Angelman Syndrome: Genotype, Phenotype and Differential Diagnosis

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Overview

- Clinical features and natural history of Angelman syndrome
- Genetic mechanisms in AS
- Genotype/phenotype correlation
- Differential Diagnosis

Harry Angelman

Characteristic features

- Learning disability
- Ataxic, jerky movements
- Seizures
- Absent speech
- Happy, sociable disposition
- Characteristic facial features
- Blonde hair/blue eyes in some

Angelman, 1965

Infancy

- Normal pregnancy and delivery
- Not dysmorphic
- Feeding difficulties
- Tremulous, easily startled
- Frequent smiling

Early Childhood

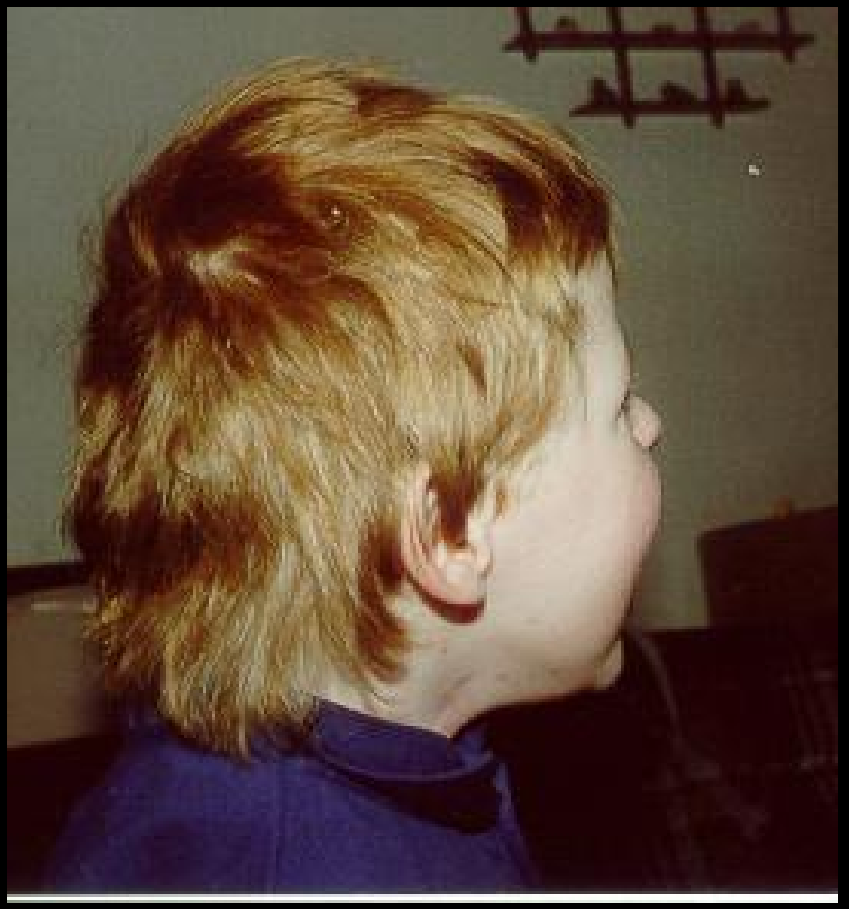
- Delayed milestones
- Decelerating OFC
- Failure to develop speech
- Onset of seizures
- Sleep disorder
- Jerky movements

Later Childhood

- Characteristic gait
- Seizures
- Sociable affect
- Jerky movements
- Microcephaly
- Dysmorphic facial features
- No/little speech

Dysmorphic Features

- Deep set eyes
- Small mid-face
- Pointed chin
- Wide, smiling mouth
- Tongue protrusion
- Relatively wide-spaced teeth
- Brachycephaly



Behavioural features of AS

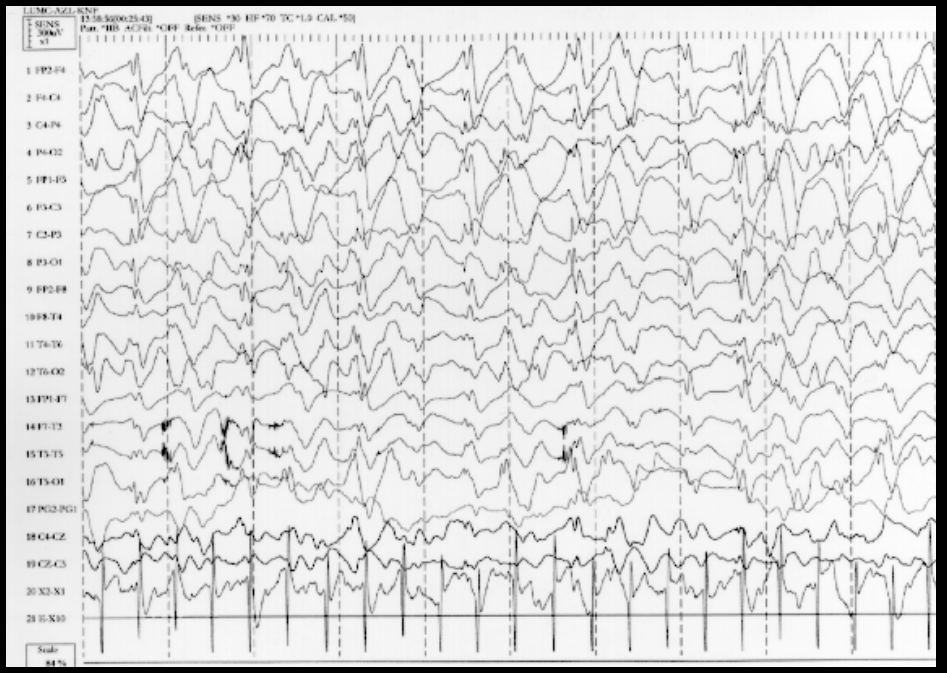
- Sociable
- Laughter easily provoked
- Love of water
- Inquisitive
- Fascination with reflections
- Sleep disorder

Movement Disorder in AS

- Hand flapping
- Athetoid-like posture to hands
- Tremor (worse with age , due to cortical myoclonus
- Lurching gait

Seizures in AS

- Present in 85%
- Onset often 12-18 months
- All seizure types
- Difficult to control
- Characteristic EEG in most but not all
- Improve with age but may return
- Cortical myoclonus



Communication in AS

- Most have <3 words
- Signing difficult
- Picture exchange system useful (PECS)
- Augmented communication
- Skills continue to improve in adulthood

Adulthood

- Most are healthy
- Obesity common
- Oesophageal reflux
- Lack of mobility and contractures may impair health
- Scoliosis 40%
- Return of seizures, cortical myoclonus
- Keratoconus

Symptoms vary from one person to another. Even with the best therapy some of these complications may arise

Facial features in adults

- Deeper set eyes
- More prominent chin
- Longer face
- Remain youthful-looking (? Degree of hypogonadism)

Skills of Daily Living

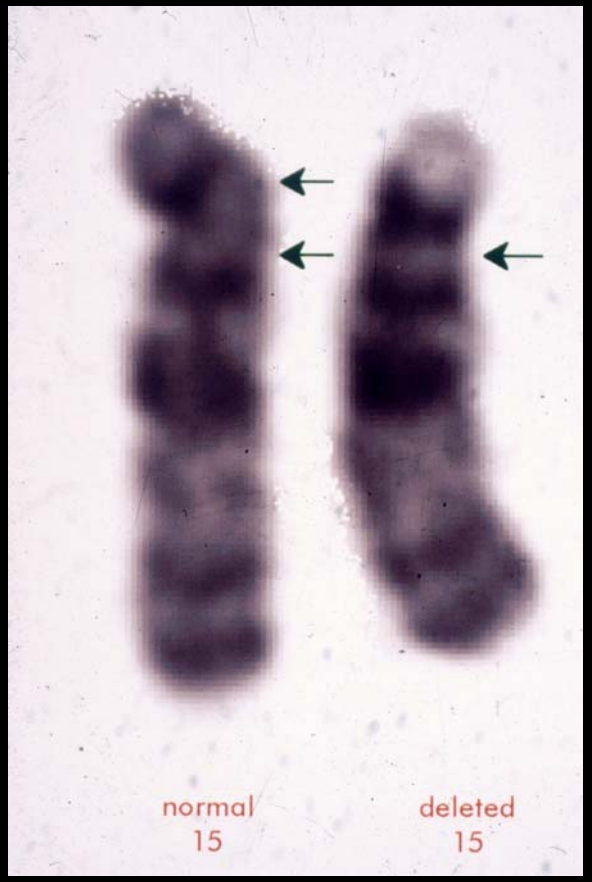
- Most toilet trained by day
- Very few dry by night
- Need 24 hr supervision
- Many able to do simple tasks eg table laying, hoovering but need supervision
- Need encouragement to "stay on task"

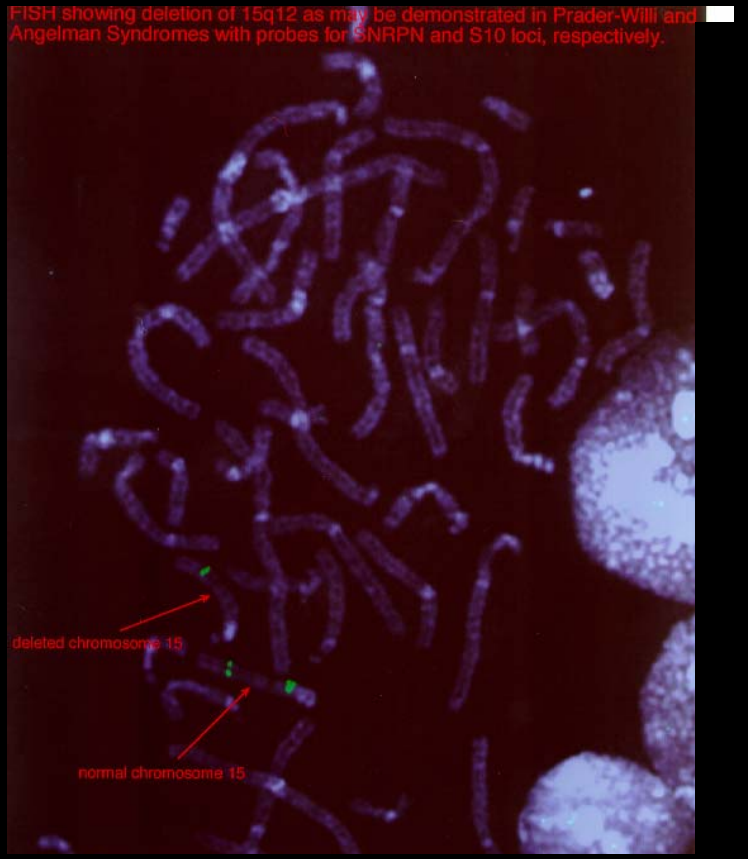
Scoliosis

- Develops in 40% adults
- Highest risk in adolescent growth spurt
- Need regular surveillance
- Surgery may be required

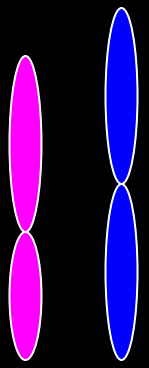
Angelman Syndrome is caused by a variety of genetic mechanisms which all interfere with expression of the UBE3A gene on chromosome 15q11-13

1. Angelman Syndrome is due to a deletion of 15q11-13 in 70% of cases



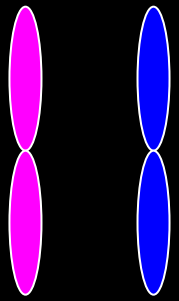


Kaplan, Magenis, 1987



m p

In Angelman syndrome the deletion arises on the maternally inherited chromosome

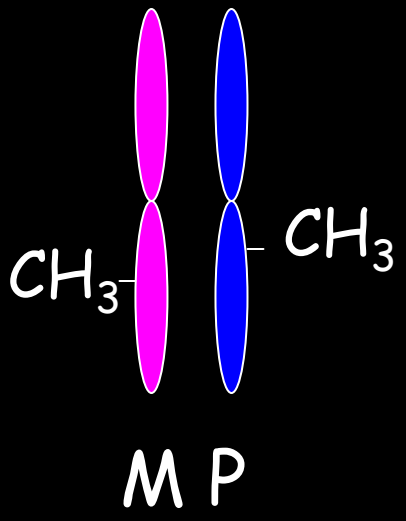


m p

An intact maternal and paternal chromosome 15q11-13 are needed for normal development

Almost all deletions arise "de novo"

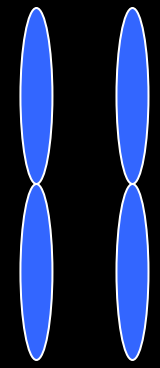
Maternal and Paternal 15q11-13 Show Differential Methylation



methylation analysis

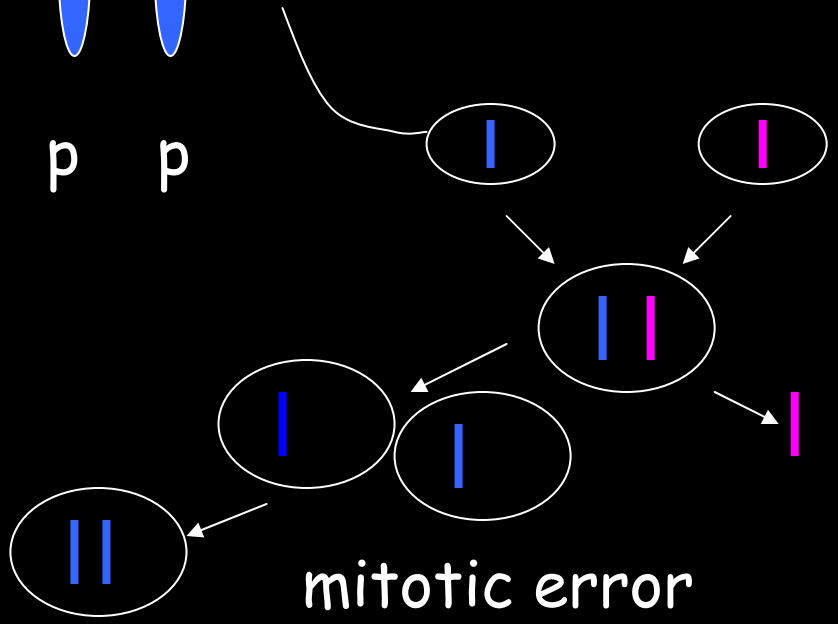
	N	AS	PWS
	—	—	—
m	—		—
p	—	—	

2. Angelman Syndrome May Arise as a Result of Paternal Uniparental Disomy

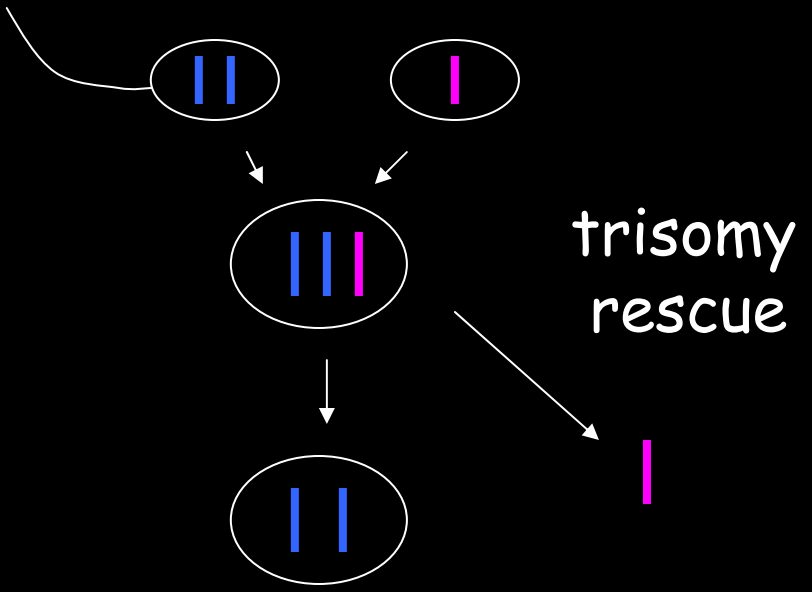


p p

Two paternal chromosome 15s
No maternal 15. Accounts for 3% AS



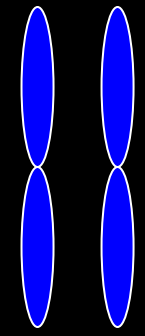
mitotic error



trisomy rescue

meiotic error

3. Angelman Syndrome may arise due to failure to reset the parental imprint during gametogenesis



m p

Imprinting defect

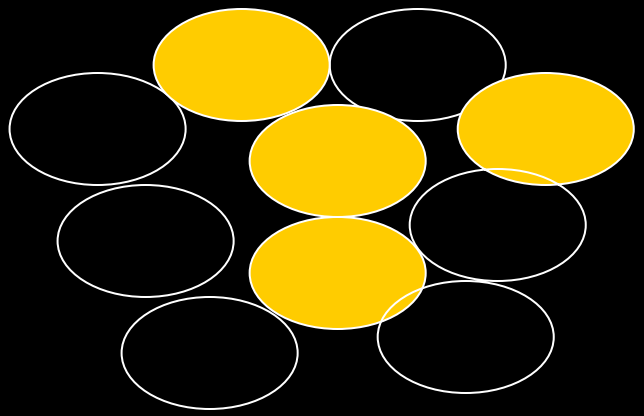
Intact chromosomes are inherited from both parents but the maternal chromosome has a paternal "imprint"

Imprinting defects

- IC deletions in 10%, often familial
- Imprinting defects with no deletion in 90%, sporadic (stochastic)

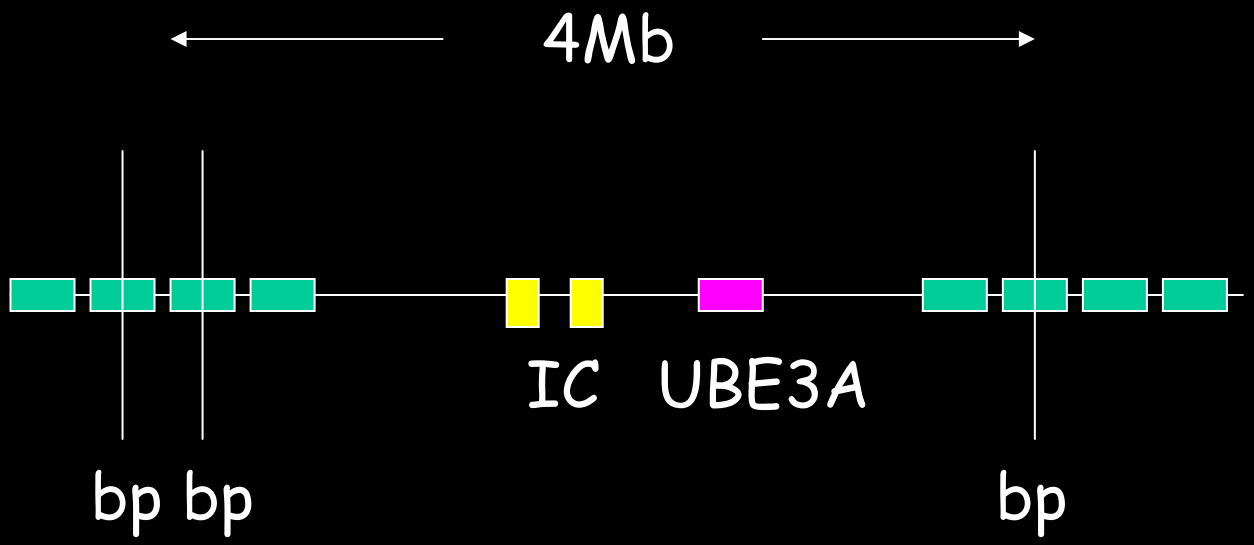
Possible association between assisted conception and/or infertility and stochastic imprinting defects

Mosaic Imprinting Problems



Only a proportion of cells are abnormally imprinted
Milder phenotype. Accounts for 27% with ID
Some have presented with hypotonia, large head and obesity

4. Angelman Syndrome may arise due to a mutation within the UBE3A gene



UBE3A gene

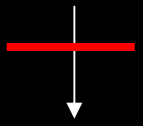
imprinting centre (IC)

UBE3A gene

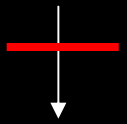
- Encodes a ubiquitin protein ligase which is involved in protein degradation within the brain
- Maternally imprinted in brain
- Expressed in hippocampus, olfactory tracts and Purkinje cells of cerebellum

UBE3A mutations and E6AP function

UBE3A gene encodes E6AP,
a protein ligase



E6AP binds thioester and accepts
ubiquitin from E2



Ubiquitin transferred to substrate

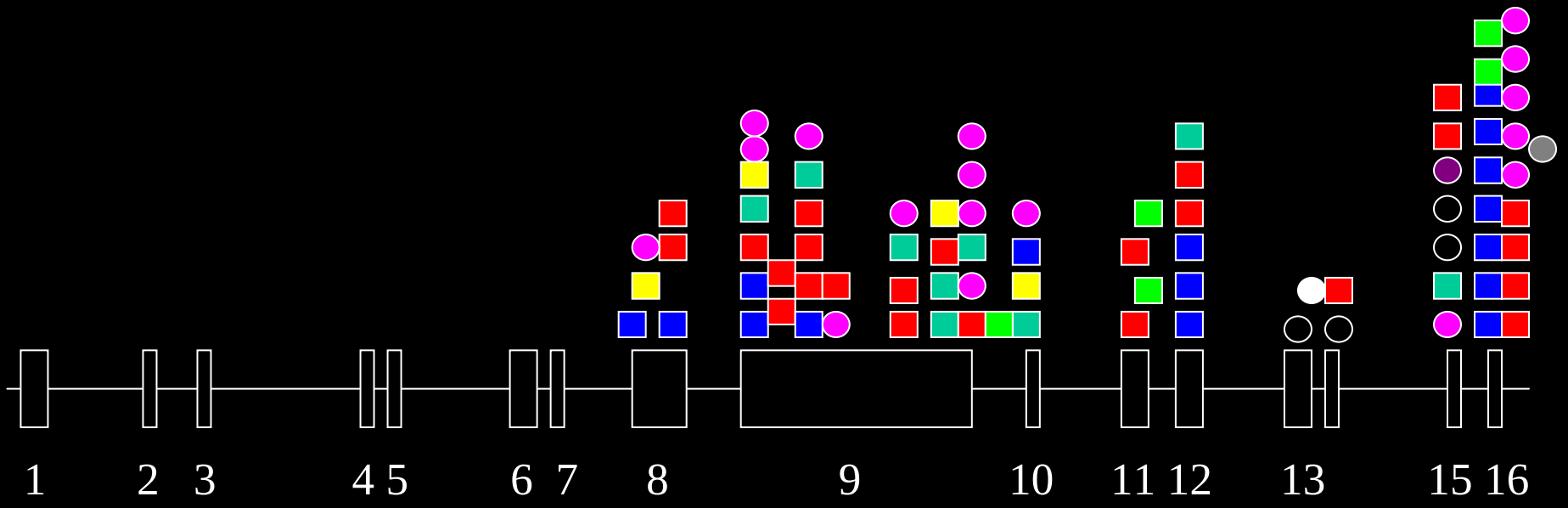
Substrate broken down

UBE 3A

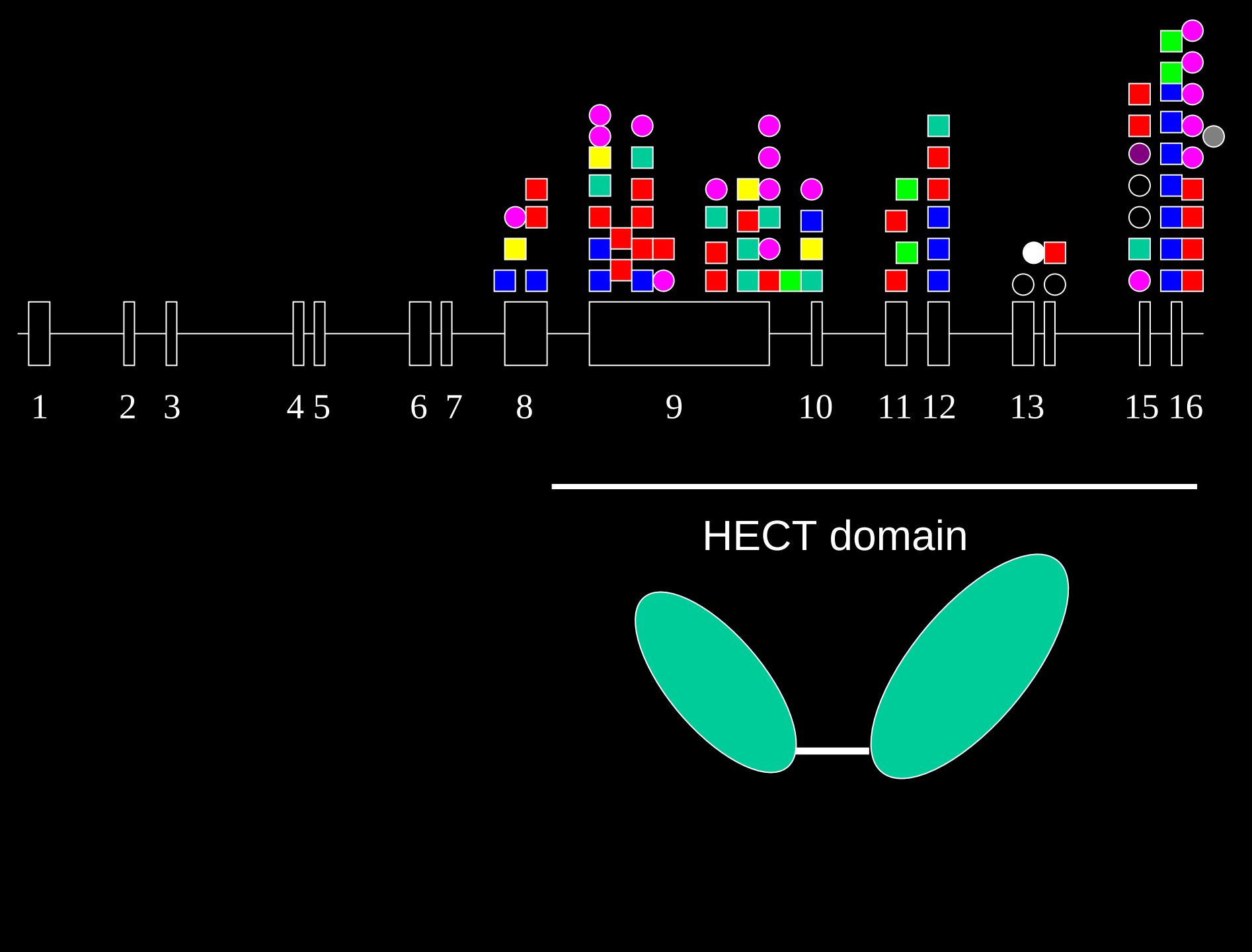
- Protein product, E6AP acts as E3 ligase in ubiquitin proteosome pathway
- Transcriptional co-activator
- Up-regulated inn neurons where it has a role in dendritic spine development

Dindot et al. Hum Mol Genetics 2008

UBE 3A Gene



- Out of frame insertion
- Out of frame deletion
- Out of frame deletion/insertion
- Splice site mutation
- Nonsense mutation
- Missense mutation
- In frame insertion
- In frame deletion
- In frame deletion, elongated protein
- Intronic change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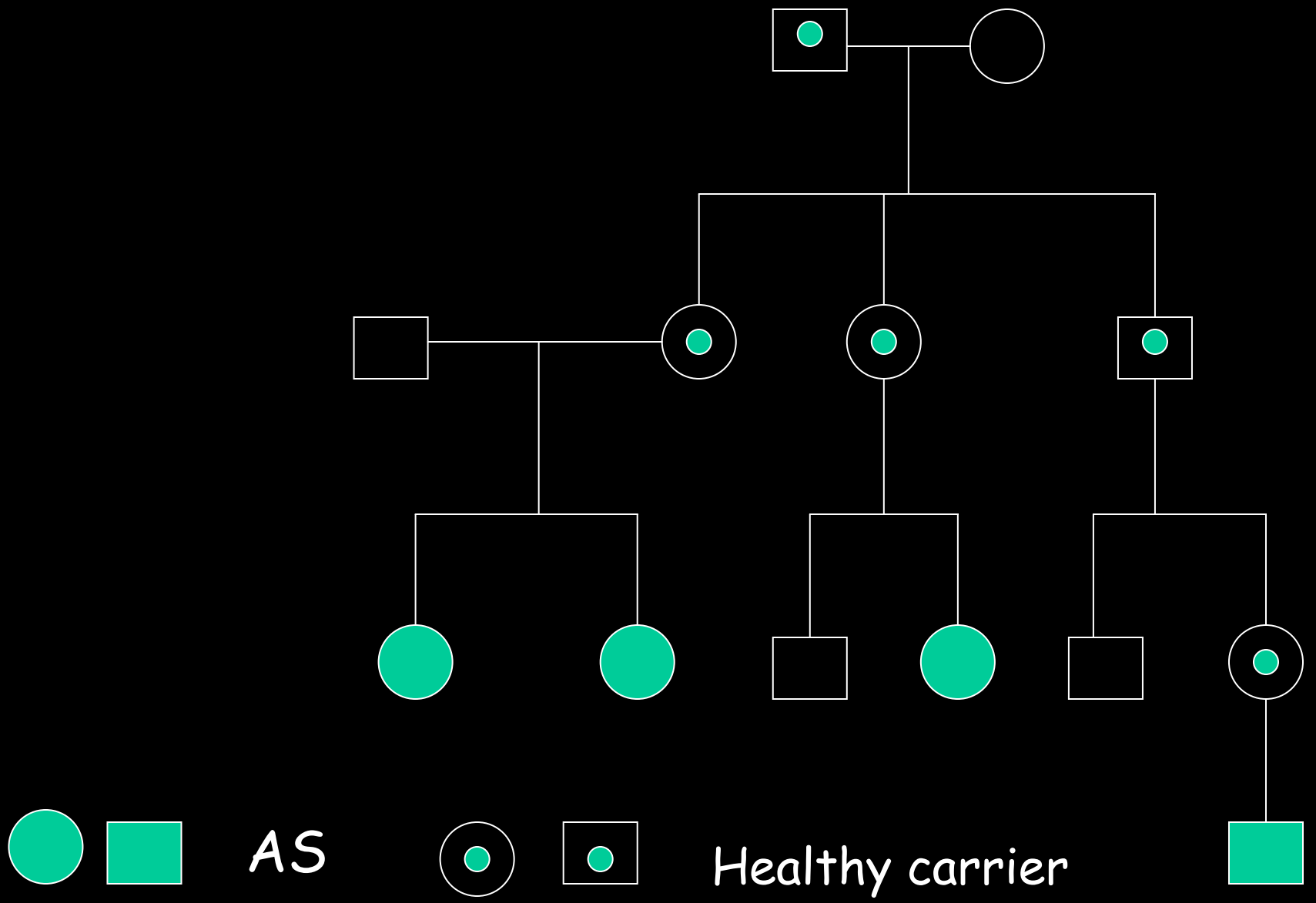
HECT domain

UBE3A mutations

- 85% familial cases
- 14-23% sporadic cases
- De novo in 70%
- Some missed on SSCP
- High incidence of gonadal mosaicism
- Arise in both maternal and paternal germline (more in mat)
- Missense probably have milder phenotype

UBE3A mutation may be familial (20%)

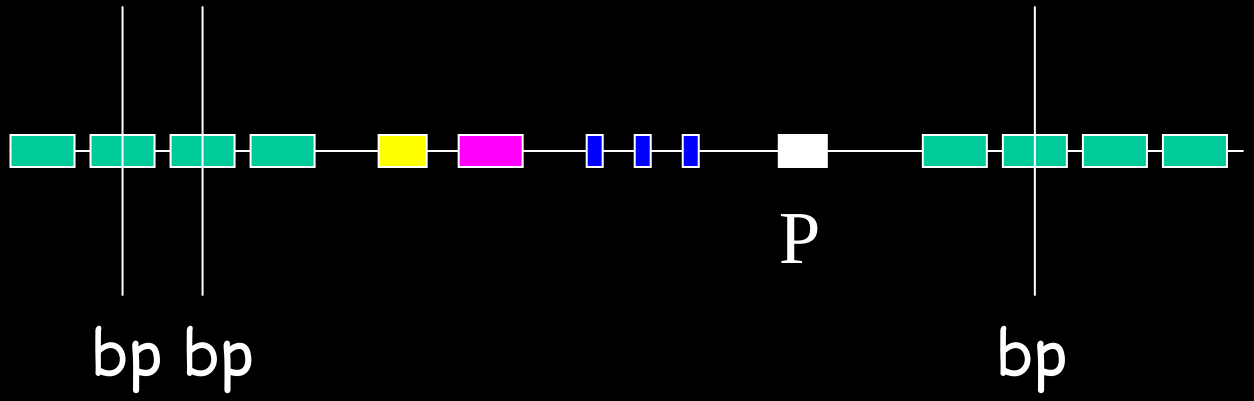


Genotype/Phenotype Correlation

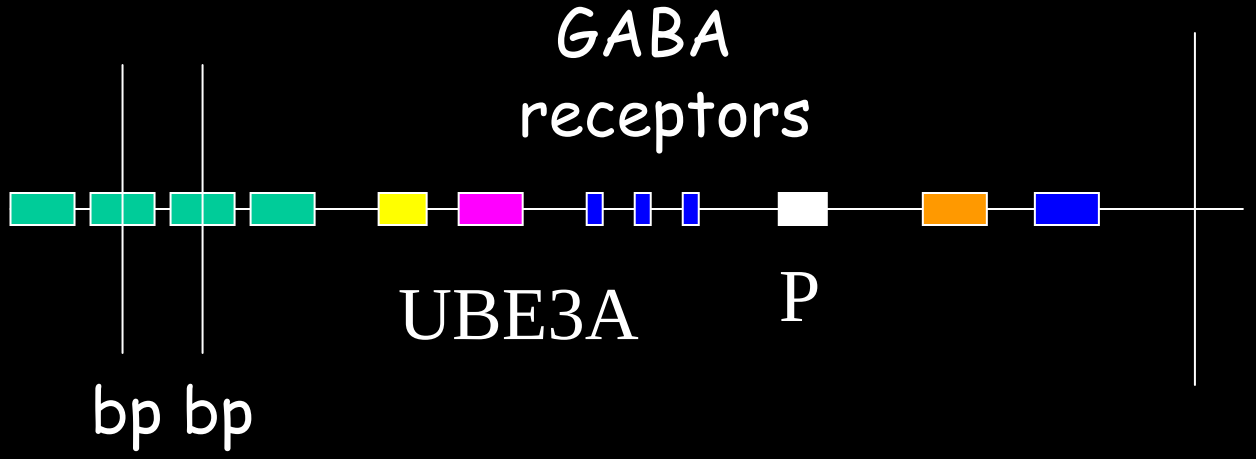
The Deletion Phenotype

- Small head size
- Seizures in 95%
- Seizures more severe
- Greater delay/inability to walk
- Hypopigmentation
- Typical facies
- More "hard" neurological signs

The P Gene Is Involved in oculocutaneous Albinism



What if the deleted segment of chromosome 15 is bigger?



…more genes might be missing

CONTIGUOUS GENE SYNDROME

The UPD Phenotype

- Walk earlier, 2-3 years
- Less ataxia
- Fewer seizures 20%
- Better comprehension and communication
- No hypopigmentation
- Less obvious facial features
- Later diagnosis
- Higher birth weight

The "Imprintor" Phenotype

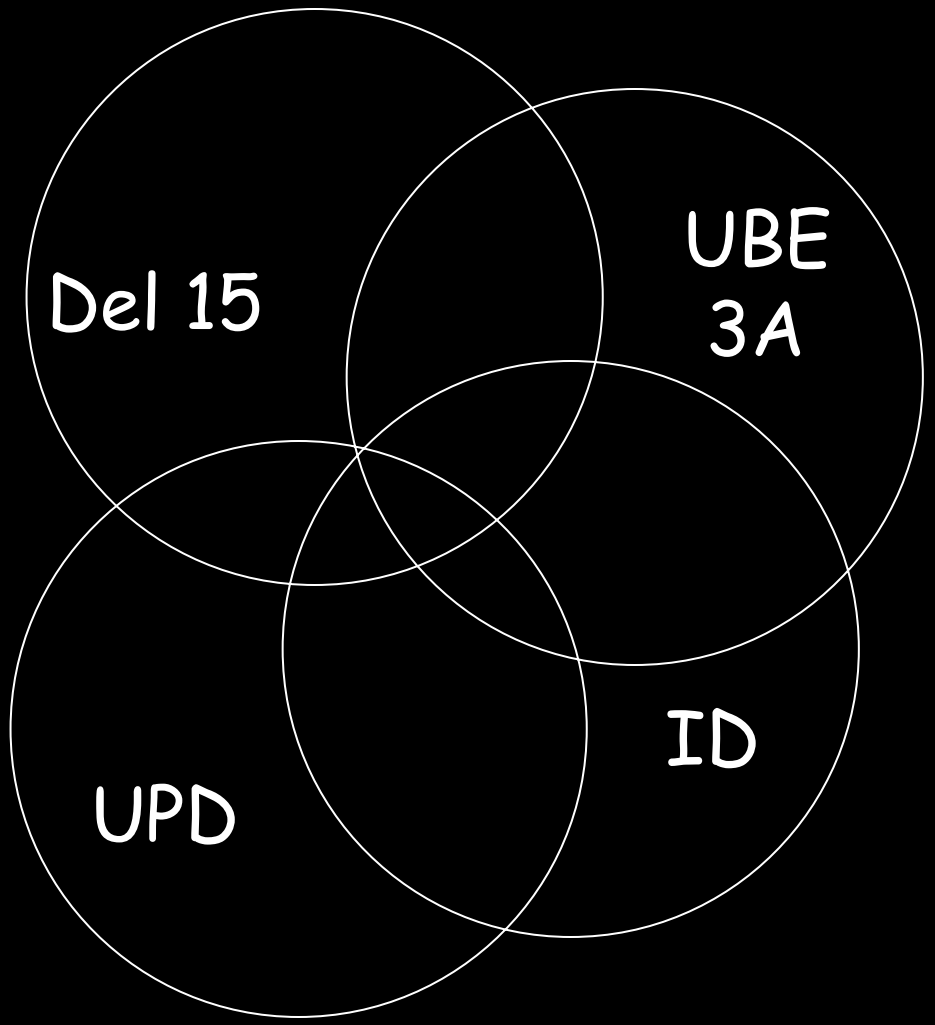
- Fewer seizures
- Better communication skills
- Less likely to have small head size
- Less ataxia
- No hypopigmentation
- ? More obesity
- Mosaics are PWS-like
- Still have AS personality

The UBE3A Phenotype

- Smallish head size
- Walk around 3 years
- Seizures in 50%
- Less ataxia
- No hypopigmentation
- Some facial features
- Better communication skills than deletion patients

What features are consistent across all groups?

- Happy, sociable behaviour
- Characteristic EEG
- Love of water
- Sleep disorder
- Scoliosis



Abilities of mosaic ID> UPD > ID > UBE > Del

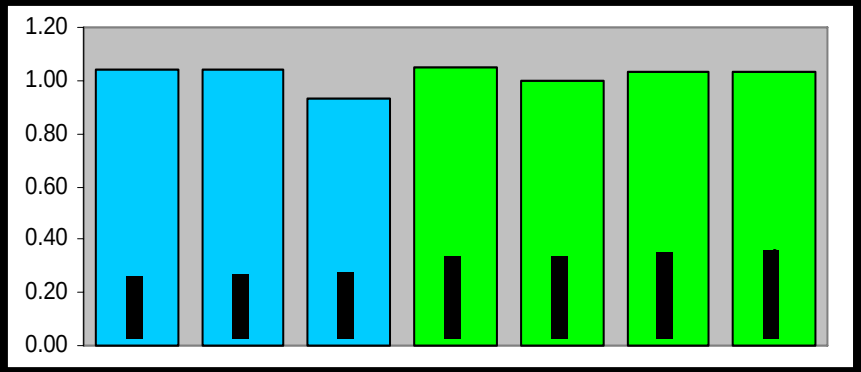
The "Quadruple-Non" Group

- Some are "typical" AS children
- On the whole a heterogeneous group
- EEG often not characteristic
- Some have structural birth defects e.g. heart problems
- May have no dysmorphic features or facial features which differ from AS

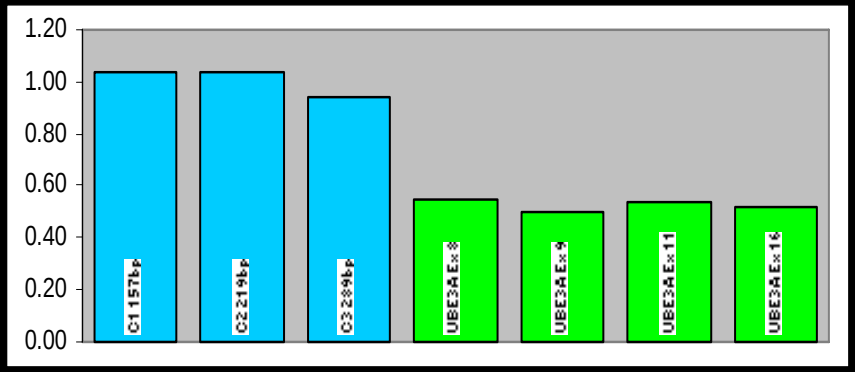
What might explain an AS phenotype with no demonstrable genetic abnormality?

- Another diagnosis.
- Mutation not detectable by current techniques
- ?Another transcript of UBE3A
- ?Another AS gene
- ?Another chromosomal microdeletion
- Mosaicism

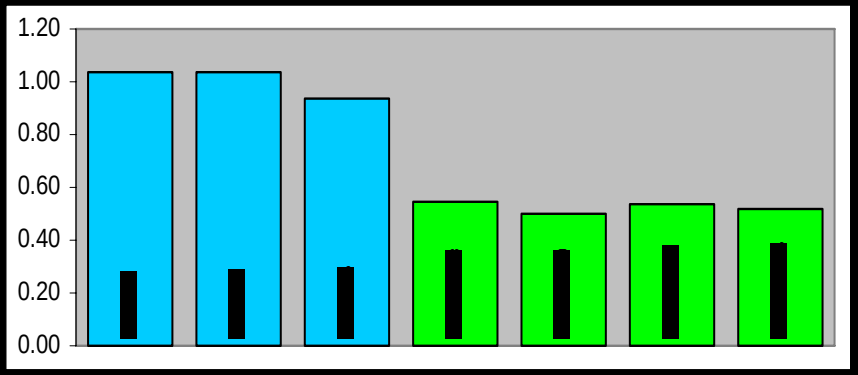
UBE3A MLPA detects smaller deletions



Normal Control



Known deletion control



PM Affected deletion carrier

Similarities in AS and RS

- Ataxia
- Deceleration of OFC
- Brachycephaly
- Seizures and abnormal EEG
- Frequent laughter
- Stereotypic hand movements
- Severe LD and absent speech
- Scoliosis

Differences between AS and RS

- No regression in AS
- Characteristic features of AS EEG
- Movement disorder
- Vasomotor instability in RS
- Hypopigmentation in AS with deletion
- Tremor prominent in RS
- RS girls are anxious, not always happy
- Rett syndrome progressive with poorer prognosis
- Type of mutation

Mowat Wilson Syndrome

- Microcephaly
- Absent corpus callosum
- Congenital heart defects
- Genitourinary malformations
- Hirschsprung's disease
- Characteristic dysmorphic features
- Upturned ear lobes
- Seizures
- Talipes deformity

ATR-X syndrome

- X- linked disorder with mutations in XNP gene at Xq13
- Characteristic facies with tented upper lip, flat nasal bridge and macrostomia
- Seizures
- Microcephaly
- Short stature
- Genital abnormalities
- Hb H inclusions

22q13-qter deletion

- Severe speech delay, often no speech
- Autistic features
- Ataxia
- Clinodactyly Vth fingers
- AS-like facies
- Overgrowth

NB sometimes picked up incidentally as absence of Control probe for 22q11 FISH

Other Chromosomal Abnormalities Resembling AS

- 9q34 deletion
- 5p-
- 17q21 microdeletion

? CGH studies will provide further clues

TCF4 gene (Pitt Hopkins)

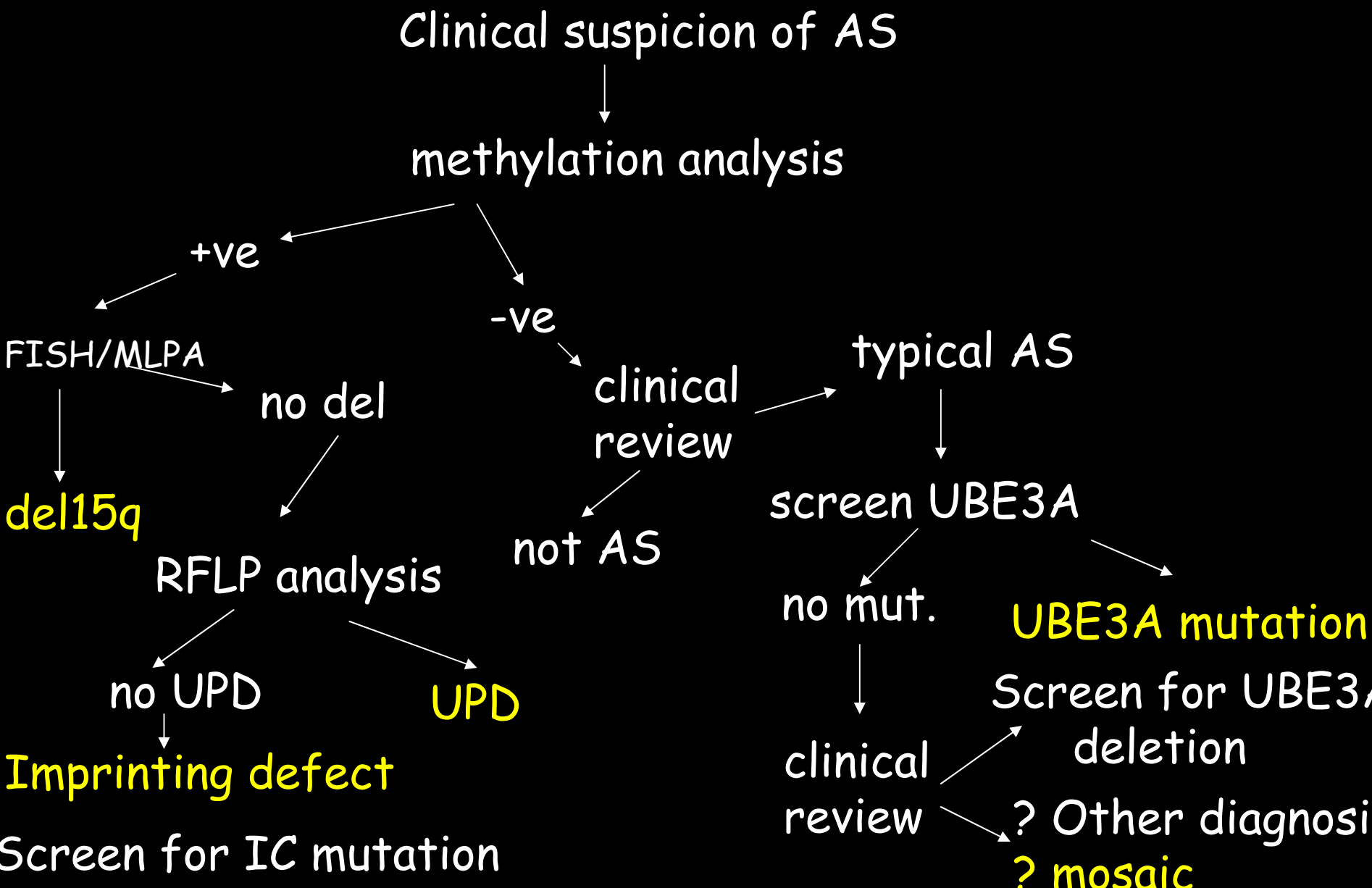
- Downstream target of WNT/catenin pathway and functions as an oncogene when mutated

  (Patient 1 has been treated for lymphoma)
- ASCL1/RET/PHOX pathway (role in congenital central hypoventilation and noradrenergic neuronal development)

Other Differential Diagnoses

- MTHFR deficiency (Arn et al. 1998)
- Perisylvian syndrome
- Lennox-Gastaut
- Ataxic cerebral palsy
- ARX syndrome

Algorithm for Genetic Testing



Current Research

- Reiter et al. Hum Mol Genet 2006
  UBE3A controls a gene called ECT2 in fruit flies
  This gene regulates brain cell growth and is probably important in AS and autism

- Beaudet et al. 2006 identified two genes that affect the activity of the imprinting centre in mice.

- Van Woerden et al. improved the behaviour of AS mice by manipulation of alphaCaMKII gene (Nature neuroscience 2007)

Acknowledgements

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ASSERT
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AS families worldwide