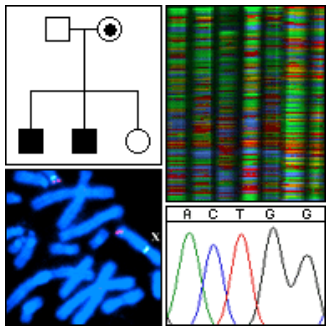

Genetics of Intellectual Disability and Autism: possibilities and limitations

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ID definition

World Health Organization
REGIONAL OFFICE FOR Europe

Definition: intellectual disability

Intellectual disability means a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning), and begins before adulthood, with a lasting effect on development.

Disability depends not only on a child's health conditions or impairments but also and crucially on the extent to which environmental factors support the child's full participation and inclusion in society.

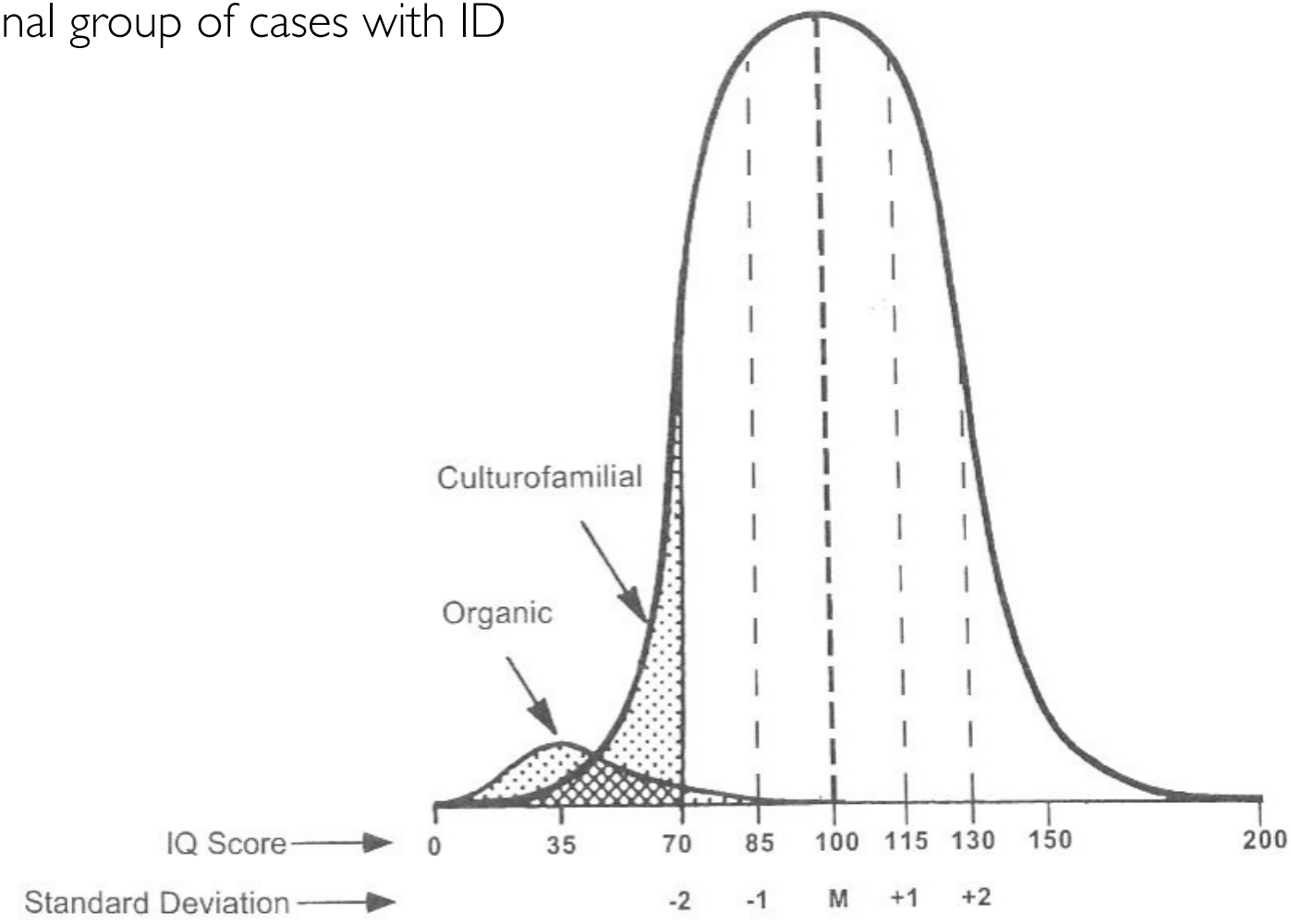
The use of the term intellectual disability in the context of the WHO initiative "Better health, better lives" includes children with autism who have intellectual impairments. It also encompasses children who have been placed in institutions because of perceived disabilities or family rejection and who consequently acquire developmental delays and psychological problems.

Epidemiology

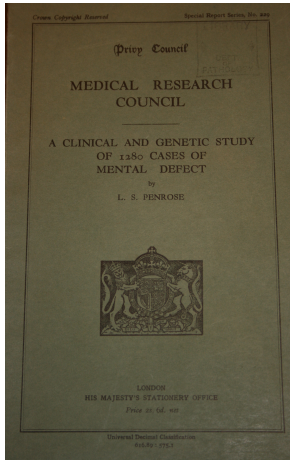
- Intellectual disability is common and affects 1-2 % population
- Developmental delay is the commonest referral reason to paediatric clinical genetics services
- Etiology is poorly understood
- In some families there is a clear X linked inheritance pattern where males are affected and it is inherited through unaffected or mildly affected females
- <90% of cases there is no family history

Epidemiology

- IQ has a normal distribution but IQ <50 presence of additional group of cases with ID



Epidemiology



Males excess 1.3:1
Penrose LS 1938 1280 inpatients

Severity	*IQ*	*Males*	*Females*	*M:F*
Profound	<20	1166	964	1.21
Severe	20–34	835	610	1.37
Moderate	35–49	833	619	1.35
Mild	50–70	1130	841	1.34
Borderline/low normal	>70	180	107	1.68

- Replicated in multiple studies internationally

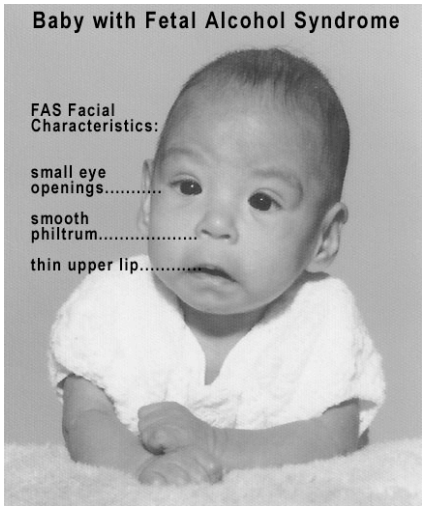
South Carolina Institutions
Anderson et al 1996

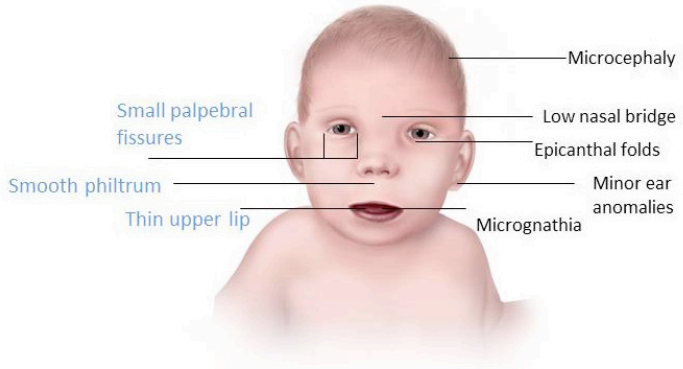
Causation	*Age < 20 Years IQ < 50*	*Age > 19 Years IQ < 50*
1 Chromosomal	123 (10.5)*	568 (15.1)
2 Single gene	113 (9.6)	238 (6.3)
3 Multifactorial	35 (3.0)	34 (0.9)
4 Culturofamilial	63 (5.4)	108 (2.9)
5 Known syndrome	30 (2.6)	55 (1.5)
6 Other genetic	10 (0.9)	45 (1.2)
7 Injury, prenatal	3 (0.3)	17 (0.5)
8 Injury, perinatal	69 (5.9)	153 (4.1)
9 Injury, postnatal	30 (2.6)	76 (2.0)
10 Infection, prenatal	17 (1.4)	44 (1.2)
11 Infection, perinatal	15 (1.3)	12 (0.3)
12 Infection, postnatal	53 (4.5)	230 (6.1)
13 Chemical, prenatal	24 (2.0)	12 (0.3)
14 Chemical, perinatal	3 (0.3)	17 (0.5)
15 Chemical, postnatal	1 (0.1)	15 (0.4)
16 Prematurity	111 (9.4)	91 (2.4)
17 Other environmental	9 (0.8)	12 (0.3)
18 Unknown	467 (39.7)	2046 (54.2)
Total	1176†	3773

Factor that influence intellectual development

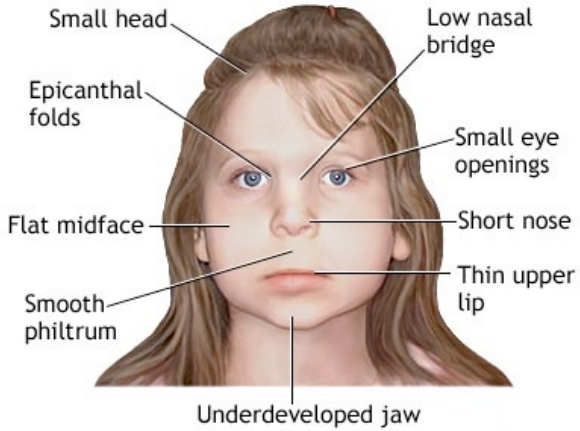
- Environmental
  - Prenatal, perinatal and postnatal infections (rubella, CNV, measles, toxoplasmosis and sepsis)
  - Drug exposure (fetal alcohol, valproate)
  - Diet (PKU, inborn errors of metabolism)
  - Prematurity
- Genetics variation
  - High penetrant aberrations of genetic material
    - Chromosomal anomalies trisomy 21, deletions
    - Copy Number Variants
    - Single gene defects
    - Genetic modifiers of disease severity
  - Culturofamilial factors e.g. parental IQ is a strong predictor within the normal range
    - Polygenic
    - Genetics modifiers of monogenic disease

Fetal Alcohol





Toxin during key stages of development
Generally affects all organs
Characteristic face
Poor concentration
Poor intellectual development
Poor growth



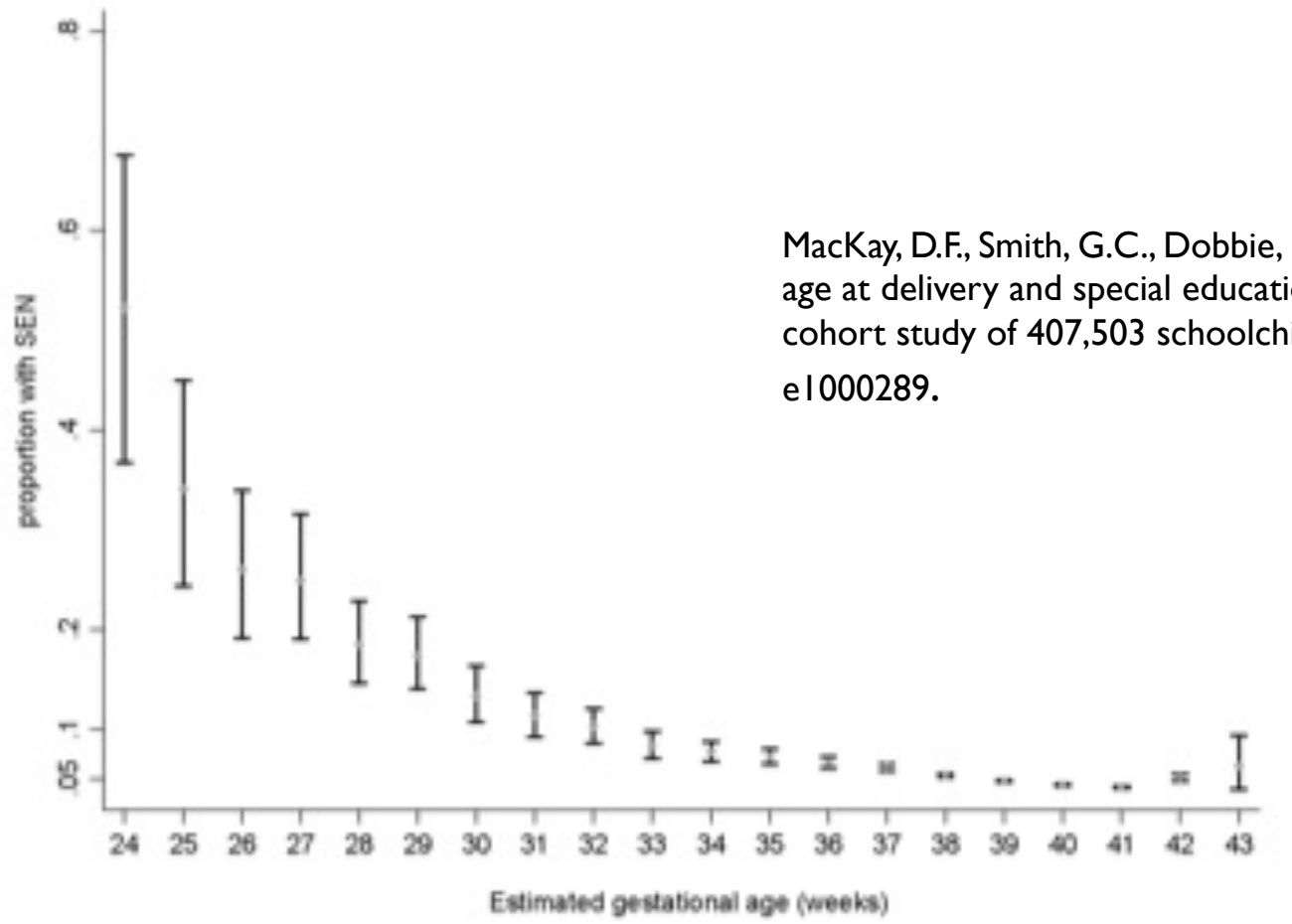
Photomontage Fetal alcohol

Fetal Valproate

Spina bifida 30X population risk

Clinical features: epicanthic folds; infraorbital groove; medial deficiency of the eyebrows;
flat nasal bridge; short nose with anteverted nares;
smooth or shallow philtrum; long thin upper lip; thick lower lip;
small, downturned mouth; spina bifida; cardiac malformations; neurodevelopmental delay

Special educational need as a function of gestation

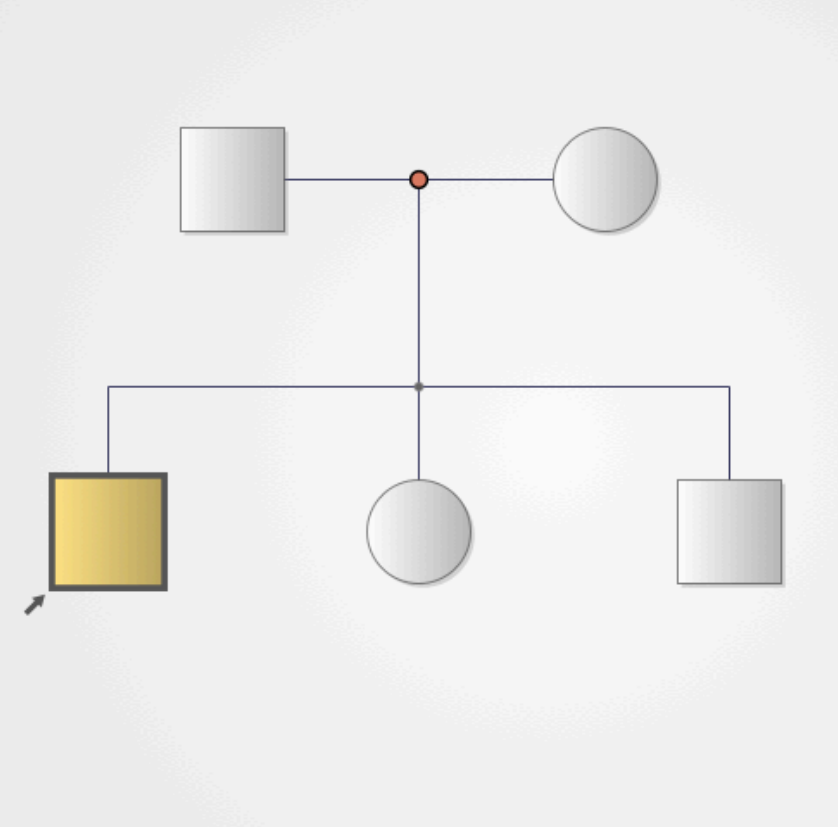


MacKay, D.F., Smith, G.C., Dobbie, R. & Pell, J.P. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med* **7**, e1000289.

Empiric recurrence risks (IQ <50)

Reference	*Male IP*			*Female IP*		
	Brother	*Sister*	*All sibs*	*Brother*	*Sister*	*All sibs*
Turner et al 1971			2-9%			3.5-4%
Bundey et al 1974	6.7%	3.2%	5%	4.4%	6.3%	5.4%
Herbst et al 1982	6%	2.3%	4.3%	2.9%	5.6%	4.2%
Bundey et al 1986	10%	5%	7.5%			
Costeff et al 1987	14%	14%	14%	8.5%	9.6%	9.2%
	6-14%	2-14%		3-8%		

Mechanism of Disease



- Environmental
- Genomics CNV abnormality
- X linked recessive
- Autosomal recessive
- De novo autosomal dominant

Population Genetics

- Frequency of a disease in the population depends on
  - New mutation rate
  - Reproductive lethality
  - Sustainability of the disease in the population
  - Degree of relatedness of parents

- Familial conditions tend to be those that do not affect fertility
- Conditions that do affect fertility tend to be new mutations or recessive where parents are unaffected

Is the male excess due to X linked disease

- ARX data 6.6% mutation in families which were research families and phenotypically variable with syndromic and non-syndromic (3.5-12.1 95%CI)
- 0.13% in sporadic males with non-syndromic disease (</= 0.45)
- If the males excess is due to XLMR then mutations should be 1.6% in sporadic cohort if the 30% male excess is due to XLMR
- Observed rates are more in keeping with 10% of male excess is XLID

European Journal of Human Genetics (2004) 12, 689–693

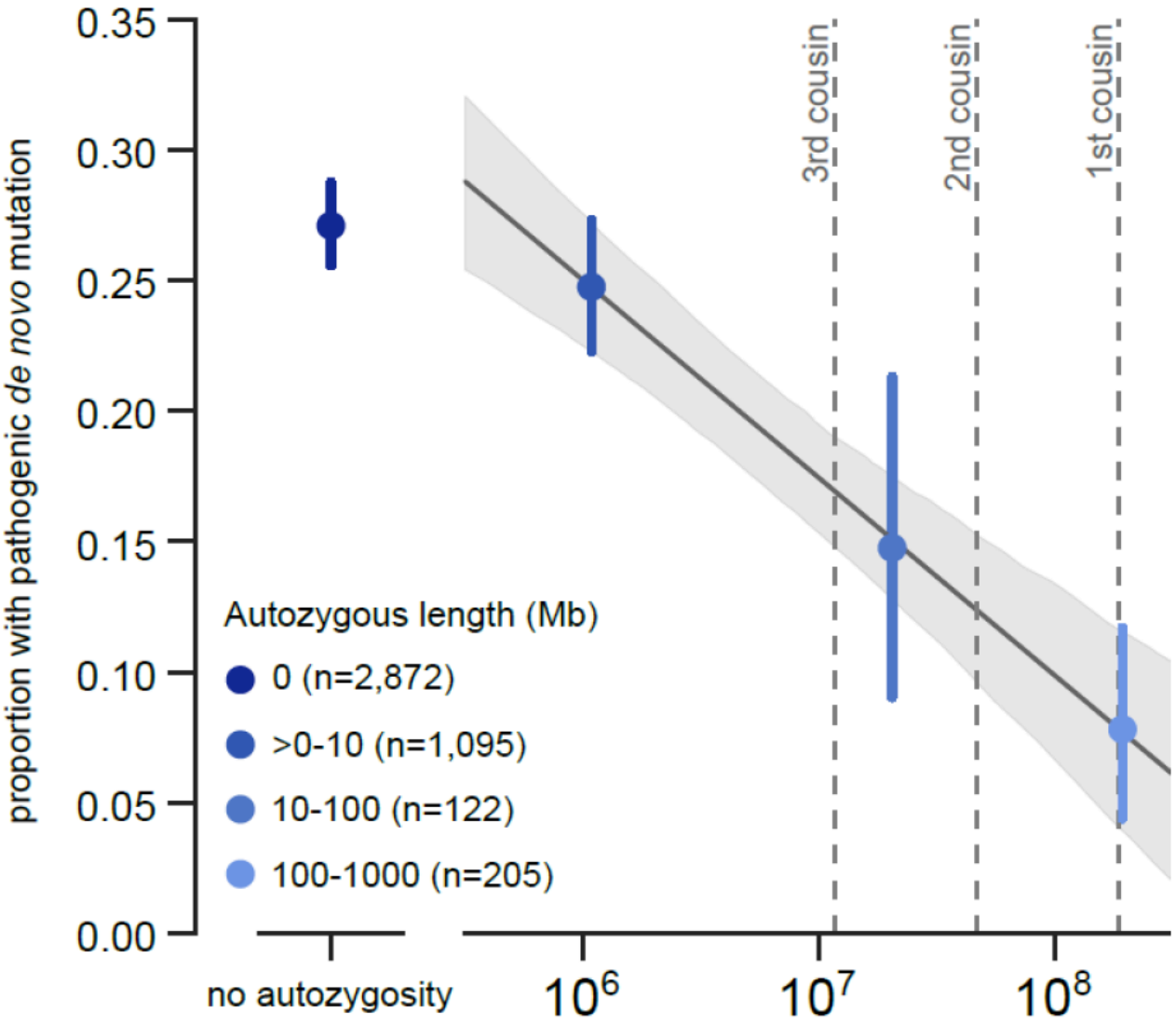
www.nature.com/ejhg

NEWS AND COMMENTARY

Monogenic X-linked mental retardation: Is it as frequent as currently estimated? The paradox of the ARX (Aristaless X) mutations

Jean-Louis Mandel*,[1,3] and Jamel Chelly[2]

De novo rates in consanguinous families



www.ddduk.org

Restoring reproductive confidence in families with X-linked intellectual disability by finding the causal mutation

Carrier status Knowledge	No. women	Reproductive Years *	Women with children (%)	Women with no children (%) †	Sons (no. affected)	Daughters	Offspring/ reproductive Year ‡
At risk	48	673	16 (33)	32 (66)	8(2)	17 #	1 in 27
Not a Carrier	23	123	18(78)	5 (21)	11(0)	7 §	1 in 6
Carrier	19	181	16(84)	3 (16)	11(2)	13 ⊙	1 in 7

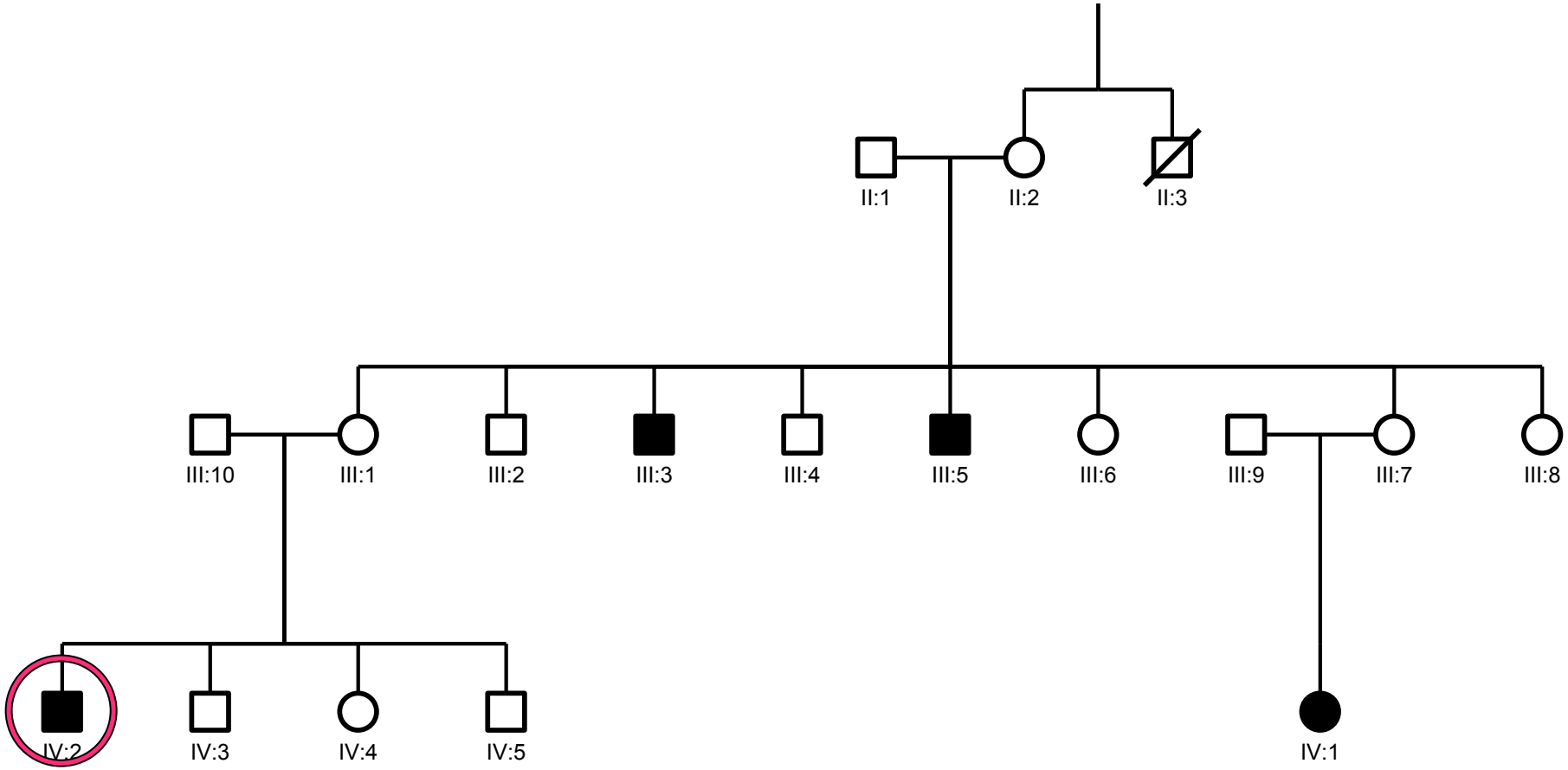
‡ **average rate in NSW = 1 in 11**; † for differences pre and post tests, X^2 =20.67, df 2, p< .0005; § plus 4 pregnancies, sex unknown; ⊙ plus 1 pregnancy, sex unknown

G Turner et al Clin Genet 2008 73:188-90

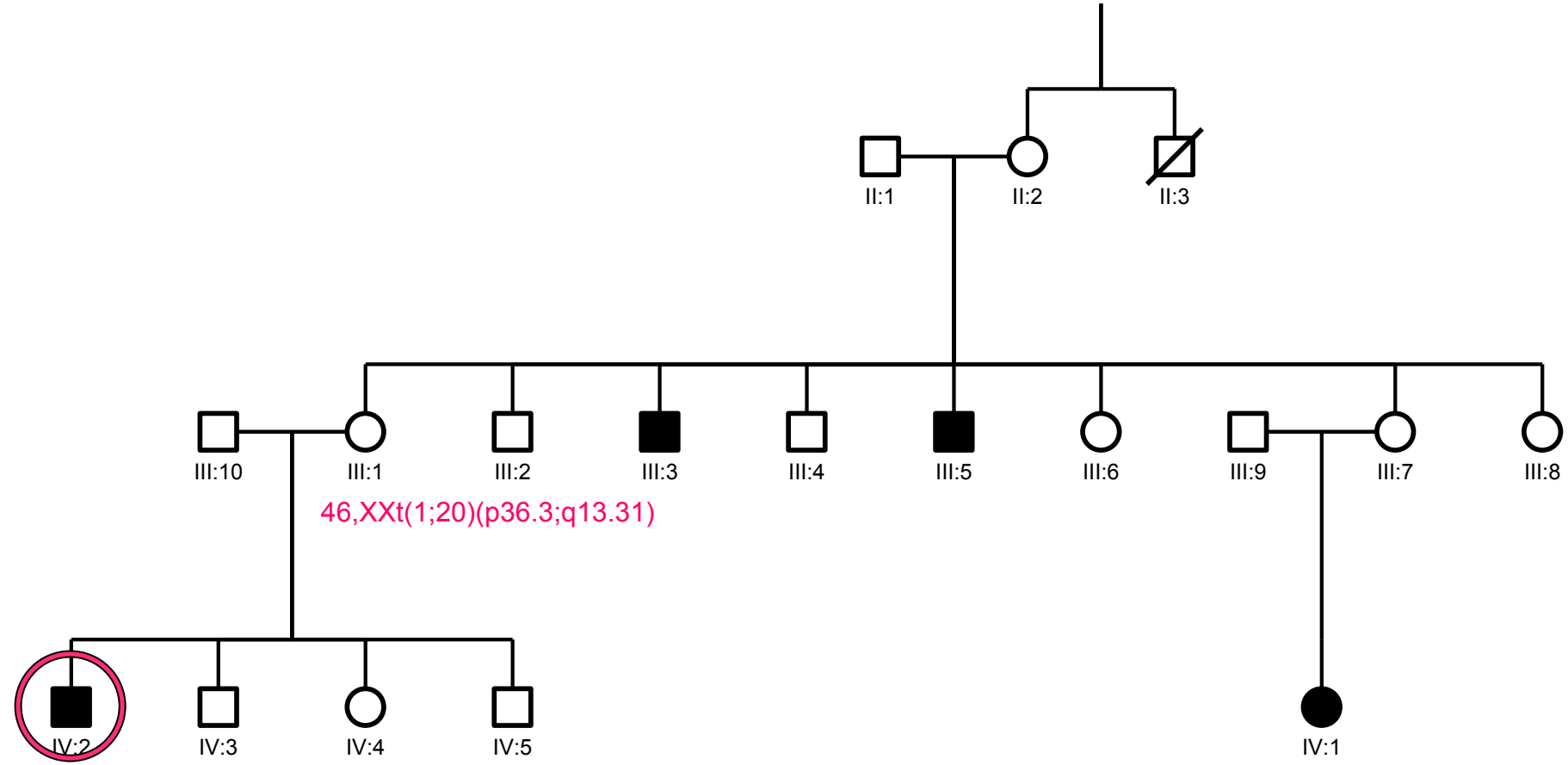
Investigation of a child with intellectual disability

- Pedigree
- Karyotype
- Microarray analysis <4 Mb resolution
- X inactivation pattern
- Selective gene analysis for specific syndromes

X-linked intellectual disability ?



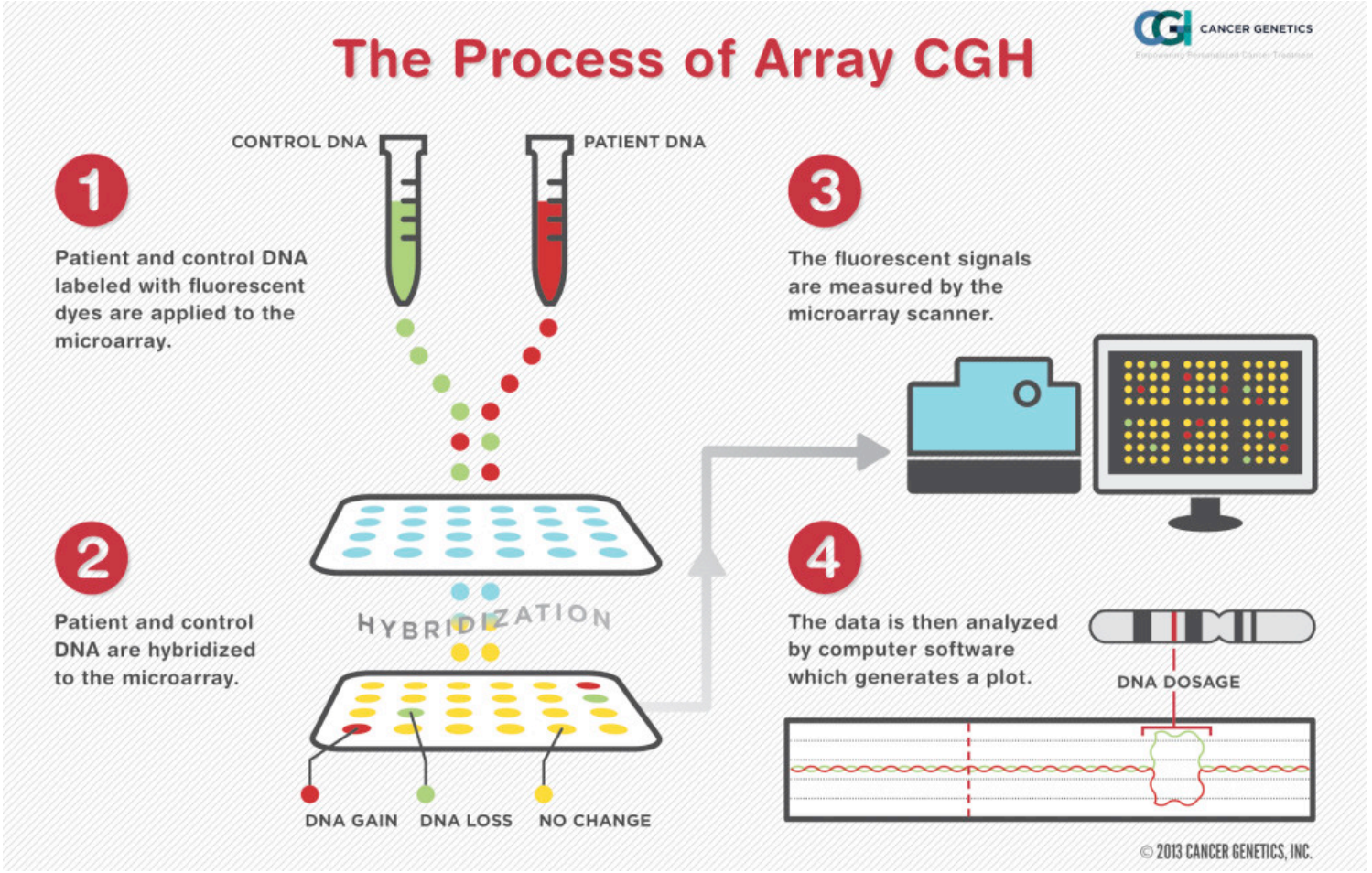
G-banding



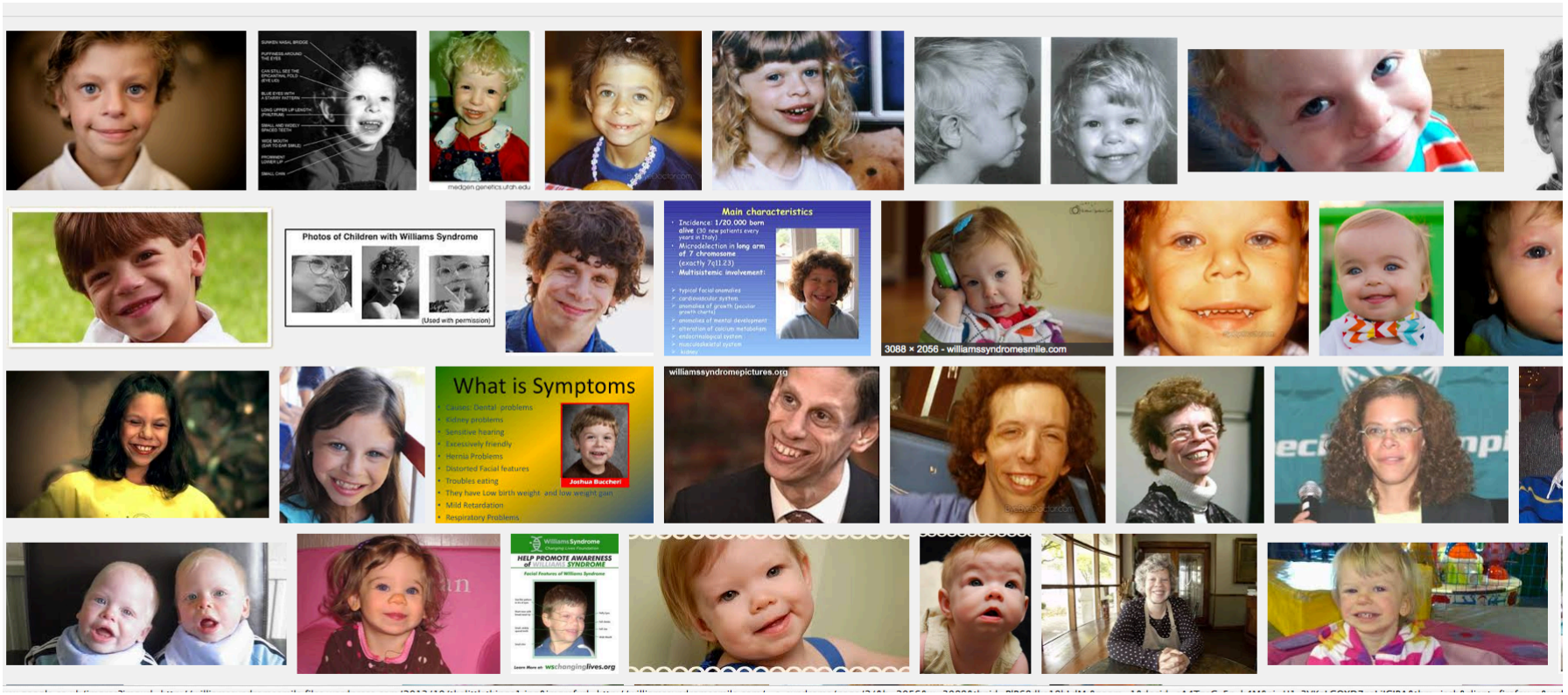
46,XY,der(1)t(1;20)(p36.3;q13.31)mat

1p36 syndrome

Array CGH

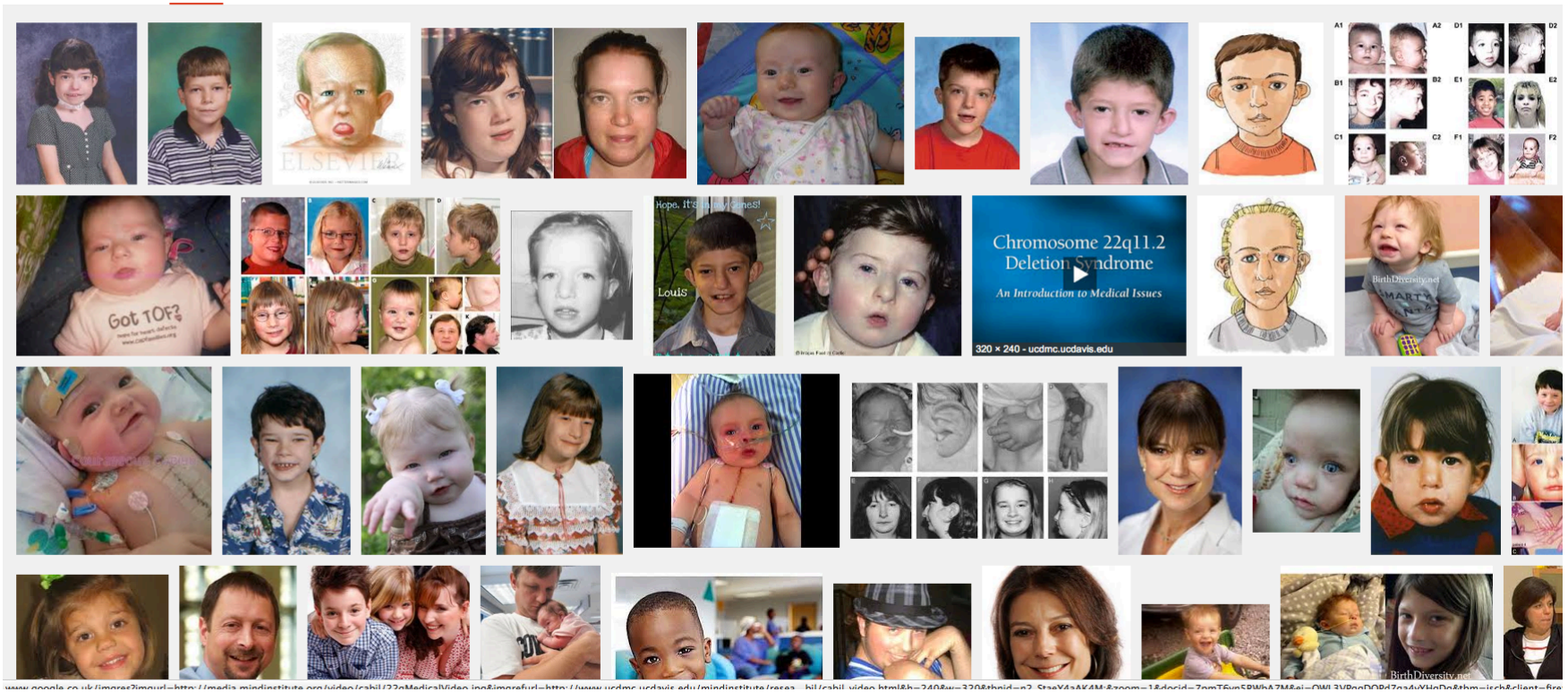

The Process of Array CGH
CANCER GENETICS
CONTROL DNA
PATIENT DNA
1
Patient and control DNA labeled with fluorescent dyes are applied to the microarray.
2
Patient and control DNA are hybridized to the microarray.
HYBRIDIZATION
DNA GAIN
DNA LOSS
NO CHANGE
3
The fluorescent signals are measured by the microarray scanner.
4
The data is then analyzed by computer software which generates a plot.
DNA DOSAGE
© 2013 CANCER GENETICS, INC.

Williams syndrome

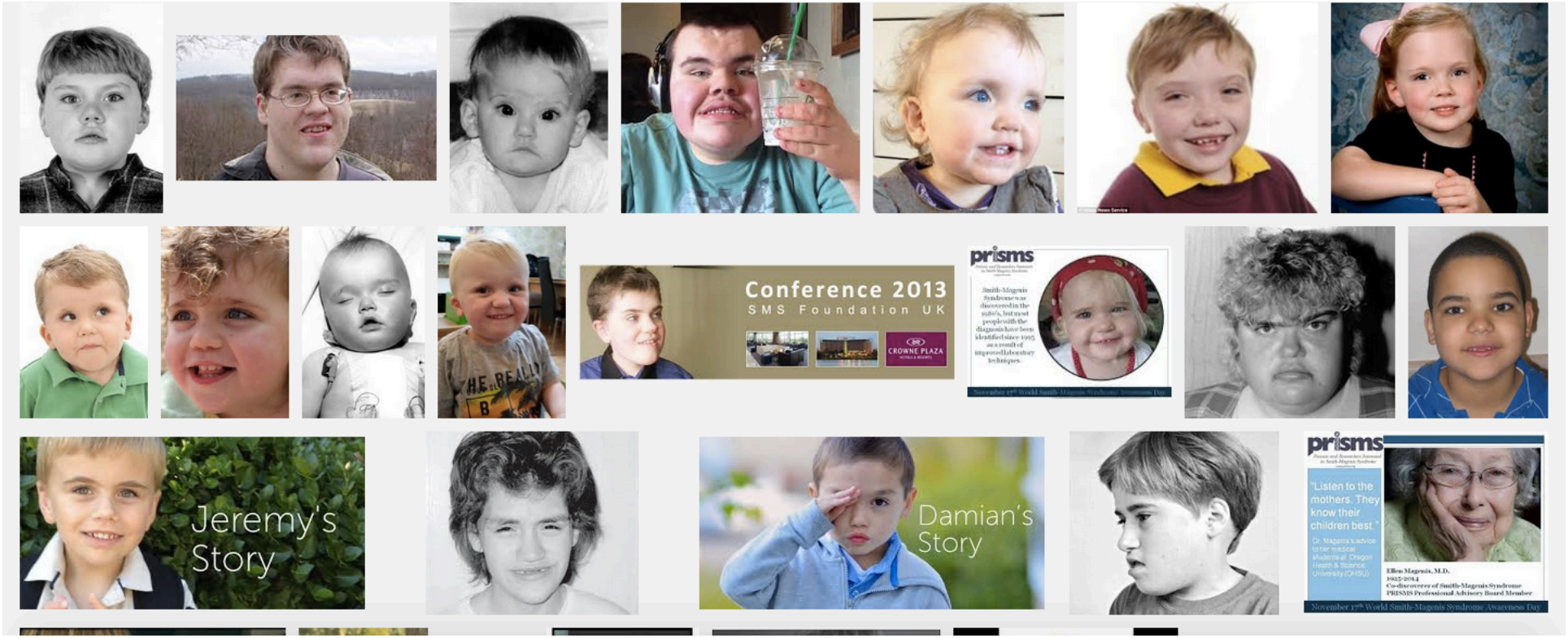


22q11 syndrome

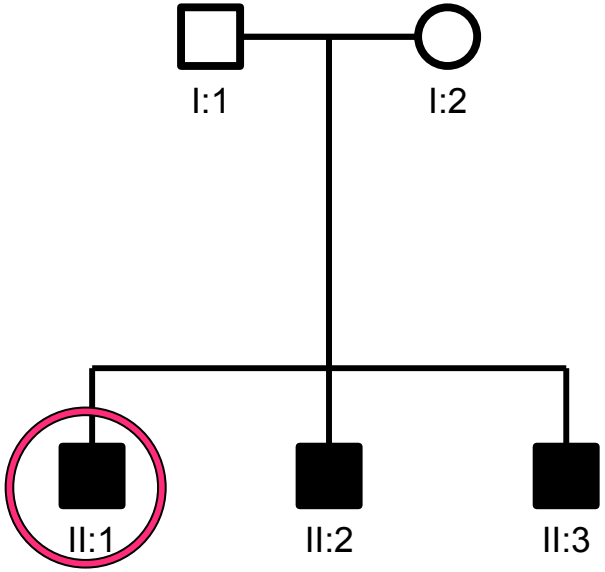
Cardiac; thymus aplasia; immundeficiency; velopharngeal insufficiency; learning disability

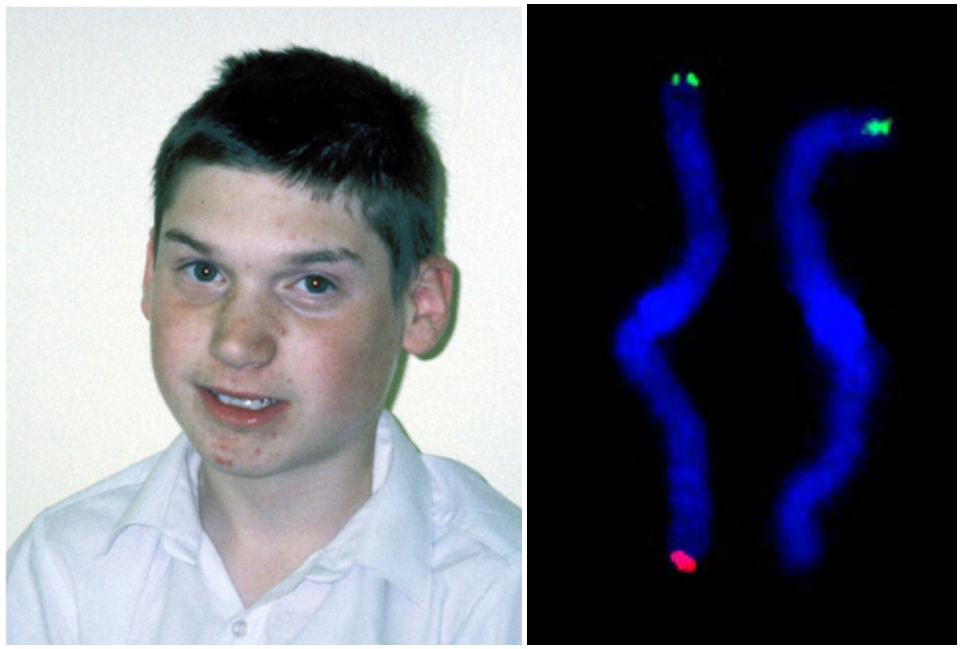


Smith Magenis syndrome



Diagnosis of 3q29 deletion





- de novo 3q29 deletion
- remember over ascertainment is common

3q29 deletion genome first diagnostics

Report

Am. J. Hum. Genet. 77:154–160, 2005

3q29 Microdeletion Syndrome: Clinical and Molecular Characterization of a New Syndrome

Lionel Willatt,[1] James Cox,[1] John Barber,[2] Elisabet Dachs Cabanas,[2] Amanda Collins
Dian Donnai,[4] David R. FitzPatrick,[5] Eddy Maher,[6] Howard Martin,[1] Josep Parnau,[1]
Lesley Pindar,[7] Jacqueline Ramsay,[5] Charles Shaw-Smith,[1] Erik A. Sistermans,[8]
Michael Tettenborn,[9] Dorothy Trump,[4] Bert B. A. de Vries,[8] Kate Walker,[2]
and F. Lucy Raymond[1]

RESEARCH ARTICLE

AMERICAN JOURN
medical gen

Novel Features of 3q29 Deletion Syndrome: Results From the 3q29 Registry

**Megan R. Glassford,[1] Jill A. Rosenfeld,[2] Alexa A. Freedman,[3] Michael E. Zwick,[1,4] Unique R
Chromosome Disorder Support Group,[5] and Jennifer G. Mulle[1,3]***

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia
[2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas
[3]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia
[4]Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia
[5]Unique Rare Chromosome Disorder Support Group, Surrey, United Kingdom

Manuscript Received: 25 August 2015; Manuscript Accepted: 9 December 2015

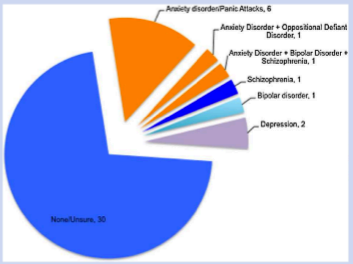
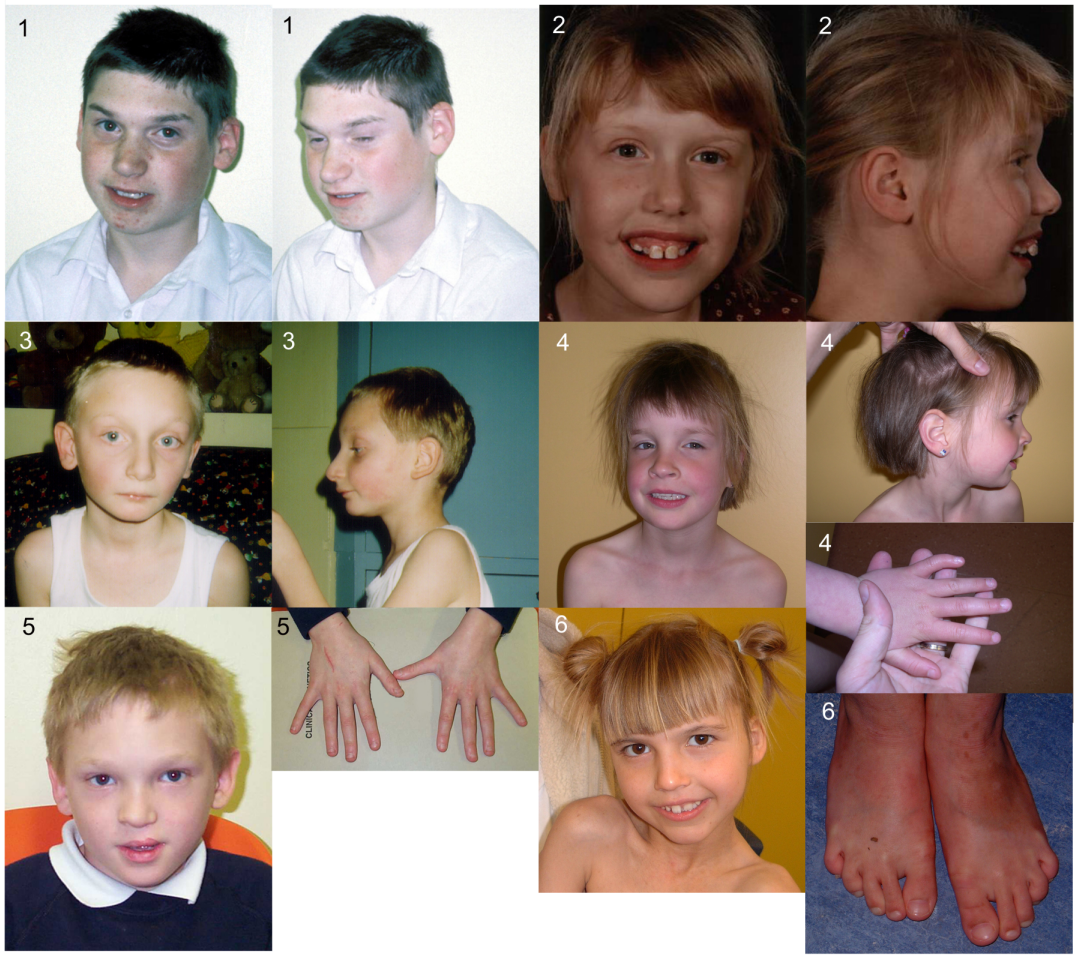


FIG. 4. The distribution of neuropsychiatric conditions reported by 3q29 deletion registry participants. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

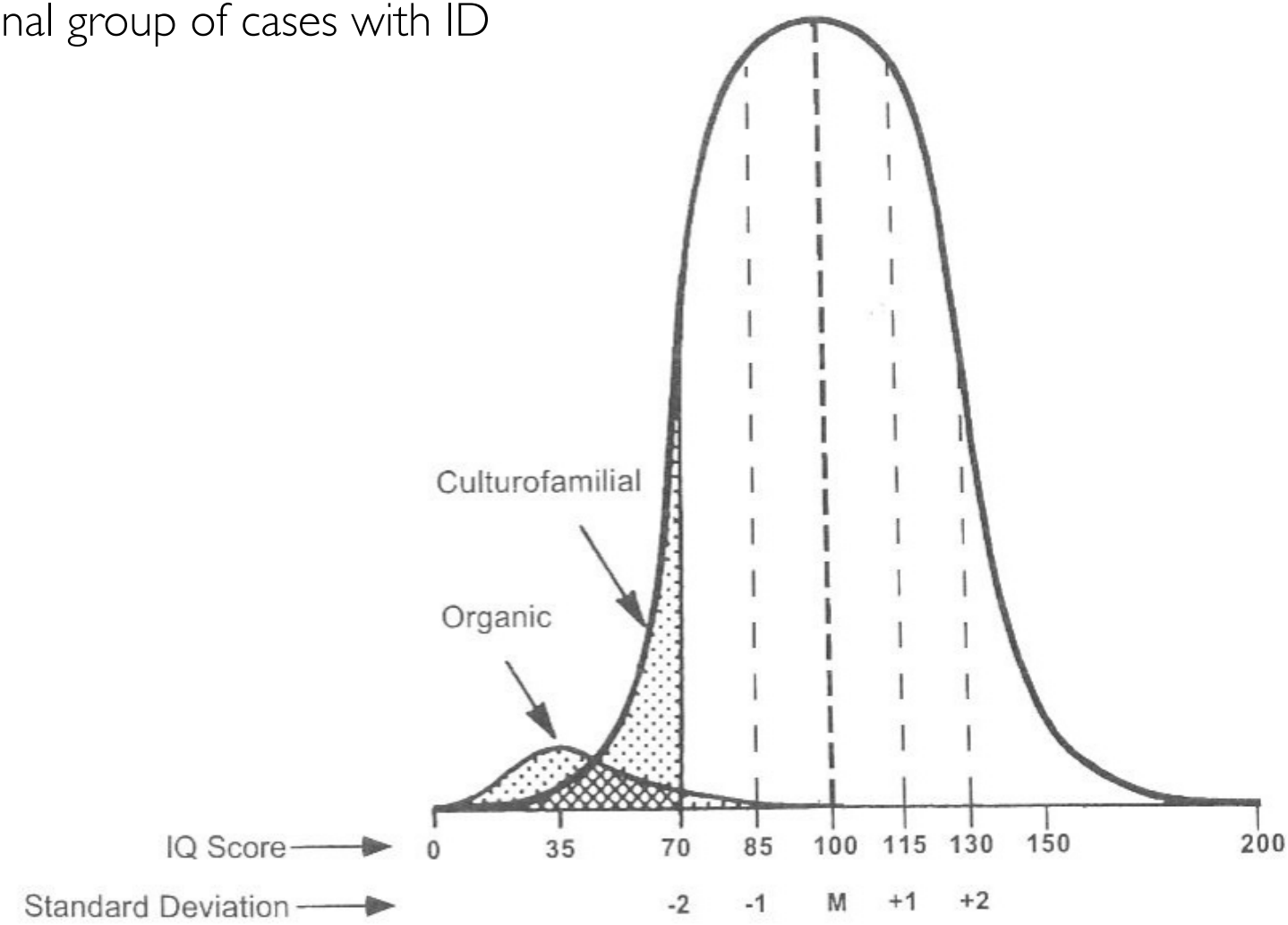


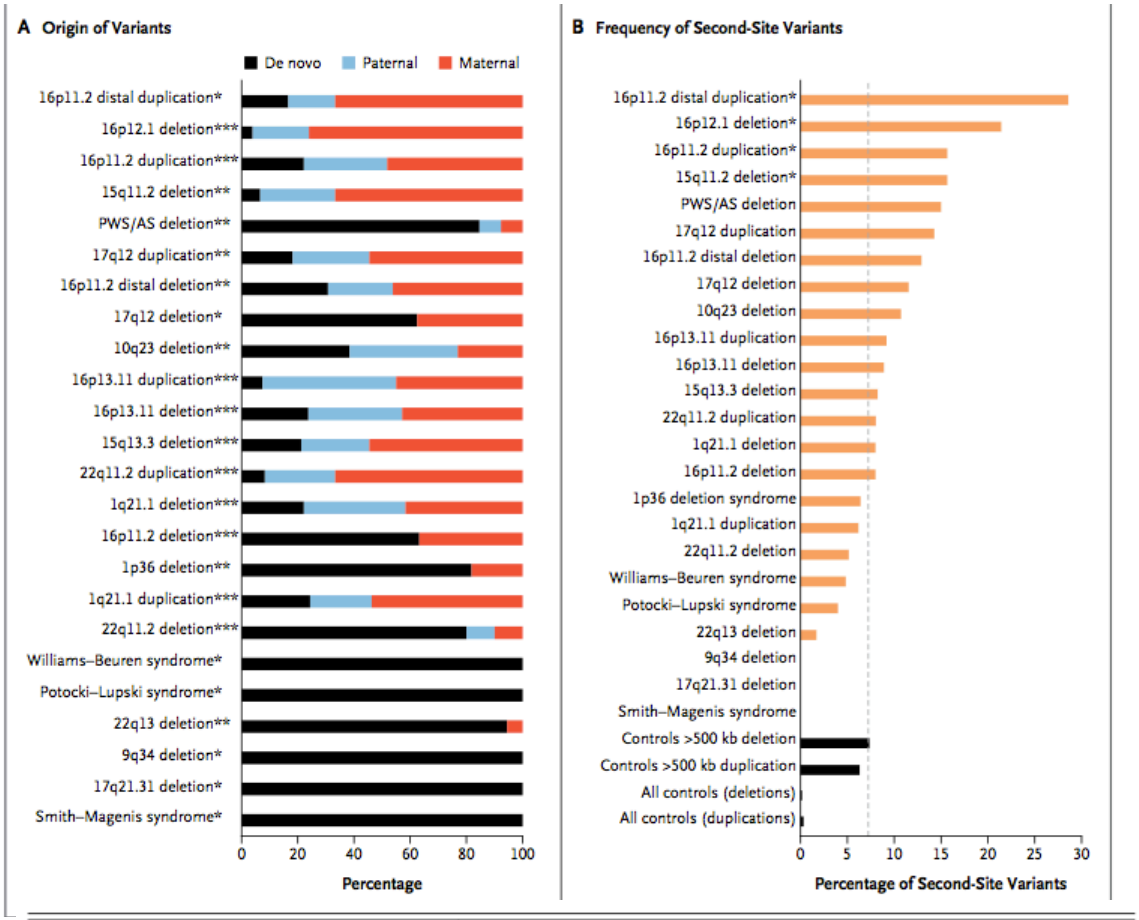
Penetrance

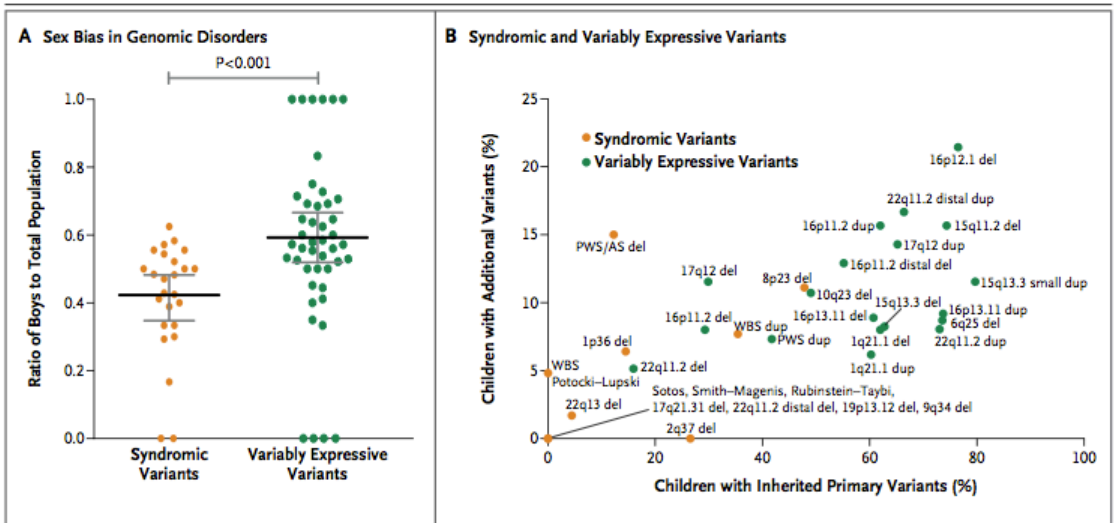
- The likelihood that the genotype will predict the phenotype
- High penetrant variants
  - Rare
  - Mendelian disease
  - More likely to be *de novo*
- Reduced penetrance
  - Associated with disease rather than necessarily completely predictive or causative and also present in unaffected cases individuals
  - More likely to be inherited
  - Less severe

Epidemiology

- IQ has a normal distribution but IQ <50 presence of additional group of cases with ID







Phenotypic Heterogeneity of Genomic Disorders and Rare Copy-Number Variants

Santhosh Girirajan, M.B., B.S., Ph.D., Jill A. Rosenfeld, M.S., Bradley P. Coe, Ph.D., Sumit Parikh, M.D., Neil Friedman, M.B., Ch.B., Amy Goldstein, M.D., Robyn A. Filipink, M.D., Juliann S. McConnell, M.S., Brad Angle, M.D., Wendy S. Meschino, M.D., Marjan M. Nezarati, M.D., Alexander Asamoah, M.D., Kelly E. Jackson, M.S., Gordon C. Gowans, M.D., Judith A. Martin, M.D., Erin P. Carmany, M.S., David W. Stockton, M.D., Rhonda E. Schnur, M.D., Lynette S. Penney, M.D., Donna M. Martin, M.D., Ph.D., Salmo Raskin, Ph.D., Kathleen Leppig, M.D., Heidi Thiese, M.S., Rosemarie Smith, M.D., Erika Aberg, M.S., Dmitriy M. Niyazov, M.D., Luis F. Escobar, M.D., Dima El-Khechen, M.S., Kisha D. Johnson, M.S., Robert R. Lebel, M.D., Kiana Siefkas, M.S., Susie Ball, M.S., Natasha Shur, M.D., Marianne McGuire, M.S., Campbell K. Brasington, M.S., J. Edward Spence, M.D., Laura S. Martin, M.D., Carol Clericuzio, M.D., Blake C. Ballif, Ph.D., Lisa G. Shaffer, Ph.D., and Evan E. Eichler, Ph.D.

NEJM 2012

- Penetrance of CNVs depends on the nature of the CNV
- 10% have additional CNV
- Reduced penetrant CNV give a phenotype in proportion to the size and number of additional CNVs
- Male genome is more susceptible to CNVs
- Analysis 2,312 / 32,587 sample set

Original Investigation

Defining the Effect of the 16p11.2 Duplication on Cognition, Behavior, and Medical Comorbidities

Debra D'Angelo, MS; Sébastien Lebon, MD; Qixuan Chen, PhD; Sandra Martin-Brevet, MS; LeeAnne Green Snyder, PhD; Loyse Hippolyte, PhD; Ellen Hanson, PhD; Anne M. Maillard, PhD; W. Andrew Faucett, MS; Aurélien Macé, MS; Aurélie Pain, MS; Raphael Bernier, PhD; Samuel J. R. A. Chawner, MA; Albert David, MD; Joris Andrieux, MD, PhD; Elizabeth Aylward, MD; Genevieve Baujat, MD; Ines Caldeira, MD; Philippe Conus, MD; Carrina Ferrari, MS; Francesca Forzano, MD; Marion Gérard, MD; Robin P. Goin-Kochel, PhD; Ellen Grant, MD; Jill V. Hunter, MD; Bertrand Isidor, MD, PhD; Aurélia Jacquette, MD; Aia E. Jønch, MD; Boris Keren, MD; Didier Lacombe, MD; Cédric Le Caignec, MD, PhD; Christa Lese Martin, PhD; Katrin Männik, PhD; Andres Metspalu, PhD; Cyril Mignot, MD; Pratik Mukherjee, MD; Michael J. Owen, PhD; Marzia Passeggeri, MD; Caroline Rooryck-Thambo, MD; Jill A. Rosenfeld, PhD; Sarah J. Spence, MD, PhD; Kyle J. Steinman, MD; Jennifer Tjernagel, MS; Mieke Van Haelst, MD; Yiping Shen, PhD; Bogdan Draganski, MD; Elliott H. Sherr, MD, PhD; David H. Ledbetter, PhD; Marianne B. M. van den Bree, PhD; Jacques S. Beckmann, PhD; John E. Spiro, PhD; Alexandre Reymond, PhD; Sébastien Jacquemont, MD; Wendy K. Chung, MD, PhD; for the Cardiff University Experiences of Children With Copy Number Variants (ECHO) Study, the 16p11.2 European Consortium, and the Simons Variation in Individuals Project (VIP) Consortium

Editorial page 7

Supplemental content at jamapsychiatry.com

IMPORTANCE The 16p11.2 BP4-BP5 duplication is the copy number variant most frequently associated with autism spectrum disorder (ASD), schizophrenia, and comorbidities such as decreased body mass index (BMI).

OBJECTIVES To characterize the effects of the 16p11.2 duplication on cognitive, behavioral, medical, and anthropometric traits and to understand the specificity of these effects by systematically comparing results in duplication carriers and reciprocal deletion carriers, who are also at risk for ASD.

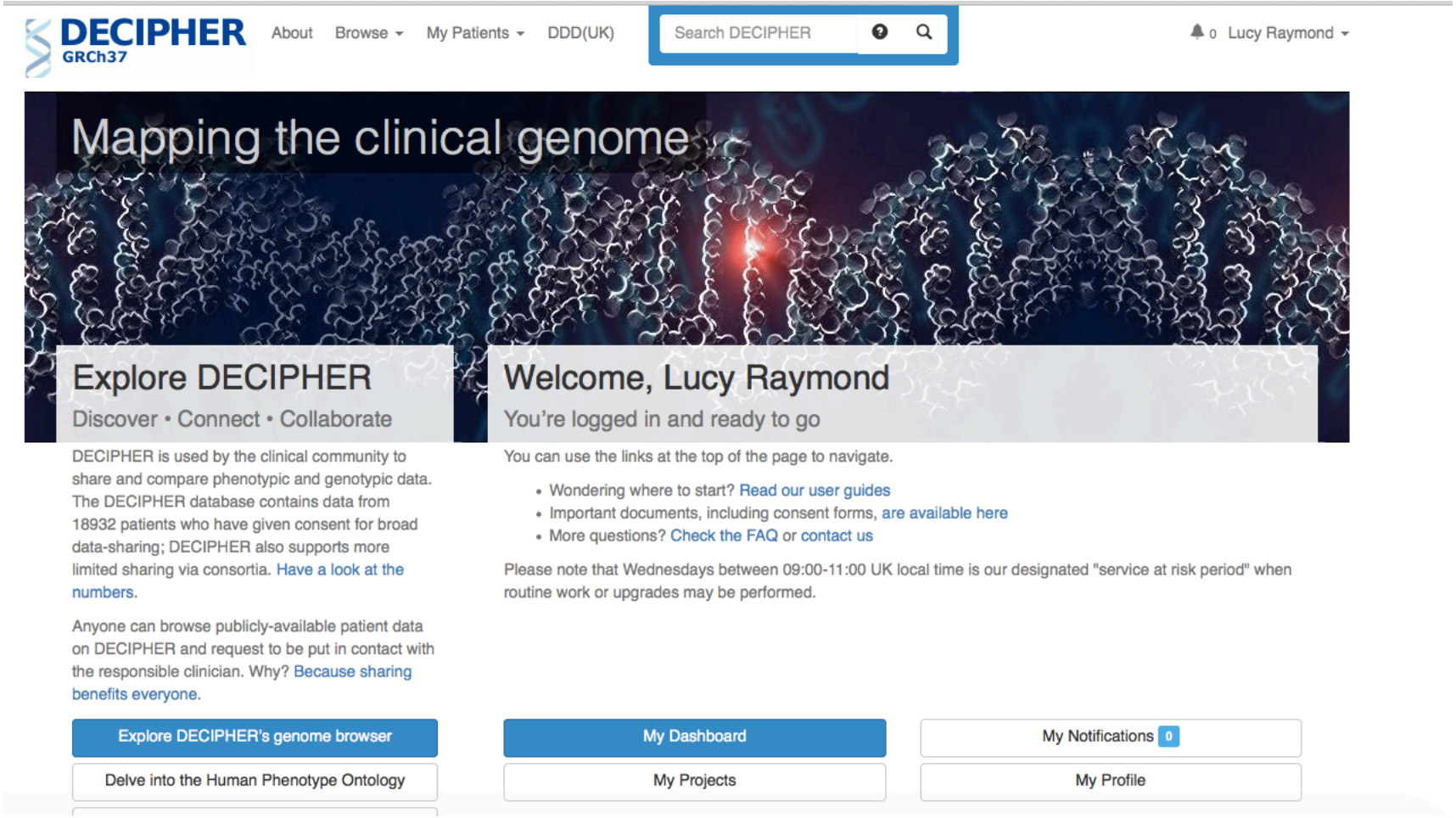
DESIGN, SETTING, AND PARTICIPANTS This international cohort study of 1006 study participants compared 270 duplication carriers with their 102 intrafamilial control individuals, 390 reciprocal deletion carriers, and 244 deletion controls from European and North American cohorts. Data were collected from August 1, 2010, to May 31, 2015 and analyzed

RESULTS Among the 1006 study participants, the duplication was associated with a mean FSIQ score that was lower by 26.3 points between proband carriers and noncarrier relatives and a lower mean FSIQ score (16.2-11.4 points) in nonproband carriers. The mean overall effect of the deletion was similar (−22.1 points; $P < .001$). However, broad variation in FSIQ was found, with a 19.4- and 2.0-fold increase in the proportion of FSIQ scores that were very low (≤40) and higher than the mean (>100) compared with the deletion group ($P < .001$). Parental FSIQ predicted part of this variation (approximately 36.0% in hereditary probands). Although the frequency of ASD was similar in deletion and duplication proband carriers (16.0% and 20.0%, respectively), the FSIQ was significantly lower (by 26.3 points) in the duplication probands with ASD. There also were lower head circumference and BMI measurements among duplication carriers, which is consistent with the findings of previous studies.

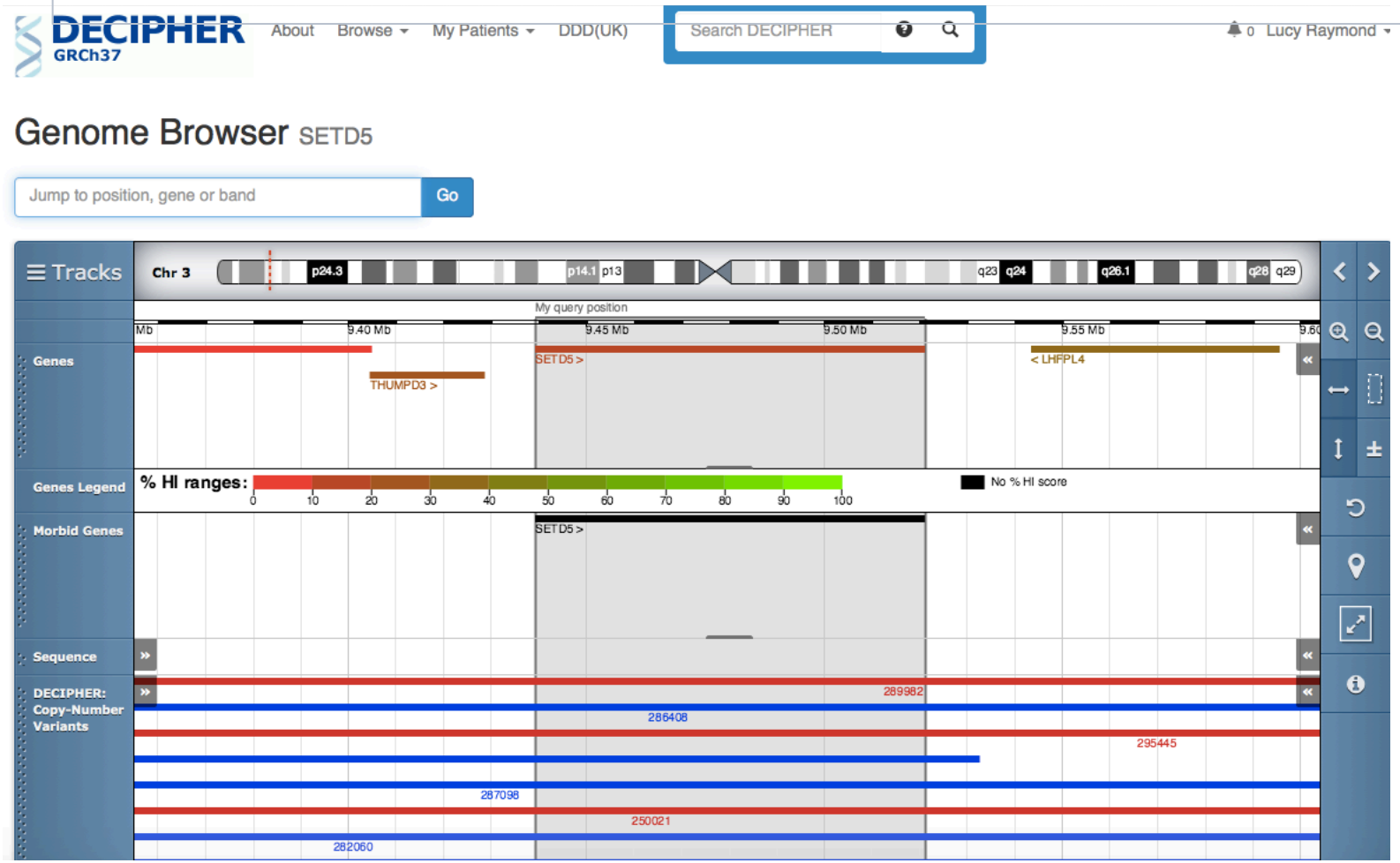
CONCLUSIONS AND RELEVANCE The mean effect of the duplication on cognition is similar to that of the reciprocal deletion, but the variance in the duplication is significantly higher, with severe and mild subgroups not observed with the deletion. These results suggest that additional genetic and familial factors contribute to this variability. Additional studies will be necessary to characterize the predictors of cognitive deficits.

JAMA Psychiatry. 2016;73(1):20-30. doi:10.1001/jamapsychiatry.2015.2123
Published online December 2, 2015.

https://decipher.sanger.ac.uk

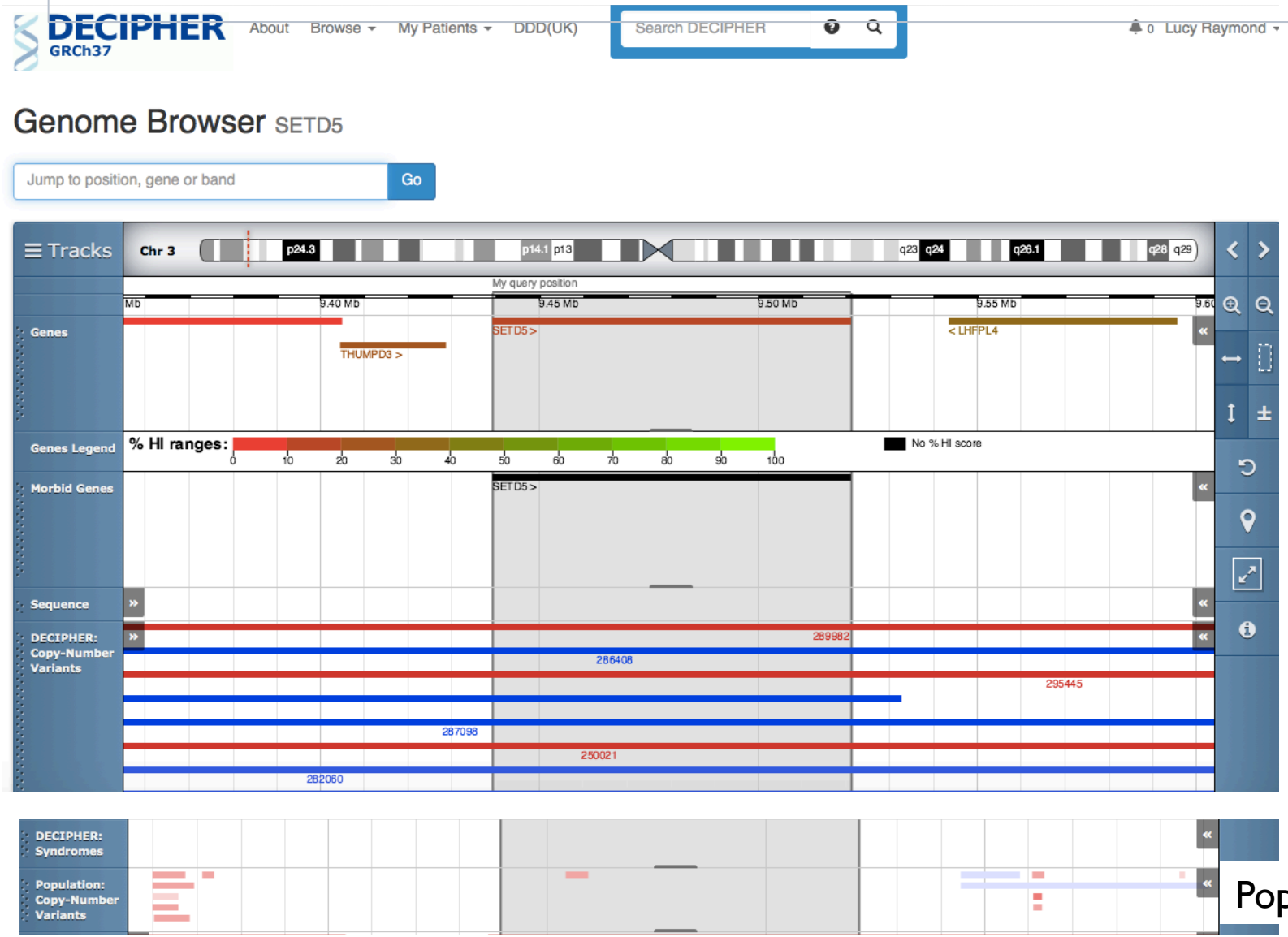


https://decipher.sanger.ac.uk



Rare CNVs

https://decipher.sanger.ac.uk



Rare CNVs

Population CNVs

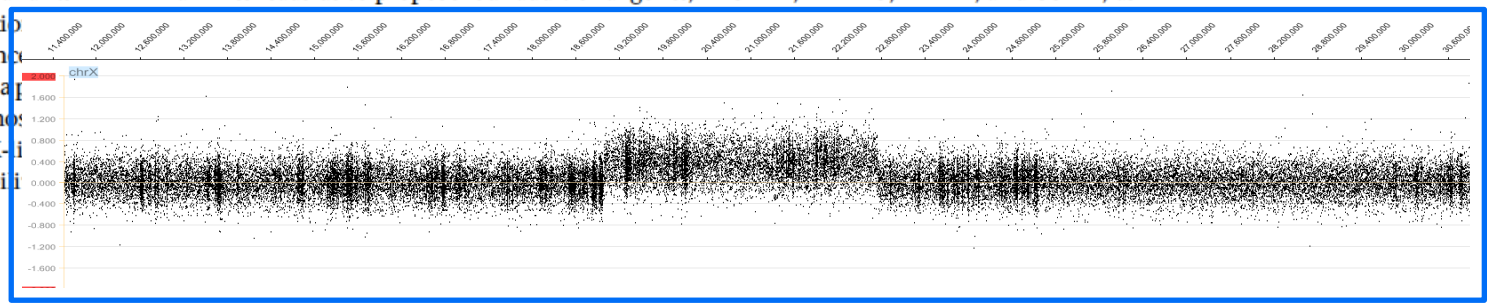
ARTICLE

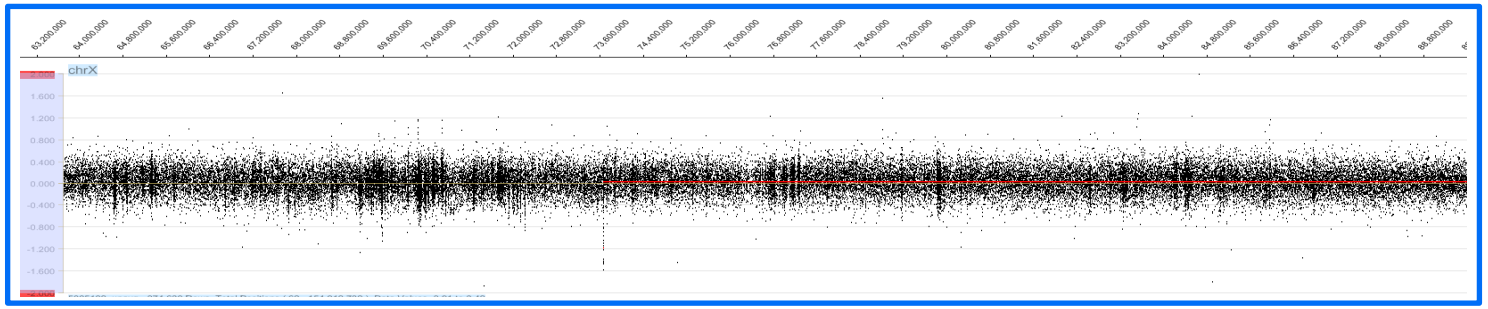
Fine-Scale Survey of X Chromosome Copy Number Variants and Indels Underlying Intellectual Disability

Single gene/exon resolution

Annabel C. Whibley,[1] Vincent Plagnol,[1,2] Patrick S. Tarpey,[3] Fatima Abidi,[4] Tod Fullston,[5,6] Maja K. Choma,[1] Catherine A. Boucher,[1] Lorraine Shepherd,[1] Lionel Willatt,[7] Georgina Parkin,[7] Raffaella Smith,[3] P. Andrew Futreal,[3] Marie Shaw,[8] Jackie Boyle,[9] Andrea Licata,[4] Cindy Skinner,[4] Roger E. Stevenson,[4] Gillian Turner,[9] Michael Field,[9] Anna Hackett,[9] Charles E. Schwartz,[4] Jozef Gecz,[5,6,8] Michael R. Stratton,[3] and F. Lucy Raymond[1,*]

Copy number variants and indels in 251 families with evidence of X-linked intellectual disability (XLID) were investigated by array comparative genomic hybridization on a high-density oligonucleotide X chromosome array platform. We identified pathogenic copy number variants in 10% of families, with mutations ranging from 2 kb to 11 Mb in size. The challenge of assessing causality was facilitated by prior knowledge of XLID-associated genes and the ability to test for cosegregation of variants with disease through extended pedigrees. Fine-scale analysis of rare variants in XLID families leads us to propose four additional genes, *PTCHD1*, *WDR13*, *FAAH2*, and *GSPT2*, as candidates for XLID causati
apparent disease consequen
mechanisms and indicated a
investigations and X chromo
coding variants and non-X-
Genetics of Learning Disabi





Whibley et al Am J Hum Genetics (2010) 87:173-88

Copy number abnormalities on the X chromosome

Detection of Genomic Copy Number Changes in Patients With Idiopathic Mental Retardation by High-Resolution X-Array-CGH: Important Role for Increased Gene Dosage of *XLMR* Genes

Guy Froyen,[1,2*] Hilde Van Esch,[3] Marijke Bauters,[1,2] Karen Hollanders,[1,2] Suzanna G.M. Frints,[4] Joris R. Vermeesch,[3] Koen Devriendt,[3] Jean-Pierre Fryns,[3] and Peter Marynen[1,2]

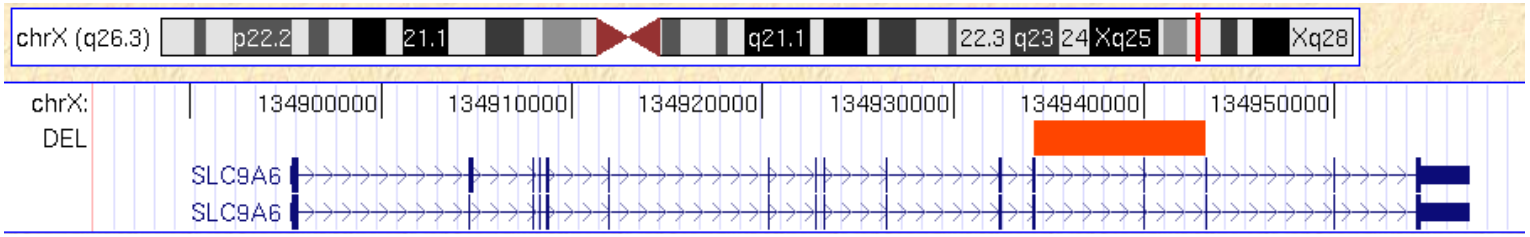
[1]Human Genome Laboratory, Department for Molecular and Developmental Genetics, VIB, Leuven, Belgium; [2]Human Genome Laboratory, Department of Human Genetics, KU Leuven, Leuven, Belgium; [3]Department of Human Genetics, University Hospital Gasthuisberg, Leuven, Belgium; [4]Department of Clinical Genetics, University Hospital, Maastricht, The Netherlands

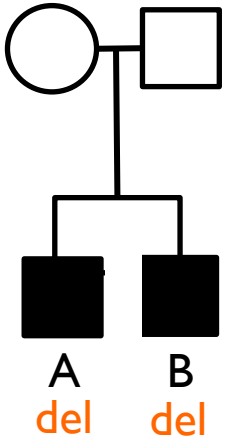
Fine-Scale Survey of X Chromosome Copy Number Variants and Indels Underlying Intellectual Disability

Annabel C. Whibley,[1] Vincent Plagnol,[1,2] Patrick S. Tarpey,[3] Fatima Abidi,[4] Tod Fullston,[5,6] Maja K. Choma,[1] Catherine A. Boucher,[1] Lorraine Shepherd,[1] Lionel Willatt,[7] Georgina Parkin,[7] Raffaella Smith,[3] P. Andrew Futreal,[3] Marie Shaw,[8] Jackie Boyle,[9] Andrea Licata,[4] Cindy Skinner,[4] Roger E. Stevenson,[4] Gillian Turner,[9] Michael Field,[9] Anna Hackett,[9] Charles E. Schwartz,[4] Jozef Gecz,[5,6,8] Michael R. Stratton,[3] and F. Lucy Raymond[1,*]

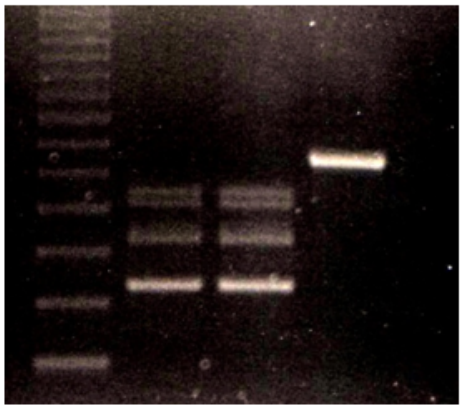
- 10-15% of cases have significant deletion or duplication
- MECP2 and HUWE1 regions are the commonest
- Find single exon deletions are detectable with high resolution array

SLC9A6 / NHE6





RT-PCR: A B WT



Exon 10 11 12 13 14 15

cDNA

REPORT

SLC9A6 Mutations Cause X-Linked Mental Retardation, Microcephaly, Epilepsy, and Ataxia, a Phenotype Mimicking Angelman Syndrome

Gregor D. Gilfillan,[1,2,15] Kaja K. Selmer,[1,2,15] Ingrid Roxrud,[3] Raffaella Smith,[4] Mårten Kyllerman,[5] Kristin Eiklid,[1] Mette Kroken,[1] Morten Mattingsdal,[1] Thore Egeland,[1] Harald Stenmark,[3] Hans Sjøholm,[6] Andres Server,[7] Lena Samuelsson,[8] Arnold Christianson,[9] Patrick Tarpey,[4] Annabel Whibley,[10] Michael R. Stratton,[4] P. Andrew Futreal,[4] Jon Teague,[4] Sarah Edkins,[4] Jozef Gecz,[11] Gillian Turner,[12] F. Lucy Raymond,[10] Charles Schwartz,[13] Roger E. Stevenson,[13] Dag E. Undlien,[1,2] and Petter Strømme[2,14,*]

AJHG (2008) 82:1003-1010

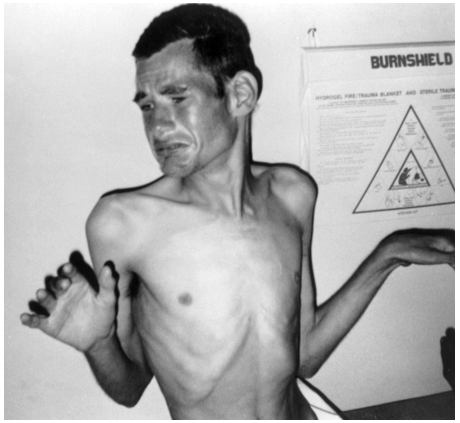
Family 115
Always moving
ataxic
Shy
No speech
Toileted
Microcephaly

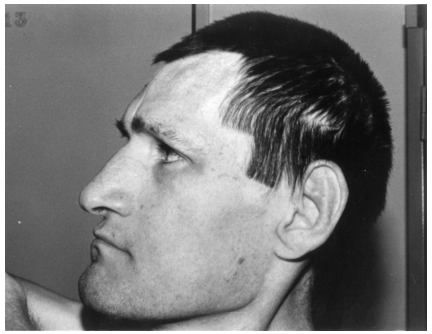
Family 115
Microcephaly
No speech
Wheelchair from aged 15
Previously very mobile
Incontinent
Kyphoscoliosis
Flexed hand postures
Moving hands

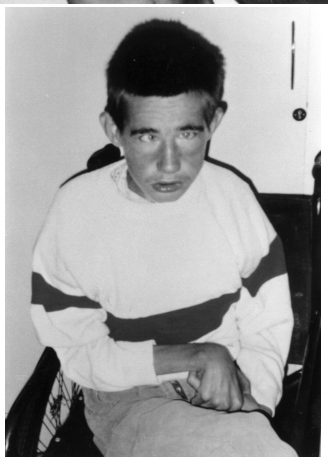
Christianson syndrome

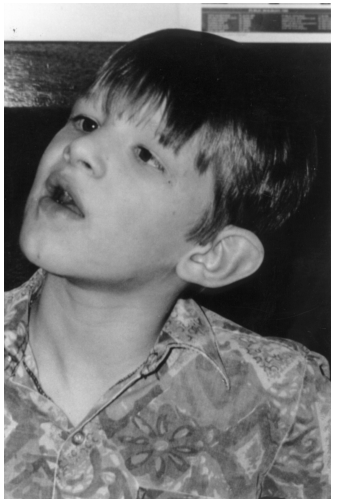
GOLD 227

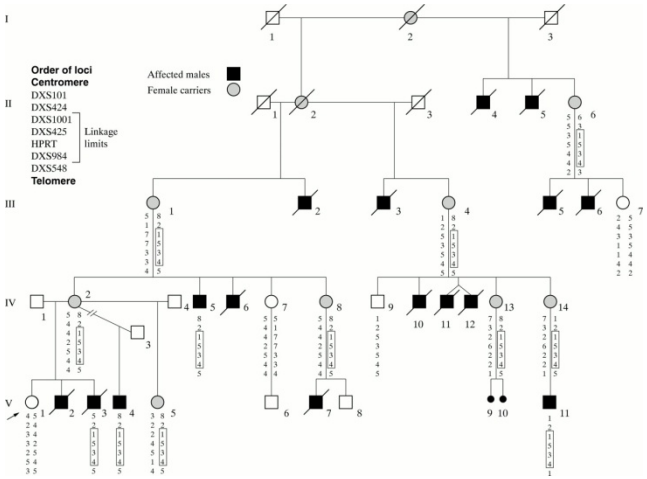
2bp deletion H171fs X





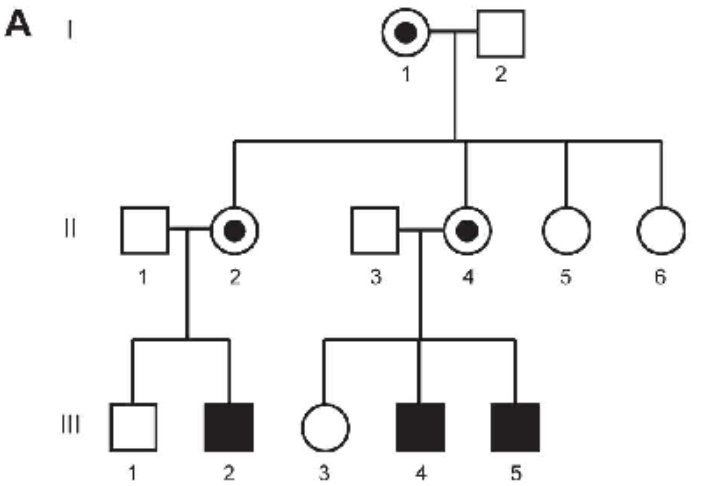


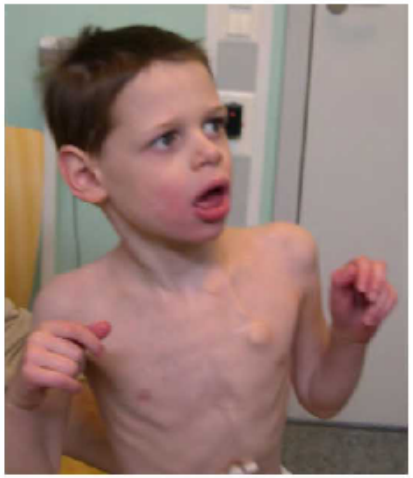




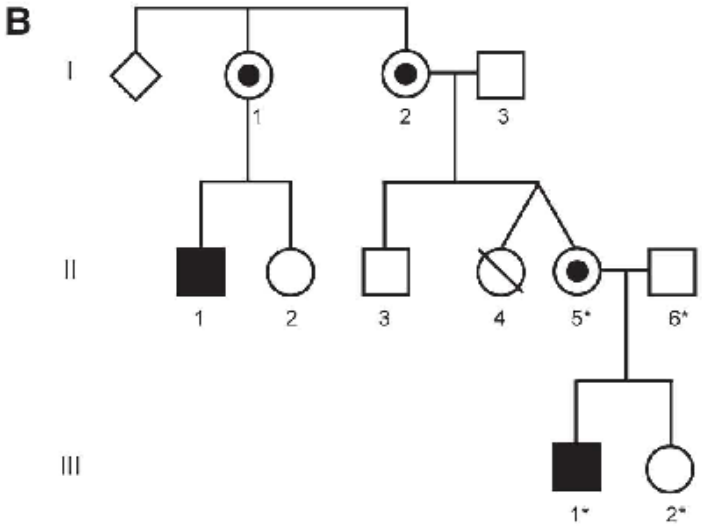
Christianson et al (1999) JMG 36 759-766

Swedish and Norwegian families





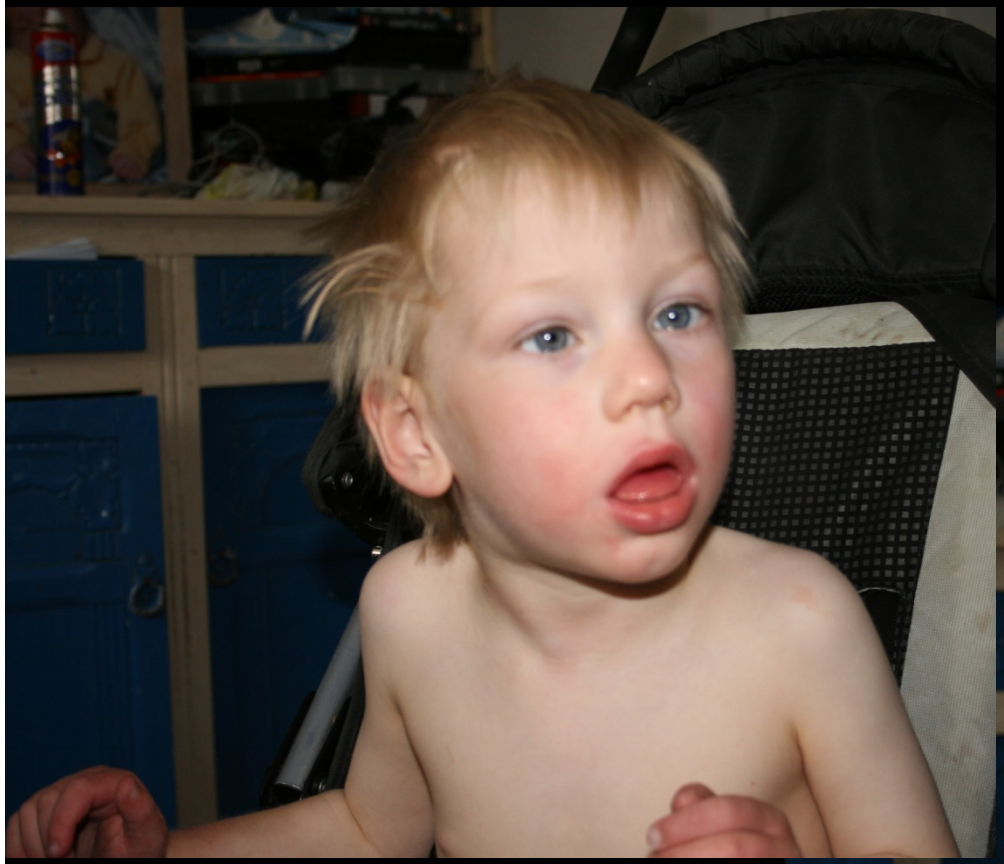
E255_256del

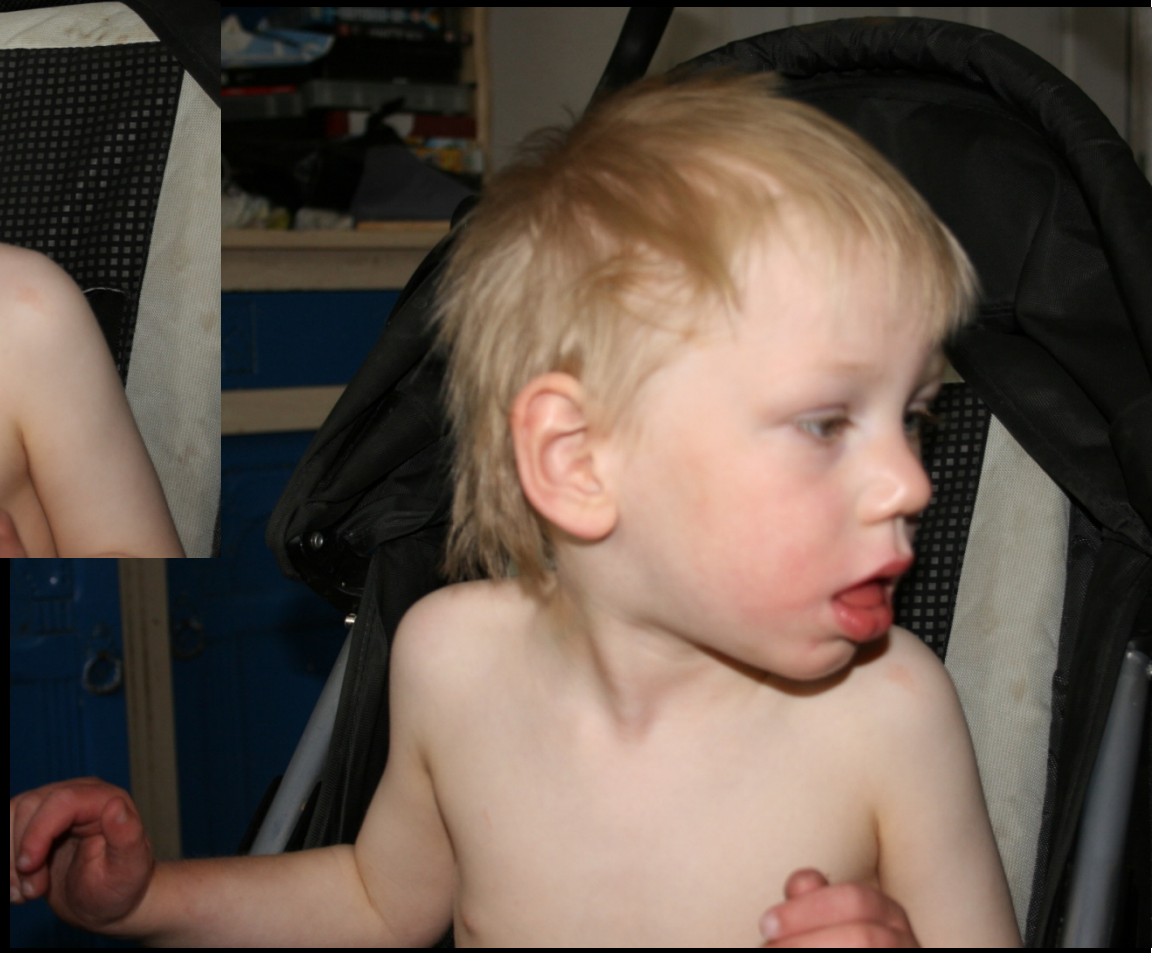


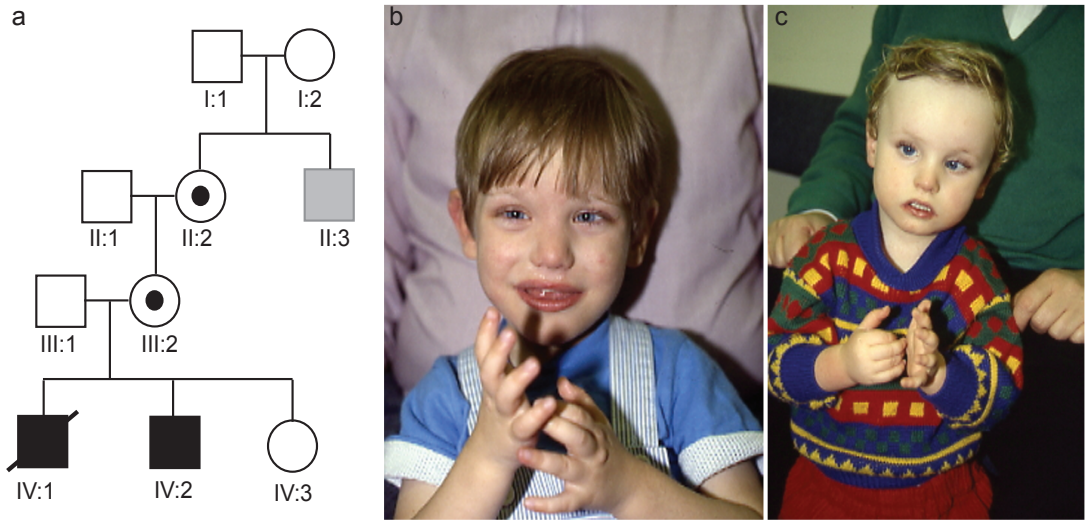
R468X

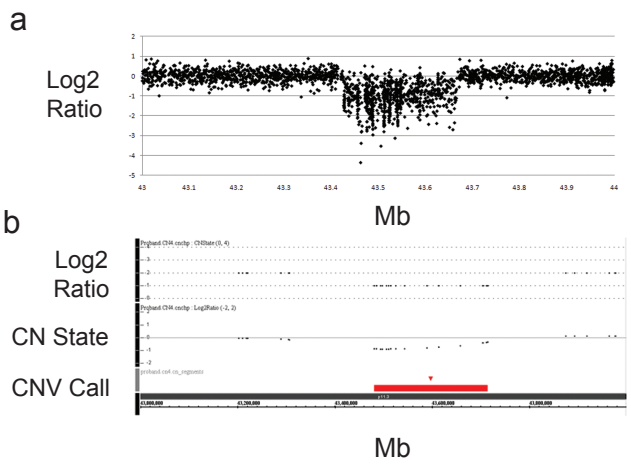
Gilfillan et al AJHG(2008)

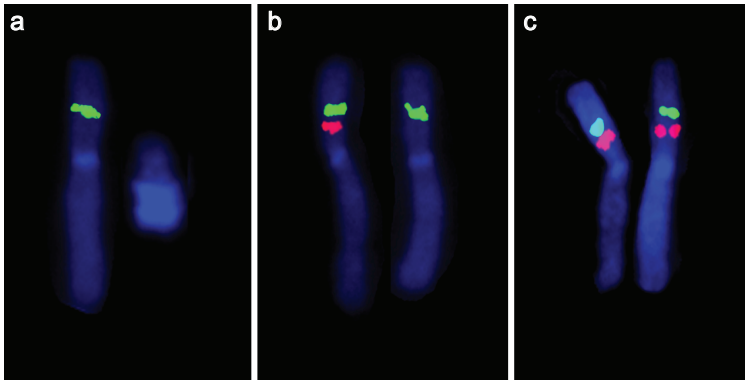

Aged 21
Severe scoliosis
Double incontinence
Gilfillan et al AJHG(2008)

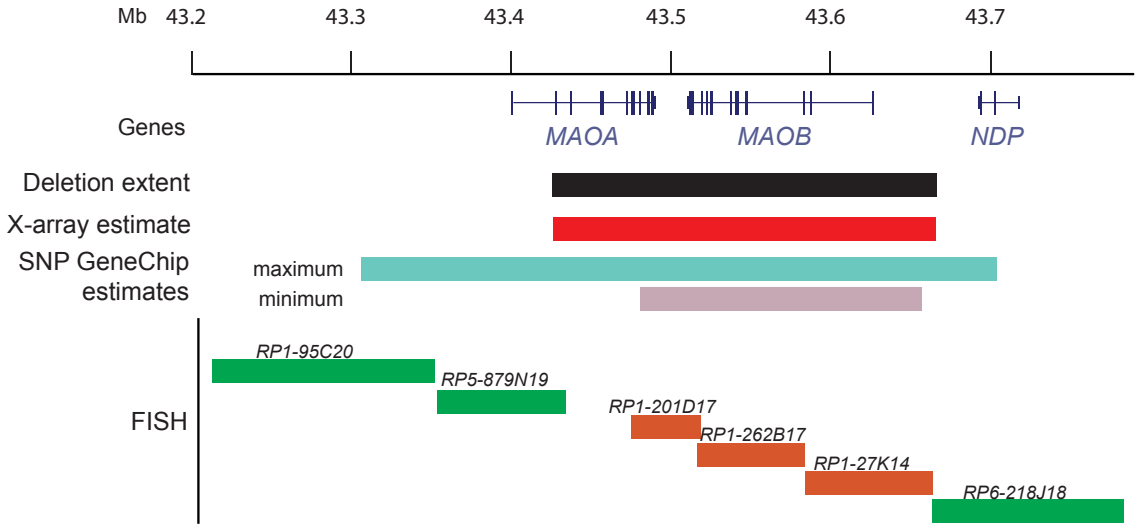


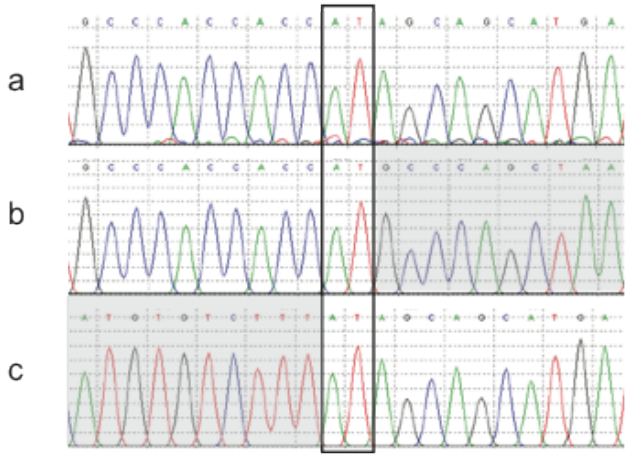












MAOA and MAOB deletion

Whibley et al Eur J Hum Genet. 18:1095-9 (2010).

Mutational mechanisms for monogenic diseases

HGMD 2010 102,433 entries

57,570 missense/nonsense mutations

9,791 splicing

8,135 small insertions or indels

74% of all entries detectable by sequencing strategy

16,080 small deletions

6,403 large deletions

1,338 large insertions or duplications

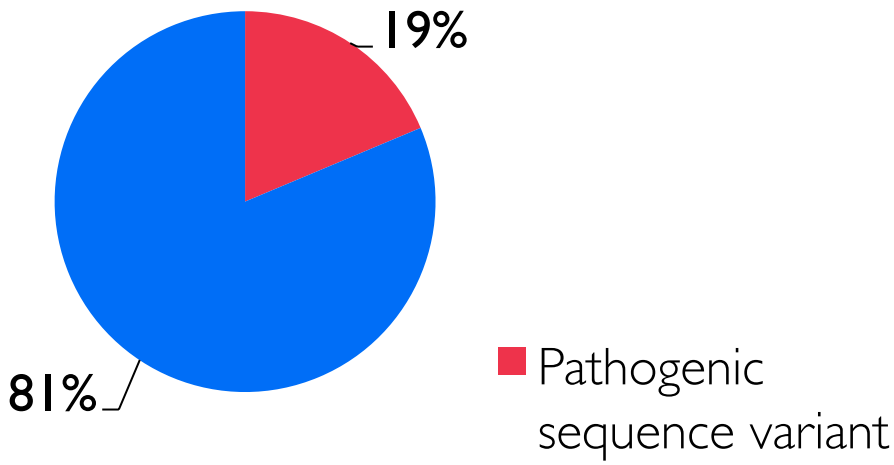
22% of all entries detectable by array CGH strategy

A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation

Patrick S Tarpey[1], Raffaella Smith[1], Erin Pleasance[1], Annabel Whibley[2], Sarah Edkins[1], Claire Hardy[1], Sarah O'Meara[1], Calli Latimer[1], Ed Dicks[1], Andrew Menzies[1], Phil Stephens[1], Matt Blow[1], Chris Greenman[1], Yali Xue[1], Chris Tyler-Smith[1], Deborah Thompson[3], Kristian Gray[1], Jenny Andrews[1], Syd Barthorpe[1], Gemma Buck[1], Jennifer Cole[1], Rebecca Dunmore[1], David Jones[1], Mark Maddison[1], Tatiana Mironenko[1], Rachel Turner[1], Kelly Turrell[1], Jennifer Varian[1], Sofie West[1], Sara Widaa[1], Paul Wray[1], Jon Teague[1], Adam Butler[1], Andrew Jenkinson[1], Mingming Jia[1], David Richardson[1], Rebecca Shepherd[1], Richard Wooster[1], M Isabel Tejada[4], Francisco Martinez[5], Gemma Carvill[6], Rene Goliath[6], Arjan P M de Brouwer[7], Hans van Bokhoven[7], Hilde Van Esch[8], Jamel Chelly[9], Martine Raynaud[10], Hans-Hilger Ropers[11], Fatima E Abidi[12], Anand K Srivastava[12], James Cox[2], Ying Luo[2], Uma Mallya[2], Jenny Moon[2], Josef Parnau[2], Shehla Mohammed[13], John L Tolmie[14], Cheryl Shoubridge[15], Mark Corbett[15], Alison Gardner[15], Eric Haan[15], Sinitdhorn Rujirabanjerd[15], Marie Shaw[15], Lucianne Vandeleur[15], Tod Fullston[15], Douglas F Easton[3], Jackie Boyle[16], Michael Partington[16], Anna Hackett[16], Michael Field[16], Cindy Skinner[12], Roger E Stevenson[12], Martin Bobrow[2], Gillian Turner[16], Charles E Schwartz[12], Jozef Gecz[15,17], F Lucy Raymond[2], P Andrew Futreal[1] & Michael R Stratton[1,18]

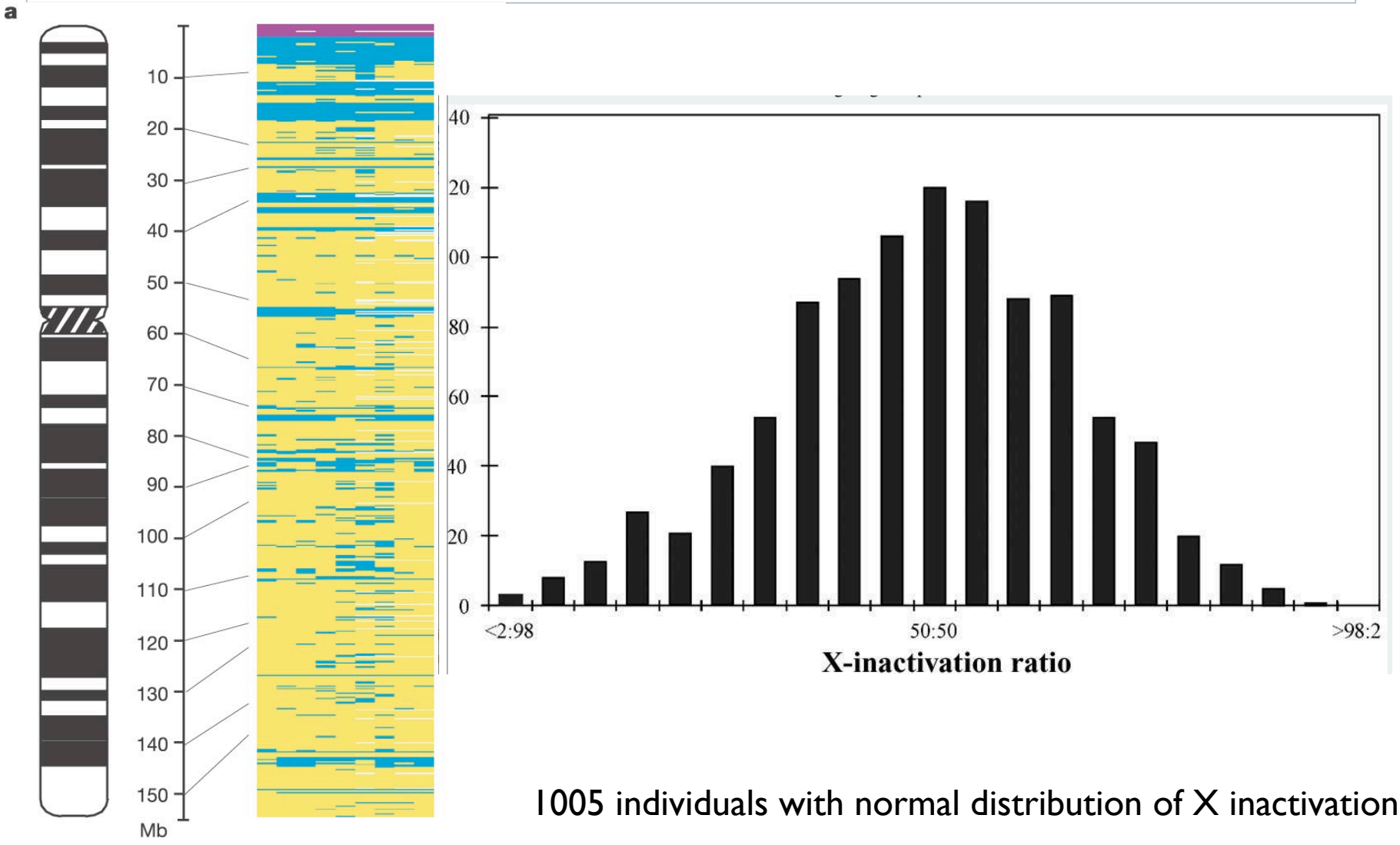
Large-scale systematic resequencing has been proposed as the key future strategy for the discovery of rare, disease-causing sequence variants across the spectrum of human complex disease. We have sequenced the coding exons of the X chromosome in 208 families with X-linked mental retardation (XLMR), the largest direct screen for constitutional disease-causing mutations thus far reported. The screen has discovered nine genes implicated in XLMR, including *SYP*, *ZNF711* and *CASK* reported here, confirming the power of this strategy. The study has, however, also highlighted issues confronting whole-genome sequencing screens, including the observation that loss of function of 1% or more of X-chromosome genes is compatible with apparently normal existence.

Tarpey et al Nature Genetics (2009) 41:536-543



DLG3
AP1S2
CUL4B
ZDHHC9
BRWD3
UPF3B
SLC9A6
MED12
IQSEC
CASK
SYP
ZNF711

X inactivation in mothers

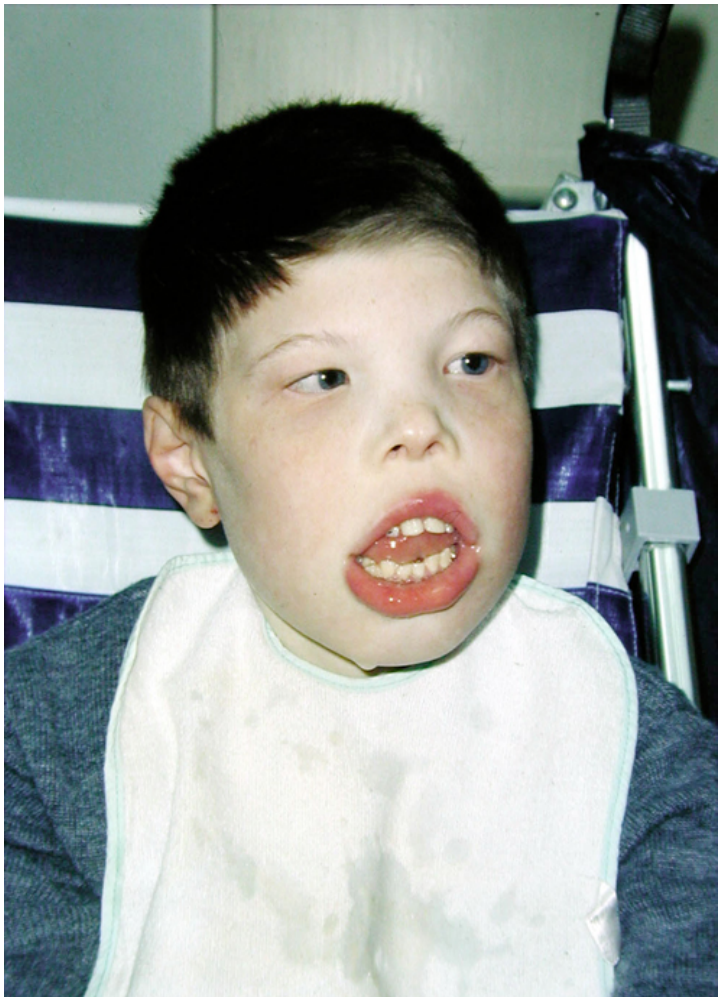


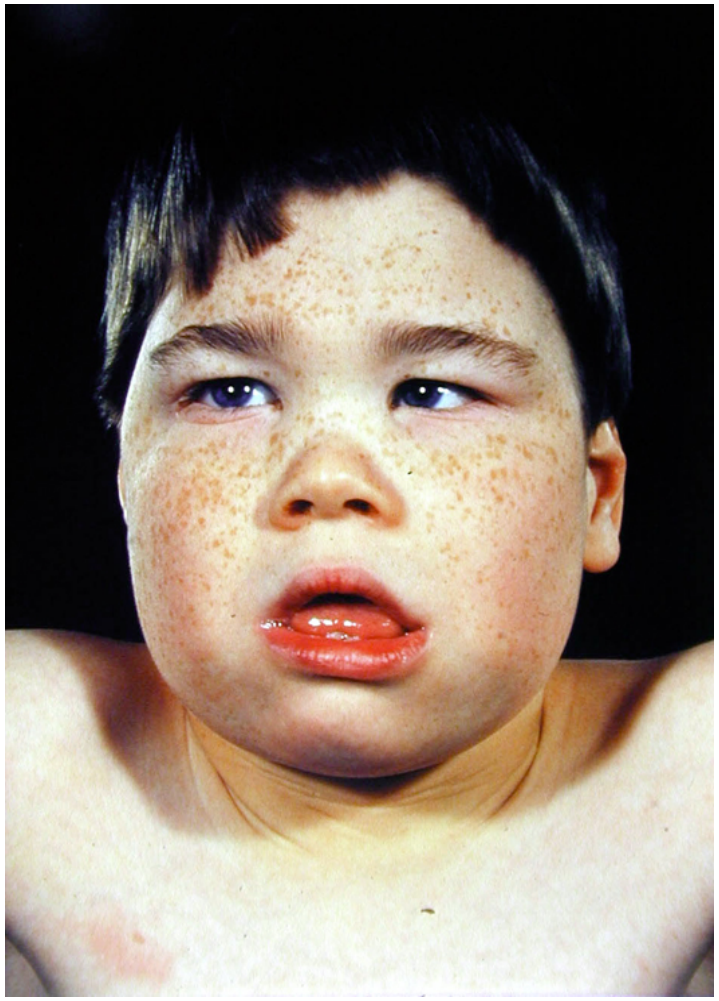
1005 individuals with normal distribution of X inactivation

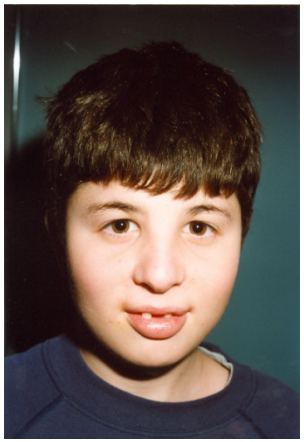
X linked genes associated with skewed X inactivation

- MECP2
- HUWE1
- UPF3B
- CUL4B
- ATRX
- Others more variable
- Skewed = >95% one allele
- Largely depends on whether the gene of interest is expressed in lymphocytes to any extent
- If skewed then X linked disease likely. If not skewed then risk of X linked disease is not significantly reduced except for a few genes

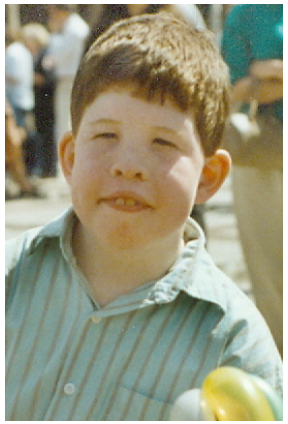
ATRX (X-linked alpha thalassaemia)

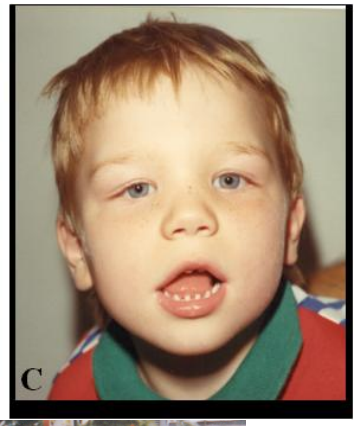
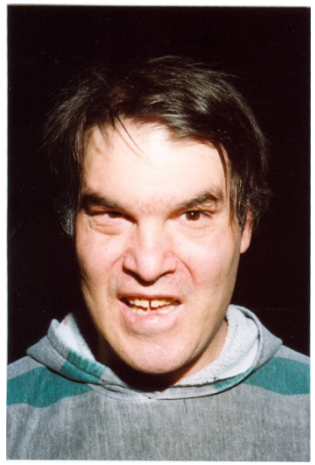


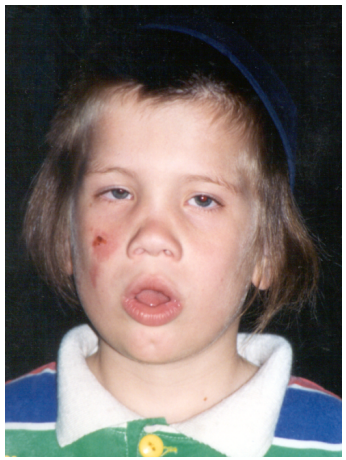


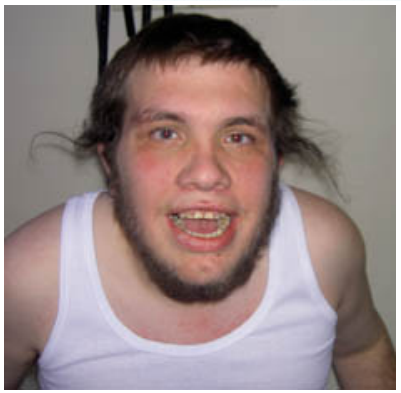



A

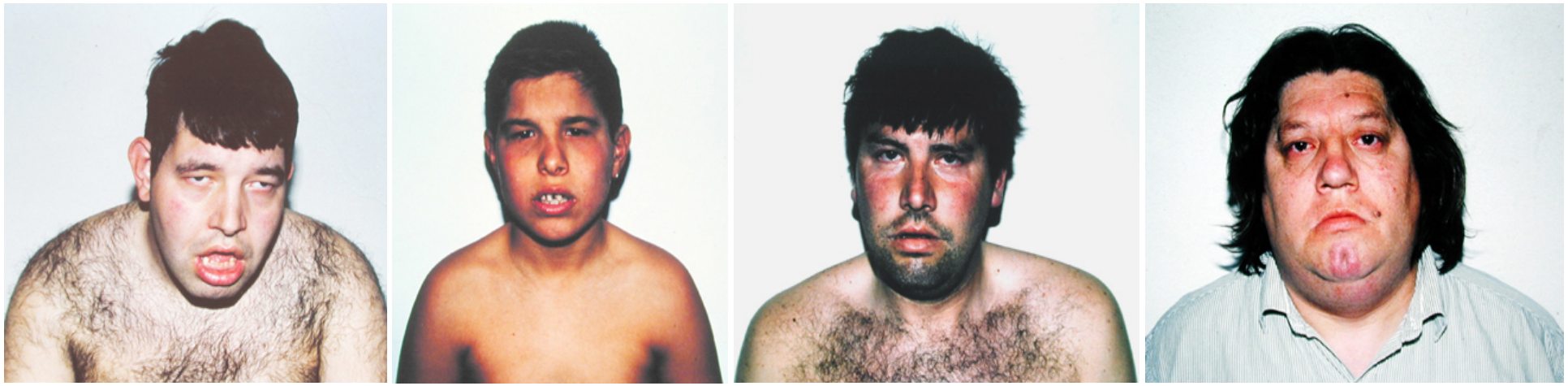
B




C




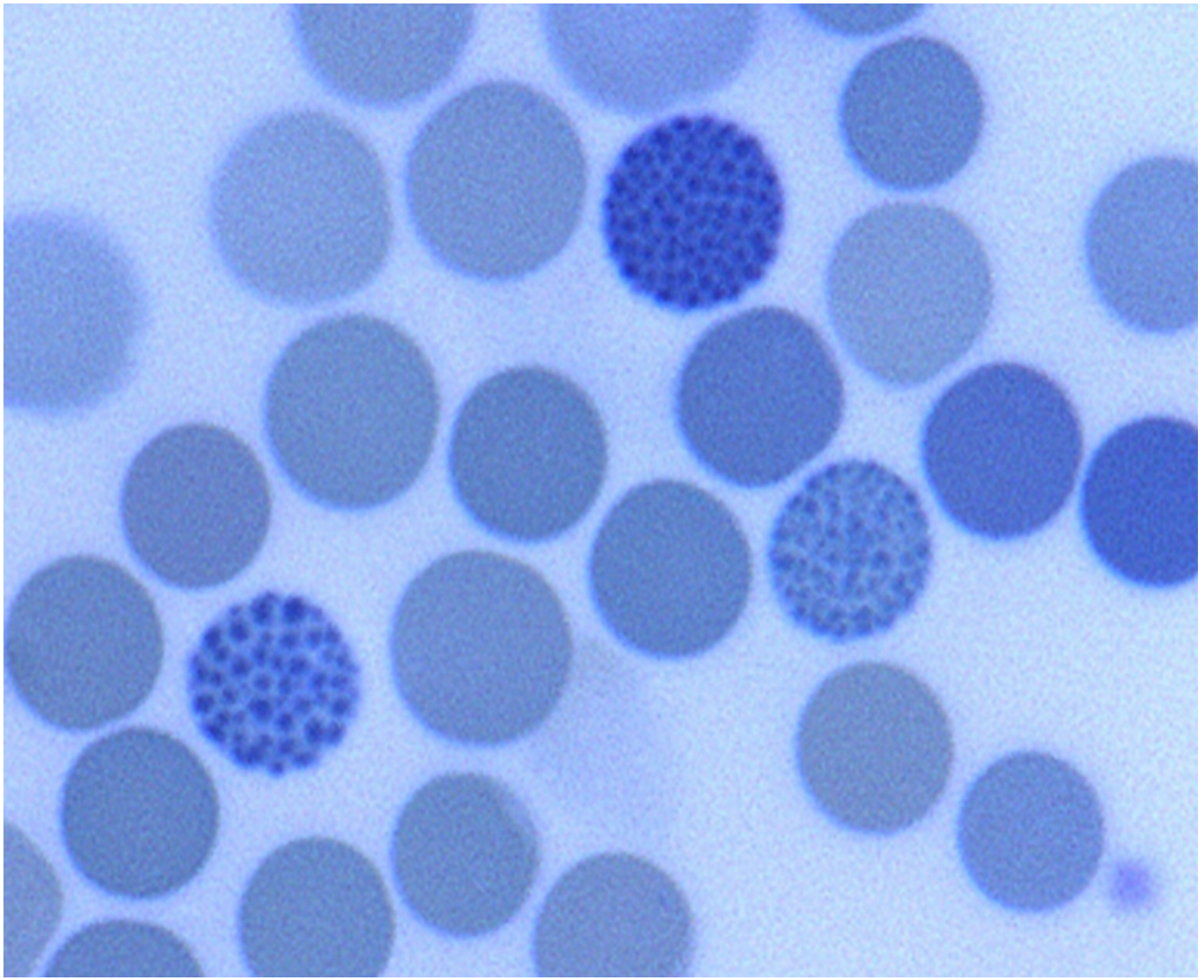


‘Milder ATRX phenotype’

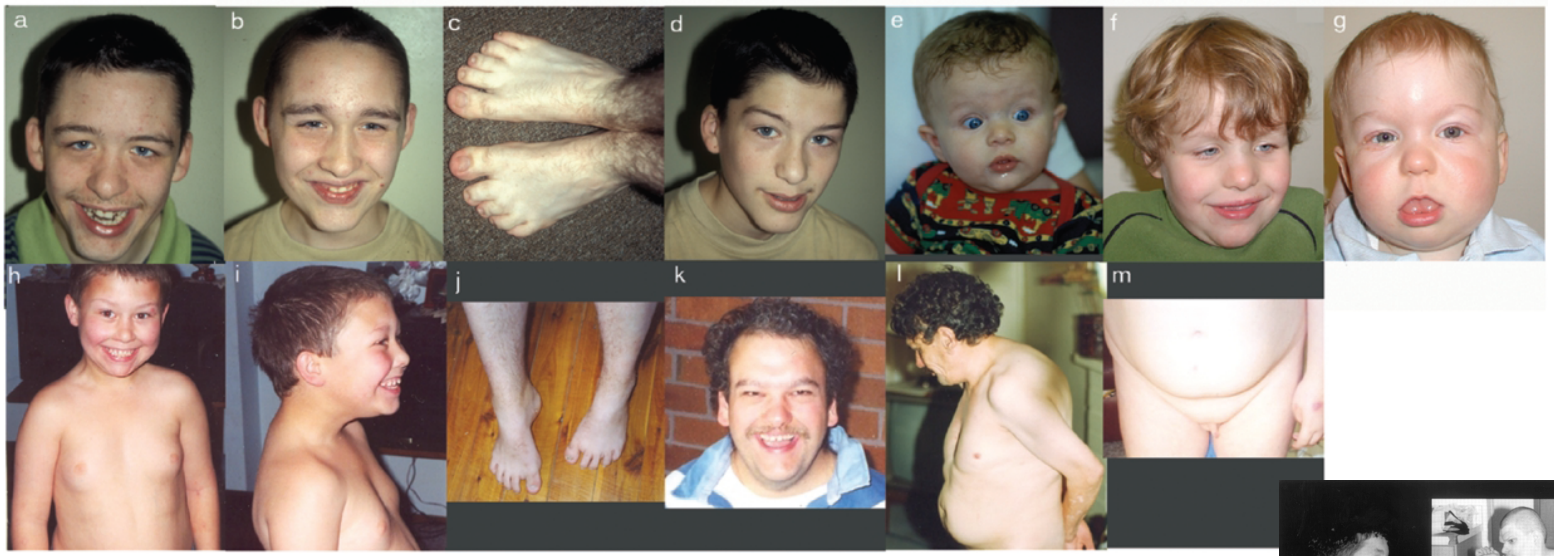


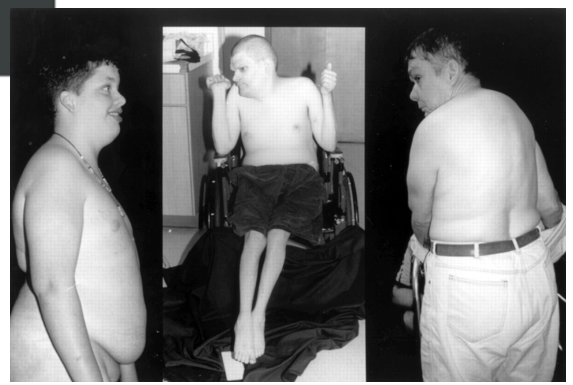
Guerrini et al. 2000 Ann Neurol 47:117-121

HbH inclusions



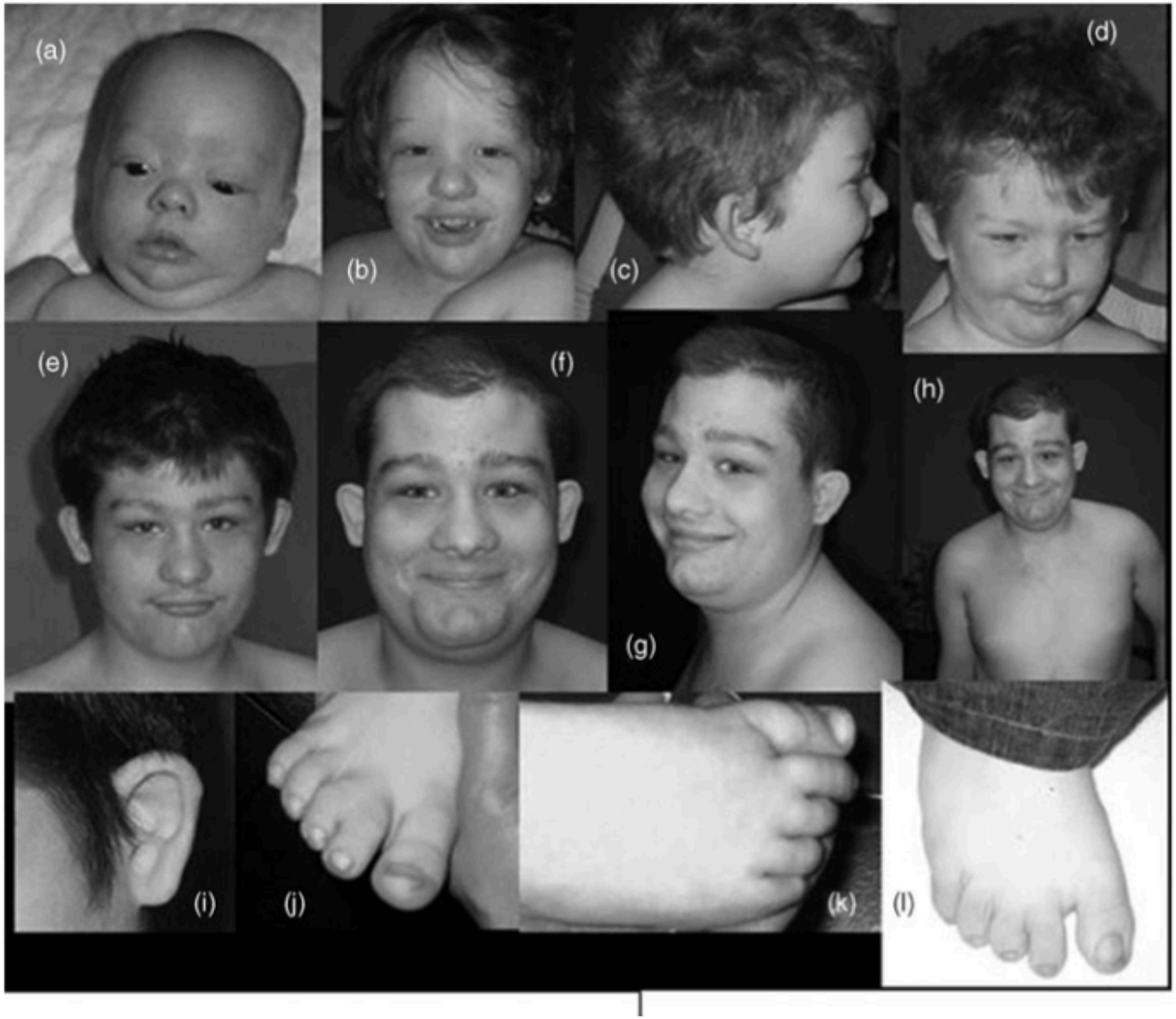
CUL4B syndrome





Mutations in *CUL4B, Which Encodes a Ubiquitin E3 Ligase* Subunit, Cause an X-linked Mental Retardation Syndrome Associated with Aggressive Outbursts, Seizures, Relative Macrocephaly, Central Obesity, Hypogonadism, Pes Cavus, and Tremor

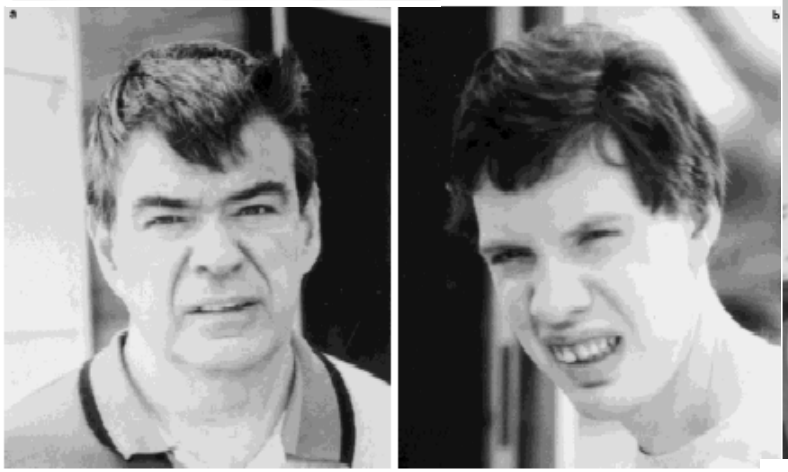
Tarpey et al AJHG 80 345-352 (2007)

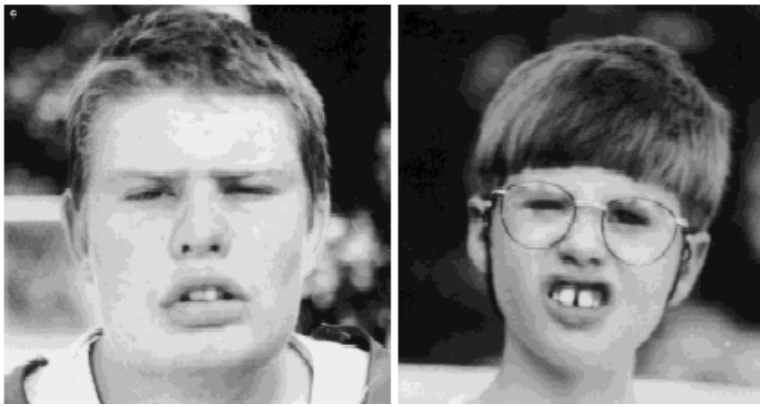


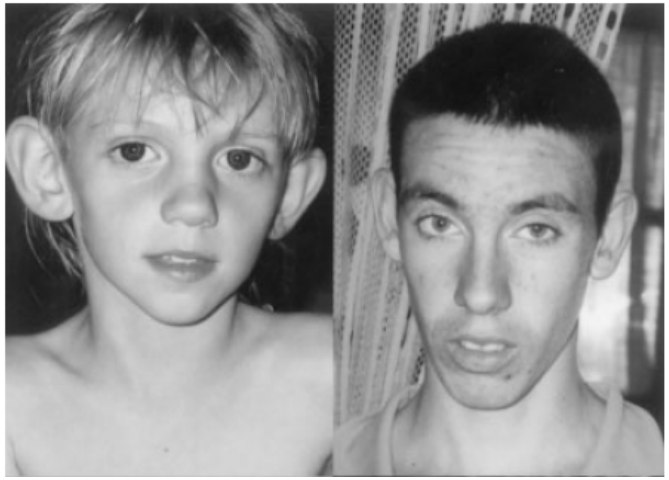
Badura-Stronka et al Clinical Genetics 2009

Severe intellectual disability
Speech impairment
Hyperactivity
Seizures
Intention tremor
Inguinal hernia
Small feet
Pes cavus

Family 502 (MRX59)







CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Deletion of the *CUL4B* Gene in a Boy With Mental Retardation, Minor Facial Anomalies, Short Stature, Hypogonadism, and Ataxia

Bertrand Isidor,[1]* Olivier Pichon,[1] Sabine Baron,[2] Albert David,[1] and Cédric Le Caignec[1,3,4,5]

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[2]Service d'Endocrinologie Pédiatrique, Centre Hospitalier Universitaire de Nantes ?, Nantes, France

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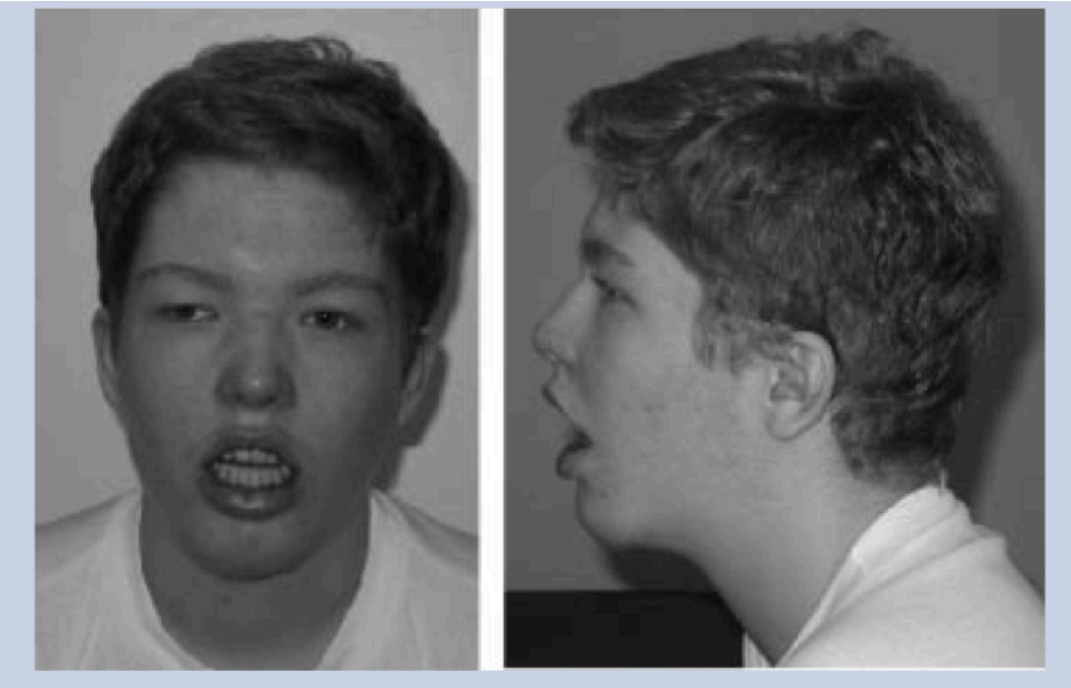
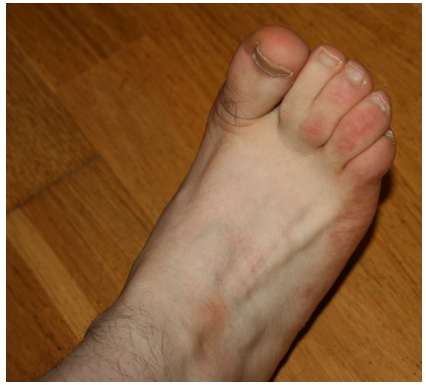
[5]Université de Nantes, Nantes, France

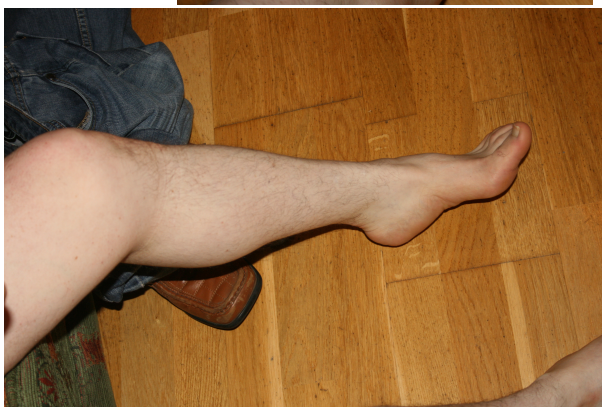
Received ? August 2009; Accepted 12 September 2009



Small palpebral fissures
Ptosis
Telecanthus
Small nose
Narrow nostrils
Prominent lower lip
Hypotonic breathing

CUL4B, MCTS1, and LAMP2 deleted





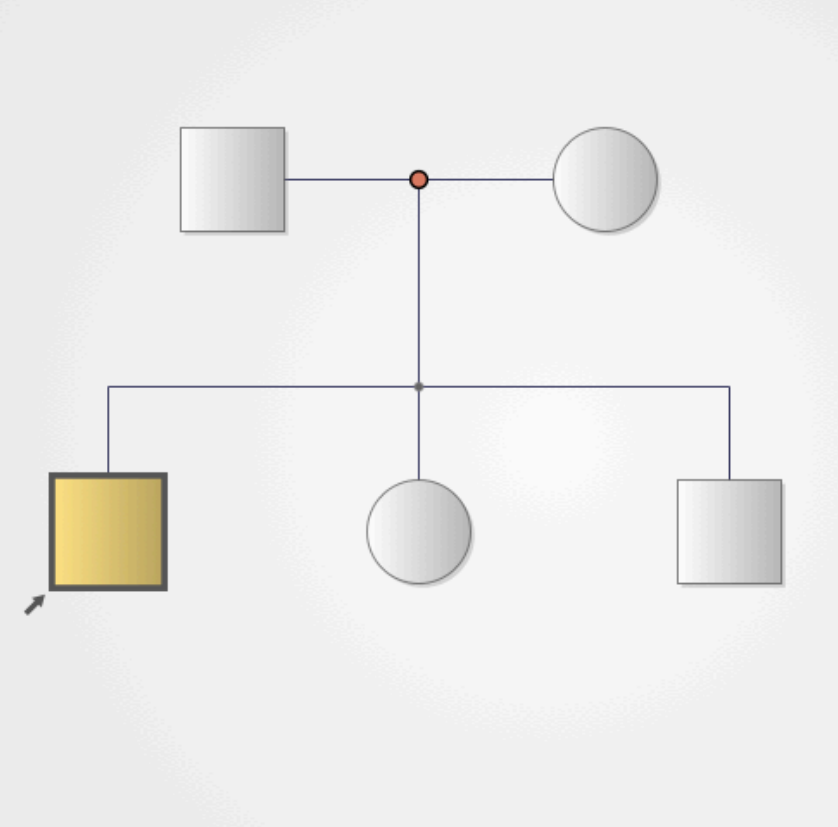
Summary of main features

TABLE I. Summary of the Findings in Patients With *CUL4B* Mutations

	Tarpey et al. [2007]	Zou et al. [2007]	Our patient	Total
Motor delay	5/5	6/6	+	12/12
Speech delay	18/18	6/6	+	25/25
Short stature	7/11	6/6	+	14/18
Macrocephaly	8/11	0/6	−	8/18
Mental retardation	22/22	6/6	+	29/29
Aggressive outbursts	12/15	0/6	+	13/22
Tremors	11/13	1/5	+	13/19
Seizures	8/11	4/5	−	12/17
Obesity	15/19	0/5	−	15/25
Pes cavus	7/8	0/5	+	8/14
Small testes	10/15	1/5	+	12/20
Prominent lower lip	6/17	5/5	+	12/23
Gait ataxia	6/12	6/6	+	13/19
Kyphosis	3/18	NR	+	4/19
Abnormal toes, with wide 1–2 gap	11/13	NR	+	11/14

Additional features emerging:
Facial grimace
Prominent front teeth
Structural brain abnormalities including abnormal ventricles, corpus callosum, PVL, hydrocephalus, porencephalic cysts

Mechanism of Disease



- Environmental
- Genomics CNV abnormality
- X linked recessive
- Autosomal recessive
- De novo autosomal dominant

NATURE GENETICS | LETTER

A *de novo* paradigm for mental retardation

Lisenka E L M Vissers, Joep de Ligt, Christian Gilissen, Irene Janssen, Marloes S
Petra de Vries, Bart van Lier, Peer Arts, Nienke Wieskamp, Marisol del Rosario, B
van Bon, Alexander Hoischen, Bert B A de Vries, Han G Brunner & Joris A Veltm

Affiliations | Contributions | Corresponding authors

Nature Genetics **42**, 1109–1112 (2010) | doi:10.1038/ng.712
Received 11 August 2010 | Accepted 18 October 2010 | Published online 14 Novem

LETTER

doi:10.1038/nature14135

Large-scale discovery of novel genetic causes of developmental disorders

The Deciphering Developmental Disorders Study*

Despite three decades of successful, predominantly phenotype-driven discovery of the genetic causes of monogenic disorders[1], up to half of children with severe developmental disorders of probable genetic

were analysed jointly in the following analyses, allowing, for example, the identification of compound heterozygous CNVs and SNVs affecting the same gene.

>1000 trios with intellectual disability

Patterns and rates of exonic *de novo* mutations in autism spectrum disorders

Benjamin M. Neale[1,2], Yan Kou[3,4], Li Liu[5], Avi Ma'ayan[3], Kaitlin E. Samocha[1,2], Aniko Sabo[6], Chiao-Feng Lin[7], Christine Stevens[2], Li-San Wang[7], Vladimir Makarov[4,8], Paz Polak[2,9], Seungtai Yoon[4,8], Jared Maguire[2], Emily L. Crawford[10], Nicholas G. Campbell[10], Evan T. Geller[7], Otto Valladares[7], Chad Schafer[5], Han Liu[11], Tuo Zhao[11], Guiqing Cai[4,8], Jayon Lihm[4,8], Ruth Dannenfelser[3], Omar Jabado[12], Zuleyma Peralta[12], Uma Nagaswamy[6], Donna Muzny[6], Jeffrey G. Reid[6], Irene Newsham[6], Yuanqing Wu[6], Lora Lewis[6], Yi Han[6], Benjamin F. Voight[2,13], Elaine Lim[1,2], Elizabeth Rossin[1,2], Andrew Kirby[1,2], Jason Flannick[2], Menachem Fromer[1,2], Khalid Shakir[2], Tim Fennell[2], Kiran Garimella[2], Eric Banks[2], Ryan Poplin[2], Stacey Gabriel[2], Mark DePristo[2], Jack R. Wimbish[14], Braden E. Boone[14], Shawn E. Levy[14], Catalina Betancur[15], Shamil Sunyaev[2,9], Eric Boerwinkle[6,16], Joseph D. Buxbaum[4,8,12,17], Edwin H. Cook Jr[18], Bernie Devlin[19], Richard A. Gibbs[6], Kathryn Roeder[5], Gerard D. Schellenberg[7], James S. Sutcliffe[10] & Mark J. Daly[1,2]

De novo mutations revealed by whole-exome sequencing are strongly associated with autism

Stephan J. Sanders[1], Michael T. Murtha[1], Abha R. Gupta[2]*, John D. Murdoch[1]*, Melanie J. Raubeson[1]*, A. Jeremy Willsey[1]*, A. Gulhan Ercan-Sencicek[1]*, Nicholas M. DiLullo[1]*, Neelroop N. Parikshak[3], Jason L. Stein[3], Michael F. Walker[1], Gordon T. Ober[1], Nicole A. Teran[1], Youeun Song[1], Paul El-Fishawy[1], Ryan C. Murtha[1], Murim Choi[4], John D. Overton[4], Robert D. Bjornson[5], Nicholas J. Carriero[5], Kyle A. Meyer[6], Kaya Bilguvar[7], Shrikant M. Mane[8], Nenad Šestan[6], Richard P. Lifton[4], Murat Günel[7], Kathryn Roeder[9], Daniel H. Geschwind[3], Bernie Devlin[10] & Matthew W. State[1]

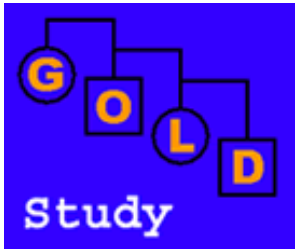
1549 variants that are de novo in autism

Targeted Exome Sequence Analysis of 1000 individuals with Intellectual Disability

- 1,000 families where a single sample was available from the proband with ID
- 2,812 sample with CHD and or other rare diseases not associated with ID

- 996 ID samples pass QC of DNA went for sequencing
- 986 QC variant calling (10 cases had >30 variants)

- 565 genes
  - 253 known genes
    (UK10K, Gilissen and DDD)
  - 312 candidate genes
    (UK10K, Rauch, de Ligt)



Results

8466 variants in 986 individuals

8011 missense and 455 LOF

8 rare variants in 253 known genes per patient

- All these variants are in

  Grozeva et al Hum Mutation (2015) PMID: 26350

  open access

- Likely pathogenic LOF and missense variants- DECIPHER

DECIPHER GRCh37

Table of 77 LoF variants in 44 known genes

Autosomal Dominant Inheritance		X-linked Inheritance		Recessive Inheritance	
Gene	**N cases**	**Gene**	**N cases**	**Gene**	**N cases**
SETD5	7	*ATRX*	6	*HEXA*	1 (comp. het.)
ARID1B	4	*CUL4B*	5	*AGA*	1 (homoz.)
TCF4	2	*IL1RAPL1*	3	*HGSNAT*	1 (homoz.+missense)
KANK1	2	*BRWD3*	2	*PAH*	1 (homoz.)
GRIN2B	2	*NLGN4X*	1		
SCN2A	2	*OPHN1*	2		
SHANK2	2	*PQBP1*	2		
CHD7	2				
CTNNB1	2				
KAT6B	2				
SETBP1	1	*ACSL4*	1		
UBE3A	1	*AFF2*	1		
ASXL1	1	*GPC3*	1		
MLL2	1	*KDM5C*	1		
CREBBP	1	*MAOA*	1		
SCN8A	1	*OFD1*	1		
EHMT1	1	*PTCHD1*	1		
FOXP1	1	*SMC1A*	1		
KANSL1	1	*SMS*	1		
MEF2C	1	*TSPAN7*	1		
NSD1	1	*USP9X*	1		
PAX6	1				
PTEN	1				
RAF1	1				

SETD5, ARID1B, ATRX and CUL4B commonest genes

Table of 77 LoF variants in 44 known genes

Autosomal Dominant Inheritance		X-linked Inheritance		Recessive Inheritance	
Gene	**N cases**	**Gene**	**N cases**	**Gene**	**N cases**
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SHANK2	2	*PQBP1*	2		
CHD7	2				
CTNNB1	2				
KAT6B	2				
SETBP1	1	*ACSL4*	1		
UBE3A	1	*AFF2*	1		
ASXL1	1	*GPC3*	1		
MLL2	1	*KDM5C*	1		
CREBBP	1	*MAOA*	1		
SCN8A	1	*OFD1*	1		
EHMT1	1	*PTCHD1*	1		
FOXP1	1	*SMC1A*	1		
KANSL1	1	*SMS*	1		
MEF2C	1	*TSPAN7*	1		
NSD1	1	*USP9X*	1		
PAX6	1				
PTEN	1				
RAF1	1				

Syndromic genes with non-syndromic phenotype

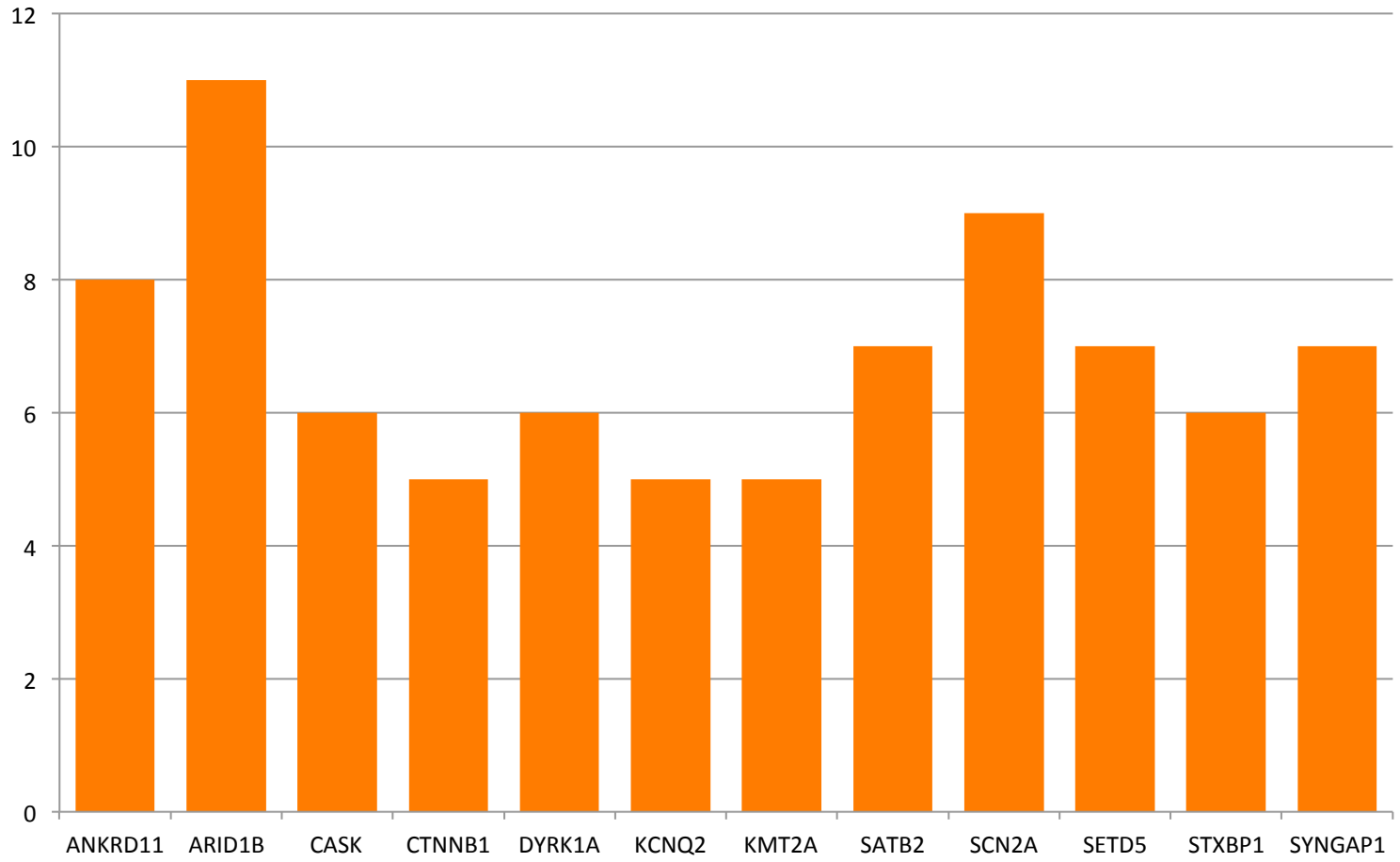
Table of 77 LoF variants in 44 known genes

Autosomal Dominant Inheritance		X-linked Inheritance		Recessive Inheritance	
Gene	**N cases**	**Gene**	**N cases**	**Gene**	**N cases**
SETD5	7	*ATRX*	6	*HEXA*	1 (comp. het.)
ARID1B	4	*CUL4B*	5	*AGA*	1 (homoz.)
TCF4	2	*IL1RAPL1*	3	*HGSNAT*	1 (homoz.+missense)
KANK1	2	*BRWD3*	2	*PAH*	1 (homoz.)
GRIN2B	2	*NLGN4X*	1		
SCN2A	2	*OPHN1*	2		
SHANK2	2	*PQBP1*	2		
CHD7	2				
CTNNB1	2				
KAT6B	2				
SETBP1	1				
UBE3A	1	*AFF2*	1		
ASXL1	1	*GPC3*	1		
MLL2	1	*KDM5C*	1		
CREBBP	1	*MAOA*	1		
SCN8A	1	*OFD1*	1		
EHMT1	1	*PTCHD1*	1		
FOXP1	1	*SMC1A*	1		
KANSL1	1	*SMS*	1		
MEF2C	1	*TSPAN7*	1		
NSD1	1	*USP9X*	1		
PAX6	1				
PTEN	1				
RAF1	1				

60/77 78% of variants not present on HGMD

DIAGNOSTIC RATE 8%

Diagnostic yield of >25% if trio analysis to identify rare de novo events



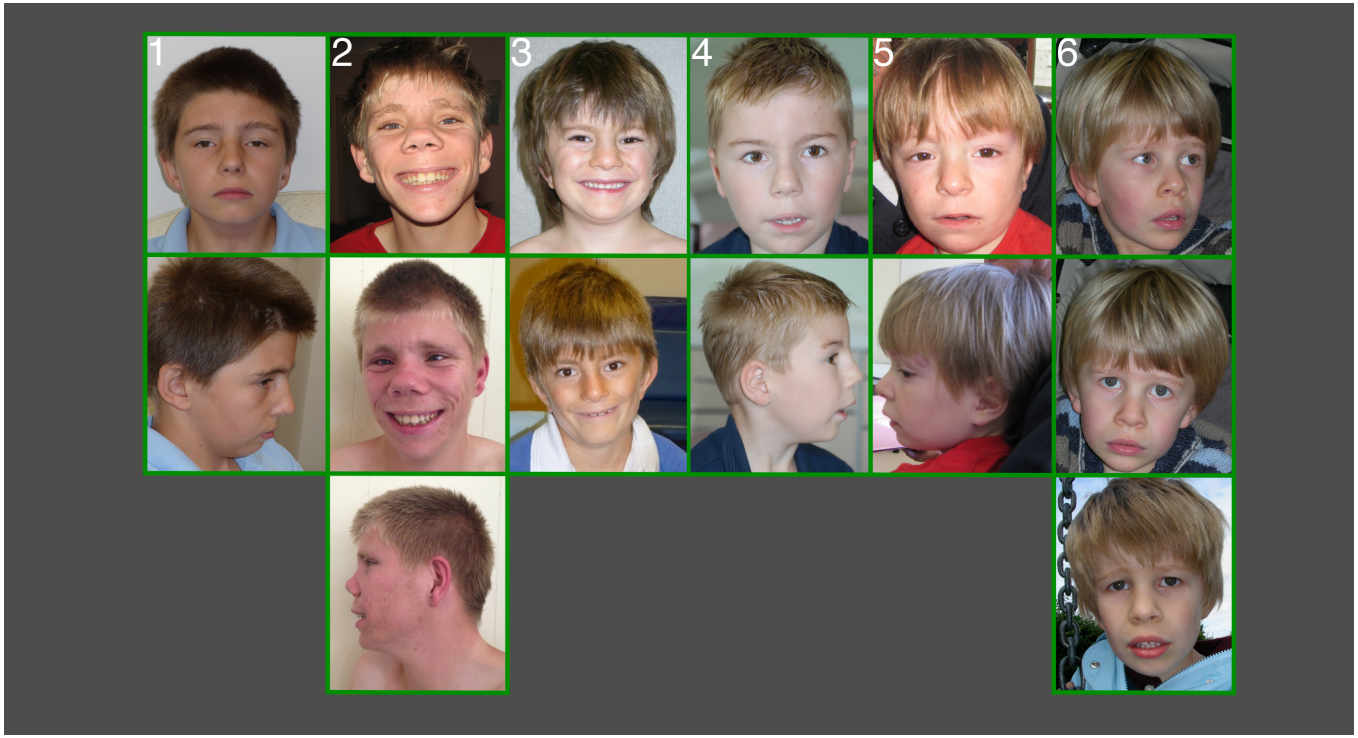
www.ddduk.org

REPORT

De Novo Loss-of-Function Mutations in *SETD5*, Encoding a Methyltransferase in a 3p25 Microdeletion Syndrome Critical Region, Cause Intellectual Disability

Detelina Grozeva,[1] Keren Carss,[2] Olivera Spasic-Boskovic,[1] Michael J. Parker,[3] Hayley Archer,[4] Helen V. Firth,[5] Soo-Mi Park,[5] Natalie Canham,[6] Susan E. Holder,[6] Meredith Wilson,[7] Anna Hackett,[8] Michael Field,[9] James A.B. Floyd,[2,10] UK10K Consortium,[2] Matthew Hurles,[2] and F. Lucy Raymond[1,*]

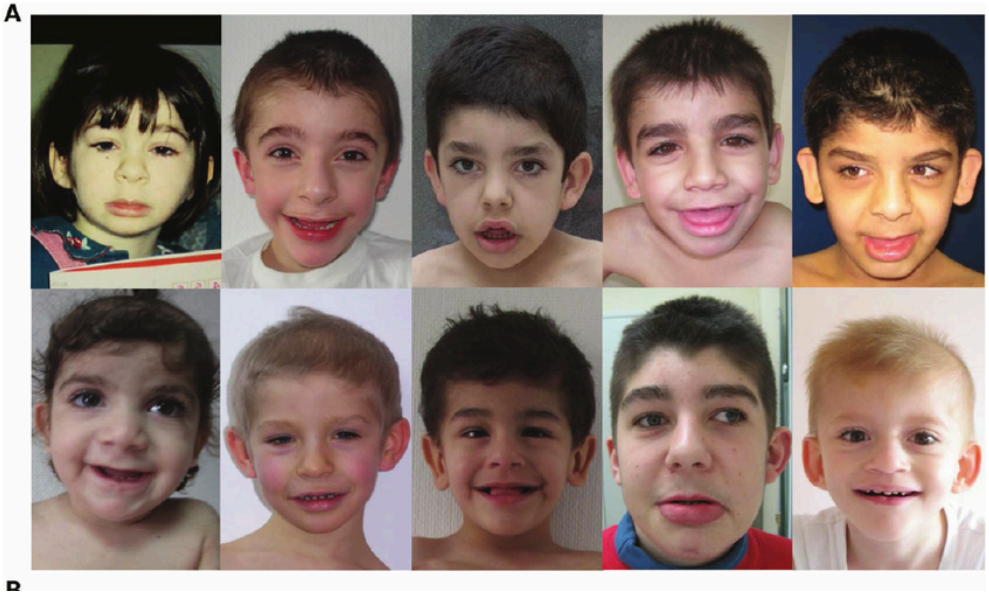
AJHG 2014



Loss of function of SETD5 is a relatively frequent cause of ID (0.7% in our ID sample)

Occurs as a rare de novo mutational event

LoF mutations within SETD5 is sufficient to cause many of the features of 3p25 microdeletion syndrome



ARID1B
Coffin-Siris or severe ID

Mutations in SWI/SNF chromatin remodeling complex gene *ARID1B* cause Coffin-Siris syndrome

Gijs W E Santen, Emmelien Aten, Yu Sun, Rowida Almomani, Christian Gilissen, Maartje Nielsen, Sarina G Kant, Irina N Snoeck, Els A J Peeters, Yvonne Hilhorst-Hofstee, Marja W Wessels, Nicolette S den Hollander, Claudia A L Ruivenkamp, Gert-Jan B van Ommen, Martijn H Breuning, Johan T den Dunnen, Arie van Haeringen & Marjolein Kriek

< Previous Article

Volume 90, Issue 3, p565–572, 9 March 2012

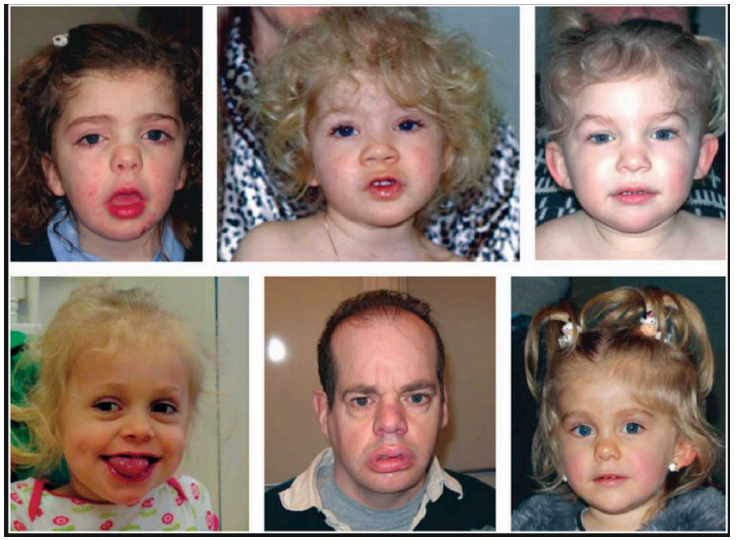
Report

Switch to Standard View

Haploinsufficiency of *ARID1B*, a Member of the SWI/SNF-A Chromatin-Remodeling Complex, Is a Frequent Cause of Intellectual Disability

Juliane Hoyer[8], Arif B. Ekici[8], Sabine Endele[8], Bernt Popp, Christiane Zweier, Antje Wiesener, Eva Wohlleber, Andreas Dufke, Eva Rossier, Corinna Petsch, Markus Zweier, Ina Göhring, Alexander M. Zink, Gudrun Rappold, Evelin Schröck, Dagmar Wieczorek, Olaf Riess, Hartmut Engels, Anita Rauch, André Reis

[8] These authors contributed equally to this work.



ANKRD11

European Journal of Human Genetics (2015) 23, 1176–1185

www.nature.com/ejhg

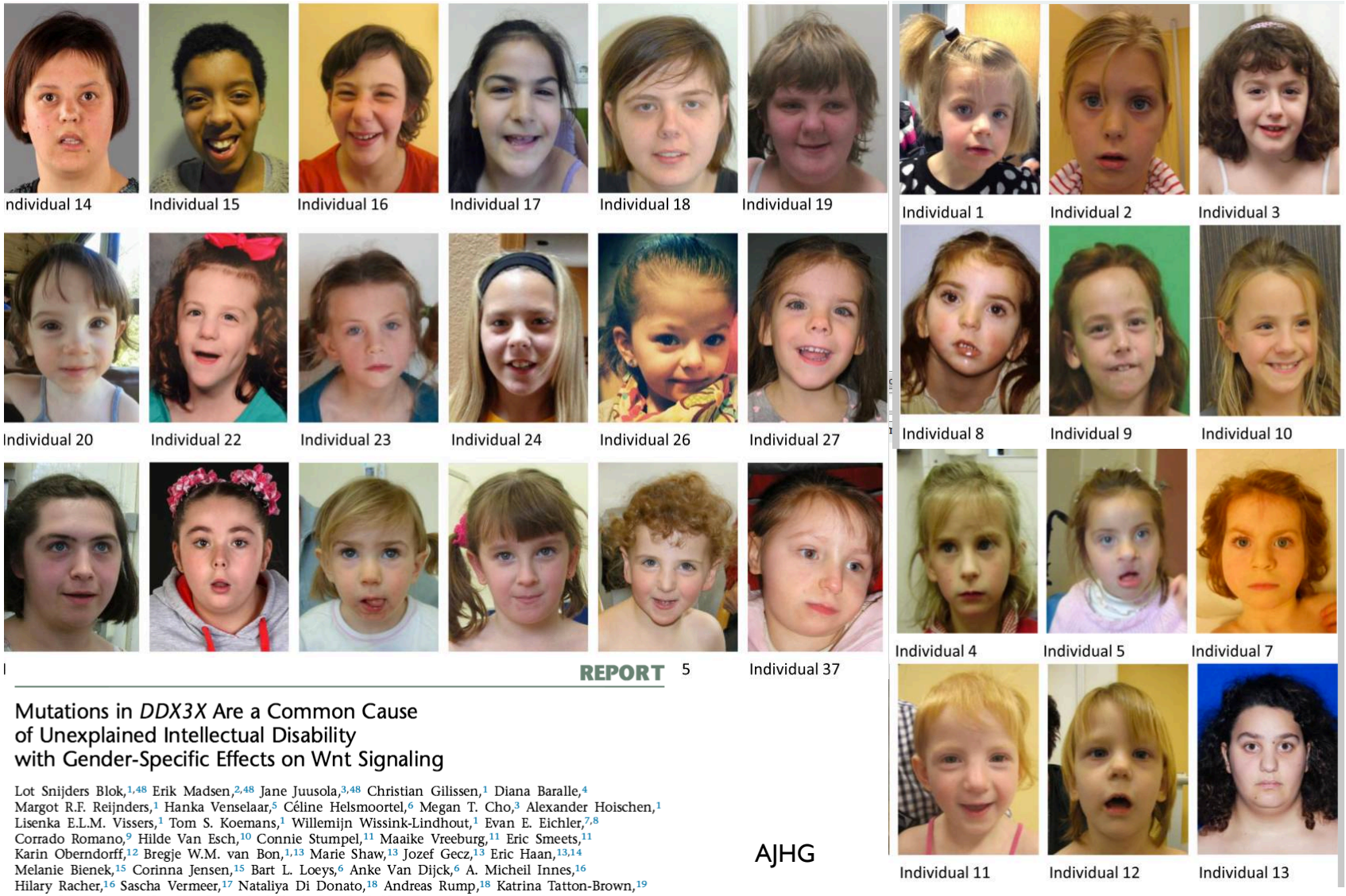
ARTICLE

Further delineation of the KBG syndrome phenotype caused by *ANKRD11* aberrations

This paper has been corrected since online publication and a corrigendum also appears in this issue

Charlotte W Ockeloen*,[1], Marjolein H Willemsen*,[1], Sonja de Munnik[1], Bregje WM van Bon[1,2], Nicole de Leeuw[1], Aad Verrips[3], Sarina G Kant[4], Elizabeth A Jones[5,6], Han G Brunner[1], Rosa LE van Loon[7], Eric EJ Smeets[8], Mieke M van Haelst[9], Gijs van Haaften[9], Ann Nordgren[10,11], Helena Malmgren[10,11], Vermeer[12], Pedro Louro[13], Lina Ramos[13], Thomas JJ Maal[14], G Yntema[1], Carine EL Carels[16,17] and Tjitske Kleefstra[1,17]

DDX3X



Mutations in *DDX3X* Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling

Lot Snijders Blok,[1,48] Erik Madsen,[2,48] Jane Juusola,[3,48] Christian Gilissen,[1] Diana Baralle,[4] Margot R.F. Reijnders,[1] Hanka Venselaar,[5] Céline Helsmoortel,[6] Megan T. Cho,[3] Alexander Hoischen,[1] Lisenka E.L.M. Vissers,[1] Tom S. Koemans,[1] Willemijn Wissink-Lindhout,[1] Evan E. Eichler,[7,8] Corrado Romano,[9] Hilde Van Esch,[10] Connie Stumpel,[11] Maaike Vreeburg,[11] Eric Smeets,[11] Karin Oberndorff,[12] Bregje W.M. van Bon,[1,13] Marie Shaw,[13] Jozef Gecz,[13] Eric Haan,[13,14] Melanie Bienek,[15] Corinna Jensen,[15] Bart L. Loeys,[6] Anke Van Dijck,[6] A. Micheil Innes,[16] Hilary Racher,[16] Sascha Vermeer,[17] Nataliya Di Donato,[18] Andreas Rump,[18] Katrina Tatton-Brown,[19] Michael J. Parker,[20] Alex Henderson,[21] Sally A. Lynch,[22] Alan Fryer,[23] Alison Ross,[24] Pradeep Vasudevan,[25] Usha Kini,[26] Ruth Newbury-Ecob,[27] Kate Chandler,[28] Alison Male,[29] the DDD Study, Sybe Dijkstra,[30]

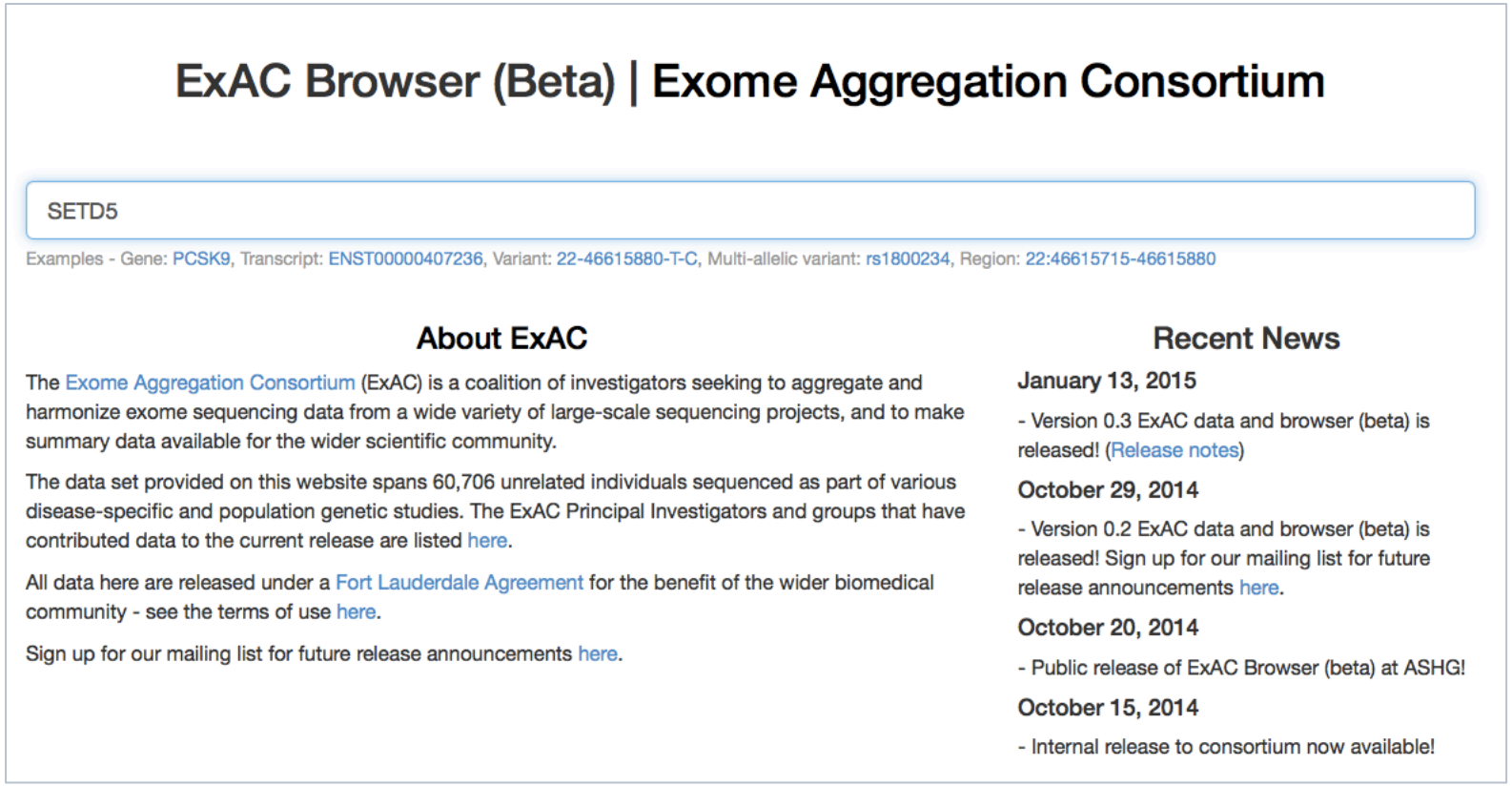
AJHG

Volume 97, Issue 2, 6 August 2015, Pages 343–352

How to assess a variant is pathogenic

- Rare
  - ExAC
- Segregates
- Present in diagnostic databases
  - HGMD and ClinVar but presence is not proof
- Clinically fits
- Still no automated variant analysis can get there
  - Multidisciplinary approach

Variant assessment in >120,000 alleles



Coverage, constraint score and individual variants

SETD5 SET domain containing 5
Number of variants 1039 (Including filtered: 1150)
UCSC Browser 3:9439299-9520924
GeneCards SETD5
Other External References

Transcripts

Constraint from ExAC	Expected no. variants	Observed no. variants	Constraint Metric
Synonymous	167.6	186	z = -0.88
Missense	442.4	444	z = -0.04
LoF	49.2	2	pLI = 1.00

Gene summary

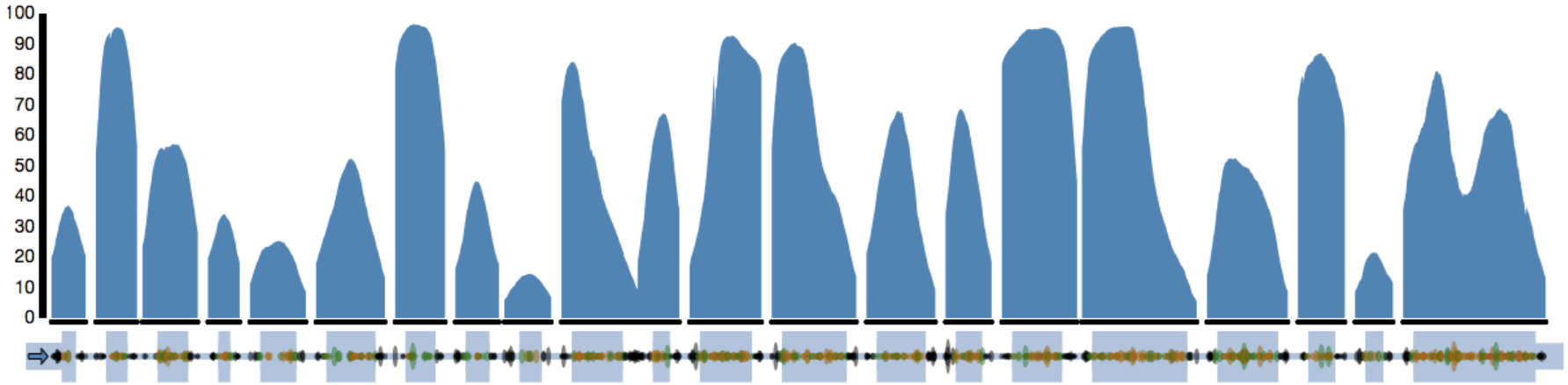
(Coverage shown for canonical transcript: ENST00000402198)

Mean coverage 51.90

Display: Overview | Detail | Include UTRs in plot

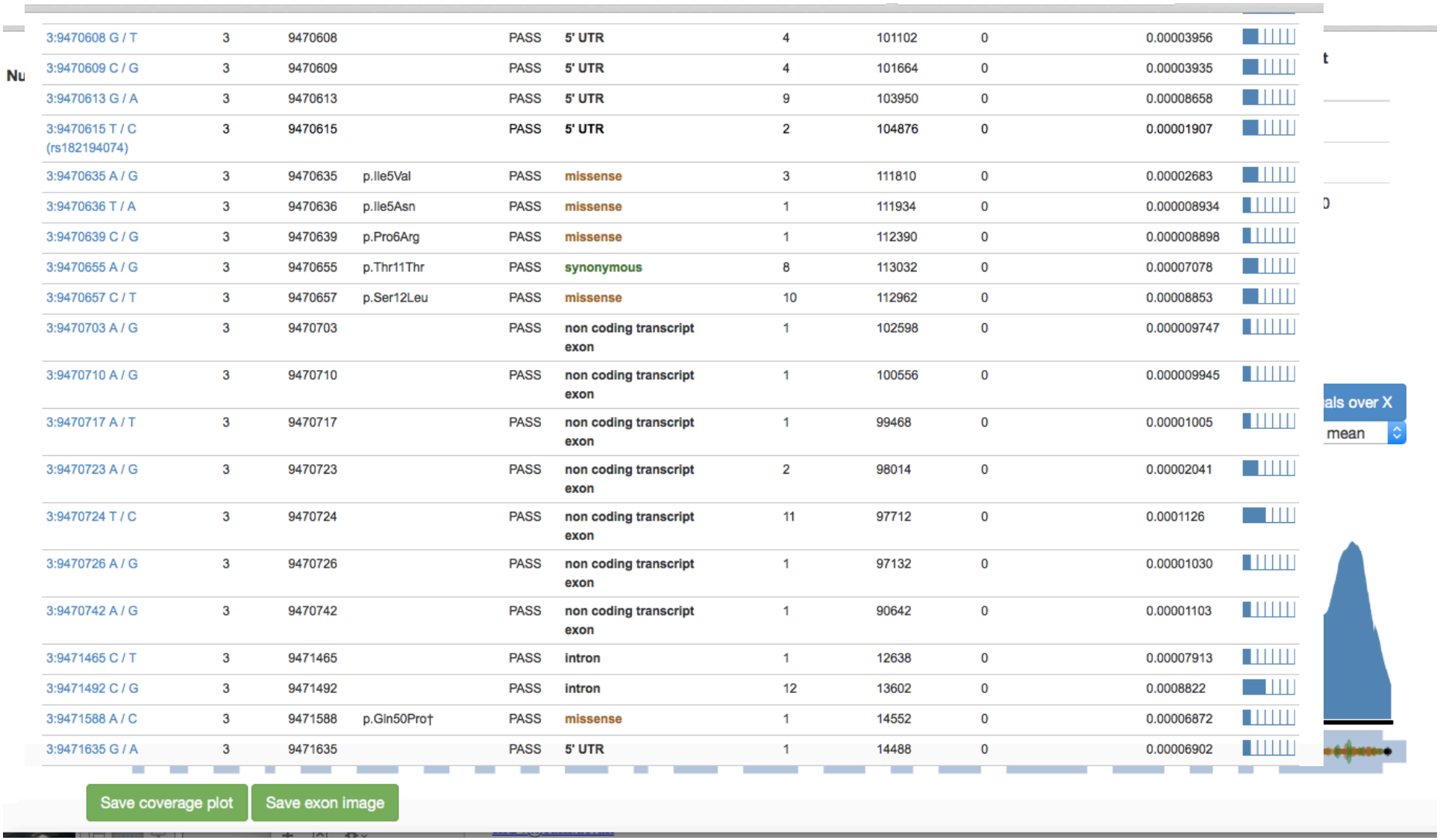
Coverage metric: Average | Individuals over X

Metric: mean



Save coverage plot | Save exon image

Coverage, constraint score and individual variants



3:9470608 G / T	3	9470608		PASS	5' UTR	4	101102	0	0.00003956
3:9470609 C / G	3	9470609		PASS	5' UTR	4	101664	0	0.00003935
3:9470613 G / A	3	9470613		PASS	5' UTR	9	103950	0	0.00008658
3:9470615 T / C (rs182194074)	3	9470615		PASS	5' UTR	2	104876	0	0.00001907
3:9470635 A / G	3	9470635	p.Ile5Val	PASS	missense	3	111810	0	0.00002683
3:9470636 T / A	3	9470636	p.Ile5Asn	PASS	missense	1	111934	0	0.000008934
3:9470639 C / G	3	9470639	p.Pro6Arg	PASS	missense	1	112390	0	0.000008898
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3:9470703 A / G	3	9470703		PASS	non coding transcript exon	1	102598	0	0.000009747
3:9470710 A / G	3	9470710		PASS	non coding transcript exon	1	100556	0	0.000009945
3:9470717 A / T	3	9470717		PASS	non coding transcript exon	1	99468	0	0.00001005
3:9470723 A / G	3	9470723		PASS	non coding transcript exon	2	98014	0	0.00002041
3:9470724 T / C	3	9470724		PASS	non coding transcript exon	11	97712	0	0.0001126
3:9470726 A / G	3	9470726		PASS	non coding transcript exon	1	97132	0	0.00001030
3:9470742 A / G	3	9470742		PASS	non coding transcript exon	1	90642	0	0.00001103
3:9471465 C / T	3	9471465		PASS	intron	1	12638	0	0.00007913
3:9471492 C / G	3	9471492		PASS	intron	12	13602	0	0.0008822
3:9471588 A / C	3	9471588	p.Gln50Pro†	PASS	missense	1	14552	0	0.00006872
3:9471635 G / A	3	9471635		PASS	5' UTR	1	14488	0	0.00006902

Save coverage plot Save exon image

Coverage, constraint score and individual variants

3:9470608 G / T	3	9470608		PASS	5' UTR	4	101102	0	0.00003956
3:9470609 C / G	3	9470609		PASS	5' UTR	4	101664	0	0.00003935
3:9470613 G / A	3	9470613		PASS	5' UTR	9	103950	0	0.00008658
3:9470615 T / C (rs182194074)	3	9470615		PASS	5' UTR	2	104876	0	0.00001907
3:9470635 A / G	3	9470635	p.Ile5Val	PASS	missense	3	111810	0	0.00002683
3:9470636 T / A	3	9470636	p.Ile5Asn	PASS	missense	1	111934	0	0.000008934
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3:9470710 A / G	3	9470710		PASS	non coding transcript exon	1	100556	0	0.000009945
3:9470717 A / T	3	9470717		PASS	non coding transcript exon	1	99468	0	0.00001005
3:9470723 A / G	3	9470723		PASS	non coding transcript exon	2	98014	0	0.00002041
3:9470724 T / C	3	9470724		PASS	non coding transcript exon	11	97712	0	0.0001126
3:9470726 A / G	3	9470726		PASS	non coding transcript exon	1	97132	0	0.00001030
3:9470742 A / G	3	9470742		PASS	non coding transcript exon	1	90642	0	0.00001103
3:9471465 C / T	3	9471465		PASS	intron	1	12638	0	0.00007913
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3:9471635 G / A	3	9471635		PASS	5' UTR	1	14488	0	0.00006902

Additional source of knowledge

- Parents
- Parents
- Parents
  - Support groups
  - Parental observations
  - Parental research
  - Internet groups

UNIQUE

Rare chromosome support charity

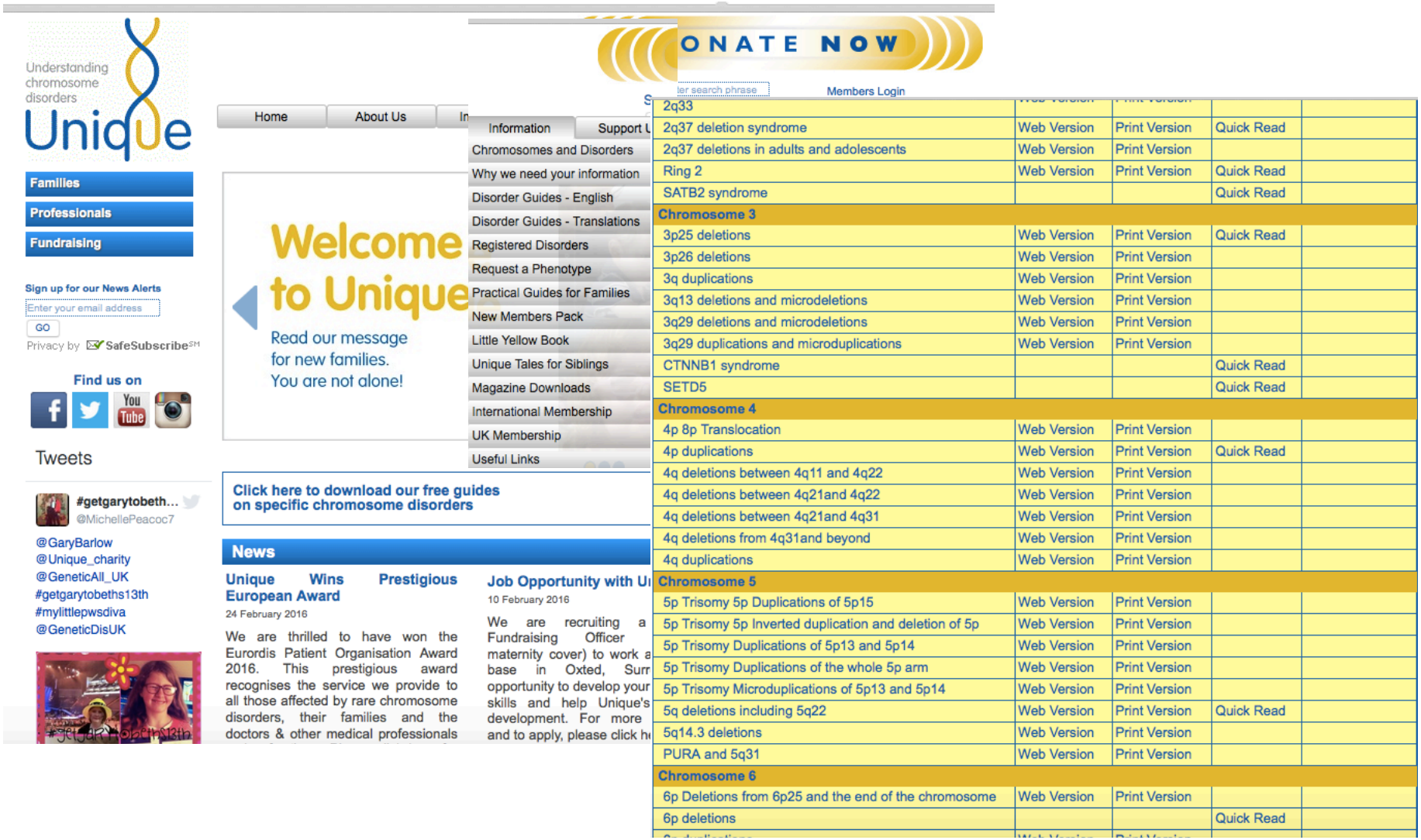
http://www.rarechromo.org

UNIQUE

http://www.rarechromo.org

UNIQUE

http://www.rarechromo.org



2q33				
2q37 deletion syndrome	Web Version	Print Version	Quick Read	
2q37 deletions in adults and adolescents	Web Version	Print Version		
Ring 2	Web Version	Print Version	Quick Read	
SATB2 syndrome			Quick Read	
Chromosome 3				
3p25 deletions	Web Version	Print Version	Quick Read	
3p26 deletions	Web Version	Print Version		
3q duplications	Web Version	Print Version		
3q13 deletions and microdeletions	Web Version	Print Version		
3q29 deletions and microdeletions	Web Version	Print Version		
3q29 duplications and microduplications	Web Version	Print Version		
CTNNB1 syndrome			Quick Read	
SETD5			Quick Read	
Chromosome 4				
4p 8p Translocation	Web Version	Print Version		
4p duplications	Web Version	Print Version	Quick Read	
4q deletions between 4q11 and 4q22	Web Version	Print Version		
4q deletions between 4q21and 4q22	Web Version	Print Version		
4q deletions between 4q21and 4q31	Web Version	Print Version		
4q deletions from 4q31and beyond	Web Version	Print Version		
4q duplications	Web Version	Print Version		
Chromosome 5				
5p Trisomy 5p Duplications of 5p15	Web Version	Print Version		
5p Trisomy 5p Inverted duplication and deletion of 5p	Web Version	Print Version		
5p Trisomy Duplications of 5p13 and 5p14	Web Version	Print Version		
5p Trisomy Duplications of the whole 5p arm	Web Version	Print Version		
5p Trisomy Microduplications of 5p13 and 5p14	Web Version	Print Version		
5q deletions including 5q22	Web Version	Print Version	Quick Read	
5q14.3 deletions	Web Version	Print Version		
PURA and 5q31	Web Version	Print Version		
Chromosome 6				
6p Deletions from 6p25 and the end of the chromosome	Web Version	Print Version		
6p deletions			Quick Read	

3p25 deletion and SETD5

What causes SETD5 syndrome?

When children are conceived their parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of children that are not seen in the DNA of their parents. SETD5 syndrome occurs when one of these random, rare changes affects the *SETD5* gene on chromosome 3. These types of change happen naturally in all species - humans, plants and animals - and are not due to your lifestyle or anything you did. In most families the DNA change in *SETD5* occurs out of the blue (de novo). In a minority of families, one parent may have the same genetic change as their child, but this is very rare.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. For SETD5 syndrome where parents do not carry the same *SETD5* change as their child, the chances of having another child are little higher than for anyone else in the population. If the genetic analysis of the parents of a child with SETD5 syndrome shows that they carry the same change in the *SETD5* gene, the chances of it happening again are much higher. Each family situation is different and a clinical geneticist or genetic counsellor can give you specific advice for your family.

How common is SETD5 syndrome?

SETD5 syndrome is a rare condition and was only identified for the first time in 2014. The first study identified changes (mutations) in the *SETD5* gene as one of the commoner causes of intellectual disability with autism and behavioural problems. In a recent study of 1000 children with moderate to severe intellectual disability a change in the *SETD5* gene was found in 6 individuals (0.7%).

Families say ...

"Our daughter made us see the world through different eyes. She is a gift to us." - 11 years

"Our son is very fond of electronics, seems to know a lot and gets excited to help others. He loves all special Olympics activities he participates in. Always excited to go and be part of the group. Always keeps us on our toes, very loving and loves to talk. One of the most special boys we have ever known." - 15 years

Inform Network Support

Understanding chromosome disorders Unique

Rare Chromosome Disorder Support Group,
GI, The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
Tel/Fax: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Understanding chromosome disorders Unique

SETD5 and 3p25 deletion syndrome

rarechromo.org

IMAGINE ID

Intellectual Disability and Mental Health: Assessing Genomic Impact on Neurodevelopment

Prof Lucy Raymond, David Skuse, Jeremy Hall, Marianne van den Bree

MRC Medical Research Council

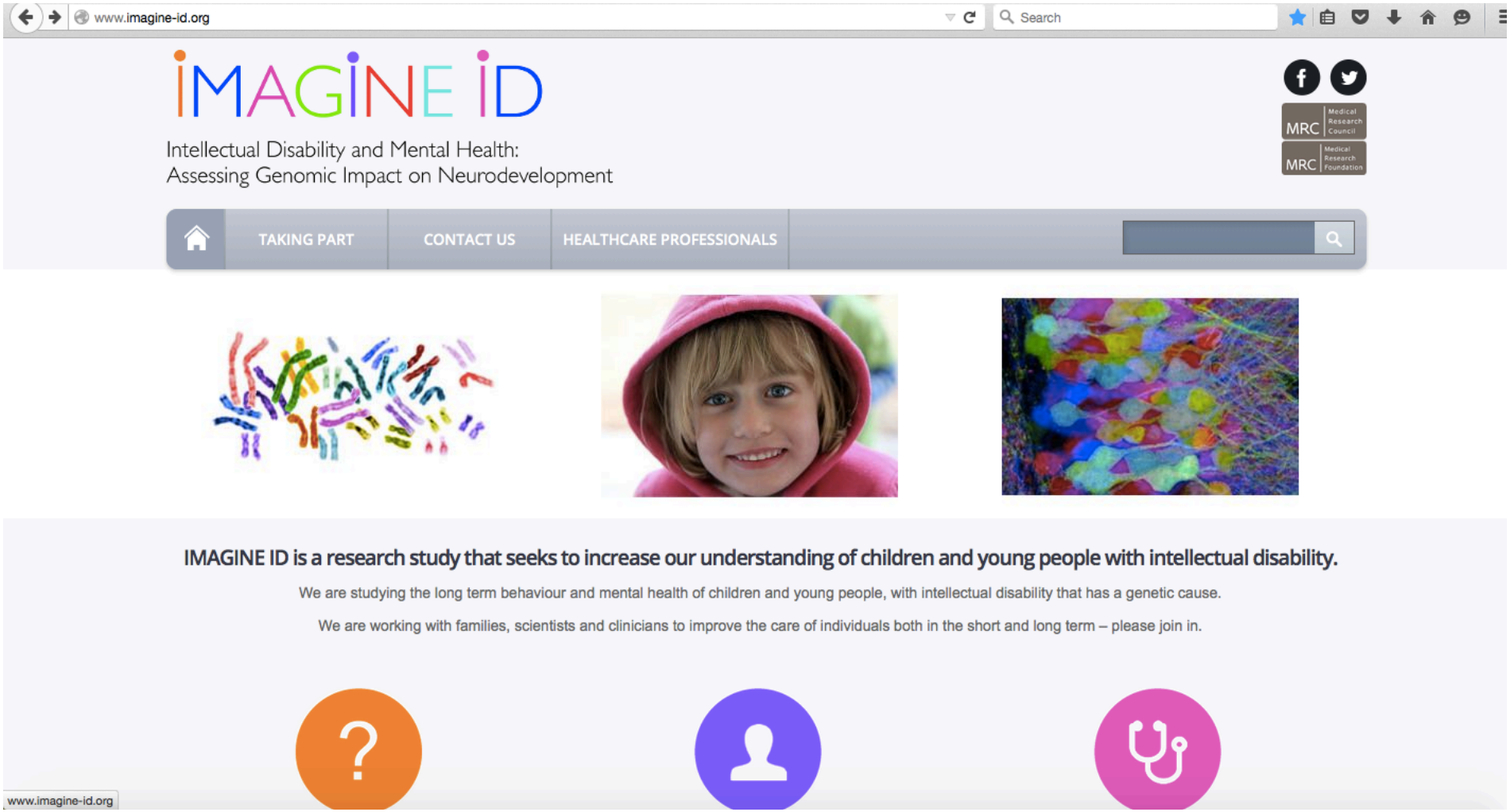
MRC Medical Research Foundation

Cambridge University Hospitals NHS Foundation Trust

UNIVERSITY OF CAMBRIDGE

CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD

UCL



www.imagine-id.org

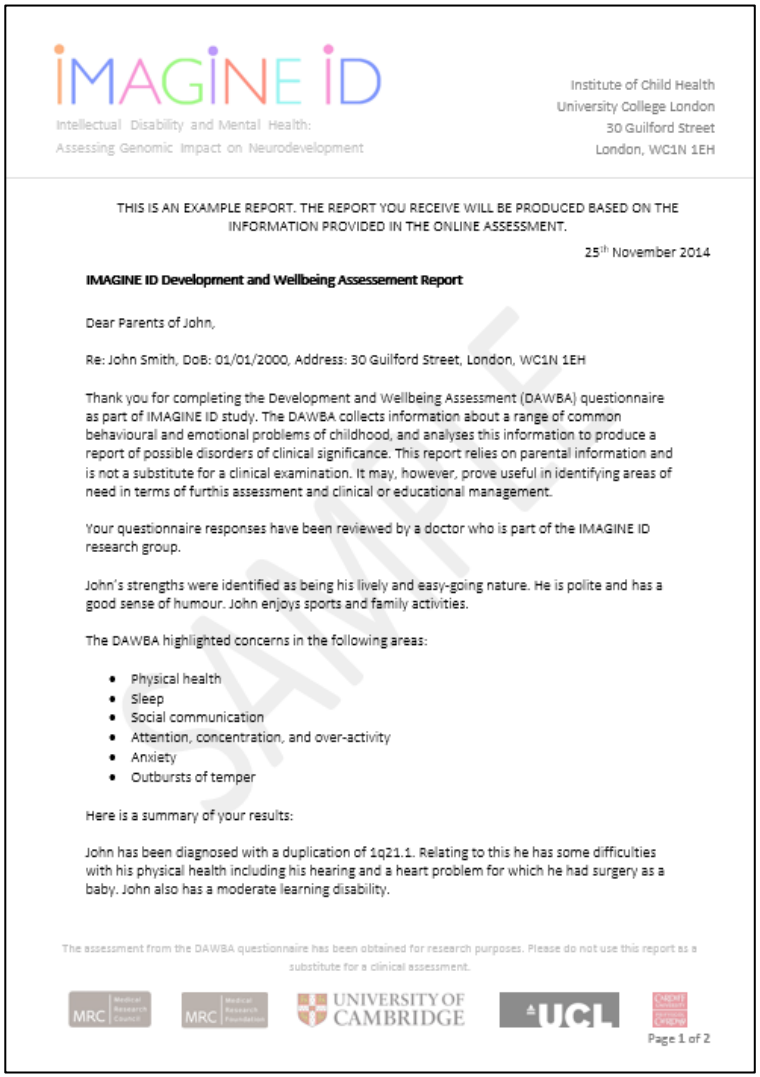
IMAGINE ID

- Aims to better understand how the genome affects the long term development, behaviour and mental health of children with intellectual disability
- MRC funded national study over 5 years
- Multidisciplinary team from University College London, University of Cambridge, and Cardiff University
- Aim to recruit10,000 patients by September 2019

Inclusion Criteria

- ✓ Child is between 4 and 18 years old
- ✓ Has likely pathogenic SNV or CNV(s)
- ✓ Has intellectual disability, learning difficulties, or developmental delay

DAWBA Report



IMAGINE ID

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

Institute of Child Health
University College London
30 Guilford Street
London, WC1N 1EH

THIS IS AN EXAMPLE REPORT. THE REPORT YOU RECEIVE WILL BE PRODUCED BASED ON THE INFORMATION PROVIDED IN THE ONLINE ASSESSMENT.

25th November 2014

IMAGINE ID Development and Wellbeing Assessement Report

Dear Parents of John,

Re: John Smith, DoB: 01/01/2000, Address: 30 Guilford Street, London, WC1N 1EH

Thank you for completing the Development and Wellbeing Assessment (DAWBA) questionnaire as part of IMAGINE ID study. The DAWBA collects information about a range of common behavioural and emotional problems of childhood, and analyses this information to produce a report of possible disorders of clinical significance. This report relies on parental information and is not a substitute for a clinical examination. It may, however, prove useful in identifying areas of need in terms of furthis assessment and clinical or educational management.

Your questionnaire responses have been reviewed by a doctor who is part of the IMAGINE ID research group.

John's strengths were identified as being his lively and easy-going nature. He is polite and has a good sense of humour. John enjoys sports and family activities.

The DAWBA highlighted concerns in the following areas:

- Physical health
- Sleep
- Social communication
- Attention, concentration, and over-activity
- Anxiety
- Outbursts of temper

Here is a summary of your results:

John has been diagnosed with a duplication of 1q21.1. Relating to this he has some difficulties with his physical health including his hearing and a heart problem for which he had surgery as a baby. John also has a moderate learning disability.

IMAGINE ID

Intellectual Disability and Mental Health:
Assessing Genomic Impact on Neurodevelopment

Institute of Child Health
University College London
30 Guilford Street
London, WC1N 1EH

John has difficulty falling and staying asleep. He takes several hours to fall asleep and often wakes up at night and moves into his parents' bed. John takes melatonin to help his sleep.

The DAWBA identified John as having some difficulties with social communication. John has difficulty with non-verbal social interaction and peer relationships. At present, these difficulties seem to be best explained by his developmental level which is lower than his chronological age. If concerns remain as John develops, furthis assessment may be beneficial.

John has difficulties with attention and over-activity which is in keeping with his diagnosis of attention deficit hyperactivity disorder (ADHD). These difficulties have a significant impact on John's learning and family life. The difficulties are currently managed by providing John with lots of short activities to help him re-focus, and by offering him regular prompts and reminders.

John experiences anxiety about a number of things; these include the dark, crowds, and separation from his mother. John gets very upset when having to leave his mother to go to school or other activities on his own. John's fear of the dark means that he prefers to sleep with the lights on and usually needs a parent in the room to settle. In addition, John's fear of crowds lead him to avoid social situations such as parties. John's fears are triggered frequently and have a significant impact on his quality of life; as such they warrant further assessment and management.

John has temper outbursts approximately 3 times a week. During these outbursts John shouts, cries, and says negative things about himself. John's outbursts mainly occur at home, but also occur at school. The triggers for these episodes are not always clear but are often related to tiredness or being told he cannot have something he wants. John's family currently manage his temper outbursts by using appropriate strategies.

John and his family receive input from range of local services; in particular, John's school was described as being very supportive of John's needs. In addition they are flexible and supportive of each other.

Yours sincerely,

IMAGINE ID Team

The assessment from the DAWBA questionnaire has been obtained for research purposes. Please do not use this report as a substitute for a clinical assessment.

NATURE GENETICS | LETTER

A *de novo* paradigm for mental retardation

Lisenka E L M Vissers, Joep de Ligt, Christian Gilissen, Irene Janssen, Marloes S
Petra de Vries, Bart van Lier, Peer Arts, Nienke Wieskamp, Marisol del Rosario, B
van Bon, Alexander Hoischen, Bert B A de Vries, Han G Brunner & Joris A Veltm

Affiliations | Contributions | Corresponding authors

Nature Genetics **42**, 1109–1112 (2010) | doi:10.1038/ng.712
Received 11 August 2010 | Accepted 18 October 2010 | Published online 14 Novem

LETTER

doi:10.1038/nature14135

Large-scale discovery of novel genetic causes of developmental disorders

The Deciphering Developmental Disorders Study*

Despite three decades of successful, predominantly phenotype-driven discovery of the genetic causes of monogenic disorders[1], up to half of children with severe developmental disorders of probable genetic

were analysed jointly in the following analyses, allowing, for example, the identification of compound heterozygous CNVs and SNVs affecting the same gene.

>1000 trios with intellectual disability

Patterns and rates of exonic *de novo* mutations in autism spectrum disorders

Benjamin M. Neale[1,2], Yan Kou[3,4], Li Liu[5], Avi Ma'ayan[3], Kaitlin E. Samocha[1,2], Aniko Sabo[6], Chiao-Feng Lin[7], Christine Stevens[2], Li-San Wang[7], Vladimir Makarov[4,8], Paz Polak[2,9], Seungtai Yoon[4,8], Jared Maguire[2], Emily L. Crawford[10], Nicholas G. Campbell[10], Evan T. Geller[7], Otto Valladares[7], Chad Schafer[5], Han Liu[11], Tuo Zhao[11], Guiqing Cai[4,8], Jayon Lihm[4,8], Ruth Dannenfelser[3], Omar Jabado[12], Zuleyma Peralta[12], Uma Nagaswamy[6], Donna Muzny[6], Jeffrey G. Reid[6], Irene Newsham[6], Yuanqing Wu[6], Lora Lewis[6], Yi Han[6], Benjamin F. Voight[2,13], Elaine Lim[1,2], Elizabeth Rossin[1,2], Andrew Kirby[1,2], Jason Flannick[2], Menachem Fromer[1,2], Khalid Shakir[2], Tim Fennell[2], Kiran Garimella[2], Eric Banks[2], Ryan Poplin[2], Stacey Gabriel[2], Mark DePristo[2], Jack R. Wimbish[14], Braden E. Boone[14], Shawn E. Levy[14], Catalina Betancur[15], Shamil Sunyaev[2,9], Eric Boerwinkle[6,16], Joseph D. Buxbaum[4,8,12,17], Edwin H. Cook Jr[18], Bernie Devlin[19], Richard A. Gibbs[6], Kathryn Roeder[5], Gerard D. Schellenberg[7], James S. Sutcliffe[10] & Mark J. Daly[1,2]

De novo mutations revealed by whole-exome sequencing are strongly associated with autism

Stephan J. Sanders[1], Michael T. Murtha[1], Abha R. Gupta[2]*, John D. Murdoch[1]*, Melanie J. Raubeson[1]*, A. Jeremy Willsey[1]*, A. Gulhan Ercan-Sencicek[1]*, Nicholas M. DiLullo[1]*, Neelroop N. Parikshak[3], Jason L. Stein[3], Michael F. Walker[1], Gordon T. Ober[1], Nicole A. Teran[1], Youeun Song[1], Paul El-Fishawy[1], Ryan C. Murtha[1], Murim Choi[4], John D. Overton[4], Robert D. Bjornson[5], Nicholas J. Carriero[5], Kyle A. Meyer[6], Kaya Bilguvar[7], Shrikant M. Mane[8], Nenad Šestan[6], Richard P. Lifton[4], Murat Günel[7], Kathryn Roeder[9], Daniel H. Geschwind[3], Bernie Devlin[10] & Matthew W. State[1]

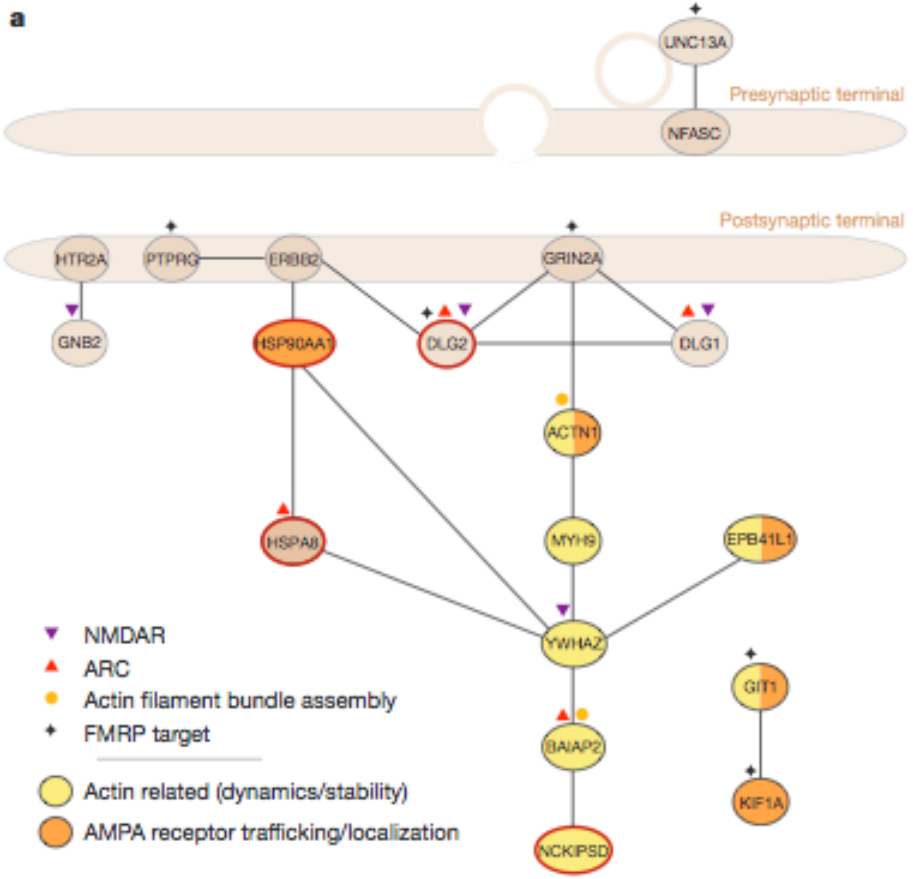
1549 variants that are de novo in autism

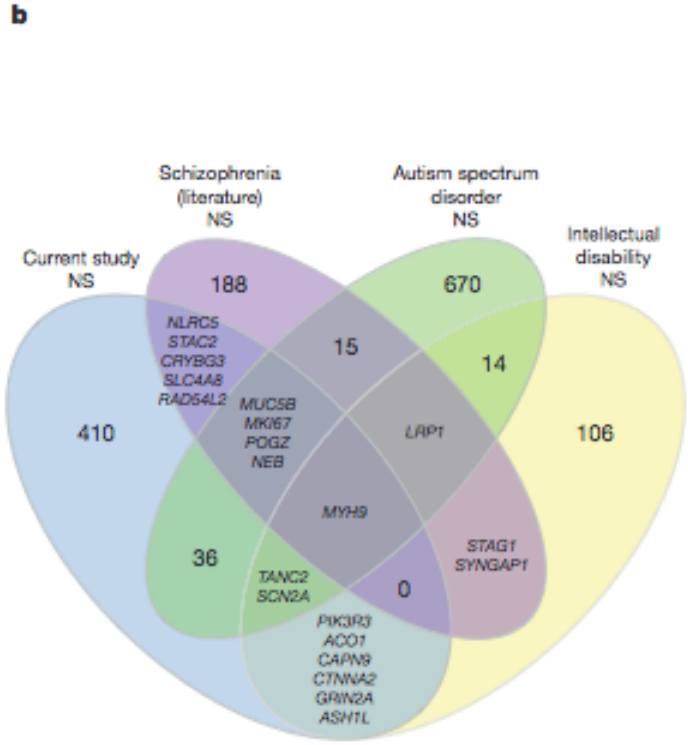
RESEARCH ARTICLE

De novo mutations in schizophrenia implicate synaptic networks

Menachem Fromer[1,2], Andrew J. Pocklington[3], David H. Kavanagh[3], Hywel J. Williams[3], Sarah Dwyer[3], Padhraig Gormley[4,5], Lyudmila Georgieva[3], Elliott Rees[3], Priit Palta[4,6,7], Douglas M. Ruderfer[1,3], Noa Carrera[3], Isla Humphreys[3], Jessica S. Johnson[1], Panos Roussos[1], Douglas D. Barker[2], Eric Banks[5], Vihra Milanova[8], Seth G. Grant[9], Eilis Hannon[3], Samuel A. Rose[2], Kimberly Chambert[2], Milind Mahajan[1], Edward M. Scolnick[2], Jennifer L. Moran[2], George Kirov[3], Aarno Palotie[4,5,7], Steven A. McCarroll[2,5,10], Peter Holmans[3], Pamela Sklar[1,11], Michael J. Owen[3], Shaun M. Purcell[1,2,12] & Michael C. O'Donovan[3]

Inherited alleles account for most of the genetic risk for schizophrenia. However, new (*de novo*) mutations, in the form of large chromosomal copy number changes, occur in a small fraction of cases and disproportionally disrupt genes encoding postsynaptic proteins. Here we show that small *de novo* mutations, affecting one or a few nucleotides, are overrepresented among glutamatergic postsynaptic proteins comprising activity-regulated cytoskeleton-associated protein (ARC) and *N*-methyl-D-aspartate receptor (NMDAR) complexes. Mutations are additionally enriched in proteins that interact with these complexes to modulate synaptic strength, namely proteins regulating actin filament dynamics and those whose messenger RNAs are targets of fragile X mental retardation protein (FMRP). Genes affected by mutations in schizophrenia overlap those mutated in autism and intellectual disability, as do mutation-enriched synaptic pathways. Aligning our findings with a parallel case–control study, we demonstrate reproducible insights into aetiological mechanisms for schizophrenia and reveal pathophysiology shared with other neurodevelopmental disorders.





Genetics of speech and language disorders

Am. J. Hum. Genet. 67:357–368, 2000

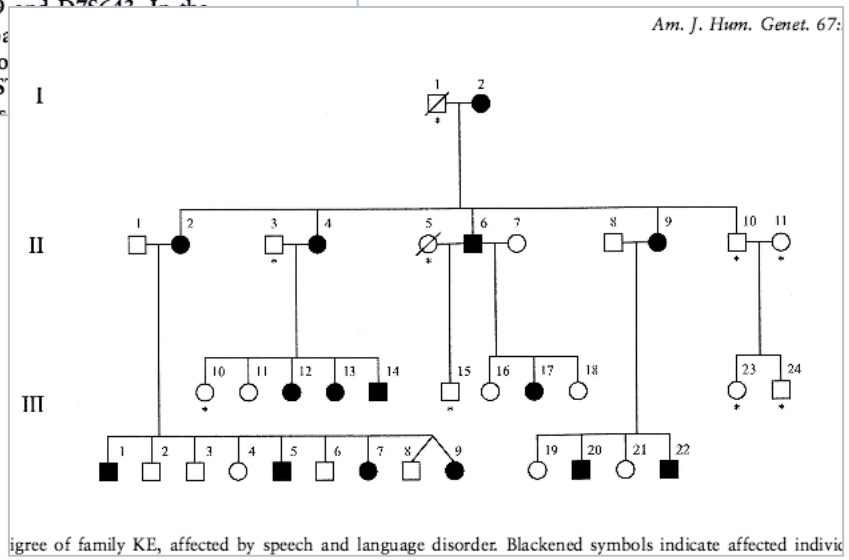
The *SPCH1* Region on Human 7q31: Genomic Characterization of the Critical Interval and Localization of Translocations Associated with Speech and Language Disorder

Cecilia S. L. Lai,[1,*] Simon E. Fisher,[1,*] Jane A. Hurst,[2] Elaine R. Levy,[1] Shirley Hodgson,[3] Margaret Fox,[4] Stephen Jeremiah,[4] Susan Povey,[4] D. Curtis Jamison,[5] Eric D. Green,[5] Faraneh Vargha-Khadem,[6] and Anthony P. Monaco[1]

[1]Wellcome Trust Centre for Human Genetics, Oxford University, [2]Department of Clinical Genetics, Oxford Radcliffe Hospital, Oxford; [3]Genetics Centre, Guy's Hospital, [4]MRC Human Biochemical Genetics Unit, University College London, and [5]Cognitive Neuroscience Unit, Institute of Child Health, Mecklenburgh Square, London; and [5]National Human Genome Research Institute, National Institutes of Health, Bethesda

The KE family is a large three-generation pedigree in which half the members are affected with a severe speech and language disorder that is transmitted as an autosomal dominant monogenic trait. In previously published work, we localized the gene responsible (*SPCH1*) to a 5.6-cM region of 7q31 between D7S2459 [illegible] present study, we have employed bioinformatic analyses to assemble a detailed BAC-/PAC-ba[illegible] this interval, containing 152 sequence tagged sites (STSs), 20 known genes, and >7.75 Mb o[illegible] sequence. We screened the affected chromosome 7 from the KE family with 120 of these S[illegible] <100 kb), but we did not detect any evidence of a microdeletion. Novel polymorphic markers

FOXP2



igree of family KE, affected by speech and language disorder. Blackened symbols indicate affected indivic

Multiple locii
but no more
single genes as yet

Table 2 Candidate language-related genes discussed in the review

Gene[a]	Chromosome	Uniprot Protein Name
ATP2C2	16q24.1	Calcium-transporting ATPase type 2C member 2
AUTS2	7q11.22	Autism susceptibility gene 2 protein
BCL11A (*CTIP1*)	2p16.1	B-cell lymphoma/leukemia 11A
CMIP	16q23.2	C-Maf-inducing protein
CNTNAP2 (*CASPR2*)	7q35	Contactin-associated protein-like 2
CTNND2	5p15.2	Catenin delta-2
DCDC2	6p22.3	Doublecortin domain-containing protein 2
DOCK4	7q31.1	Dedicator of cytokinesis protein 4
DYX1C1	15q21.3	Dyslexia susceptibility 1 candidate gene 1 protein
ERC1 (*ELKS*)	12p13.33	ELKS/Rab6-interacting/CAST family member 1
FOXP1	3p13	Forkhead box protein P1
FOXP2	7q31.1	Forkhead box protein P2
GCFC2 (*C2ORF3*)	2p12	GC-rich sequence DNA-binding factor 2
GNPTAB	12q23.2	N-acetylglucosamine-1-phosphotransferase subunits alpha/beta
GNPTG	16p13.3	N-acetylglucosamine-1-phosphotransferase subunit gamma
GRIN2A (*NR2A*)	16p13.2	Glutamate receptor ionotropic, NMDA 2A
IMMP2L	7q31.1	Mitochondrial inner membrane protease subunit 2
KIAA0319	6p22.3	Dyslexia-associated protein KIAA0319
MRPL19	2p12	39S ribosomal protein L19, mitochondrial
NAGPA	16p13.3	N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase
NFXL1	4p12	NF-X1-type zinc finger protein NFXL1
NOP9	14q12	Nucleolar protein 9
PCDH11X	Xq21.31	Protocadherin-11 X-linked
PCDH11Y	Yp11.2	Protocadherin-11 Y-linked
PLCL1 (*PRIP*)	2q33.1	Inactive phospholipase C-like protein 1
ROBO1	3p12.3	Roundabout homolog 1
ROBO2	3p12.3	Roundabout homolog 2
SCN1A	3p22.2	Sodium channel protein type 11 subunit alpha
SETBP1	18q12.3	SET-binding protein
SRPX2	Xq22.1	Sushi repeat-containing protein SRPX2
TBR1	2q24.2	T-box brain protein 1
TM4SF20	2q36.3	Transmembrane 4 L6 family member 20
ZNF277	7q31.1	Zinc finger protein 277

[a]Gene symbol approved by Human Genome Nomenclature Committee. Common alternative names are given in brackets.

Invaluable tools for all

- DECIPHER https://decipher.sanger.ac.uk/
- ExAC http://exac.broadinstitute.org/
- ClinVar http://www.ncbi.nlm.nih.gov/clinvar/
- UNIQUE http://www.rarechromo.org

- Arrays 10-15% yield
- X inactivation if X linked and familial
- Limited single gene analysis of 20-30 genes further 10-20%
- Whole exome and whole genome sequence
- Recruitment into longitudinal studies of phenotypes
- Parents
- Clinical skills…..!!!