Boston, June 30th 2018

Kleefstra syndrome and the EHMT1 gene
Past-Present-Future

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The Netherlands

Human Genetics Nijmegen

Donders Institute
for Brain, Cognition and Behaviour

Radboudumc

Repetition – Novelty

Meet and exchange experience

My ‘conclusion’ slide Boston 2016

- **Large variability both clinically and molecularly**
- **What about natural history and phenotype?**
  - **> Need for registry of natural history**
  - **> Emphasis on behaviour and psychopathology, but also different topics**
- **International collaboration on the syndrome is warranted**
  - **> Network of dedicated professionals (> foundation/patient network)**
- **Funding is hard, particularly because of rare ID/autism disorder**
  - **> Foundation**


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Samuel

Inleiding door redacteur **ROEL VAN DIEPEN**

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zijn leeservaring van het boek

WILLEM VISSERS leest voor
en reikt het eerste exemplaar uit

DAG **Dinsdag 7 november**

TIJD **17.30 uur stipt**
(inloop vanaf 17.00 uur)

LOCATIE **Cafe Czaar**
Czaar Peterstraat 281 | Amsterdam

Graag even aanmelden via **LILI.BURKI@LEBOWSKIPUBLISHERS.NL**

Weekly columns Dutch National Newspaper

Willem Vissers schrijft wekelijks over het leven van zijn gehandicapte zoon Samuel.

Samuel

WILLEM VISSERS

Ziekenhuis

Een dag onderzoeken in Nijmegen, van de fysio naar de sciencefictionafdeling.

Foto's **Marijn Scheeres**

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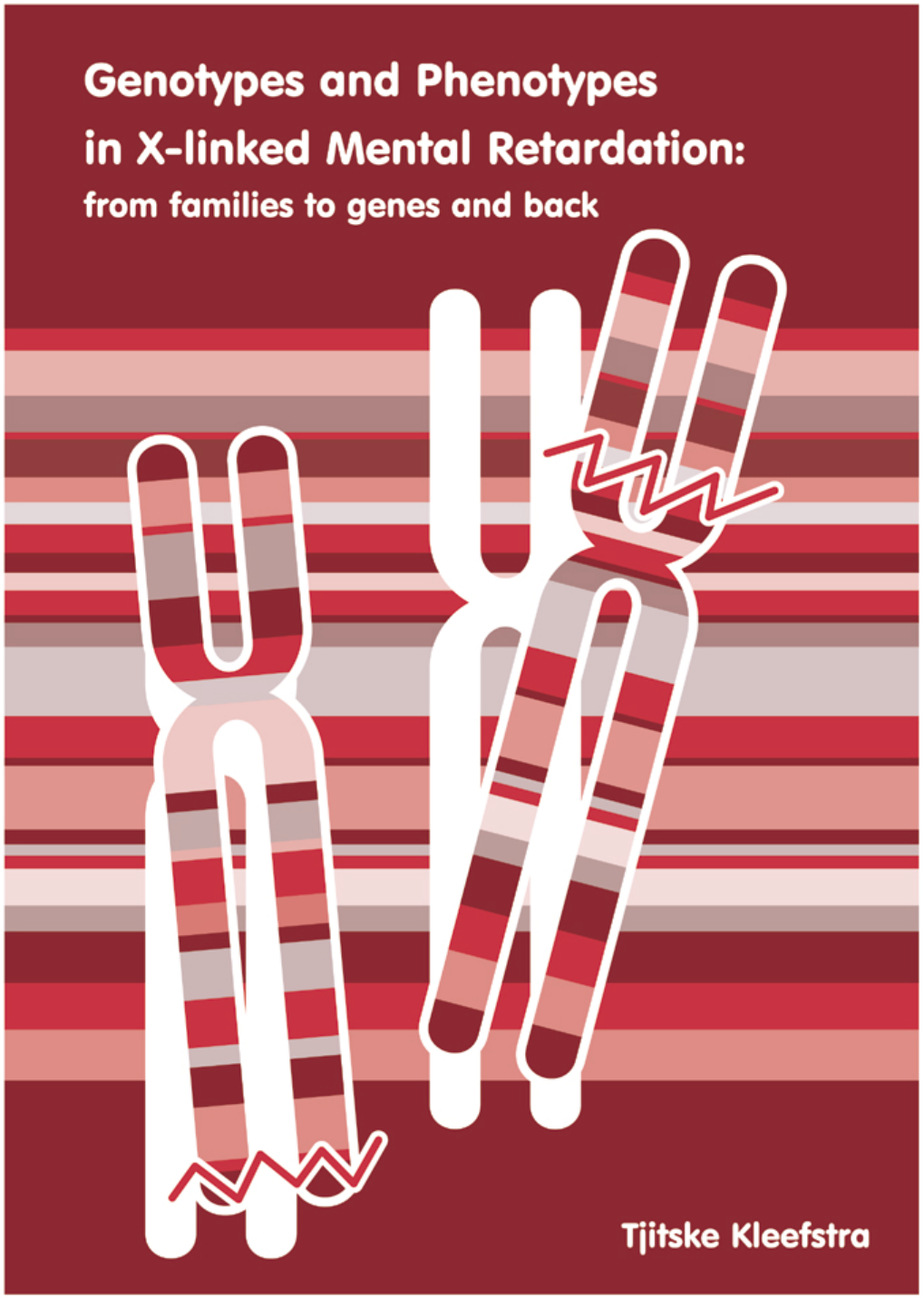
2005



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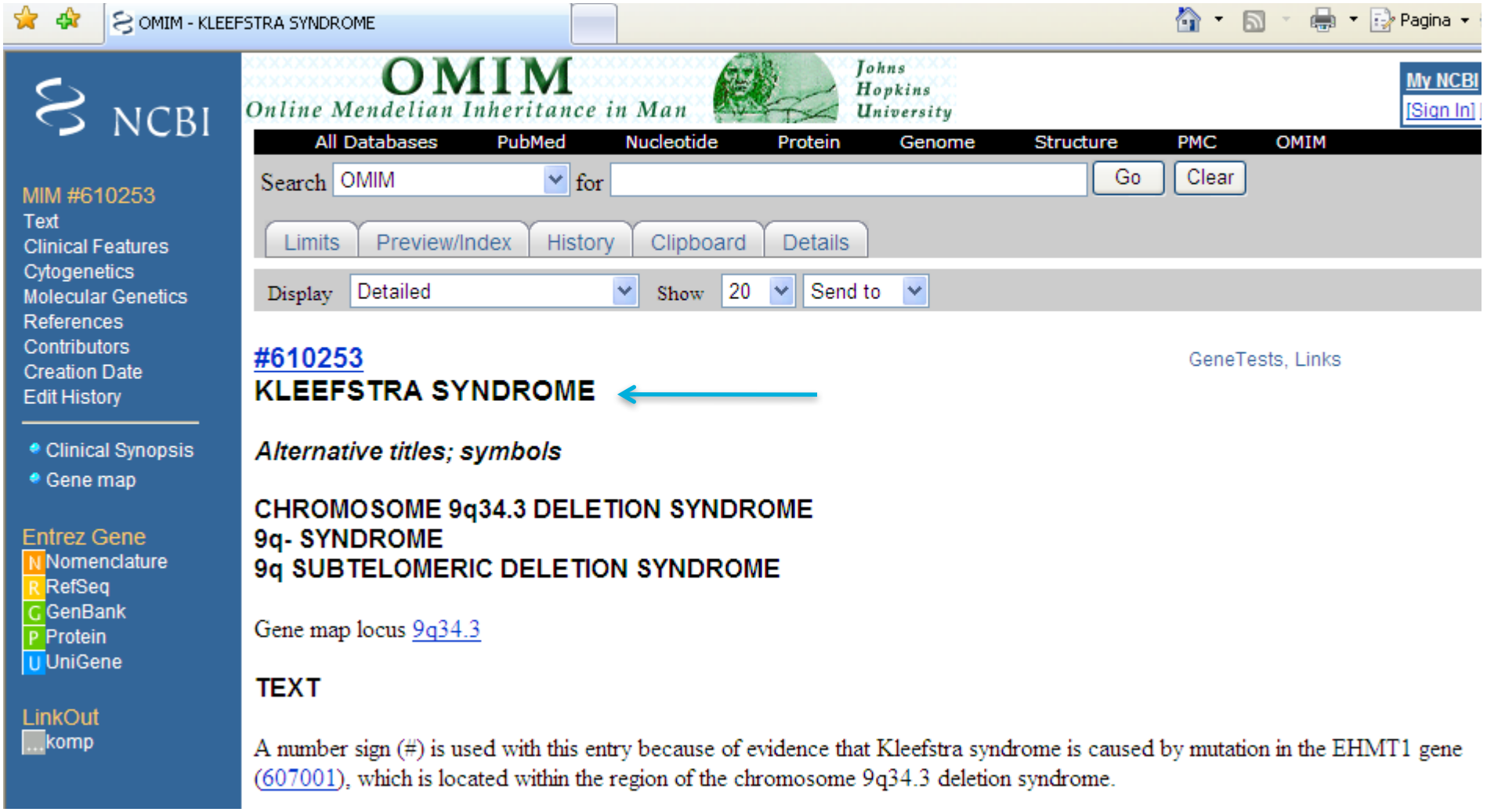
OMIM - KLEEFSTRA SYNDROME
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Johns Hopkins University
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All Databases PubMed Nucleotide Protein Genome Structure PMC OMIM
Search OMIM for Go Clear
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Text
Clinical Features
Cytogenetics
Molecular Genetics
References
Contributors
Creation Date
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Clinical Synopsis
Gene map
Entrez Gene
Nomenclature
RefSeq
GenBank
Protein
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LinkOut
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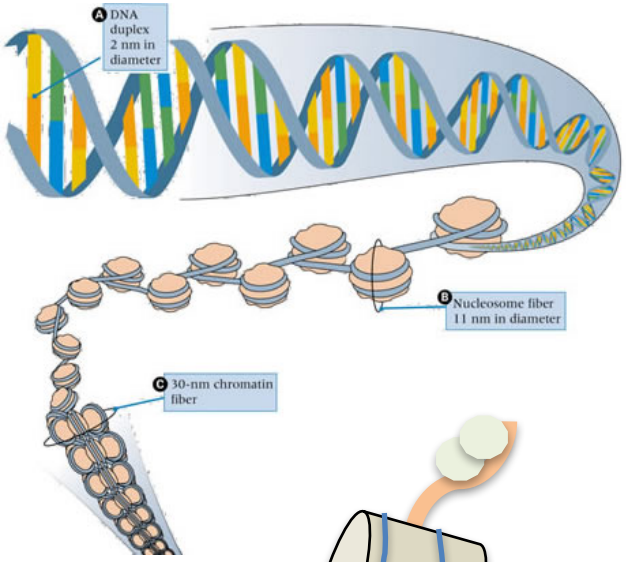
#610253
KLEEFSTRA SYNDROME
GeneTests, Links
Alternative titles; symbols
CHROMOSOME 9q34.3 DELETION SYNDROME
9q- SYNDROME
9q SUBTELOMERIC DELETION SYNDROME
Gene map locus 9q34.3
TEXT
A number sign (#) is used with this entry because of evidence that Kleefstra syndrome is caused by mutation in the EHMT1 gene (607001), which is located within the region of the chromosome 9q34.3 deletion syndrome.

EHMT1
Gene and protein



EHMT1

"epigenetic" gene regulation

Histon tail

on

gene

DNA

EHMT1

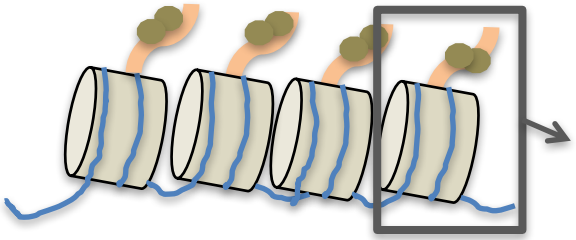
Me

Me

off

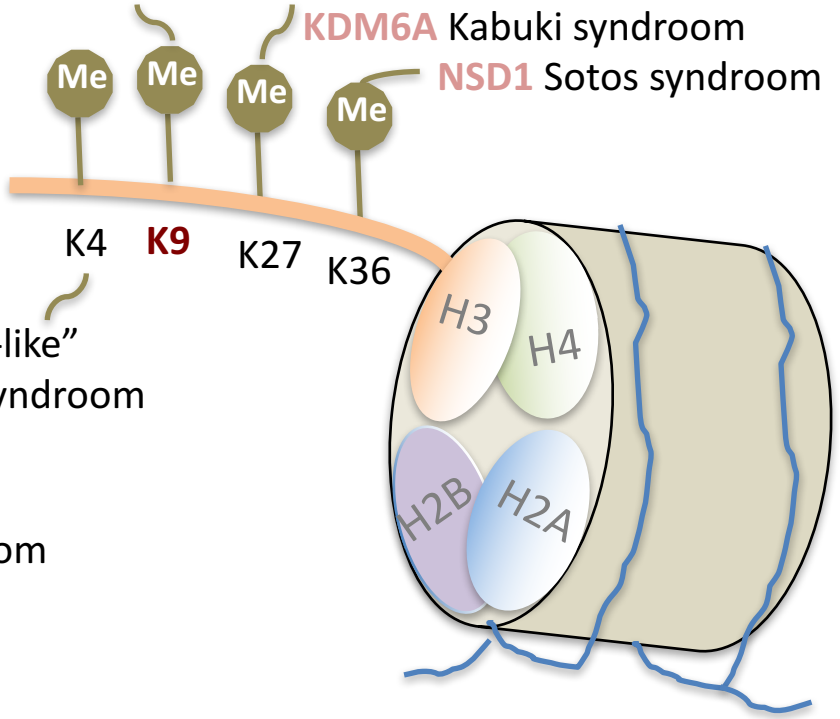
gene

Defective epigenetic machinery in Kleefstra syndrome
and comparable Mendelian syndromes



EHMT1 Kleefstra syndroom

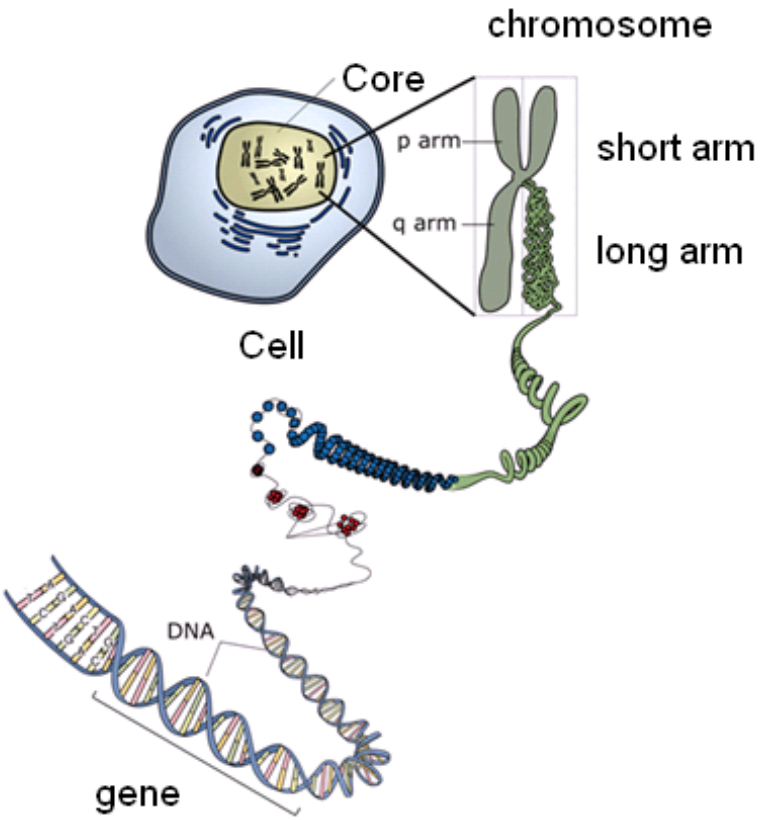
EZH2 Weaver syndroom
KDM6A Kabuki syndroom
NSD1 Sotos syndroom



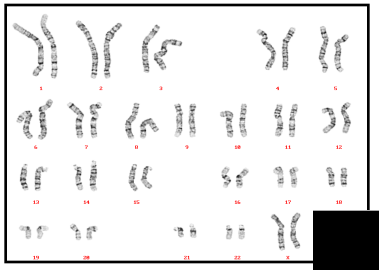
KMT2C "Kleefstra syndroom-like"
KMT2A Wiedeman Steiner syndroom
KMT2D Kabuki syndroom
SETD1A Schizophrenia
KDM5C Claes-Jensen syndroom

How to find?

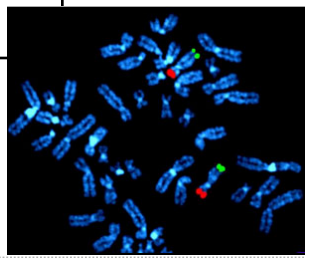
The humane genome and the genes



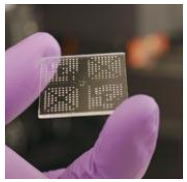
1950s

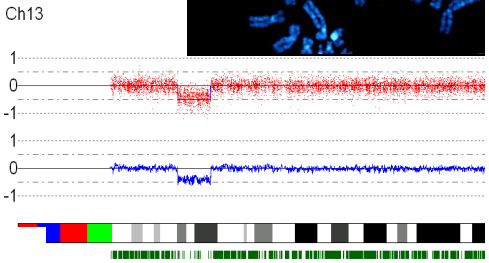


1990s



2005





2011

Human Genetics Nijmegen

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

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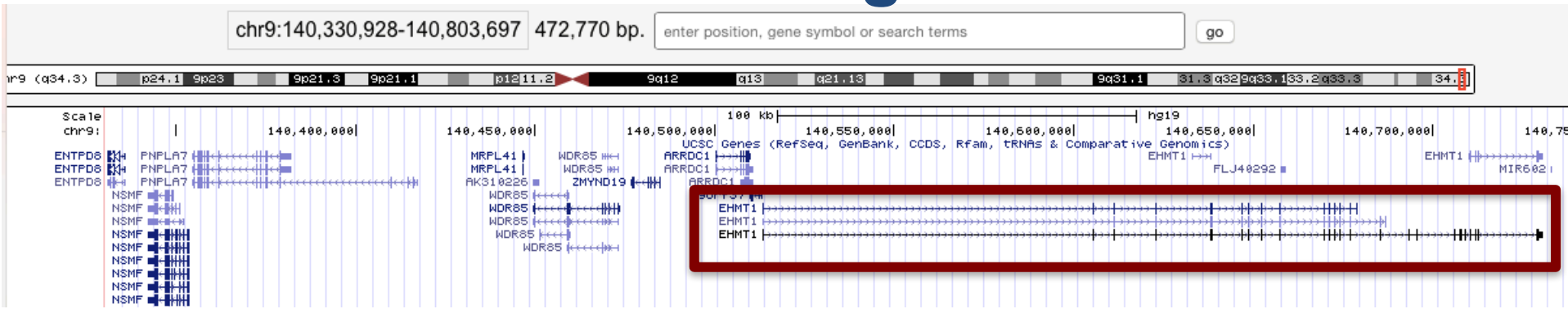
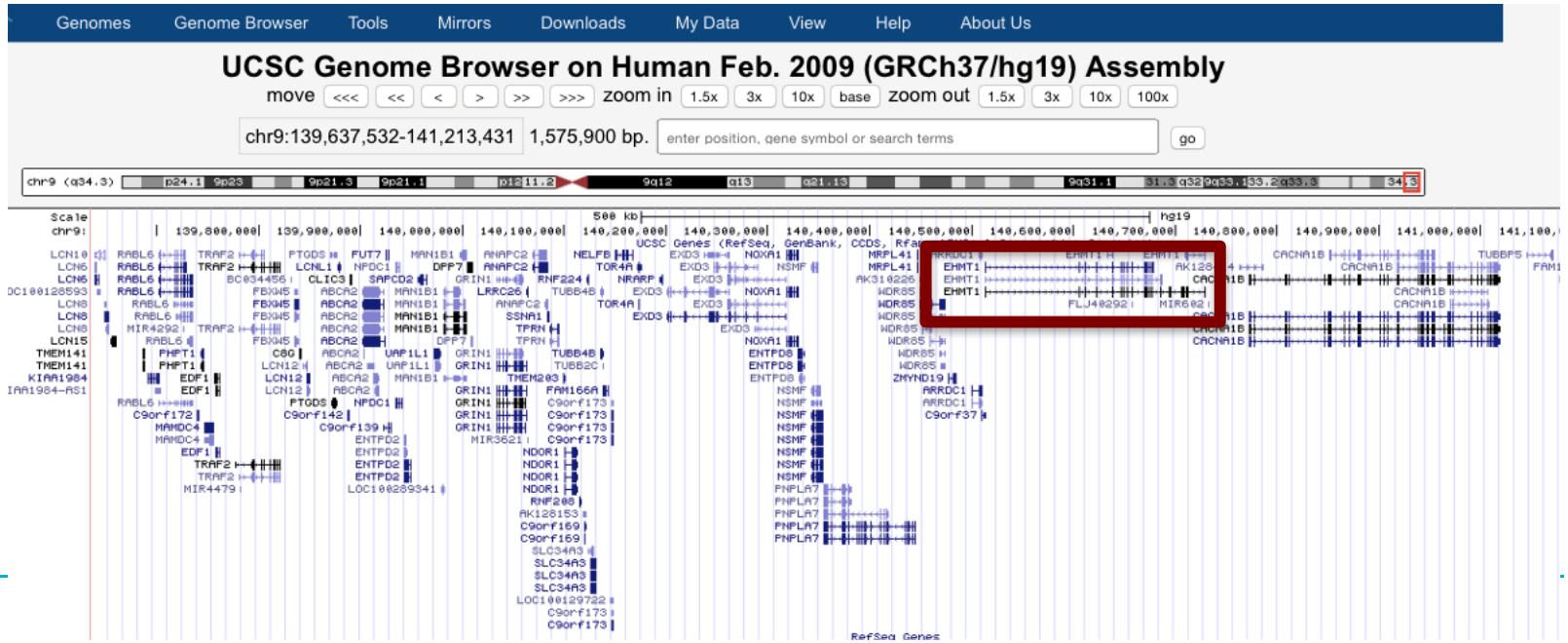
Sizes and gene number differ considerably

472 kb: 12 genes



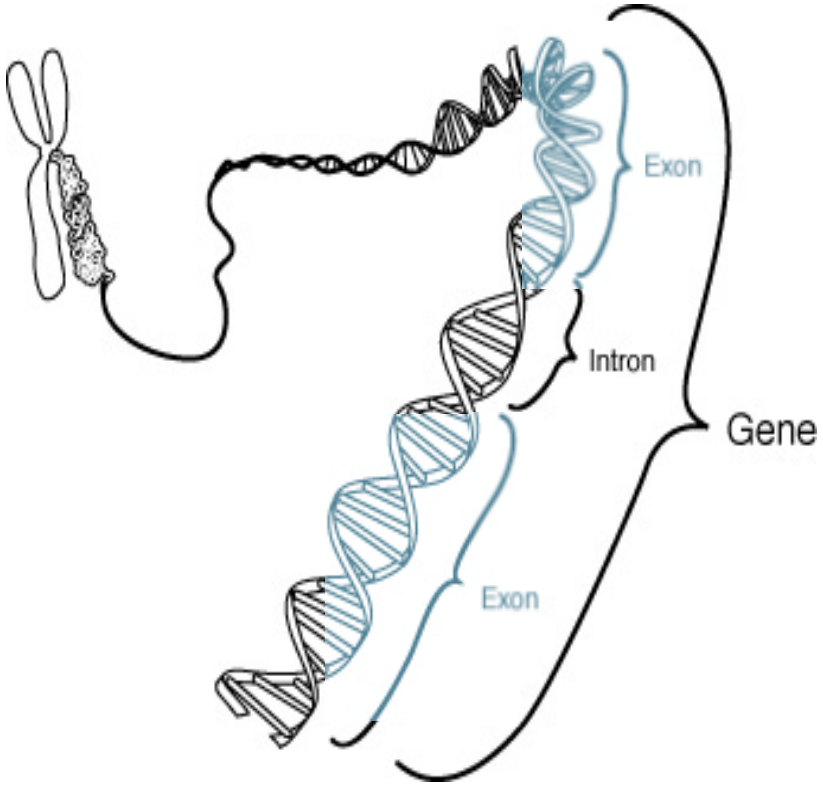
1.5 Mb: 50 genes



NGS → Exome sequencing

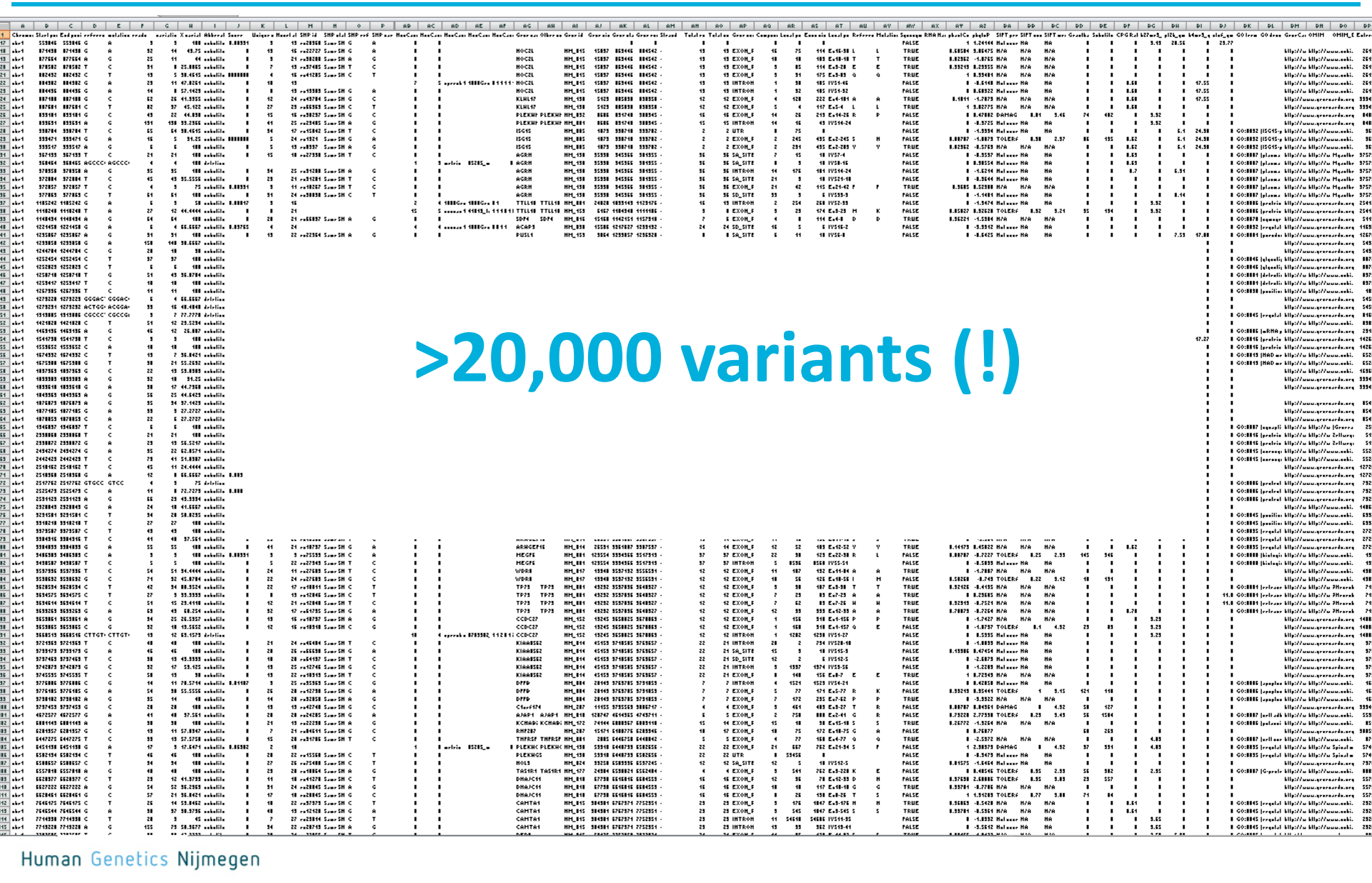
'Exome' (all exons of a genome)

~1% of the human genome



All coding sequences of a human genome (>200,000 exons), sequenced and analyzed in **one** experiment

Bioinformatics pipeline

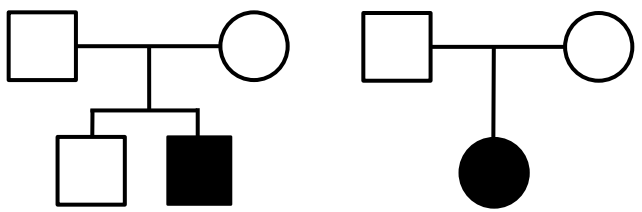


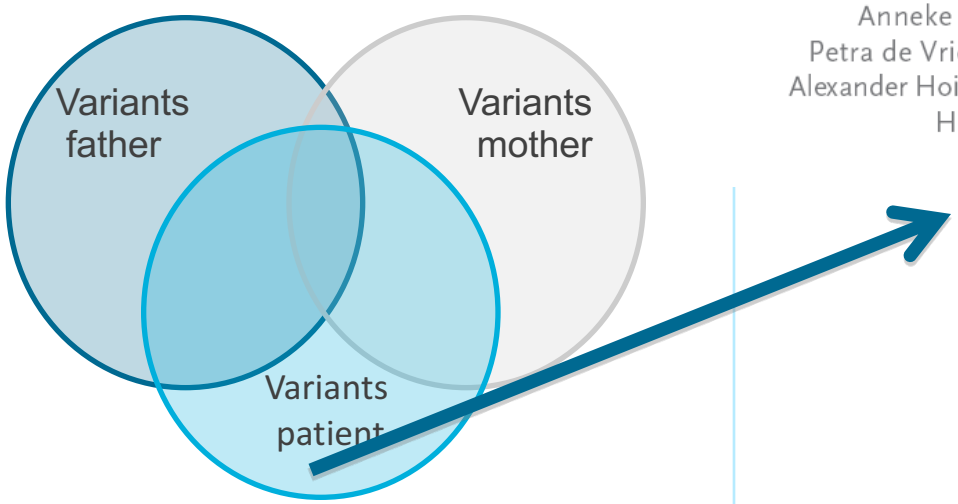
>20,000 variants (!)

‘Trio sequencing’

Study design ‘child-parent trio’s’

patients
(and parents)





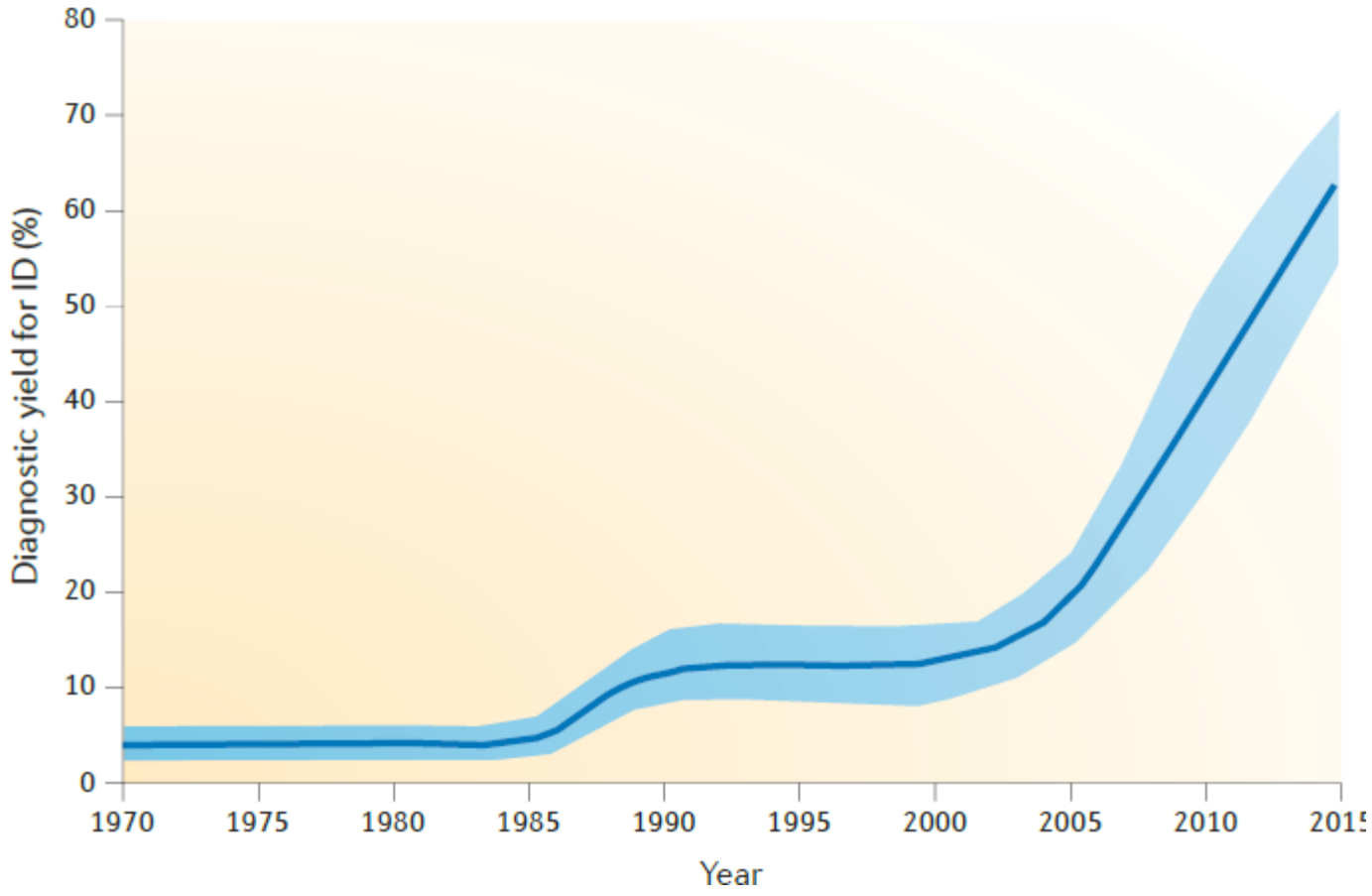
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability

Joep de Ligt, M.Sc., Marjolein H. Willemsen, M.D., Bregje W.M. van Bon, M.D., Ph.D., Tjitske Kleefstra, M.D., Ph.D., Helger G. Yntema, Ph.D., Thessa Kroes, B.Sc., Anneke T. Vulto-van Silfhout, M.D., David A. Koolen, M.D., Ph.D., Petra de Vries, B.Sc., Christian Gilissen, Ph.D., Marisol del Rosario, B.Sc., Alexander Hoischen, Ph.D., Hans Scheffer, Ph.D., Bert B.A. de Vries, M.D., Ph.D., Han G. Brunner, M.D., Ph.D., Joris A. Veltman, Ph.D., and Lisenka E.L.M. Vissers, Ph.D.

Diagnostic yield for ID



Vissers, Gillissen&Veltman; Nat Rev Genet 2016

Broadening clinical spectrum

Gene, 2016

Research paper

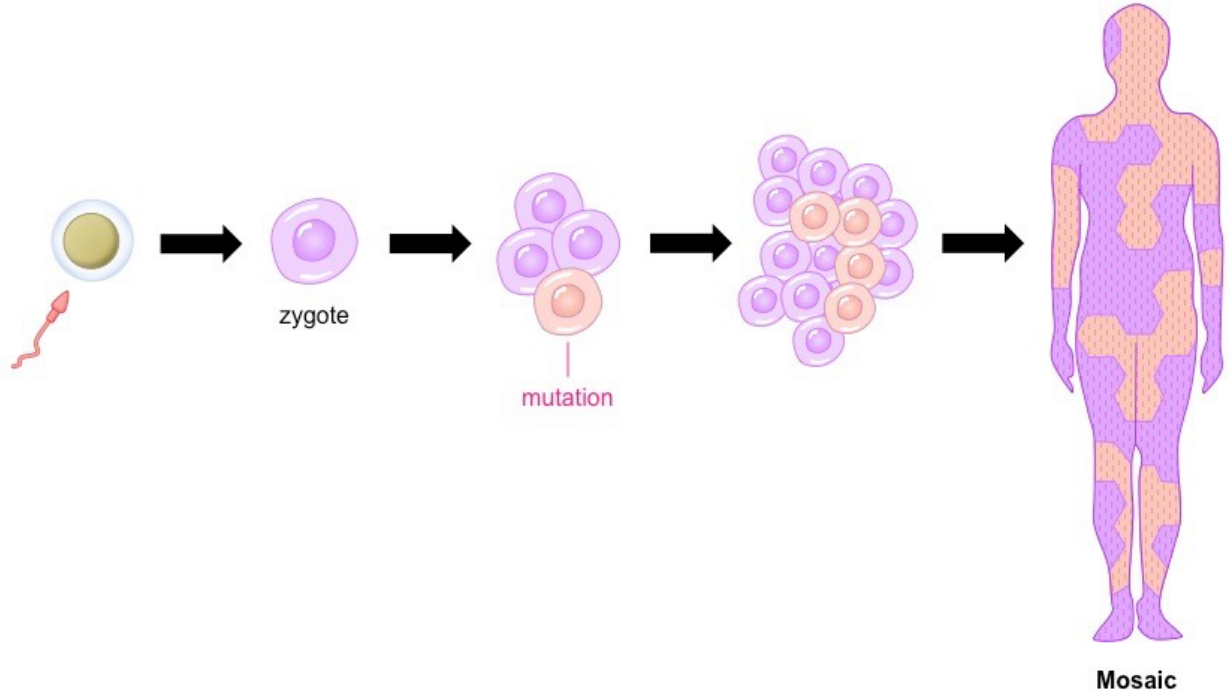
Targeted next generation sequencing of a panel of autism-related genes identifies an *EHMT1* mutation in a Kleefstra syndrome patient with autism and normal intellectual performance

Table 2
Patient characteristics.

Characteristics	
Sex (M/F)	F
Age (y)	12
Family history[a]	Brother with ASD
ADOS classification[b]	autism
ADOS communication social interaction total	*10*
ADI-R social diagnostic score	*12*
ADI-R communication diagnostic score	17
ADI-R repetitive behaviors diagnostic score	4
WISC-IV[c] FSIQ	92 (87–97)
Verbal comprehension index	96 (90–105)
Perceptual reasoning index	92 (86–99)
Working memory index	103 (94–113)
Processing speed index	86 (76–100)
Vineland-II score[c]	75 (70–80)
Communication skills	77 (70–84)
Daily living skills	81 (73–89)
Social skills	73 (65–81)
Maladaptive behavior index	Elevated

9q34 deletions and EHMT1 mutations

mostly occur novel…



Mosaic parents may have significant problems

de Boer *et al. Molecular Autism* (2018) 9:5
DOI 10.1186/s13229-018-0193-9

Molecular Autism

RESEARCH Open Access

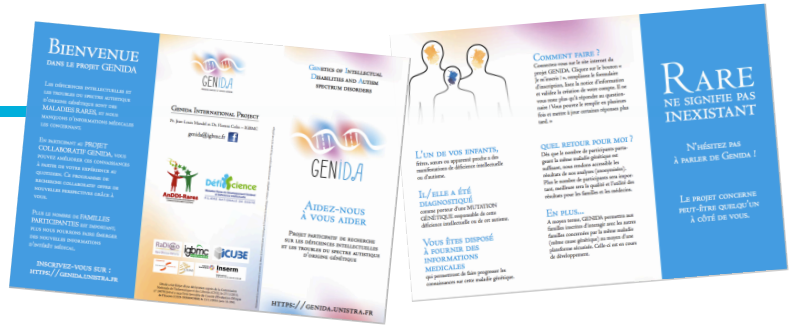
EHMT1 mosaicism in apparently unaffected parents is associated with autism spectrum disorder and neurocognitive dysfunction

Anneke de Boer[1,3†], Karlijn Vermeulen[1,2,3†], Jos I. M. Egger[4,5,6], Joost G. E. Janzing[3], Nicole de Leeuw[7], Hermine E. Veenstra-Knol[8], Nicolette S. den Hollander[9], Hans van Bokhoven[2,7], Wouter Staal[1,2,3,10,11] and Tjitske Kleefstra[2,7*]

My conclusion slide - 2016

- **Large variability both clinically and molecularly**
- **What about natural history and phenotype?**
  - **> Need for registry of natural history**
  - **> Emphasis on behaviour and psychopathology, but also different topics**
- **International collaboration on the syndrome is warranted**
  - **> Network of dedicated professionals (> foundation/patient network)**
- **Funding is hard, particularly because of rare ID/autism disorder**
  - **> Foundation**

GENIDA
https://genida.unistra.fr



GENIDA – **Gen**etics of **I**ntellectual **D**isability and **A**utism spectrum disorders

A participatory research program for families and professionals

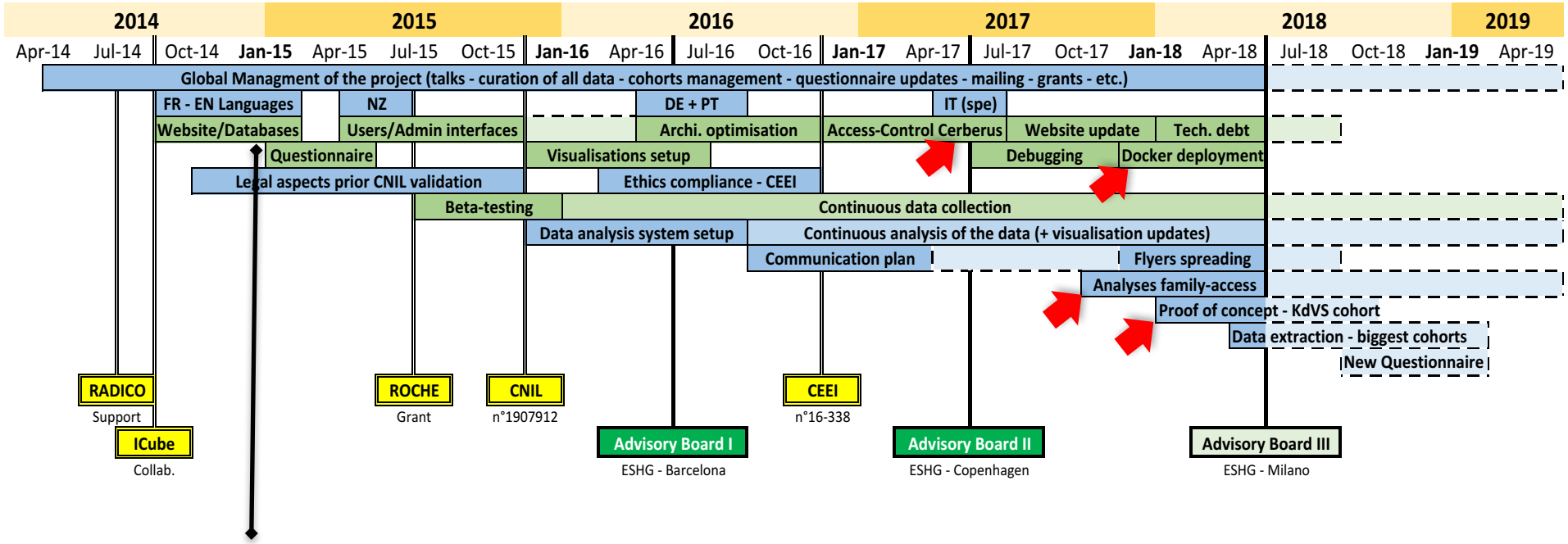
Florent Colin
Jean-Louis Mandel

https://genida.unistra.fr

RaDiCo Rare Disease Cohorts
iCUBE Laboratoire des sciences de l'ingénieur de l'informatique et de l'imagerie
igbmc institut de génétique et de biologie moléculaire et cellulaire
USIAS
FONDATION UNIVERSITÉ DE STRASBOURG
AnDDI-Rares Filière de Santé Anomalies du Développement et Déficience Intellectuelle de Causes Rares
DéfiScience Maladies Rares du Développement Cérébral et Déficience Intellectuelle FILIÈRE NATIONALE DE SANTÉ

GENIDA route

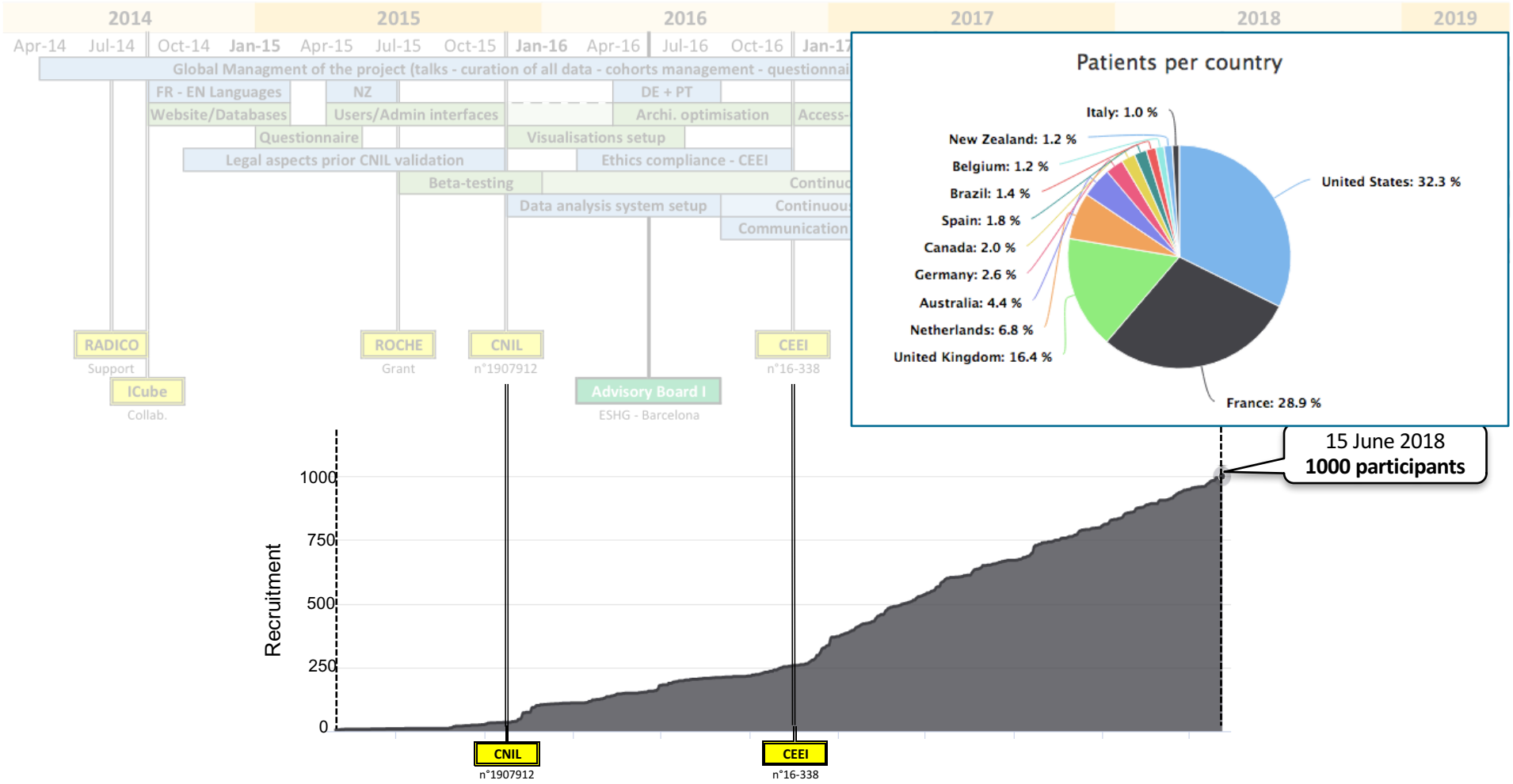
https://genida.unistra.fr



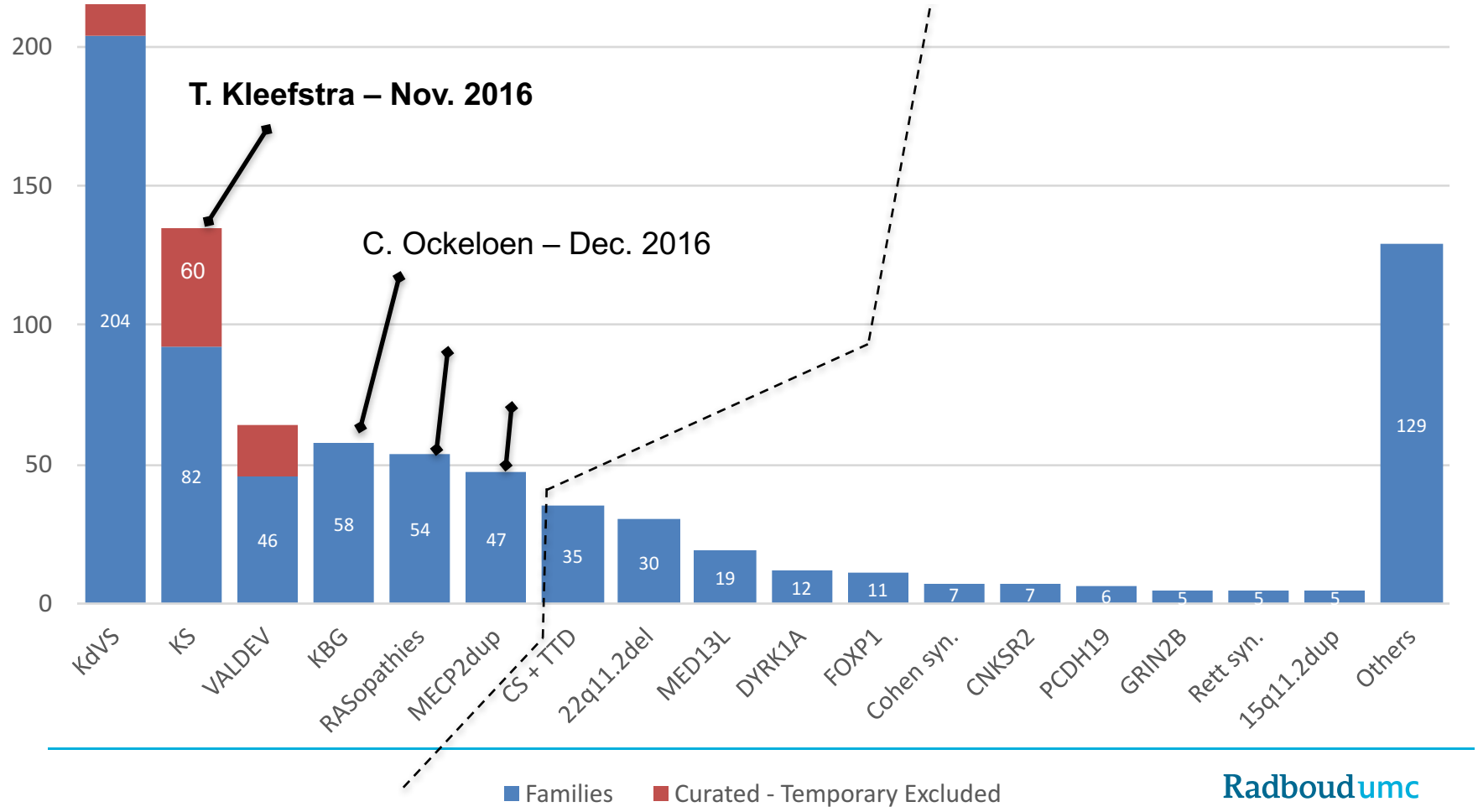
Collaboration David Koolen and Tjitske Kleefstra

GENIDA project families recruitment status

https://genida.unistra.fr



	num	avr nbr of answers
Excellent participation (above full completion >46)	38	50,8
Good participation (>10 and <46	26	36,2
Low participation (>1 and <10)	18	4,5
Total participation	**82**	**36,0**
No participation (=0)	**60**	**0**
Total KS families	**142**	



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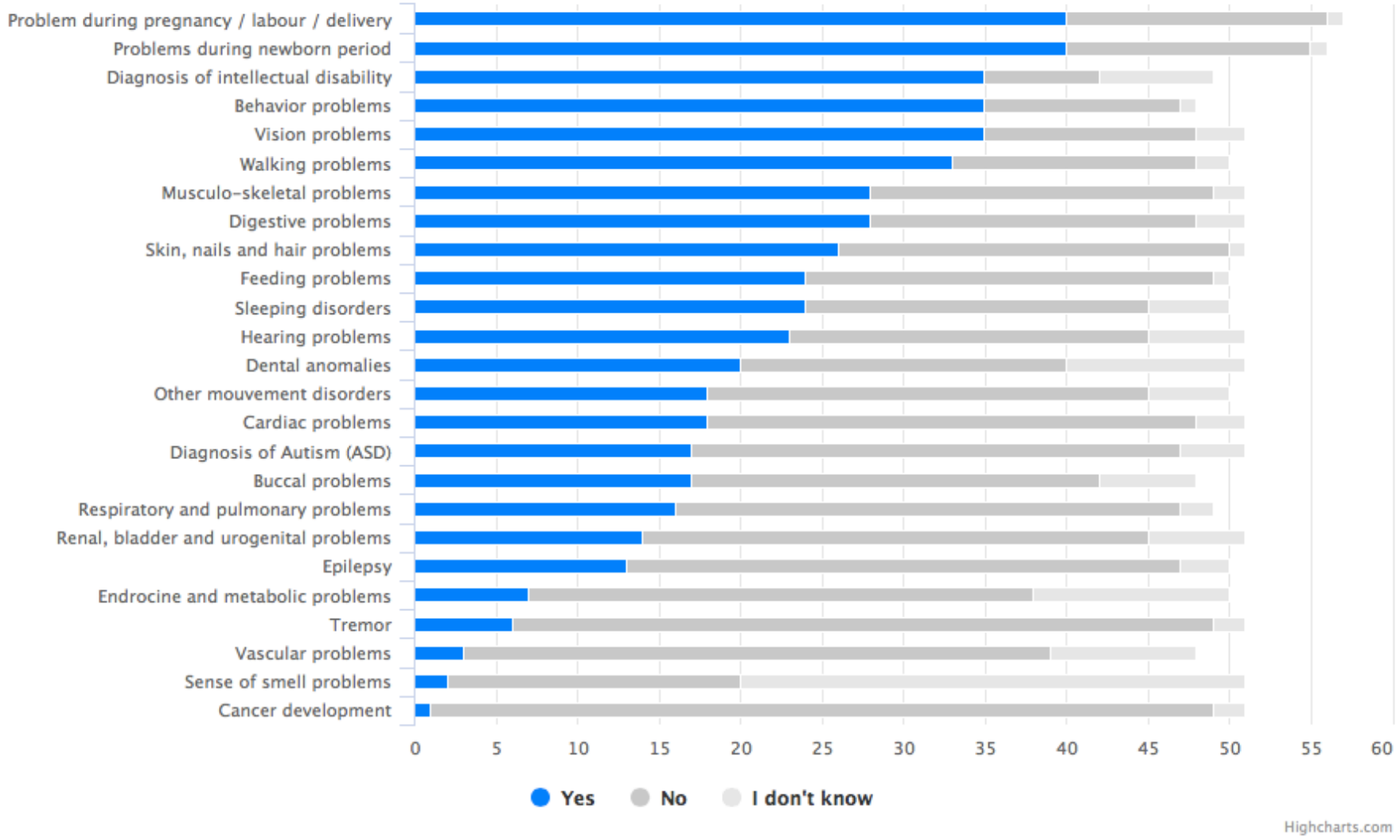
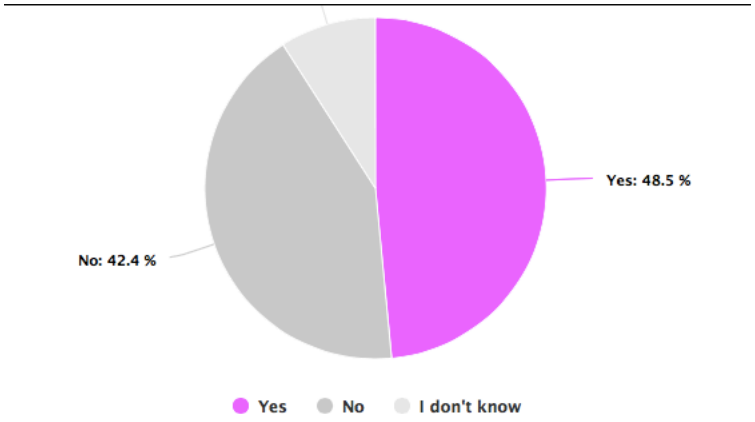
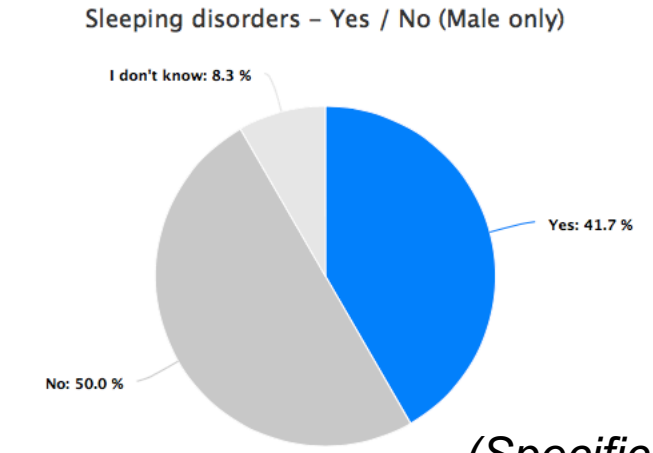
Overview - GenIDA



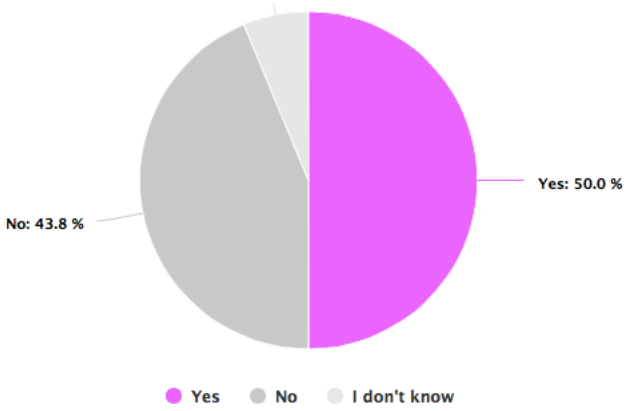
Sleep disorders (0-10 years):



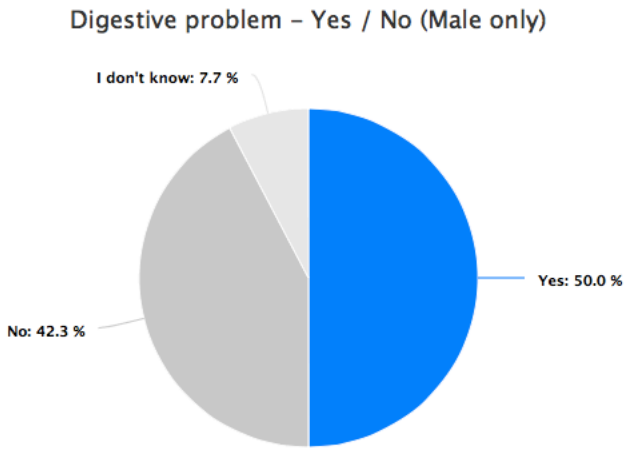


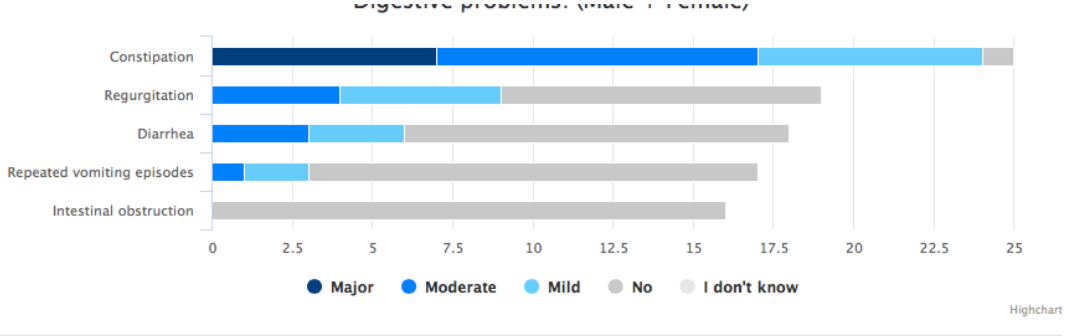
(Specific study on sleep will follow)

Digestive problems

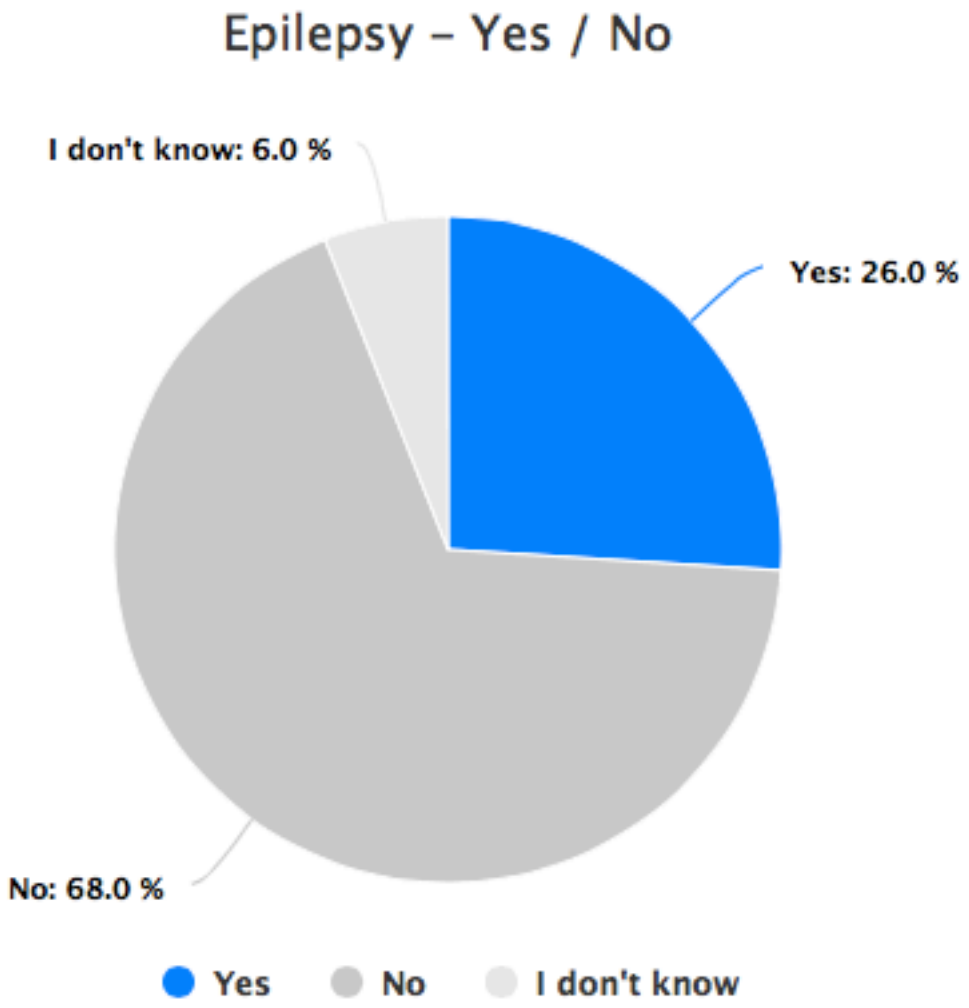


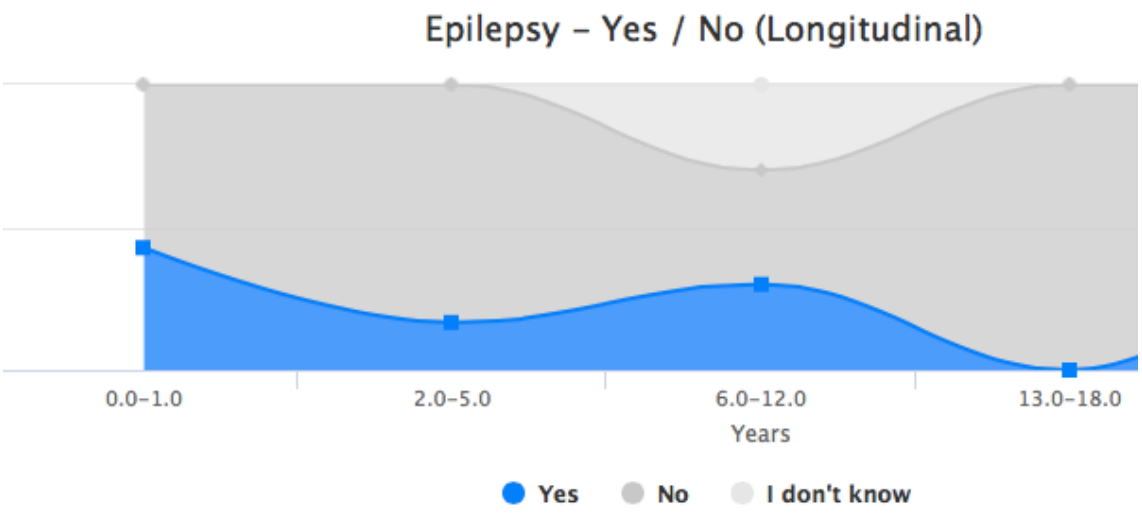
- laxative: Forlax, Miralax, etc
- enema
- cecostomy
- cyclic vomiting: topiramate (?)

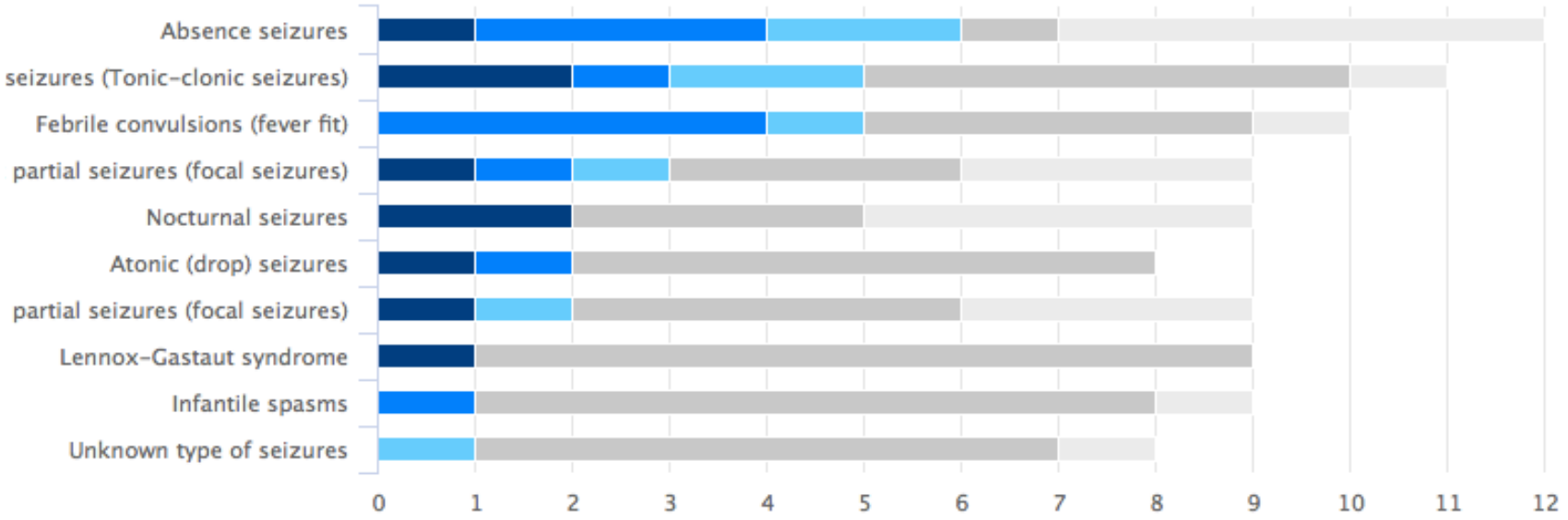




Epilepsy




Epilepsy – Yes / No (Longitudinal)
0.0–1.0
2.0–5.0
6.0–12.0
13.0–18.0
Years
Yes
No
I don't know


Absence seizures
seizures (Tonic–clonic seizures)
Febrile convulsions (fever fit)
partial seizures (focal seizures)
Nocturnal seizures
Atonic (drop) seizures
partial seizures (focal seizures)
Lennox–Gastaut syndrome
Infantile spasms
Unknown type of seizures
0
1
2
3
4
5
6
7
8
9
10
11
12

https://genida.unistra.fr

- Enter as much as possible details
- E-mails are sent by curator
- Also adults!

Future Studies: My conclusion slide - 2016

- **Large variability both clinically and molecularly**

- **What about natural history and phenotype?**
  - **> Need for registry of natural history**
  - **> Emphasis on behaviour and psychopathology, but also different topics**

- **International collaboration on the syndrome is warranted**
  - **> Network of dedicated professionals (> foundation/patient network)**

- **Funding is hard, particularly because of rare ID/autism disorder**
  - **> Foundation**

Zorg **O**nderzoek **N**ederland/**M**edische **W**etenschappen

Dutch Health Organisation

800.000 Euro

kinder- en jeugdpsychiatrie karakter

Donders Institute for Brain, Cognition and Behaviour

Dr Karlijn Vemeulen, (child- and adolescent))psychiatrist

PhD studies:

Neurocognitive endophenotypes: on the intersection of genetic syndromes and psychiatry

Psychopathology research project

- Developmental disability

- **Psychopathology**: KS patients have a vulnerable brain!
  - Autisme Spectrum Disorder (typical hand/finger posture/movements)
  - Sleep problems
  - Psychotic periods
  - Mood and anxiety disorders

- Regression in young adulthood, with loss of functioning and (enhancement) of sleep problems and hypoactivity.

Regression?

- In our experience > 18 years
- regression in general functioning
- Preceded by severe sleepproblems

- Paradoxal reaction to benzodiazepines
- Some severe agression

- Reaction on Olanzapine (or aripripazole), high doses(!)
- As soon as sleeppattern restores, right dosis
- Hypothesis: (manic) psychoses → schizophrenia/schizoaffective development

Radboudumc

Patiëntenzorg Research Onderwijs

Radboudumc Expertisecentrum
Zeldzame aangeboren ontwikkelingsstoornissen

Contact
Expertisecentrum zeldzame aangeboren ontwikkelingsstoornissen
(024) 361 39 46

neem contact op

Over

Samenwerkingen

Naast intensieve samenwerking tussen afdelingen genetica, geneeskunde voor mensen met verstandelijke beperkingen en het Amalia kinderziekenhuis is er ook een samenwerkingsverband met het Vincent van Gogh Topklinisch Centrum voor Neuropsychiatrie en met kinder- en jeugdpsychiatrisch centrum Karakter.

Expertisecentrum Zeldzame aangeboren ontwikkelingsstoornissen

Vincent van Gogh voor geestelijke gezondheidszorg

kinder- en jeugdpsychiatrie karakter

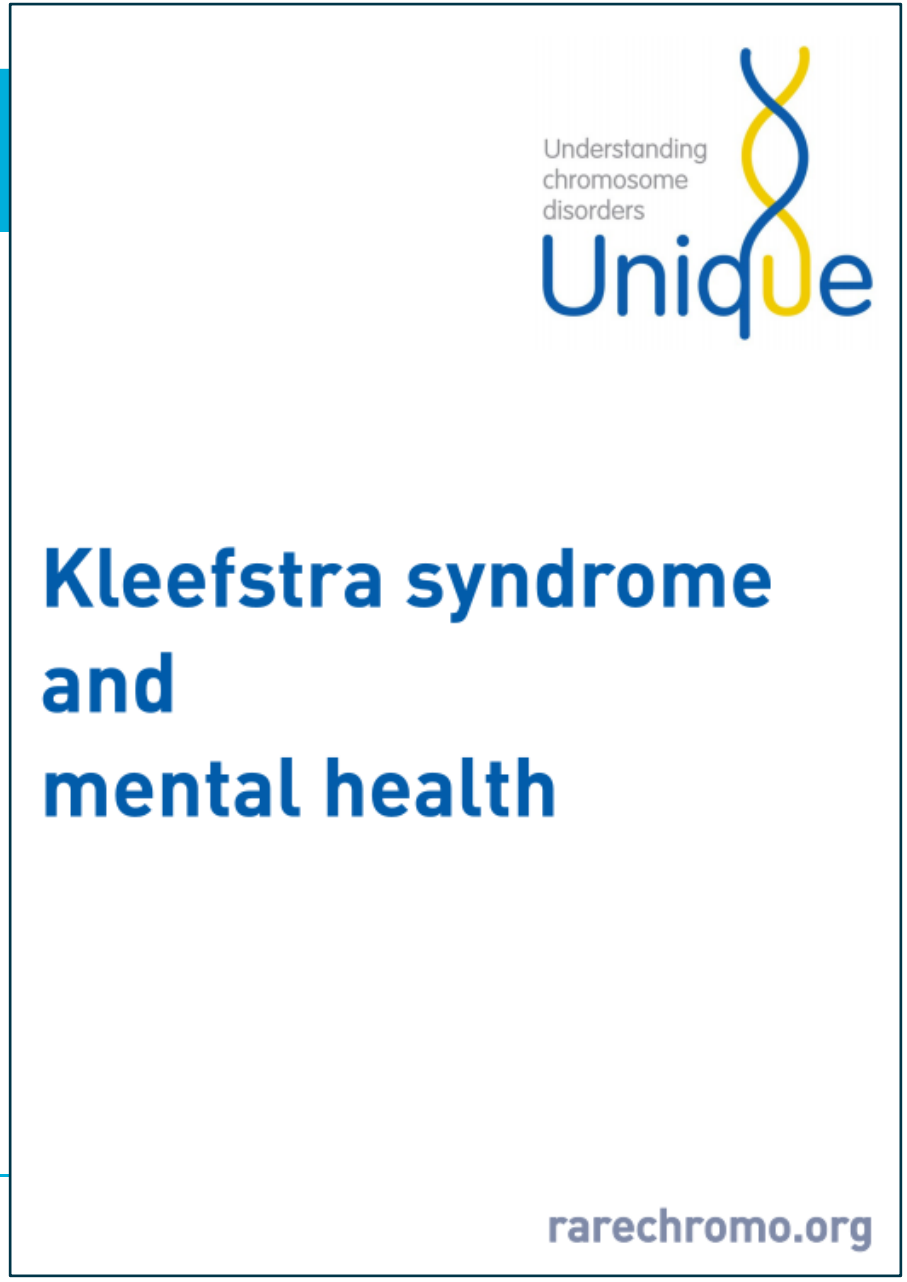
Radboudumc

Radboudumc expert center

- Intervention program

parents and children with Kleefstra Syndrome

- 12 jr: psycho-education/leaflet mental health
- From 16 year, 1- to 2-yearly follow up



Aims of the study

To develop and implement intervention strategies for Mendelian disorders affecting the epigenetic machinery

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

Objective 2: to understand the pathophysiology of the regression observed in KS and the mechanism of olanzapine using patient-derived induced neurons **>Nael**

Objective 3: to perform an international clinical effect study to prevent general regression in patients with KS syndrome

Follow up strategy

Tests	Test Characteristics	P / C	t_0 Inclusion	t_1 1 year	t_2 2 years	t_3 3 years	t_4 4 years
General examination *	Includes height, weight, blood pressure, heartbeat frequency, abdominal circumference, biobank sampling (t_0) and video-monitoring	P	+	+	+	+	+
VABS[25,26]	*The Vineland Adaptive Behavior Scale* to assess developmental age and possible developmental regression	C	+	+	+	+	+
PANSS[27,28]	*Positive And Negative Syndrome Scale* to measure both positive and negative psychotic symptoms	P/ C	+	+	+	+	+
Mini PAS-ADD[29,30]	*Mini Psychiatric Assessment Schedules for Adults with Developmental Disabilities* to measure a broad range of psychopathology	C	+	+	+	+	+
ADOS-2[31,32]	*Autism Diagnostic Observation Schedule* Standardized psychiatric observation of Autismspectrum symptoms	P	+		+		+
CBCL	*Child behavior checklist* to asses behavioural difficulties	C	+	+	+	+	+
Beery-VMI[33]	Test for Visual-Motor Integration	P	+	+	+	+	+
LLT[34]	*Location Learning Test to* asses spatial learning and memory	P	+	+	+	+	+
(IQ test)*	Wechsler scale (WAIS-IV/WISC-III)	P	(+)				
(CANTAB) [35]**	*CAmbridge Neuropsychological Test Automated Battery* Computer based assessment of attention, memory and reaction time	P	(+)	(+)	(+)	(+)	(+)

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Center UK
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Points to consider

- Recruitment

Also ‘older’ adults!

- Dedicated professionals

- Co-funding

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