - 19 genes associated with Rett/Angelman
• Whole exome sequencing
• Whole genome sequencing
RETT-Like Conditions

Chromosomal locations of the MECP2, CDKL5 and FOXG1 genes

- MECP2: Xq28
- CDKL5: Xp22.13
- FOXG1: 14q12
Schematic of CDKL5 and Specific Domains

- ATP-binding site (aa 14–47)
- ST kinase active site (aa 127–144)
- T-X-Y conserved motif (aa 169–171)
- Putative nuclear localization signals (aa 312–315 and aa 784–789)
- Putative nuclear export signals (aa 836–845)
- Signal peptidase I serine active site (aa 971–978)

Catalytic domain
Figure 2. Schematic gene structure of FOXG1. The 3 main functional domains are shown, namely, the DNA binding fork-head domain (FHD), the Groucho binding domain (GBD), and the JARID1B binding domain (JBD). Twenty reported pathogenic variants and their positions are indicated.\textsuperscript{18}
Chromosome to Gene to Protein

Cell
Each chromosome is composed of one large continuous DNA molecule.

Chromosomes

Gene
A gene is a segment of DNA that encodes a protein product.

Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.

DNA

Nucleotides
- Adenine
- Thymine
- Guanine
- Cytosine
### DNA Alphabet

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- **A** – adenine
- **T** – thymine
- **C** – cytosine
- **G** – guanine
**DNA Code for Amino Acids**

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Terminology

• **Deletions:**
  Deletion exon 3
  Deletion exon 3 and 4
  c.806delG
  c.1154_1185del32
  c.488_489delGG

• **Missense/Nonsense Mutations:**
  p.T158M
  p.R270X
  p.G269fs
Exon 4  
c.473C>T  
p.T158M

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**MUTATION**
Missense Mutations

c.11A>C  or p.H4P

Missense mutation

Original DNA code for an amino acid sequence.

DNA bases

CATCATCATCATCATCAT

Amino acid

Pro

Replacement of a single nucleotide.

Incorrect amino acid, which may produce a malfunctioning protein.
Nonsense (Stop) Mutations
c.10C>T or p.G4X
**CDKL5**

Exon 12
c.1675C>T
p.R559X

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**MUTATION**
Deletion causes a Frameshift
c.11delA  or p.H4fs
Insertion causes a Frameshift

c.9_10insA or p.H4fs

Original DNA code for an amino acid sequence.

DNA bases

CATCATCATCATCATCATCAT

Amino acid

His His His His His His

Insertion of a single nucleotide.

CATCATCATCATACATCATCA

Incorrect amino acid sequence, which may produce a malfunctioning protein.
Does Mutation Predict Severity? Sometimes, but Not Always

- Specifics of mutation
- Location of mutation
- Impact of other genes
- X-inactivation (in Rett and CDKL5)
X Inactivation

- Both X chromosomes active
- Maternal X chromosome active
- Paternal X chromosome active

Fertilized egg

Early embryo

Random X chromosome inactivation in each cell

Fixed X chromosome inactivation in all descendant cells

Random X chromosome inactivation

Skewed X chromosome inactivation
Genetic Counseling Issues for Rett Syndrome (And Perhaps CDKL5 and FOXG1)

• Most (>99%) are sporadic:
  – <1% recurrence risk
  – New mutation in sperm or egg
  – Most new mutations occur in the sperm (in Rett)

• MECP2 Duplication:
  - most inherited from carrier mother
  - de novo mutations do occur
X-Linked Inheritance for MECP2 and CDKL5

Son receives Y from father
Daughter receives X from father

Males and females receive an X from mother
Germline Mosaicism

- Rare (<1% of families)
- Occurs in both males and females
- No easy, non-invasive test
- Higher recurrence risk (???%)

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Mosaicism

- Normal Cells
- Cells With Genetic Change

Cell Division

Mosaic Tissue
Testing Other Family Members

• Mothers - offer to rule out rare carriers (MECP2 and CDKL5)

• Fathers and brothers - not needed if typically developing

• Sisters – if typically developing, rare to be carriers, but offer prior to reproductive years (MECP2 and CDKL5)
Prenatal Diagnosis

• If mutation known, can be done either by CVS or Amniocentesis
• Individual choice
• Usually only check for known mutation in family
Duplications of MECP2, CDKL5 and FOXG1

- Typically involve other genes
- All associated with developmental and medical problems, but different from mutations in the individual genes
- Implications regarding treatment
Thank You to:

• Rettsyndrome.org
• NIH
• All the patients and families that inspire us and have taught us so much