Ljubljana Scientific meeting, June 1-2 2023

The Journey of Kleefstra syndrome and the EHMT1 gene

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

Clinical Genetics Department Erasmus MC

Human Genetics Nijmegen

Erasmus MC University Medical Center Rotterdam

ITHACA

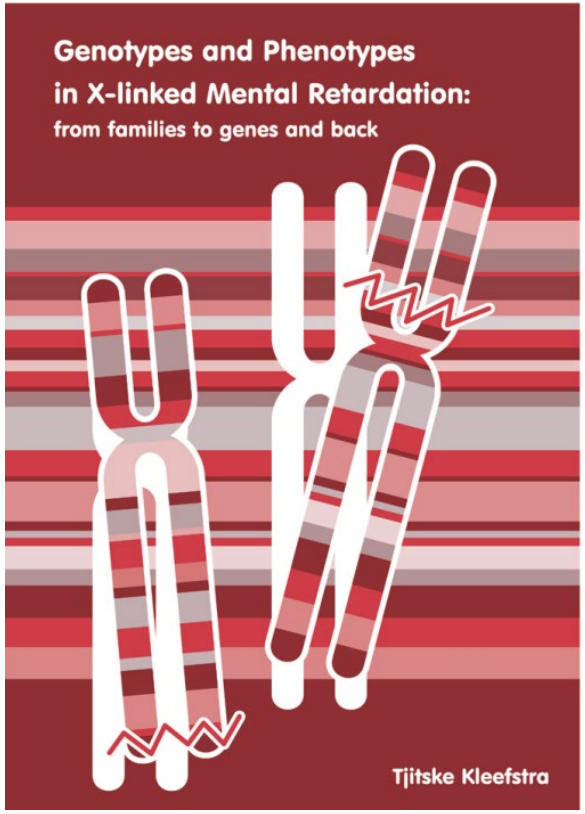
Radboudumc

Disclosure

Center of excellence in neuropsychiatry Vincent van Gogh

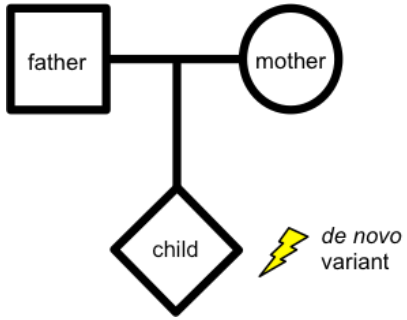
CENTRUM VOOR
NEUROPSYCHIATRIE

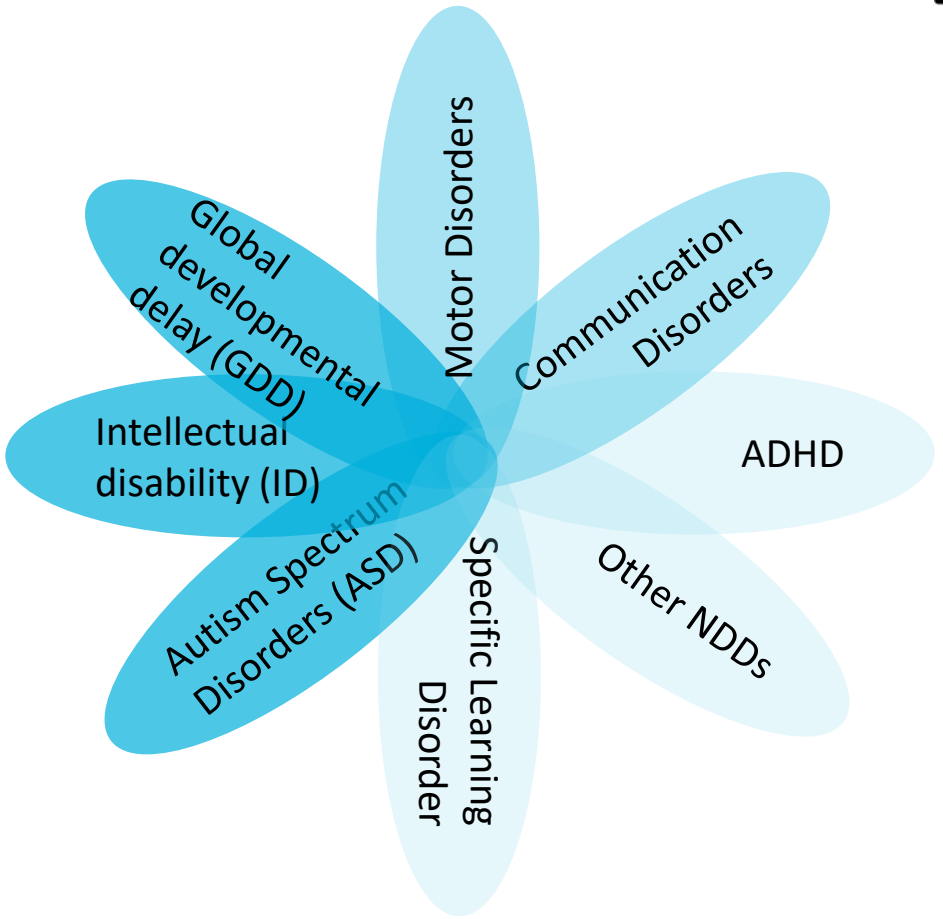
Starting 2002…



Monogenic Neurodevelopmental disorders NDDs

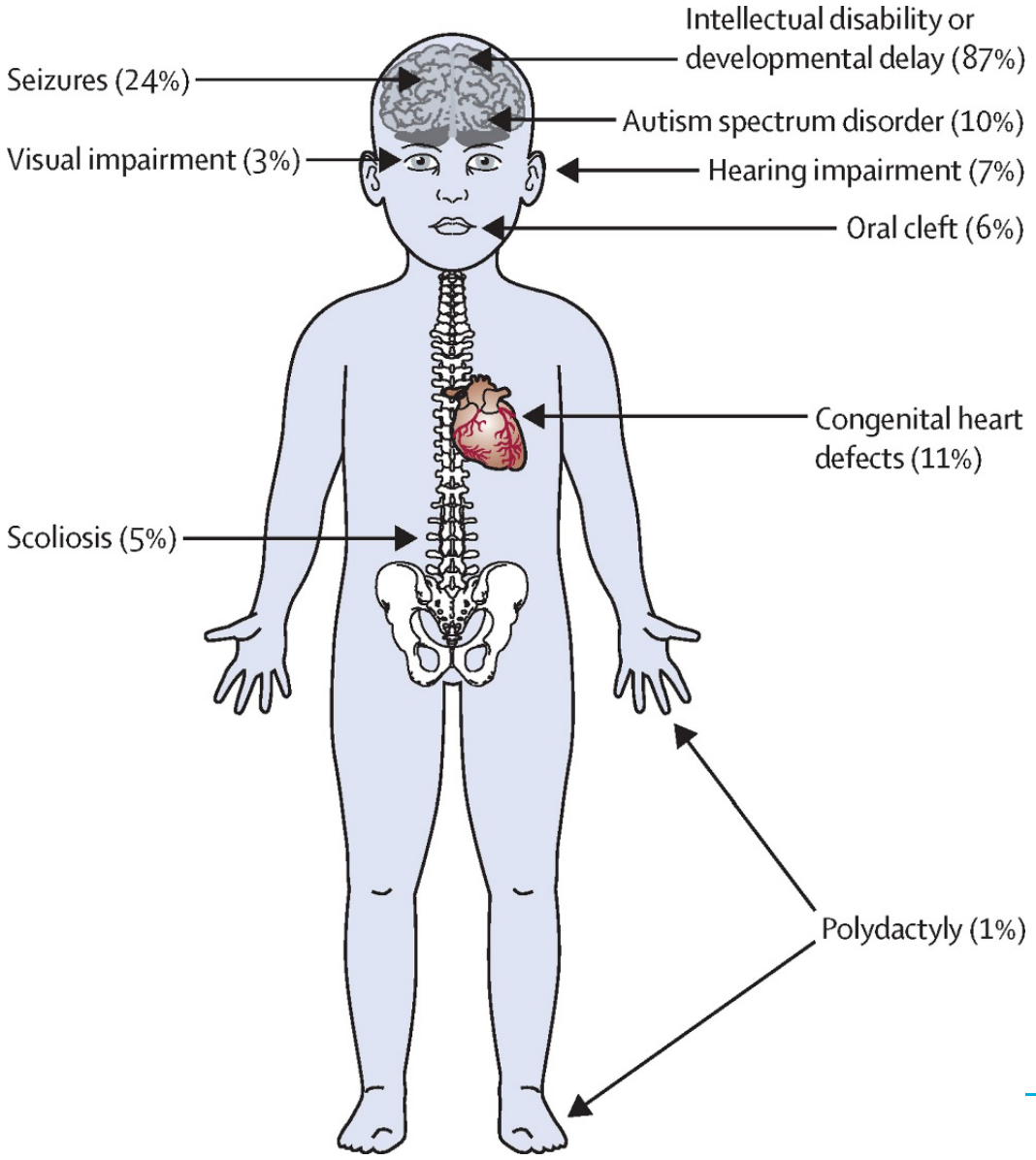
- The neurodevelopmental disorders are a group of conditions with onset in the developmental period





DSM-5, 2013

Typical NDD patient we see



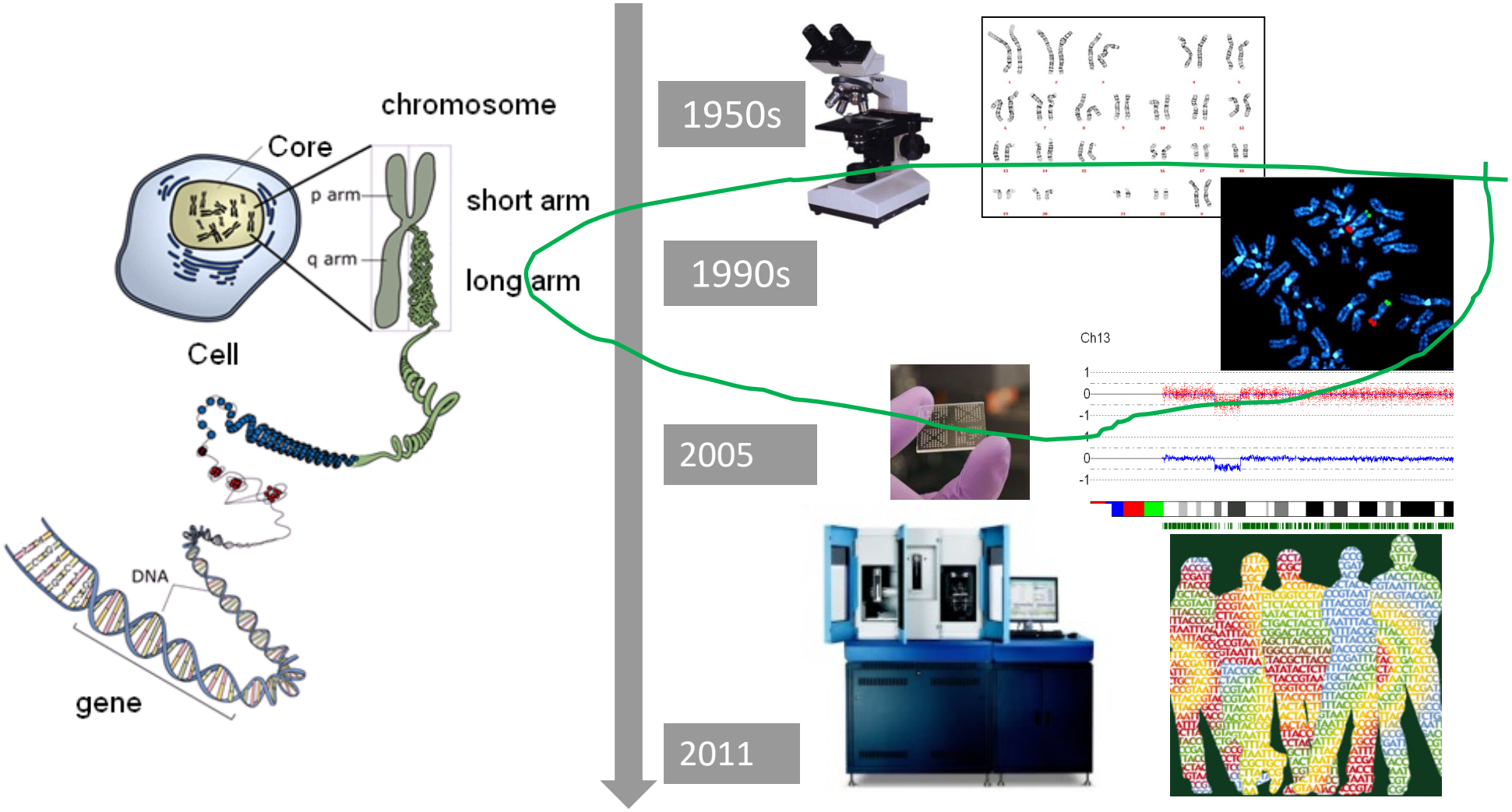
- Prevalence 2% population
- Over 1600 different ‘Mendelian’ genes

Deciphering Developmental Disorders study

Wright C. et al, 2015

Radboudumc

The humane genome: chromosomes and genes



Human Genetics Nijmegen

Willemsen&Kleefstra; Clin Genet 2013
Making headway with genetic diagnostics of intellectual disabilities.

Radboudumc

Breakthrough 1999

THE LANCET

Submit Artic

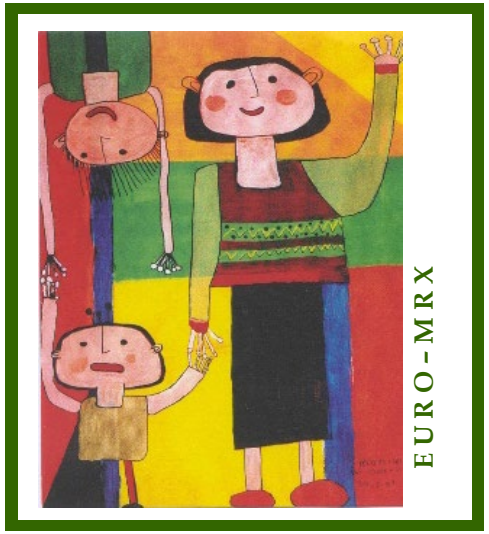
ARTICLES | VOLUME 354, ISSUE 9191, P1676-1681, NOVEMBER 13, 1999

Subtle chromosomal rearrangements in children with unexplained mental retardation

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

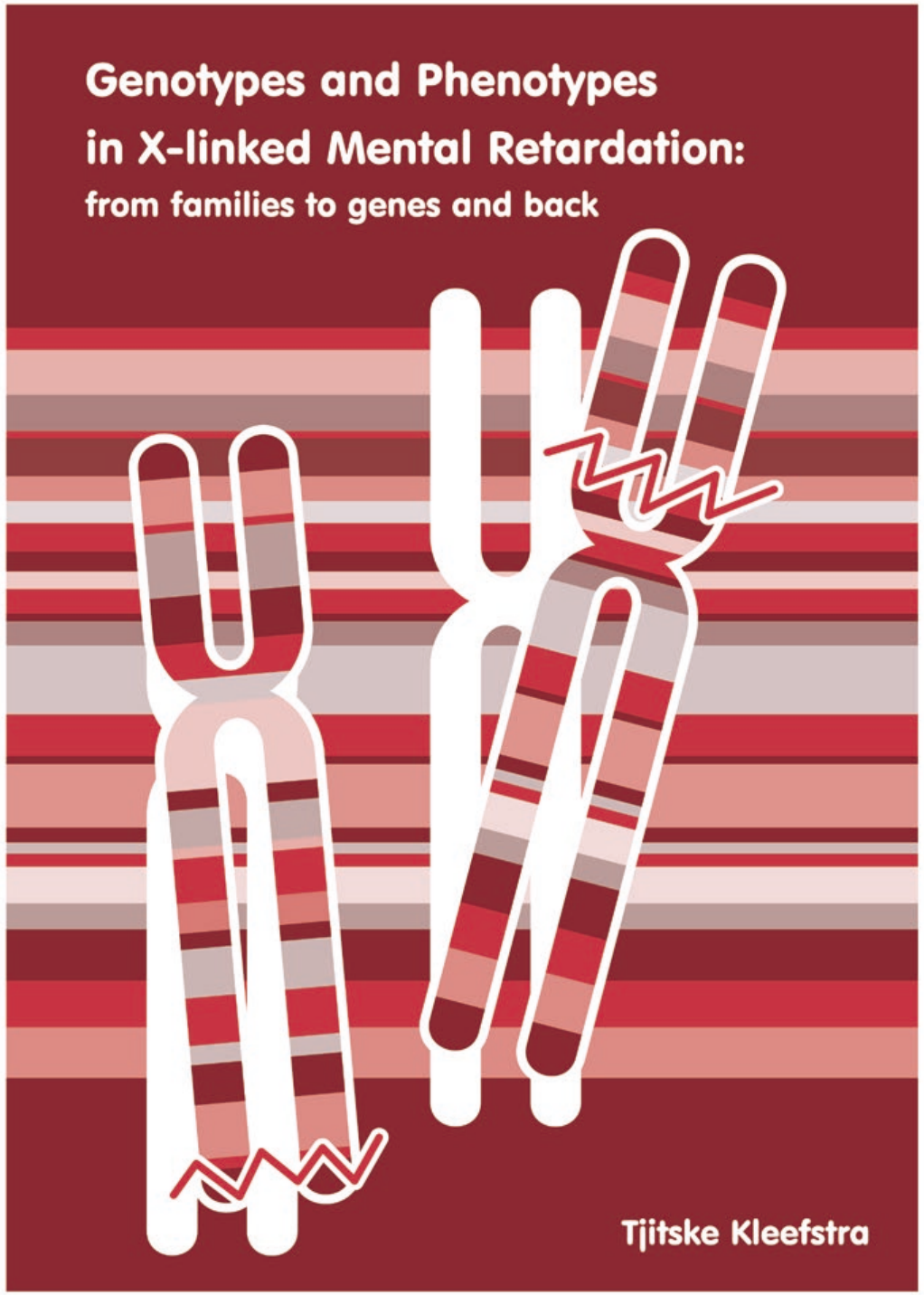
Published: November 13, 1999 • DOI: https://doi.org/10.1016/S0140-6736(99)03070-6

Nijmegen XLMR team

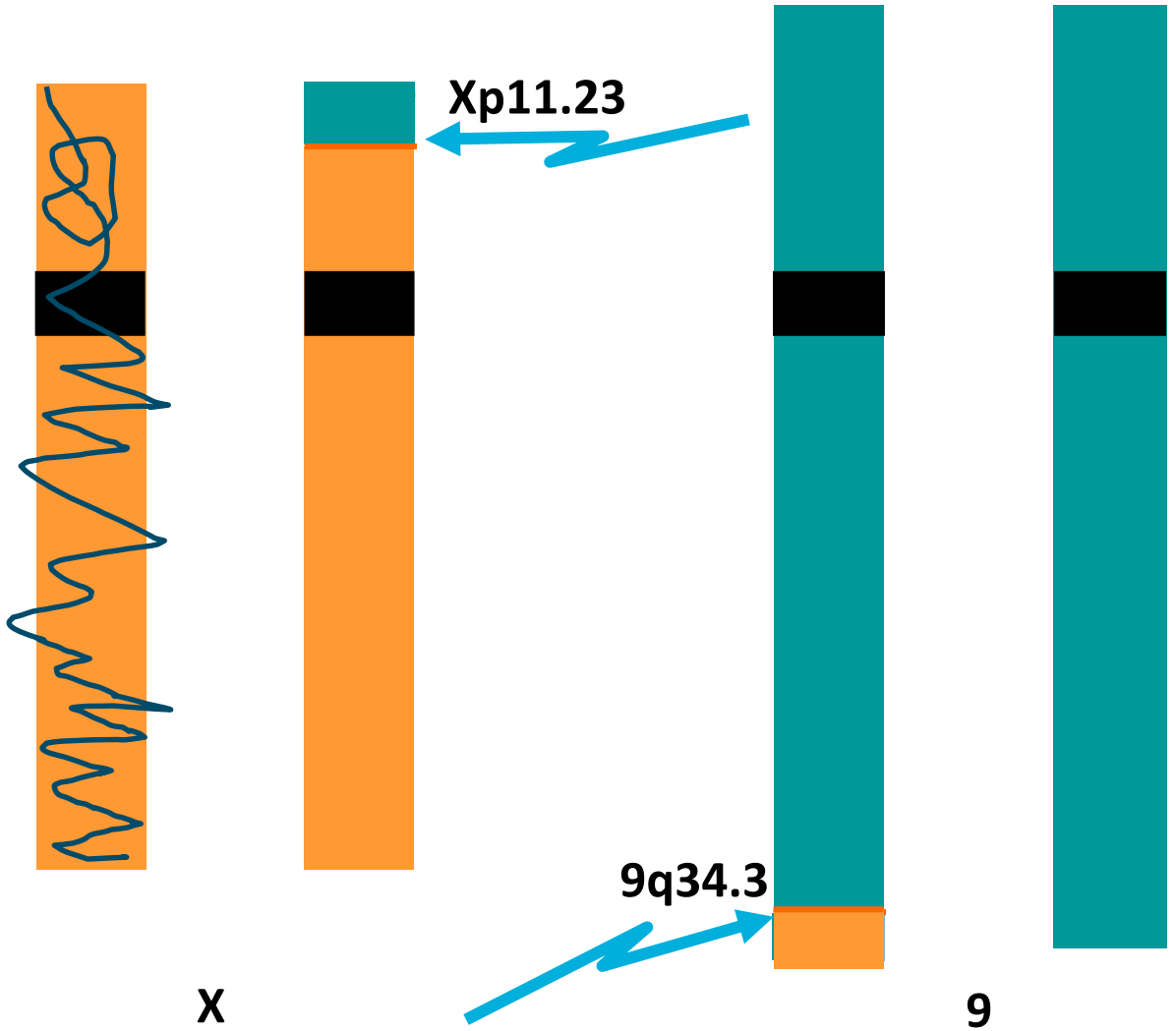


2002

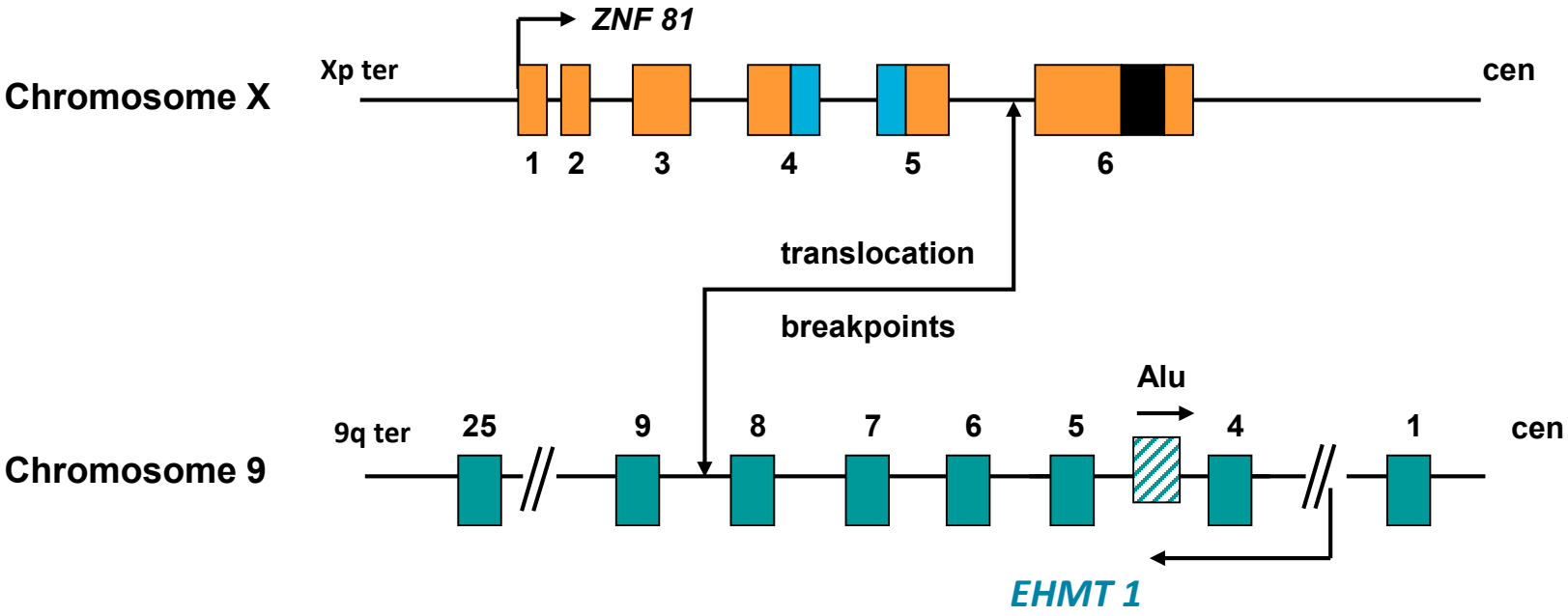
2005


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*



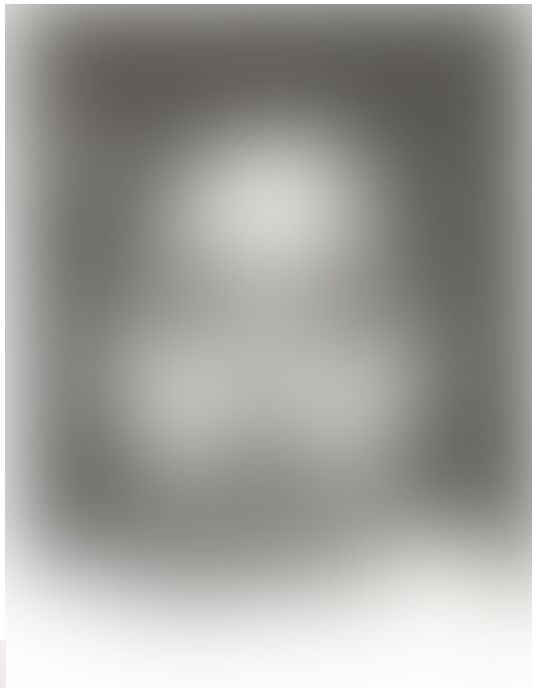
Eu-chromatin Histon Methyl Transferase 1

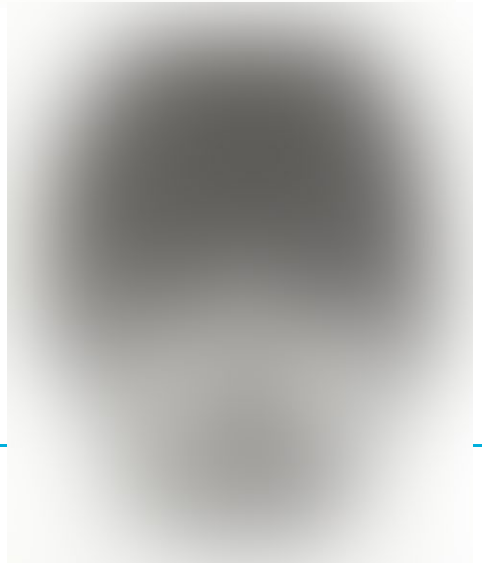
Subtelomere 9q deletion by FISH

Knight *et al*, Lancet 1999

Dawson *et al*, Clin Genet 2002

Cormier-Daire *et al*, J Med Genet 2003





AJHG

Volume 79, Issue 2, August 2006, Pages 370–377

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. Oudakker[a], Willy M. Nillesen[a], Alex Magee[c], David Geneviève[b], Valérie Cormier-Daire[b], Hilde van Esch[d], Jean-Pierre Fryns[d], Ben C.J. Hamel[a], Erik A. Sistermans[a], Bert B.A. de Vries[a], Hans van Bokhoven[a]

NDROME

OMIM
e Mendelian Inheritance in Man
Johns Hopkins University

My NCBI
[Sign In]

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | PMC | OMIM

Search OMIM for Go Clear

Limits | Preview/Index | History | Clipboard | Details

Display Detailed Show 20 Send to

MIM #610253
Text
Clinical Features
Cytogenetics
Molecular Genetics
References
Contributors
Creation Date
Edit History

Clinical Synopsis
Gene map

Entrez Gene
Nomenclature
RefSeq
GenBank
Protein
UniGene

LinkOut
komp

GeneTests, Links

#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….

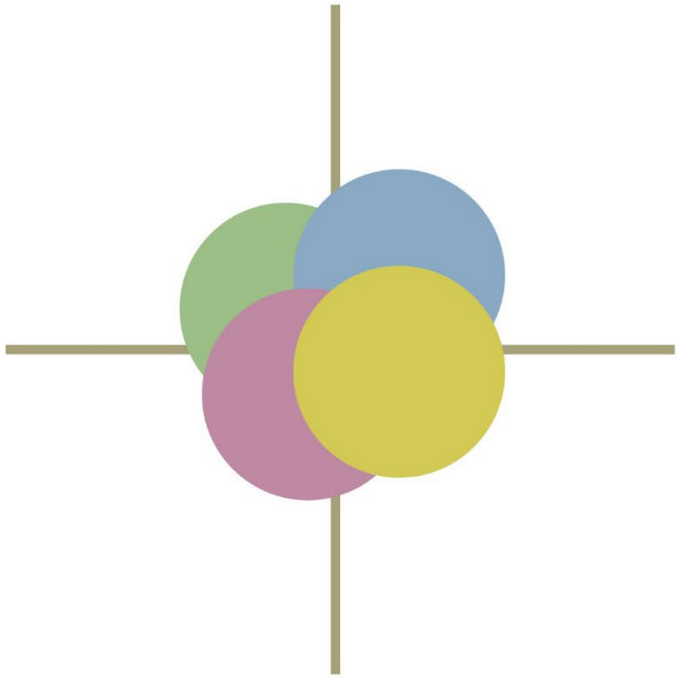
- Genome First: broadening molecular and clinical spectra
- Clinical follow up/natural history
- Pre-clinical studies
- “Kleefstra syndrome type 2”

Rare genetic syndromes

Aim: optimal treatment trough knowledge integration

Psychiatry

(Clinical) Genetics



‘personalised’
intervention strategies

Biology

Psychology

umc

Neuropsychiatric deterioration

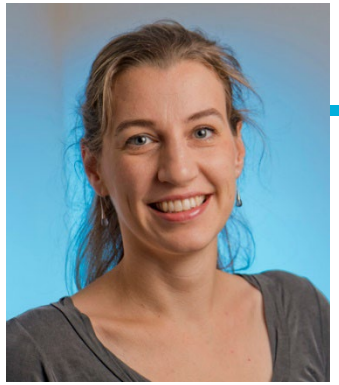
AJMG AMERICAN JOURNAL OF medical genetics PART A

Research Article | Full Access

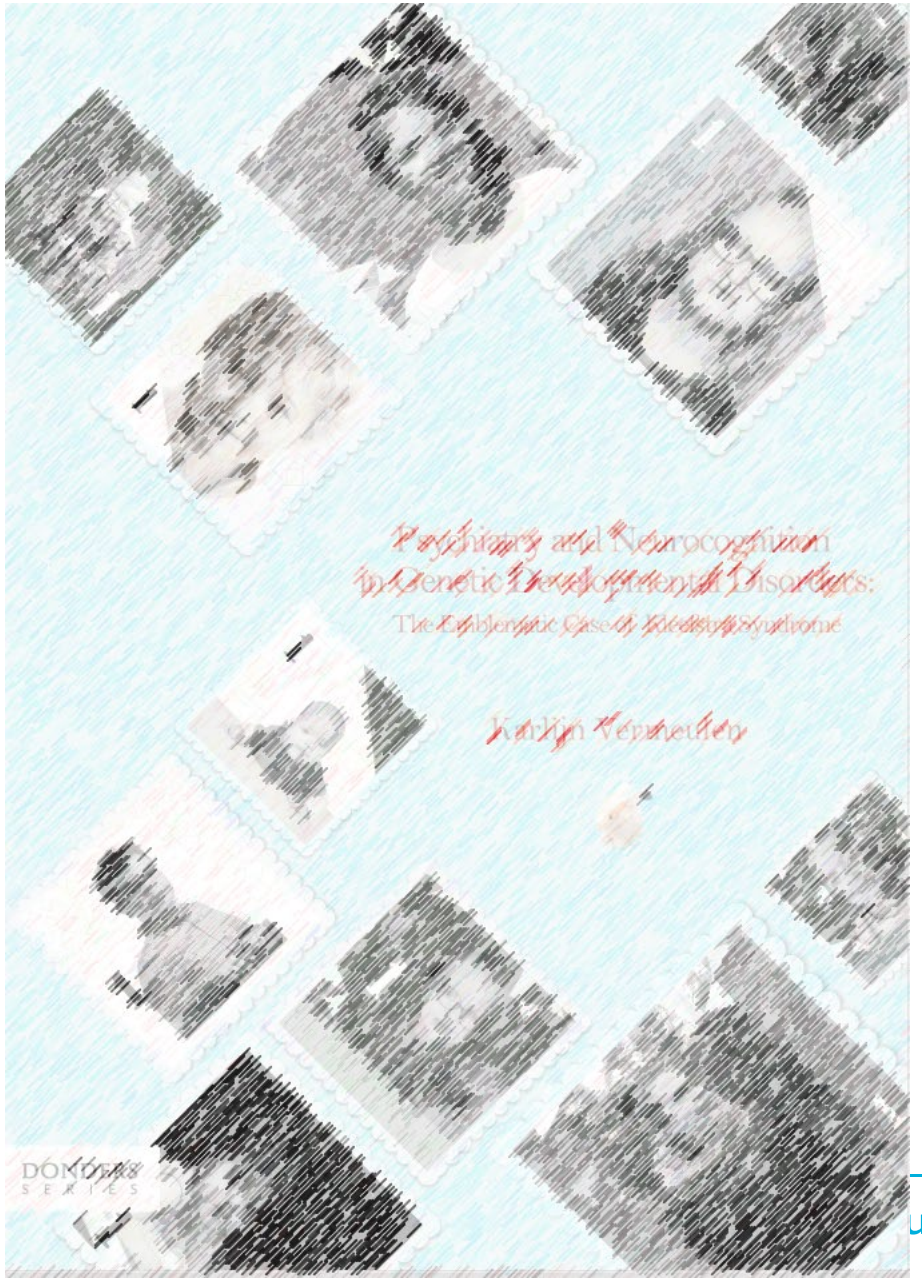
Kleefstra syndrome in three adult patients: Further delineation of the behavioral and neurological phenotype shows aspects of a neurodegenerative course*

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



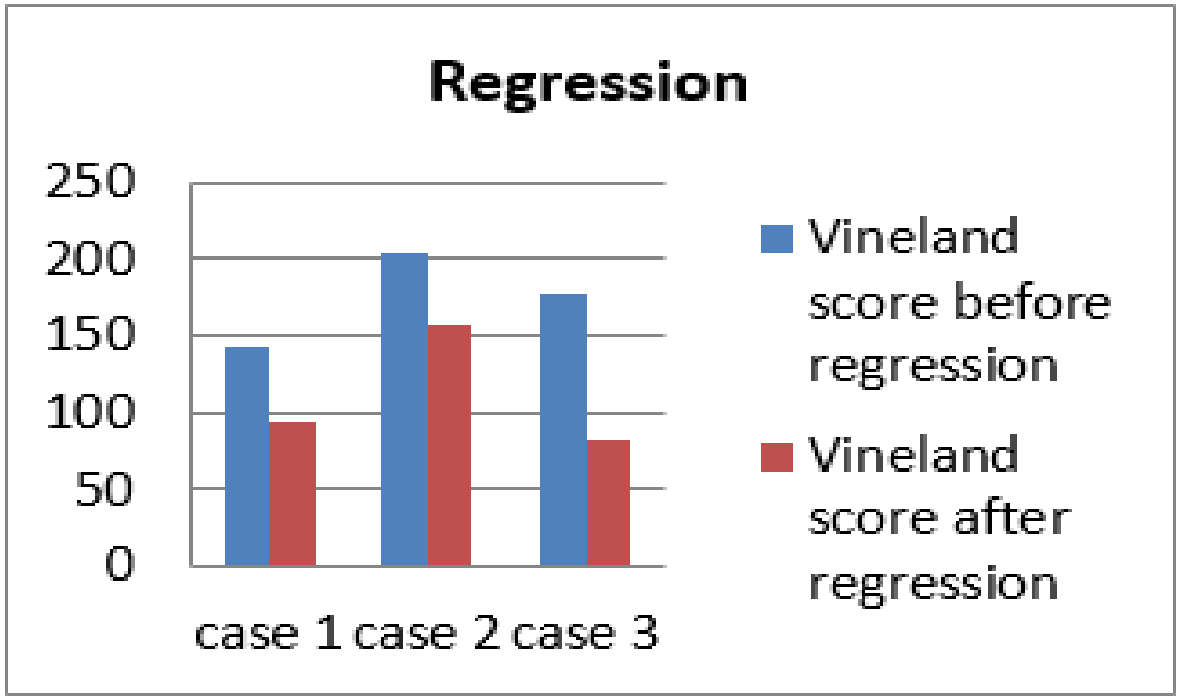
Vincent van Gogh voor geestelijke gezondheidszorg

kinder- en jeugdpsychiatrie karakter

umc

Severe loss of function post-puberty!

Adaptive functioning: Vineland-Z: Clinical interview



Vineland-Z Adaptive Behavior Domains		
Communication (Com)	Daily living skills (Day)	Socialization (Soc)
Receptive	Personal	Interpersonal Relationships
Expressive	Domestic	Play and Leisure
Written Language	Community	Social skills

225 items, maximum 450 points (0,1,2 points per item)

Natural History

Joost Kummeling

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

ZonMw

Radboudumc

Sequential design

Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

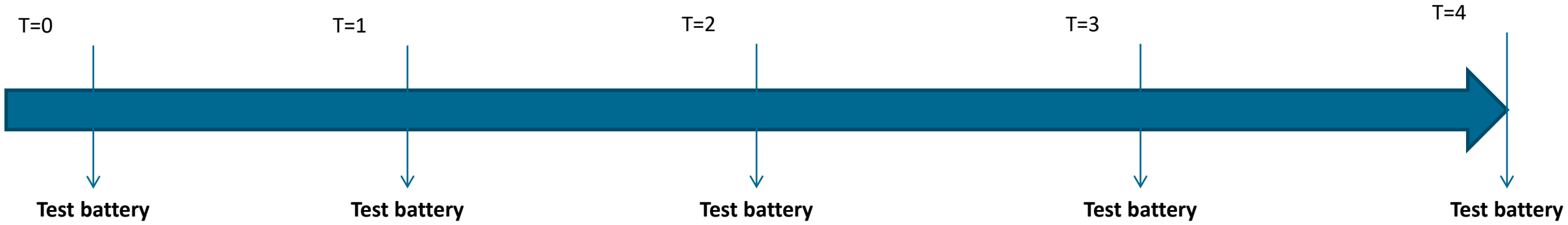
Statistical Methods in Medical Research
0(0) 1–13

DOI: 10.1177/0962280216653778
smm.sagepub.com
SAGE

Sequential designs with small samples: Evaluation and recommendations for normal responses

Stavros Nikolakopoulos, Kit CB Roes and Ingeborg van der Tweel

- *Treatment starts when symptoms of psychosis/regression occur*
- *Early Deteciont Cohort with psychosis and Late Detection Cohort will be treated*



Boston Children's Hospital

Where the world comes for answers

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.

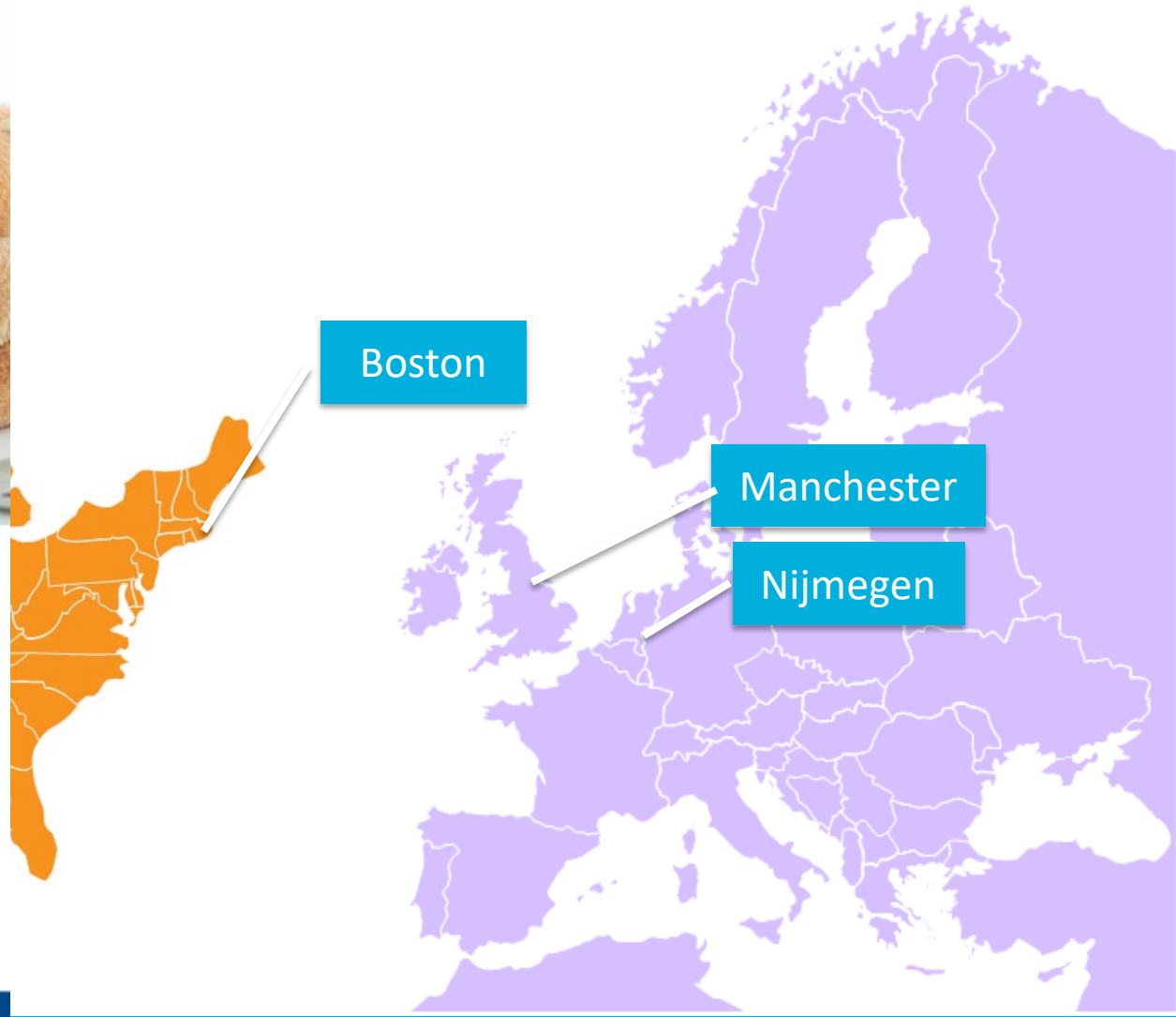
Who can participate in this study?
Anyone genetically diagnosed with Kleefstra Syndrome (EHMT1 deletion or pathogenic variant) that is 13 years of age or older.

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.Drew@childrens.harvard.edu.



Radboudumc

“ Kleefstra syndrome type 2”

What about Kleefstra syndrome type 2……..

#617768
Table of Contents

ICD+

617768

KLEEFSTRA SYNDROME 2; KLEFS2

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
7q36.1	Kleefstra syndrome 2	617768	AD	3	KMT2C	606833

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

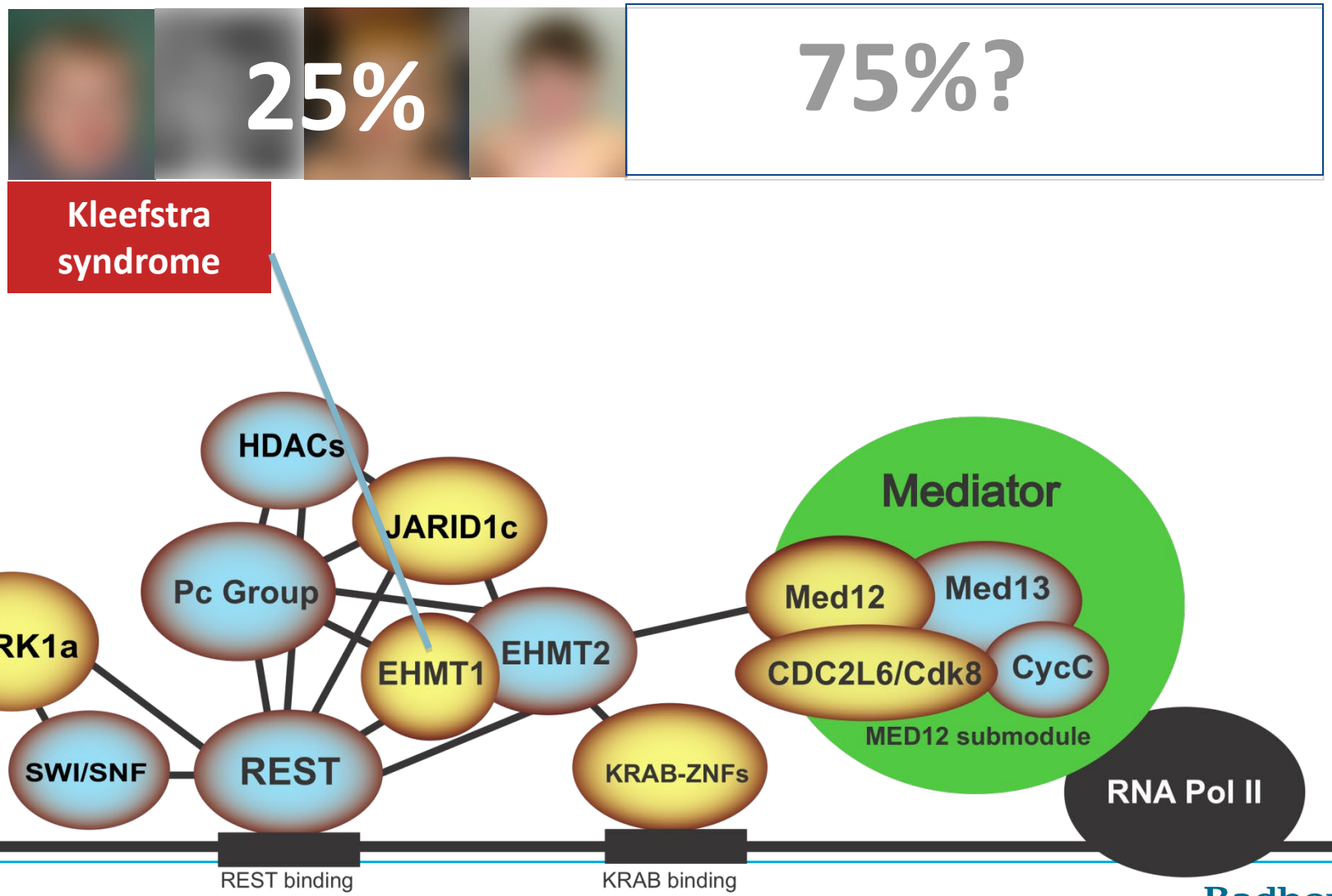
TEXT

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.

External Links

- Protein
- Clinical Resources
  - Clinical Trials
  - EuroGentest
  - GTR
  - OrphaNet
  - POSSUM
- Animal Models

2011: Module: Chromatin modification



Finding the other causes

10 cases:

- **Targeted: 5 cases**

  Gene Ontology (GO) term: ‘chromatin modification’

  String database/Known EHMT1 interactors

  Total ≈ 400 genes

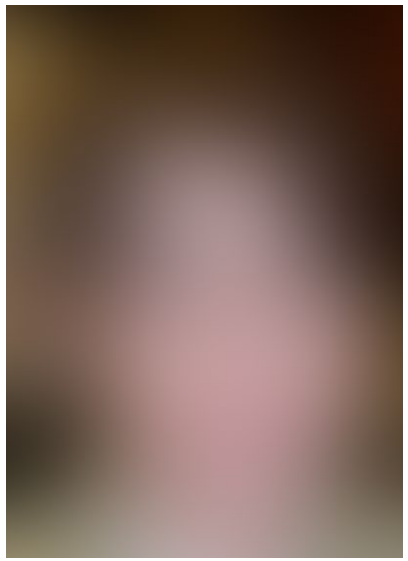
- **Whole Exome: 5 cases**

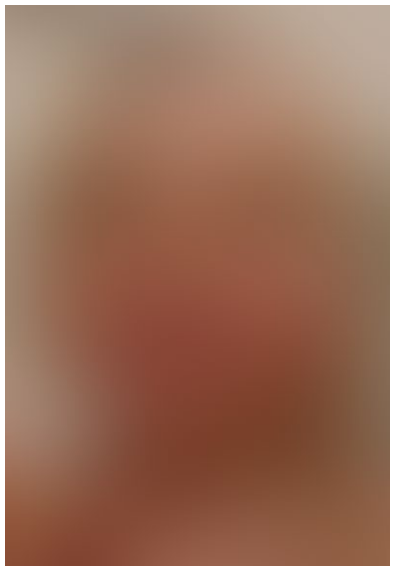
  ≈ 18000 genes

  ‘Trio screening’

Genetic causes in ‘EHMT1-negative’ patients

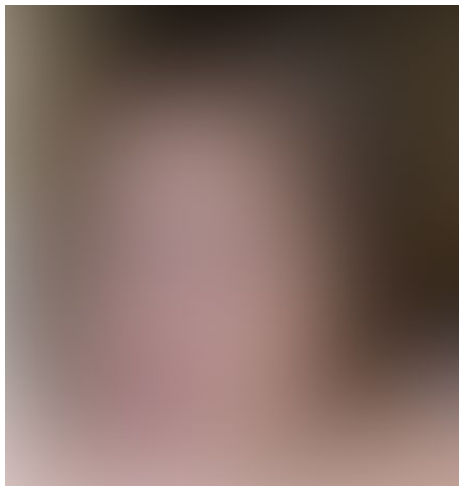
Whole Exome

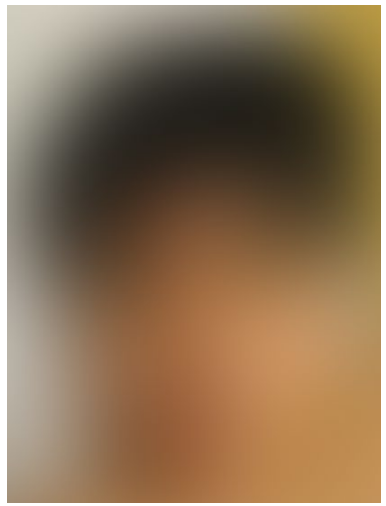




MBD5 ***NR1I3***

Targeted



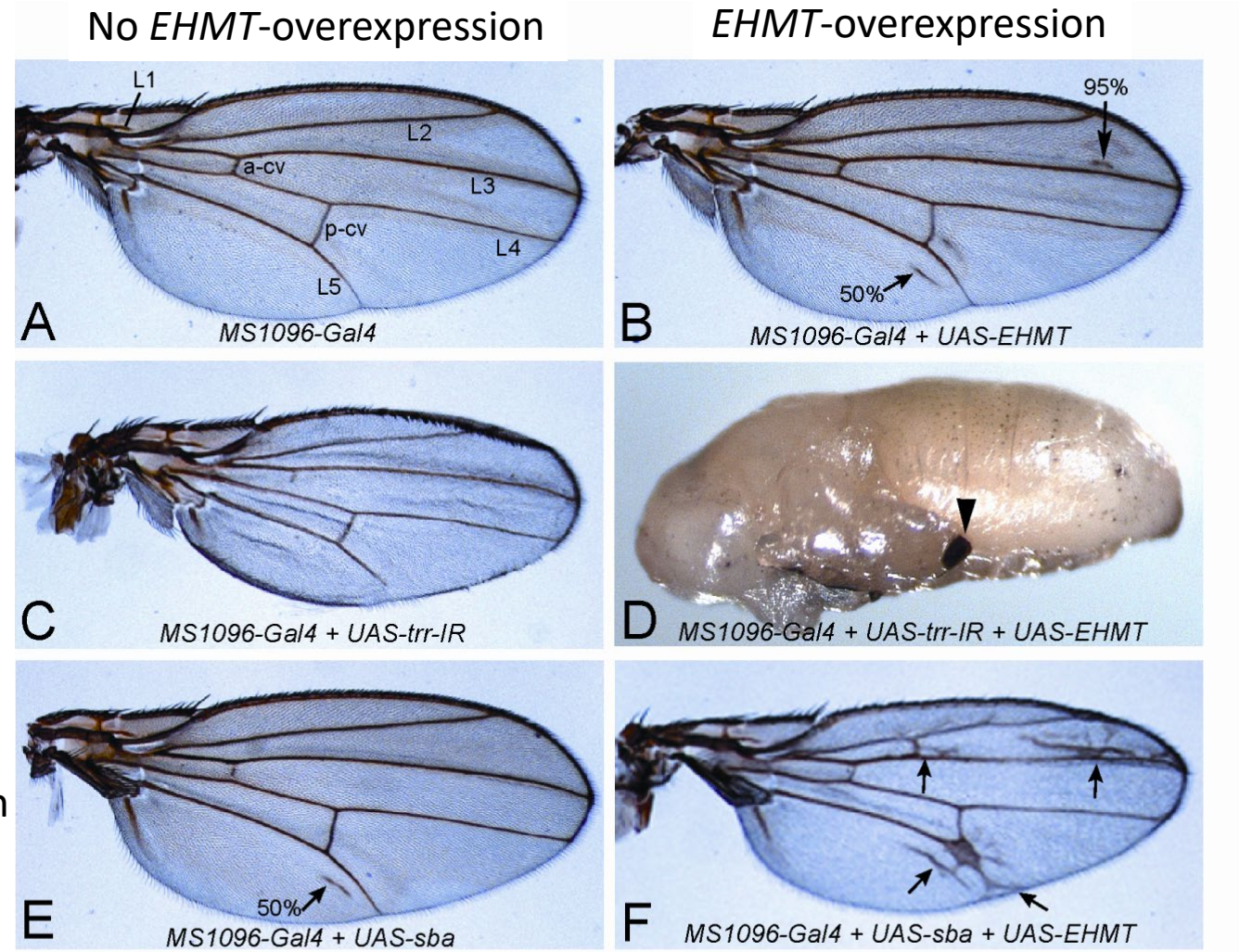


SMARCB1 ***MLL3***

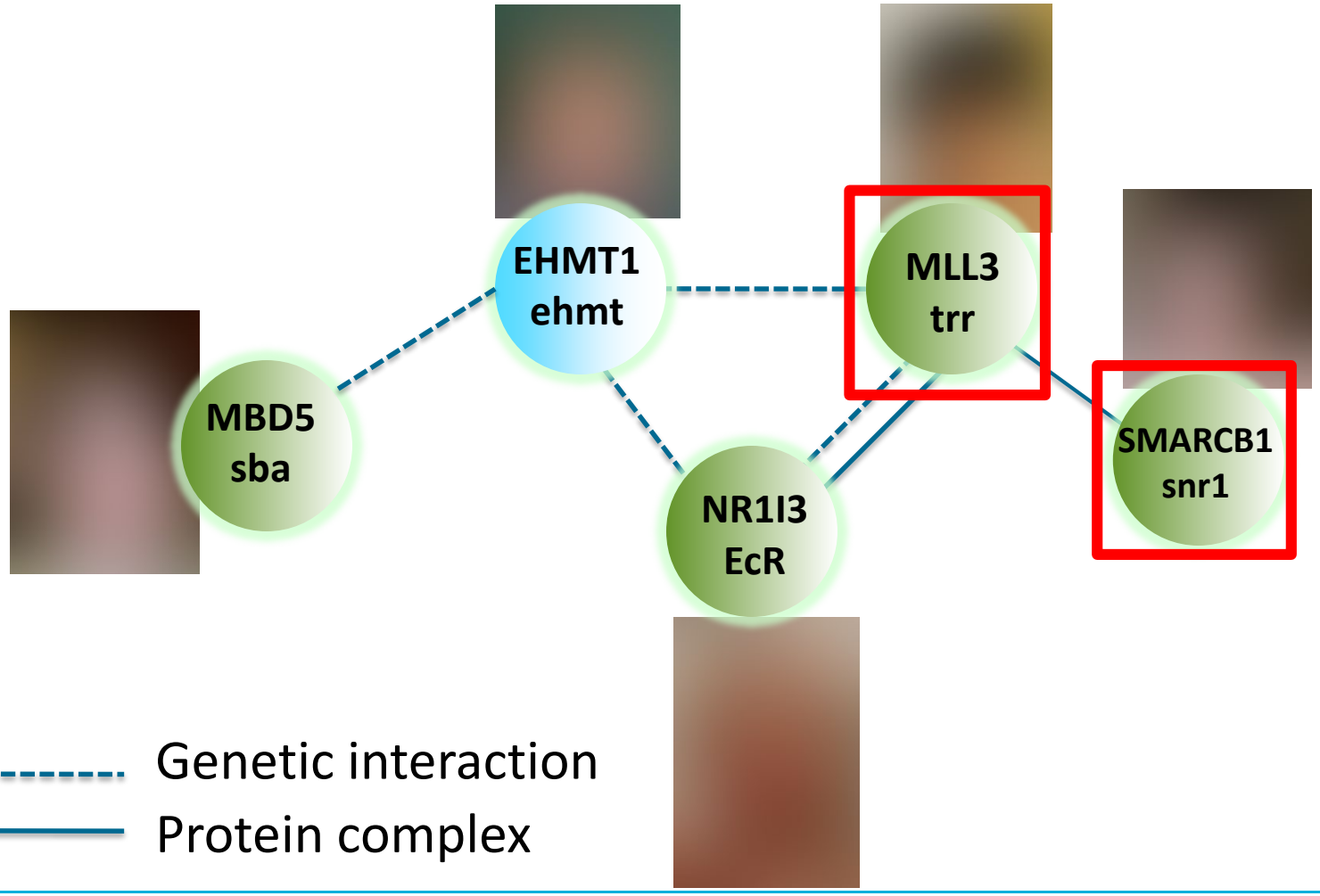
Any interactions of these genes/proteins known?

Kleefstra et al., AJHG 2012

Collaboration
Jamie Kramer
Annette Schenck
Radboudumc

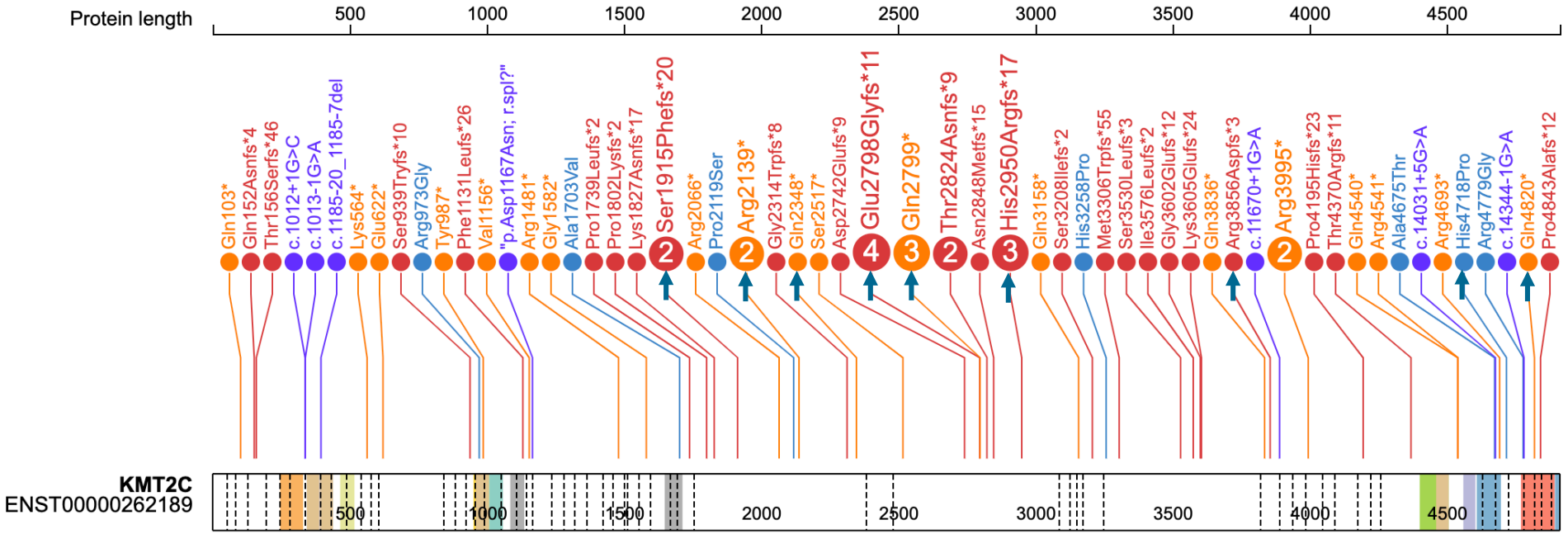


Establishment of *EHMT1* associated genotype and phenotype networks



MLL3
trr

Ongoing collection: *KMT2C*-related NDD cohort n=90



- ePHD1_KMT2C — Extended PHD finger 1 found in histone-lysine N-methyltransferase 2C (KMT2C)
- RING — Ring finger
- PHD2_KMT2C — PHD finger 2 found in Histone-lysine N-methyltransferase 2C (KMT2C)
- PHD3_KMT2C — PHD finger 3 found in Histone-lysine N-methyltransferase 2C (KMT2C)
- PHD4_KMT2C — PHD finger 4 found in Histone-lysine N-methyltransferase 2C (KMT2C)
- PHD5_KMT2C_like — PHD finger 5 found in Histone-lysine N-methyltransferase 2C (KMT2C) an ...
- PHD6_KMT2C — PHD finger 6 found in Histone-lysine N-methyltransferase 2C (KMT2C)
- HMG — high mobility group
- ePHD2_KMT2C — Extended PHD finger 2 found in histone-lysine N-methyltransferase 2C (KMT2C)
- FYRN — FY-rich domain
- FYRC — FY-rich domain
- SET — SET (Su(var)3-9
- PostSET — Cysteine-rich motif following a subset of SET domains

- NONSENSE, n=23
- FRAMESHIFT, n=31
- MISSENSE, n=7
- SPLICE, n=7
- Inherited

KMT2C variants compared to EHMT1 and KMT2D

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

Conclusion: Cohort differences on all levels

- Distinctive methylation signatures

- HPO terms + facial symptoms

Koemans et al., Plos Genet 2017 and Rots et al., m*anuscript in preparation*

guideline

Kleefstra syndrome

Rare

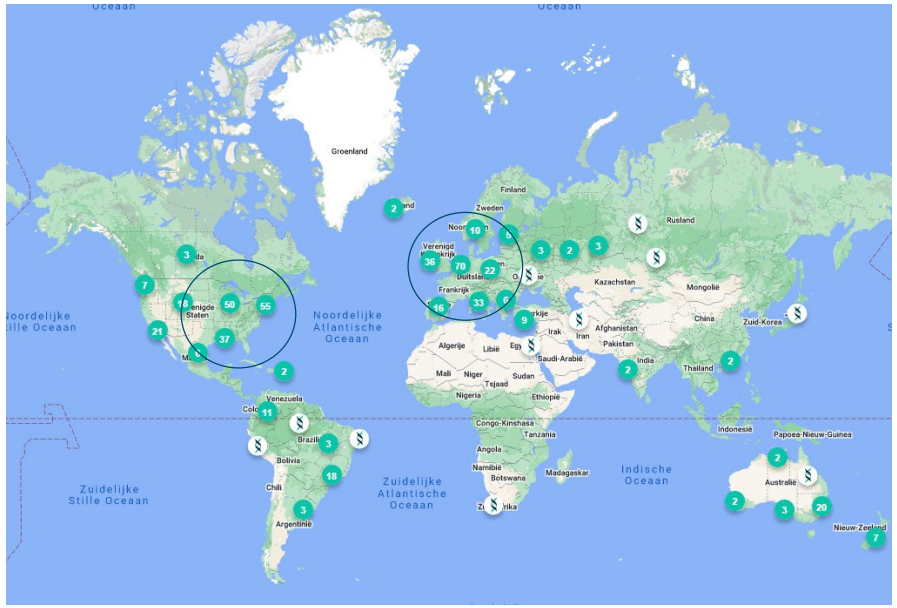
Limited studies

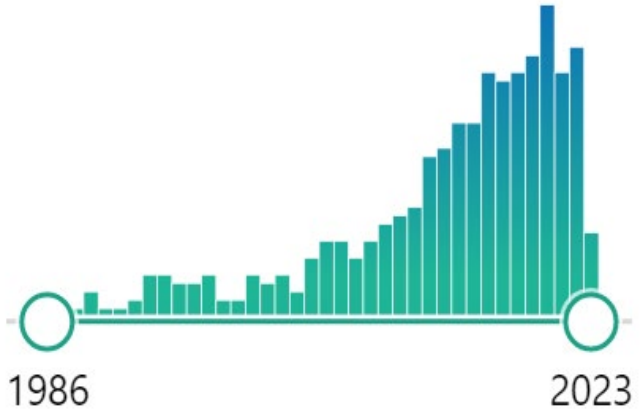
Lack of knowledge

Inadequate surveillance and follow-up

High burden

Need for guideline development





Pubmed: 365 results

Kleefstra Syndrome
Kleefstra-syndrom*
Ehmt1
Ehmt-1
9q34.3
9q-Subtelomeric-Delet*
9qSTDS
9q-STDS

Consortium aim

To develop a clinical consensus guideline

-achieve an uniform, minimum standard of care

-support clinical decision making

- *Clinical*

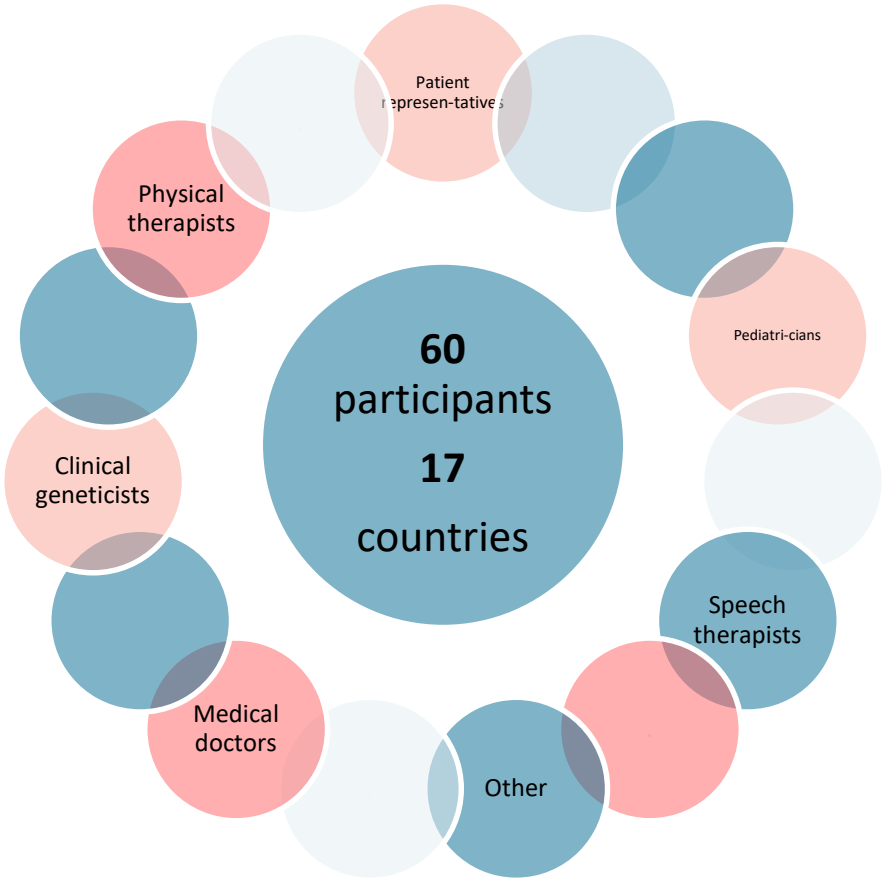
Based on clinical questions

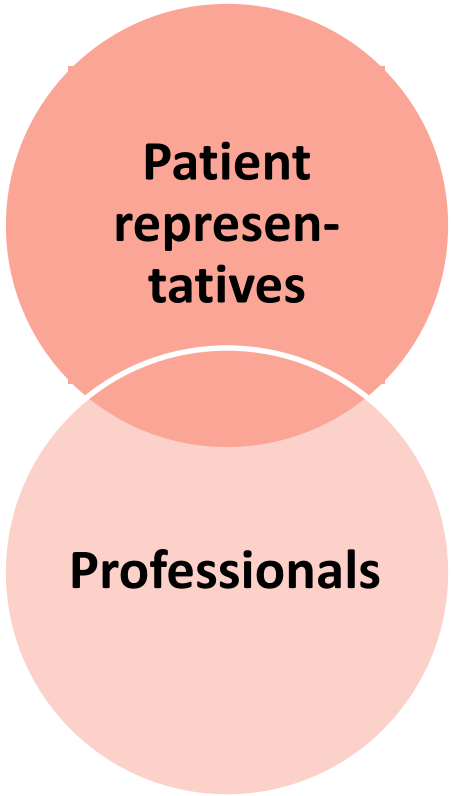
- *Consensus*

- *Guideline*

Recommendations to use in clinical practice

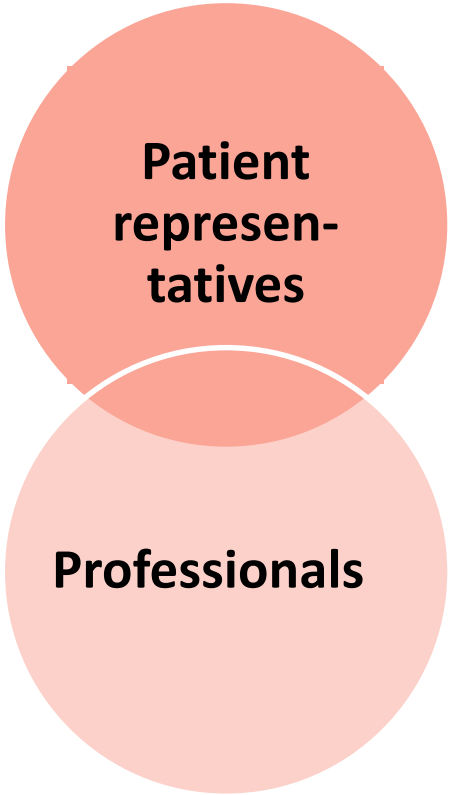
Guideline process





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
Arianne 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