Early identification of genetic anomalies

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April 7, 2016
• Syndromes that may escape immediate detection
• What test to order
• What to do next
Case study

- 3 day old girl born at term by C-section weighing 2.6 kg
- Significantly hypotonic with weak cry
- Normocephalic
- Absent suck
A diagnostic study was performed.
PWS arises from lack of paternally expressed genes on 15q11-q13:

- Paternal deletion of 15q11-q13 (75%)
  - type I: Much larger
  - type II

- Maternal uniparental disomy (24%)

- Deletion in the imprinting center (1%)

- Translocation of the PWS critical region (<1%)
When should you consider the diagnosis (and testing) for PWS?

- “Floppy” infant
- Obese children with significant LD, slowed growth velocity, and hx neonatal hypotonia
- Adolescents and adults with the above with delayed pubertal maturation
Endocrinology in PWS

- Variable degrees of GH deficiency
- If untreated, estimated 50% would fail to reach a normal adult height
- GH increases height velocity and final height
Case study #2

- 8 year old boy with problems in reading and spelling
- Anxiety over new people and new situations
- Cannot ride a bike or tie his shoes
• Problems with stressed gaits
• Intention tremor
• Otherwise normal
A diagnostic test was performed
LEARN ABOUT
KLINEFELTER'S SYNDROME
WITH PROJECT 47XXY
• X inactivation patterns
• X-linked androgen receptor gene allele length (CAG repeats)
• The longer the gene, the more severe the phenotype and the earlier the diagnosis
• 1 in 660 males
• The vast majority diagnosed in adulthood
• Less than 10 per cent diagnosed prior to puberty
• Why?
KS is also associated with physical, neurocognitive, and psychosocial comorbidities, including infertility and high risk for the development of cardiovascular disease, diabetes, osteoporosis, autoimmune disorders, and certain kinds of cancers.3
Testosterone therapy

- Normalize pubertal development
- Increase muscle mass
- Preservation of bone density
- Mood and energy levels
- Cognition
When to test?

- Cognitive phenotype tends to present with nonverbal skills much better developed than verbal skills
- Social anxiety is common
- Tremor
- Balance issues
- Cryptorchidism
Case #3

- 4 year old M presents with speech delay
- Vomits when family takes him out in public
- Chews on clothes
On exam

- Macrocephaly
- Tubes in both ears, one is draining
- Prominent ear cartilages
- Hypermobile joints
- Flat feet
- Delayed speech and flapping hands
Why do we call it *fragile X*?
GENE LOCATION

- Fragile X Mental Retardation 1 (FMR1) gene on the end of the X chromosome

- Normally about 30 repeats of CGG
- Premutation: 55-200 repeats
- Full mutation: more than 200 repeats
Epidemiology

- 1 in 3600 to 400 males estimated to have the full mutation
- 1 in 4000 to 6000 females estimated to have full mutation
- 1 in 800 males estimated to have premutation
- 1 in 260 women estimated to have premutation
Mode of inheritance

A typical fragile X family tree
Clinical features increase in frequency and severity in succeeding generations

CGG-repeat size

- Normal individual
- Carrier (premutation)
- Full mutation

Women have two copies of the gene. Shades of pink indicate variable degree of involvement (ratio of normal to premutation genes active)

Child with fragile X syndrome - first family member brought to clinic

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Fragile X tremor-ataxia syndrome (FXTAS)

- Seen in 25-30% men > 50 years old who have the premutation
- Limb and truncal ataxia, tremor, cognitive symptoms
- Misdiagnosed as Parkinson’s disease
Fragile X-associated premature ovarian insufficiency (FXPOI)

- 25 per cent of women with the premutation
- Irregular menses
- Reduced bone density
- Infertility
- Menopause prior to 40 years
Other problems associated with the premutation

- ADHD, autism spectrum d/o, learning issues
- Social anxiety, phobias, and depression
- SLE, other autoimmune disease
- Thyroid dysfunction
- Hypertension
- Chronic muscle pain syndrome
Who should be tested for fragile X?

- Any woman with premature ovarian failure
- Anyone presenting with parkinsonism in middle age
- Anyone with autism
- The family members of people with fragile X
What test do you order?

- FMR1 gene sequencing
- Usually does NOT show up on CMA or karyotype
- Up to 40 per cent of these individuals are mosaic
- Prognosis is not related to the length of the allele but to the amount of FMRP produced