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
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
In Angelman syndrome the deletion arises on the maternally inherited chromosome.

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

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

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

mitotic error

meiotic error

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

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

- 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 in neurons where it has a role in dendritic spine development

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

Clinical suspicion of AS

methylation analysis

+ve

FISH/MLPA

no del

del15q

RFLP analysis

no UPD

UPD

Imprinting defect

Screen for IC mutation

-ve

clinical review

not AS

typical AS

screen UBE3A

no mut.

UBE3A mutation

Screen for UBE3A deletion

? Other diagnosis

? mosaic
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)
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