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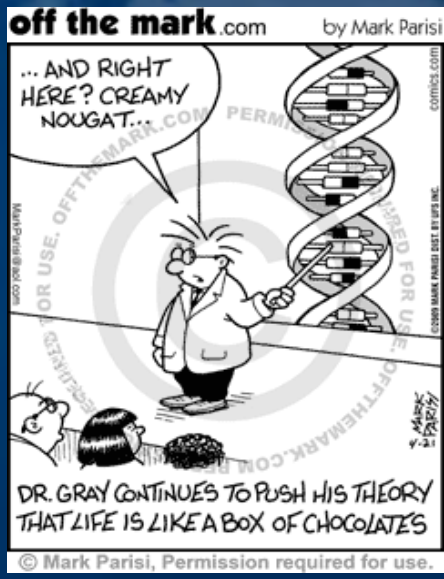
SPECIALTY: Psychiatry and Autism Specialist

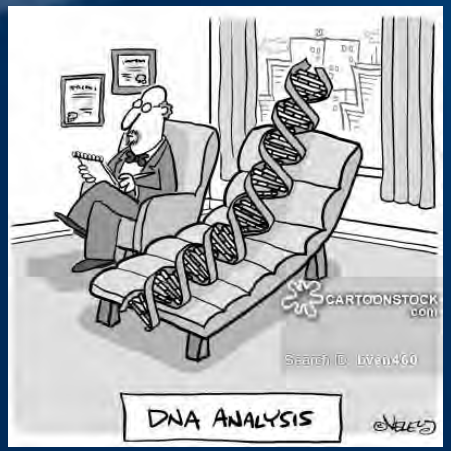
UNDERGRADUATE SCHOOL: University of California, Santa Barbara

DOCTORATE: University of Idaho

RESIDENCY: Cold Spring Harbor Laboratory (New York)

FELLOWSHIP: Cold Spring Harbor Laboratory (New York)





Rady Children's Specialists of San Diego
A Medical Foundation

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Jonathan Sebat, Ph.D.

Autism doesn't run in my family. How can my child's autism be genetic?

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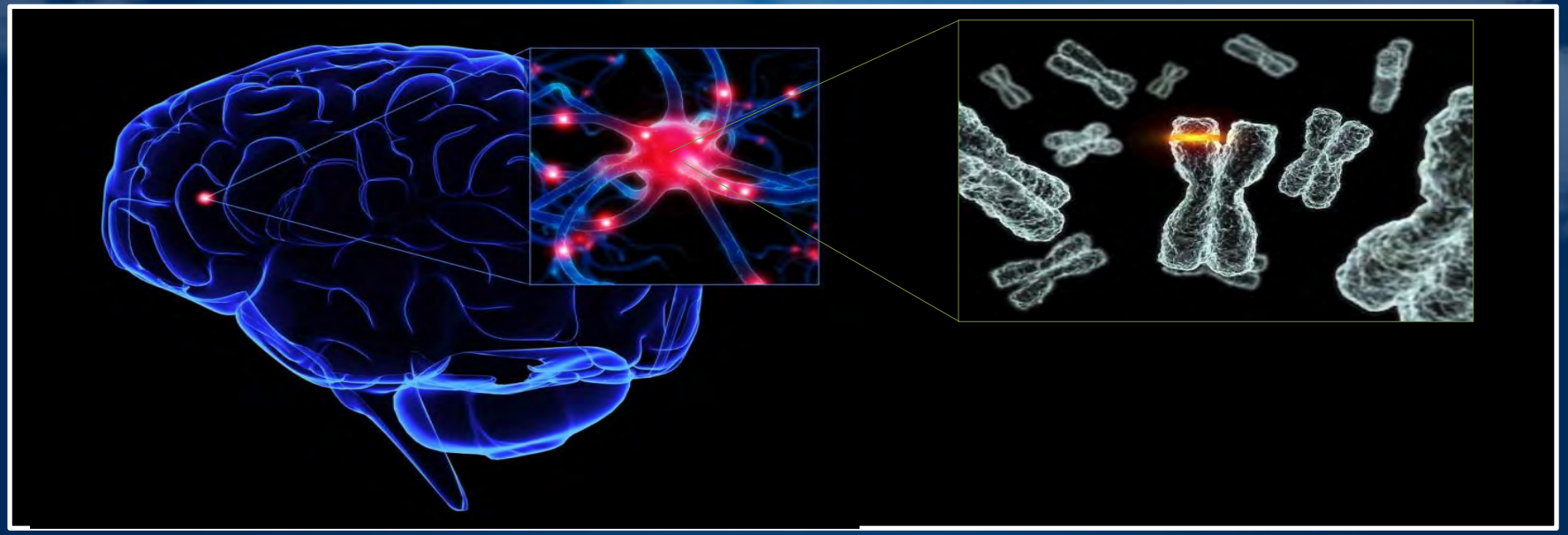

Department of Psychiatry, Cellular & Molecular Medicine ,
Institute for Genomic Medicine
UCSD

Disclosures

- None

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Outline

- Myths about the causes of autism
- CNVs & the paradigm shift in autism genetics
- New Discoveries from Exome and Whole Genome Sequencing

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A vaccine health scare is born (Wakefield et al., *The Lancet* ,1998)

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associ… by the parents, with measles, mumps, and rub… vaccination in eight of the 12 children, with measl… infection in one child, and otitis media in a… All 12… children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to a… oid ul…ration. Histology showed patchy chronic inflam…tion i… in 11 children and reactive ileal lymphoi… perplasia in seven, but no granulomas. Be…viour…l disor…rs included autism (nine), disintegrativ… sis (one), a… possible postviral or vaccinal encephalitis (…o). There were no focal neurological ab…rmalities and …l and EEG tests were normal. Abno…al laboratory results …ere significantly raised urinary …ethylmal… acid compared with age-matched control… (p=0.003), low haemoglobin in four children, … low s…m IgA in …r children.

Interpretation …e iden… associated gastrointestinal di…se and …evelopmental regression in a group of previ…ly …mal chil…n, which was generally associated in time … possible environmental triggers.

Lancet 199… **351:** 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP,), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a pe…d of apparent normality, lost acquired skills, includ…g com…nication. They all had gastrointestinal …mptoms, …luding abdominal pain, diarrhoea, and …ating and, in some cases, food intolerance. We …scribe… a clinical fi…lings, and gastrointestinal featur… of these chi…en.

Patients and meth…ds

12 children, cons…tively …rred to th… department of paediatric gastr…terology … a hi…y of a pervasive developmental …der with loss …ired skills and intestinal symptoms …arrh… abdominal …in, bloating and food intolerance), were inv…gated. All children were admitted to the ward for …week, accomp…ed by their parents.

Clinical investigations

… took histori… including details of immunisations and e…posure to infect…us diseases, and assessed the children. In 11 ca… the history …as obtained by the senior clinician (JW-S). Neur…logical …d psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental …s included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done

- 12 children (mean age of 6) referred to gastroenterology
  - Regressive developmental delay
  - Diarrhea
  - Abdominal pain
- Performed GI and neurological exams under sedation
  - Colonoscopy and biopsy
  - MRI, EEG
  - Spinal tap
- Parents reported that onset of symptoms were coincident with receiving MMR vaccinations

Yes, that's all.

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"Conclusions" of the Wakefield study are speculation

"Intestinal and behavioural pathologies may have occurred together by chance, reflecting a selection bias in a self-referred group"

"however, the uniformity of the intestinal pathological changes and the fact that previous studies have found intestinal dysfunction in children with autistic-spectrum disorders, suggests that the connection is real and reflects a unique disease process."

*Later, Wakefield and other hypothesize that the "toxic agent" in vaccines is the vaccine preservative Thimerosal (which contains trace amounts of mercury)

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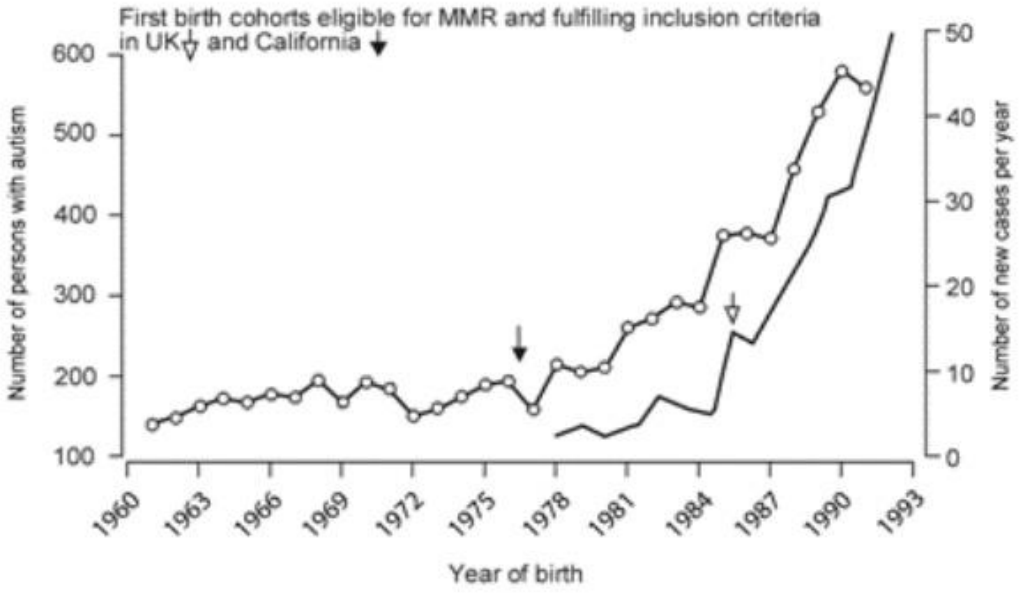
Wakefield argues for an MMR vaccine cause based on temporal correlation of vaccine introduction and rise in prevalence



Wakefield AJ. MMR vaccination and autism. *Lancet* 1999;**354**:949-50.

By this logic, we could infer a causal role for handheld calculators, Astroturf and the Environmental Protection Agency

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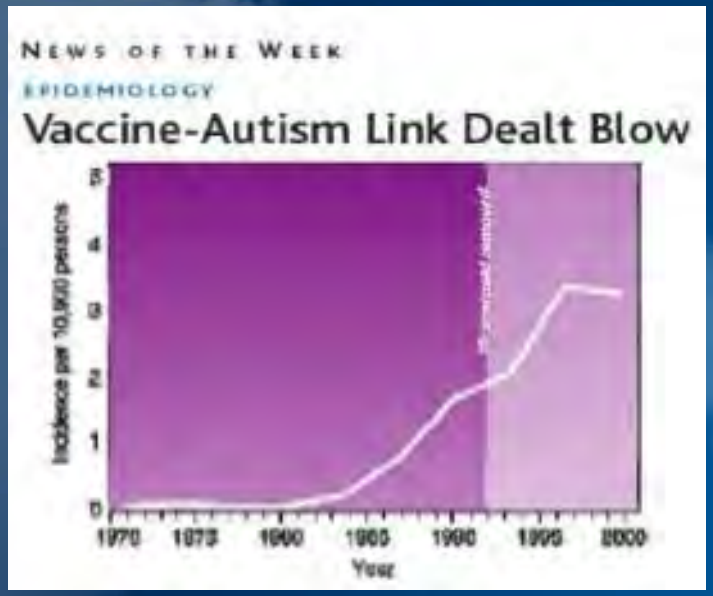
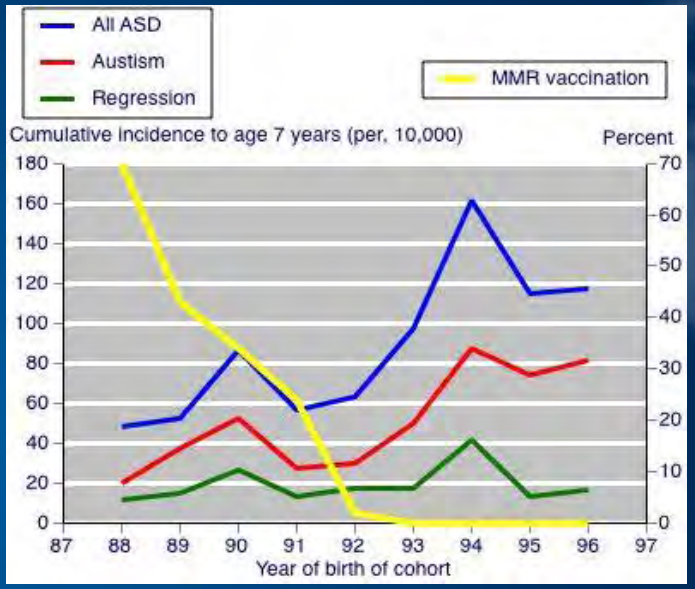
Autism-vaccine link begins to unravel

Stokstad et al Science 2003



Danish Study Shows that Autism rates continued to rise after Thimerosal is removed from Vaccines

Honda et al, 2005



Autism rates continued to rise in Yokohama Japan after withdrawal of the MMR vaccine

And many other studies find no link…

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A timeline of the Wakefield retraction

28 February Gastroenterologist Andrew Wakefield reports in *The Lancet* that his team has found a "genuinely new syndrome"—a link between the measles, mumps and rubella (MMR) vaccine and an increased risk of autism (*Lancet* **351**, 637–641, 1998).

2002–2004 Numerous studies published in *BMJ*, *The New England Journal of Medicine*, *The Lancet* and other journals find no link between MMR and autism.

28 January The UK General Medical Council rules that Wakefield acted "dishonestly and irresponsibly," and showed "callous disregard" for the suffering of children involved in his controversial research.

1998 **2000** **2004** **2010**

6 April Wakefield and Dublin pathologist John O'Leary present research to a US congressional committee showing that 24 of 25 autistic children tested had traces of the measles virus in their gut.

6 March Ten authors on the 1998 paper issue a retraction (*Lancet* **363**, 750, 2004), and *The Lancet*'s editor says the journal, in hindsight, should not have published the study (*Lancet* **363**, 747–749, 2004).

2 February *The Lancet* retracts Wakefield's 1998 paper, noting elements of the manuscript proved to be false (*Lancet* doi:10.1016/S0140-6736(10)60175-7, 2010).

But it can take decades to get to the truth

-The original paper was shown to be fraudulent.

-But where was the credibility of a possible autism-vaccine in the first place?

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In typically developing children, higher cognitive abilities come online between 1 and 3 years of age

By coincidence, failure to meet these milestones appears to coincide with the recommended vaccine schedule

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Then what causes autism?

Autism is a heritable disorder

Heritability is the proportion of autism that can be explained by genes.
A classical way to measure heritability is through *twin studies*

MZ twins

(genetically identical)

DZ twins

(50% genetically identical)

Siblings

(50% genetically identical)

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Degree of shared environment is very similar in MZ & DZ twins

	MZ twins	DZ twins	Siblings
Amniotic	only in 5%	No	No
Uterine	Yes	Yes	No
Home environment	Yes	Yes	Yes

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Recurrence risk for Autism Spectrum Disorders

MZ twins

70-90%

DZ twins

10-20%

Siblings

10-20%

General population

1%

Recurrence risk

The proportion of autism that can be explained by genes is estimated at 90%

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Bolton et al 1994

The search for genes 1990-2007

Linkage studies reported findings chromosomes 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 15, 16, 17, 18, 19, 20, 22 and X

- Signals were weak and did not replicate well across studies

Candidate gene studies were not reproducible

Cytogenetic Abnormalities have been reported in >5% of cases

Some rare single gene disorders meet criteria for ASDs

- Fragile X syndrome (FMR1)
- Rett Syndrome (MECP2)
- Tuberous Sclerosis (TSC2)
- Cowden Syndrome (PTEN)
- Sotos Syndrome (NSD1)

Genetics of autism is heterogenous. No one gene accounts for a large proportion of the disorder

Phenotypic heterogeneity

Mental Retardation

Sensory Problems

Impaired ability to communicate

Poor physical coordination

Seizures

Autoimmune Problems

Difficulty with Social Interaction

Restricted & Repetitive Behavior

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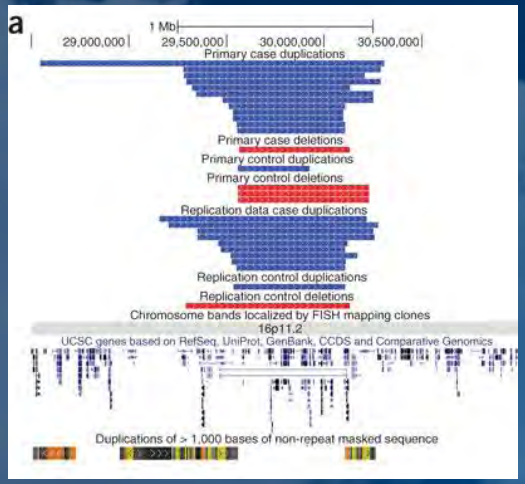
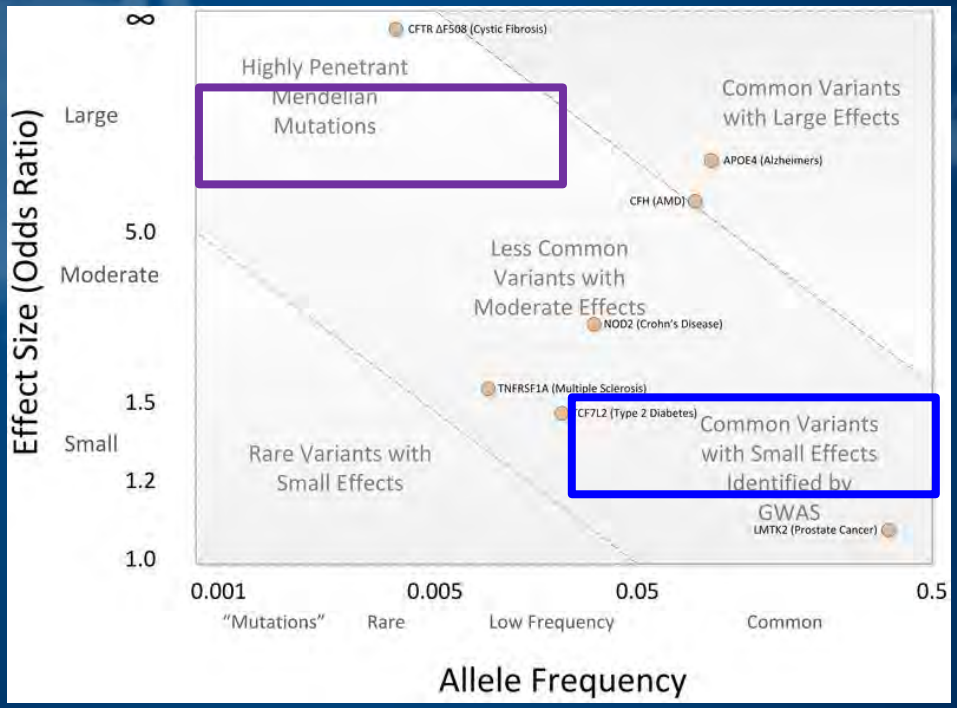
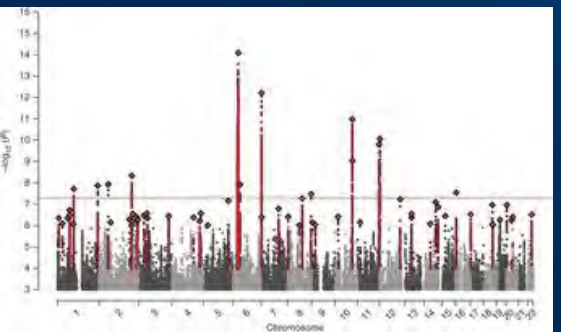
Rare variants of large effect (CNVs)







Common variants of modest effect (SNPs)

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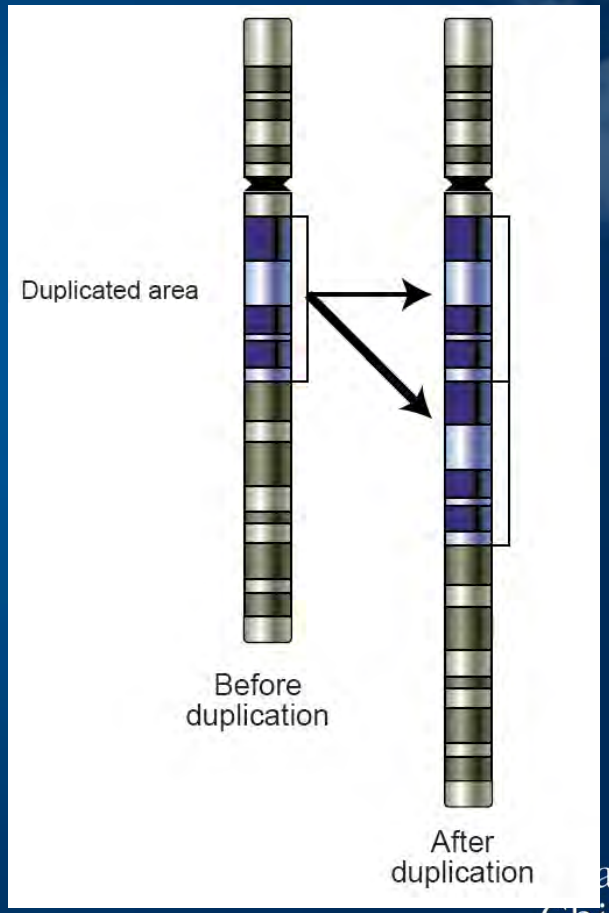
Copy number variation

Large-Scale Copy Number Polymorphism in the Human Genome

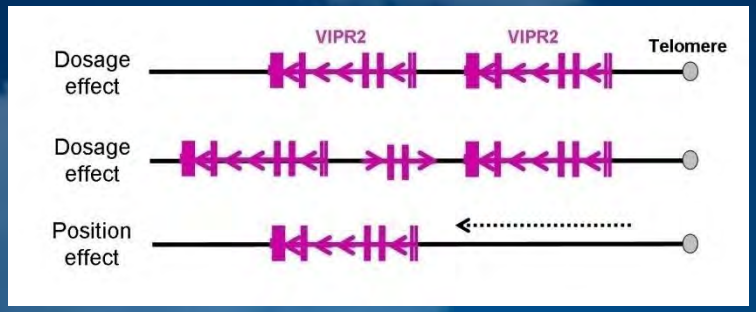
Jonathan Sebat,[1] B. Lakshmi,[1] Jennifer Troge,[1] Joan Alexander,[1] Janet Young,[2] Pär Lundin,[3] Susanne Månér,[3] Hillary Massa,[2] Megan Walker,[2] Maoyen Chi,[1] Nicholas Navin,[1] Robert Lucito,[1] John Healy,[1] James Hicks,[1] Kenny Ye,[4] Andrew Reiner,[1] T. Conrad Gilliam,[5] Barbara Trask,[2] Nick Patterson,[6] Anders Zetterberg,[3] Michael Wigler[1]*

Sebat et al. Science. 2004. 23;305(5683):525-8

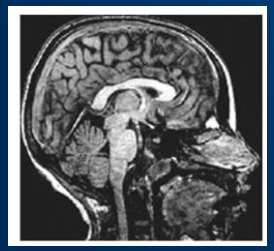


CNV-based approach to disease

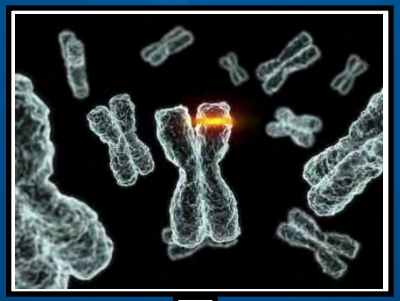
Genetic Mechanism



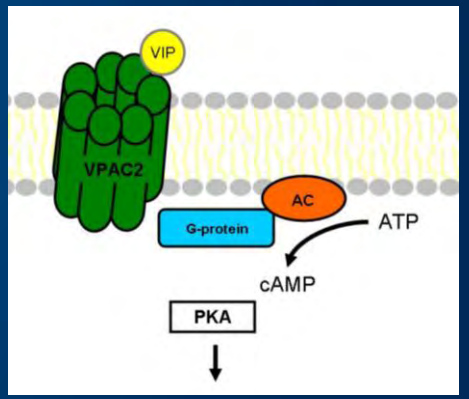
Clinical Characterization



CNV Discovery



Biochemical Mechanism



Cognition and Behavior

Copy number = 0 1 2 3 4

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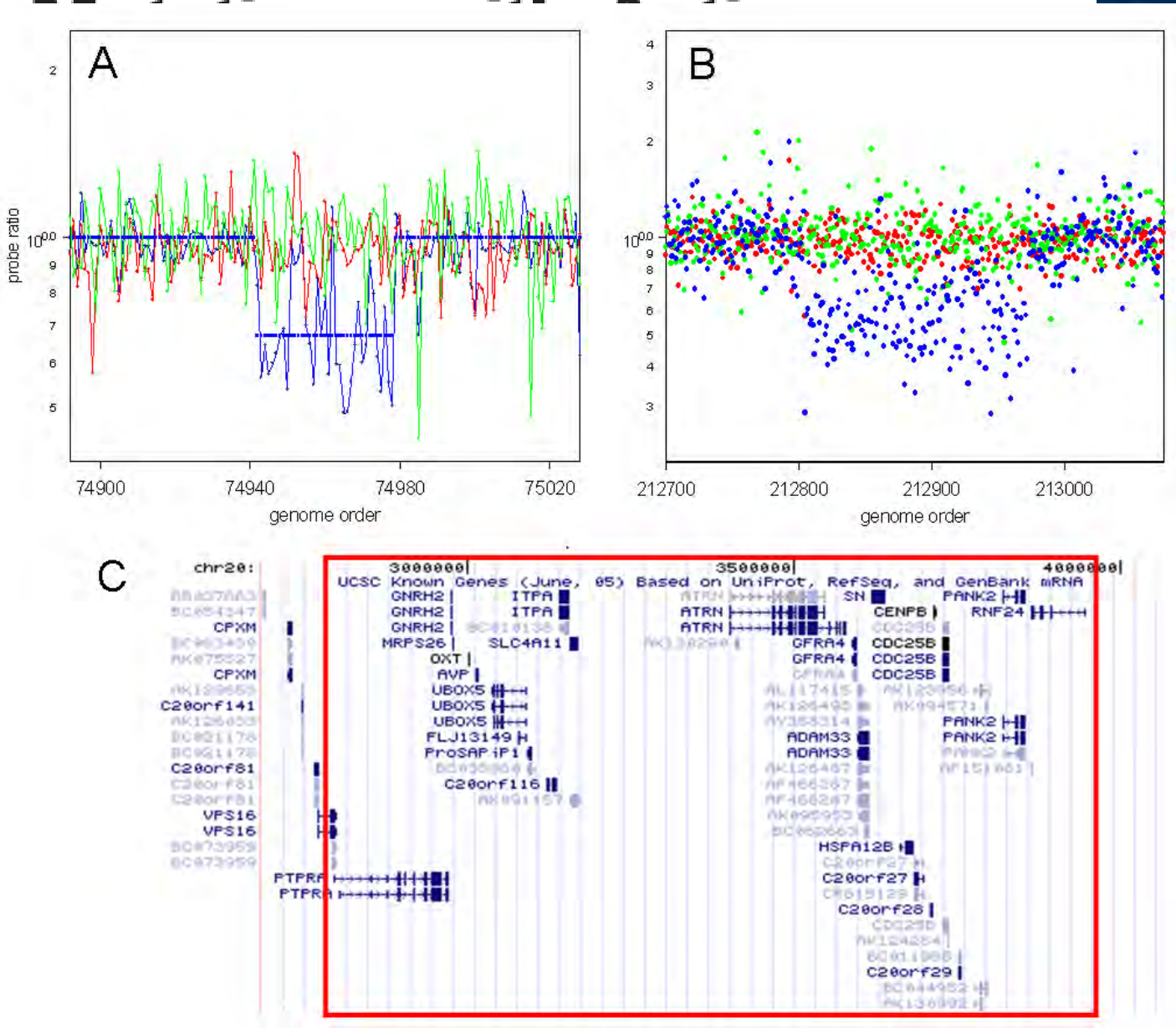
Strong Association of De Novo Copy Number

Jonathan Sebat,[1*] Tom Walsh,[3] Boris
Deepa Pai,[1] Ray Zl
Kaija Puura,[6] Terh
James S. Sutcliffe,
Mary-Claire King,[3]
Kenny Ye,[14] Micha



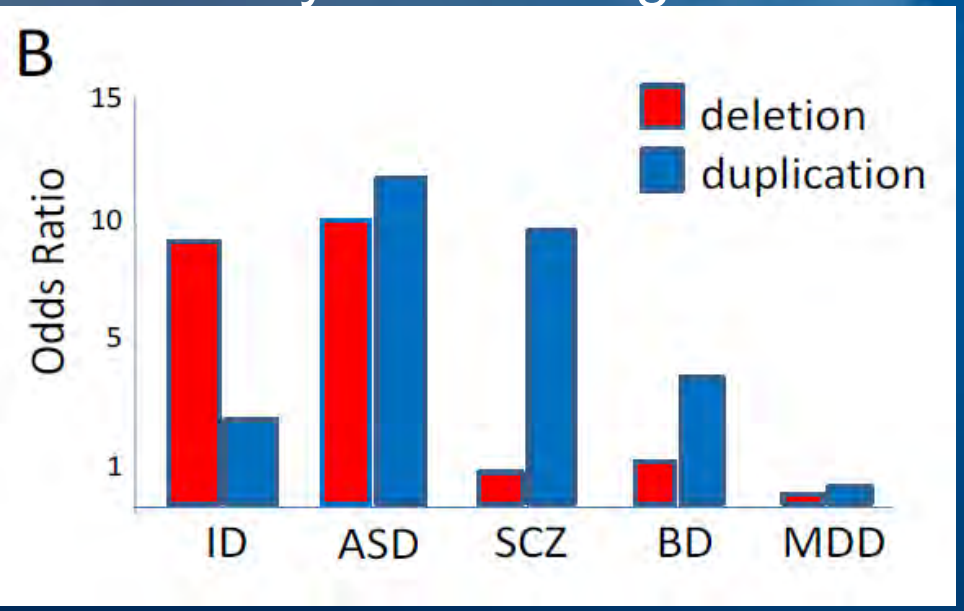
De novo CNVs detected in subjects

Table 1. Spontaneous CNVs detected by ROMA. A description of 17 de novo CNVs in 16 subjects is provided, along with the methods used for its validation. The number of unique RefSeq genes within each CNV region is indicated, and when the locus apparently encompasses only a single gene, the gene symbol is listed. Types of validation included (A) higher-resolution microarray scans by 390K ROMA or Agilent 244K CGH, (B) G-banded karyotype, (C) FISH, and (D) microsatellite genotyping. References are listed for four cases where similar de novo CNVs were previously reported in the literature.

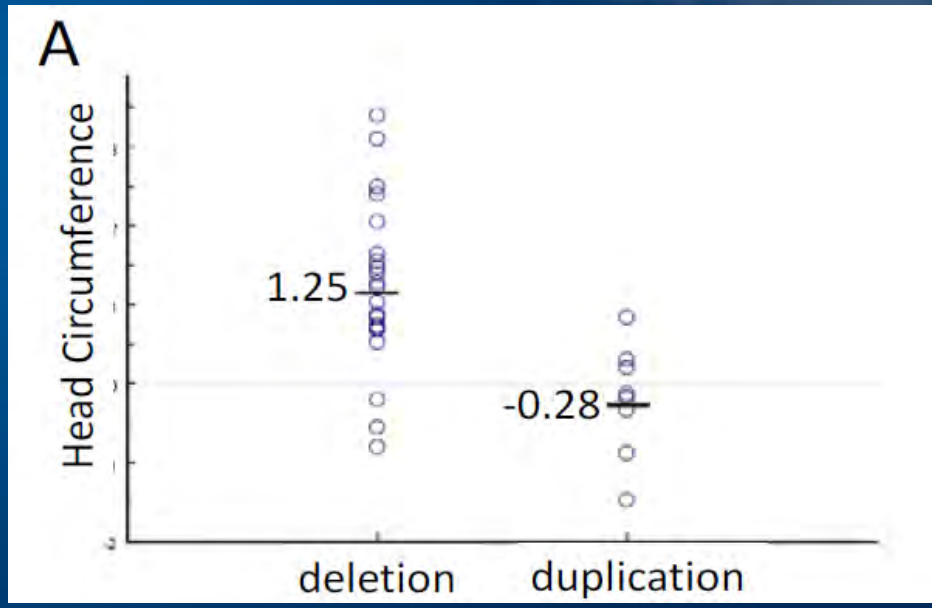
Individual	Locus	Start position	Length	CN change	Family type	Diagnosis	Gender	Validation	# Genes	Single-gene targets	Ref.
63-144-2575 and 2667	2q24.2	162,212,720	99,252	Loss	Simplex	Autism	Female	A	1	SLC4A10	
61-2710-3	2q37.2-q37.3	236,414,455	6,286,648	Loss	Simplex	Autism	Male	A, B, D	50		(*19*)
Van69-258900	2q37.3	238,217,066	4,484,037	Loss	Simplex	Autism	Male	A, D	43		(*19*)
89-3507-1	3p14.2	60,746,033	101,507	Loss	Simplex	Autism	Male	A	1	FHIT	
63-562-6612	3p14.2	61,072,100	293,096	Gain	Simplex	Autism	Male	A	1	FHIT	
AU010604	6p23	13,997,280	1,264,651	Loss	Multiplex	Autism	Male	A, D	2		
	13q14.12-q14.13	44,199,441	1,943,737	Loss				A, D	13		
AU072203	7p21.1	15,160,118	151,880	Loss	Simplex	Autism	Male	A	1	FLJ16237	
AU032903	10q11.23-q21.2	50,562,149	10,916,362	Gain	Multiplex	Autism	Male	A, B	23		
60-3061-4	15q11-q13.33	18,526,971	12,229,800	Gain	Simplex	Autism	Male	A, B	30		(*21*)
AU077504	16p13.3	5,992,836	207,980	Loss	Simplex	Autism	Female	A, B, C, D	1	A2BP1	
CG2061	16p11.2	29,578,715	502,574	Loss	Simplex	Asperger's	Female	A, C, D	27		
71-259100	20p13	75,912	291,959	Loss	Simplex	Autism	Female	A, C, D	7		
SK-135-C	20p13	2,785,194	1,169,205	Loss	Simplex	Asperger's	Male	A, D	23		
89-3524-100	22q13.31-q13.33	45,144,027	4,321,856	Loss	Simplex	Autism	Female	A, B, C, D	30		(*20*)
NA10857	2p16.1	58,394,177	2,786,284	Gain	Control	Unaffected	Male	A	7		
AU070807	20p13-p12.3	111,824	5,316,286	Gain	Simplex	Unaffected	Female	A	69		

Correlating CNV genotype with clinical phenotype (reciprocal deletions and duplications of 16p11.2)

Psychiatric diagnosis



Head Size



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McCarthy et al, Nat Gen 2009

Lessons learned

There is a strong association of de novo CNVs and sporadic autism

- –10% in sporadic cases, 3% in multiplex, 1% in controls

9/14 (>60%) of *de novo* CNVs were "private mutations"

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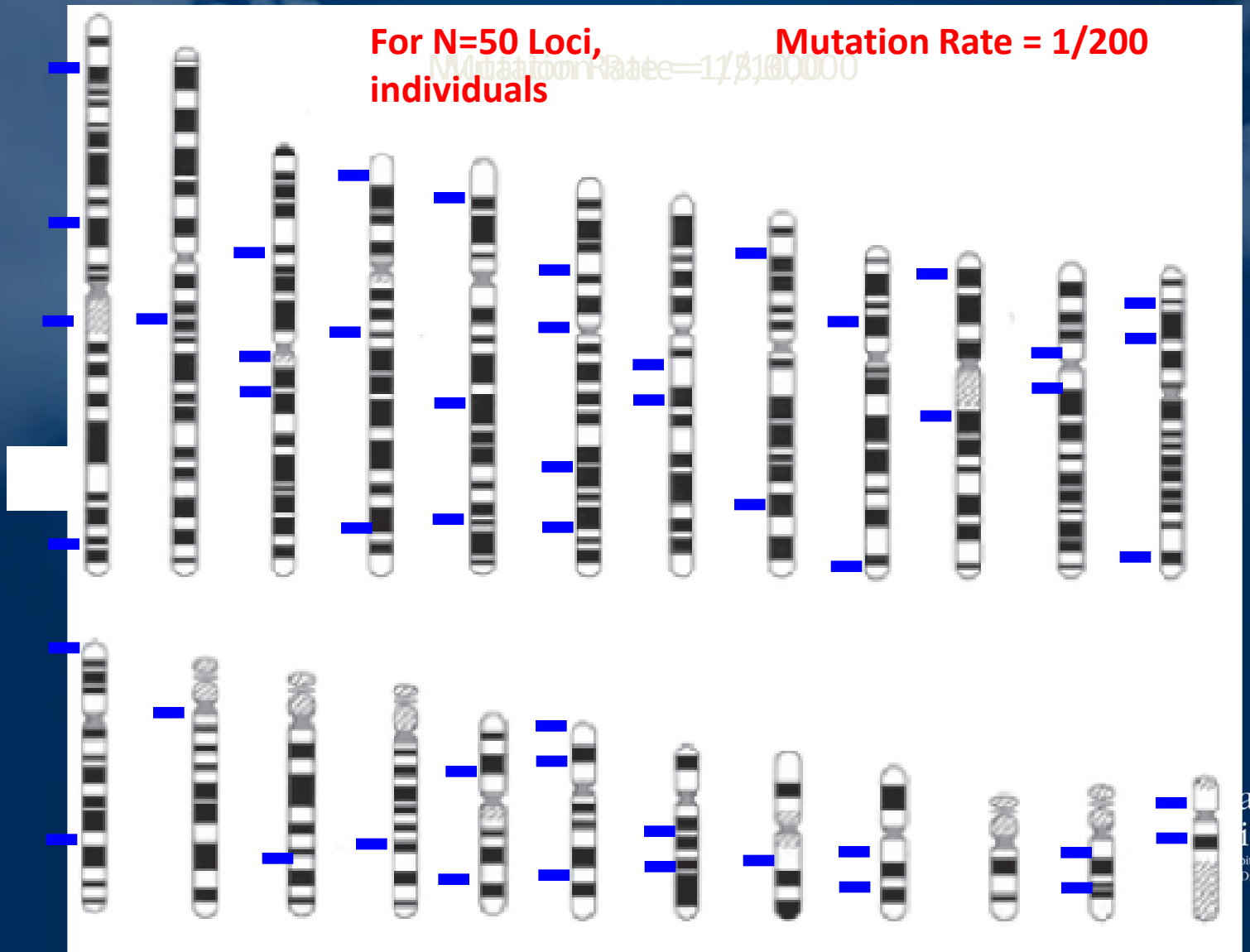
Autism: a common disorder caused by rare mutations



Beyond CNVs

To rare variants in the DNA sequence

De novo point mutations in exons contribute to autism

Matthew State

LETTER

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]

Michael Wigler

Neuron

Article

De Novo Gene Disruptions in Children on the Autistic Spectrum

Ivan Iossifov,[1,6] Michael Ronemus,[1,6] Dan Levy,[1] Zihua Wang,[1] Inessa Hakker,[1] Julie Rosenbaum,[1] Boris Yamrom,[1] Yoon-ha Lee,[1] Giuseppe Narzisi,[1] Anthony Leotta,[1] Jude Kendall,[1] Ewa Grabowska,[1] Beicong Ma,[1] Steven Marks,[1] Linda Rodgers,[1] Asya Stepansky,[1] Jennifer Troge,[1] Peter Andrews,[1] Mitchell Bekritsky,[1] Kith Pradhan,[1] Elena Ghiban,[1] Melissa Kramer,[1] Jennifer Parla,[1] Ryan Demeter,[2] Lucinda L. Fulton,[2] Robert S. Fulton,[2] Vincent J. Magrini,[2] Kenny Ye,[3] Jennifer C. Darnell,[4] Robert B. Darnell,[4,5] Elaine R. Mardis,[2] Richard K. Wilson,[2] Michael C. Schatz,[1] W. Richard McCombie,[1] and Michael Wigler[1,*]

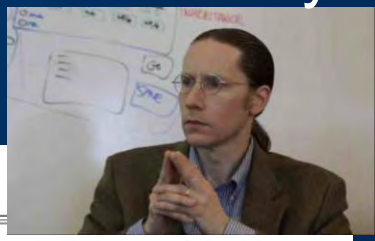
Evan Eichler

LETTER

Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations

Brian J. O'Roak[1], Laura Vives[1], Santhosh Girirajan[1], Emre Karakoc[1], Niklas Krumm[1], Bradley P. Coe[1], Roie Levy[1], Arthur Ko[1], Choli Lee[1], Joshua D. Smith[1], Emily H. Turner[1], Ian B. Stanaway[1], Benjamin Vernot[1], Maika Malig[1], Carl Baker[1], Beau Reilly[2], Joshua M. Akey[1], Elhanan Borenstein[1,3,4], Mark J. Rieder[1], Deborah A. Nickerson[1], Raphael Bernier[2], Jay Shendure[1] & Evan E. Eichler[1,5]

Mark Daly



LETTER

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

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Autism is a disorder of the synapse…

… and the rest of the cell

Class	Gene	Function
Synapse	*CHRNA7*	cholinergic receptor
	KATNAL2	microtubule assembly
	TUBA1A	microtubule assembly; neuronal migration
	NLGN3	neuronal cell adhesion via interaction with neurexins
	STXBP1	neurotransmitter release at synapses
	GRIN2B	NMDA receptor
	SHANK2	postsynaptic scaffold protein
	SHANK3	postsynaptic scaffold protein
	SCN2A	propagation of neuronal action potentials
	SYNE1	synaptic nuclear envelope
	NRXN1	synaptic receptor / cell adhesion
Cell Signaling	*DYRK1A*	cell proliferation
	PTEN	cell proliferation; inhibition of AKT signaling pathway
	SYNGAP1	dendritic spine development and maturation
	MAPK3	extracellular signal-regulated kinase
	POGZ	mitotic cell cycle progression
	MVP	nucleo-cytoplasmic transport
	TSC2	regulates mTORC1 / PI3K signaling
	TSC1	regulates mTORC1 / PI3K signaling
	TRIO	Rho signalling
Translational Regulation	*CUL3*	protein ubiquitination and degradation
	UBE3A	protein ubiquitination and degradation
	KCTD13	protein ubiquitination and degradation
	CYFIP1	translational repression
	FMR1	translational repression
Transcriptional Regulation	*CHD8*	chromatin remodelling
	CHD2	chromatin remodelling
	ADNP	chromatin remodelling
	SATB2	chromatin remodelling
	ARID1B	chromatin remodelling
	DNMT3A	DNA methytransferase
	HDAC4	histone deacetylase
	SUV420H1	histone methyltransferase
	SETD5	histone methyltransferase
	NSD1	histone methyltransferase
	MED13L	transciptional cofactor
	TBR1	transcription factor; differentiation and migration of neurons
	TBL1XR1	transcriptional activation
	MECP2	transcriptional repression through binding methylated DNA
	FOXP1	transcriptional repressor

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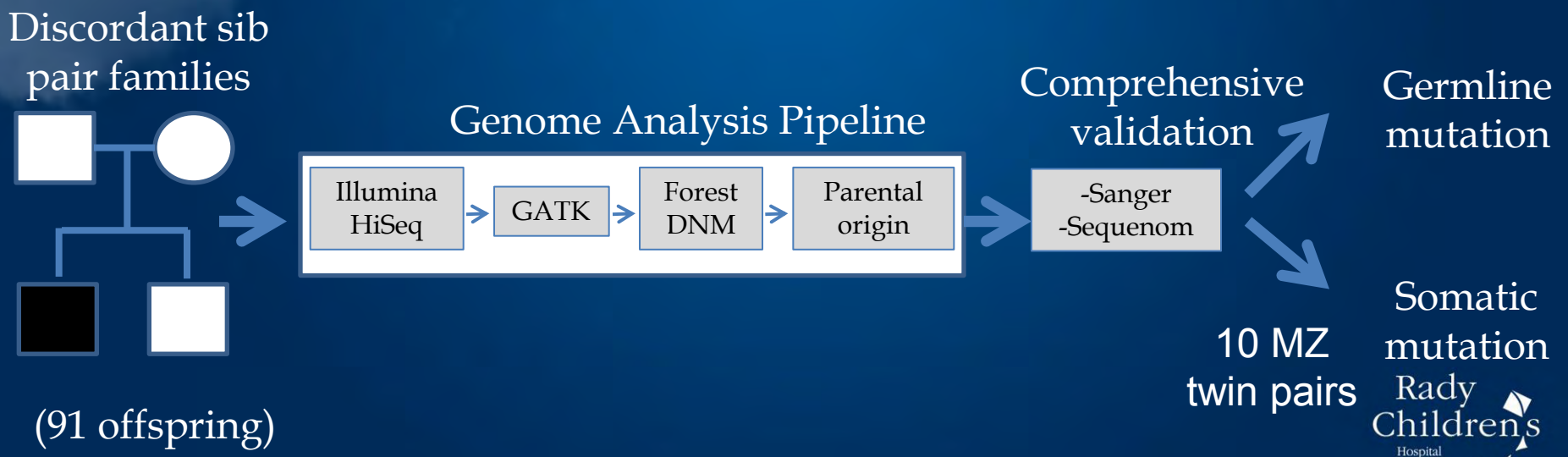
Moving beyond the exome

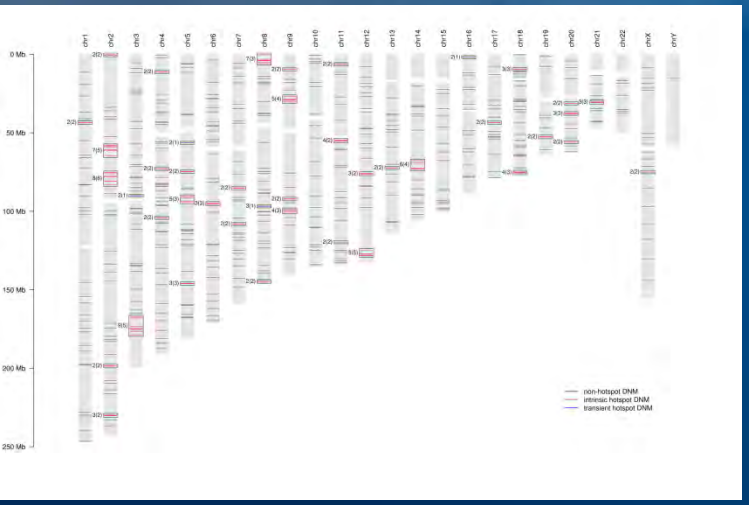
Toward all variation in all of the genome

Determining patterns of de novo mutation by Whole Genome Sequencing

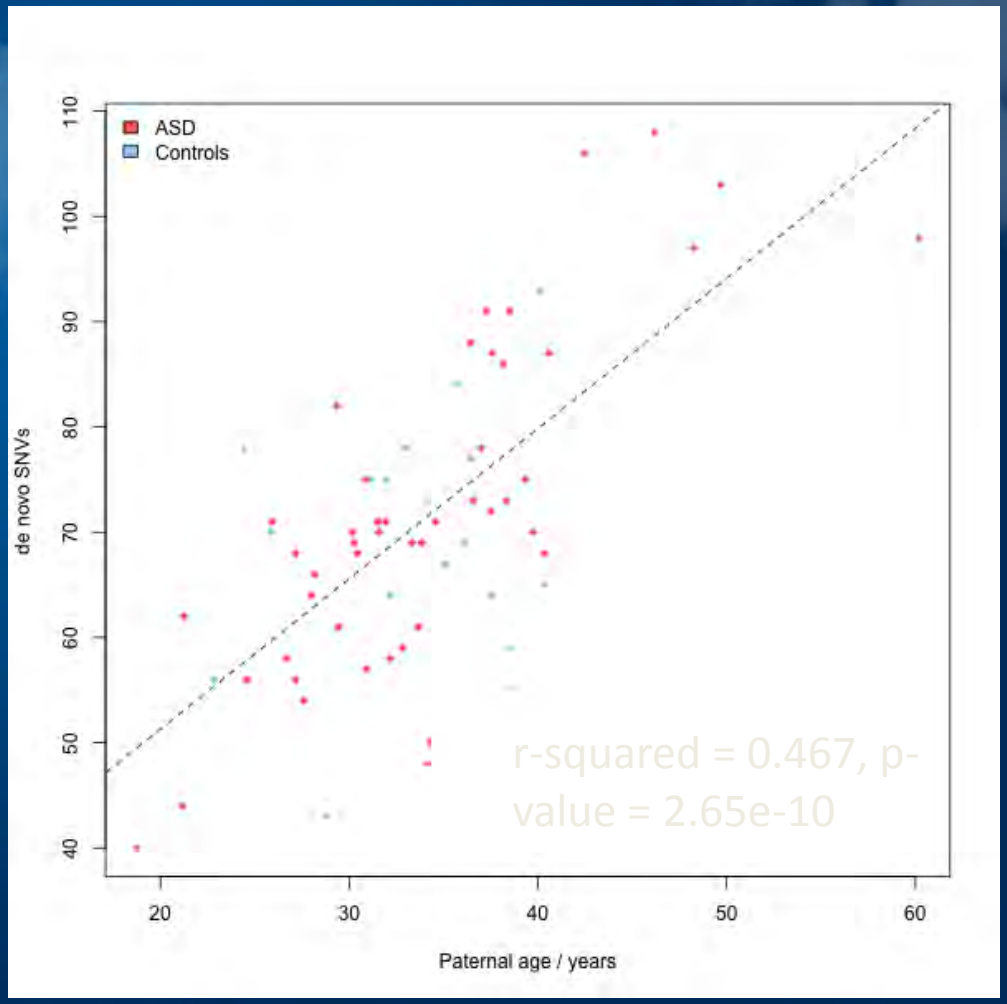


50% of variance in germline mutation rate is explained by father's age

5,586 mutations detected in 71 offspring



Average mutation rate = $1X10^{-8}$



Older reproductive age (>40) is a significant risk factor ASD

Advancing Paternal Age and Autism

Abraham Reichenberg, PhD; Raz Gross, MD, MPH; Mark Weiser, MD; Michealine Bresnahan, PhD; Jeremy Silverman, PhD; Susan Harlap, MBBS; Jonathan Rabinowitz, PhD; Cory Shulman, PhD; Dolores Malaspina, MD; Gad Lubin, MD; Haim Y. Knobler, MD; Michael Davidson, MD; Ezra Susser, MD, DrPH

	mother	**father**
	No effect	5-fold greater risk

Reichenberg, Susser et al, Arch Gen Psych 63:1026-1032, 2006

Estimated Autism Risk and Older Reproductive Age

Marissa D. King, PhD, Christine Fountain, PhD, Diana Dakhlallah, BA, and Peter S. Bearman, PhD

	1.3-1.8 fold	1.3-1.7 fold

King et al, Am Jnl Public Health 99(9):1673-1679, 2009

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This finding may also relate to genetic risk factors

Hypermutability is a common feature of brain and autism genes

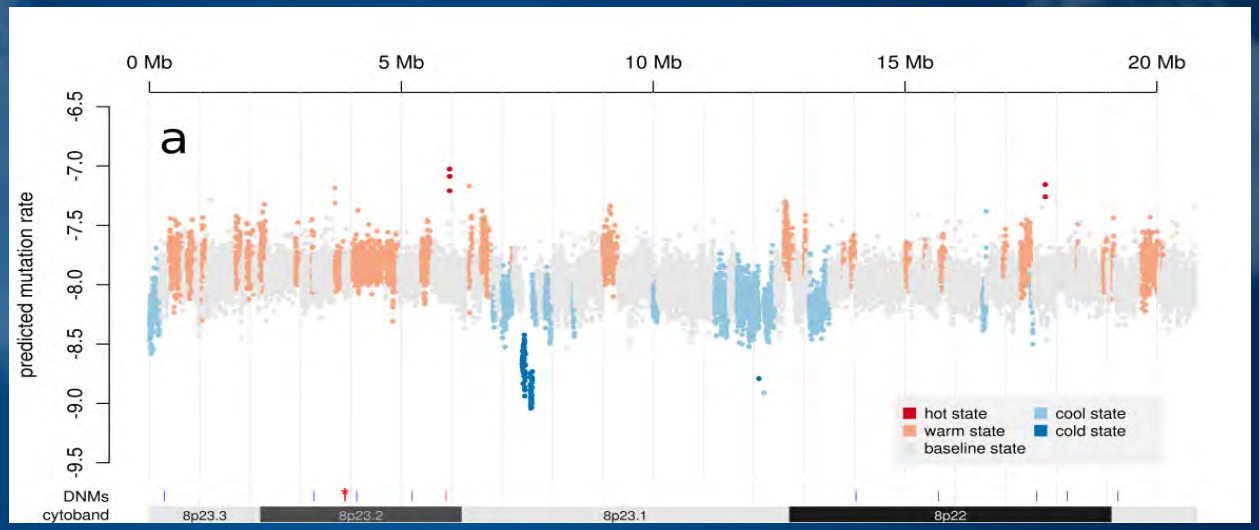
Includes hotspots for nucleotide substitution, CNV or both

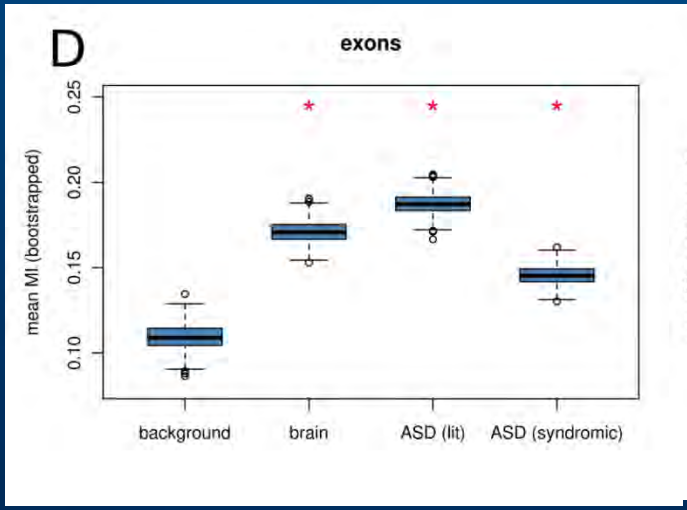
Michaelson et al 2012

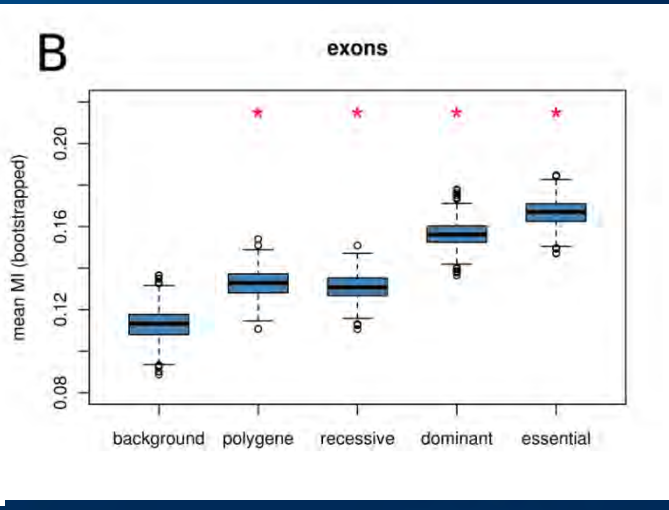
Jake Michaelson

Madhu Gujral

Dheeraj Malhotra







De novo protein coding SNVs in our study overlap with genes hit by *de novo* coding mutations in studies of neurodevelopmental disorders

Case vs Case

DNM type	n DNMs	observed overlap	Cases (ASD, ID, SZ) LOF+NS expected (95%CI)	fold	P
LOF+NS	49	28	14.8(10-20)	1.84	0.000078
lof	8	6	2.6(1-5)	1.92	0.019
NS	41	22	12.1(8-17)	1.75	0.001
SYN	25	11	7.2(4-11)	1.47	0.057

Case vs Control

DNM type	n DNMs	observed overlap	Controls LOF+NS expected (95%CI)	fold	P
LOF+NS	49	6	6.5(3-10)	0.93	0.5
lof	8	0	0.8(0-2)	0.55	0.4
NS	41	6	5.6(2-9)	1.06	0.49
SYN	25	0	2.9(1-6)	0.25	0.041

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Missense variants are driving the association

P-value

Case vs Case

Primary \ Replication	LOF	NS	SYN
LOF	0.002	0.57	0.63
NS	0.095	0.0001	0.14
SYN	0.44	0.16	0.22

Case vs Control

Primary \ Replication	LOF	NS	SYN
LOF	0.5	0.47	0.44
NS	0.4	0.9	0.51
SYN	0.49	0.51	0.57

Nonsynonymous and Loss-of-Function mutations impact different genes

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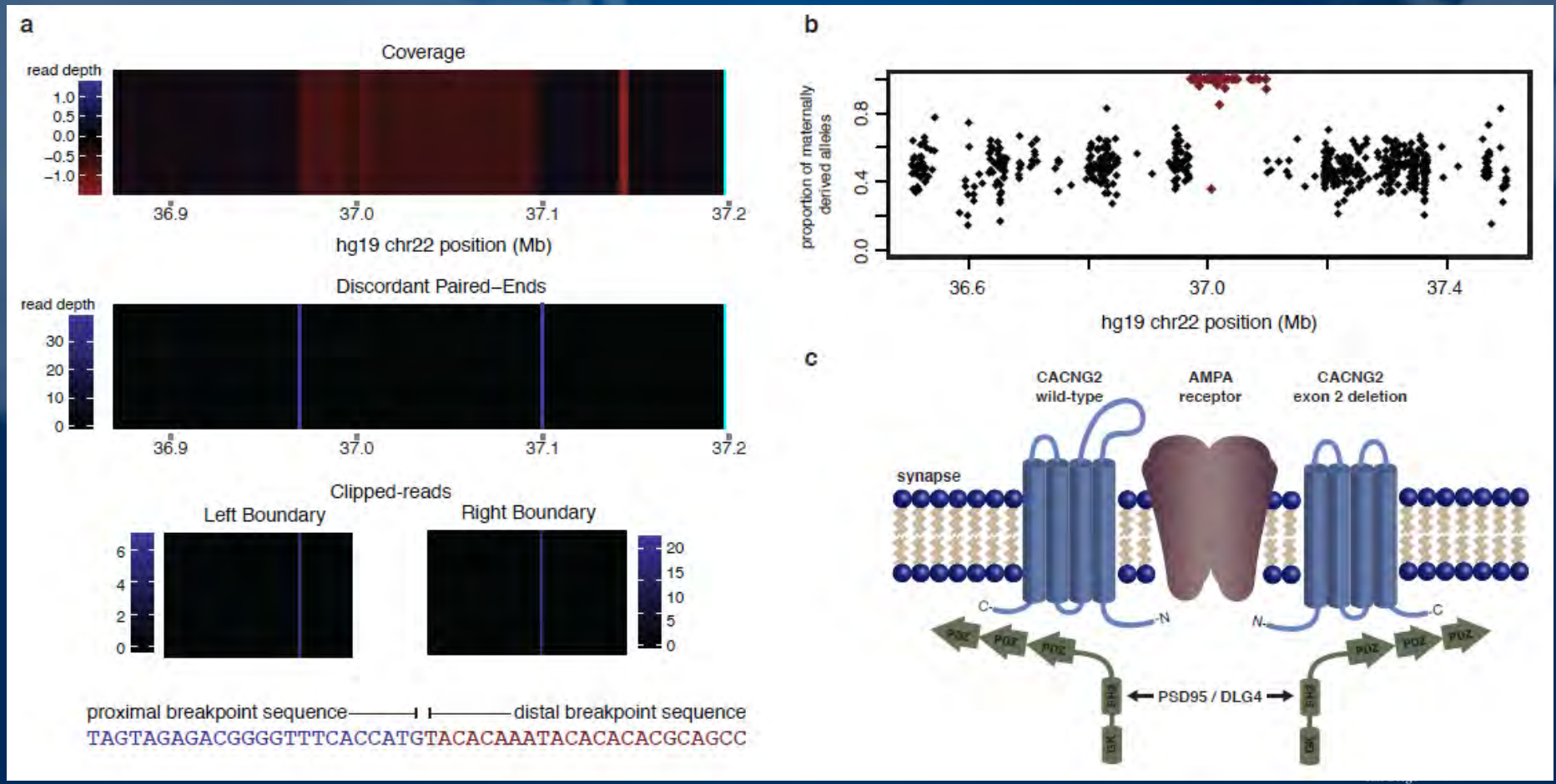
Genes overlapping with exome studies

Gene	function	WES_WGS_hits
NAV1	nonsynonymous	ASD
CUL9	splicing	ASD
PRPS1L1	nonsynonymous	ASD
ERP44	nonsynonymous	ASD
FTSJ3	nonsynonymous	ASD
LAMB2	nonsynonymous	ASD,ASD
FOXP1	stopgain	ASD,ASD
GIGYF1	stopgain	ASD,ASD
GPR98	nonsynonymous	ASD,ASD,EE
SETD5	nonsynonymous	ASD,ASD,ID
FCGBP	nonsynonymous	ASD,SZ
NLRP8	nonsynonymous	EE

Gene	function	WES_WGS_hits
GRB14	nonsynonymous	ID
POP1	nonsynonymous	ID
KIF20B	nonsynonymous	ID
PHIP	nonsynonymous	ID,ASD
PDCD11	nonsynonymous	SZ
TEKT5	nonsynonymous	SZ
SHKBP1	nonsynonymous	SZ
CERK	nonsynonymous	SZ
TAF7L	nonsynonymous	SZ
HIVEP3	stopgain	SZ,ASD
KMT2D	nonsynonymous	SZ,ASD
RYR3	nonsynonymous	SZ,SZ,ASD

Sequence level characterization of de novo CNVs



De novo and rare mutations contribute to ~30% of ASDs

Mutation Type	% cases	% controls	odds ratio	% ASD explained
de novo copy number variation	8	2	4	6
de novo loss of function	20	10	2	10
De novo missense (recurrent in this study)	22	12	1.8	10
rare complete gene knock-out	6	3.3	1.8	2.7
rare ♂ X-linked loss of function	4.8	3.1	1.5	1.7

How do we explain the 'missing heritability'?

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Conclusions

De novo mutation is an important contributor to risk for ASDs

- CNVs, SNVs, indels in coding regions contribute to ~20% of cases

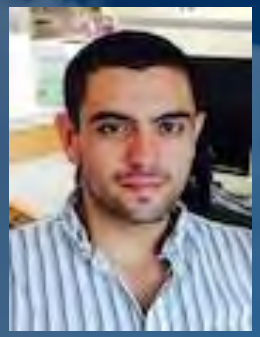
Rare variants and de novo mutation in the other 99% of the (non-coding) remain largely unexplored

Rare mutations in regulatory elements of genes may explain some of the missing heritability of Autism

Special Thanks

Sebat Lab


William Brandler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SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Thank You

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