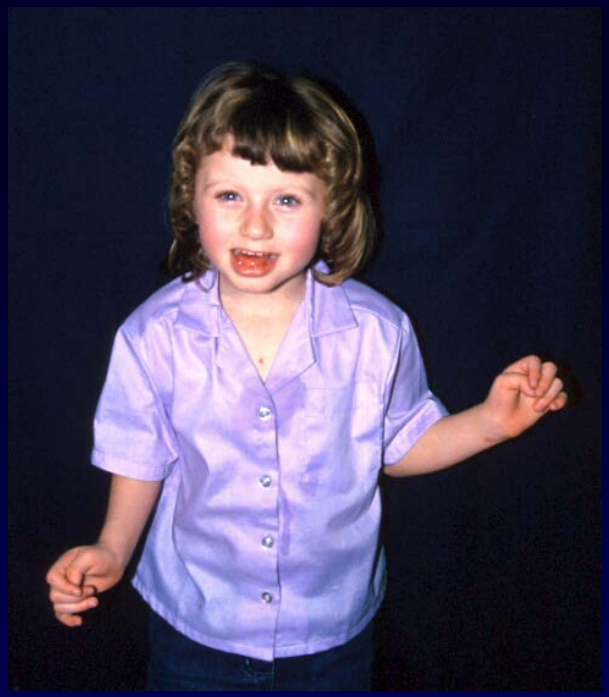
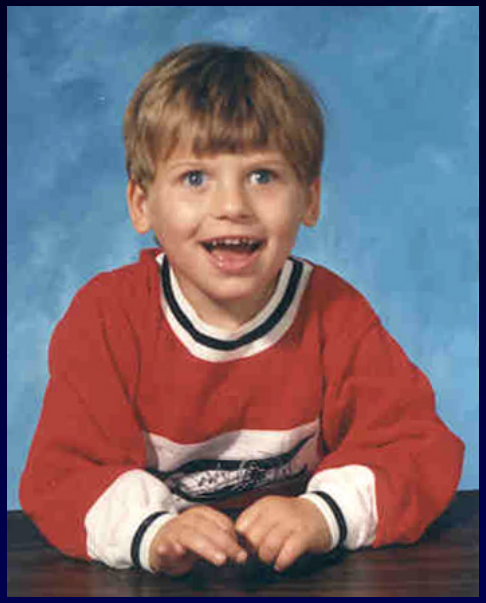
Angelman Syndrome

- Severe mental retardation
- Absent speech, jerky limb movements
- Ataxia, excessive laughter
- No malformations, minimal facial dysmorphia





AS Consensus Criteria

- Consistent (100%)
  - Developmental delay, severe
  - Speech impairment
  - Movement or balance disorder
  - Behavioral uniqueness (e.g., happy, hypermotoric)
- Frequent (more than 80%)
  - Delayed or disproportionate cranial growth
  - Seizures
  - Abnormal EEG (e.g., slow/spike waves)
- Associated (20-80%)
  - E.g., strabismus, frequent drooling, protruding tongue, flat occiput, attraction to or fascination with water

Am J Med Genet, 1995

AS: Clinical Aspects

- **Movements**
- **Behaviors**
- **Language and Speech Abilities**
- **Seizure Disorders**

AS: Movement Disorder

- Wide-based gait, truncal ataxia
- Stiff, jerky or robot-like gait
- General tremulousness of limbs
- Lurching, forward gait, uplifted arms
- Hyperkinetic limb movements
- Clumsy movements, worse upon intention
- No nystagmus, athetosis, resting tremor, chorea

AS: Behaviors

- Excessive laughter/happiness
- Easily excitable personality, often with hand-flapping movements
- Hypermotoric/hyperactive behavior
- Absent speech, decreased vocalizations
- Increased mouthing of objects
- Fascination with tiny objects, crinkly paper, water

AS: Language and Speech

- **Babies and infants typically quiet**
- **Correct single word usage is rare**
- **Some vocal mimicry (high functioning AS)**
- **Gestures, some signing possible**
- **Receptive skills may be impressive**
  - understanding complex verbal requests
  - knowledge of many body parts, colors, etc.
  - understanding of social interactions

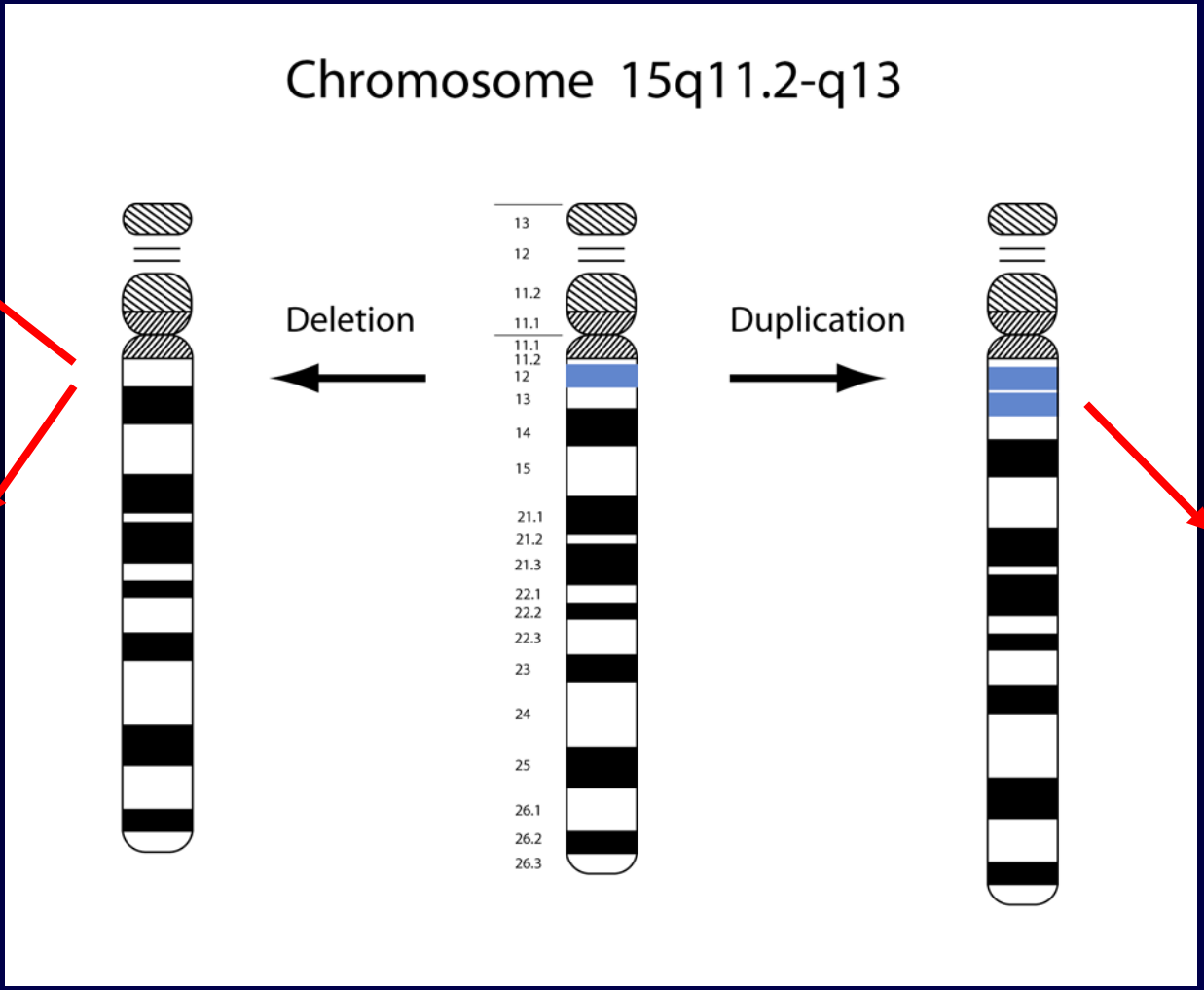
AS: Seizures

- Onset usually before age 3 years
- EEG is usually abnormal:
  - runs of rhythmic 2-3/s high voltage activity
  - ill defined slow spike /wave complexes
  - persistent rhythmic 4-6/s activities
- Many types: myoclonic, atypical absence, etc.
- Brain MRI/CT shows nonspecific changes
- Seizure severity improves with age

Deletion on the maternally-derived 15 can cause Angelman syndrome

Angelman
Maternal 15

Prader-Willi
Paternal 15



Autism-like
Maternal 15

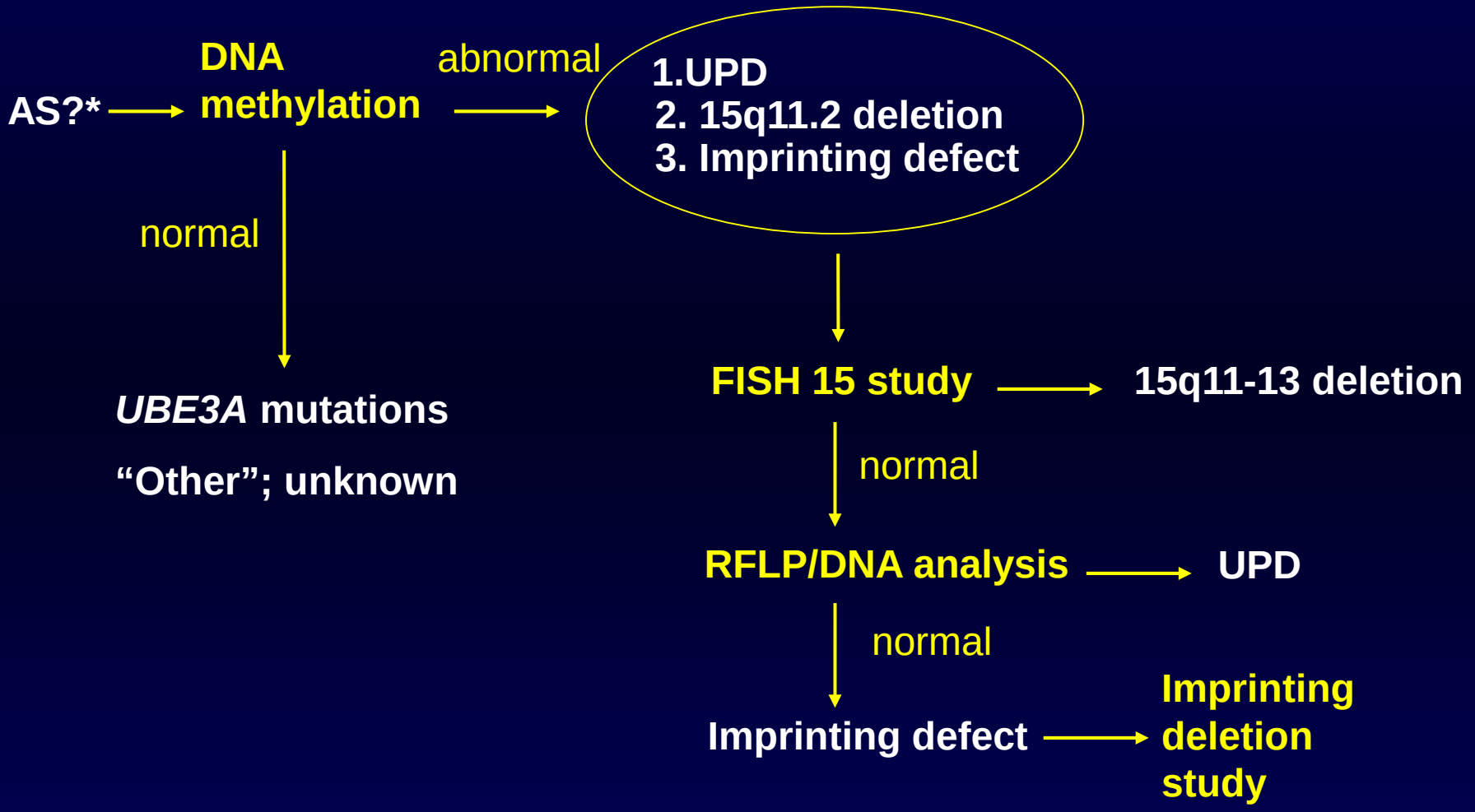
Angelman Syndrome

- Etiology: abnormal function of maternal Ubiquitin Ligase Gene (UBE3A) in the CNS.

- Mechanisms that disrupt UBE3A:
  - 70%: microdeletion of 15q11.2-13
  - 10%: mutation of UBE3A
  - 5%: paternal uniparental disomy (UPD) of 15
  - 3%: abnormal maternal imprinting center
  - 12%: unknown

- Diagnosis: DNA methylation testing screens for deletion, imprinting and UPD; FISH 15q11.2-13 detects microdeletion;DNA micro-satellite studies detect UPD; UBE3A sequencing detects intragene mutations.

Diagnostic Approach to AS



*Note: Ensure routine chromosome study for all cases regardless of mechanism