Early identification of genetic anomalies

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- Syndromes that may escape immediate detection
- What test to order
- What to do next

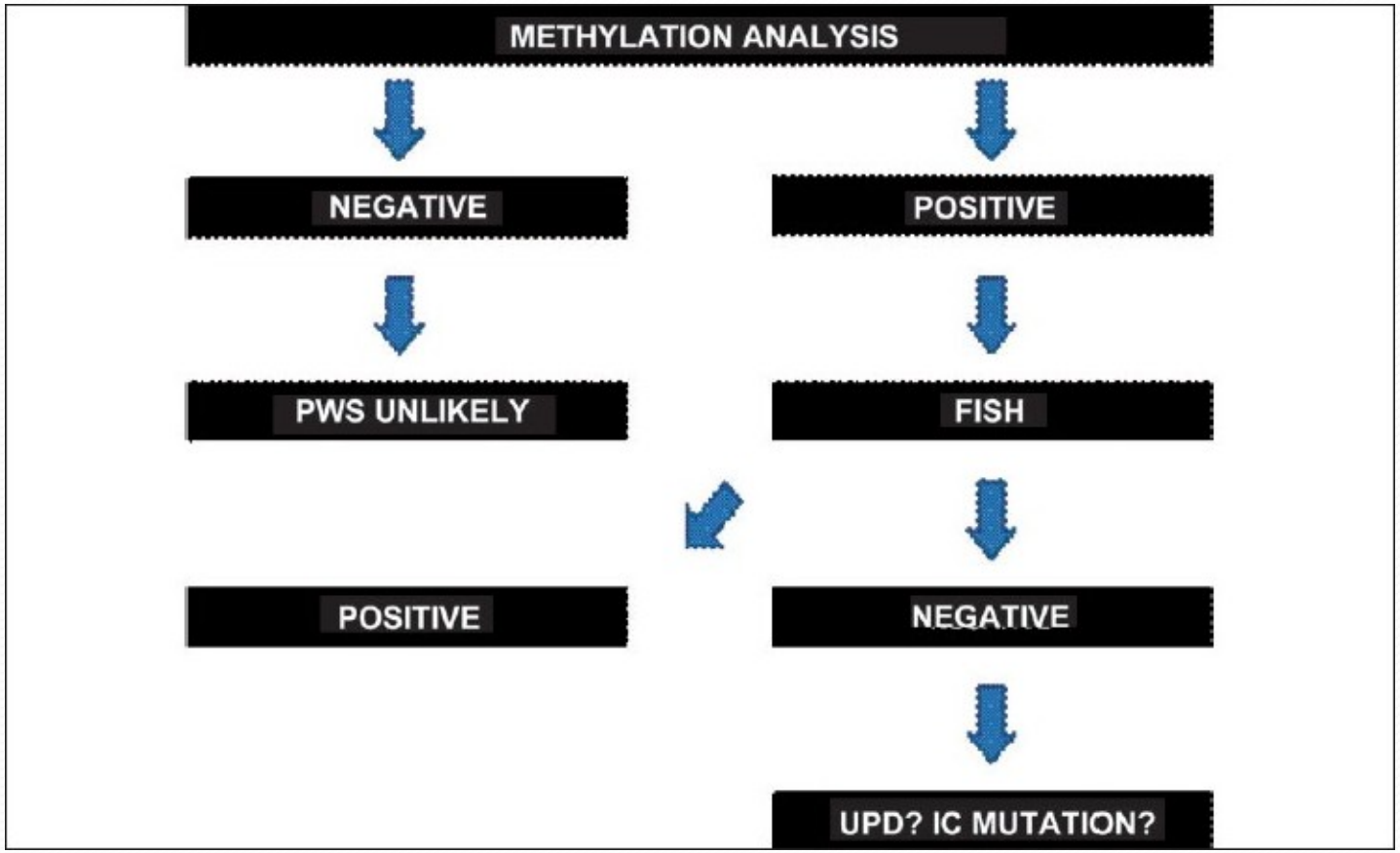
Case study

- 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

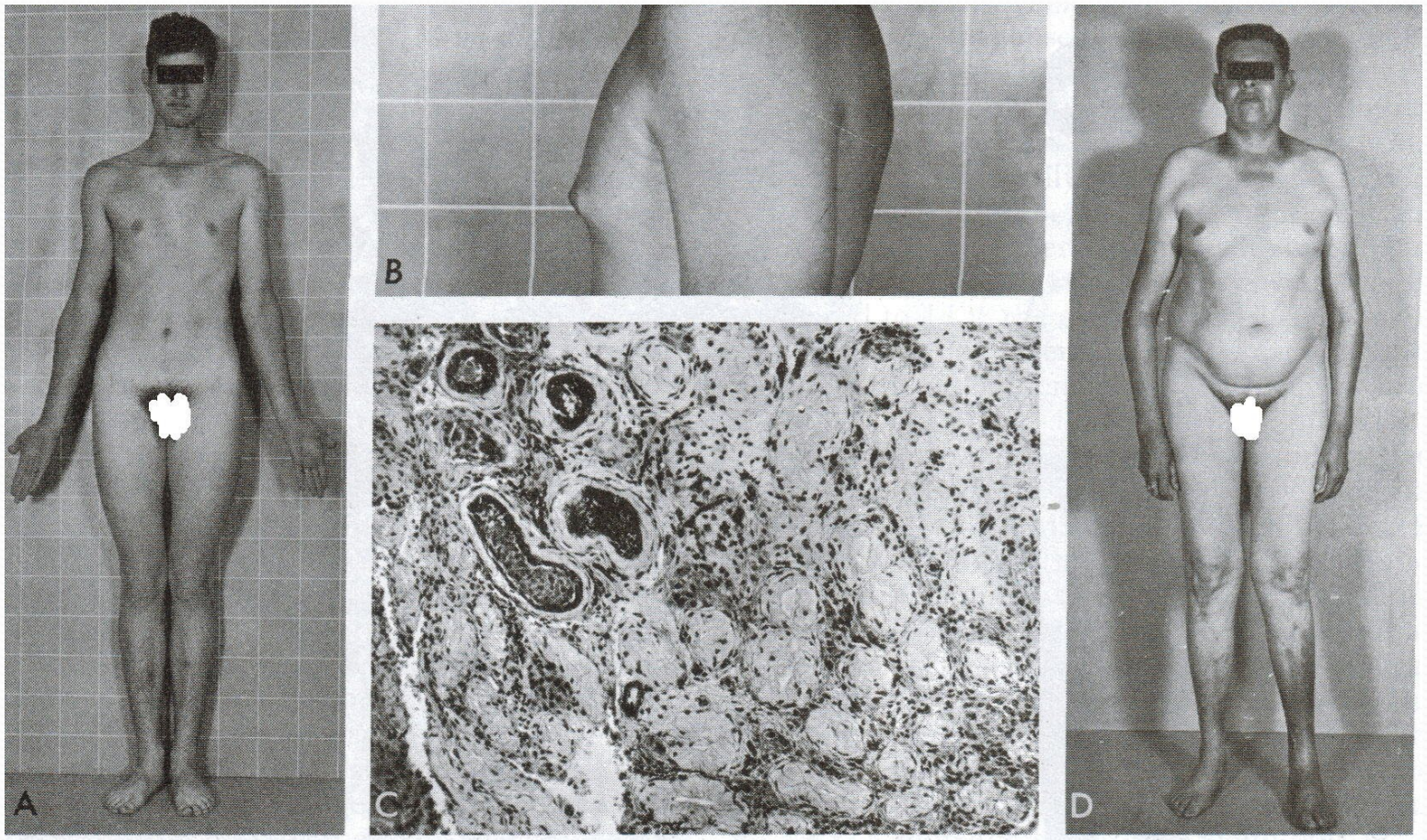
- Variable degrees of GH deficiency
- If untreated, estimated 50% would fail to reach a normal adult height
- GH increases height velocity and final height

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



- 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

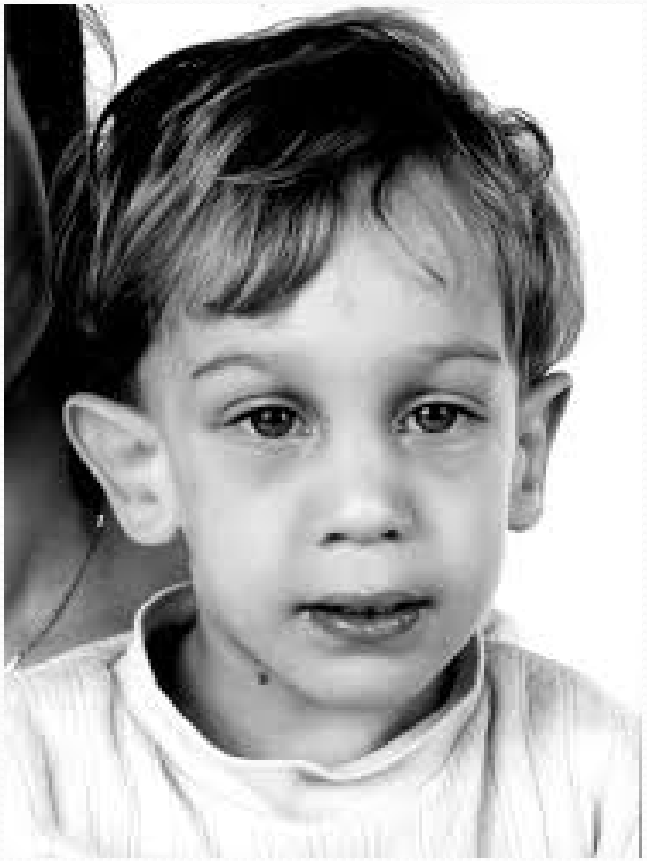
- Normalize pubertal development
- Increase muscle mass
- Preservation of bone density
- Mood and energy levels
- ?Cognition

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

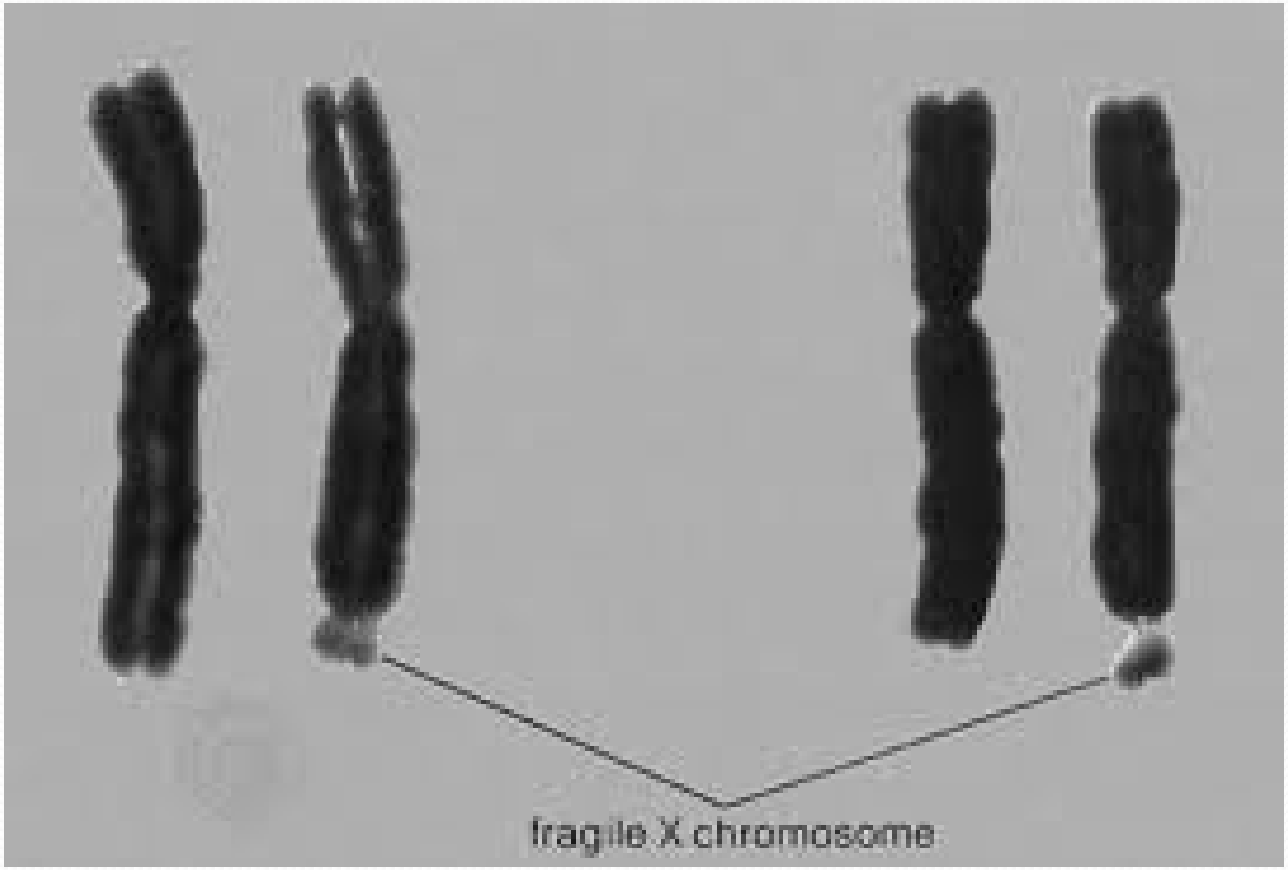
- 4 year old M presents with speech delay
- Vomits when family takes him out in public
- Chews on clothes



On exam

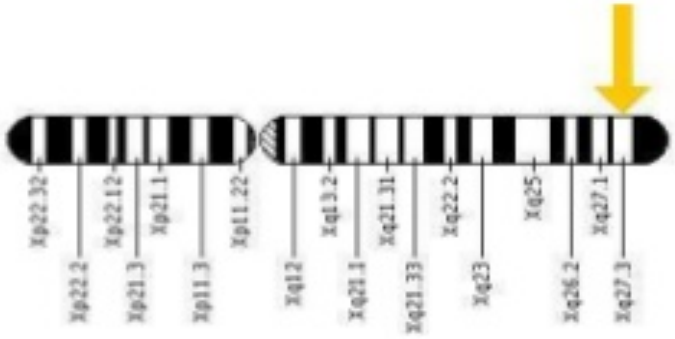
- Macrocephaly
- Tubes in both ears, one is draining
- Prominent ear cartilages
- Hypermobile joints
- Flat feet
- Delayed speech and flapping hands

Why do we call it *fragile* X?



GENE LOCATION

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

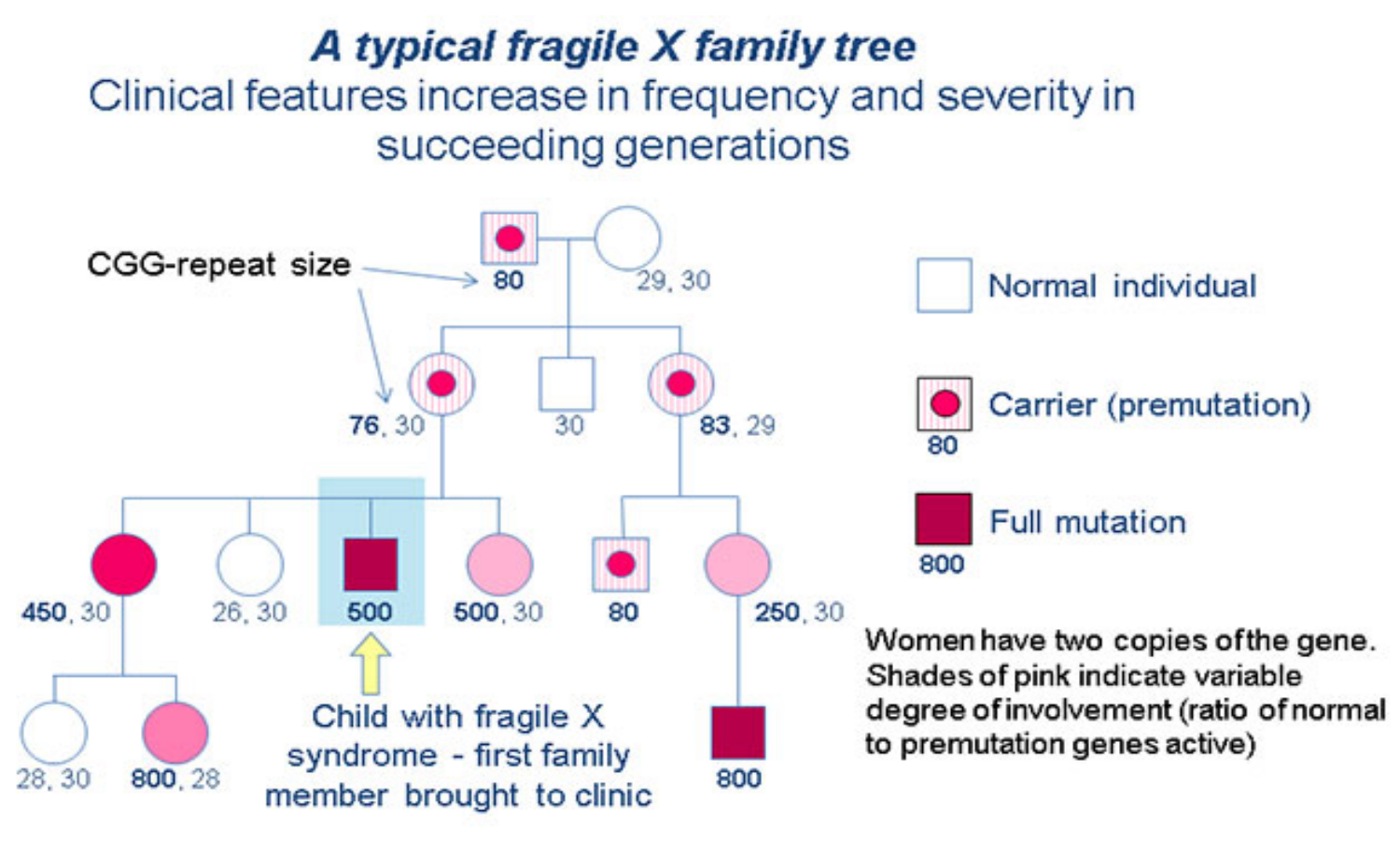


- Normally about 30 repeats of CGG
- Premutation: 55-200 repeats
- Full mutation: more than 200 repeats

Epidemiology

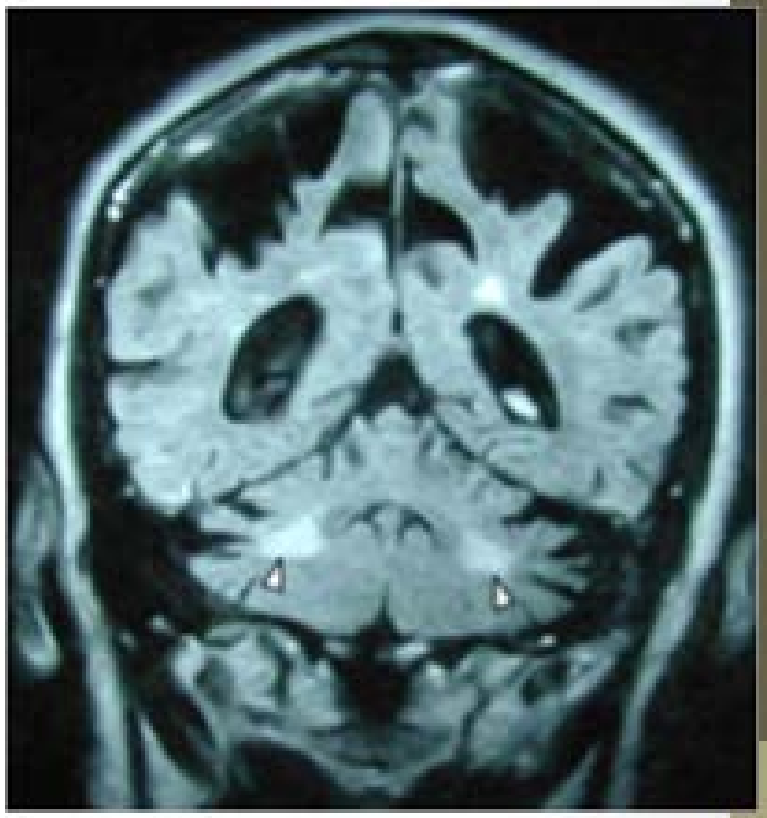
- 1 in 3600 to 400 males estimated to have the full mutation
- 1 in 4000 to 6000 females estimated to have full mutation
- 1 in 800 males estimated to have premutation
- 1 in 260 women estimated to have premutation

Mode of inheritance



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

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