Early identification of genetic anomalies
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- 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.
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?
Epidemiology

- 1 in 3600 to 4000 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
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