ERN ITHACA

Webinar 2025

Navigating Angelman syndrome in clinical practice

Tuesday 13 May, 17:30 – 18:00 (CET time)

Chaired by Ellen Koekoeckx, FAST

Speakers:
Dr. Karen Bindels-de Heus (MD, Phd)
Dr. Ana Roche (MD, Phd)

European Commission

EUROPEAN REFERENCE NETWORKS

Helping patients with rare or low-prevalence complex diseases

Project Manager Anne Hugon

2025

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Welcome – Technical points

- We are please to be numerous > 100 registrations
- Webinar being recorded

- Thank you for
  - Turn off your microphone and disconnect your camera
  - Raise your hand at the time of the questions and discussions
  - We will answer the questions sent in the registration form
  - A satisfaction survey will be sent to you :

- Webinars # will be available on ITHACA's Website
- https://ern-ithaca.eu/webinars/

- Anne Hugon Project Manager ERN ITHACA - anne.hugon@aphp.fr

Welcome and Introduction

- **Public:** Clinical geneticists, neurologists, pediatricians & AS caregivers

- This webinar is the second of a webinar series dedicated to Angelman syndrome, a neurogenetic disorder. In this session we'll focus on how Angelman syndrome presents in clinical practice. Join us for an insightful webinar exploring how different genotypes in Angelman Syndrome influence development and medical outcomes.

- Chaired by **Ellen Koekoeckx** on behalf of **FAST** (Foundation of Angelman Syndrome Therapeutics)

- Invited expert speakers:
  - **Dr. Karen Bindels-de Heus (MD, PhD),** Pediatrician, Erasmus MC, Rotterdam, the Netherlands
  - **Dr. Ana Roche (MD, PhD**), Pediatric neurologist & Angelman syndrome Clinic coordinator, Parc Tauli, Barcelona, Spain

Agenda

Our expert speakers will provide insights on the following topics:

- **Genotype-phenotype differences in Angelman Syndrome (20 min)**
  - Overview of the different genotypes
  - Impact of genotype on developmental outcomes and severity of symptoms
  - Angelman syndrome in adulthood

- **Medical conditions related to Angelman Syndrome (50 min)**
  - Seizures
  - Movement disorders
  - Anxiety and behavioral concerns
  - Sleep disturbances
  - Gastrointestinal issues
  - Hyperphagia, growth & puberty
  - Bone health concerns

- **Q&A**

Genotype-phenotype differences in Angelman Syndrome

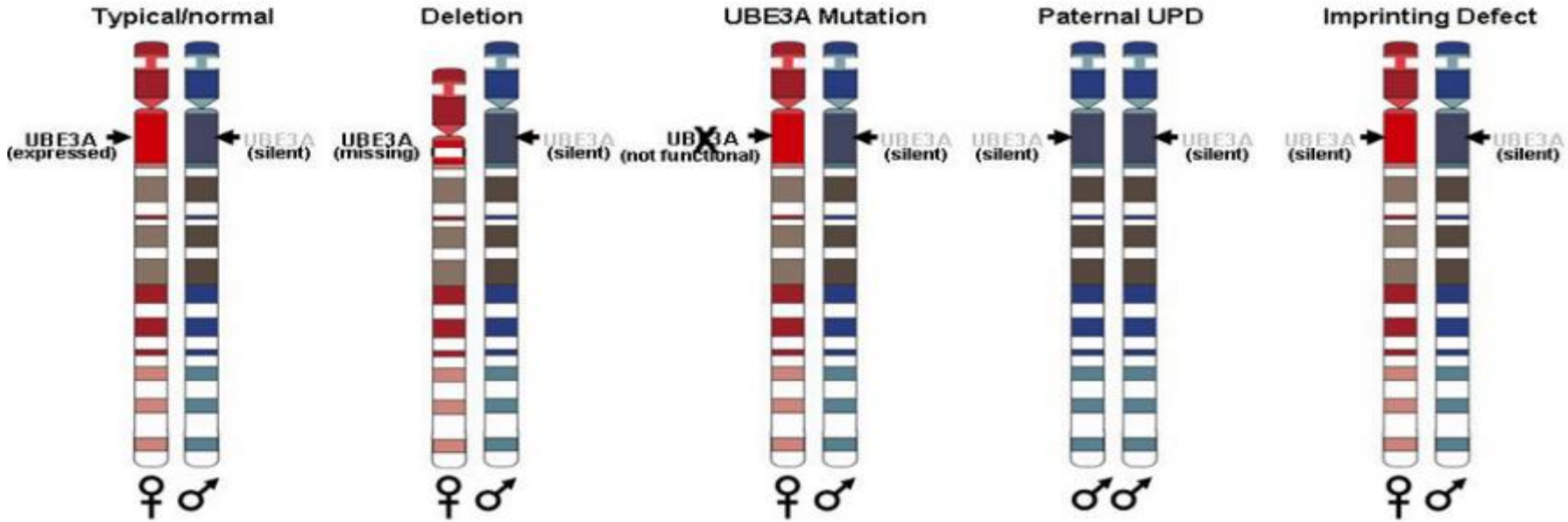
Genotype-phenotype differences in Angelman Syndrome

Overview of the different genotypes

Impact of genotype on developmental outcomes
- gross motor
- fine motor
- cognition
- communication

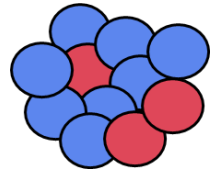
and severity of symptoms

Overview of the different genotypes



~70-80% | ~10% | ~3% | ~1%

Mosaicism



Combination of cells expressing UBE3A and cells that do not express UBE3A

~1%

1. Dagli A, Buiting K, Williams C. Molecular and Clinical Aspects of Angelman Syndrome. Mol Syndromol 2011; 2:100-112.
2. Dagli A, Mueller D, Williams C. Angelman Syndrome. GeneReviews, 2017. Editor, Adam. Seattle, WA. [https://www.ncbi.nlm.nih.gov/books/NBK1144/]
3. Williams C, Driscoll D, Dagli A. Clinical and genetic aspects of Angelman syndrome. Genet Med. 2010; 12(7): 385-395.

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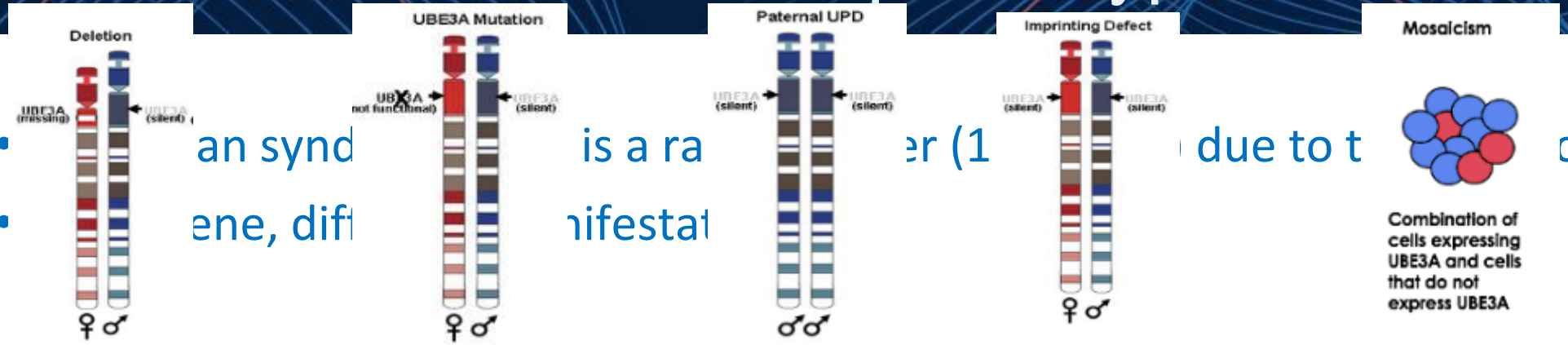
Overview of the different phenotypes



- an synd is a ra er (1 due to t ce of UB3A protein
- ene, dif nifestat

- Deletion type I and II: 70%-80% "de novo" interstitial deletion of the long arm region of the maternally inherited chromosome, include genes coding for GABA A receptors
- Mutations of the maternal *UBE3A* gene, 10% (truncated or missense)
- Paternal uniparental disomy (UPD): 3%, the child has inherited both chromosomes 15 from the father (silenced).
- Imprinting defects (ID): 1%, maternal *UB3A* is silenced
- Mosaicism: 1%, various populations of cells (different tissues) with different genetic information

Genotype-phenotype correlations

- Clinical manifestations include
- Severity may vary among the different genotypes: genotype-phenotype correlation

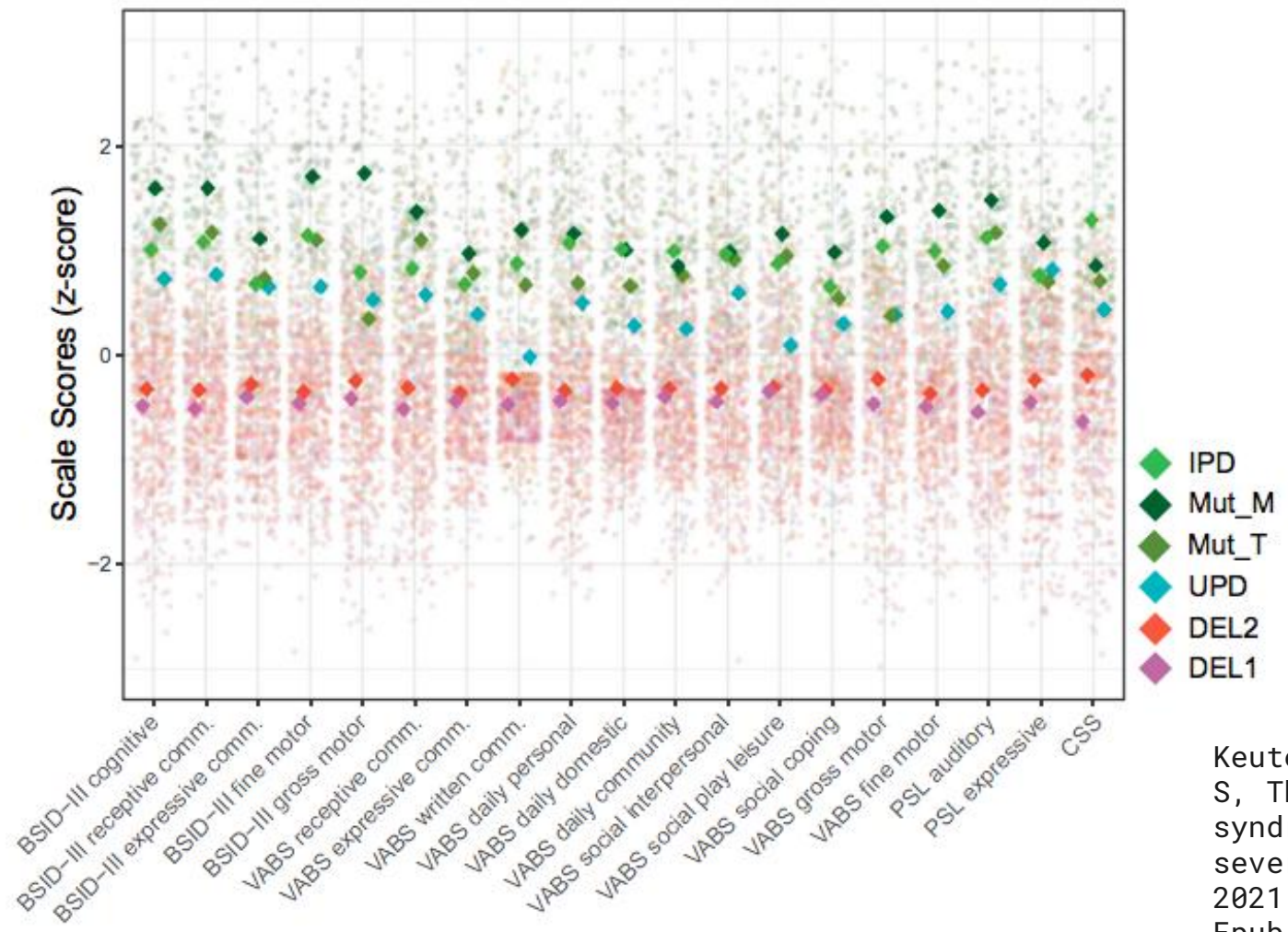
- Severe neurodevelopmental delay
- Autism Spectrum
- Lack of speech
- Sleep disorders
- Ataxia
- Apraxia
- Gastrointestinal issues
- Complicated behaviors
- Refractive errors (hyperopia/ astigmatism, esotropia

- Could we predict the future?
- Could we adjust expectations? Improve clinical follow up?

Behaviour

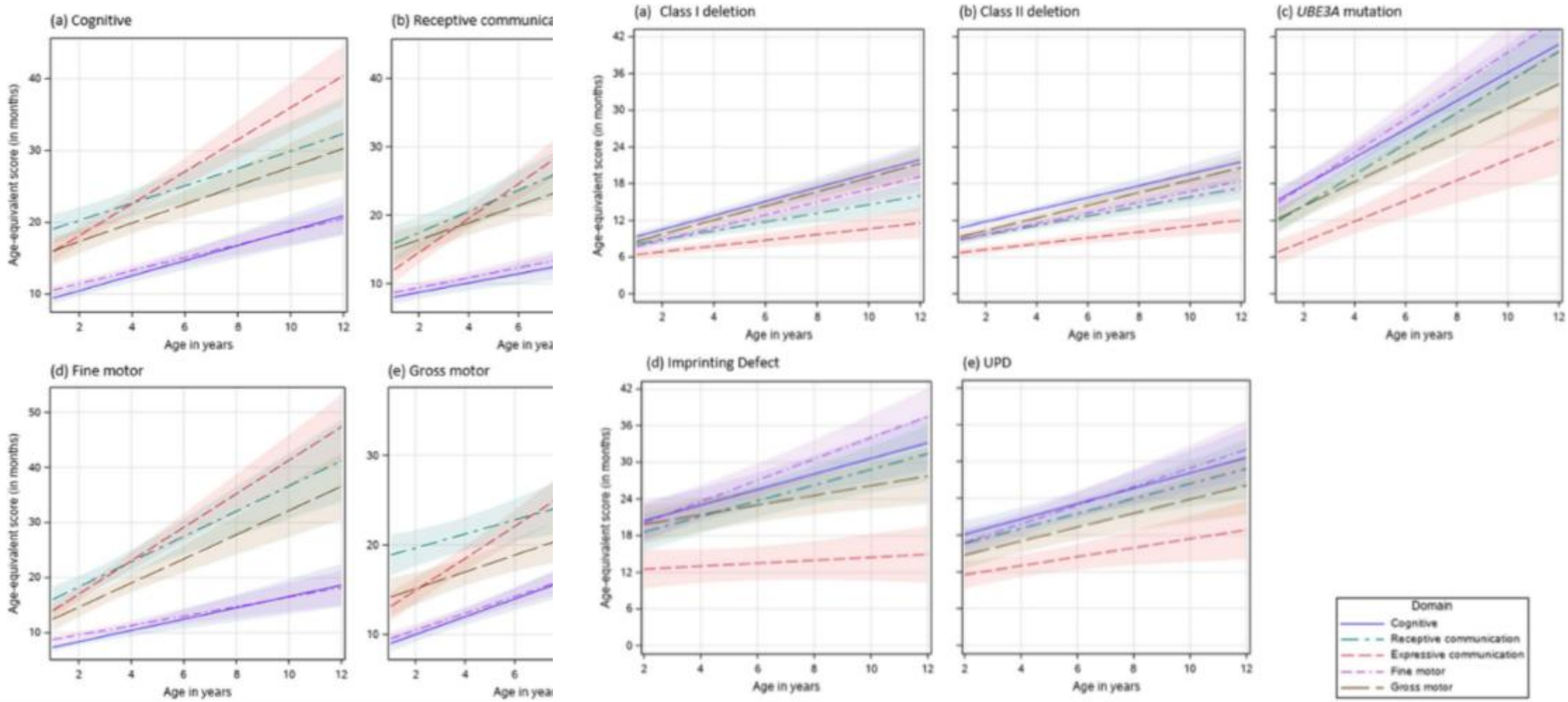
- Happy demeanor, easily provoked laughter,
- Short attention span / hypermotoric behavior, become more focus after adolescense.
- Mouthing objects → behavioural estrategias or baby teether
- Affinity for water
- General irritability may happen in early infancy → rule out intestinal troubles
- Disruptive behaviors by the majority of patients: biting, pinching, hair-pulling, and grabbing, usually in response to frustration, easy excitability, desire for attention, poor control over movements, reduced comunication skills

Impact of genotype on developmental outcomes



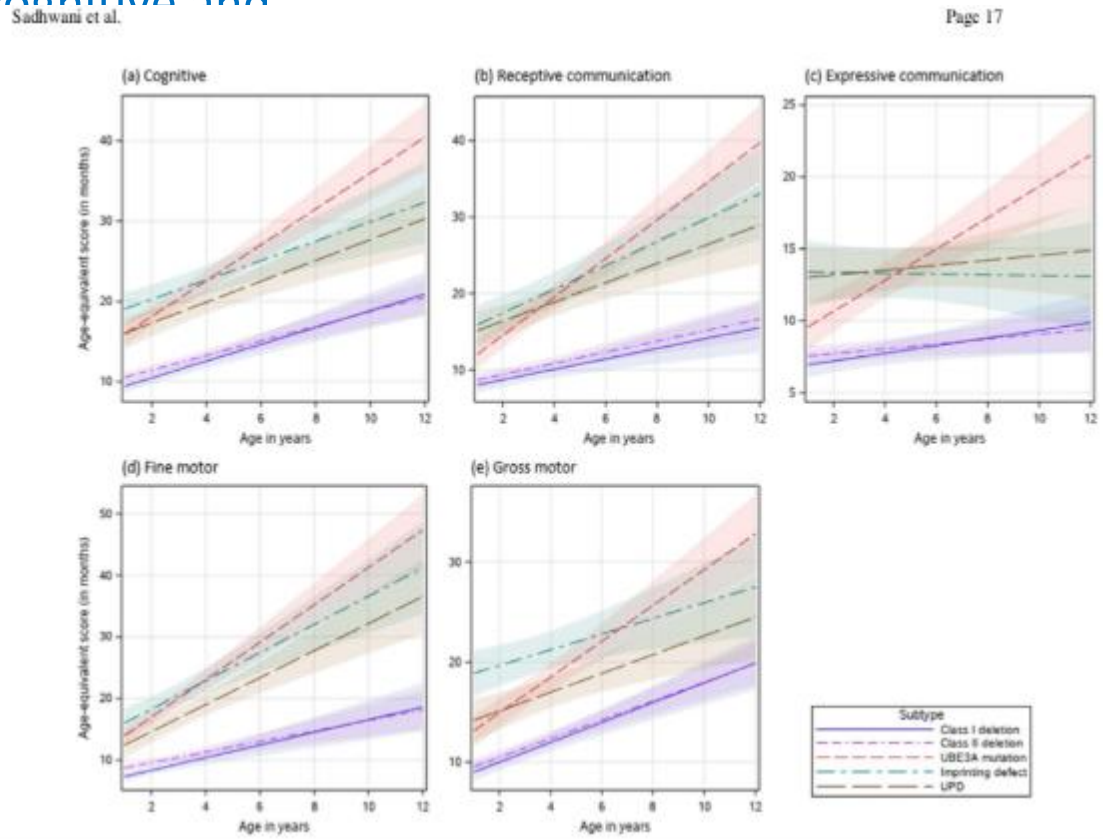
Keute M, Miller MT, Krishnan ML, Sadhwani A, Chamberlain S, Thibert RL, Tan WH, Bird LM, Hipp JF. Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment. Mol Psychiatry. 2021 Jul;26(7):3625-3633. doi: 10.1038/s41380-020-0858-6. Epub 2020 Aug 13. PMID: 32792659; PMCID: PMC8505254.

Every Angelman patient will improve



Deletion

- Generally considered the most severe phenotype
  - Highest prevalence of seizures, up to 95%
  - Lower scores on cognitive and language assessm
  - More motor diffic
  - Microcephaly is m
  - Classic phenotype
  - Lighter and shorte
- Likely a result of the d
- Unclear if there is a di
- Hypopigmentation for



lepsy and developmental delay

d deletion classes

Del I
Del II

UAB Universitat Autònoma de Barcelona

Parc Taulí Institut d'Investigació i Innovació I3PT

Parc Taulí Consorci Corporació Sanitària

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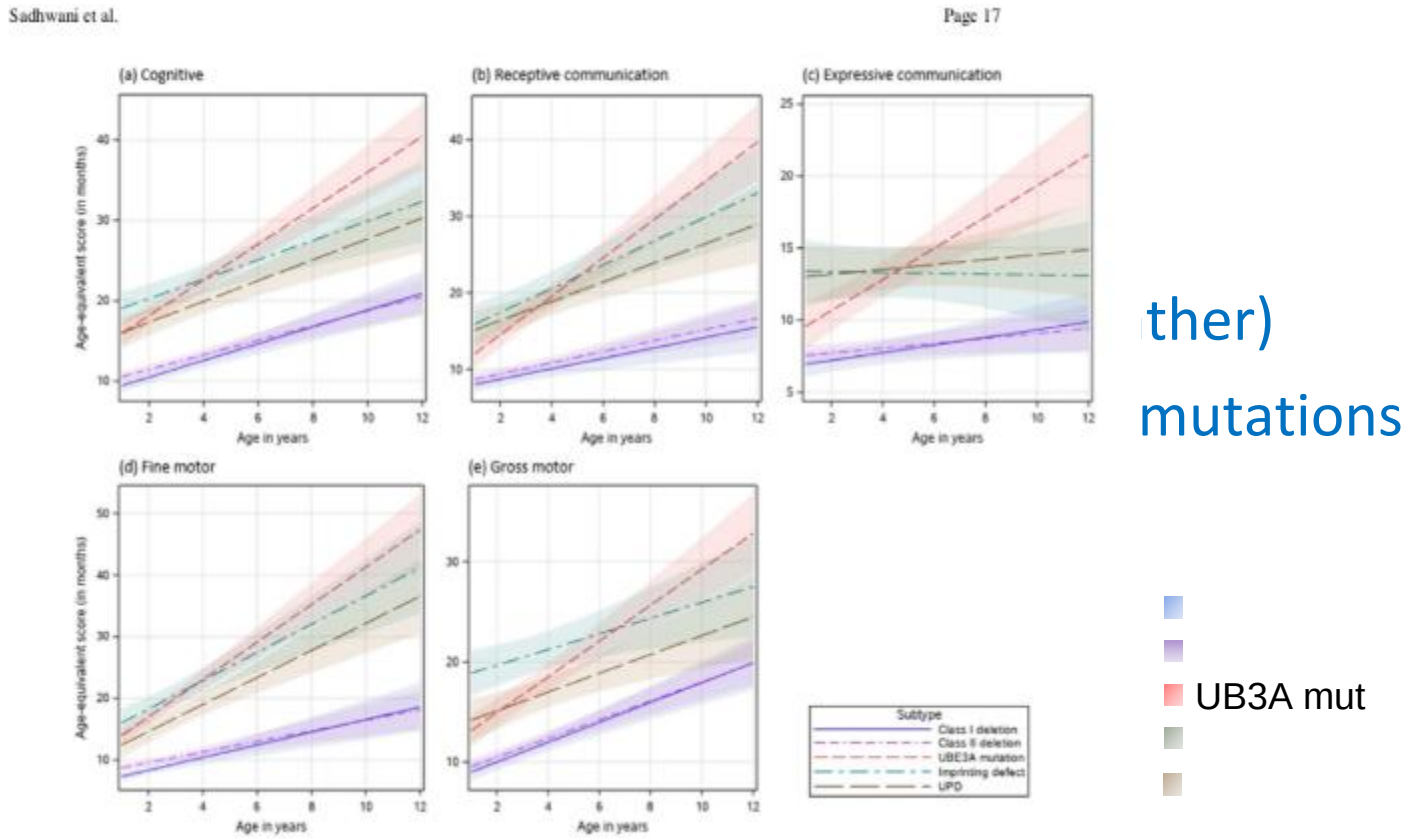
UB3A mutation

- Patients are similar to deletion patients for
  - Seizures
  - Microcephaly

But higher performance in moto

May appear de novo or be inhe ther)

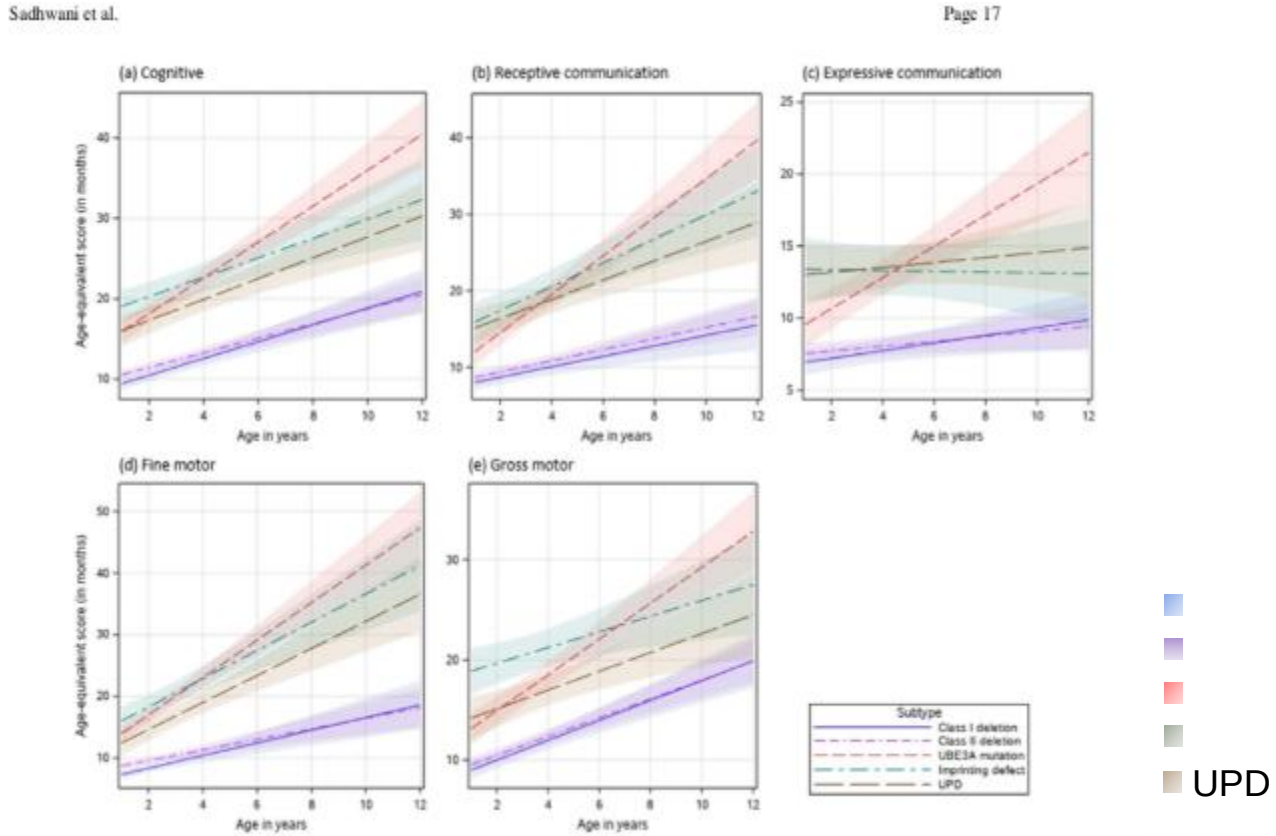
Missense mutations may have s mutations generally don’t



UB3A mut

Uniparental disomy

- Generally less severe phenotype
- Diagnosis comes later
  - Lower prevalence of epile
  - Less severe epilepsy
  - Better motor performanc
  - Higher risk of obesity
  - Verbal language



UPD

Imprinting Disease

Patients with imprinting anomalies have a even milder course with less seizures and better communication skills.

- epigenetic events (~85%
- deletions within the AS

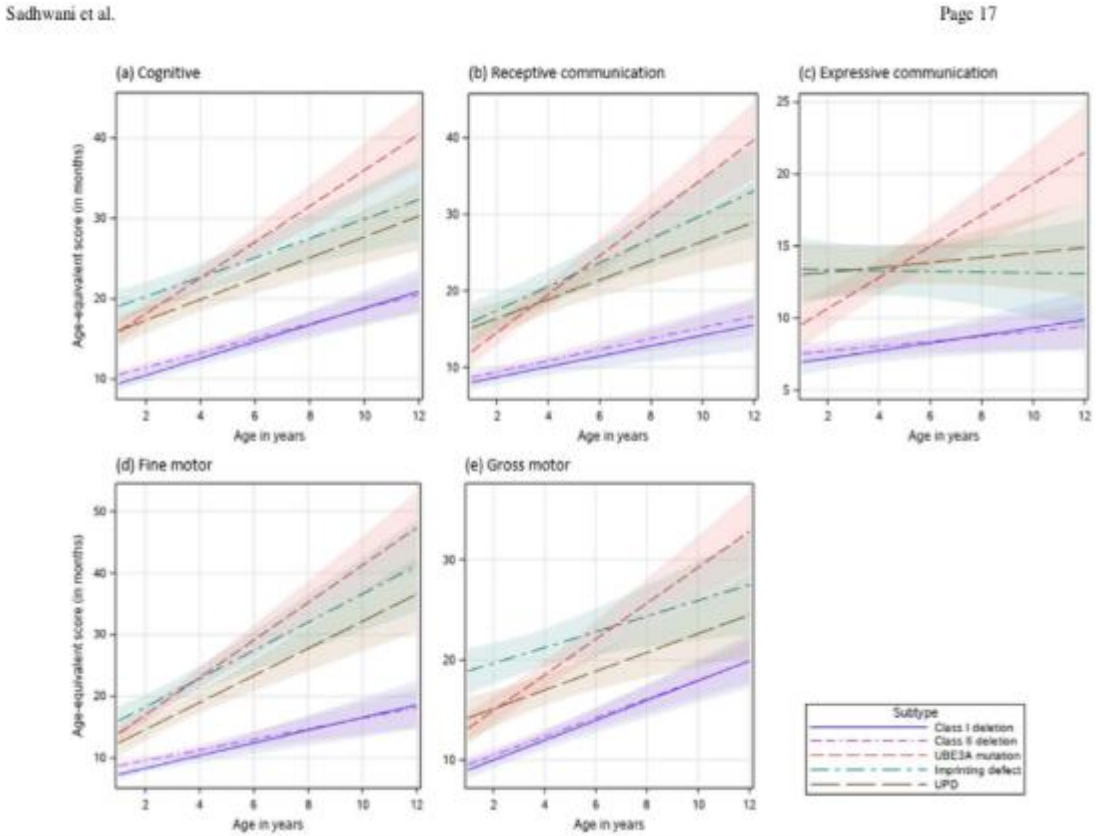
the maternal chrom e the paternal copy.

→similar to UPD phenotype

- (~30%) of individuals wi fect only

in a subset of cells) [

Mosaicism in patients ma



ID

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Sadhwani *et al.*
Journal of Neurodevelopmental Disorders (2024) 16:32
https://doi.org/10.1186/s11689-024-09548-7

Journal of
Neurodevelopmental Disorders

RESEARCH Open Access

Developmental milestones and daily living skills in individuals with Angelman syndrome

Anjali Sadhwani[1,2*], Sonya Powers[3,10], Anne Wheeler[3], Hillary Miller[4,11], Sarah Nelson Potter[3], Sarika U. Peters[5], Carlos A. Bacino[6], Steven A. Skinner[7], Logan K. Wink[8,12], Craig A. Erickson[8], Lynne M. Bird[9] and Wen-Hann Tan[1,13]

challenging

challenge

chance

change

Daily living skills

- Toileting and feeding
- Brushing teeth
- Bathing
- Dressing themselves

only a small minority of the participants achieving these skills, especially among deletion-positive individuals

Medical conditions related to Angelman Syndrome

Epilepsy

- Epilepsy comprises a broad group of disorders/diseases with diverse etiologies, diverse electroclinical presentations, and marked variability in clinical outcomes

- The International League Against Epilepsy (ILAE) Classification of the Epilepsies defined three diagnostic levels including
  - (1) seizure type: descriptions of movemnets and duration
  - (2) epilepsy type: based on seizure type and EEG
  - (3) epilepsy syndrome: based also in aetiology

  emphasizing that etiology and comorbidities must be considered at each level

- Importance of home videos

Epidemiology of epilepsy

Image Source: freepik

- 90% of cases experience epileptic seizures during their lifetime
- 25% of patients develop them in the first year of life
- 35% of epileptic seizures in AS start a a febrile spell
- most common during the first three years of life
- Under control after adolescescense in most cases (65%), but…

- Many patients experience daily seizures during a limited period in infancy.
- 60% of patients experience seizures which are daily life limiting
- 35% to 85% status epilepticus
- Around 20s, or after adolescence, number of seizures decrease, new peak around 30-40 years old.
- Absence seizures and myoclonic seizures until adulthood.

- 90-95% of children with deletions will develop epilepsy
- 75% of mutations and UPD
- 50% of ICD
- Seizure types as initial seizure presentation include
  - myoclonic—25%
  - Atonic- drop attack—23%
  - generalized tonic-clonic—21%
  - and atypical absences—12%.
- infantile spasms generally rare in AS.
- AS seizures are typically generalized, but up to 30% may also have focal seizures

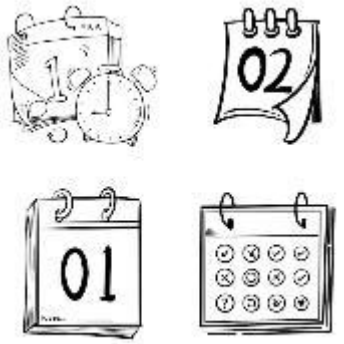
It's sometimes difficult to determine...

Types of seizures

- Different types of seizures at the same time
- Generalized more frequent
- Atonic absences and atypic absence seizures
- In infancy, myoclonic seizures are more frequent
- 50% focal seizures
- Particularities: fever is often a trigger, heat intolerance

Special situations: be ware of the non-convulsive status

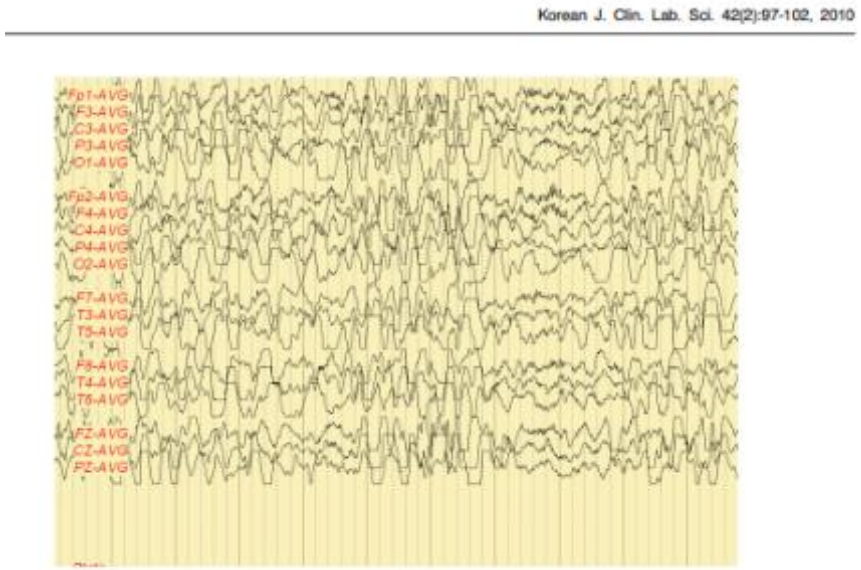
- Non-convulsive status epilepticus (NCSE) is common:
  - periods of decreased responsiveness or alertness, which may last hours to days, often with loss of developmental skills.
  - typically no clinical seizures, it may go unrecognized.
  - 50–90% of the population in older studies,
  - Recent studies show 19%-20% of NCSE



  - Rarely accompanied by frequent myoclonic jerks, which is known as myoclonic status in non-progressive encephalopathies (MSNPE, Dalla Bernardina syndrome)

Video- EEG as an important tool

- There are 3 typical EEG patterns, that can be observed after 4 months of age, and can be isolated or combined.
- Pattern I, after 12 yo
  - Persistent Rhythmic theta activity at 4-6 Hz, >200 V amplitude, generalized, without somnolence
  - Persists with eyes shut
- Pattern II, children and adults
  - Rhythmyc activity at 2-3 Hz, 200-500 V amplitude, anterior, interictal epileptiform discharges
- Pattern III
  - Spikes and waves at 3-4 Hz, >200 V amplitude, posterior, enhanced when eyes are shut



Video- EEG as an important tool

- EEG delta power is elevated in Angelman syndrome patients, compared to tipically developing population
- The origin of this frequency-unspecific increase of EEG signal power is unknown
- (1 – 18 years) and showed that delta power increase (relative to TD controls) is stable across development
- delta-band AS phenotype is more pronounced for deletion as compared to non-deletion AS

EEG might be a biomarker

AS physiopathology?
Prognostic factor?
Evolution assessment?
Treatment response?

Treatment

- No comparative trials for AED or anticonvulsant drugs (ACDs) → clinical practice based on case series and own experience

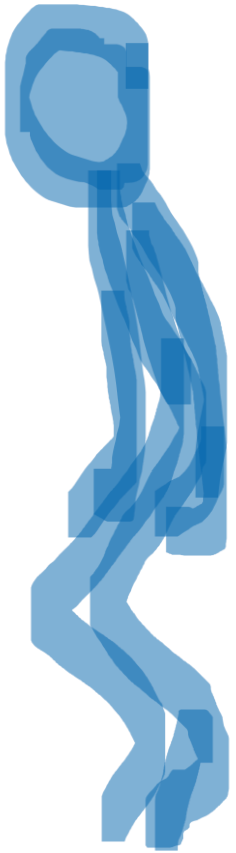
- **Likely to provide benefit** with **limited adverse effects** include **clobazam, levetiracetam**, and clonazepam
  - Levetiracetam or clobazam as first line therapy
  - consider dietary intervention, including a **ketogenic diet** (KD)- feeding tube- or low glycemic index therapy (LGIT)

- Generalized seizures are prominent → broad spectrum ACDs are recommended.
  - Phenobarbital, primidone, carbamazepine, phenytoin, and vigabatrin are contraindicated
  - High rate of motor side effects with valproic acid: sparing use unless as a bridge medication or failure of other ACDs and diet
- Cannabidiol: little evidence but a promising medication for seizures, behaviour and NEM
- Rescue medication such as rectal diazepam gel or intranasal / bucal midazolam for prolonged seizures.
- **Interruption therapy** for episodes of **NCSE** with diazepam divided 2–3 times daily with a taper over 5–7 days has benefit
- Interruption therapy for **clusters of seizures** may benefit from clobazam c/12h for 3-5 days

Non epileptic movement disorders

Ataxic/jerky movements were the only initially considered phenotypic of Angelman syndrome, but:

- Axial hypotonia, triple flexor pattern
- Ataxia
- Tremor
- Dystonia
- Stereotypies
- Non epileptic myoclonus



Ataxia / Jerky movements

- Neurological sign: lack of coordination in the movement of different muscles in the body.
- abnormalities in gait, abnormal eye movements such as nystagmus.
- Prevalence 70%-100% of patients
- Treatment: physical therapy, rehabilitation, occupational tehrapy…

Tremor

- Tremor is a neurological condition: shaking or trembling movements in one or more parts of the body, most commonly affecting a person's hands.
- It may be constant, or only happen sometimes
- Prevalence 25% of patients with AS in some series, but in our experience might be 40-50%, often inconstant
- Often action tremor, more evident if tired or overexcited
- Differential diagnosis with cortical myoclonus (jerky, tremulous, dystonic movements, pathologically hyperexcitable sensorimotor cortex.)

Levodopa responsive Parkinsonism in adults with Angelman Syndrome

M. Harbord, MBBS FRACP

Affiliations & Notes Article Info

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Abstract

Two intellectually disabled adults with Angelman Syndrome are reported who developed intermittent episodes of a severe resting tremor, cogwheel rigidity and bradykinesia in their late teens. The Parkinsonism was not due to medications and there was a dramatic improvement with levodopa therapy. The association between Angelman Syndrome and Parkinsonism has not previously been described.

Harbord M. Levodopa responsive Parkinsonism in adults with Angelman Syndrome. J Clin Neurosci. 2001 Sep;8(5):421-2. doi: 10.1054/jocn.2000.0753. PMID: 11535008.

Dystonia

- Involuntary, maintained contraction of agonist and antagonist muscles → abnormal posturing, twisting and repetitive movements, or tremulous
- Can be initiated or worsened by attempted movement → changes in severity based on the activity and posture.

J Neurol. 2021 Jun;268(6):2208-2212. doi: 10.1007/s00415-020-10395-4. Epub 2021 Jan 23.

Dystonia in Angelman syndrome: a common, unrecognized clinical finding

Edoardo Ferlazzo [1 2 3], Michele Ascoli [1 2], Francesca Abate [1], Sara Gasparini [1 2], Giovanni Mastroianni [2], Vittoria Cianci [2], Giulia Ferrigno [1], Chiara Sueri [2], Tiziana D'Agostino [2], Umberto Aguglia [4 5 6]

Affiliations + expand

PMID: 33484323 DOI: 10.1007/s00415-020-10395-4

30 subjects (15 F) (range 15–51).
Dystonia was present in 93.3%

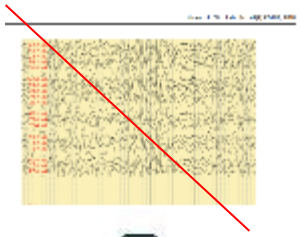
- upper limbs 100%
- lower limbs 28.5%
- mouth 25%
- neck 10.7%
- trunk in 3.6%
- Severity slight to moderate
- Correlation between severity of dystonia and increasing age
- There was no difference in terms of severity of dystonia among genetic subgroups

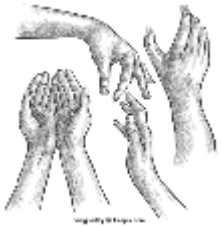
Stereotypies

- Motor stereotypies are common, repetitive, rhythmic movements with typical onset in early childhood.
- No treatment is usually used, but correlation with anxiety, overexcitement → distract attention, provide an object to hold…
- → investigate if there is a trigger

Non epileptic myoclonus

- 40% of AS children > 10years of age
- Puberty or later
- No electrographic correlate on EEG if captured during registration.
- Seconds to hours
- Start on hands and spread to the face and all extremities in some individuals.
- No postictal period, no consciousness decline, no developmental regression.
- Difficult to treat and are often refractory to medication; levetiracetam, clobazam, clonazepam, and perampanel





Possible triggers:
poor sleep
anxiety

Anxiety

- Difficult to evaluate by selfreported scales, limited studies
- Anxiety, Depression, and Mood Scale (ADAMS)

- Parents of children with AS have reported higher levels of parenting stress related to child factors including intellectual abilities, physical abilities and mood characteristics
- Anxiety persists through lifespan in AS
- Hipersensitivity (noises, strong smells…) may trigger anxiety reactions
- **Behavioral responses** include avoidance, head banging or slapping, pacing, cyclic vomiting, and behavioral outbursts
- Influences many aspects of daily life:

Attention, learning
Social interactions
Rutines, selfcare
Sleep
Feeding

Behavioral Measures

- **Aberrant Behavior Checklist-Community Version.—**The Aberrant Behavior Checklist-Community Version (ABC-C; Aman et al., 1985) is a 58-item questionnaire
- **DBC-P Version.—**The DBC-P (Einfeld & Tonge, 2002), is a 96-item questionnaire used to assess behavior and emotional problems in youth ages 4–18 years with developmental and intellectual disabilities

Developmental Measures

- **Bayley Scales of Infant and Toddler Development, Third Edition.—**
- Neurodevelopment was assessed at each visit with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2005)
- **Vineland Adaptive Behavior Scales, 2nd Edition.—**The Vineland Adaptive Behavior Scales, 2nd Edition

Am J Intellect Dev Disabil. Author manuscript; available in PMC: 2022 Feb 1.

Published in final edited form as: Am J Intellect Dev Disabil. 2022 Jan 1;127(1):1–10. doi: 10.1352/1944-7558-127.1.1

Anxiety in Angelman Syndrome

Stacey C Grebe [1], Danica L Limon [2], Morgan M McNeel [3], Andrew Guzick [4], Sarika U Peters [5], Wen-Hann Tan [6], Anjali Sadhwani [7], Carlos A Bacino [8], Lynne M Bird [9], Rodney C Samaco [10], Leandra N Berry [11], Wayne K Goodman [12], Sophie C Schneider [13], Eric A Storch [14]

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PMCID: PMC8803540 NIHMSID: NIHMS1771053 PMID: 34979033

Treatment?

- 26% percent of the sample (n = 11) was classified as experiencing elevated anxiety through a questionnaire, parents' interpretation, young sample (other series 40-50%)

- How do we identify anxiety in Consultation?
  - Eating anxiety? Is Hyperfagia alone?
  - Estereotipies?
  - Irritability? Is it desconfort? Is there a medical cause beneath?
  - Self regulation actions (Bitting clothes or objects...)

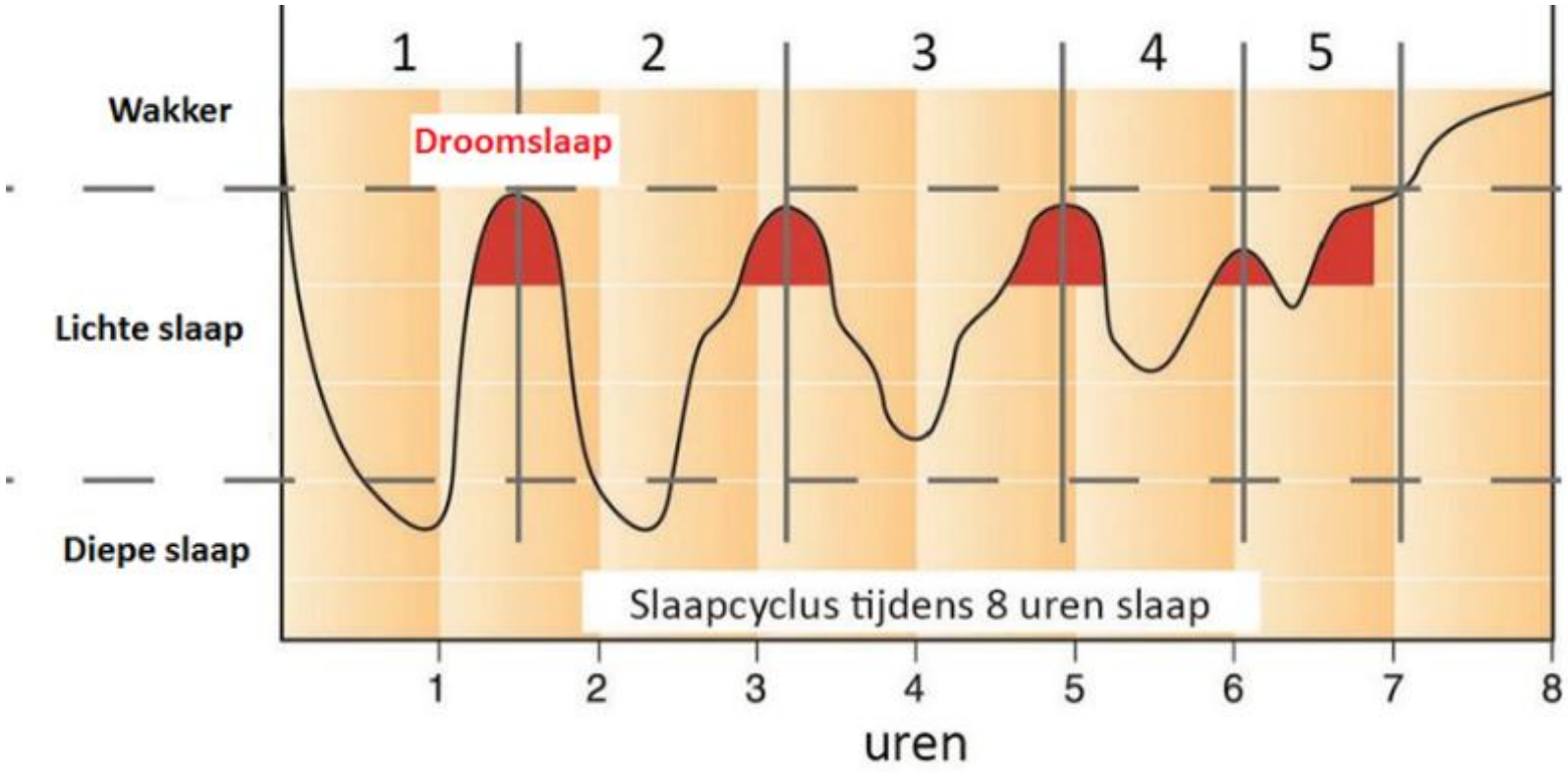
Cognitive training?
Relaxing techniques?
Medical treatment? Sertraline?
Aripiprazol?

Sleep problems

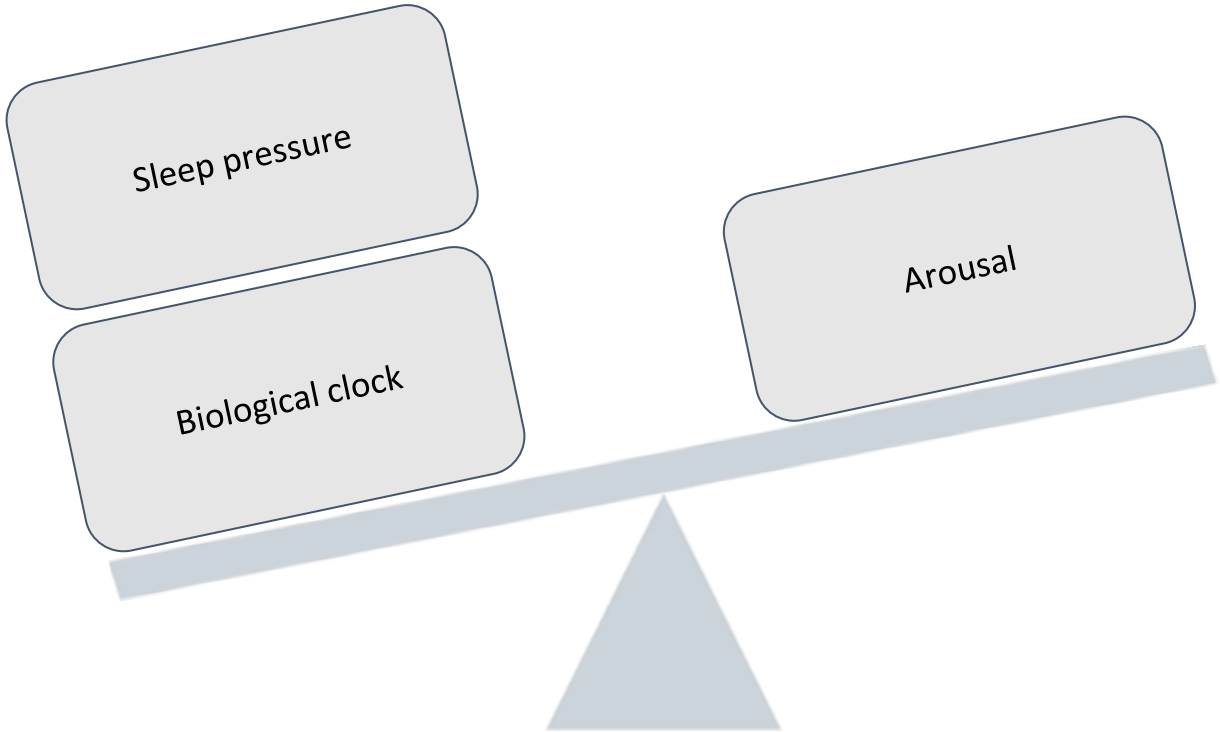
- Sleep problems in AS 50-90%
- Settling, sleep onset latency, frequent awakenings and/ or early awaking
- Mostly in children, but can persist into adulthood
- No genotype difference
- Biological, physical and behavioral factors
- Large impact on the family
- Intervention options an unmet clinical need

Bindels-de Heus et al., 2020; Bruni et al., 2004; Didden et al., 2004; Goldman et al., 2012; Grieco et al., 2019, Khan et al., 2019; Pereira et al., 2020; Spruyt et al., 2018; Trickett et al., 2017, 2018, 2019, Wheeler et al., 2017, Willgoss, 2021

Sleep problems: normal sleep architecture

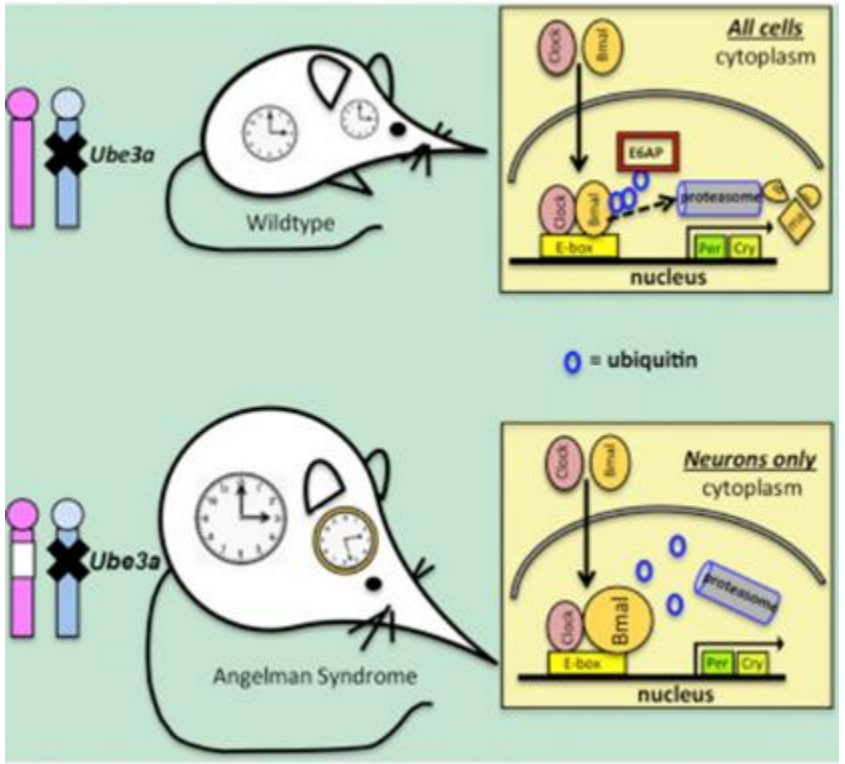


Sleep problems: sleep balance



Sleep problems: biological factors

- UBE3A involved in circadian rythm regulation
- Polysomnography: disturbed sleep architecture, delayed sleep phase
- Melatonin peak later and lower



Braam, 2008, Miano, 2004, Shi, 2018, 2022, Takaesu, 2012

Sleep problems: physical factors

- Side effects medication
- Upper air way problems, OSAS, central apnoeas, OME
- GER/ micro-aspiration
- Constipation
- Pain/ discomfort
- Epilepsy
- Itch
- Nightly feeding

Sleep problems: behavioral factors

- Behavioral problems don’t stop at night…
  - pervasive behavior and hyperactivity
- Sensory processing issues
- Emotional regulation, limited self-soothing skills
- Anxiety, separation anxiety
- Developmental age not synchronised calender age (both ways!)
- Environmental factors:
  - family stress
  - housing issues (noise, more children in 1 room etc)
  - safety issues

Allen 2013, Egan et al., 2020, Goldman et al., 2012; Pelc et al., 2008, Spruyt et al., 2015; Trickett et al., 2019

Sleep problems: diagnostics

- History taking:
  - sleep schedule, bedding rituals, sleep hygien, differences school- and weekend days and location, mobility, being outside, medication, stressors etc
- Physical examination
- Sleep questionnaires:
  - Sleep Behavior Questionnaire (SP-SQ)
  - Slaap Hygiene Balance for Children (SHBK)
  - Sleep Disturbance Scale for Children (SDSC)
- Sleep diary
- Actigraphy
- Videosomnography
- Polysomnography

Sleep problems: treatment

- General sleep advices including sleep hygiene
- Behavioral techniques
- Medication

Sleep problems: general sleep advices

- Sufficient exercise and sunlight exposition
- Bedroom dark & cool and only for sleeping, if possible soundproof
- Sleeping bag, zipper on the back
- Tent or high fence bed
- Weighted blanket, deep pressure massage
- > 1 pacifier in bed…
- Sleep ritual:
  - fixed bed times, also in weekends
  - cooling down min 30 min before bedtime, no screens
  - sleep ritual same all caregivers, max 30 min

Sleep problems: general sleep advices

- Bed time should suit age
- Evaluate day program
- Use AAC for day and night concept
- Falling asleep in own bed
- Sleeptrainer for early birds
- Evaluate function of sleep problem?
  - anxiety, need for closeness
  - attention seeking
  - I'm on, so you should be too…

Allen et al., 2013, Didden & Sigafoos, 2001; Jan et al., 2008; Spruyt & Curfs, 2015, Bindels et al, 2023

Sleep problems: general sleep advices & techniques

- When awake at night:
  - Don’t get the child out of its bed/ bedroom
  - Use dim light, low voice
  - No food (of course if possible!)
  - Repeat part of the evening ritual
  - Camera in bedroom, only go if necessary
- Behavioral techniques:
  - Bedtime fading
  - Gradual distancing
  - Differentiated extinction

Allen et al., 2013, Didden & Sigafoos, 2001; Jan et al., 2008; Spruyt & Curfs, 2015, Bindels et al, 2023

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Sleep problems in children with Angelman Syndrome: The effect of a behavioral intervention program

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Sleep problems: medication

- Melatonin:
  - indications
    - 1. influence biological clock:
      - max 0.3-0.5 mg, fixed time, around 18.00/ 19.00
    - 2. diminish arousal:
      - 0.1-2 mg, 30-60 min before sleeping
    - 3. sleeping in and through the night with ASS
      - long-acting version option, 0.5-5 mg, short time before sleeping
    - wash-out 2 weeks in case of accumulation
  - Antiallergic drugs: alimemazine, hydroxyzin, ketotifen, promethazine (> 2 jaar)
  - Clonidin
  - Pipamperon
  - Clobazam in case of epilepsy
  - Gabapentin

Gastro-intestinal problems

1. Swallowing problems
2. GER/ gastric motility problem
3. Constipation

Gastro-intestinal problems: swallowing

Eating behavior:

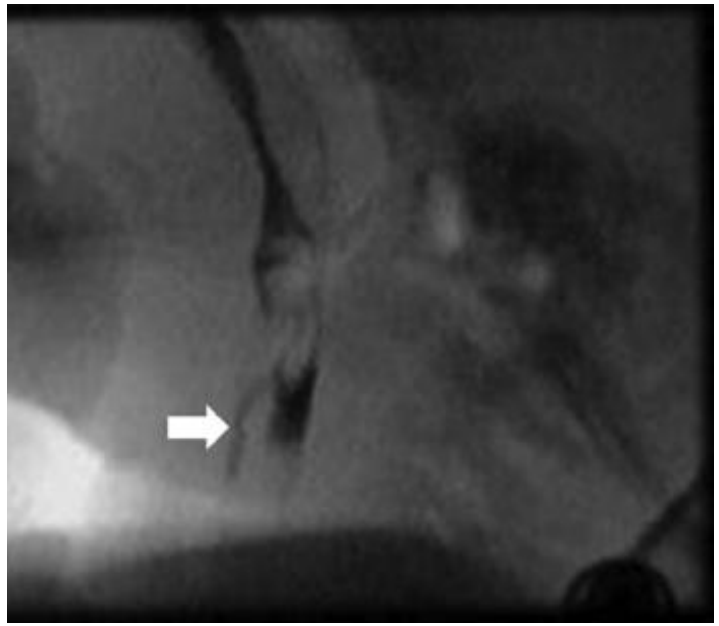
- tendency to stuff without chewing
- real risk of choking
- control eating: offer small bites

Glassman, 2016, Bindels, 2020

Gastro-intestinal problems: swallowing

Swallowing dysfunction with risk of micro-aspiration:

- deletion subtype most affected
- gurgling, gagging, coughing during or after eating, but mostly drinking
- sometimes only symptom is recurrent pneumonia!
- swallowing function evaluation by speech- and language therapist
  - clinical
  - radiographic swallowing video with contrast
- treatment:
  - thickening fluids
  - adjustments in posture etc
  - sometimes need for percutaneous gastric tube



Glassman, 2016, Bindels, 2020

Gastro-intestinal problems: swallowing

angelman SYNDROME FOUNDATION

FAMILIES. RESEARCH. CLINICS. COMMUNITY.

WITH YOU FOR THE JOURNEY.

Aspiration Prevention in Angelman Syndrome

A Practical Guide for Caregivers and Care Teams

What is Aspiration?

Aspiration happens when food, liquid, saliva, or other substances are not swallowed correctly and enter the airway instead of going down the esophagus to the stomach. In individuals with Angelman syndrome (AS), aspiration may go unnoticed (silent aspiration) and can lead to:

- Recurrent pneumonia or respiratory infections
- Chronic coughing or choking
- Poor weight gain or nutrition challenges

https://www.angelman.org/wp-content/uploads/2025/04/ASF_Aspiration-Prevention_Apr2025.pdf

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Gastro-intestinal problems: GER/ gastric motility

- GER:
  - 40-44%, persists into adulthood, deletion subtype most affected
  - can lead to micro-aspirations and oesophagitis
  - treatment:
    - tickening fluids
    - proton pomp inhibitor
    - prokinetic
- Gastric motility disorder
  - mostly cause of GER
  - can worsen over time
  - treatment:
    - blended diet
    - semi-elementary feeding
    - continuous feeding
    - sometimes need for postpyloric feeding: duodenal tube, PEG-J, jejunostomia

Glassman, 2016, Bindels, 2020

Gastro-intestinal problems: constipation

- Highly prevalent, 38-71%
- Persists into adulthood
- Deletion subtype most affected
- Hard stools, low frequency, abdominal distention and pain
- Can lead to worsening of GER, epilepsy and/ or behavioral problems
- Treatment:
  - sufficient fluid and fiber intake and exercise
  - osmotic laxative: macrogol 4000/ polyethylene glycol 3500
  - as needed rectal enema

Glassman, 2016, Bindels, 2020

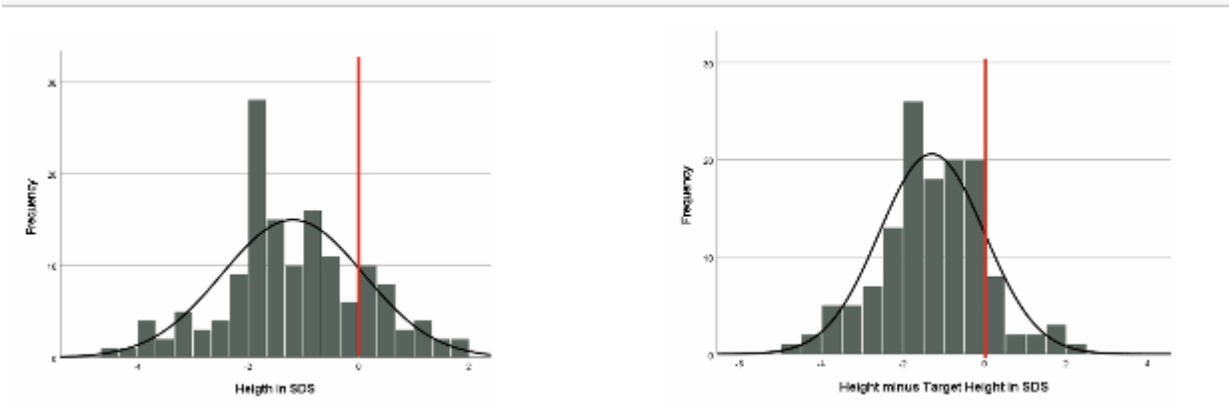
Hyperphagia

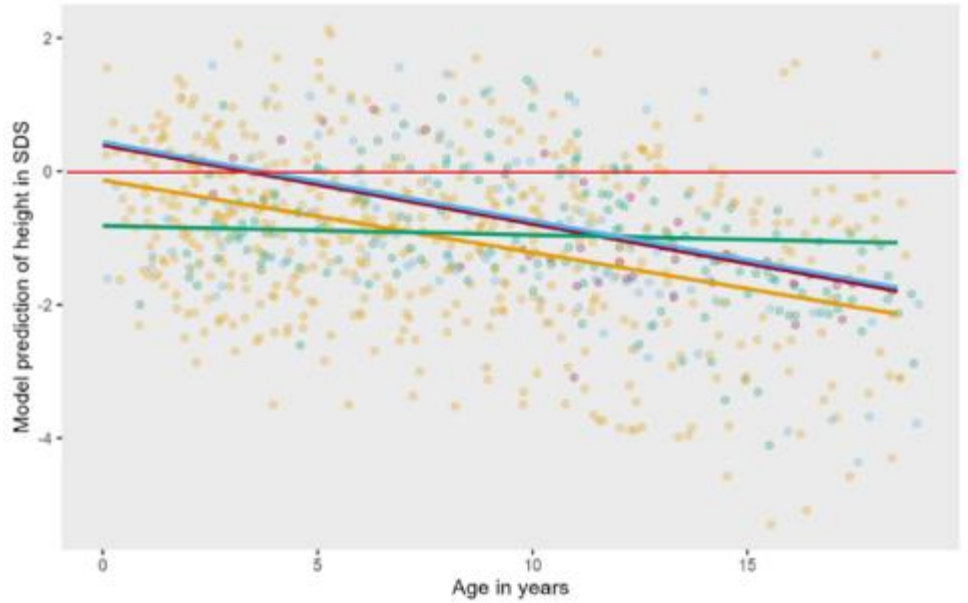
- High interest in food
- Hyperphagia questionnaire Dykens: mean score 25 (11 = no interest, 55 is extreme interest)
- Almost comparable with children with Prader Willi Syndrome (means around 27)
- No genotype differences!
- Higher score associated with higher BMI
- Mechanism?
  - *UBE3A* involved in circadian rhythm regulation
  - sensory processing issues
  - lower impuls control in ID

Bindels, 2020 & 2024, Andrews, 2024

Growth: height

- Lower mean height
  - -1.2 SDS
  - 144 children
  - no genotype difference
  - also compared to target height
- Height SDS decreased with age
  - 822 measurements
  - decrease starts around age of 6 years
  - children with a mutation seem less affected
- Study in Israel same findings
  - 88 patients, 280 measurements
  - final height -1.2 SDS
  - lower IGF-1 levels, mean -0.55 SDS
  - deletion subtype more affected
- Mechanism unknown





Bindels, 2020 & 2024, Gruber 2023

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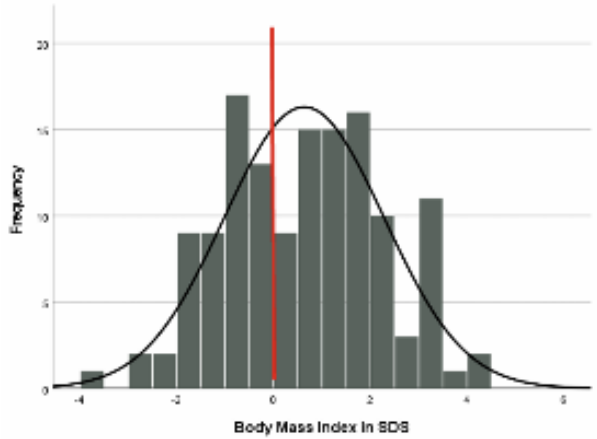
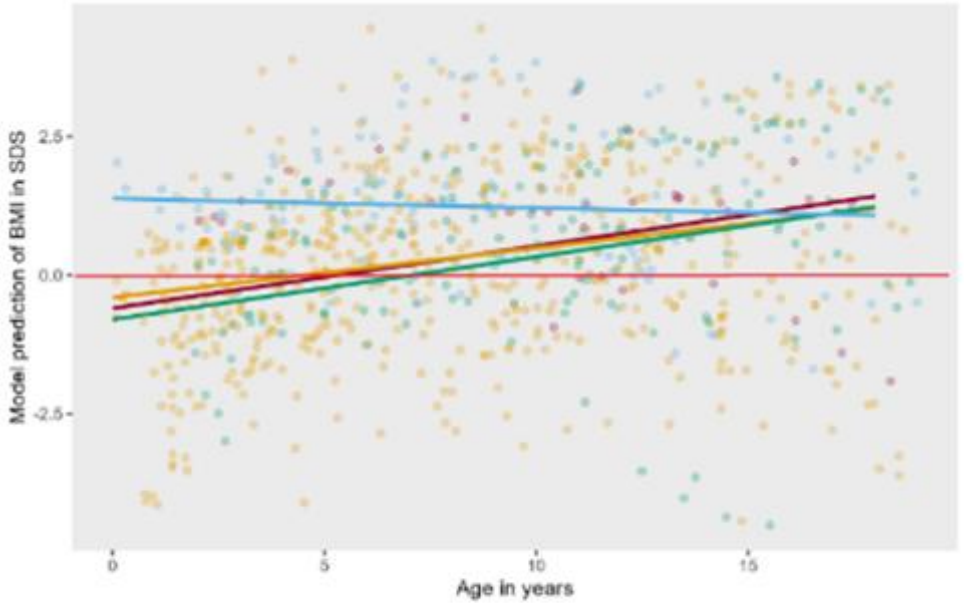
Growth: weight/ BMI

- Higher mean BMI
  - 145 children
  - +0.4 SDS deletion subtype
  - +1 SDS non-deletion subtypes
  - 21% BMI >1 - < 2 SDS (overweight)
  - 19% BMI > 2 SDS (obesity)
- BMI SDS increases with age
  - 853 measurements
  - no significant genotype differences
- Mechanism unknown
  - *UBE3A* involved in circadian rhythm regulation and nuclear transcription hormone receptors
  - hyperphagia and higher BMI associated





Bindels, 2020 & 2024

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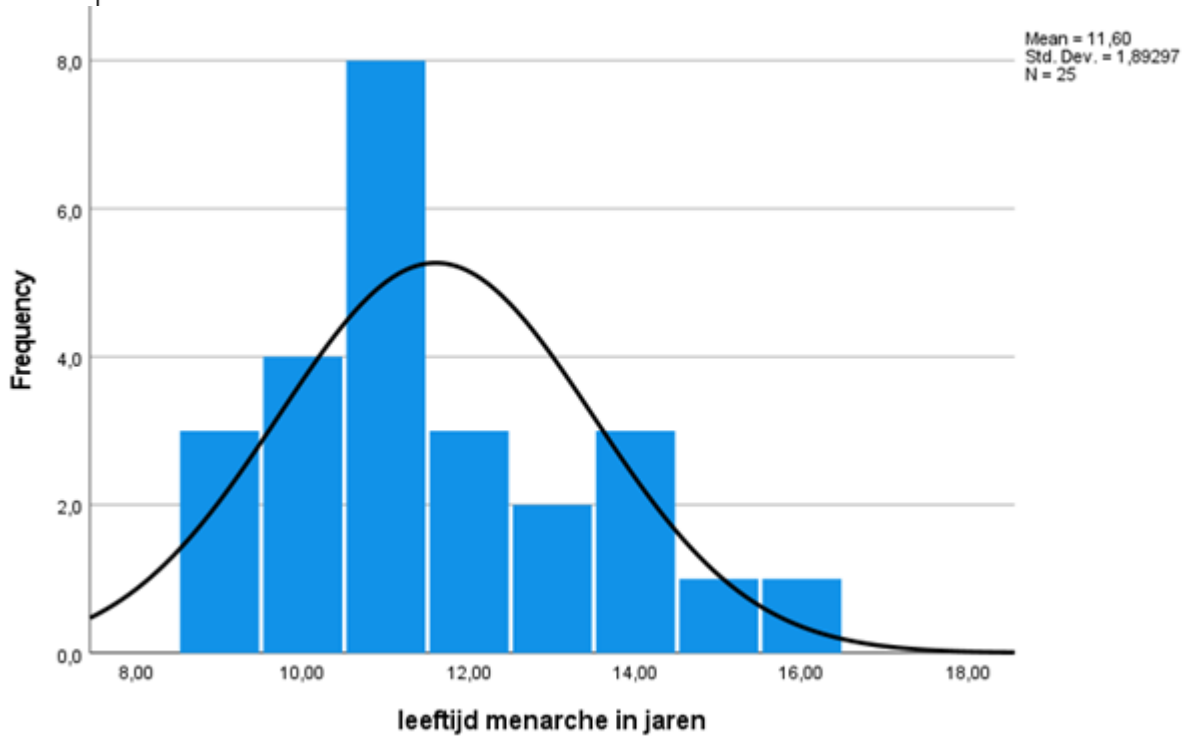
Growth

- Nutritional assessment dietician
- Exercise
- Instruct family on use of treats
- If height decreases < -2 SDS and/ or BMI > 1 SDS, pediatric screening

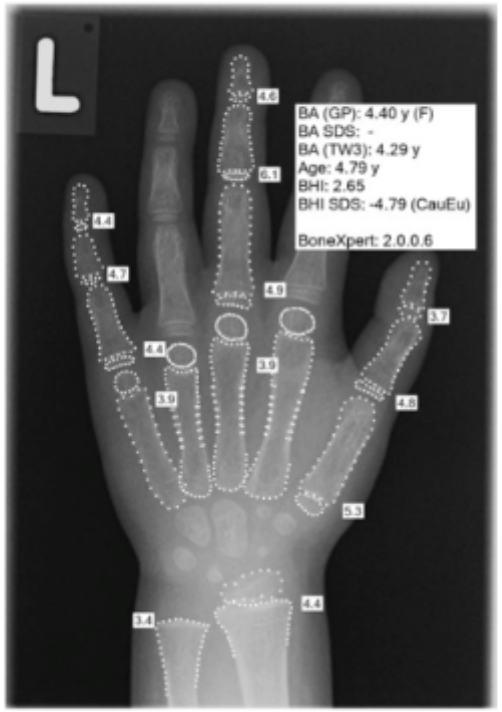
Further research needed on endocrine function, body composition, energy expenditure and role of exercise

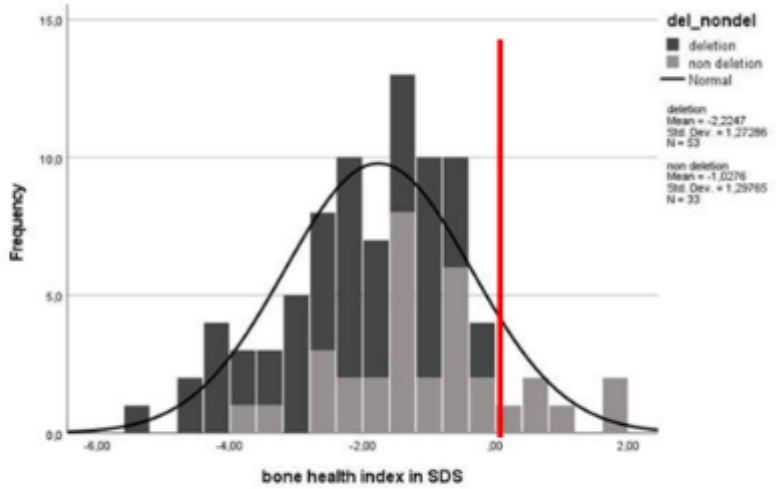
Puberty

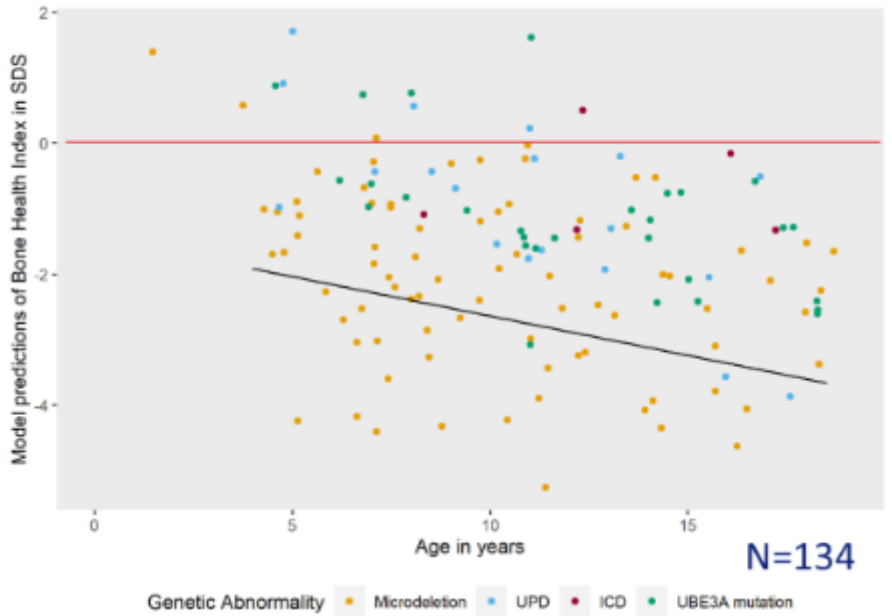
	Girls (N)	Boys (N)	Total (N)
Prepubertal	27	32	59
Early	3	-	3
Normal	33	38	71
Late	4	8	12
Total	67	78	145



Bone health







BHI-SDS low and significantly lower in deletion group

BHI-SDS significantly decreases with age

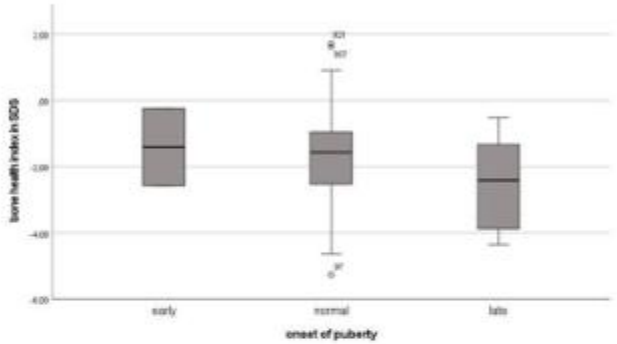
	Deletion	Non-deletion	Total	N
BHI-SDS (SD)**	-2.22 (1.3)	-1.02 (1.3)	-1.77 (1.4)	86

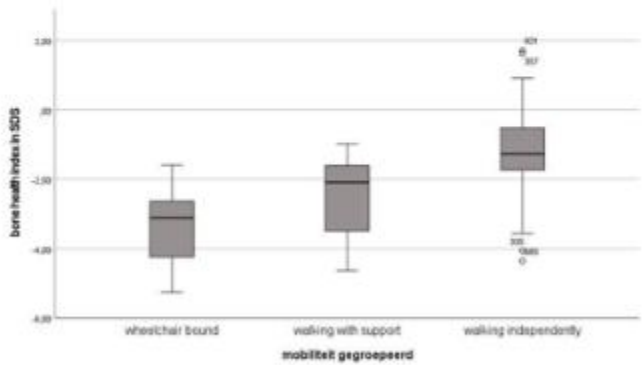
** *Significant difference between deletion & non-deletion (P<.001)*

Bindels, 2024

Bone health

		Mean BHI-SDS (SD)	Uncorrected for covariates	Corrected for predictors and covariates	N
Genotype	*Deletion*	-2.22 (0.2)	**<.001**	**.027**	53
	Non-deletion	-1.02 (0.2)			33
	UPD/IDC	*-0.93 (1.5)*			*16*
	UBE3A	*-1.1 (1.1)*			*17*
Sex (m/f)	*Male*	-1.85 (1.1)	.579	.439	47
	Female	-1.66 (1.7)			39
Epilepsy	*Yes*	-1.89 (1.4)	**.031**	.380	72
	No	-1.13 (1.5)			14
AED yes/no	*Yes*	-1.92 (1.4)	**.026**	.629	71
	No	-1.04 (1.5)			15
VPA	*No*	-1,24 (1.2)	**<.001**	.476	50
	Yes	-2.41 (1.4)			41
AED number	*1*	-1.57 (1.5)	**.029**	.767	30
	2	-1.99 (1.2)			26
	3 or more	-2.46 (1.2)			15
Mobility: *Walking independently*		-1.23 (1.2)	**<0.001**	**<.001**	54
Walking with support		-2.44 (1.1)			20
Wheel chair		-3.30 (1.1)			10
BMI			.521	.398	87
Vitamin D	*Yes*	-1.98 (1.7)	.398	-	30
	No	-1.70 (1.3)			52
Walking ability duration			.152	-	54
Onset of puberty	*Early*	-1.41 (1.7)	.329	**.036**	2
	Normal	-1.78 (1.4)			47
	Late	-2.53 (1.4)			9
Age menarche			.404	-	16





Bone health

- 22% one or more fractures with significantly lower BHI (-2.60 SDS) vs children without (-1.56 SDS)
- Prevalence of # and BHI-SDS in adulthood?
- DEXA versus BoneXpert discussion
- Secundary low bone health
- Primary factors?
  - *Role of UBE3A gene in hormone receptor function?*
  - *NIPA2 gene in deletion type involved with bone turnover?*

➢ Further research needed

➢ Preventive measures:

  ➢ *Sun exposure, vit D suppletion, choice of AED, late puberty, mobility!*

  ➢ *X-hand at the age of 7, 13-14 and 17*

  ➢ *Consider bisphospanate when osteoporosis is diagnosed*

Bishop, 2014, Edouard, 2020, Shalof, 2021, Zhao, 2020

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AS in adulthood: health issues

- 2 large cohort studies
  - den Besten: 95 adults, age 18-83
  - Larson: 110 adults, age 16-50
- Main health problems:
  - epilepsy 41- 57%
  - sleep problems 65 - 72%
  - behavioral problems 86 - 72%
  - GER 33 - 47%
  - constipation 90 - 85%
  - overweight & obesity 37 - 32%, female >> male
  - hyperphagia 45 - 50%
  - scoliosis 42 - 50%
  - fractures hip/ femur 7% (Larson)

den Besten, 2020, Larson, 2015

AS in adulthood: daily functioning

- walking independently 65 & 68%
- **decline in mobility 49% (den Besten)**
- eating independently 59 & 71%
- use of gestures 26-68%, picto's 28-33% and speech generators 4-15%
- toilet trained daytime 50 & 39%
- over time improvement: hyperactivity!
- over time declination:
  - daily living skills > age 60
  - mobility > age of 40

AS & mortality

- Normal life expectancy
- 2013 Facebook group “sharing causes of mortality in AS” started
- Data combined with Global Registry and NHS
- 2022 analysis of 220 reported deaths from 19 countries
  - range 1-78 years of age
  - 150 known cause
  - causes varied with age
  - leading causes:
    - respiratory illness
    - accidents
    - seizures
    - SUDEP
    - cancer

Gomes, 2024

AS & mortality

TABLE 1 | Reported causes of death in people with Angelman syndrome, by age group.

Cause of death	Ages 1–5	Ages 6–12	Ages 13–18	Ages 19–29	Ages 30+	Totals
Pneumonia/respiratory illness	3	5	5	14	5	32
Accidents	6	13	3	5	1	28
Seizures	7	5	0	9	2	23
Sudden unexpected death in sleep (SUDS)	2	3	5	3	4	17
Cancer	0	2	0	5	10	17
Post-operative complications	1	2	4	4	0	11
Homicide (Filicide)	1	0	3	2	0	6
Sepsis	0	2	2	0	0	4
Meningitis	0	2	0	0	0	2
Heart failure	0	1	0	0	1	2
COVID-19	0	0	0	1	1	2
Renal failure	0	0	0	0	2	2
Bowel perforation/obstruction	0	0	0	0	2	2
Unexpected death	0	0	1	0	0	1
Pancreatitis	0	0	0	0	0	0
Neurodegeneration	0	0	0	0	1	1
Pulmonary fibrosis	0	0	0	0	1	1
Unspecified illness	0	1	2	4	4	11
No cause listed	11	9	5	16	17	58
Totals	31	45	30	63	51	220

Gomes, 2024

European Reference Networks ITHACA

AS & mortality

- Respiratory illness
  - high prevalence in people with intellectual & motor disabilities
  - risk factors are micro-aspiration and diminished mucus clearance
- Accidents
  - leading cause in children
  - drowning specific risk
- Seizures
- SUDs/ SUDEP
  - not previously reported in AS
  - difficult diagnosis, per excusionem
- Cancer
  - leading cause in adults, no specific type of cancer
- Filicide in 6 cases…

Gomes, 2024

European AS network for professionals

European Reference Networks ITHACA

European AS network for professionals: why & how

- **Access to an Expertise Center for every individual with Angelman Syndrome in Europe**
- Supporting professionals in (set up of) AS care in Europe
- Enhancing quality of care
- Collaborating in large cohort studies
- Prepare for future therapeutic options
- How?
  - online and live meetings
  - development of European AS guideline (with help of ERN Ithaca)
  - share parent information materials
  - set up a database format for individual use and a medical database board
  - cohort studies with use of standard scripts, combined meta-analysis
  - working group PhD's
- Interested?

angelman@erasmusmc.nl

European Reference Networks ITHACA

Discussion time - Conclusion with speakers and moderator

Discussion & Conclusion

- Time for questions

- Satisfaction Survey :
  - https://forms.office.com/e/BfFD5F6U99
- Website :
  - https://ern-ithaca.eu
  - https://ern-ithaca.eu/webinars/

Thank you for your participation