RACP Congress 2017

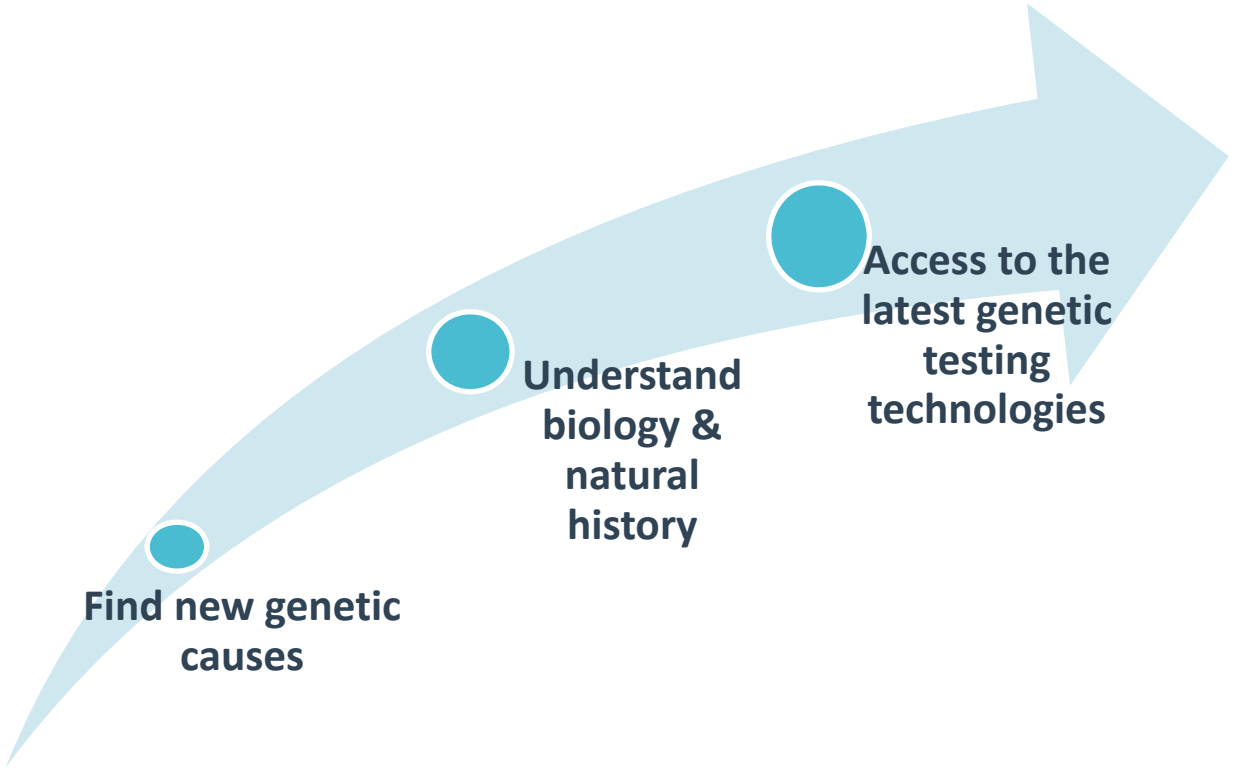
Genetics of Intellectual Disability and Autism: Past Present and Future

9th May 2017

Why causation?

- Explanation for family
- Prognosis
- Recurrence risk and reproductive options
- Guide medical management
- Avoid unnecessary investigations
- Promise of new targeted treatments
- Support groups and international community
- Prevention

Goal: to identify a precise cause of all children with genetically determined neurodisability



- **Prevention**
- **Novel treatments**
- **Improved clinical care**

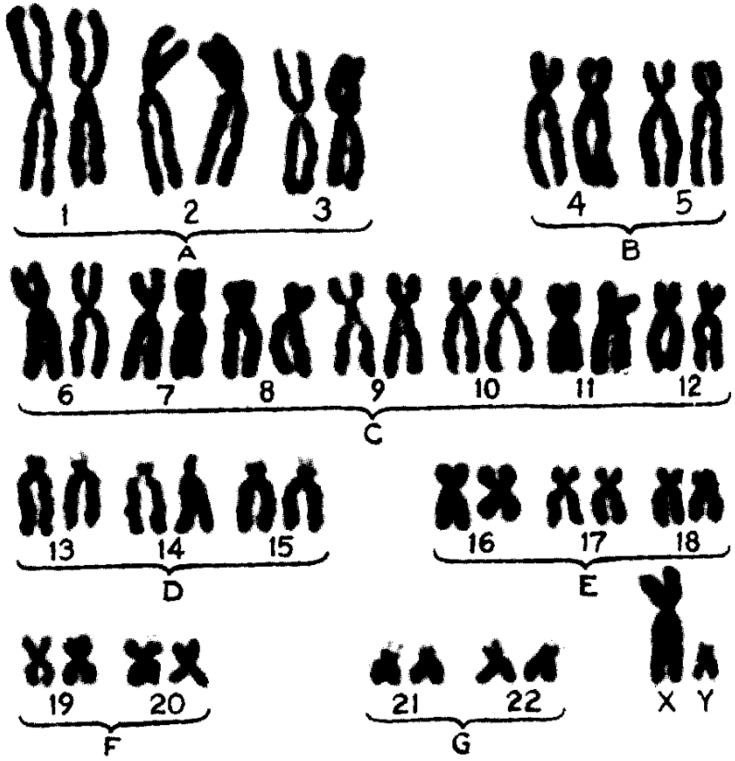
Causes of neurodisability

Genetic	• Gross chromosomal imbalance • Copy number variants • Monogenic conditions • Polygenic conditions
Environmental factors	• Malnutrition • Vascular accidents • Asphyxia • Polutants • Alcohol exposure • Iodine deficiency
Other	• Unknown

Intellectual Disability

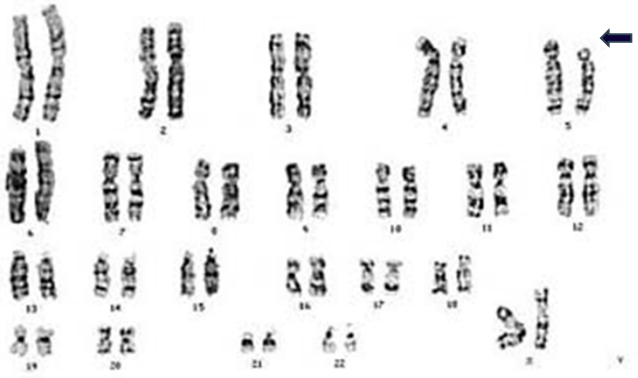
- **Normal (IQ >70)**
- **Mild ID (IQ 50-70)**
  - 1-3%
  - Behaves genetically as the lower end of the normal distribution
  - Polygenic factors plus environment
  - Many do not have a single identifiable cause
- **Moderate-Severe ID (IQ <50)**
  - 0.3-0.5%
  - Parental intelligence usually normal
  - Discontinuity between intelligence of affected and unaffected family members
  - More common in males than females
  - Identifiable genetic cause in >50%

1959 identification of aneuploidy



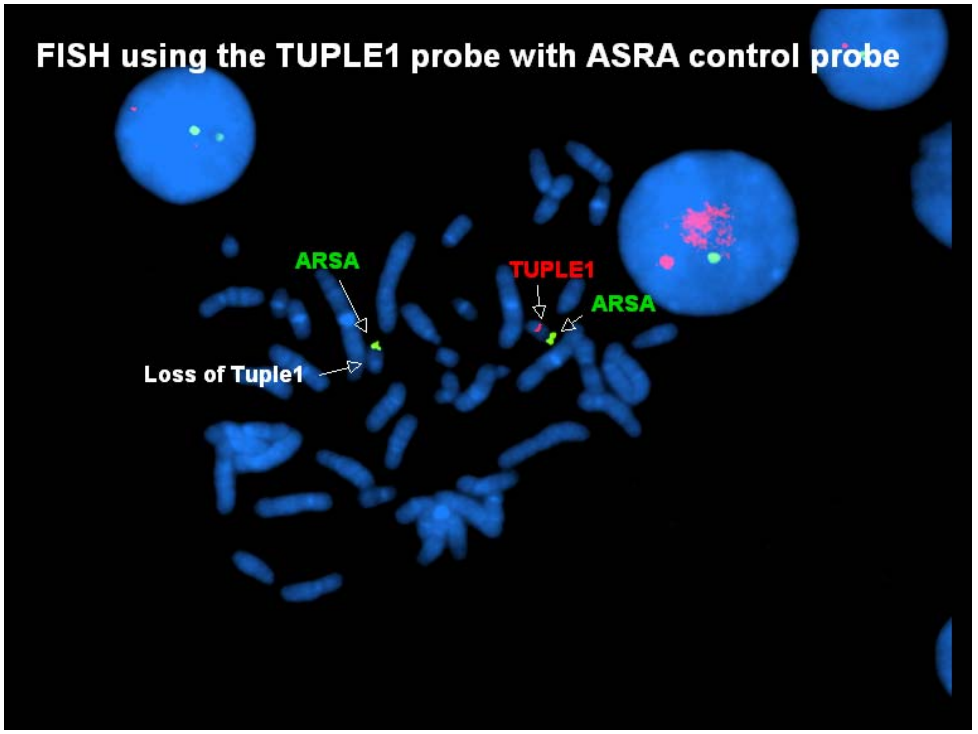
Karyotype

- Yield is 4%
- Common abnormalities incl.
  - Trisomy 21
  - Sex chromosome aneuploidy
  - Small deletions/duplications
- Yield increased if additional features:
  - Dysmorphic features
  - Growth retardation
  - Organ defects

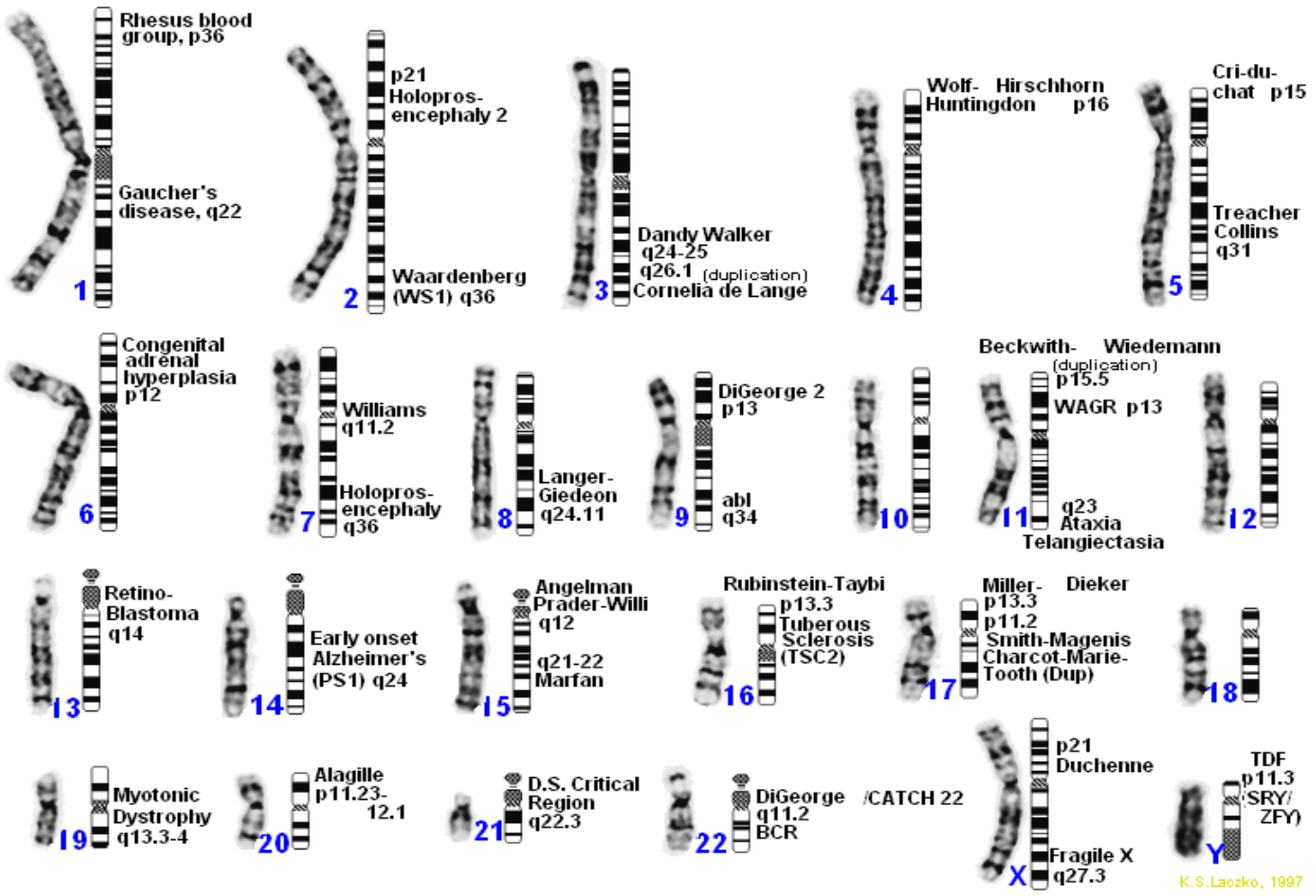


Del 5p: Cri du chat syndrome

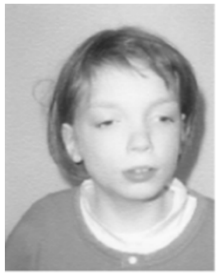
1990s - Targeted FISH, microdeletion syndromes



1990s – Multiple microdeletion syndromes



2000s - Molecular cytogenetic screening including subtelomeric chromosome rearrangements



del 11q25

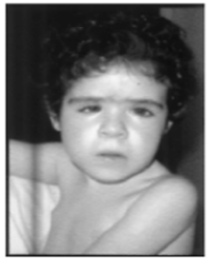
del 2q37

del 1p36

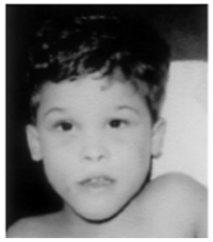
del 9q34

del 1pter

del 18qter

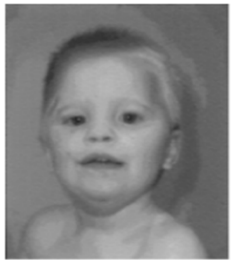


del 1pter



del 2q37

Complete isodisomy of paternal X chromosom



Partial maternal heterodisomy of 17qter

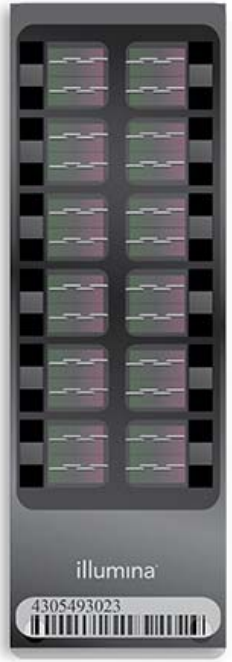
Era of genomic medicine

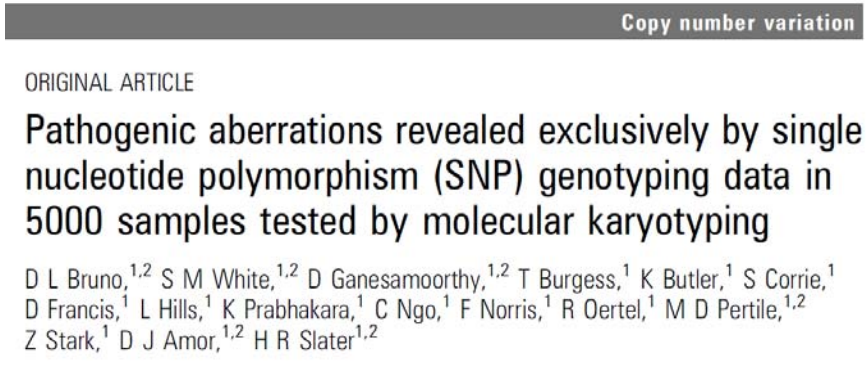
- Genomic medicine: an emerging practice of medicine that involves using genomic data to better predict, diagnose, and treat disease

- New technologies continue to drive advances in genomic medicine in last 10 years and the future

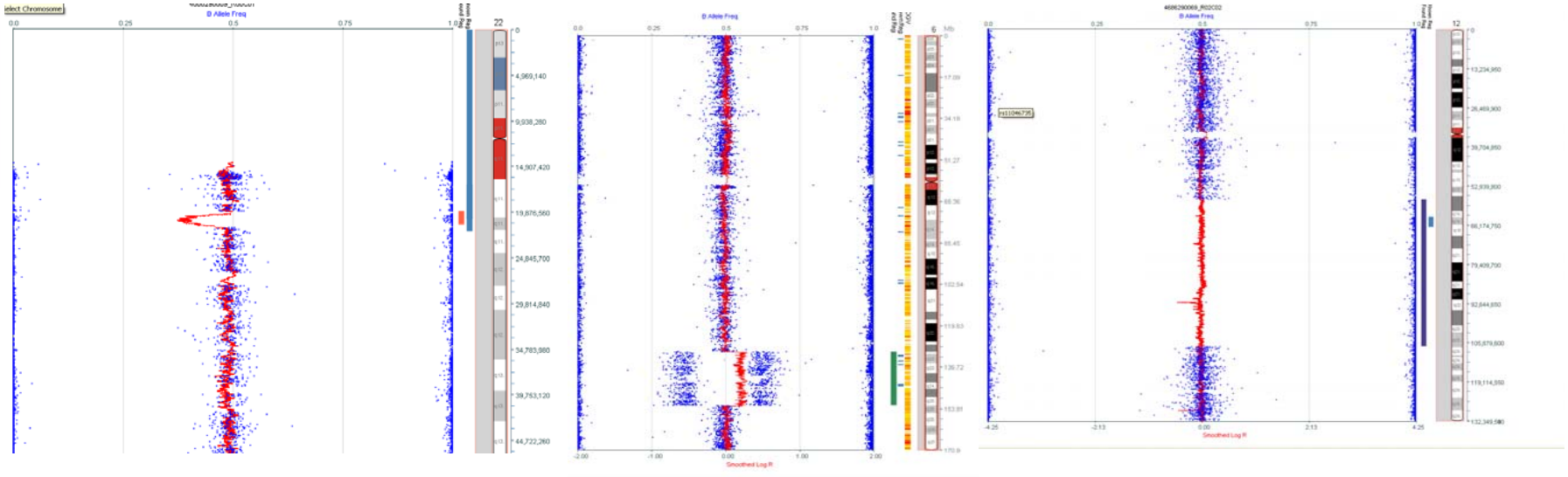
Molecular karyotyping using microarray based testing

- Has replaced conventional karyotyping for paediatric indications
- Whole genome copy number analysis
- Detects pathogenic CNVs in 15% of undiagnosed ID
- Many inherited CNVs associated with learning problems, behaviour
- Many new syndromes defined
- Does not detect Fragile X syndrome





SNP microarray



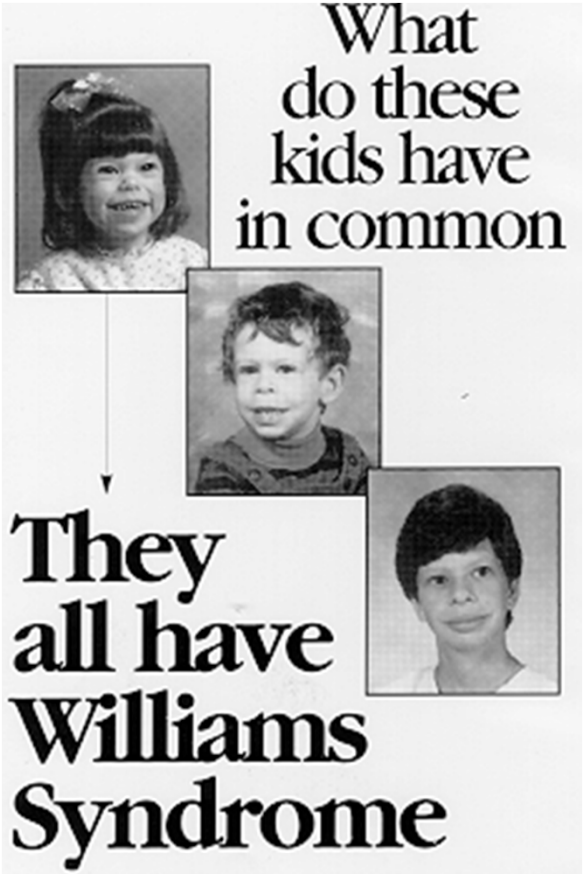
Deletion

Duplication

LCSH

1. Pathogenic Copy Number Changes

- These are well established ‘pathogenic’ copy number change
- Already described and verified in the literature
- Include common microdeletion and microduplication syndromes, e.g.
  - Prader-Willi syndrome
  - Angelman syndrome
  - 22q11 microdeletion syndrome (VCFS)
  - Cri-du-chat syndrome



2. Copy number changes with incomplete penetrance

- Known association with phenotypic abnormality
- But also be found in phenotypically normal parents/healthy controls.
- Therefore likely to be a contributing factor but not in itself sufficient to cause the abnormality

- **16p11.2 deletion**
  - IQ low normal/ mild ID
  - Language difficulties
  - Overweight
- **16p11.2 duplication**
  - Found in normal individuals
  - Increased risk of in dev delay and psychiatric disorders
- **15q11.2 deletion**
  - Found in normal individuals
  - Penetrance estimate 10% for neurodevelopmental disorders

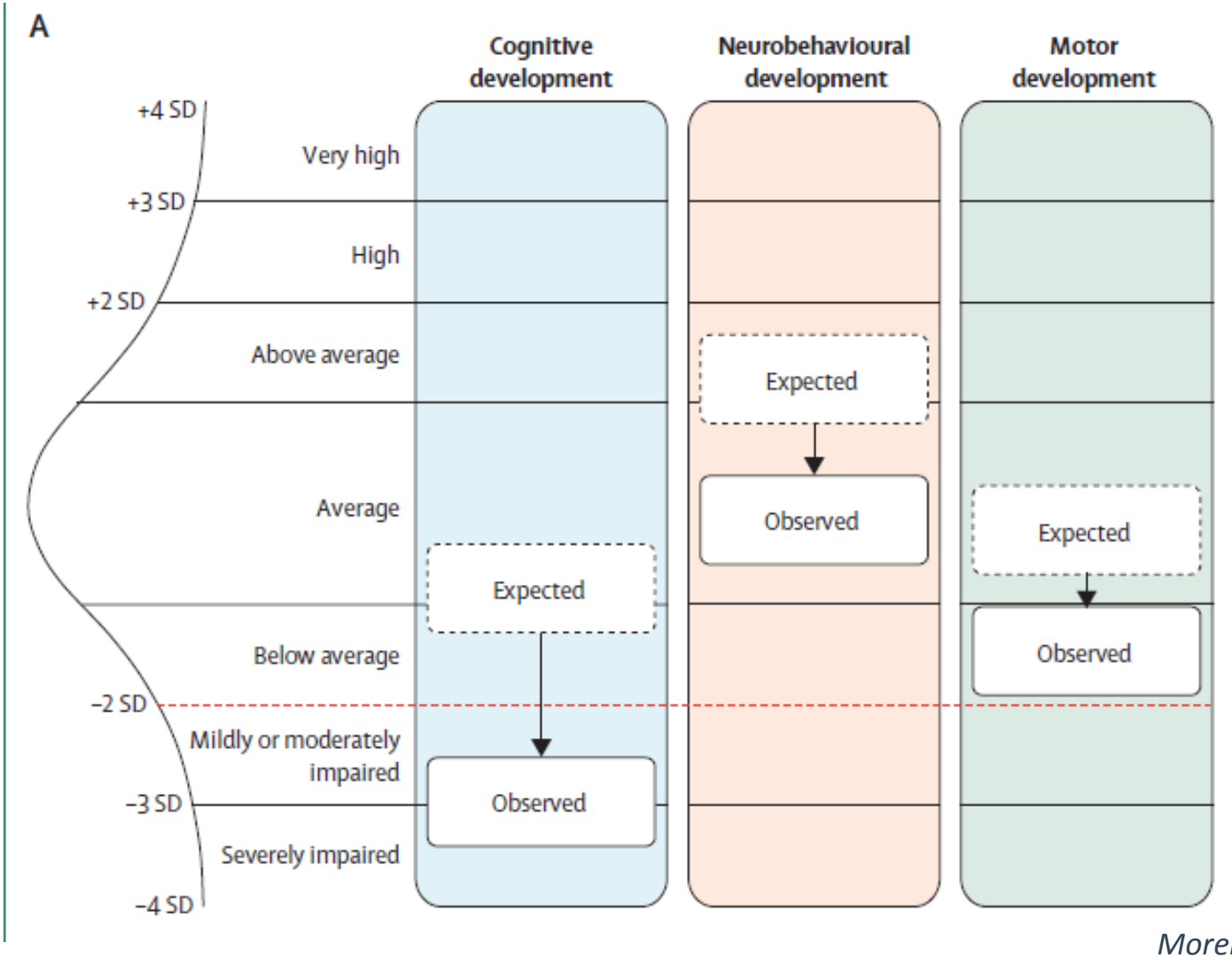
Table 1 Penetrance estimates with case and control frequencies for recurrent CNVs

Region (gene within region)	Copy number	Coordinates (hg18)	Frequency, postnatal aCGH cases	Frequency, controls	*P* value (Fisher exact one-tailed test)	Frequency of *de novo* occurrence in cases	Penetrance estimate, % (95% CI)
Proximal 1q21.1 (*RBM8A*)	Duplication	chr1: 144.0–144.5 Mb	85/48,637 (0.17%)	10/22,246 (0.04%)	<<0.0001	0/13 (0%)	17.3 (10.8–27.4)
Distal 1q21.1 (*GJA5*)	Deletion	chr1: 145.0–146.35 Mb	97/33,226 (0.29%)	6/22,246 (0.03%)	<<0.0001	7/39 (17.9%)	36.9 (23.0–55.0)
Distal 1q21.1 (*GJA5*)	Duplication	chr1: 145.0–146.35 Mb	68/33,226 (0.20%)	6/22,246 (0.03%)	<<0.0001	5/30 (16.7%)	29.1 (16.9–46.8)
15q11.2 (*NIPA1*)	Deletion	chr15: 20.3–20.8 Mb	203/25,113 (0.81%)	84/22,246 (0.38%)	<<0.0001	0/27 (0%)	10.4 (8.45–12.7)
16p13.11 (*MYH11*)	Deletion	chr16: 14.9–16.4 Mb	50/33,226 (0.15%)	12/22,246 (0.05%)	<0.0005	5/23 (21.7%)	13.1 (7.91–21.3)
16p12.1 (*CDR2*)	Deletion	chr16: 21.85–22.4 Mb	62/33,226 (0.19%)	16/22,246 (0.07%)	<0.0002	1/28 (3.6%)	12.3 (7.91–18.8)
Distal 16p11.2 (*SH2B1*)	Deletion	chr16: 28.65–29.0 Mb	46/33,226 (0.14%)	1/22,246 (0.005%)	<<0.0001	7/21 (33.3%)	62.4 (26.8–94.4)
Distal 16p11.2 (*SH2B1*)	Duplication	chr16: 28.65–29.0 Mb	35/33,226 (0.11%)	10/22,246 (0.04%)	<0.01	1/8 (12.5%)	11.2 (6.26–19.8)
Proximal 16p11.2 (*TBX6*)	Deletion	chr16: 29.5–30.15 Mb	146/33,226 (0.44%)	6/22,246 (0.03%)	<<0.0001	33/47 (70.2%)[a]	46.8 (31.5–64.2)
Proximal 16p11.2 (*TBX6*)	Duplication	chr16: 29.5–30.15 Mb	93/33,226 (0.28%)	9/22,246 (0.04%)	<<0.0001	7/30 (23.3%)	27.2 (17.4–40.7)
17q12 (*HNF1B*)	Deletion	chr17: 31.8–33.3 Mb	29/33,226 (0.09%)	2/22,246 (0.01%)	<0.0001	5/9 (55.6%)	34.4 (13.7–70.0)
17q12 (*HNF1B*)	Duplication	chr17: 31.8–33.3 Mb	37/33,226 (0.11%)	5/22,246 (0.02%)	<0.0001	2/9 (22.2%)	21.1 (10.6–39.5)
22q11.21 (*TBX1*)	Duplication	chr22: 17.2–19.9 Mb	136/48,637 (0.28%)	12/22,246 (0.05%)	<<0.0001	12/47 (25.5%)	21.9 (14.7–31.8)

aCGH, microarray-based comparative genomic hybridization; CI, confidence interval; CNV, copy-number variation; <<, much less than.

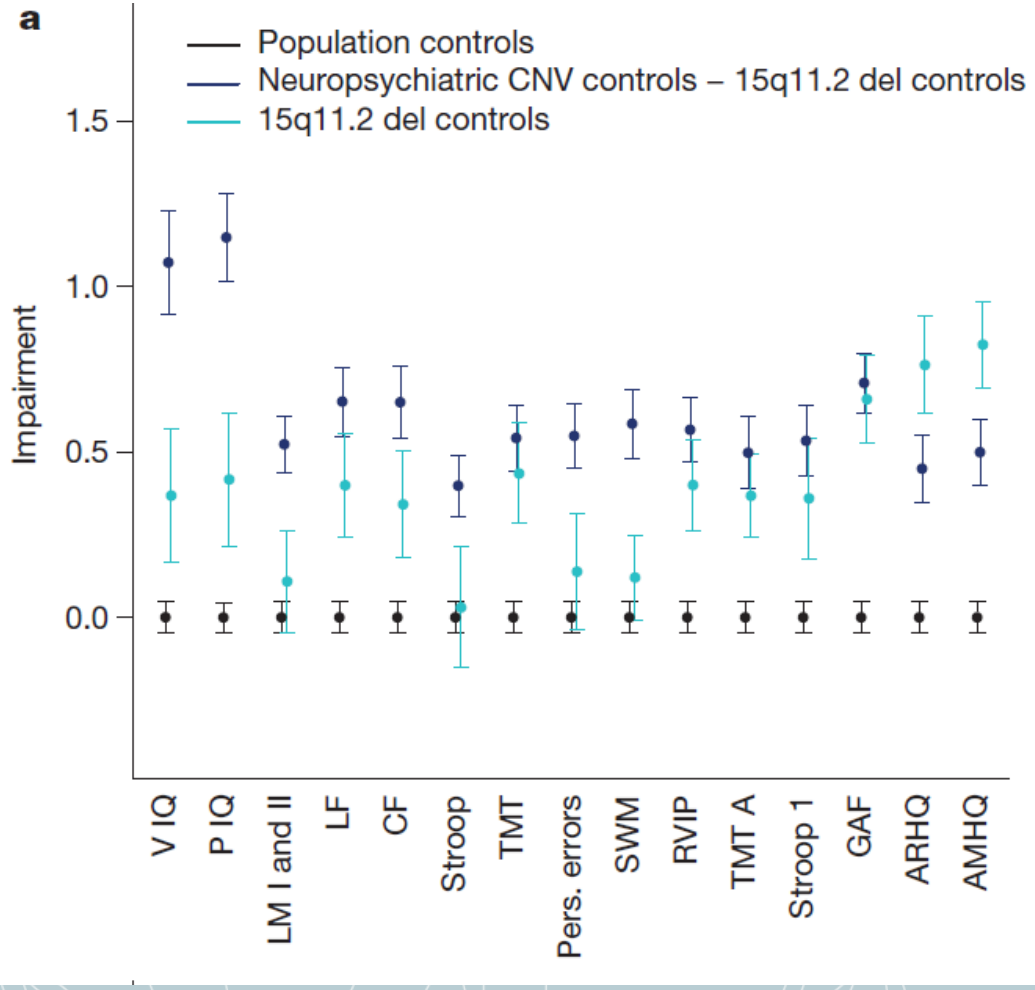
[a]Deletions of the proximal 16p11.2 region showed a maternal transmission bias (14/68 mothers identified to be carriers vs. 0/38 fathers; two-tailed $P = 0.0018$, Fisher exact test); no parental transmission bias was detected for any other CNV.

Concept of penetrance may not be appropriate for CNVs



Moreno-de-Luca 2013

Controls carrying neuropsychiatric CNVs have lower cognitive scores than population controls



Stefansson et al. Nature 2014

Original Investigation

Copy Number Variations and Cognitive Phenotypes in Unselected Populations

Katrin Männik, PhD; Reedik Mägi, PhD; Aurélien Macé, MSc; Ben Cole, BS; Anna L. Guyatt, MBChB; Hashem A. Shihab, PhD; Anne M. Maillard, PhD; Helene Alavere, MD, MSc; Anneli Kolk, MD, PhD; Anu Reigo, MD; Evelin Mihailov, MSc; Liis Leitsalu, MSc; Anne-Maud Ferreira, MSc; Margit Nõukas, MSc; Alexander Teumer, PhD; Erika Salvi, PhD; Daniele Cusi, PhD; Matt McGue, PhD; William G. Iacono, PhD; Tom R. Gaunt, PhD; Jacques S. Beckmann, PhD; Sébastien Jacquemont, MD; Zoltán Kutalik, PhD; Nathan Pankratz, PhD; Nicholas Timpson, PhD; Andres Metspalu, MD, PhD; Alexandre Reymond, PhD

Table 2. Educational Attainment in Estonian Genome Center, the University of Tartu Cohort (Joint Analysis of Discovery and Replication Cohorts)[a]

Cohort	Sample Size	Mean Education Attainment (95% CI)[b]	*P* Value[c]	No. of Individuals Not Reaching Secondary Education	Prevalence, %	No. of Individuals Not Reaching Secondary Education, OR (95% CI)	*P* Value[c]
Estonian population	7877	4.08 (4.10-4.05)		2000	25.4		
DECIPHER-listed CNV carriers	56	3.64 (3.92-3.37)	3.0e-03	28	50	2.94 (1.67-5.16)	8.334e-05
Deletion carrier by CNV size							
≥1 Mb	37	3.51 (3.80-3.22)	4.0e-04	17	46	2.5 (1.23-5.03)	7.2e-03
≥500 kb	84	3.75 (3.98-3.52)	5.7e-03	33	39.3	1.9 (1.18-3.01)	5.4e-03
≥250 kb	248	3.81 (3.94-3.67)	1.06-e04	83	33.5	1.48 (1.12-1.95)	5.0e-03
500 kb ≤ to <1 Mb	47	3.93 (4.28-3.59)	3.83e-01	16	34.0	1.52 (0.77-2.87)	1.8e-01
250 kb≤ to <500 kb	164	3.84 (4.00-3.67)	4.1e-03	50	30.5	1.29 (0.9-1.82)	1.5e-01
Duplication carrier by CNV size							
≥1 Mb	115	3.69 (3.87-3.51)	5.024e-05	45	39.1	1.89 (1.27-2.8)	1.6e-03
≥500 kb	264	3.92 (4.05-3.79)	2.5e-02	86	32.6	1.42 (1.08-1.86)	1.0e-02
≥250 kb	583	4.04 (4.13-3.95)	4.93e-01	164	28.1	1.15 (0.95-1.39)	1.54e-01
500 kb ≤ to <1 Mb	149	4.10 (4.29-3.93)	8.19e-01	43	28.9	1.19 (0.81-1.72)	3.4e-01
250 kb≤ to <500 kb	319	4.14 (4.27-4.02)	2.95e-01	78	24.5	0.95 (0.72-1.24)	7.4e-01

Abbreviations: CNV, copy number variations; EGCUT, Estonian Genome Center, the University of Tartu; kb, kilobase; OR, odds ratio.

[a] The results are presented as cumulative or as size-separated groups.

primary, 1; primary, 2; basic, 3; secondary, 4; professional or college, 5; university or academic, 6; scientific degree, 7.

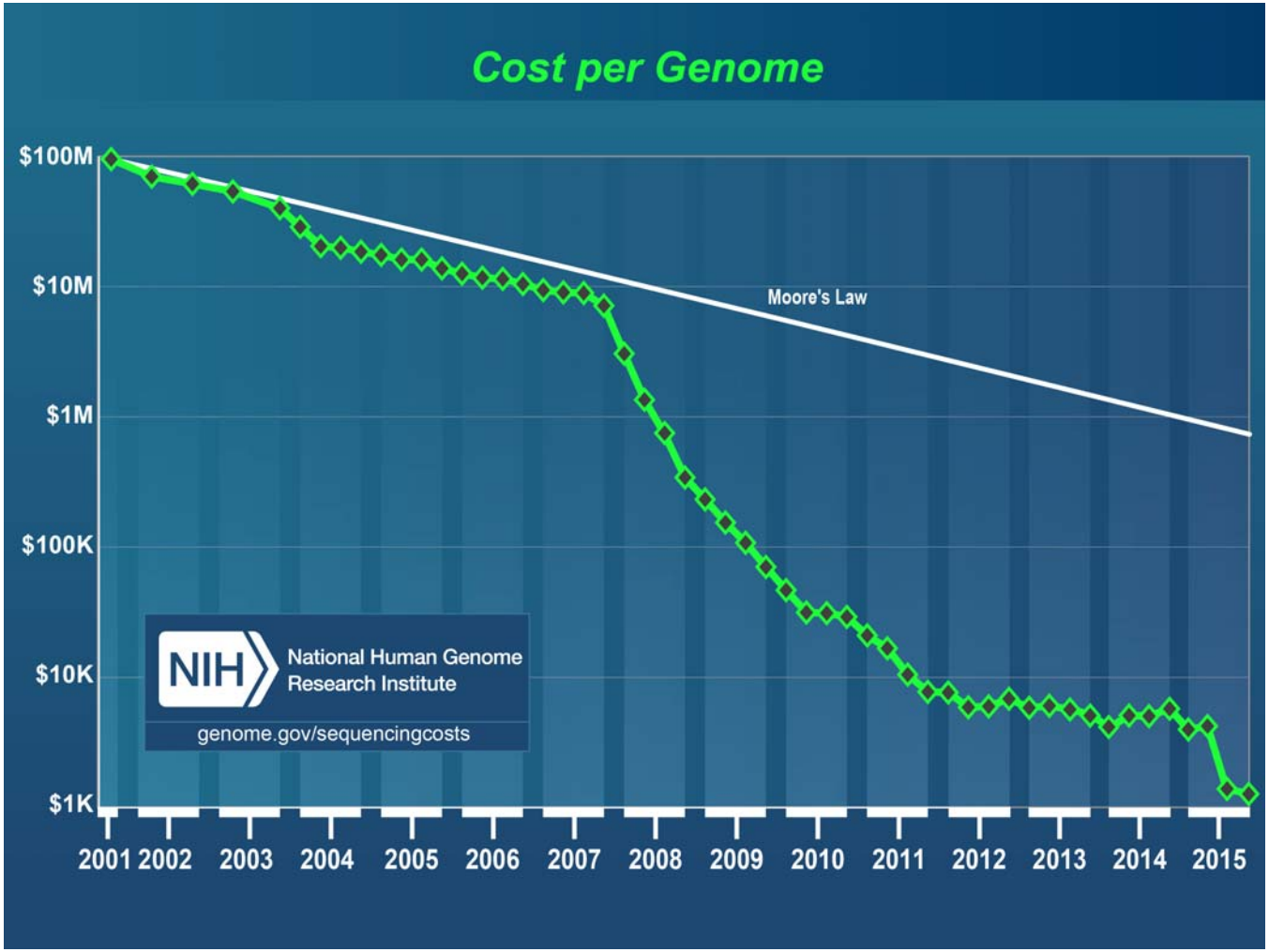
[c] Statistical significance was determined by comparing the educational

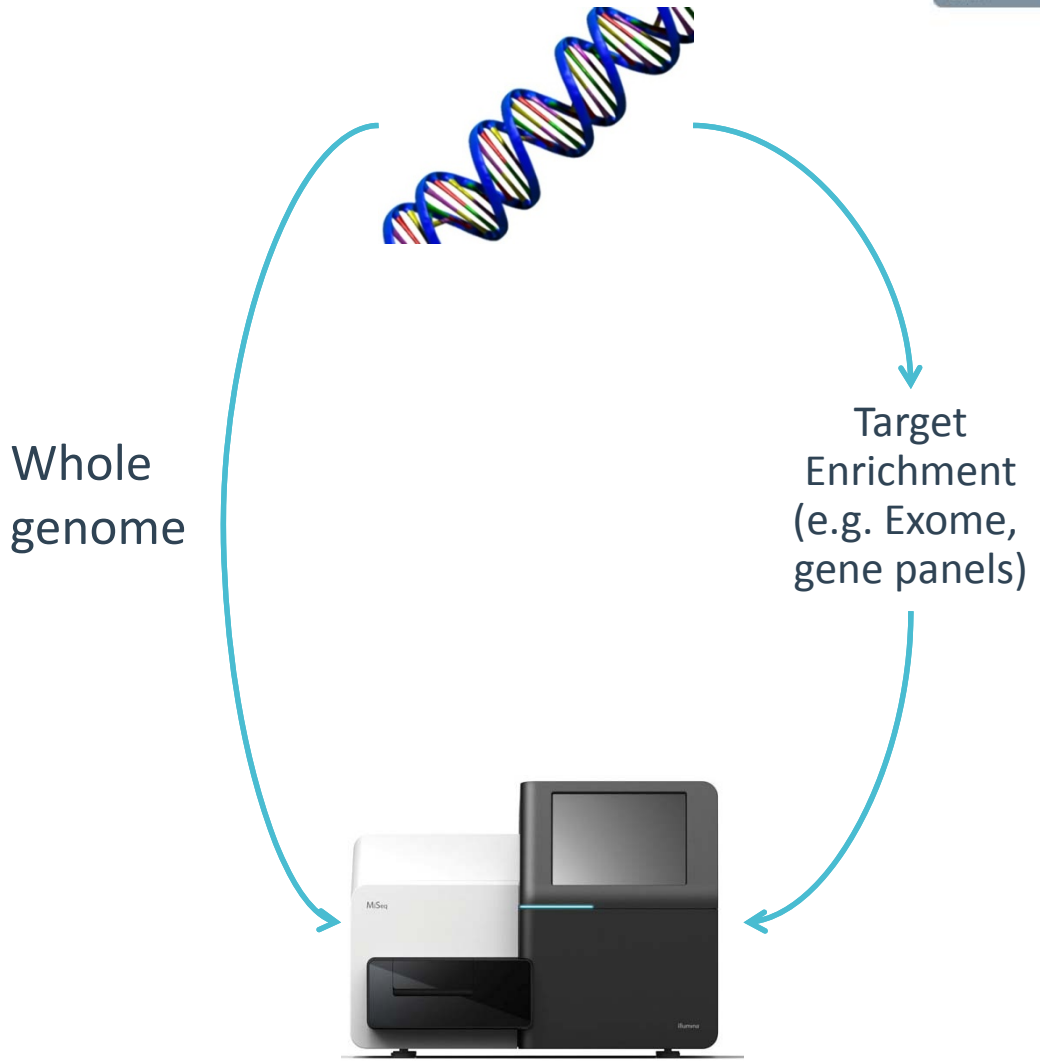
JAMA 2015

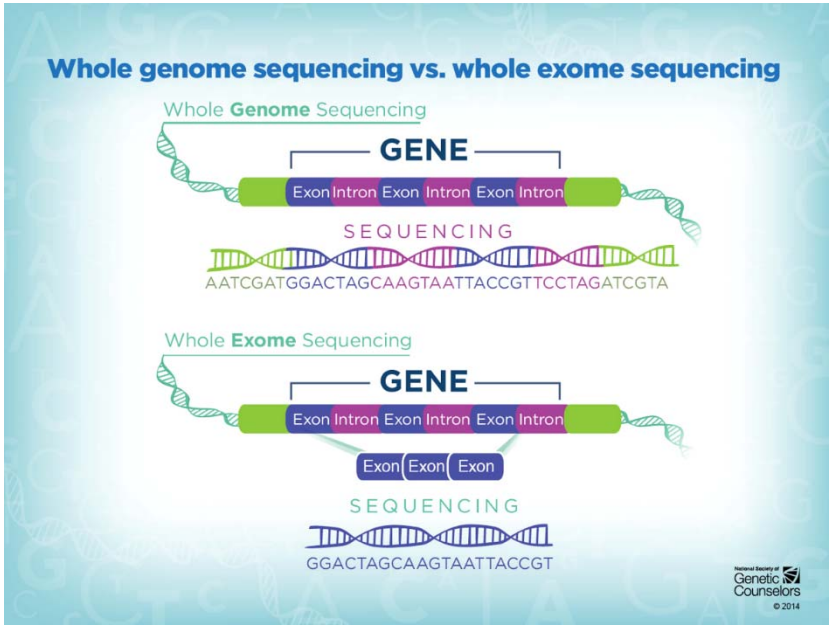
3. Copy number changes of unknown significance

- These are changes that have not been described and verified in the literature, but which contain genes, therefore potentially relevant.
- Standardised workflow to determine pathogenicity:
  - Size of CNV
  - Inherited vs. de novo
  - If inherited, does it track with phenotype in family?
  - Gene content
  - Information from databases
    - Healthy control
    - Developmental disability

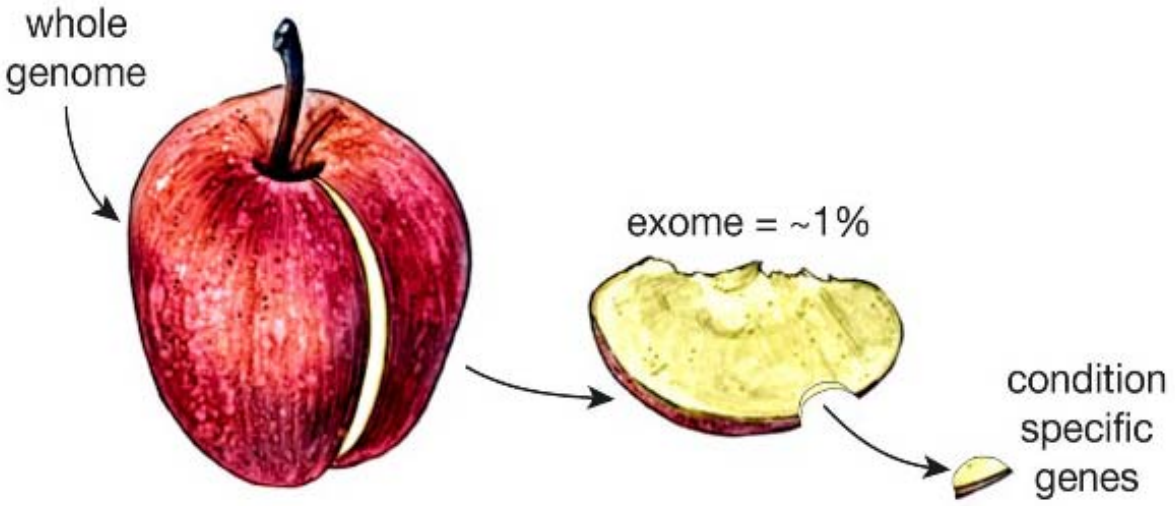
Cost of sequencing a genome




Whole genome
Target Enrichment (e.g. Exome, gene panels)



Melbourne Children's
A world leader in child and adolescent health



Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study

Anita Rauch*, Dagmar Wieczorek*, Elisabeth Graf*, Thomas Wieland*, Sabine Endele, Thomas Schwarzmayr, Beate Albrecht, Deborah Bartholdi, Jasmin Beygo, Nataliya Di Donato, Andreas Dufke, Kirsten Cremer, Maja Hempel, Denise Horn, Juliane Hoyer, Pascal Joset, Albrecht Röpke, Ute Moog, Angelika Riess, Christian T Thiel, Andreas Tzschach, Antje Wiesener, Eva Wohlleber, Christiane Zweier, Arif B Ekici, Alexander M Zink, Andreas Rump, Christa Meisinger, Harald Grallert, Heinrich Sticht, Annette Schenck, Hartmut Engels, Gudrun Rappold, Evelin Schröck, Peter Wieacker, Olaf Riess, Thomas Meitinger, André Reis†, Tim M Strom†

- 45/51 (88%) of ID patients had de novo variants (1.71/generation)
- 16/51 (31%) of ID patients had de novo mutations in known ID genes
- Plus 6/51 (12%) of ID patients had de novo mutations in novel genes predicted to be disease causing
- = total yield 43%
- 14/20 (70% of controls had de novo variants (1.2/generation)
- Little role for autosomal recessive genes

Lancet 2012; 380: 1674–82

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.

- 100 patients with IQ <50 and parents
- 53/100 patients (53%) had one or more de novo mutations
- 13/100 (13%) of patients had mutations in known autosomal or X-linked genes
- Additional 22/100 (22%) patients had mutations in candidate ID genes
- = total yield 35%
- No causative autosomal recessive gene mutations detected

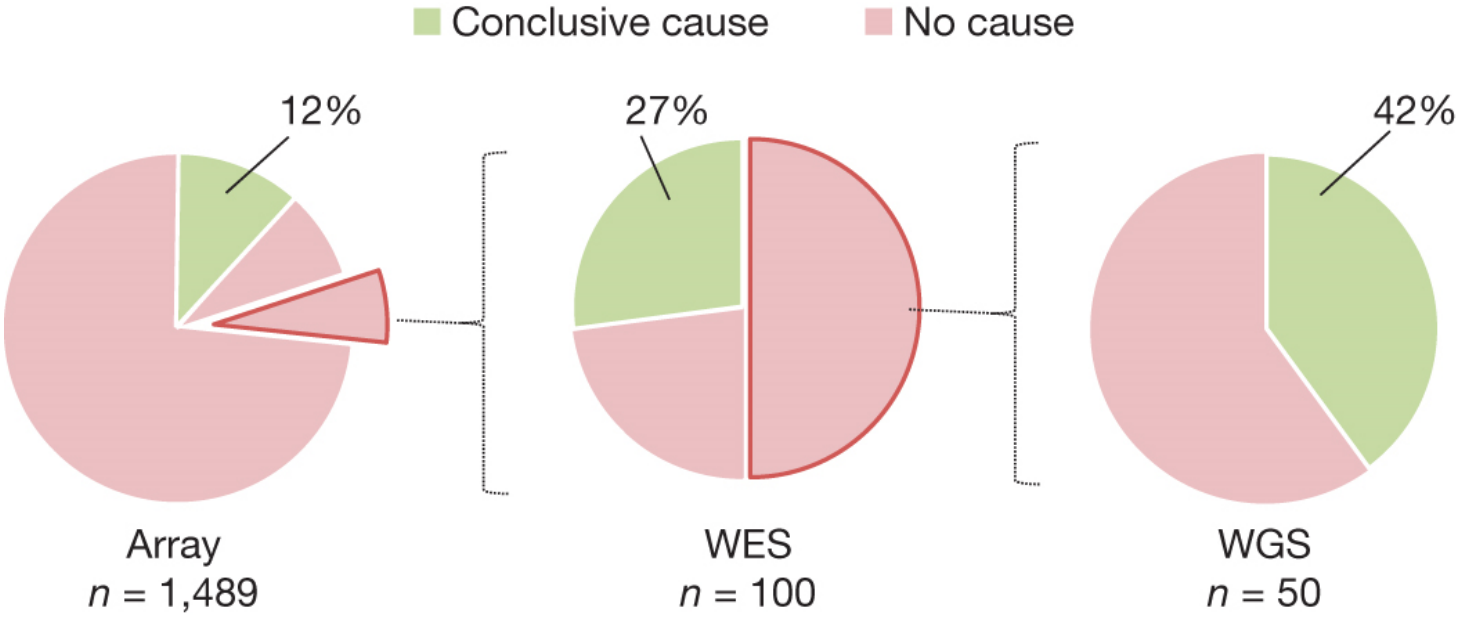
2013

LETTER

doi:10.1038/nature13394

Genome sequencing identifies major causes of severe intellectual disability

Christian Gilissen[1]*, Jayne Y. Hehir-Kwa[1]*, Djie Tjwan Thung[1], Maartje van de Vorst[1], Bregje W. M. van Bon[1], Marjolein H. Willemsen[1], Michael Kwint[1], Irene M. Janssen[1], Alexander Hoischen[1], Annette Schenck[1], Richard Leach[2], Robert Klein[2], Rick Tearle[2], Tan Bo[1,3], Rolph Pfundt[1], Helger G. Yntema[1], Bert B. A. de Vries[1], Tjitske Kleefstra[1], Han G. Brunner[1,4]*, Lisenka E. L. M. Vissers[1]* & Joris A. Veltman[1,4]*



Cumulative	12%	39%	70%

C Gilissen *et al. (2014) Nature*

Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data

Caroline F Wright, Tomas W Fitzgerald, Wendy D Jones, Stephen Clayton, Jeremy F McRae, Margriet van Kogelenberg, Daniel A King, Kirsty Ambridge, Daniel M Barrett, Tanya Bayzetinova, A Paul Bevan, Eugene Bragin, Eleni A Chatzimichali, Susan Gribble, Philip Jones, Netravathi Krishnappa, Laura E Mason, Ray Miller, Katherine I Morley, Vijaya Parthiban, Elena Prigmore, Diana Rajan, Alejandro Sifrim, G Jawahar Swaminathan, Adrian R Tivey, Anna Middleton, Michael Parker, Nigel P Carter, Jeffrey C Barrett, Matthew E Hurles, David R FitzPatrick, Helen V Firth, on behalf of the DDD study*

- 1133 children
- UK and Ireland
- 87% ID/DD
- Exome sequencing <u>trios</u> and arrayCGH
- Mean per child
  - SNVs 19,811
  - Indels 491
  - CNVs 148
  - De novo variant 1.2

LETTER

doi:10.1038/nature14135

Large-scale discovery of novel genetic causes of developmental disorders

2015

The Deciphering Developmental Disorders Study*

- 317 (28%) had pathogenic variants in known ID genes
- 35 patients had mutations in ‘new’ ID genes identified by this study
- = <u>total yield 31%</u>
- 17 had mutations in 2 different genes (composite phenotype)

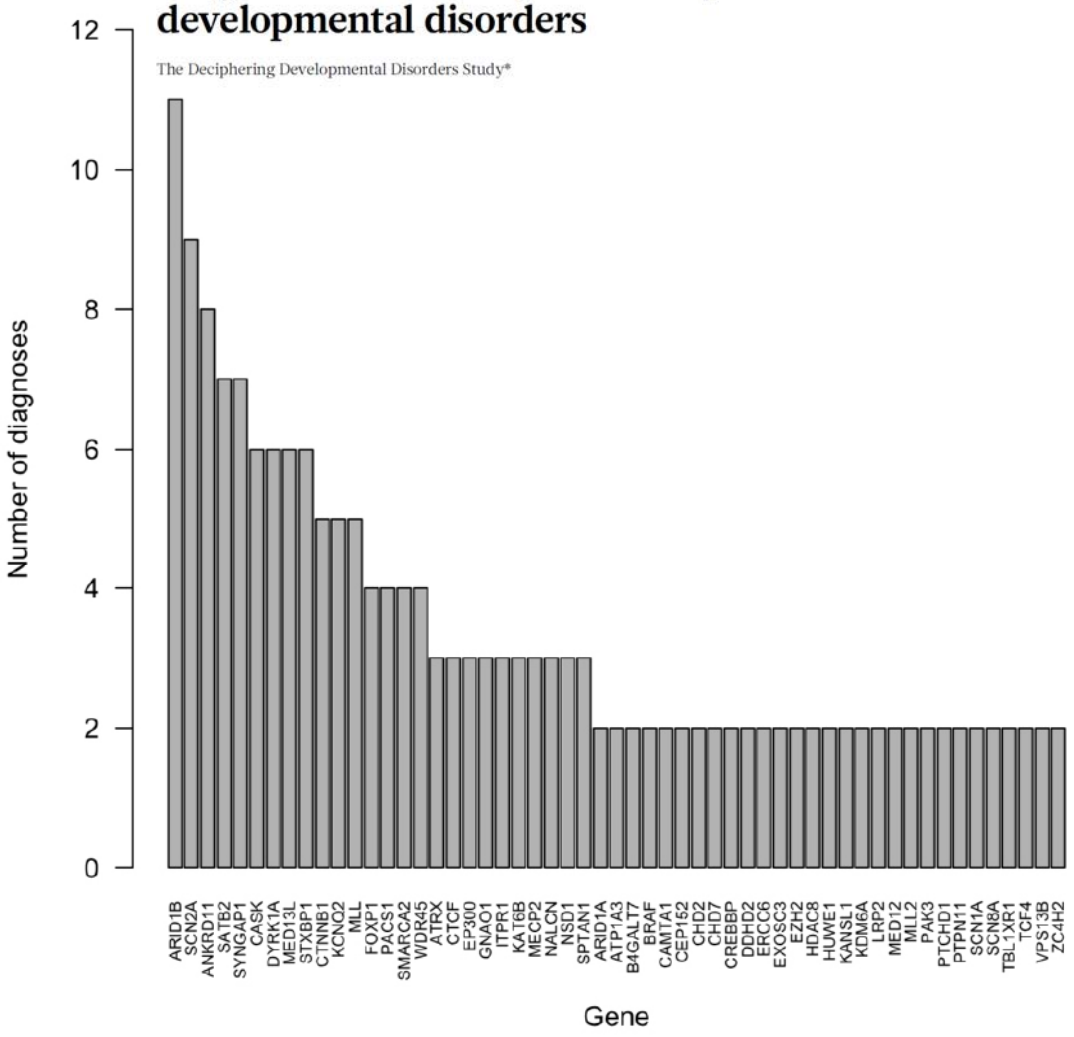
ARID1B (1%)
SCN2A
ANKRD11
SATB2
SYNGAP1
CASK
DYRK1A
MED13L
STXBP1

LETTER

doi:10.1038/nature14135

Large-scale discovery of novel genetic causes of developmental disorders

The Deciphering Developmental Disorders Study*



167 genes represented only once

Extended Data Figure 3 | Number of diagnoses per gene. Histogram showing the number of diagnoses per gene for genes with at least two diagnoses from different proband samples.

ARTICLE

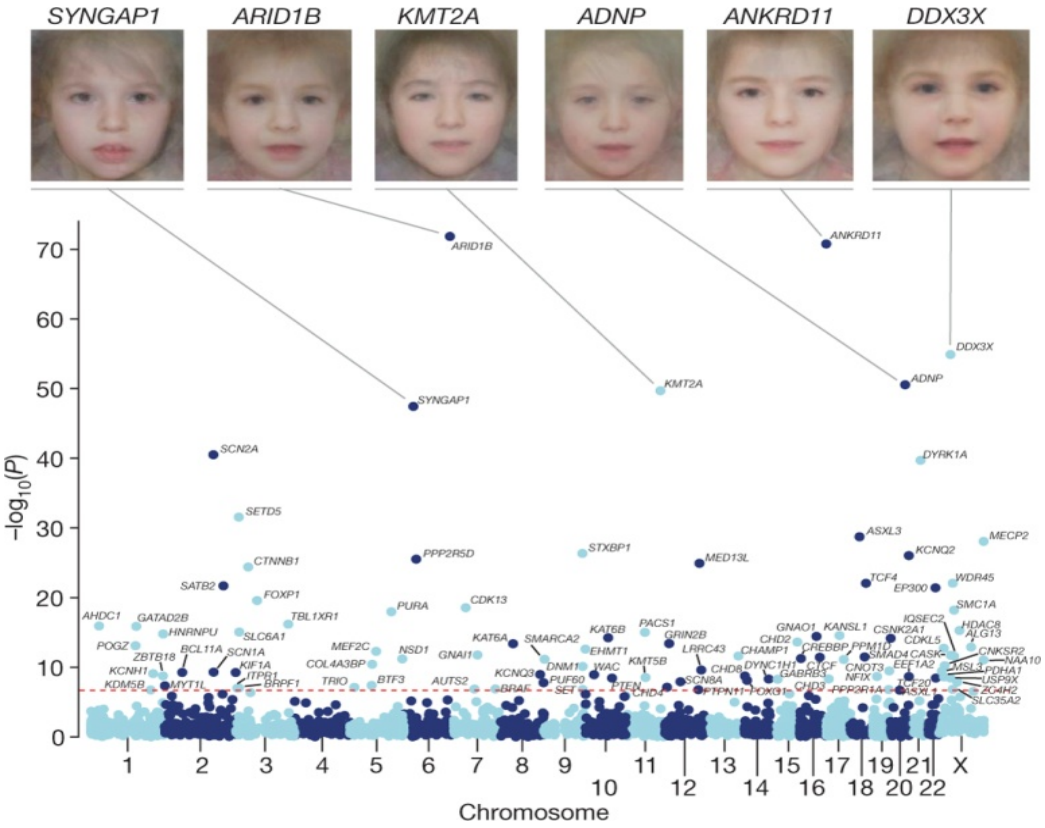
doi:10.1038/nature21062

Prevalence and architecture of *de novo* mutations in developmental disorders

Deciphering Developmental Disorders Study*

- Further data from the DDD study + 13 other studies
- Exomes from 7,580 individuals with developmental disability
- 42% have pathogenic de novo mutations
- Developmental disorders caused by de novo mutation have prevalence of 1:213 to 1:448 depending on parental age

Excess of de novo mutations



J F McRae *et al. Nature* 1–6 (2017) doi:10.1038/nature21062

JAMA Psychiatry | Original Investigation

Diagnostic Yield and Novel Candidate Genes by Exome Sequencing in 152 Consanguineous Families With Neurodevelopmental Disorders

Miriam S. Reuter, MD; Hasan Tawamie, MA; Rebecca Buchert, MA; Ola Hosny Gebril, MD; Tawfiq Froukh, PhD;

- ES in 152 consanguineous families with 1 or more child with ID
- Clear genetic cause in 55 families (37%) (50 genes)
  - 46AR
  - 2 XLR
  - 2 de novo
- Plausible genetic cause in another 48 (32%)
- Higher yield in severe ID, additional clinical features and multiplex families

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders

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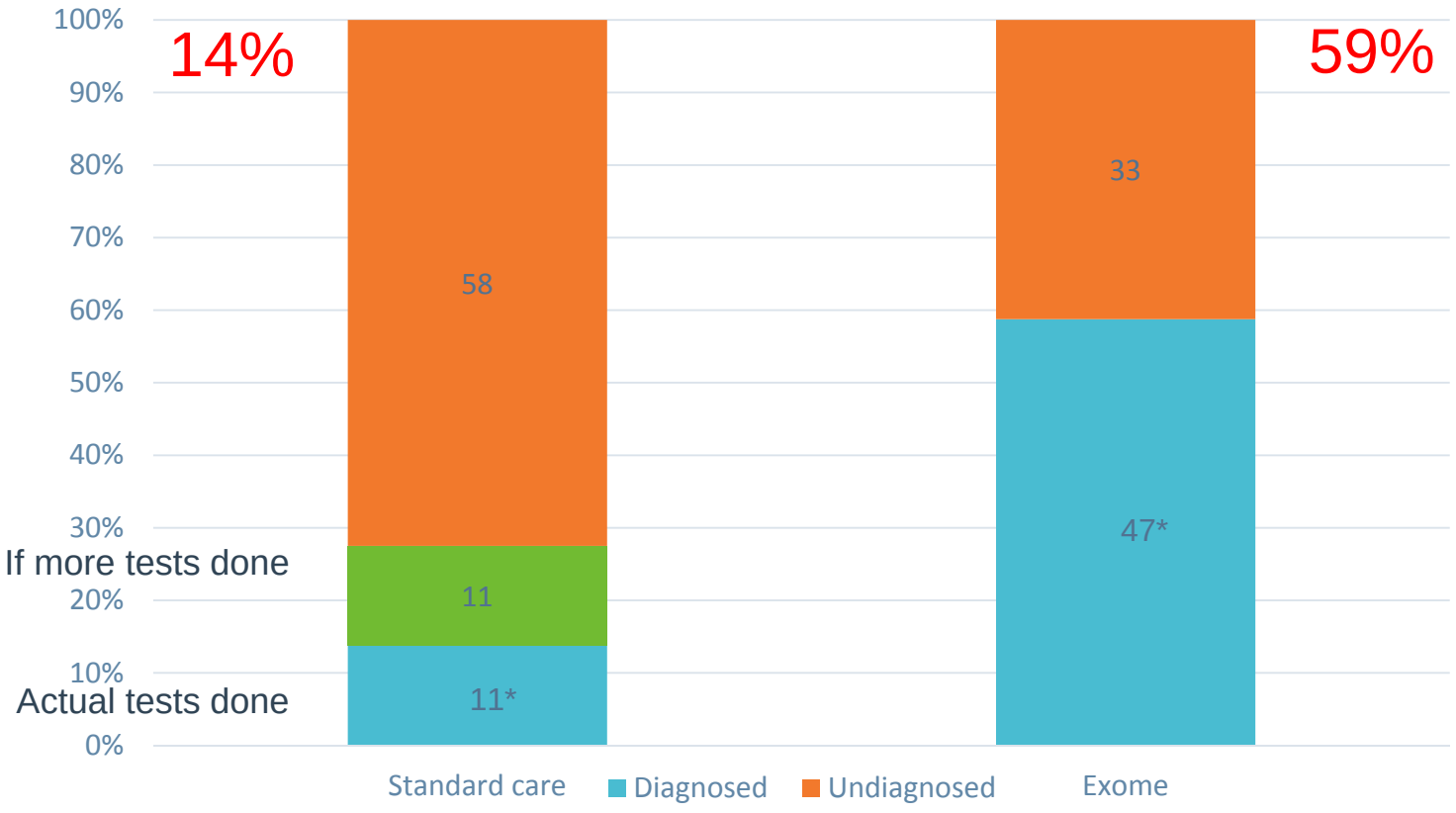
Standard Care vs Exome

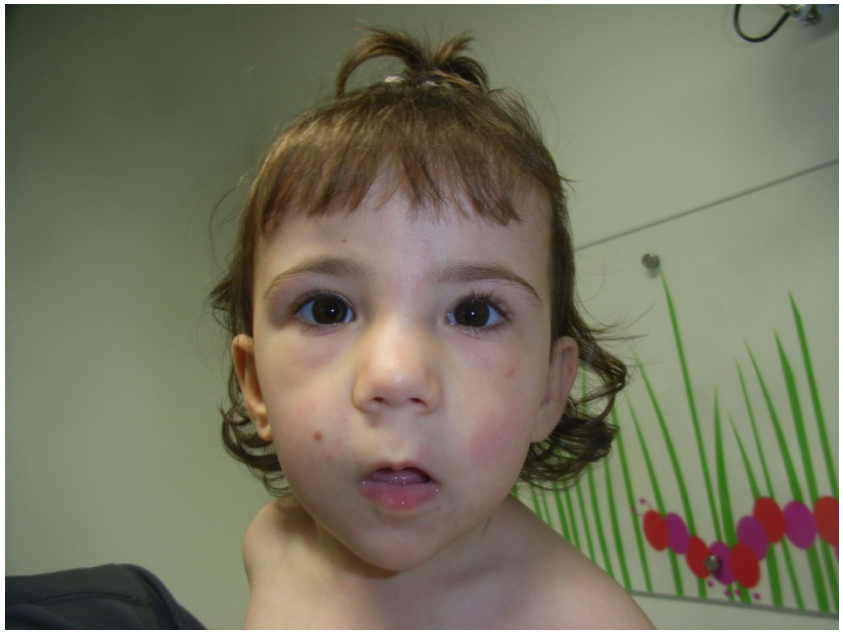


Our local ID data

- Singleton exomes at VCGS
  - funded by MCRI translational genomics grant
- Cohort of 15 children
  - Severe ID (non verbal)
  - Normal microarray and Fragile X
  - No clear syndromal features
- Likely pathogenic mutations found in 7/15 patients (47%)

KT

- 6 year old girl with global developmental delay
  - Walked at 2 years
  - Non-verbal
  - Loves water, sensory stimulation
- Calcaneovalgus deformity
- Bilateral esotropia
- 2 x UTIs
- Growth parameters all 3rd-50th centile
- Normal CMA, UMS, FX, MRI



Prominent peri-orbital fullness, short palpebral fissures, prominent mid-face, small mouth and thin upper lip

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

Lot Snijders Blok,[1,48] Erik Madsen,[2,48] Jane Juusola,[3,48] Christian

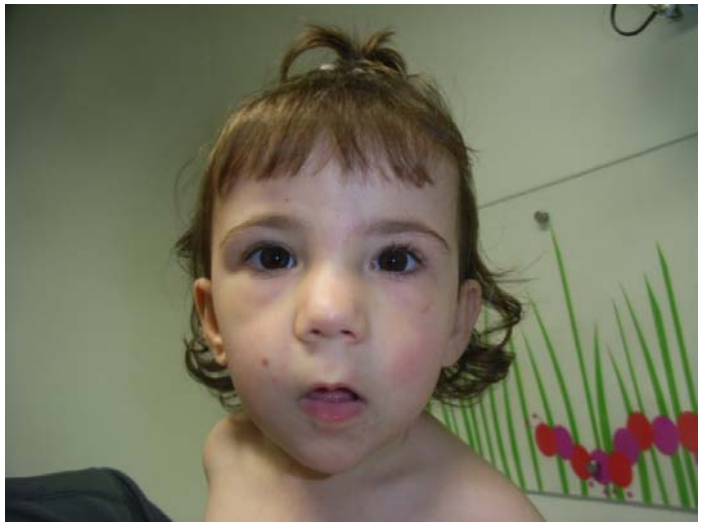
- DDX3X (XLMR)
  - c.1122dupG
  - p. Q374fs

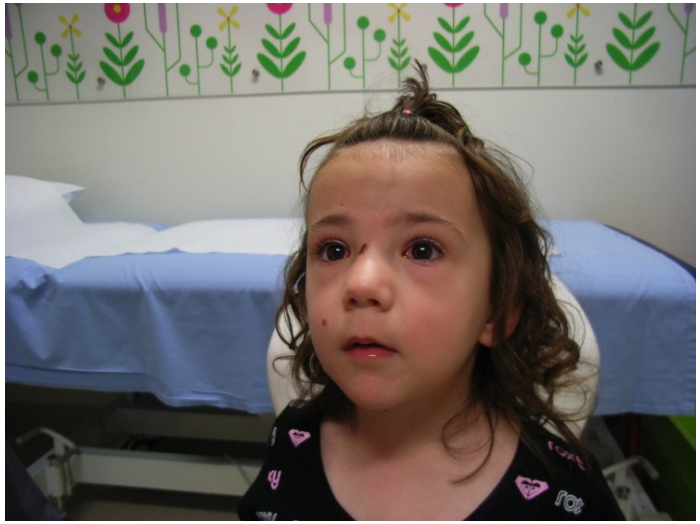
- In three large cohorts, mutations in 1.9%, 1.1%, 2.9% of females with ID
- Total 38 females with 35 distinct mutations
  - 19/35 LOF
  - 15 missense, 1 in frame deletion

Table 2. Clinical Features of Females with De Novo *DDX3X* Mutations

	Percentage	Number
Development		
Intellectual disability or developmental delay	100%	38/38
Mild or mild-moderate disability	26%	10/38
Moderate or moderate-severe disability	26%	10/38
Severe disability	40%	15/38
Developmental delay	8%	3/38
Growth		
Low weight	32%	12/38
Microcephaly	32%	12/38
Neurology		
Hypotonia	76%	29/38
Epilepsy	16%	6/38
Movement disorder (including spasticity)	45%	17/38
Behavior problems	53%	20/38
Brain MRI		
Corpus callosum hypoplasia	35%	13/37
Cortical malformation	11%	4/37
Ventricular enlargement	35%	13/37

2015





Block et al. 2015

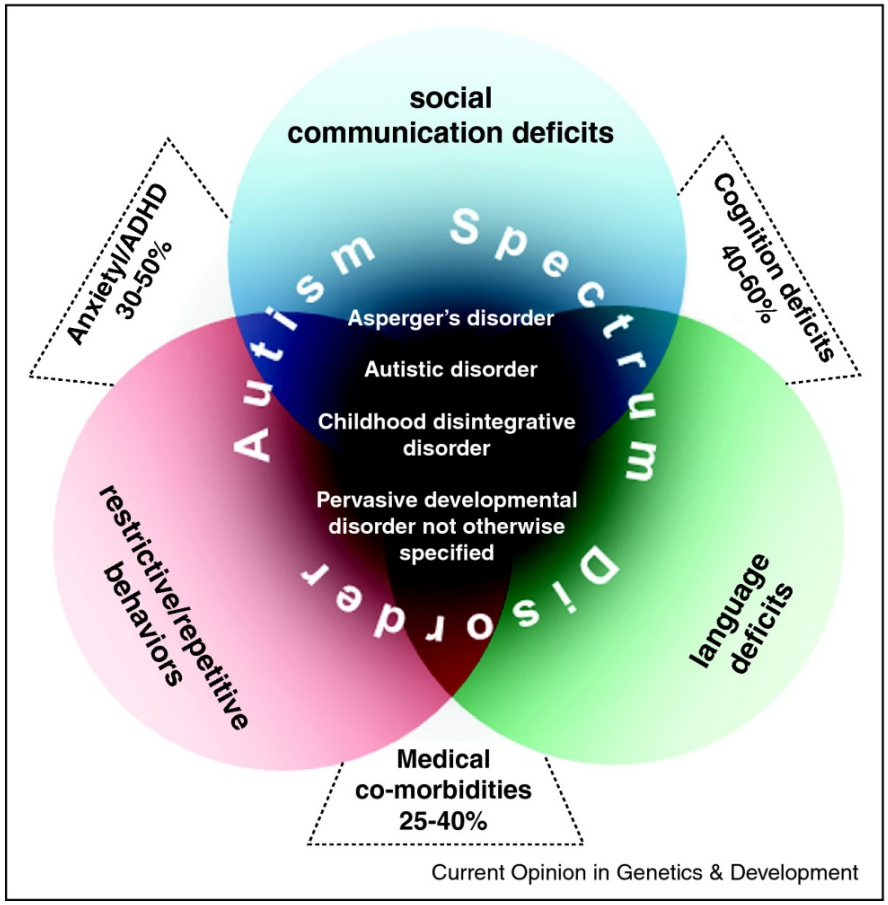
Causative mutations in 7/15 patients

- MAGEL2*
  - Heterozygous mutations cause Prader-Willi phenotype and autism
- ASLX3*
  - Heterozygous mutations cause Bainbridge-Ropers syndrome
- STXBP1
  - Heterozygous mutations cause epileptic encephalopathy and intellectual disability
- DDX3*
  - X-linked dominant mutations cause intellectual disability in females
- FOXG1
  - Heterozygous mutations cause congenital variant of Rett syndrome
- GAMT
  - Autosomal recessive mutations cause cerebral creatine deficiency syndrome
  - Therapy including creatine supplementation causes improvement of stabilization of symptoms
- CTNNB1*
  - De novo heterozygous mutations cause severe intellectual disability, microcephaly, and spasticity

* identified since 2013

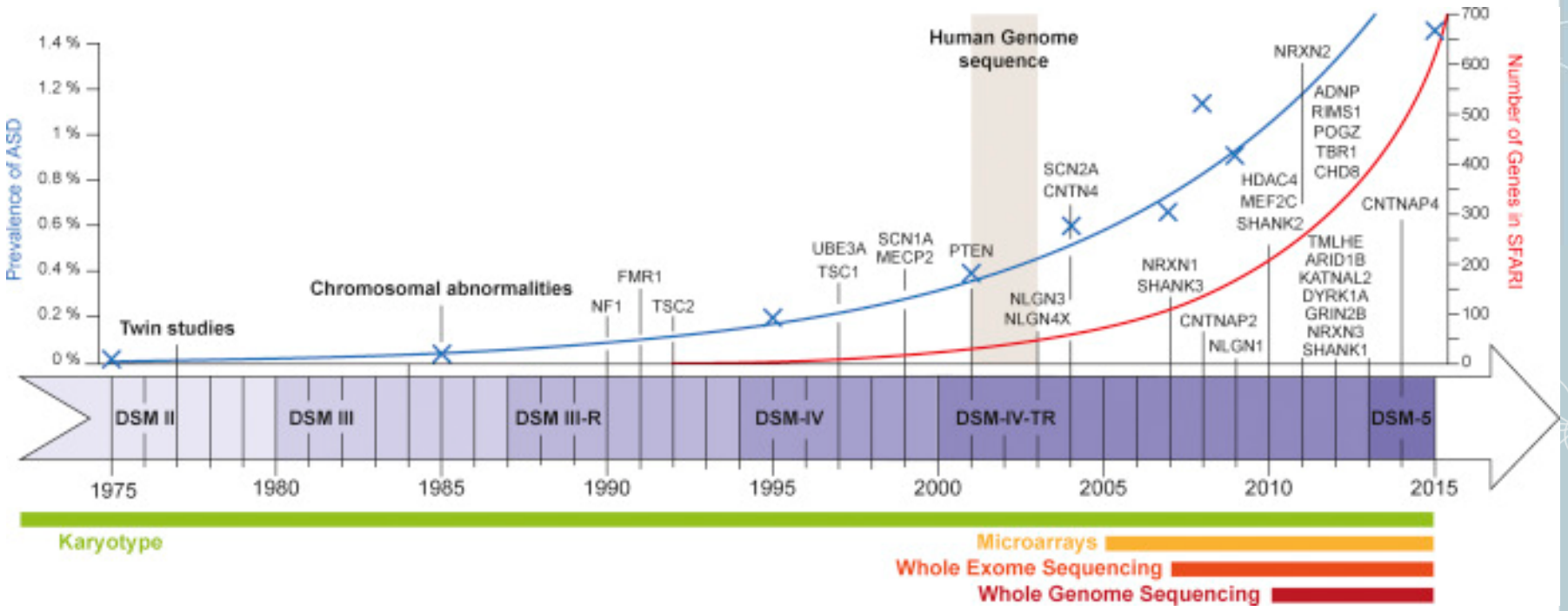
Autism

- Frequency 1:100-1:200
- 4:1 male to female gender bias
  - higher for Asperger syndrome
  - Lower when ID/dysmorphism
- Comormidities
  - intellectual disability, epilepsy, motor control difficulties, ADHD, tics, anxiety, sleep disorders, depression, gastrointestinal problems
- ASD phenotype extends into the subclinical realm – the 'Broader Autism Phenotype'
  - Autistic traits are normally distributed in clinical cases as well as in the general population.
- Twin concordance
  - 50% MZ
  - 15% DZ



Devlin and Scherer 2013

The history of the genetics of autism from 1975 to 2015



Bourgeron 2016

Table 1 | **Recurrent structural abnormalities consistently reported in association with ASDs**

Abnormality	ASD penetrance* (rate of ASD in carriers; %)	Neuropsychiatric pleiotropy‡ (associated neuropsychiatric phenotypes)	Somatic pleiotropy‡ (associated somatic phenotypes)
Del1q21.1	8 (REF. 129)	ID[130], ADHD[129], schizophrenia[131]	Microcephaly[129], heart defect[132], eye abnormalities[129], short stature[129], epilepsy[129]
Dup1q21.1	36 (REF. 133)	ID[133], schizophrenia[133]	Epilepsy[133,134], macrocephaly[133], heart defect[133]
Del2q23.1	100 (REF. 135)	ID[135], ADHD[135], language disorder[136], motor delay[136]	Epilepsy[135,136], obesity[136], brachycephaly[136], microcephaly[136], short stature[136]
Del2q37	25–42 (REFS 137,138)	ID[139], ADHD[138]	Epilepsy[137], short stature[139], obesity[139], heart defect[137]
Del3q29	27 (REFS 63,140)	ID[63], speech delay[63], language disorder[63], anxiety disorders[63], schizophrenia[63], bipolar disorder[63]	Gastrointestinal problems[63], heart defect[63], feeding problems[63], recurrent ear infections[63], abnormal dentition[63]
Del5q14.3	43 (REFS 141,142)	ID[141], absent speech[141]	Epilepsy[141,142], capillary malformation[141,142]
Dup7q11.23	41 (REF. 143)	ID[143], ADHD[144,145], anxiety disorders[145,146], oppositional defiant disorders[145], speech delay[134,145]	Epilepsy[143], macrocephaly[145], brachycephaly[147], dilatation of ascending aorta[145,147], patent ductus arteriosus[147], chronic obstipation[147], kidney abnormalities[147]
Del8p23	Unknown	ID[148], ADHD[138]	Heart defect[148], congenital diaphragmatic hernia[148]
Dup15q11–q13	69 (REF. 149)	ID[150], ADHD[151]	Epilepsy[134,152], heart defect[134], muscle hypotonia[153], short stature[153]
Del15q11.2	32 (REFS 154,155)	ID[154,155], ADHD[154,155], schizophrenia[156], OCD[156], speech delay[155]	Epilepsy[154,155], ataxia[156], heart defect[156]
Dup15q11.2	43 (REF. 155)	ID[154], ADHD[155], speech delay[155]	Epilepsy[154,155], ataxia[155], hypotonia[155]
Dup15q13.2–q13.3	80 (REF. 157)	ID[134], speech delay[134]	Epilepsy[134], urogenital anomalies[134], recurrent infections[134]
Del15q13.2–q13.3	60 (REF. 157)	ID[157], ADHD[157]	None reported
Del16p11.2	15 (REF. 158)	ID[158]	Epilepsy[158], hypotonia[159], sacral dimples[159], speech articulation problems[159]
Dup16p11.2	Unknown	Schizophrenia, bipolar disorder[160]	Epilepsy[159], hypotonia[159], tremor[159], ataxia[159], sacral dimples[159], speech articulation problems[159]
Dup16p13.11	25 (REF. 161)	ADHD[161], speech delay	Epilepsy[134]
Del17p11.2	Unknown	None reported	Epilepsy[134]
Del17q12	Unknown	Schizophrenia[122]	Macrocephaly[122], renal anomalies[122]
Del22q11.2	30 (REF. 106)	Schizophrenia, ADHD, speech delay[115], anxiety disorders[115]	Heart defect[115], palate abnormalities[115], hypocalcaemia[115], feeding difficulties[115], recurrent infections[115] (among others)
Dup22q11.2	18 (REF. 162)	ID[162], ADHD[162]	Heart defect[163], hearing loss[163], urogenital anomalies[163], palate abnormalities[163]
Del22q13.3	>50 (REF. 123)	ID[123], language disorder[123]	Epilepsy[123], heart defect[123], renal anomalies[123], strabismus[123]

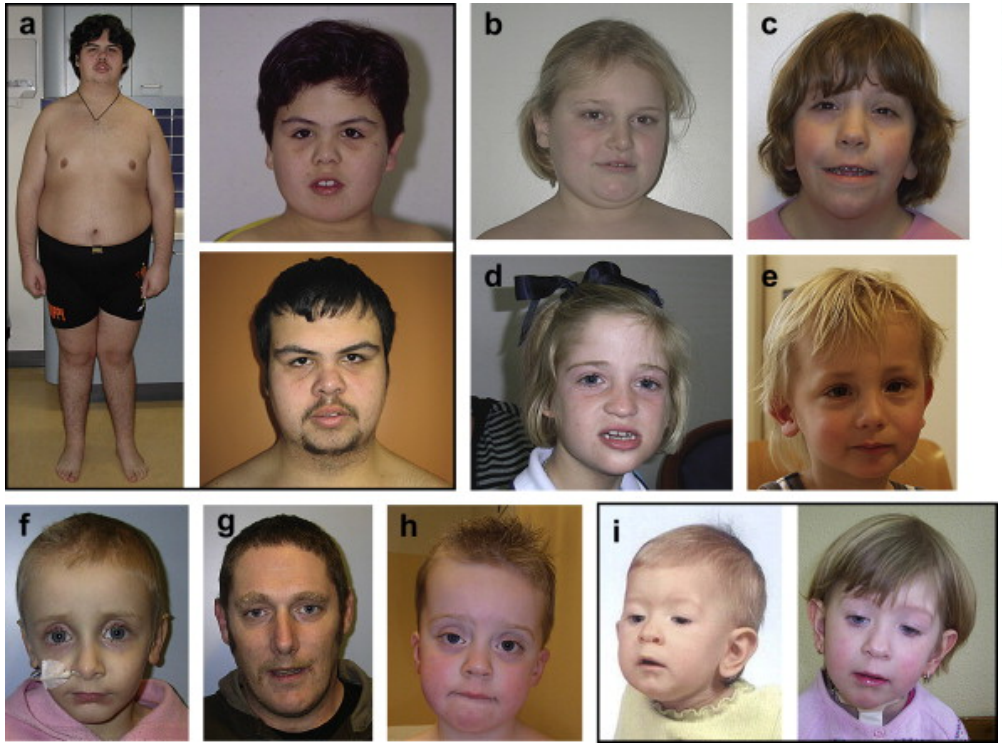
Melbourne Children's
A world leader in child and adolescent health

- CNVs detected in 5-10% of ASD patients
- De novo and inherited
- Some patients with ASD have two or more CNVs and they tend to have a more severe presentation
- Incomplete penetrance (8-100%)

Data from Vorstman et al. NRG 2017

Most common CNV in ASD is deletion/duplication at 16p11.2

- Seen in 0.8% ASD
- Also seen in
  - ASD with additional dysmorphology
  - dev delay without ASD
  - Non-ASD psychiatric disorders
  - Some unaffected individuals



ASD
Data from WES/WGS

- 18 WES/WGS performed, using >4000 families
- 3.6-8.8% of patients carry a de novo causative mutation
- Little evidence for recessive mutations
  - ? 3%

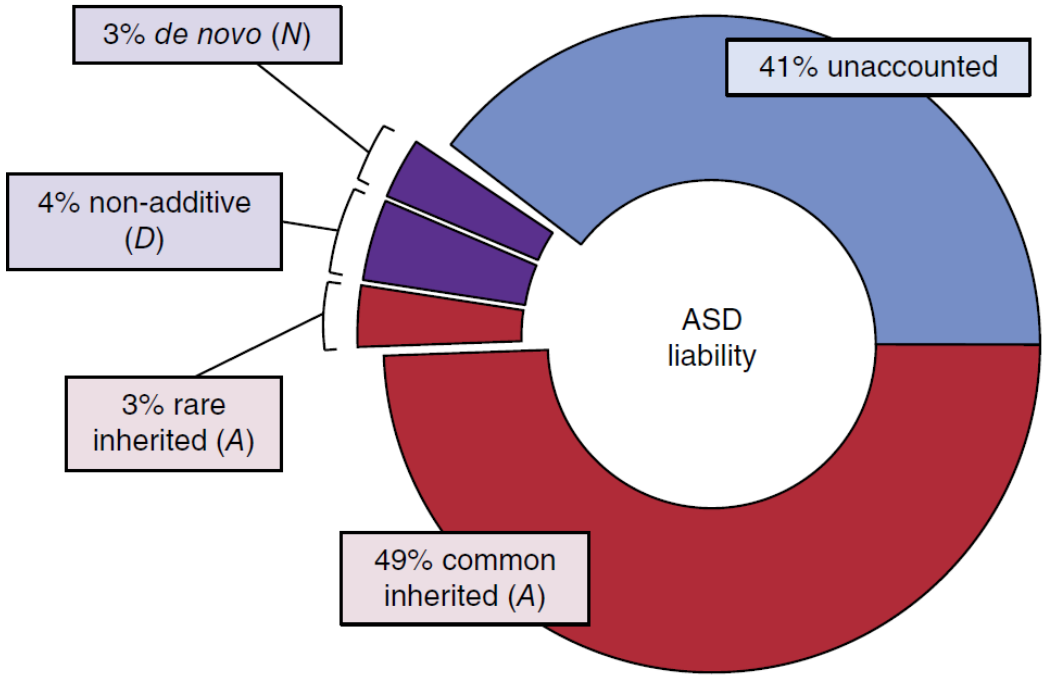
Bourgeron 2016

nature genetics

Most genetic risk for autism resides with common variation

Trent Gaugler[1], Lambertus Klei[2], Stephan J Sanders[3,4], Corneliu A Bodea[1], Arthur P Goldberg[5–7], Ann B Lee[1], Milind Mahajan[8], Dina Manaa[8], Yudi Pawitan[9], Jennifer Reichert[5,6], Stephan Ripke[10], Sven Sandin[9], Pamela Sklar[6–8,11,12], Oscar Svantesson[9], Abraham Reichenberg[5,6,13], Christina M Hultman[9], Bernie Devlin[2], Kathryn Roeder[1,14] & Joseph D Buxbaum[5,6,8,11,15,16]

- Gaugler (2014) estimated the genetic contribution to ASD:
  - 49% common inherited variants
  - 3% rare inherited variants
  - 3% de novo
  - 4% Mendelian (dominant, recessive)



Genes associated with ASDs from sequencing studies
(Vortman et al. NRG 2017)

Gene	Chromosomal location	Estimated percentage of individuals with an ASD in whom this variant is identified	ASD penetrance* (rate of ASD in carriers)	Neuropsychiatric pleiotropy‡ (associated neuropsychiatric phenotypes)	Somatic pleiotropy‡ (associated somatic phenotypes)
KATNAL2 (REF. 37)	18q21.1	0.08	Unknown	Unknown	Unknown
POGZ[37]	1q21.3	0.08	Incomplete[164]	ID[164,165], speech delay[164], language delay[164], schizophrenia[61]	Microcephaly[164], obesity[164], impaired vision[164]
TBR1 (REFS 37,166)	2q24.2	0.08	Unknown	ID[167]	Unknown
ADNP[37]	20q13.13	0.10	Complete[118]	ID[118,165], ADHD[118]	Recurrent infections[118], short stature[118], heart defect[118], hypotonia[118], hypermetropia[118], epilepsy[118], hyperlaxity[118]
SYNGAP1 (REF. 37)	6p21.32	0.10	Unknown	ID[168,169]	Epilepsy[168]
GRIN2B[37,166]	12p13.1	0.13	Unknown	ID[170]	Epilepsy[170]
ANK2 (REF. 37)	4q25-q26	0.13	Unknown	None reported	Heart arrhythmia[171]
ARID1B[37]	6q25.3	0.13	Incomplete[172]	ID[172], speech impairment[172,173]	Short stature[174], hypertrichosis[173], cryptorchidism[173], epilepsy[173], vision impairment[173]
SCN2A[37]	2q24.3	0.13	Incomplete[59]	ID[60], schizophrenia[61]	Epilepsy[62], episodic ataxia[62]
DYRK1A[37,166]	21q22.13	0.13	Incomplete[175]	ID[175,176], speech impairment[175,176], ADHD[175], anxiety[175]	Microcephaly[175,176], epilepsy[175,176], vision impairment[175], short stature[175], gastrointestinal symptoms or feeding difficulties[175,176]
CHD8 (REFS 37,166)	14q11.2	0.21	Incomplete[32]	ID[32,177], schizophrenia[177], speech delay[177], sleep problems[32]	Macrocephaly[32,177], gastrointestinal symptoms[32]

ASD Genetic Landscape

ASD-related syndromes	Rare chromosome abnormalities	Rare CNVs	Rare penetrant genes	Multigenic including rare and common variation	Environment effects
10%	5%	5%	5%	? 50% unknown	% unknown
e.g. FXS, TS	e.g. Trisomy 21, XXY	e.g. 16p11.2, 22q11.2, 17p12	e.g. PTCHD1, NRXN1, SHANK1/2		

Genes converge in a limited number of biological pathways including chromatin remodelling, protein translation, actin dynamics, and synaptic functions

Complex interplay between common and rare variants:
For some individuals, a single de novo mutation is sufficient to cause autism vs. for others, it is the accumulation of many (>1000) risk alleles

Original Investigation

Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder

JAMA 2015

Kristiina Tammimies, PhD; Christian R. Marshall, PhD; Susan Walker, PhD; Gaganjot Kaur, MRes; Bhooma Thiruvahindrapuram, MSc; Anath C. Lionel, PhD;

(High Functioning)

Positive Results	Essential Group	Equivocal Group	Complex Group	*P* Value for 3-Group Comparison
CMA, No./total No.	7/168	4/37	13/53	<.001
% (95% CI)	4.2 (1.7-8.4)	10.8 (3.0-25.4)	24.5 (13.8-38.3)	
WES, No./total No.	2/64	2/7	4/24	.02
% (95% CI)	3.1 (0.0-10.8)	28.6 (3.7-71.0)	16.7 (4.7-37.4)	
CMA and/or WES, No./total No.	4/64	2/7	9/24	.001
% (95% CI)	6.3 (1.7-15.2)	28.6 (3.7-71.0)	37.5 (18.8-59.4)	

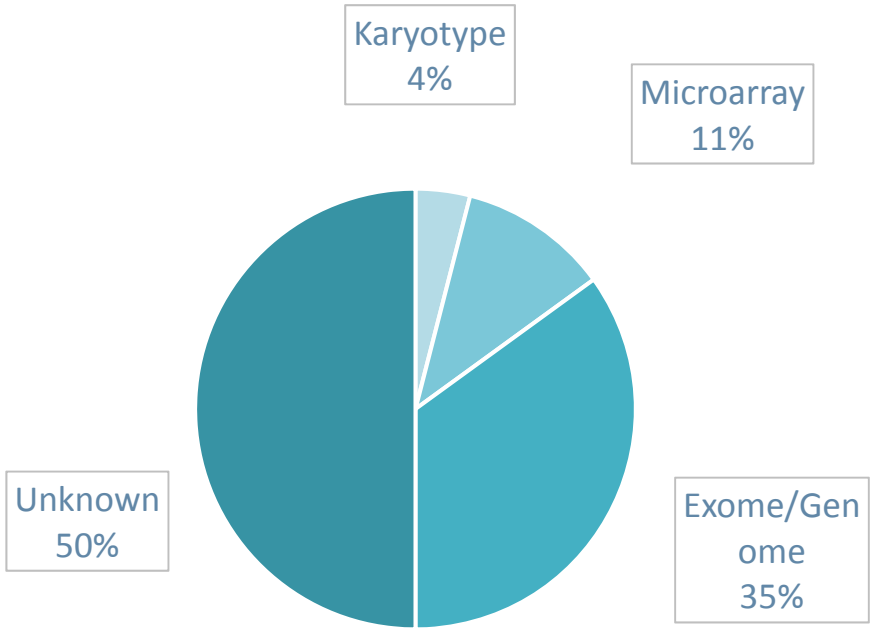
CONCLUSIONS AND RELEVANCE Among a heterogeneous sample of children with ASD, the molecular diagnostic yields of CMA and WES were comparable, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes in comparison with the children in the essential category. If replicated in additional populations, these findings may inform appropriate selection of molecular diagnostic testing for children affected by ASD.

The Future I:

We owe it to our families to provide an explanation for their child's disability

The Future II: What about the other 50%?

- New genes
- Non-coding DNA
- Complex genetics
  - Digenic/polygenic
- Mutation types not detected by NGS
  - Mosaicism
  - Epigenetic
  - Trinuclueotide repeats
- Non genetic



The Future III

- Biological research and improved medical care must be accompanied by *innovations to provide a more inclusive world for people with neurodisabilities*