The Journey of Kleefstra syndrome and the EHMT1 gene

Tjitske Kleefstra
Clinical Geneticist
ErasmusMC Rotterdam and Radboudumc Nijmegen, The Netherlands
Disclosure

Center of excellence in neuropsychiatry Vincent van Gogh
Starting 2002...
Monogenic Neurodevelopmental disorders NDDs

- The neurodevelopmental disorders are a group of conditions with onset in the developmental period.

DSM-5, 2013
Typical NDD patient we see

- Intellectual disability or developmental delay (87%)
- Autism spectrum disorder (10%)
- Hearing impairment (7%)
- Oral cleft (6%)
- Seizures (24%)
- Visual impairment (3%)
- Scoliosis (5%)
- Congenital heart defects (11%)
- Polydactyly (1%)

- Prevalence 2% population
- Over 1600 different ‘Mendelian’ genes

Deciphering Developmental Disorders study
Wright C. et al, 2015
The humane genome: chromosomes and genes

Human Genetics Nijmegen

Willemsen & Kleefstra; Clin Genet 2013
Making headway with genetic diagnostics of intellectual disabilities.
Subtle chromosomal rearrangements in children with unexplained mental retardation

Samantha JL Knight, PhD  •  Regina Regan, MSc  •  Allison Nicod, BSc  •  Sharon W Horsley, BSc  •  Lyndal Kearney, PhD  •  Tessa Homfray, MD  •  et al.  Show all authors

Published: November 13, 1999  •  DOI: https://doi.org/10.1016/S0140-6736(99)03070-6
Nijmegen XLMR team
Genotypes and Phenotypes in X-linked Mental Retardation: from families to genes and back

Tjitske Kleefstra
Translocation t(X;9)(p11.23;q34.3)
Breakpoints ZNF81 and EHMT1

Eu-chromatin Histon Methyl Transferase 1
Subtelomere 9q deletion by FISH

Knight et al, Lancet 1999
Dawson et al, Clin Genet 2002
Cormier-Daire et al, J Med Genet 2003
Report
Loss-of-Function Mutations in *Euchromatin Histone Methyl
Transferase 1 (EHMT1)* Cause the 9q34 Subtelomeric Deletion Syndrome

Tjitske Kleefstra\(^a\), Han G. Brunner\(^a\), Jeanne Amiel\(^b\), Astrid R. Oudekerk\(^a\), Willy M. Nillesen\(^a\), Alex Magee\(^b\), David Geneviève\(^b\), Valérie Cormier-Daire\(^b\), Hilde van Esch\(^d\), Jean-Pierre Fryns\(^c\), Ben C.J. Hamel\(^a\), Erik A. Sistermans\(^a\), Bert B.A. de Vries\(^a\), Hans van Bokhoven\(^a\)

**OMIM**

#610253
KLEEFSTRA SYNDROME

**Alternative titles; symbols**

CHROMOSOME 9q34.3 DELETION SYNDROME
9q- SYNDROME
9q SUBTELOMERIC DELETION SYNDROME

Gene map locus *9q34.3*

**TEXT**

A number sign (°) is used with this entry because of evidence that Kleefstra syndrome is caused by mutation in the EHMT1 gene (607001), which is located within the region of the chromosome 9q34.3 deletion syndrome.
EHMT1 after 2006....

- Genome First: broadening molecular and clinical spectra
- Clinical follow up/natural history
- Pre-clinical studies
- “Kleefstra syndrome type 2”
Rare genetic syndromes
Aim: optimal treatment through knowledge integration

Psychiatry

(Clinical) Genetics

‘personalised’ intervention strategies

Biology

Psychology
Neuropsychiatric deterioration

Kleefstra syndrome in three adult patients: Further delineation of the behavioral and neurological phenotype shows aspects of a neurodegenerative course*

Willem M.A. Verhoeven, Jos I.M. Egger, Karlijn Vermeulen, Bart P.C. van de Warrenburg, Tjitske Kleefstra

AMJG 2011; 155(10):2409-2415
Psychiatry in Kleefstra syndrome
Severe loss of function post-puberty!

Adaptive functioning: Vineland-Z: Clinical interview

![Graph showing regression](image)

<table>
<thead>
<tr>
<th>Vineland-Z Adaptive Behavior Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication (Com)</td>
</tr>
<tr>
<td>Daily living skills (Day)</td>
</tr>
<tr>
<td>Socialization (Soc)</td>
</tr>
<tr>
<td>Receptive</td>
</tr>
<tr>
<td>Personal</td>
</tr>
<tr>
<td>Interpersonal Relationships</td>
</tr>
<tr>
<td>Expressive</td>
</tr>
<tr>
<td>Domestic</td>
</tr>
<tr>
<td>Play and Leisure</td>
</tr>
<tr>
<td>Written Language</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Social skills</td>
</tr>
</tbody>
</table>

225 items, maximum 450 points (0,1,2 points per item)
To develop and implement intervention strategies for Kleefstra syndrome

Objective 1: to develop a follow-up strategy for KS patients with special attention to behavioral development changes

Objective 2: to perform an international clinical effect study to prevent general regression in patients with KS syndrome

Objective 3: to understand the pathophysiology of the regression observed in KS and the mechanism of olanzapine using patient-derived induced neurons
Sequential design

- Treatment starts when symptoms of psychosis/regression occur
- Early Detection Cohort with psychosis and Late Detection Cohort will be treated
Help Us Investigate the Natural History of Kleefstra Syndrome

At Boston Children’s Hospital, we are conducting a research study for individuals ages 13 years and older who have been diagnosed with Kleefstra Syndrome. The goals of this research are to study the natural history of Kleefstra Syndrome and determine best practices for treating the mental health challenges such as psychosis and behavioral regression that can be associated with Kleefstra Syndrome.

Who can participate in this study?
A person genetically diagnosed with Kleefstra Syndrome (SEPT9 deletion or pathogenic variant) that is 13 years of age or older.

How long will the study last?
This will be a four-year natural history, observational study. You will be asked to visit Boston Children’s Hospital at least four times during the study or you may participate through a yearly virtual study visit.

What will participants do during this study?
- Participant/caregiver will need to sign our informed consent form which will provide details of the study and ensure everyone’s understanding.
- Participants will have behavioral and cognitive testing, physical exams, and blood tests (for safety).
- Parents/caregivers will answer questions about the participant’s behavior and medical history.
- If a participant shows clear signs of psychosis or a deterioration in behavioral functions, we may ask the participant to come in additional times.

This is an international study. Patients and their caregivers will be seen at the Radboud University Medical Center, Manchester Centre for Genomic Medicine, or Boston Children’s Hospital. If you are interested in participating in this important study, please contact Jacqueline.Browne@childrens.harvard.edu.
“Kleefstra syndrome type 2”
A number sign (#) is used with this entry because of evidence that Kleefstra syndrome-2 (KLEFS2) is caused by heterozygous mutation in the KMT2C gene (606833) on chromosome 7q36.
2011: Module: Chromatin modification

Kleefstra syndrome

25%  75%?
Finding the other causes

10 cases:

- **Targeted: 5 cases**
  - Gene Ontology (GO) term: ‘chromatin modification’
  - String database/Known EHMT1 interactors
  - Total ≈ 400 genes

- **Whole Exome: 5 cases**
  - ≈ 18000 genes
  - ‘Trio screening’
Genetic causes in ‘EHMT1-negative’ patients

**Whole Exome**
- MBD5
- NR1I3

**Targeted**
- SMARCB1
- MLL3
Any interactions of these genes/proteins known?

Collaboration
Jamie Kramer
Annette Schenck
Radboudumc

Kleefstra et al., AJHG 2012

Control

No EHMT-overexpression

EHMT-overexpression

Trr/Mll3-Knock Down

No EHMT-overexpression

EHMT-overexpression

Sba/MBD5-overexpression

No EHMT-overexpression

EHMT-overexpression
Establishment of *EHMT1* associated genotype and phenotype networks

Kleefstra et al., AJHG 2012
Ongoing collection: *KMT2C*-related NDD cohort n=90
KMT2C variants compared to EHMT1 and KMT2D

Conclusion: Cohort differences on all levels

- Distinctive methylation signatures

- HPO terms + facial symptoms

Collaboration
Rosanna Weksberg Sick Kids, Toronto
Sid Banka, Genomic Medicine, Manchester

Koemans et al., Plos Genet 2017 and Rots et al., manuscript in preparation
guideline
Kleefstra syndrome

- Rare
- Limited studies
- Lack of knowledge

- Inadequate surveillance and follow-up

- Need for guideline development

- High burden

Pubmed: 365 results
Kleefstra Syndrome
Kleefstra-syndrom*
Ehmt1
Ehmt-1
9q34.3
9q-Subtelomeric-Delet*
9qSTDS
9q-STDS
To develop a clinical consensus guideline

- achieve an uniform, minimum standard of care
- support clinical decision making

• Clinical
  Based on clinical questions

• Consensus

  Evidenced-based  Consensus-based

• Guideline
  Recommendations to use in clinical practice
Guideline process

60 participants
17 countries

Patient representatives
Professionals

Physical therapists
Patient representatives
Clinical geneticists
Speech therapists
Medical doctors
Other
Main topics

Survey and consortium meeting

Working groups (WG)
1. General care: patients and families
2. Development, Speech, Communication
3. Behavior, Sleep, Neurology
4. Cardiology, Digestive tract
5. Genetic testing and counseling
Final product

- 12 chapters
  - Including 12 clinical topics + recommendations: prenatal period -> adulthood
- Clinical synopsis
- Lay version in different languages

- Guideline update plan
- Research agenda

- Planning: November 2023: Consensus meeting
Acknowledgements

Human Genetics Nijmegen
Ariannie Bouwman
Joost Kummeling
Dmitrijs Rots
Lara van Renssen
Dr Nicole de Leeuw
Prof Lisenka Vissers
Dr Rolph Pfundt
Prof Han Brunner
Prof Hans van Bokhoven
Prof Nael Nadif Kasri
Prof Annette Schenck

Amalia Children Hospital
Dr Joyce Geelen

(Child)psychiatry Nijmegen
Dr Joost Janzing
Dr Monica Pop
Prof Nanda Lambregts

Clinical Neuropsychology,
Vincent van Gogh, Venray
Prof Jos Egger
Dr Karlijn Vermeulen

Guideline committee