



KLEEFSTRA SYNDROME AND MENTAL HEALTH

November 10, 2017 (10:00am EST)



Advancing drug development for
Kids with Intellectual Disability Syndromes

Submit Your Questions



To send in questions, please use
WebEx's Q&A feature

(located on the right-hand side of your screen, or at the top of your screen if you're in full view mode).

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What We'll Cover Today



- ❑ What is Kleefstra syndrome (KS)
- ❑ What is the relationship between KS and mental Health
- ❑ Clinical Research
- ❑ Regression
- ❑ Treatment options
- ❑ Q&A session

Today's Webinar Panelists



Braden Root-McCaig (Moderator)

- ▣ Executive Director, K.I.D.S. IQ Project



Dr. Karlijn Vermeulen

- ▣ Child and Adolescent Psychiatrist, Junior Researcher, Nijmegen, The Netherlands



Dr. Miranda Coberman

- ▣ General Physician, Mother of KS child

Conflicts of Interest



Conflicts of interests	None
Cooperation with pharmaceutical companies	None
Research finances •Grant	•AGIKO grant (2013) from Radboud University Nijmegen, the Netherlands, Donders Institute.

EHMT-1 Gene

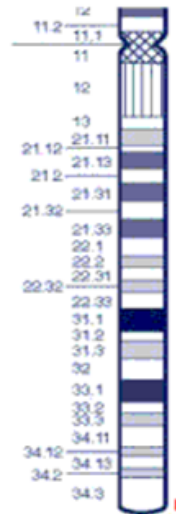
Location: 9q34.3

Gene defect:

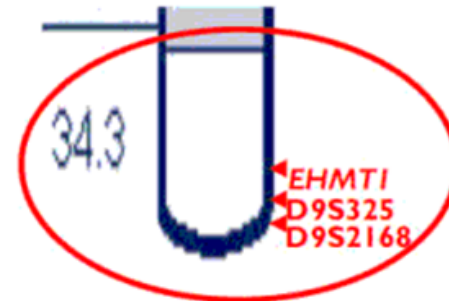
- microdeletion
- Intragenic mutation

Function:

- Histone modulation



The long arm of chromosome 9. The red line marks the approximate site of the 9q34.3 deletion. The diagram below shows an enlargement, with approximate site of the *EHMT1* gene and two markers commonly used in FISH diagnosis.



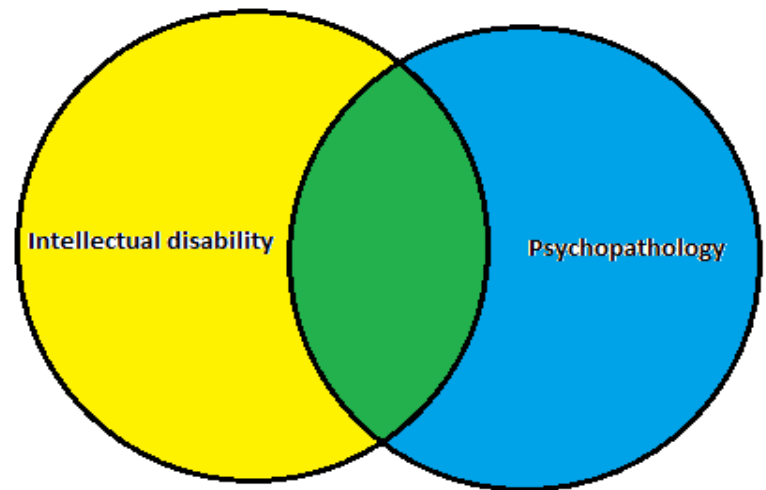
Kleefstra Syndrome

- ❑ Caused by EHMT1 gene microdeletion/mutations



Examining behavior in people with intellectual disabilities

- Attribution to the intellectual disability or not?
- ▣ Start with investigation of their normal functioning rather than focus on behavioral problems
 - Developmental age

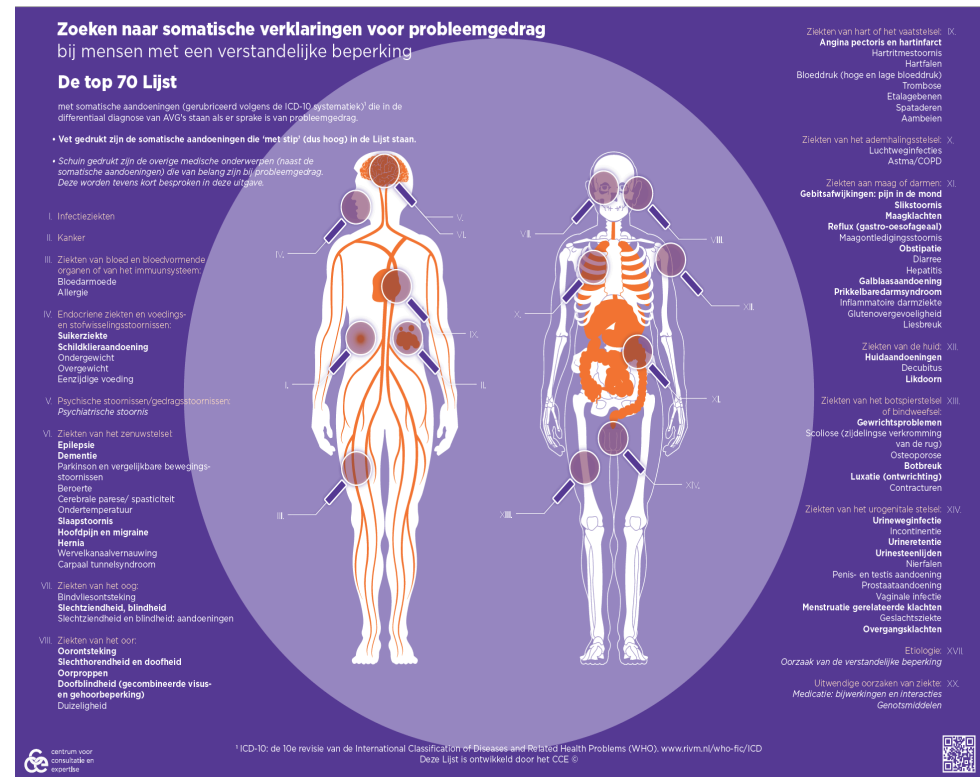


Behavioral problems? Rule out a physical cause first

- Over 70 physical illnesses can present with problem behaviors!

- **KS**

- Infections/inflammation
- Hormonal problems
- epilepsy
- Heart disease



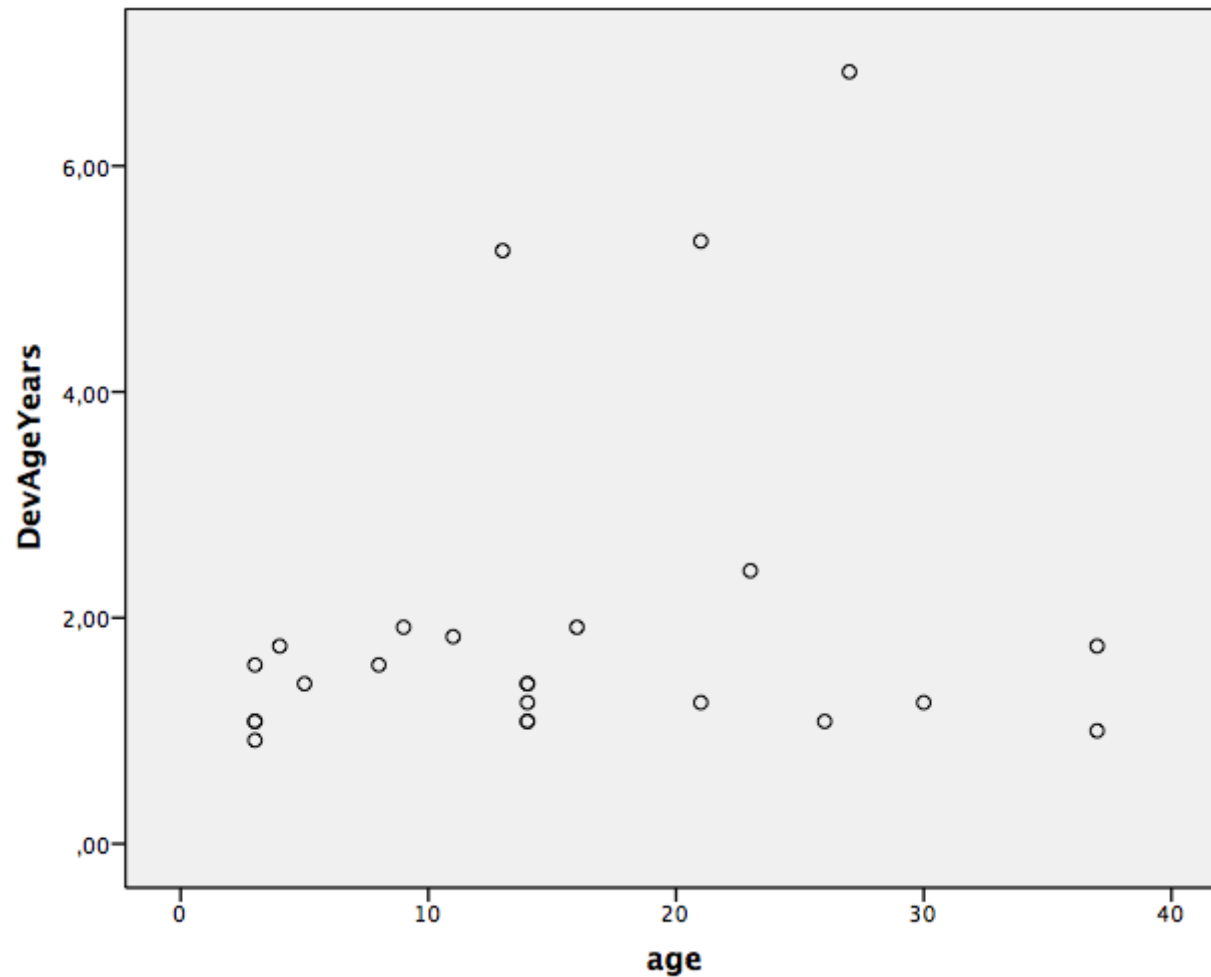
Study subjects

N (number)= 24 patients with KS

- comprising causative microdeletions as well as mutations
- Biological age= 3- 37 years (9 adults (>18 years), 15 children (<18 years). *Mean age 15,4 years.*

Assessments included: level of daily functioning, interviewing parents about psychiatric symptoms, psychiatric observation.

Results: Adaptive functioning



Results: total psychiatric comorbidity

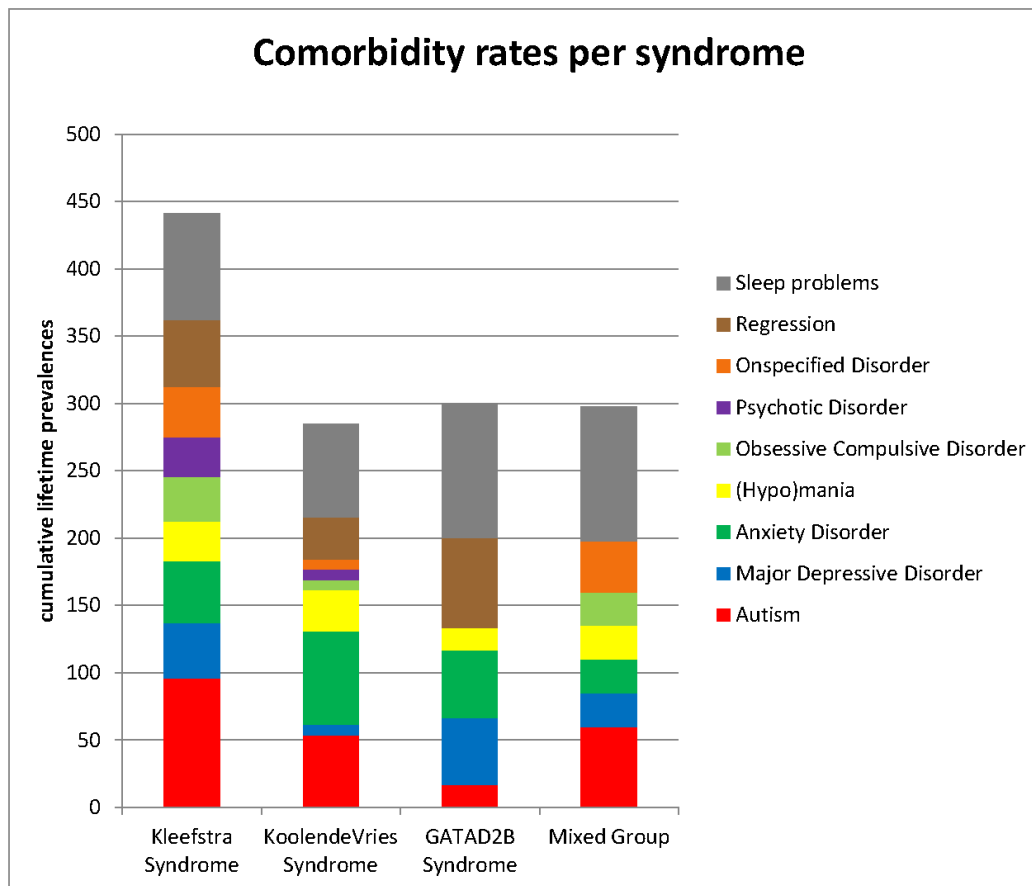


Figure 3: Comorbidity rates per syndrome. At the Y-axis are the cumulative lifetime prevalences (expressed in percentages) for each of the psychopathology categories.

Regression

- **Definition:** loss of skills

- EX: stops talking in words/ sentences (only vocalising)/ ability to walk or cycle/ toilet trainedness

Kleefstra Syndrome

- Most patients >18 years (biological age)
 - Starting age ≥ 12 years of age (but the eldest were around 25-30 years before they got their first episode)
 - Often there is a hormonal shift at that particular moment
 - Pubertal hormones
 - Shift/ start of contraception meds
 - But also... falling in love (which is of course puberty related ;-))
- >30% loss of functioning on the Vineland scale of daily functioning
- **Preceded by sleep problems (extreme!)**

Regression

CASE REPORT

Sleep Disturbance as a Precursor of Severe Regression in Kleefstra Syndrome Suggests a Need for Firm and Rapid Pharmacological Treatment

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Hans van Bokhoven, PhD,‡§// Jos I.M. Egger, PhD,¶#** and Tjitske Kleefstra, MD, PhD,‡§*

Regression

Summary of clinical features

	Case 1	Case 2	Case 3
	Sex/age genetic defect Female, 15 y <i>EHMT1</i> mutation c.3072_3073del (p.Val1026fs)	Female, 23 y 46,XX.ishdel(9)(q34.3) no micro array data available	Female, 23 y 450 kb deletion (140.67–141.12) Hg19
Current psychiatric diagnosis	Bipolar I disorder, manic episode	Major depressive episode with psychotic features	Psychotic disorder, not otherwise specified
Effective pharmacological intervention	Olanzapine additional to valproic acid	Aripiprazole 15 mg daily	Clozapine, 50 mg daily
Medical history	Perinatal complications Regurgitation Developmental delay Mild hearing and visual difficulties Irregular periods Extreme constipation polydipsia- and polyuria	Developmental delay Constipation Irregular periods	Pulmonary surgery Recurrent upper airway infections Developmental delay Hypertension Constipation Behavioral problems during (irregular) periods
Psychiatric history	ASD and ADHD Mood disorder	ASD	ASD symptoms
Somatic medication	Desmopressin Macrofol	Provera	Macrofol Oral contraception
Regression: lost skills	Talking Continence	Talking in sentences Dressing and personal hygiene Simple reading and writing	Talking Dressing Continence Swimming Decency
% Decline in developmental age	29	37	54
Absolute reduction of VABS score, points	49	45	96

*Based on the population KS patients in the Netherlands and Belgium (N = 24).

[†]Based on the Autism Diagnostic Observation Scale-2nd version (ADOS-2). The total score of 1 subject was below the “high suspicion cut-off” due to severe sedation, which made it impossible to evaluate several key items of the ADOS-2. Another subject dropped out, because he became too aggressive to complete the ADOS2 schedule.

[‡]Not all the participants completed their puberty at this age.

[§]Sleep disturbances and regression measured by the mini Psychiatric Assessment Schedule for Adults with Developmental Disabilities interview (interviewing relatives).

^{||}Measured by the percentage reduction of the total score on the VABS.⁵

Regression (2)

- Paradoxical reaction on benzodiazepines
 - ▣ Results in severe aggression or exhaustion → forced admissions
 - ▣ Olanzapine in high dosages seems to work best to acutely restore sleep
 - ▣ As soon as the sleep recovers, the dosage is right.
- Hypothesis: psychotic development, resulting neuronal loss and an old-fashioned “dementia praecox”
 - ▣ Characterised by loss of functioning. (Bleuler, Kraepelin)

Regression (3)

□ **Psychotic disorder: characteristics in Kleefstra Syndrome**

- “positive” symptoms: disorganisation, sometimes observable hallucinations, aggressive outbursts
- “negative” symptoms: 4 “A”s= Apathy, Avolition (loss of motivation), Affect flattening (no/less facial expressions) and Awake (stop sleeping).

→ Best results on Olanzapine and Clozapine for acute phase (but side-effects occur!! So close monitoring is needed!)

□ **Sometimes this psychotic disorder mixes with mood problems:**

- Manic symptoms: non-stop vocalisation (“verbal diarrhoea”), increased motor activity

→ Olanzapine is still first choice, but sometimes Lithium or Valproic acid need to be added.

Even if it is well-treated and recovery occurs, another episode may start

What To Do When Your Child Shows Behavioral Problems

- Find entrance to a doctor (young ones → pediatric, older ones → GP)

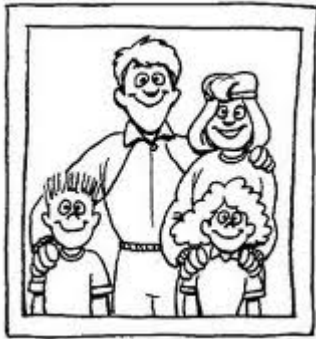
Instruments & Procedures:

- Medical doctor should exclude a physical reason for the problem behavior
- Psychiatrist perform a psychiatric observation:
 - ▣ Direct (with a familiar person close)
 - ▣ Also indirect, by watching short video's that parents made
- interview with parents (Vineland, mini PAS-ADD)
- Play observation (ADOS-2) with participant
- Simplified CANTAB with participant (special touchscreen)



Questionnaires to screen for behavioral issues seem not to measure behavioral problems, but rather complexity of the clinical picture and/ or parental stress (e.g. CBCL)

Family Functioning



- General Functioning:
mean score 1,9
- Cut-off for pathological scoring= 2.17.
- In our sample (n=23) 30,7% of the families were suffering from pathological family functioning.



This is higher than in other chronic diseases of childhood

- ▣ *Diabetes mellitus* → 1,76
- ▣ *“simple” ADHD* → 1,75

Puberty

- Early in girls if younger than age 8.
 - ▣ Signs are formation of breast buds.
- Spots are not signs of premature puberty.
- Early in boys if younger than age 10.
 - ▣ Signs are growth of the external genitalia.
- Investigations for premature puberty are complex and include blood tests, MRIs, CTs and X-rays for bone age.
 - ▣ There are reported cases of premature puberty with deletions involving chromosome 9, hence the relevance for KS.

Advantages vs Disadvantages of delaying puberty

- Not extensively studied, especially not in the intellectually disabled population.
 - ▣ Potential Advantages;
 - Possible more emotional maturity /cognitive development prior to possible regression.
 - Possible increased height (if this is an advantage ?)
 - ▣ Potential Disadvantages;
 - Possible negative impact on bone density (osteopenia or bone thinning)

Sleep Disturbances

If persistent/prolonged/unusual;

- ▣ Exclude medical causes;
- ▣ Reflux/constipation.
- ▣ ENT
- ▣ Dental
- ▣ Orthopaedic
- ▣ Restless legs (iron deficiency)
- ▣ Neurological (Esp nocturnal seizures)
- ▣ EARLY PSYCHIATRIC INPUT WHILST THE ABOVE IS HAPPENING ESPECIALLY IF AROUND PUBERTY OR POST PUBERTY.

Thanks to:

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kinder- en jeugdpsychiatrie
karakter



Key Takeaways

- High prevalence of autism spectrum disorders, measured by “ golden standard” (almost 100%)
(Vermeulen et al, 2017, AJMG-a)
- High prevalence of regression (hypothesis: psychotic disorder) and requires a specific treatment (Vermeulen et al, 2017, Clinical Neuropharmacology).
- Treatments are symptomatic
- Parents have to deal with a lot of stress:
 - ▣ Please take care of yourself and of each other