Investigating the Genetic and Biological Mechanisms That Predispose to Early-Onset Psychotic Illnesses

Catherine Brownstein, MPH, PhD

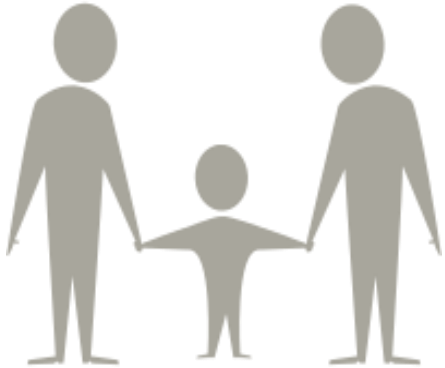
Early Psychosis Investigation Center (EPICenter),
Boston Children's Hospital

Learning objectives

1. Better recognize the signs and symptoms of psychosis in youth and how those change over development
2. Familiar with current genetic findings in early onset psychosis
3. Review the impact of early life adversity on early onset psychosis
4. Develop an understanding of why studying child onset psychosis is an important strategy for understanding idiopathic adult psychosis

Patients and families come to BCH with two fundamental questions

What's wrong?



What's next?

For many patients, genetic testing (and clinical expertise) can be used to answer these questions

Manton Center For Orphan Disease Research

Alan Beggs, PhD
Director, Manton Center

Pankaj Agrawal, MD
Division of Newborn Med.

Infants were presenting in the NICU with seemingly genetic disorders with limited means for research follow-up (for both clinically diagnosed and undiagnosed)

Find an established study in which the patient can enroll

Create an IRB protocol to enroll the patient

Boston Children's Hospital | The Manton Center for Orphan Disease Research

About Us

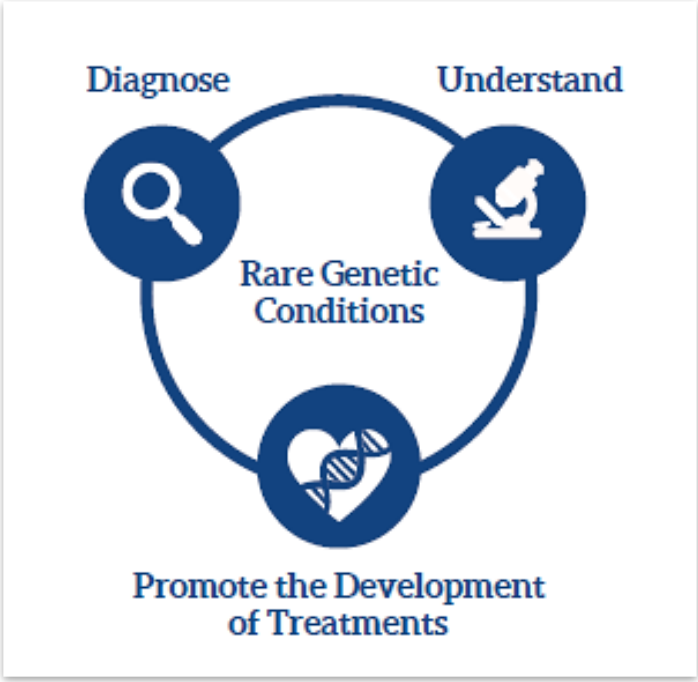
- A philanthropically funded center at Boston Children's Hospital dedicated to rare genetic disease research

Our Mission

- To understand, diagnose, and promote development of treatment for rare genetic disorders through collaboration with physicians/institutions and enrollment of patients

Gene Discovery Core (GDC)

- Research study within The Manton Center focused on creating a database and repository to learn more about rare and undiagnosed genetic disorders



Process

1. Referral to Boston Children's Hospital
2. Enrollment in the Manton Center for Orphan Disease Research
3. Biospecimen collection (blood or saliva, local or from all over the world)
4. Sequencing (exome, genome, long-range mapping)
5. Analysis (trio, suspected disease model)
6. Confirmation (protein model, animal model)
7. Confirmation (CLIA, result return)

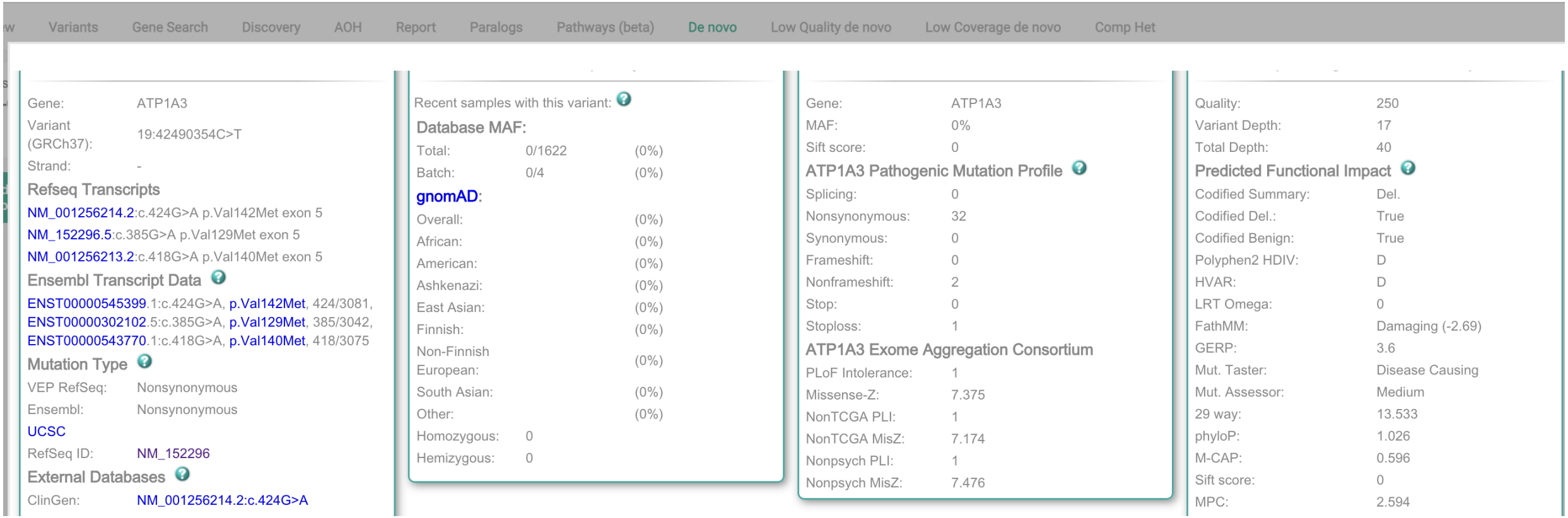
Enabling gene discovery

- 6700 participants
- 23 Departments
- 50 US States
- 53 Countries
- 6 Continents

Referred to Manton Center

- Presented with command hallucinations and behavioral
- He was described as having mood swings, lack of emotional control, and severe separation anxiety.
- He had severe self-injurious behaviors.
- Sudden onset behavioral regression:
  - aggression towards his sister and dog worsened and became highly unpredictable, to the extent that he could not be left alone with them or any other children.
- He was found hitting himself in the head and said he was trying to get two small boys “in my head” to shut up. These boys often said “bad things,” told him to hurt himself and others, and he felt he needed to obey them. He had delusional conviction that the boys in his head were real.

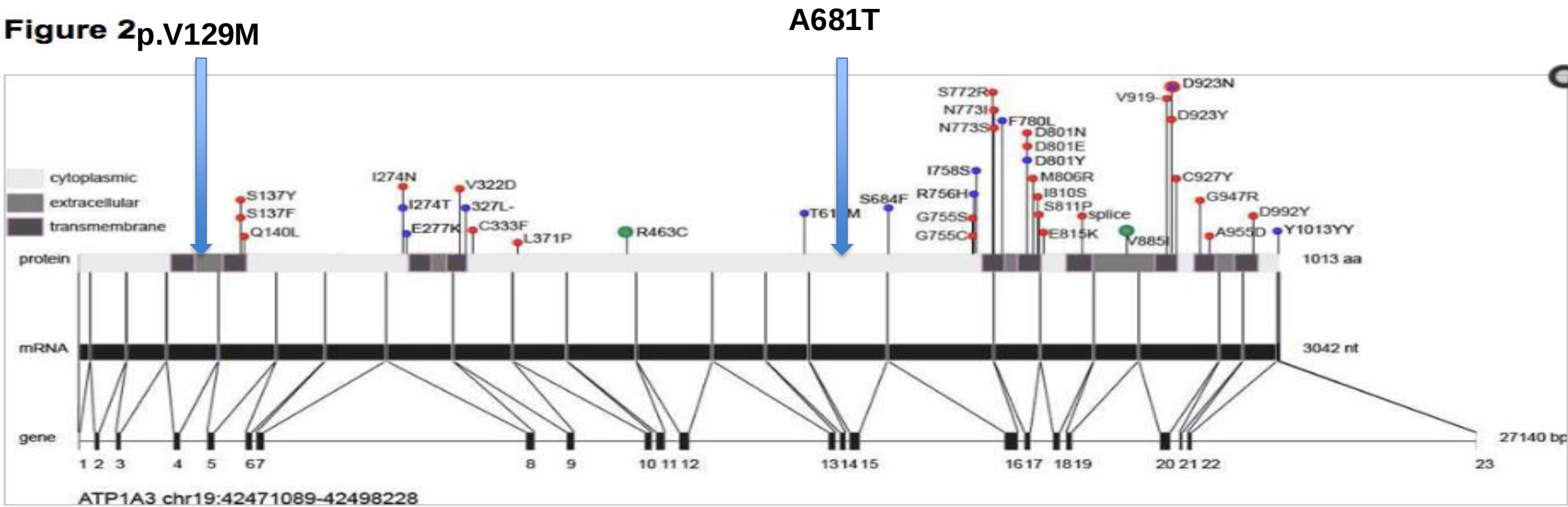
Novel *de novo* variant in *ATP1A3*



ATP1A3 is an interesting gene

PMC full text: Lancet Neurol. Author manuscript; available in PMC 2015 May 1.
Published in final edited form as:
Lancet Neurol. 2014 May; 13(5): 503–514.
doi: 10.1016/S1474-4422(14)70011-0

Figure 2



Schematic depicting the location of AHC-causing (red dots) and RDP-causing (blue dots) mutations in *ATP1A3*, mRNA and protein. The one mutation shared between disease phenotypes is located at D923N (blue dot with a red dot inside). Two rare polymorphisms identified in the general population are indicated by the green dots. Amino acid modifications are provided to the right of the dots.

Unbiased analysis of differentially expressed genes returned SCZ

DAVID: Functional Gene Classification Tool:

Category	Term	RT	Genes	Count	%	P-Value
GAD_DISEASE	Diabetes mellitus type II|Diabetes Mellitus, Type 2	RT		4	2.2	5.9E-3
GAD_DISEASE	Schizophrenia	RT		15	8.4	5.5E-3
GAD_DISEASE	Type 2 diabetes	RT		9	5.1	8.4E-3
GAD_DISEASE	oxidative stress	RT		3	1.7	1.0E-2
GAD_DISEASE	Total IgE	RT		3	1.7	5.0E-3

› Cold Spring Harb Mol Case Stud. 2016 Sep;2(5):a001008. doi: 10.1101/mcs.a001008.

A novel de novo mutation in ATP1A3 and childhood-onset schizophrenia

Niklas Smedemark-Margulies [1], Catherine A **Brownstein** [2], Sigella Vargas [3], Sahil K Tembulkar [3], Meghan C Towne [4], Jiahai Shi [5], Elisa Gonzalez-Cuevas [4], Kevin X Liu [3], Kaya Bilguvar [6], Robin Timothy W Yu [2], Alan H

Affiliations + expand

PMID: 27626066 PMC

Free PMC article

Case Reports › Mol Genet Metab Rep. 2018 Jun 15;16:23-29.

doi: 10.1016/j.ymgmr.2018.06.001. eCollection 2018 Sep.

***De novo ATP1A3* and compound heterozygous *NLRP3* mutations in a child with autism spectrum disorder, episodic fatigue and somnolence, and muckle-wells**

ne A **Brownstein** [2 3 4], Sahil K Tembulkar [3 5], Kelsey Graber [3 5], n J Kleiman [4 6], Kathleen J Sweadner [4 7], Chrystal Mavros [2], Smedemark-Margulies [8], Kiran Maski [4 9], Edward Yang [4 10], , Jiahai Shi [11], Alan H Beggs [2 4], Eugene D'Angelo [3 4 5], [5], Devon Carroll [5], Fatma Dedeoglu [12], William A Gahl [13], [12 14], Kathryn J Swoboda [4 15], Gerard T Berry [2 4], drich [2 3 4]

RESEARCH ARTICLE | BIOLOGICAL SCIENCES

Early role for a Na^+,K^+-ATPase (*ATP1A3*) in brain development

Richard S. Smith, Marta Florio, Shyam K. Akula, +16, and Christopher A. Walsh Authors Info & Affiliations

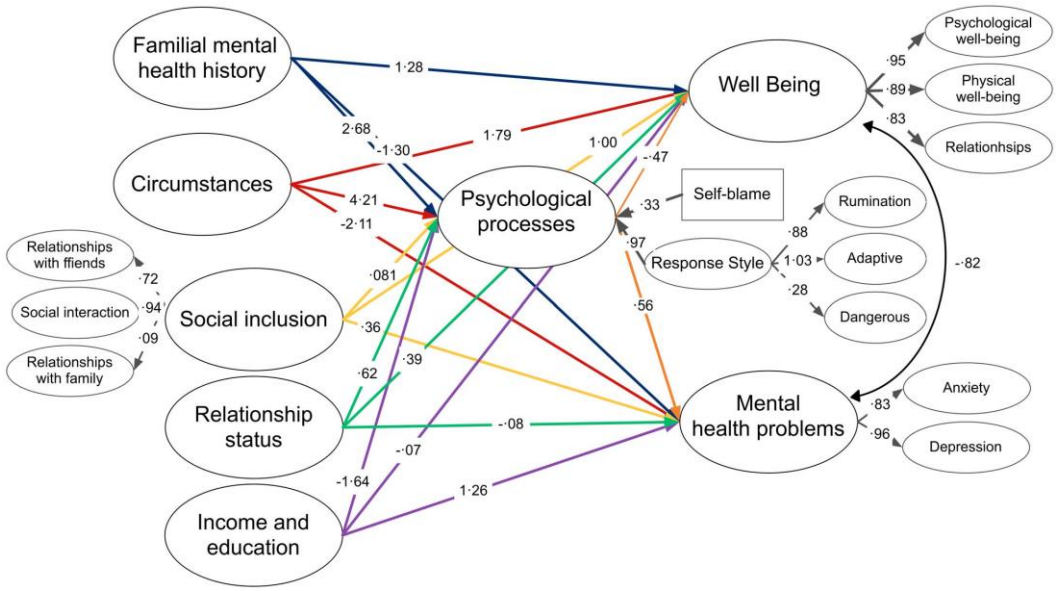
Contributed by Christopher A. Walsh, April 5, 2021 (sent for review December 1, 2020; reviewed by Simon Hippenmeyer and Denis Jabaudon)

June 14, 2021 | 118 (25) e2023333118 https://doi.org/10.1073/pnas.2023333118

Conceptualizing psychosis in youth

Learning Objective 1. To better recognize the signs and symptoms of psychosis in youth and how those change over development

Mental health is multifactorial

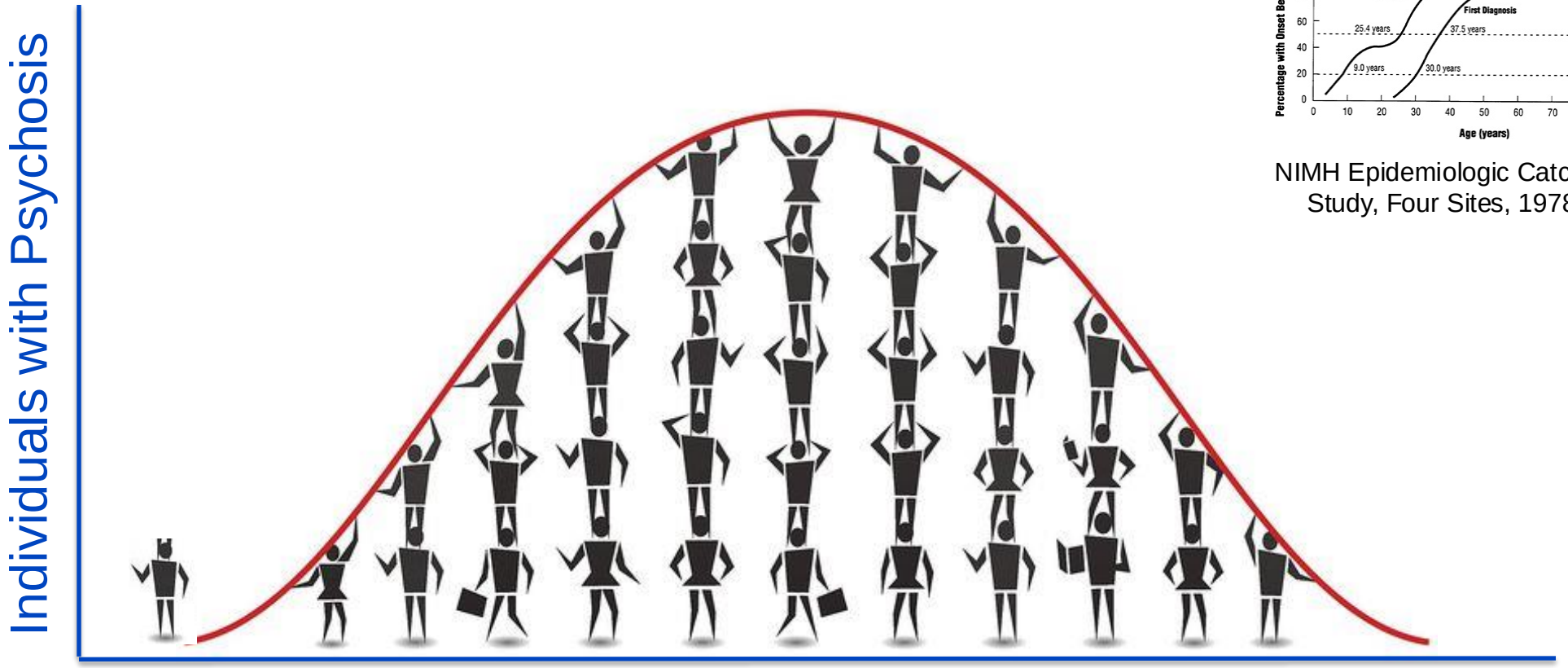


- Mental illnesses clearly include genetic, environmental, psychological and social causes.
- Typically, more than one of these factors is needed to cause illness

Psychological Processes Mediate the Impact of Familial Risk, Social Circumstances and Life Events on Mental Health

Peter Kinderman[1]*, Matthias Schwannauer[2], Eleanor Pontin[1], Sara Tai[3]

Extreme phenotypes



NIMH Epidemiologic Catchment Area Study, Four Sites, 1978 to 1983

Psychosis in children & adolescents

- Psychotic-like symptoms: transient unusual thoughts or beliefs
- Clinical high risk: some signs and symptoms of psychosis w/o dx
- Early onset psychosis (EOP): psychosis dx <19 years (very early onset <13 years)
- Childhood Onset Schizophrenia (COS): schizophrenia dx <13 (adolescent <19 years)

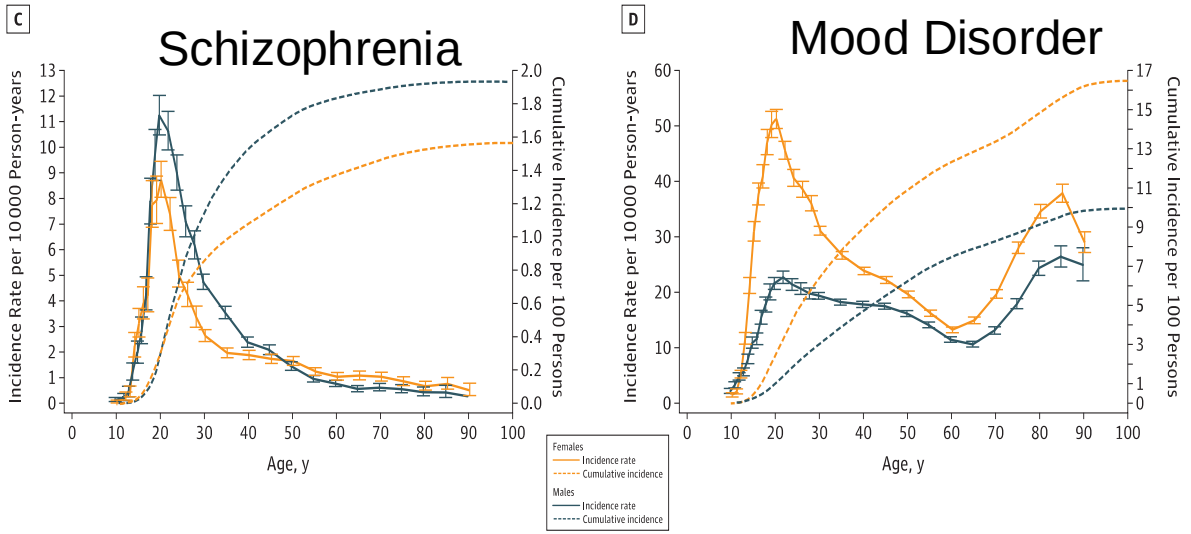
EOP Prevalence

- Lifetime prevalence of psychosis varies from ~2-3.5%
- 12.3% before 18 years
- 3% before 14 years

Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses

Berta Moreno-Küstner[1,2]*, Carlos Martín[3], Loly Pastor[1]

PLOS ONE | https://doi.org/10.1371/journal.pone.0195687 April 12, 2018



Adolescent-onset psychosis: prevalence, needs and service provision

LEONIE BOEING, VAL MURRAY, ANTHONY PELOSI, ROBERT McCABE, DOUGLAS BLACKWOOD and ROBERT WRATE

BRITISH JOURNAL OF PSYCHIATRY (2007), 190, 18–26. doi: 10.1192/bjp.190.1.18

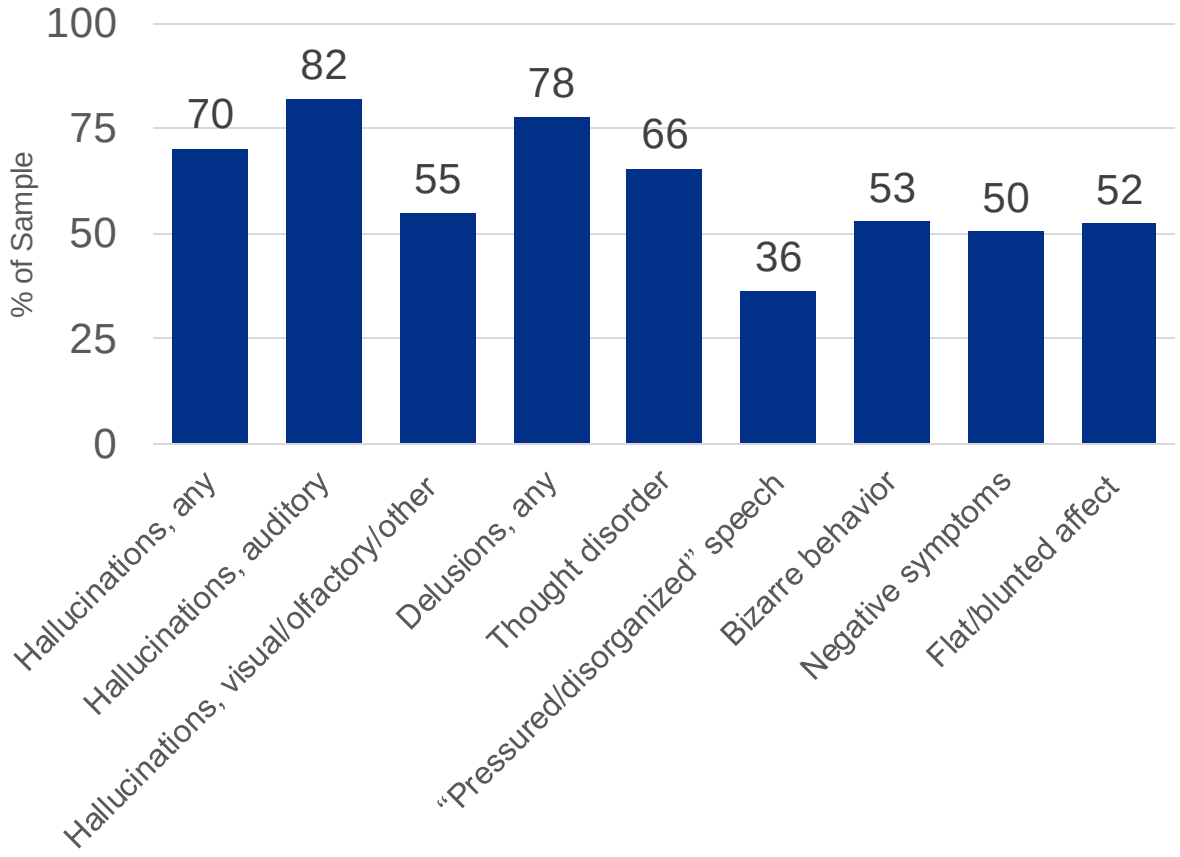
Original Investigation

A Comprehensive Nationwide Study of the Incidence Rate and Lifetime Risk for Treated Mental Disorders

Carsten Bøcker Pedersen, DrMedSc; Ole Mors, PhD; Aksel Bertelsen, MD; Berit Lindum Waltoft, MSc; Esben Agerbo, DrMedSc; John J. McGrath, MD; Preben Bo Mortensen, DrMedSc; William W. Eaton, PhD

JAMA Psychiatry May 2014 Volume 71, Number 5

Symptoms observed in EOP



Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review

Marie Stentebjerg-Olesen, MD,[1,2] Anne K. Pagsberg, MD,[1,2] Anders Fink-Jensen, MD,[3,4] Christoph U. Correll MD,[5,6,7,8*] and Pia Jeppesen, MD [1,2*]

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 26, Number 5, 2016

1506 EOP patients at baseline
773 at follow-up (2.2 – 1.7 years)

Another referral to the Manton Center

- The proband is a 12-year old boy who first presented to neurology at age 5 for concerns about school performance
- Evaluation showed delays in gross motor skills and some behavioral concerns but above average intelligence
- At age 7, concern for ADHD and compulsive behaviors (severity decreased over time) and mild social delays.
- At age 9, proband referred for psychotherapy evaluation for paranoia and hallucinations.
- Diagnosed with major depression with psychotic features in the context of NVLD (non-verbal learning disability) and OCD
- Fear of being hunted, voices listening to him, mortality

De novo variant in *TRRAP*

Parent	Allele Frac.	Variant	
1081-02	0/93	G	0/0:0.0,-27.37,-300.0:5:99:93:0
1081-03	0/147	G	0/0:0.0,-43.6,-300.0:4:99:147:0

Variant Information

Gene: TRRAP
Variant (GRCh37): 7:98553863G>A
Strand: +

Refseq Transcripts

NM_001375524.1:c.6032G>A p.Arg2011Gln exon 42
NM_001244580.2:c.6011G>A p.Arg2004Gln exon 41
NM_003496.4:c.5957G>A p.Arg1986Gln exon 40

Ensembl Transcript Data

ENST00000359863.4:c.6011G>A, p.Arg2004Gln, 6011/11580, ENST00000355540.3:c.5957G>A, p.Arg1986Gln, 5957/11493

Mutation Type

VEP RefSeq: Nonsynonymous
Ensembl: Nonsynonymous

UCSC

RefSeq ID: NM_003496

External Databases

ClinGen: NM_001375524.1:c.6032G>A

Allele Frequency Data

Recent samples with this variant:

Database MAF:

Total:	0/1622	(0%)
Batch:	0/4	(0%)

gnomAD:

Overall:	(0%)
African:	(0%)
American:	(0%)
Ashkenazi:	(0%)
East Asian:	(0%)
Finnish:	(0%)
Non-Finnish European:	(0%)
South Asian:	(0%)
Other:	(0%)
Homozygous:	0
Hemizygous:	0

Mutational Profile

Gene: TRRAP
MAF: 0%
Sift score: 0.016

TRRAP Pathogenic Mutation Profile

Splicing:	0
Nonsynonymous:	0
Synonymous:	0
Frameshift:	0
Nonframeshift:	0
Stop:	0
Stoploss:	0

TRRAP Exome Aggregation Consortium

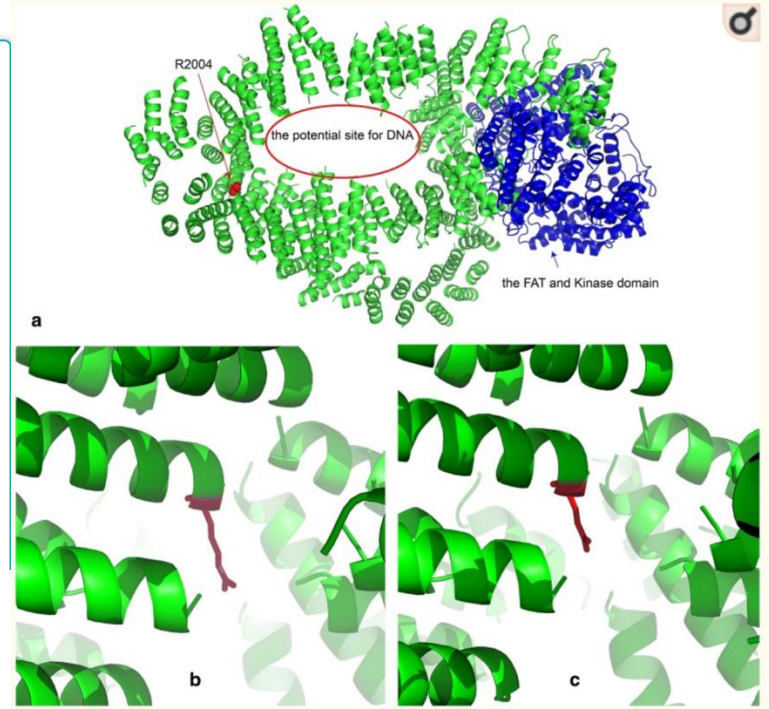
PLoF Intolerance:	1
Missense-Z:	9.823
NonTCGA PLI:	1
NonTCGA MisZ:	9.851
Nonpsych PLI:	1
Nonpsych MisZ:	10.165

Sequencing & Functional Impact

Pileup: A.AaAa,.,a,..AAaa.a,,..AAa.a,..A,Aa,.Aa,Aa.aAAaa.aAAaA.a,a.Aa.,aa.AaAa,a,A,,..A.a..aA,,..,a.,AaA.aa,..A..,aaA,.aaAAA
Quality: 250
Variant Depth: 71
Total Depth: 127

Predicted Functional Impact

Codified Summary:	Benign
Codified Del.:	False
Codified Benign:	False
Polyphen2 HDIV:	P;D
HVAR:	B
LRT Omega:	0.04711
FathMM:	Tolerated (3.98)
GERP:	4.14
Mut. Taster:	Disease Causing
Mut. Assessor:	Low



BMC Medical Genetics

BMC Med Genet. 2018; 19: 197. PMCID: PMC6234620
Published online 2018 Nov 13. doi: 10.1186/s12881-018-0711-9 PMID: 30424743

De novo variant of *TRRAP* in a patient with very early onset psychosis in the context of non-verbal learning disability and obsessive-compulsive disorder: a case report

Chrystal F. Mavros,[#1,2] Catherine A. Brownstein,[✉#1,2] Roshni Thyagrajan,[1,2] Casie A. Genetti,[1,2] Sahil Tembulkar,[3] Kelsey Graber,[3] Quinn Murphy,[1,2] Kristin Cabral,[1,2] Grace E. VanNoy,[1,2] Matthew Bainbridge,[4] Jiahai Shi,[5] Pankaj B. Agrawal,[1,2] Alan H. Beggs,[1,2] Eugene D'Angelo,[3] and Joseph Gonzalez-Heydrich[2,3]

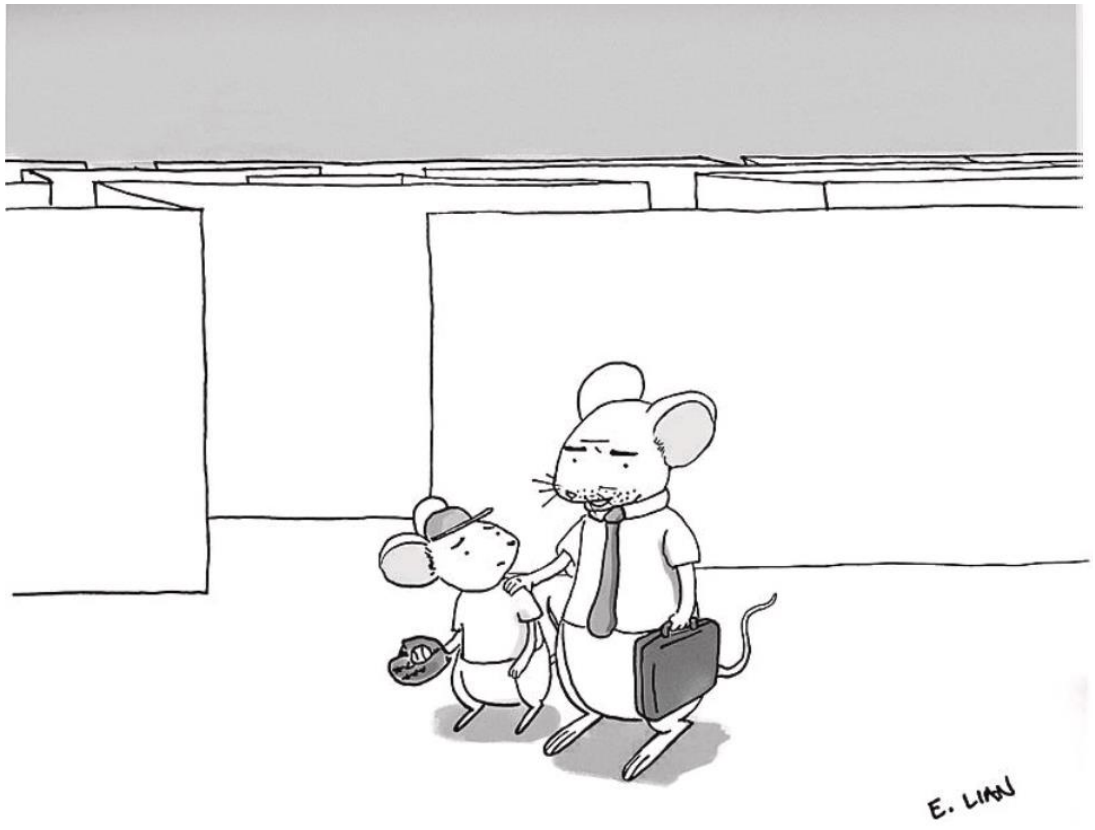
Fig. 1

Modeling of the Arg1986 residue in TRRAP. **a** The yeast homologue of TRRAP, Tra1(5OEJ), was chosen as a template to model TRRAP, as Tra1 is matched at position Arg2004 to Arg1986 in human TRRAP. The variant is removed from the kinase domain (noted in blue), and close to the central cavity. **b** Wild-type Arg1986. **c** Arg1986Gln. This substitution may reduce the side chain volume and decrease the binding between TRRAP and DNA

Mouse model

- Using CRISPR/Cas9 to create a mouse model of the patient

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants



"Sorry, kiddo. Your old man has to work so you can go to the best drug trials in the country."

Infrastructure for gene discovery

Research programs on:

- *ATP1A3*
- *TRRAP*
- *RCL1*
- *ZMYM2*
- *ATP1B1*
- *FOXP1*
- *CMIP*
- 16p13.11 del/dup

Joseph Gonzalez-Heydrich, MD

Journal List › Mol Genet Metab Rep › v.16; 2018 Sep › PMC6005789

ELSEVIER Guide for Authors | About | Explore this Journal — MGM Reports

Mol Genet Metab Rep. 2018 Sep; 16: 23–29. PMCID: PMC6005789
Published online 2018 Jun 15. doi: 10.1016/j.ymgmr.2018.06.001 PMID: 29922587

De novo ATP1A3 and compound heterozygous *NLRP3* mutations in a child with autism spectrum disorder, episodic fatigue and somnolence, and muckle-wells syndrome

Alcy Torres, Catherine A. Brownstein, Sahil K. Tembulkar, Kelsey Graber, Casie Genetti, Robin J. Kleiman, Kathleen J. Sweadner, Chrystal Mavros, Kevin X. Liu, Niklas Smedemark-Margulies, Kiran Maski, Edward Yang, Pankaj B. Agrawal, Jiahai Shi, Alan H. Beggs, Eugene D'Angelo, Sarah Hope Lincoln, Devon Carroll, Fatma Dedeoglu, William A. Gahl, Catherine M. Biggs, Kathryn J. Swoboda, Gerard T. Berry, and Joseph Gonzalez-Heydrich

Author information › Article notes › Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

Abstract Go to:

Complex phenotypes may represent novel syndromes that are the composite interaction of several genetic and environmental factors. We describe an 9-year old male with high functioning autism spectrum disorder and Muckle-Wells syndrome who at age 5 years of age manifested perseverations that interfered with his functioning at home and at school. After age 6, he developed intermittent episodes of fatigue and

COLD SPRING HARBOR Molecular Case Studies

HOME | ABOUT | ARCHIVE | SUBMIT | AUTHOR INFO | ADVERTISE | ALERTS / RSS

A novel de novo mutation in *ATP1A3* and childhood-onset schizophrenia

Niklas Smedemark-Margulies, Catherine A. Brownstein, Sigella Vargas, Sahil K. Tembulkar, Meghan C. Towne, Jiahai Shi, Elisa Gonzalez-Cuevas, Kevin X. Liu, Kaya Bilguvar, Robin J. Kleiman, Min-Joon Han, Alcy Torres, Gerard T. Berry, Timothy W. Yu, Alan H. Beggs, Pankaj B. Agrawal and Joseph Gonzalez-Heydrich

BMC Part of Springer Nature

BMC Medical Genetics

Home About Articles Submission Guidelines

Case report | Open Access | Published: 13 November 2018

De novo variant of *TRRAP* in a patient with very early onset psychosis in the context of non-verbal learning

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics

Overlapping 16p13.11 Deletion and Gain of Variations Associated With Childhood Onset Psychosis Include Genes With Mechanistic Implications for Autism Associated Pathways: Two Case Reports

Catherine A. Brownstein, Robin J. Kleiman, Elizabeth C. Engle, Meghan C. Towne, Eugene J. D'Angelo, Timothy W. Yu, Alan H. Jonathan Picker, Jason M. Fogler, Devon Carroll, Rachel C. O Robert R. Wolff, Yiping Shen, Va Lip, Kaya Bilguvar, April Kim, Kyle O'Donnell, and Joseph Gonzalez-Heydrich

Article | Open Access | Published: 17 February 2021

RCL1 copy number variants are associated with a range of neuropsychiatric phenotypes

Catherine A. Brownstein, Richard S. Smith, [...] Joseph Gonzalez-Heydrich

Molecular Psychiatry (2021) | Cite this article

2 Altmetric | Metrics

Abstract

Mendelian and early-onset severe psychiatric phenotypes often involve genetic variants having a large effect, offering opportunities for genetic discoveries and early therapeutic interventions. Here, the index case is an 18-year-old boy, who at 14 years of age had a decline in cognitive functioning over the course of a year and subsequently presented with

EPICenter: Early Psychosis Investigation Center

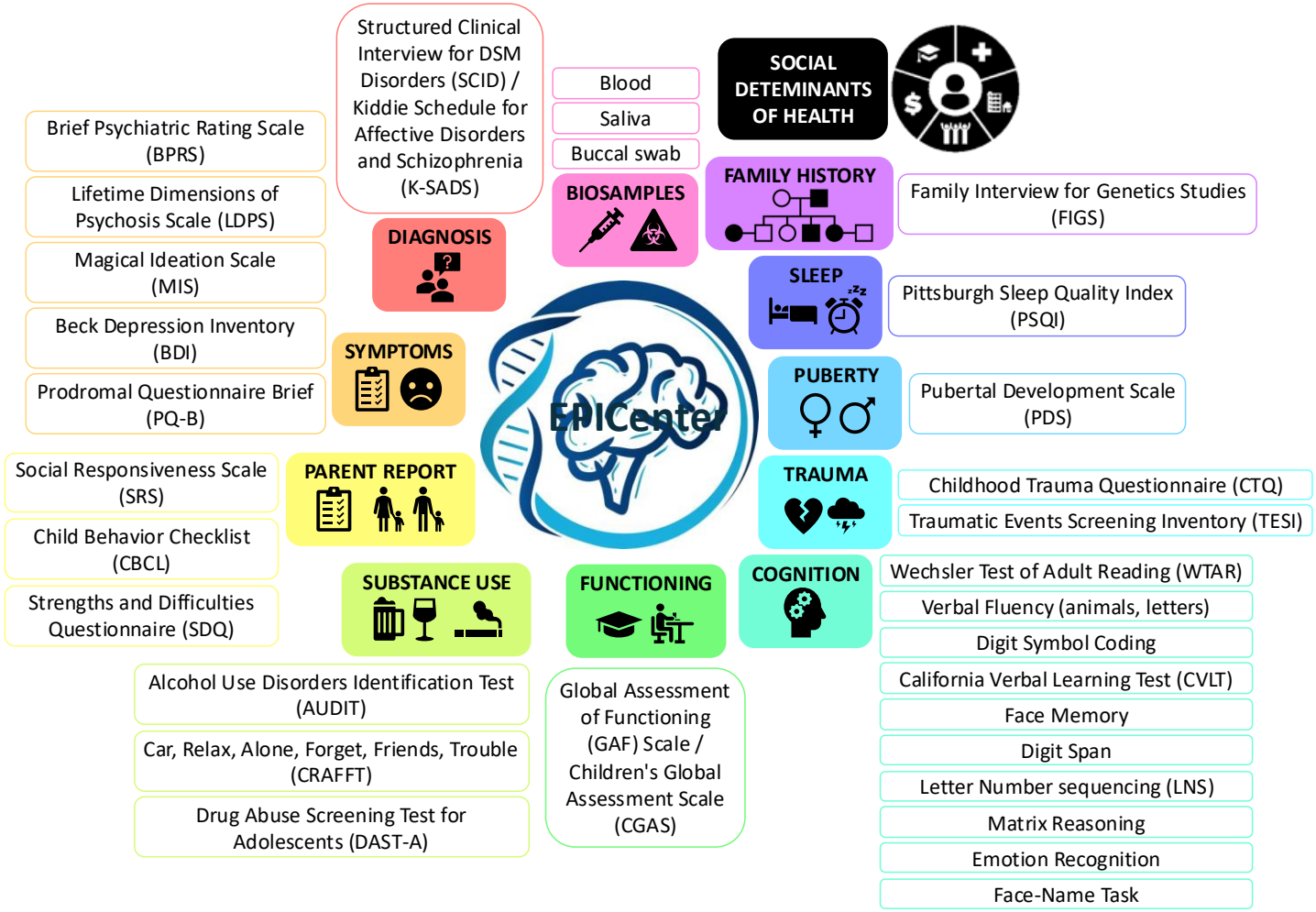
Integrates clinical, translational and basic research for children and adolescents with EOP

A well phenotyped EOP/family cohort with biosamples

Expansion of the BCH Developmental neuropsychiatry clinic (Gonzalez-Heydrich)

Funded by the Fuss Center

EPICenter Protocol & Current Enrolment



October 29, 2024	
Probands	142
Controls	66
Family Members	234
Total	442

Comparison of our cohort to other cohorts

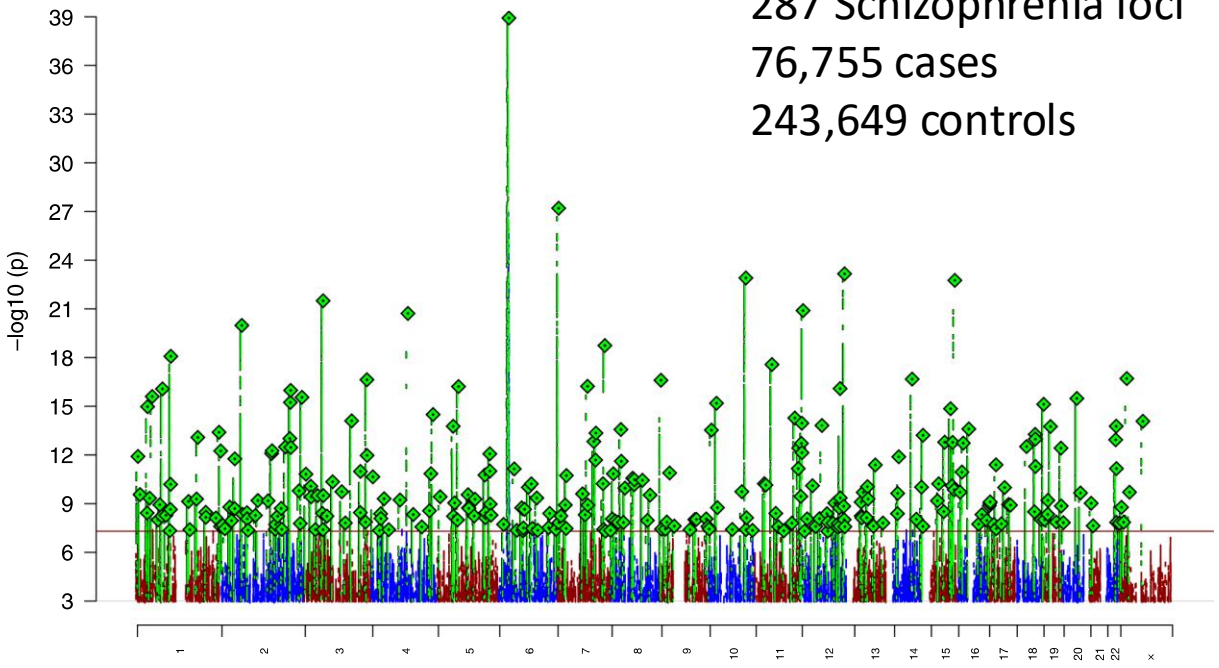
	B	C	D	E	F	G	H	I	J	K	L	M	N
	Chr	Cytoban	Start	Stop	#Probe	Amplificat	Gain	Loss	Deletio	pval	Gene Nan	size	Notes
	normal											0	
	chr10	q21.1	55538186	56676426		Duplication (4 copies)		0	0		PCDH15	1138.24	
	chr22	q11.22 - q11	23301480	24995964			0.430054		0		RTDR1, GNA	1694.484	
	chr7	q31.33	126457718	126536646				-0.888408	0		GRM8	78.928	
	chr8	q23.3	112317029	112392656			0.761195		0			75.627	
	normal											0	
	chr16	p13.11	14897761	16276117			Gain (3 copies)					1378.356	
	chX	q28	152955334	152961664			Gain (3 copies)					6.33	
	chr7	q34	141921825	142017021					Deletion		PRSS58, MO	95.196	
	chr6	q12	63543898	64025806				-0.816626	0		LGSN	481.908	
	chr19	q13.42 - q13	56238724	56515068			0.539167		0		NLRP9,RFPL4	276.344	
	chr6	p22.2	25419199	26457539			Gain					1038.34	
	chr20	q13.2	53396513	53490076				-0.845608				93.563	
	chr4	q28.3	134943258	135195162				-0.685215			PABPC4L	251.904	
	chr6	q24.2	144328804	144329441			0.855806				PLAGL1,HYM	0.637	
	chr9	q33.3	129373899	129379296			0.648742				LMX1B	5.397	
	chr10	q26.3	135270324	135377390			0.499949				LOC619207,	107.066	
	chr16	q24.1	86600972	86602522			0.550839				FOXC2	1.55	
	chr14	q31.1	79943567	80411918				-0.672448	0		NRXN3	468.351	
	chr7	p21.3	8201938	8520075			Gain				NXPH1	318.137	
	chr8	q24	125977314	126,458,921		Duplication					ZNF572, SQL	481.607	
	chr3	p26.3	270300	283433				-0.900347			CHL1	13.133	
	chr9	q33.3	129373899	129379296			0.744815				LMX1B	5.397	
	chr17	q25.3	79792272	79953020			0.657531				DYSFIP1, P4H	160.748	
	chrX	p11.1	58543266	58544060			1.173287					0.794	
	chr3	p14.2	60217711	60395355				-0.786369			FHIT	177.644	
	chrX	p22.33	3313959	3912069			0.541216				PRKX,LOC389	598.11	
	chrX	p22.2	15950430	16439709			0.489037				GRPR	489.279	

Sebastien Jacquemont, MD

Genetic influences on early onset psychosis

Learning Objective 2. To become familiar with current genetic findings in early onset psychosis

Common Genetic Variants Influence EOP Risk



287 Schizophrenia loci
76,755 cases
243,649 controls

Mapping genomic loci implicates genes and synaptic biology in schizophrenia

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

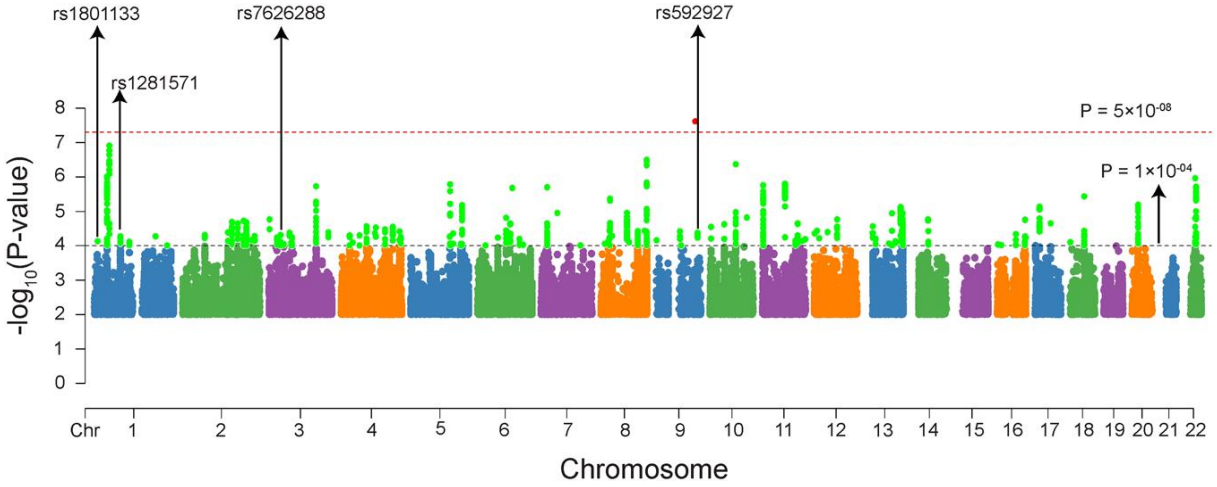
| Nature | Vol 604 | 21 April 2022

Genome wide association study identifies four loci for early onset schizophrenia

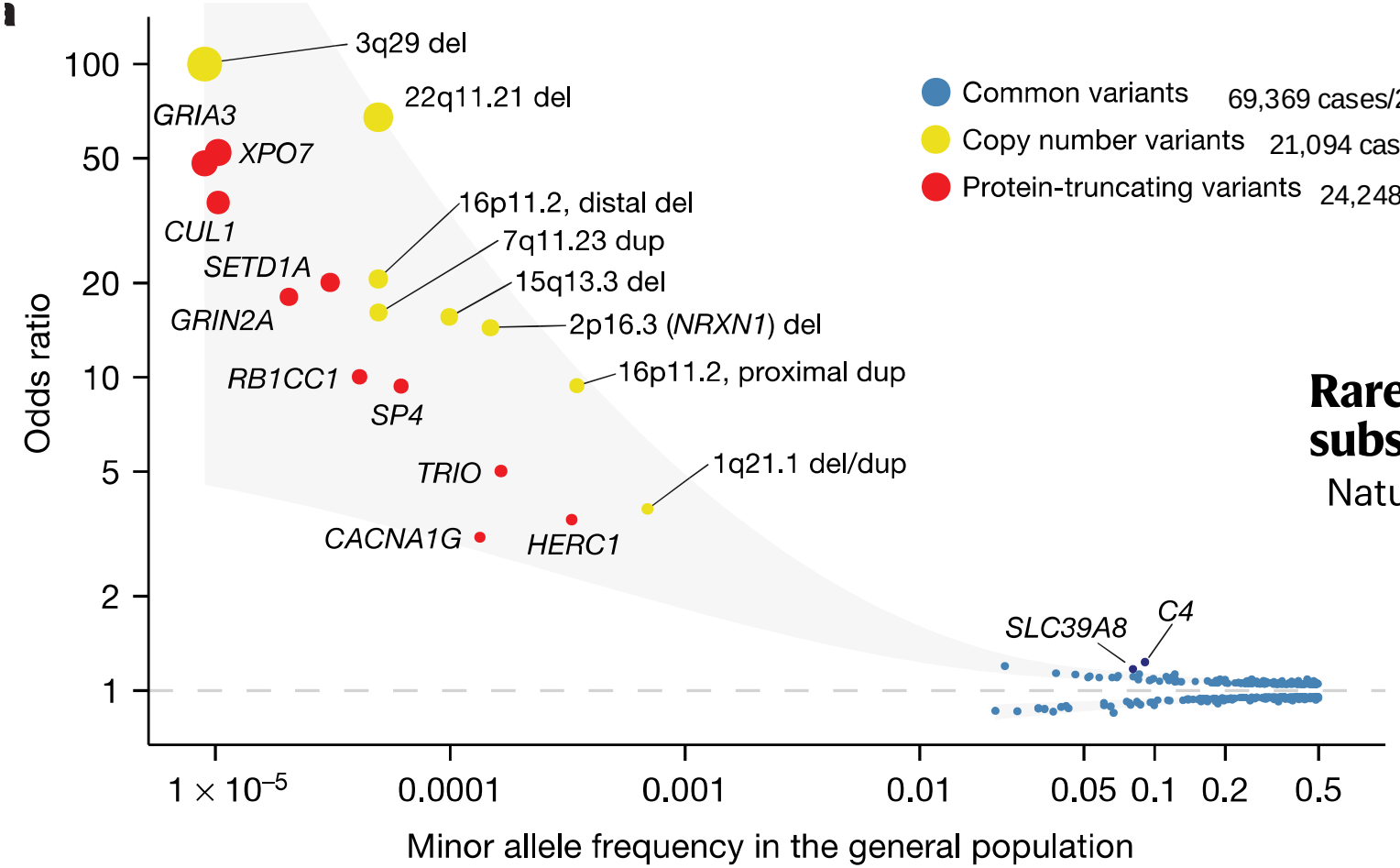
Suqin Guo[1,2], Jiewei Liu[3], Wenqiang Li[1,2], Yongfeng Yang[1,2], Luxian Lv[1,2], Xiao Xiao[3], Ming Li[3], Fanglin Guan[4] and Xiong-Jian Luo[3,5,6]

Guo et al. *Translational Psychiatry* (2021)11:248

4 EOP loci
1,256 cases
2,661 controls



Variants across the allelic spectrum influence schizophrenia risk



Rare coding variants in ten genes confer substantial risk for schizophrenia

Nature | www.nature.com |

https://schema.broadinstitute.org/results

Searching for rare genetic influences on psychosis risk

Rare structural variants in schizophrenia: one disorder, multiple mutations; one mutation, multiple disorders

Jonathan Sebat[1], Deborah L. Levy[2] and Shane E. McCarthy[1]

Trends in Genetics Vol.25 No.12

Phenotypic and genetic complexity of psychosis

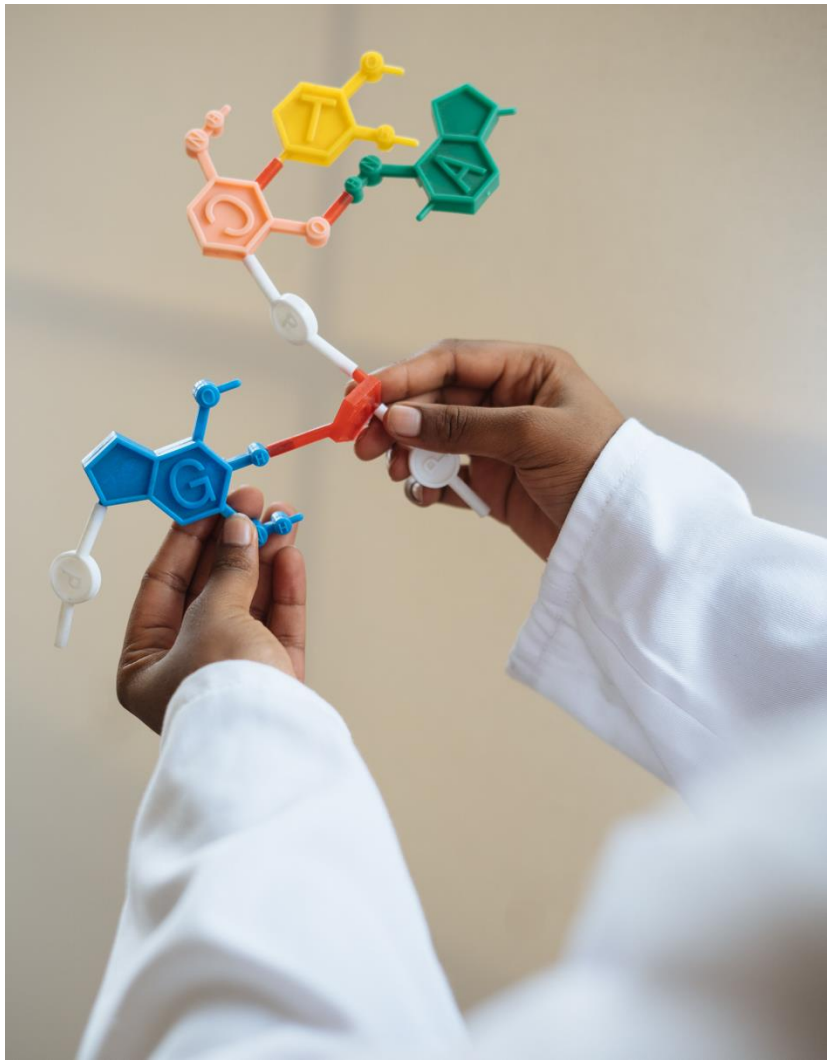
NICK CRADDOCK, MICHAEL C. O'DONOVAN and MICHAEL J. OWEN

BRITISH JOURNAL OF PSYCHIATRY (2007), 190, 200–203. doi: 10.1192/bjp.bp.106.033761

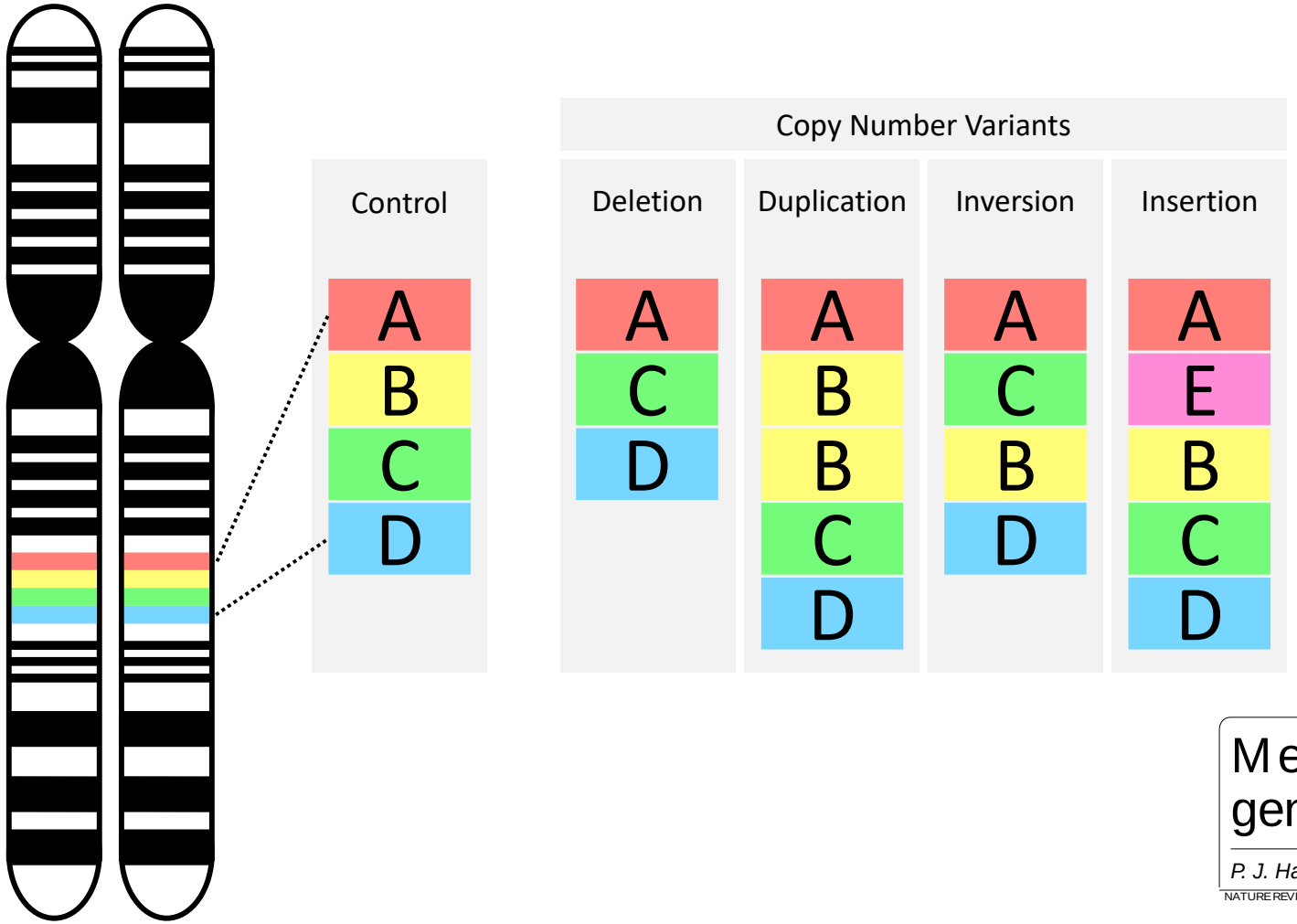
Genetic Theorizing and Schizophrenia*

By IRVING I. GOTTESMAN and JAMES SHIELDS

Brit. J. Psychiat. (1973), 122, 15–30



Copy Number Variant (CNV)



Structural variation involving unbalanced rearrangements of DNA segments (≥50 Kb) which can alter the diploid status

Mechanisms of change in gene copy number

P. J. Hastings , James R. Lupski* ‡§, Susan M. Rosenberg* ||¶# and Grzegorz Ira**

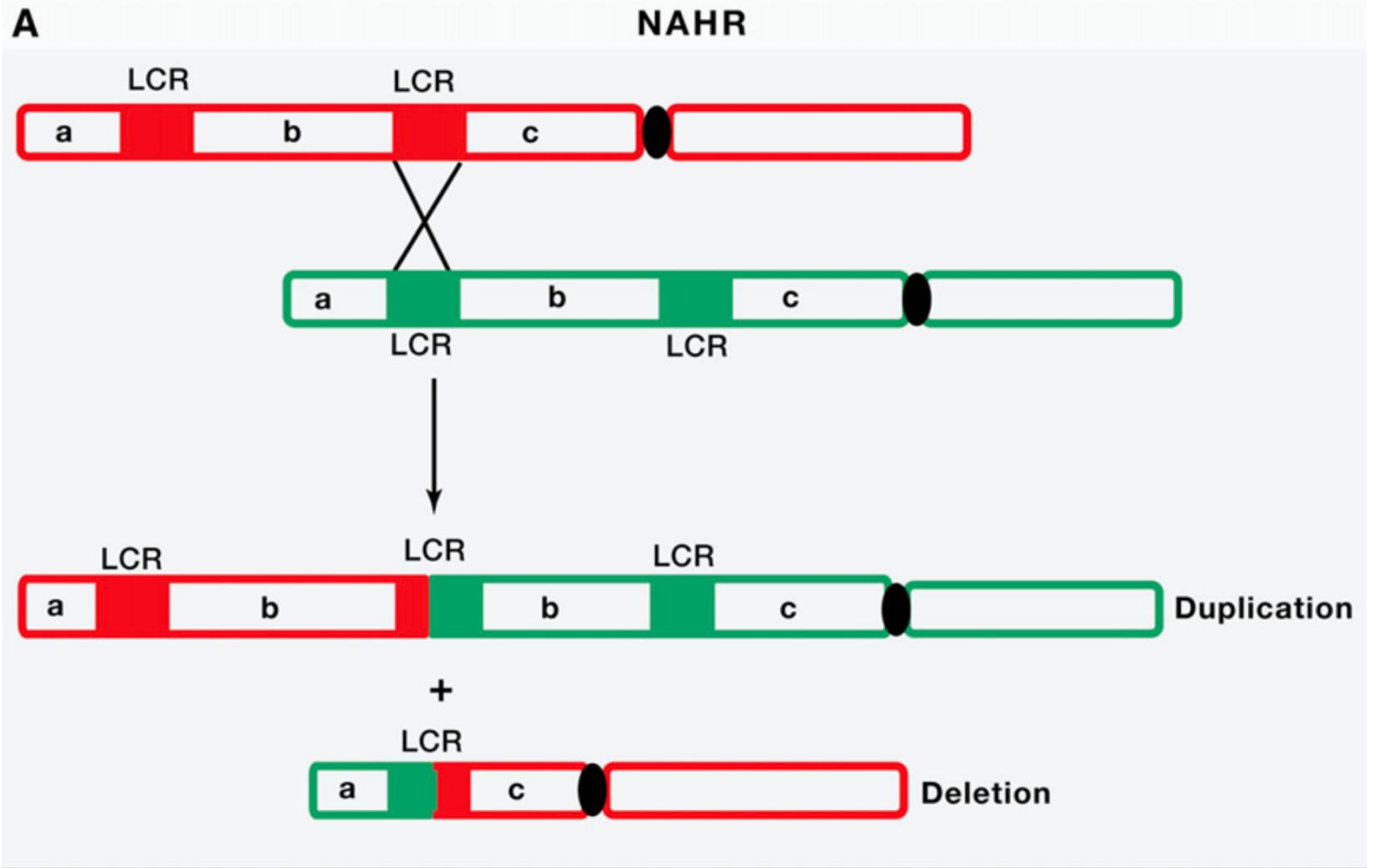
Recurrent CNVs

CNVs: Harbingers of a Rare Variant Revolution in Psychiatric Genetics

Dheeraj Malhotra[1,2] and Jonathan Sebat[1,2,3,4,*]

Cell *148*, March 16, 2012 ©2012 Elsevier Inc. 1223

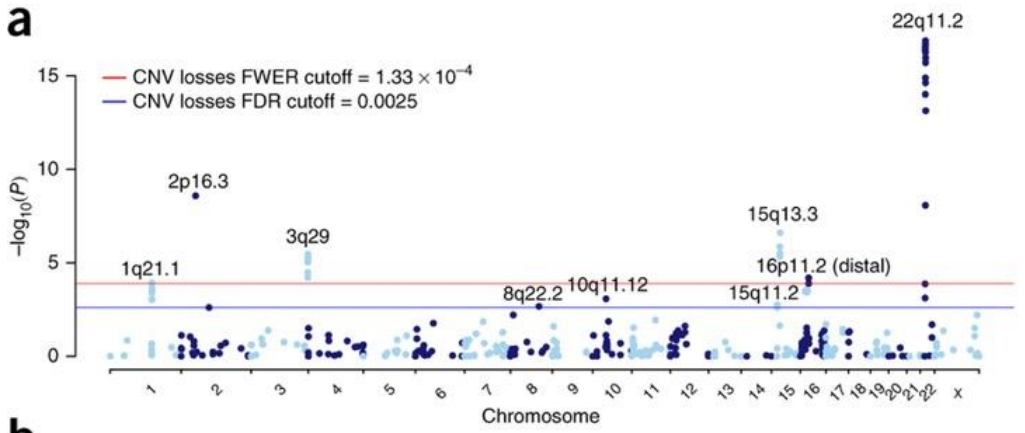
Non-allelic homologous recombination (NAHR) is typically mediated by low-copy repeats (LCRs) with recombination hotspots, gene conversion and apparent minimal efficient processing segments. NAHR that share a common size, show clustering of breakpoints, and recur in multiple individuals



Recurrent CNVs influence adult idiopathic schizophrenia risk

Genome-wide significant evidence was obtained for 1q21.1, 2p16.3 (NRXN1), 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2 and 22q11.2

Deletions



21,094 SCZ & 20,227 controls

Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects

Marshall on behalf of the CNV & Schizophrenia PGC

NATURE GENETICS VOLUME 49 | NUMBER 1 | JANUARY 2017

Recurrent CNVs in childhood schizophrenia

ORIGINAL ARTICLE

High rate of disease-related copy number variations in childhood onset schizophrenia

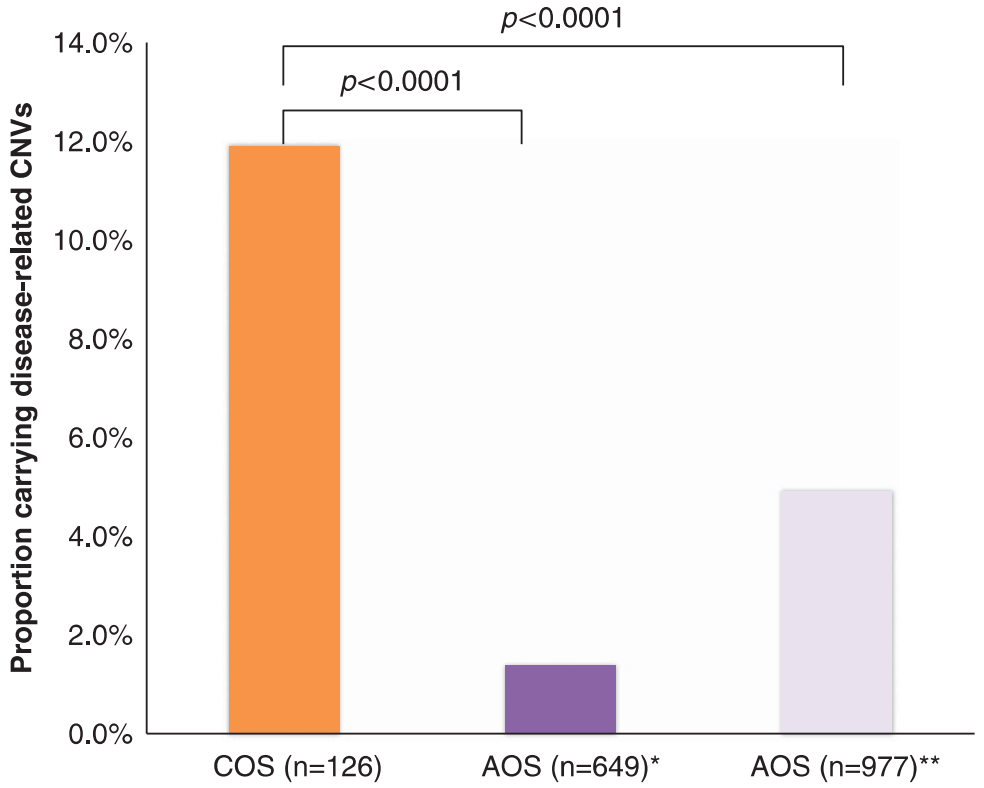
K Ahn[1], N Gotay[1], TM Andersen[1], AA Anvari[1], P Gochman[1], Y Lee[1], S Sanders[2], S Guha[3], A Darvasi[4], JT Glessner[5], H Hakonarson[5], T Lencz[3], MW State[2], YY Shugart[6] and JL Rapoport[1]

Molecular Psychiatry (2014) 19, 568–572

Rare Structural Variants Disrupt Multiple Genes in Neurodevelopmental Pathways in Schizophrenia

Tom Walsh,[1]* Jon M. McClellan,[2]*† Shane E. McCarthy,[3]* Anjené M. Addington,[4]* Sarah B. Pierce,[1] Greg M. Cooper,[5] Alex S. Nord,[5] Mary Kusenda,[3,6] Dheeraj Malhotra,[3] Abhishek Bhandari,[3] Sunday M. Stray,[1] Caitlin F. Rippey,[5] Patricia Roccanova,[3] Vlad Makarov,[3] B. Lakshmi,[3] Robert L. Findling,[7] Linmarie Sikich,[8] Thomas Stromberg,[4] Barry Merriman,[9] Nitin Gogtay,[4] Philip Butler,[4] Kristen Eckstrand,[4] Laila Noory,[4] Peter Gochman,[4] Robert Long,[4] Zugen Chen,[9] Sean Davis,[10] Carl Baker,[5] Evan E. Eichler,[5] Paul S. Meltzer,[10] Stanley F. Nelson,[9] Andrew B. Singleton,[11] Ming K. Lee,[1] Judith L. Rapoport,[4] Mary-Claire King,[1,5] Jonathan Sebat[3]

www.sciencemag.org SCIENCE VOL 320 25 APRIL 2008



* Samples in Guha *et al.* [32]

** Samples in Glessner *et al.* [31]

N=126 childhood onset schizophrenia

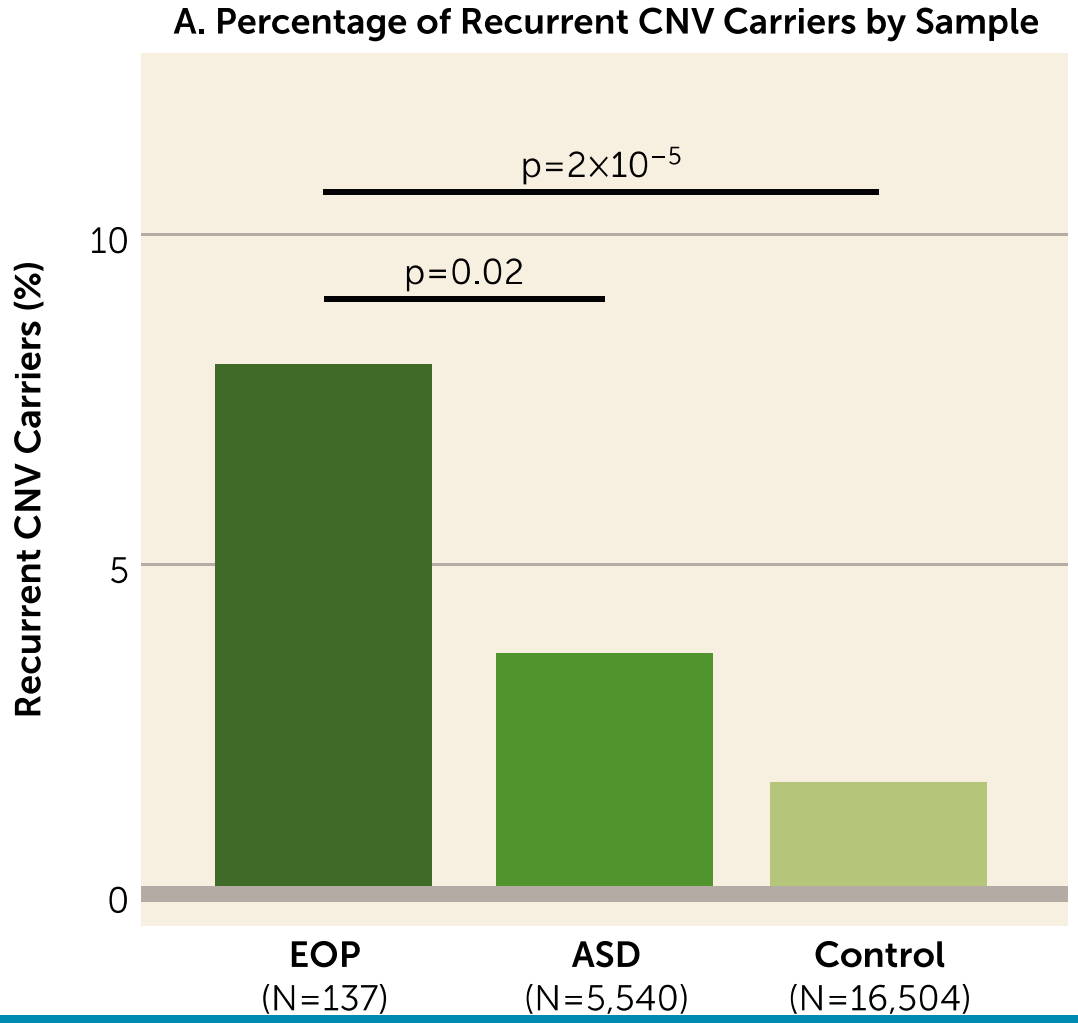
Prevalence of Recurrent CNVs in EOP

Sensitivity	EOP vs. ASD p-value	EOP vs. CT p-value
EOP Full Sample (N=137)	0.02	$3x10^{-5}$
EOP without ASD (N=90)	0.16	$6x10^{-3}$
EOP without ID (N=120)	0.16	$6x10^{-3}$
EOP without schizophrenia (N=98)	0.02	$3x10^{-3}$
EOP < 13 years old (N=99)	0.40	0.02

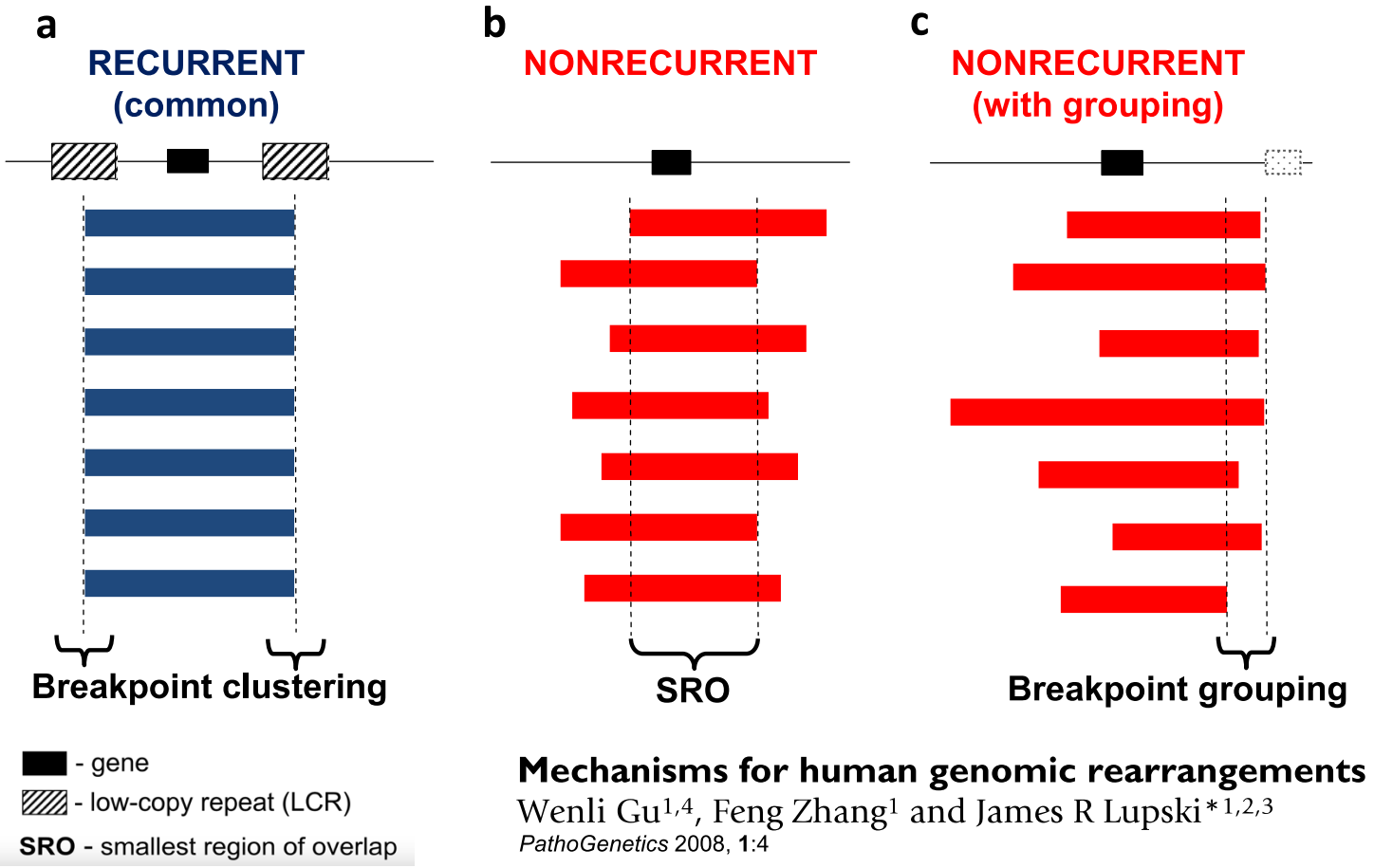
Similar Rates of Deleterious Copy Number Variants in Early-Onset Psychosis and Autism Spectrum Disorder

Catherine A. Brownstein, Ph.D., Elise Douard, M.Sc., Josephine Mollon, Ph.D., Richard Smith, Ph.D., Margaret A. Hojlo, B.A., Ananth Das, B.A., Maria Goldman, B.A., Emily Garvey, B.A., Kristin Cabral, B.S., Jianqiao Li, B.S., Joshua Bowen, B.S., Abhijit S. Rao, B.S.A., Casie Genetti, M.S., C.G.C., Devon Carroll, A.P.R.N.-B.C., Emma E. M. Knowles, Ph.D., Emma Deaso, B.A., Pankaj B. Agrawal, M.D., Alan H. Beggs, Ph.D., Eugene D'Angelo, Ph.D., Laura Almasy, Ph.D., Aaron Alexander-Bloch, M.D., Ph.D., Zohra Saci, Ph.D., Clara A. Moreau, Ph.D., Guillaume Huguet, Ph.D., ~~Anthony Dec~~, M.D., Ph.D., Sébastien Jacquemont, M.D., David C. Glahn, Ph.D., Joseph Gonzalez-Heydrich, M.D.

Am J Psychiatry 179:6, ■■ 2022



Diversity in genomic rearrangements



Mechanisms for human genomic rearrangements
Wenli Gu[1,4], Feng Zhang[1] and James R Lupski*[1,2,3]
PathoGenetics 2008, **1**:4

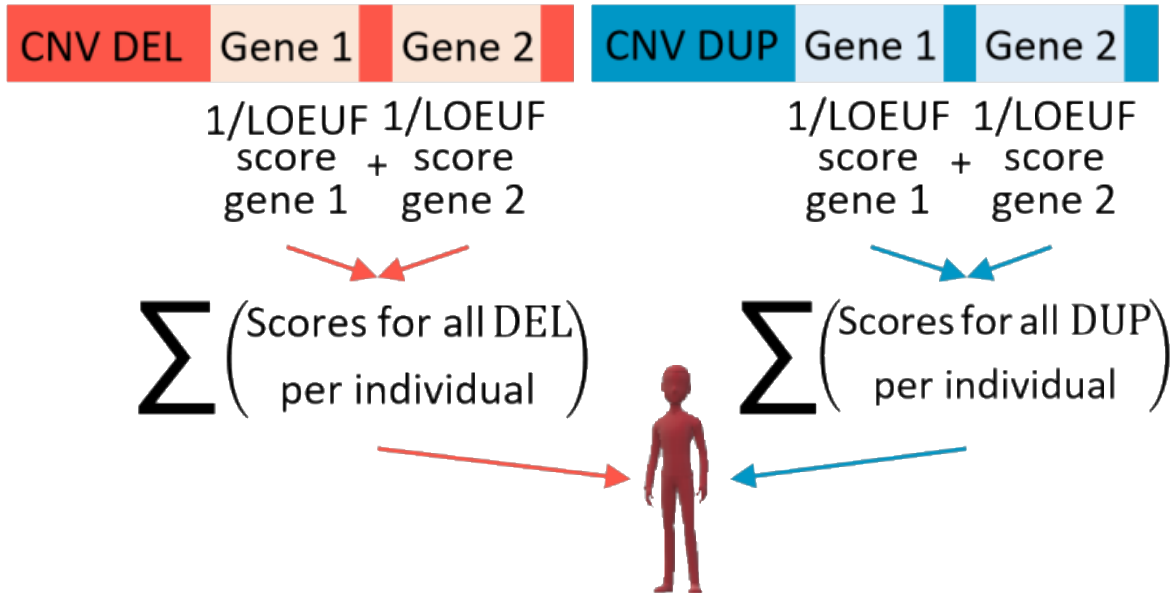
~90% of CNVs identified in the clinic are non-recurrent and are therefore too rare (i.e., insufficient copies) for association studies of individual CNVs to be practical

A large data resource of genomic copy number variation across neurodevelopmental disorders

Mehdi Zarrei[1,2], Christie L. Burton[3], Worrawat Engchuan[1,2], Edwin J. Young[4], Edward J. Higginbotham[1,2,5], Jeffrey R. MacDonald[1], Brett Trost[1,2], Ada J. S. Chan[1,2,5], Susan Walker[1], Sylvia Lamoureux[1], Tracy Heung[6], Bahareh A. Mojarad[2], Barbara Kellam[1], Tara Paton[1], Muhammad Faheem[1,2], Karin Miron[1,2], Chao Lu[1], Ting Wang[1], Kozue Samler[1], Xiaolin Wang[1], Gregory Costain[7,8], Ny Hoang[2,5,9], Giovanna Pellecchia[1], John Wei[1], Rohan V. Patel[1], Bhooma Thiruvahindrapuram[1], Maian Roifman[7,10,11], Daniele Merico[1,12], Tara Goodale[3], Irene Drmic[13], Marsha Speevak[14], Jennifer L. Howe[1], Ryan K. C. Yuen[1,2], Janet A. Buchanan[1], Jacob A. S. Vorstman[15,16], Christian R. Marshall[1,4,17], Richard F. Wintle[1], David R. Rosenberg[18,19], Gregory L. Hanna[20], Marc Woodbury-Smith[1,21], Cheryl Cytrynbaum[2,5,7,22], Lonnie Zwaigenbaum[23], Mayada Elsabbagh[24], Janine Flanagan[11], Bridget A. Fernandez[25], Melissa T. Carter[26], Peter Szatmari[15,27,28], Wendy Roberts[16], Jason Lerch[29,30], Xudong Liu[31], Rob Nicolson[32,33], Stelios Georgiades[34], Rosanna Weksberg[2,7,5], Paul D. Arnold[2,35,36], Anne S. Bassett[6,15,37], Jennifer Crosbie[3,15], Russell Schachar[3,15,38], Dimitri J. Stavropoulos[4], Evdokia Anagnostou[39] and Stephen W. Scherer[1,2,5,40*]

npj Genomic Medicine (2019) 26

Genome-Wide CNV Risk Score (CRS)



The mutational constraint spectrum quantified from variation in 141,456 humans

434 | Nature | Vol 581 | 28 May 2020

Measuring and Estimating the Effect Sizes of Copy Number Variants on General Intelligence in Community-Based Samples

Guillaume Huguet, PhD; Catherine Schramm, PhD; Elise Douard, MSc; Lai Jiang, PhD; Aurélie Labbe, PhD; Frédérique Tihy, PhD; Géraldine Mathonnet, PhD; Sonia Nizard, MD; Emmanuelle Lemyre, MD; Alexandre Mathieu, MSc; Jean-Baptiste Poline, PhD; Eva Loth, PhD; Roberto Toro, PhD; Gunter Schumann, PhD; Patricia Conrod, PhD; Zdenka Pausova, MD; Celia Greenwood, PhD; Tomas Paus, MD, PhD; Thomas Bourgeron, PhD; Sébastien Jacquemont, MD; for the IMAGEN Consortium

JAMA Psychiatry May 2018 Volume 75, Number 5

Effect Sizes of Deletions and Duplications on Autism Risk Across the Genome

Elise Douard, M.Sc., Abderrahim Zeribi, M.D., Catherine Schramm, Ph.D., Petra Tamer, B.Sc., Mor Absa Loum, Ph.D., Sabrina Nowak, B.Sc., Zohra Saci, Ph.D., Marie-Pier Lord, M.Sc., Borja Rodríguez-Herreros, Ph.D., Martineau Jean-Louis, M.Sc., Clara Moreau, M.Sc., Eva Loth, Ph.D., Gunter Schumann, Ph.D., Zdenka Pausova, M.D., Mayada Elsabbagh, Ph.D., Laura Almasy, Ph.D., David C. Glahn, Ph.D., Thomas Bourgeron, Ph.D., Aurélie Labbe, Ph.D., Tomas Paus, M.D., Ph.D., Laurent Mottron, M.D., Ph.D., Celia M.T. Greenwood, Ph.D., Guillaume Huguet, Ph.D., Sébastien Jacquemont, M.D.

Am J Psychiatry 178:1, January 2021

Genome-wide analysis of gene dosage in 24,092 individuals estimates that 10,000 genes modulate cognitive ability

Guillaume Huguet[1,2] · Catherine Schramm[1,2,3] · Elise Douard[1,2] · Petra Tamer[1,2] · Antoine Main[2,4] · Pauline Monin[2,5] · Jade England[1,2] · Khadije Jizi[1,2] · Thomas Renne[2,6] · Myriam Poirier[1,2] · Sabrina Nowak[1,2] · Charles-Olivier Martin[1,2] · Nadine Younis[1,2] · Inga Sophia Knoth[1,2] · Martineau Jean-Louis[1,2] · Zohra Saci[1,2] · Maude Auger[1,2] · Frédérique Tihy[1,2] · Géraldine Mathonnet[1,2] · Catalina Maftei[1,2] · France Léveillé[1,2] · David Porteous[7,8,9] · Gail Davies[7] · Paul Redmond[7] · Sarah E. Harris[7] · W. David Hill[7] · Emmanuelle Lemyre[1,2] · Gunter Schumann[10] · Thomas Bourgeron[11,12,13] · Zdenka Pausova[14] · Tomas Paus[15] · Sherif Karama[16,17,18] · Sarah Lippe[2,19] · Ian J. Deary[8] · Laura Almasy[20] · Aurélie Labbe[5] · David Glahn[21,22] · Celia M. T. Greenwood[3,23] · Sébastien Jacquemont[1,2]

Molecular Psychiatry (2021) 26:2663–2676

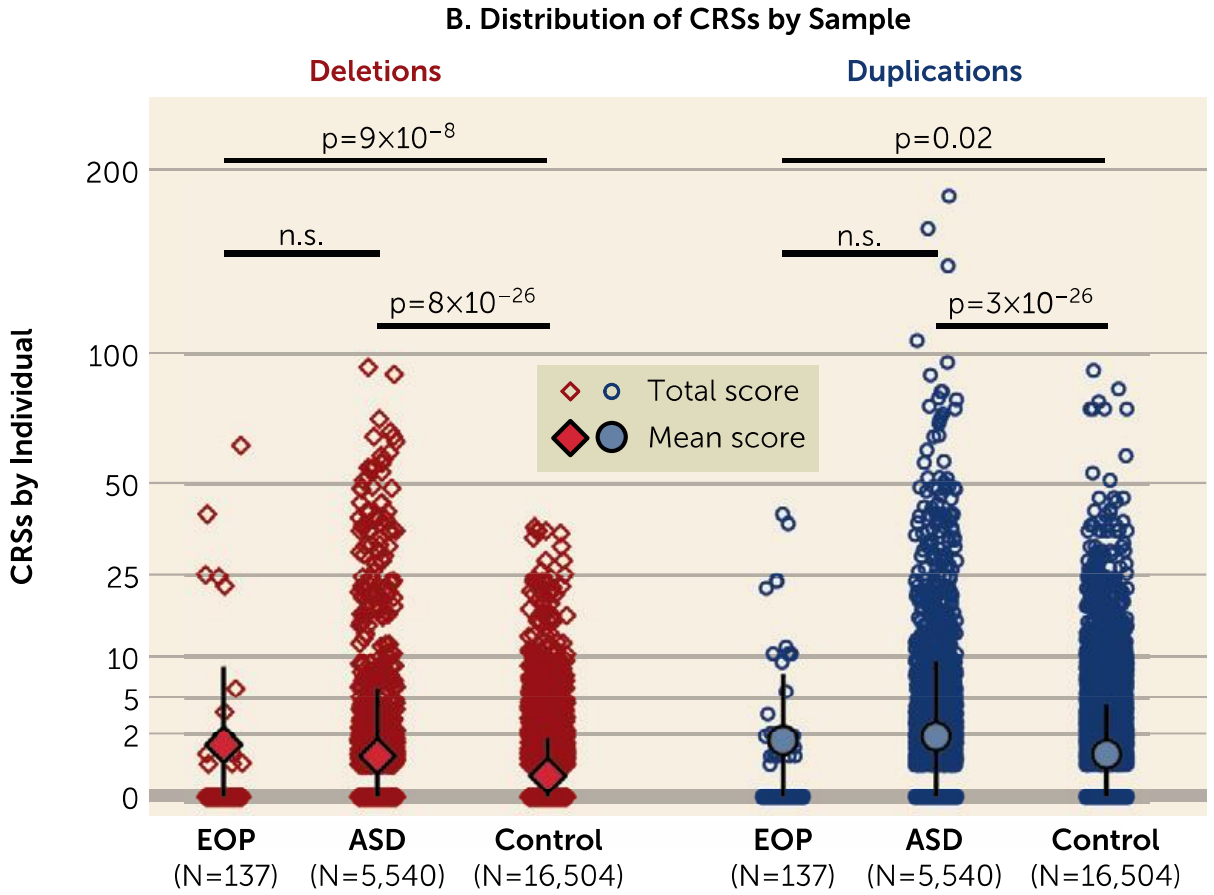
CRS in EOP, ASD and Controls

Similar Rates of Deleterious Copy Number Variants in Early-Onset Psychosis and Autism Spectrum Disorder

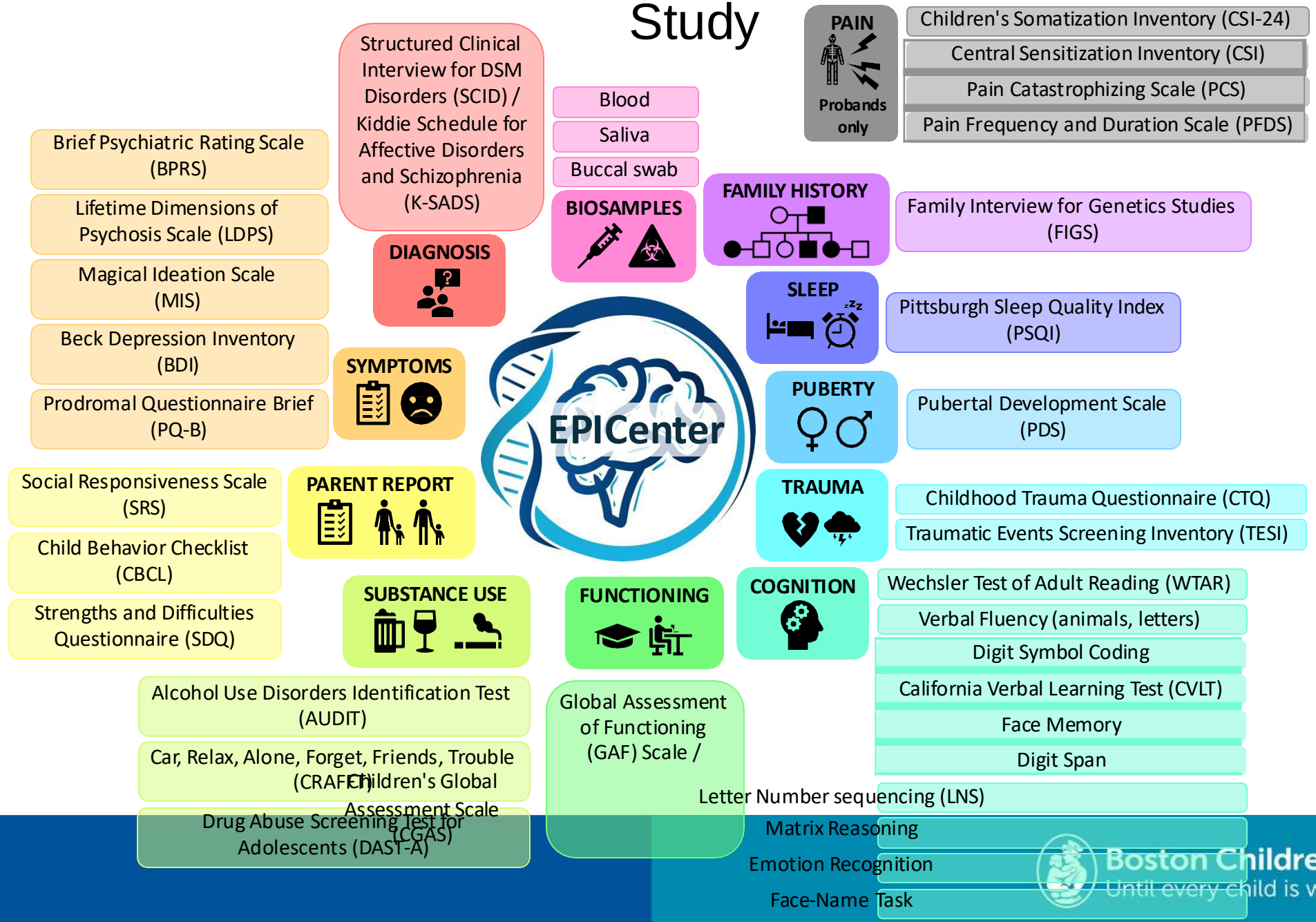
Catherine A. Brownstein, Ph.D., Elise Douard, M.Sc., Josephine Mollon, Ph.D., Richard Smith, Ph.D., Margaret A. Hojlo, B.A., Ananth Das, B.A., Maria Goldman, B.A., Emily Garvey, B.A., Kristin Cabral, B.S., Jianqiao Li, B.S., Joshua Bowen, B.S., Abhijit S. Rao, B.S.A., Casie Genetti, M.S., C.G.C., Devon Carroll, A.P.R.N.-B.C., Emma E. M. Knowles, Ph.D., Emma Deaso, B.A., Pankaj B. Agrawal, M.D., Alan H. Beggs, Ph.D., Eugene D'Angelo, Ph.D., Laura Almasy, Ph.D., Aaron Alexander-Bloch, M.D., Ph.D., Zohra Saci, Ph.D., Clara A. Moreau, Ph.D., Guillaume Huguet, Ph.D., Anthony J. Deo, M.D., Ph.D., Sébastien Jacquemont, M.D., David C. Glahn, Ph.D., Joseph Gonzalez-Heydrich, M.D.

Am J Psychiatry 179:11, November 2022

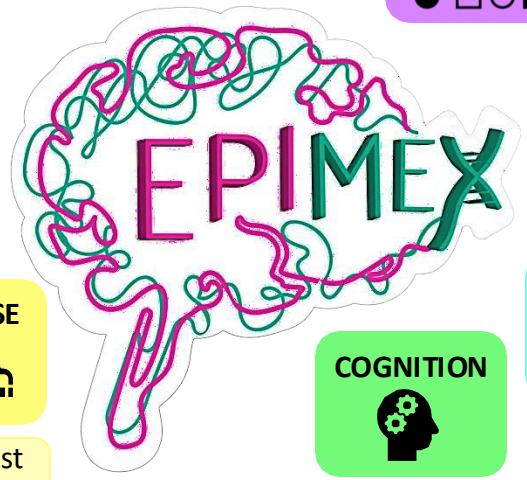
Sensitivity EOP vs. CT	Deletions p-value	Duplications p-value
EOP Full Sample (N=137)	$9x10^{-8}$	0.02
EOP without ASD (N=90)	$3x10^{-4}$	0.17
EOP without ID (N=120)	0.04	0.03
EOP without schizophrenia (N=98)	$3x10^{-7}$	0.02
EOP < 13 years old (N=99)	$3x10^{-7}$	0.22



Protocol of the Early Psychosis Investigation Center (EPICenter) Study



Protocol of the Early Psychosis Investigation in Mexico City (EPIMex) Study



DIAGNOSIS

Structured Clinical Interview for DSM Disorders (SCID) / Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)

BIOSAMPLES

- Blood
- Saliva
- Buccal swab

SOCIAL DETEMINANTS OF HEALTH

FAMILY HISTORY

Family Interview for Genetics Studies (FIGS)

SYMPTOMS

- Brief Psychiatric Rating Scale (BPRS)
- Revised Children's Anxiety and Depression Scale (RCADS)
- Generalized Anxiety Disorder 7-item (GAD-7)
- Patient Health Questionnaire (PHQ-9)
- Child Behavior Checklist (CBCL)

PUBERTY

Pubertal Development Scale (PDS)

TRAUMA

Adverse Childhood Experiences (ACEs)

SUBSTANCE USE

- Alcohol Use Disorders Identification Test (AUDIT)
- Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT)

COGNITION

- Orientation
- Verbal Fluency (animals, letters)
- Digit Symbol Coding
- California Verbal Learning Test (CVLT)
- Face Memory
- Digit Span
- Letter Number sequencing (LNS)
- Matrix Reasoning

FUNCTIONING

- Global Assessment of Functioning (GAF) Scale / Children's Global Assessment Scale (CGAS)
- WHO Disability Assessment Schedule (WHODAS)

“Genetic Architecture of Early-Onset Psychosis in Mexicans” EPIMex

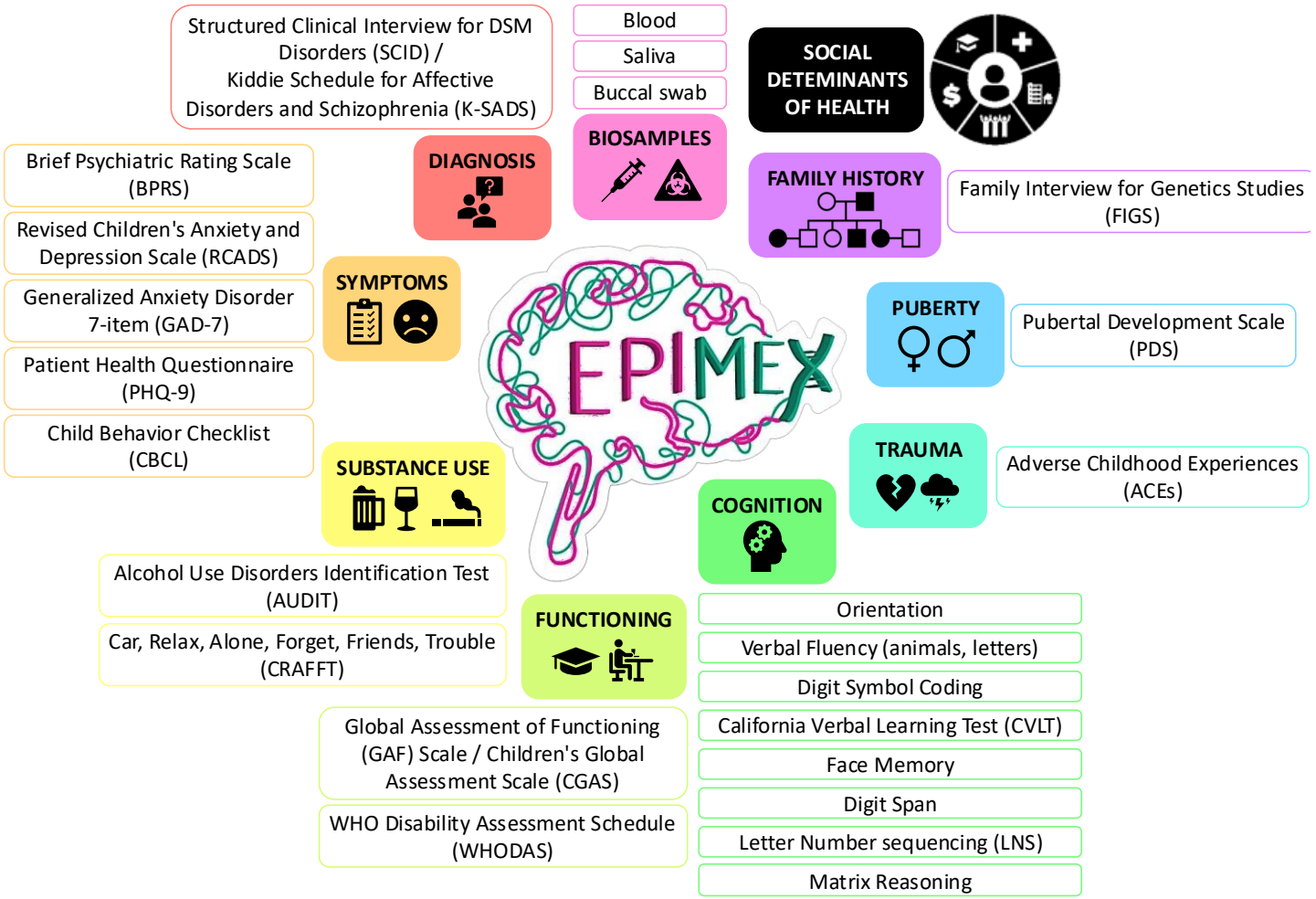
5000 individuals recruited from a single public psychiatric hospital in Mexico City to search for inherited and *de novo* mutations:

- 1900 children & adolescents with early onset psychosis (EOP)
- 1900 non-psychotic, demographically matched youth
- 1200 family members: both parents and a non-psychotic sibling for 400 probands



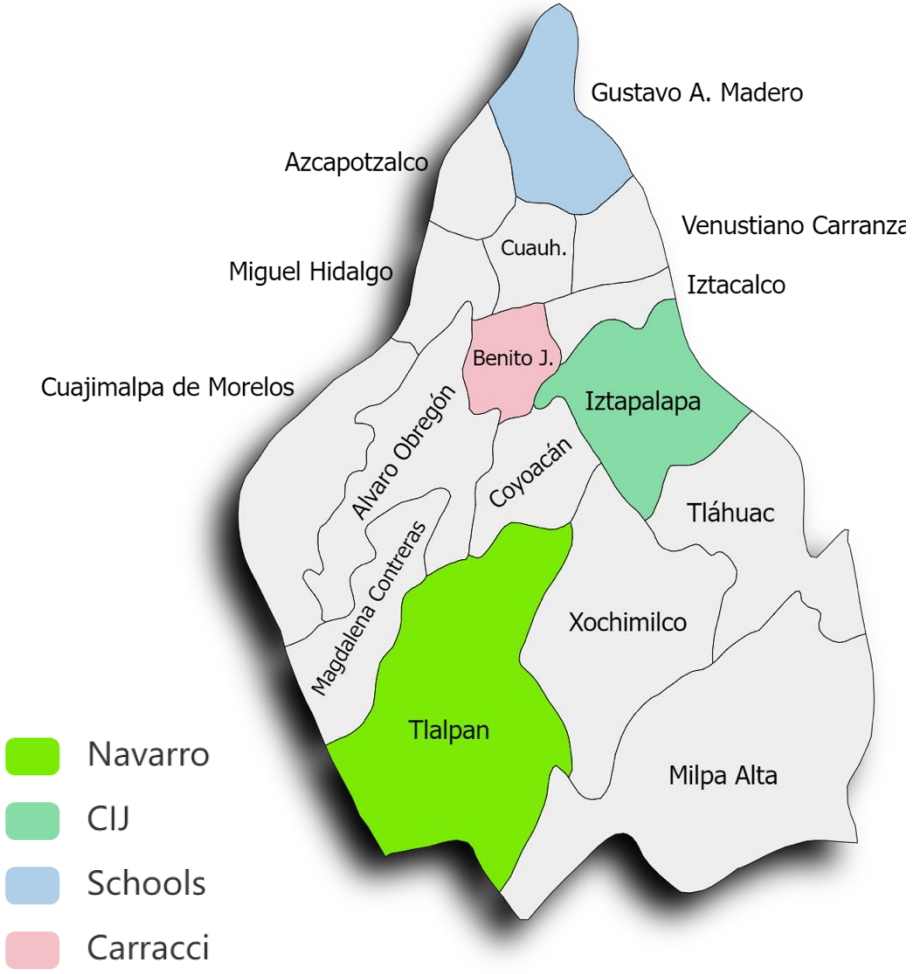
R01 MH133621

Current Enrolment



October 25, 2024	
Probands	729
Controls	777
Family Members	414
Complete quads	101
Total	1920

Hospital Psiquiátrico Infantil Dr. Juan Navarro



Culturally sensitive diagnosis

ind a second one, concerned with the incorporation of cultural variables in the
ormulation of the psychiatric diagnosis in order to make it more useful for
reatment planning and health promotion. These efforts are not merely academic,
hey are necessary for clinical practice, as ethnic and cultural diversity of those
eeking mental health services increase around the world, especially in devel-
oped societies, such as the United States.[11]

Among recent efforts to update diagnostic validity, existing universalistic
diagnostic systems are being examined critically in order to pay closer attention
o local realities and the uniqueness of the individual patient. The first type of
hese developments involves adaptations of the international classification sys-
em to regional or national clinical patterns and needs.[21] A second one is the
ecognition of the practical importance of making contextual factors an im-
portant part of the diagnostic formulation, including the perspectives of the

CULTURAL PSYCHIATRY: INTERNATIONAL PERSPECTIVES 0193–953X/01 $15.00 + .00

Enculturation and acculturation's relationship to suicidal ideation in Hispanic/Latinx individuals with psychotic spectrum disorders

Amy Weisman de Mamani, Daisy Lopez *

Psychiatry Research 307 (2022) 114298

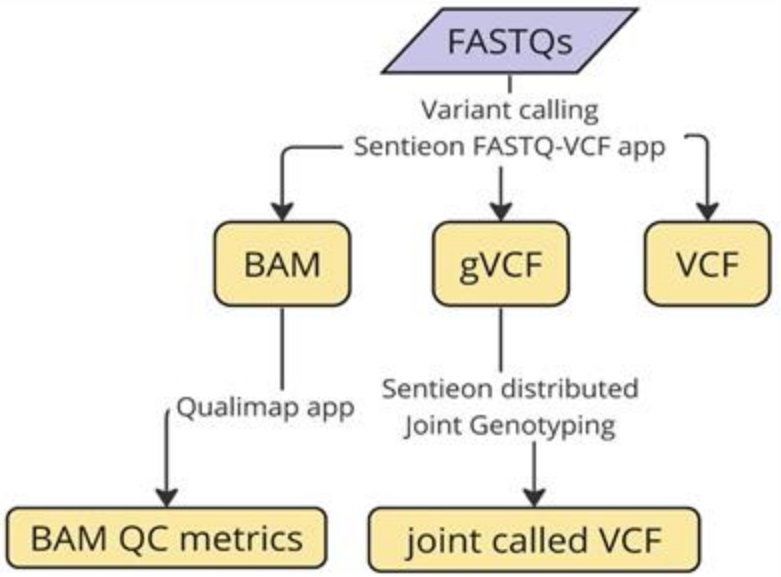
Differential diagnosis between non-pathological psychotic and spiritual experiences and mental disorders: a contribution from Latin American studies to the ICD-11

Alexander Moreira-Almeida,[1] Etzel Cardeña[2]

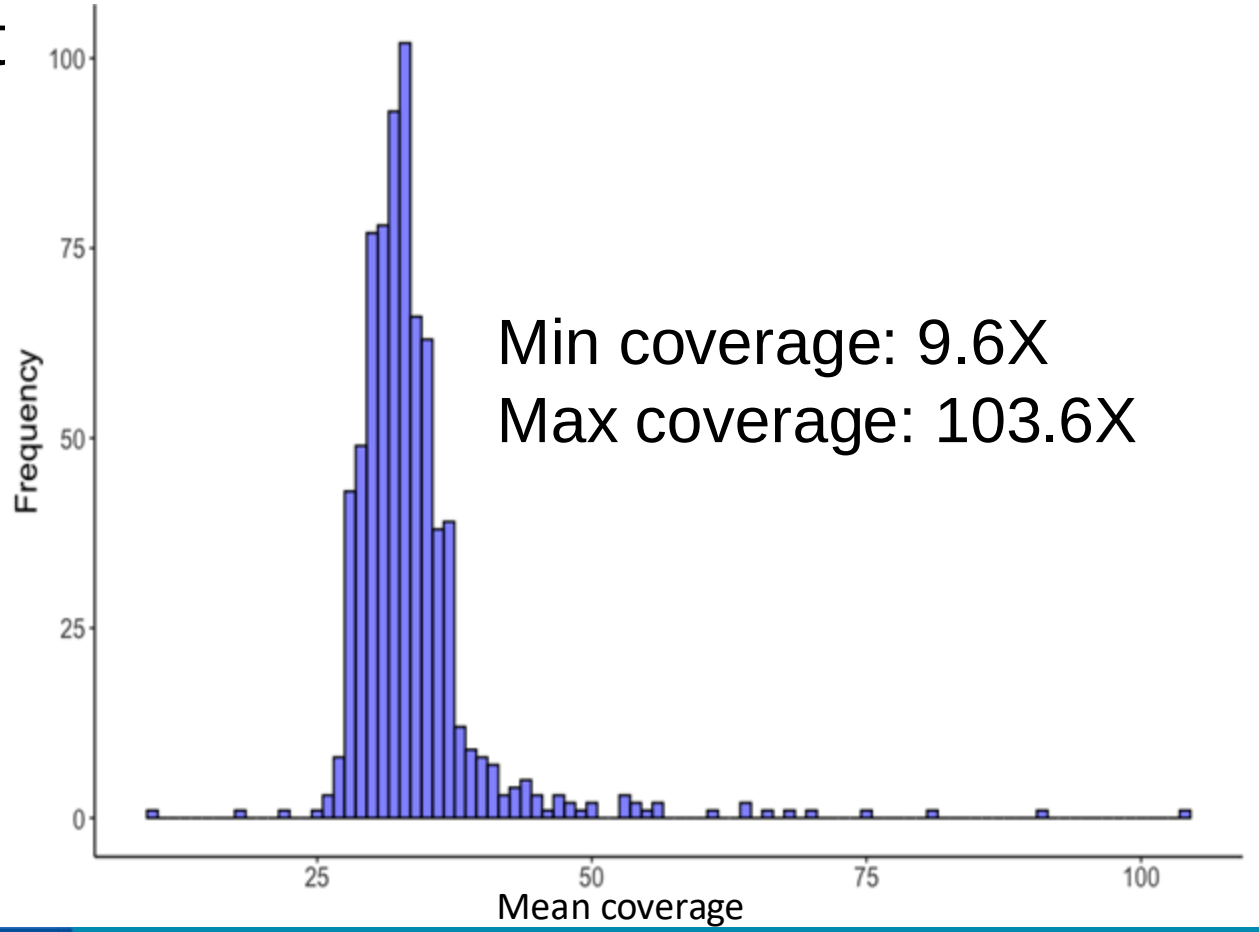
Revista Brasileira de Psiquiatria • vol 33 • Supl I • mai2011 • **S30**

EPIMex: Whole Genome Sequence

- 806 participants sequenced at Hudson Alpha



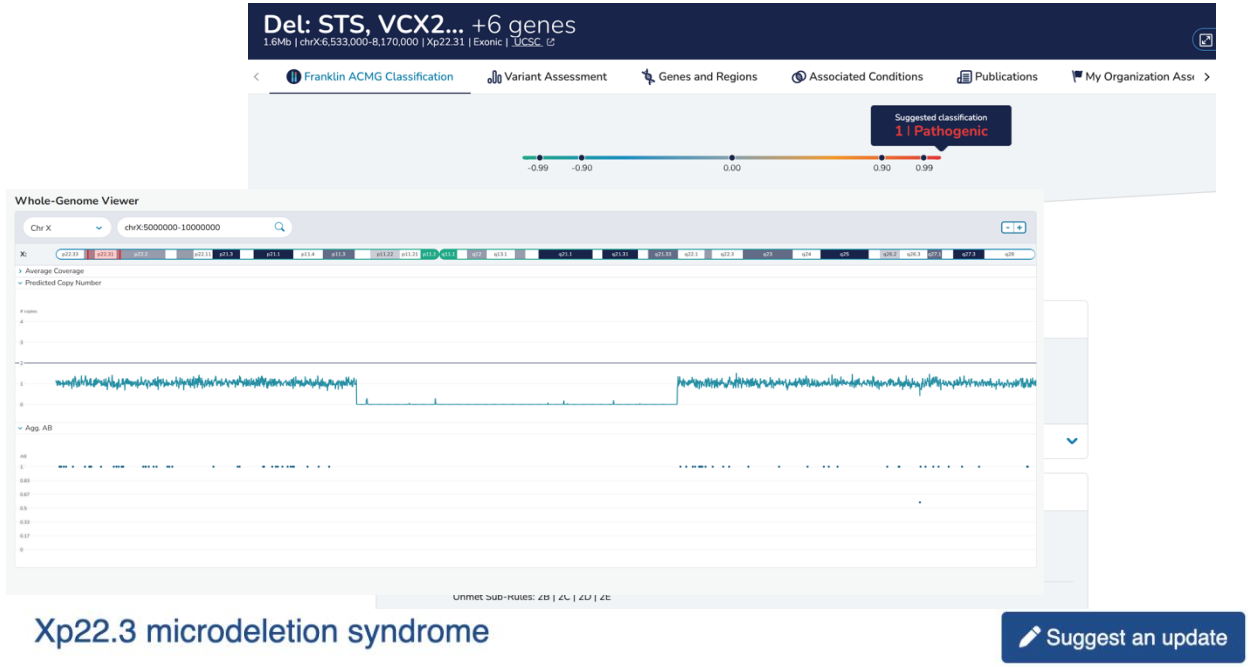
Mean coverage across samples: 33.7X



Min coverage: 9.6X
Max coverage: 103.6X

Xp22.31 deletion

- 1 case, 2 unaffected family members (mother, sister)
- 1 unrelated singleton case



Internal Occurrence

4 Samples carrying similar variants in your organization

0 Number of Homozygote

Sample	Zygosity	Confidence	Overlap	Location	Affected genes	Phenotypes	Ethnicity	Gender
40437	Heterozygote	High	69.15% : 100%	chrX:6,602,000-7,734,000	MIR4767, PUDP, STS	N/A	N/A	Unknown
40702	Homozygote	High	100% : 100%	chrX:6,533,000-8,170,000	VCX2, PUDP, MIR651, VCX3A, VCX ... read more	Psychosis	N/A	Unknown
40755	Heterozygote	High	100% : 99.94%	chrX:6,532,000-8,170,000	VCX2, PUDP, MIR651, VCX3A, VCX ... read more	N/A	N/A	Unknown
40756	Heterozygote	High	100% : 100%	chrX:6,533,000-8,170,000	VCX2, PUDP, MIR651, VCX3A, VCX ... read more	N/A	N/A	Unknown

Minimize

Family Zygosity

Sample	Relation	Zygosity	Confidence	Location	Overlap	Affected genes
40702	Proband	Homozygote	High	chrX:6,532,999-8,170,000		STS
40755	Sibling	Heterozygote	High	chrX:6,531,999-8,170,000	100% : 99.94%	STS
40756	Mother	Heterozygote	High	chrX:6,532,999-8,170,000	100% : 100%	STS

Disease definition

Xp22.3 microdeletion syndrome is a microdeletion syndrome resulting from a partial deletion of the chromosome X. Phenotype is highly variable (depending on length of deletion), but is mainly characterized by X linked ichthyosis, mild-moderate intellectual deficit, Kallmann syndrome, short stature, chondrodysplasia punctata and ocular albinism. Epilepsy, attention deficit-hyperactivity disorder, autism and difficulties with social communication can be associated.

Family 40577- paternally inherited *NRXN1* loss

- Also in an unrelated case

Article | Published: 23 May 2012

Phenotypic spectrum and genotype–phenotype correlations of *NRXN1* exon deletions

Christian P Schaaf, Philip M Boone, Srirangan Sampath, Charles Williams, Patricia I Bader, Jennifer M Mueller, Oleg A Shchelochkov, Chester W Brown, Heather P Crawford, James A Phalen, Nicole R Tartaglia, Patricia Evans, William M Campbell, Anne Chun-Hui Tsai, Lea Parsley, Stephanie W Grayson, Angela Scheuerle, Carol D Luzzi, Sandra K Thomas, Patricia A Eng, Sung-Ha… Pawel Stankiewicz & Sau W Cheung

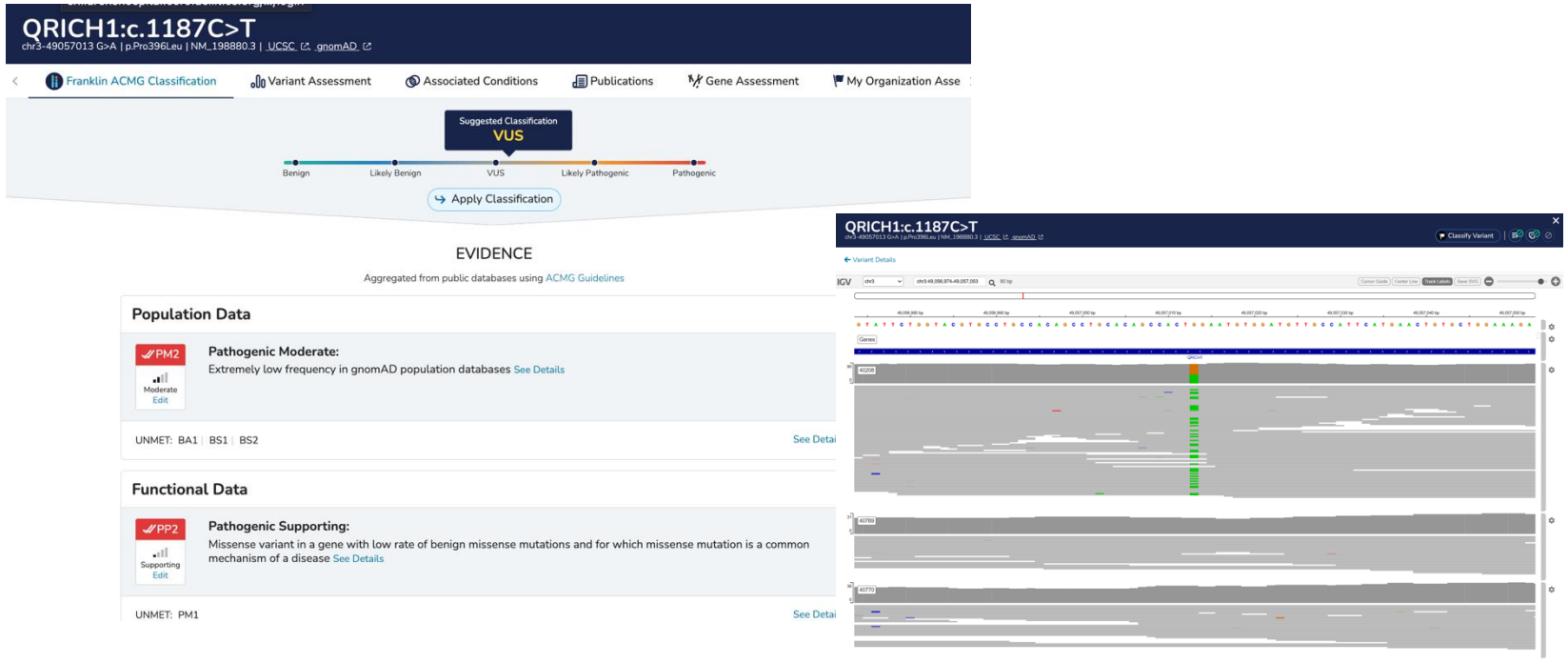
European Journal of Human Genetics **20**, 1240–1247 (2012) | Cite this artic…

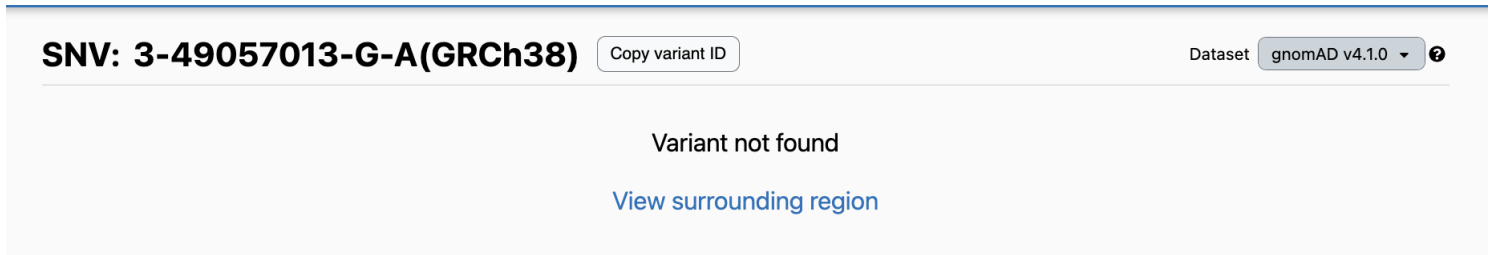
5393 Accesses | **88** Citations | **1** Altmetric | Metrics

Abstract

Copy number variants (CNVs) and intragenic rearrangements of the *N*… are associated with a wide spectrum of developmental and neuropsyc… including intellectual disability, speech delay, autism spectrum disord… and schizophrenia. We performed a detailed clinical and molecular ch… patients who underwent clinical microarray analysis and had intrageni… Seventeen of these deletions involved exons of *NRXN1*, whereas seven deleted intronic sequences only. The patients with exonic deletions manifested developmental delay/intellectual disability (93%), infantile hypotonia (59%) and ASDs (56%). Congenital malformations and dysmorphic features appeared infrequently and inconsistently among this population of patients with *NRXN1* deletions. The more C-terminal deletions, including those affecting the *β* isoform of neurexin 1, manifested increased head size and a high frequency of seizure disorder (88%) when compared with N-terminal deletions of *NRXN1*.

Family 40208- *QRICH1 de novo*





Clin Genet. 2021 Jan;99(1):199-207. doi: 10.1111/cge.13853. Epub 2020 Nov 10.

QRICH1 variants in Ververi-Brady syndrome-delineation of the genotypic and phenotypic spectrum

Melanie Föhrenbach [1], Rami Abou Jamra [2], Arndt Borkhardt [3], Triantafyllia Brozou [3], Petra Muschke [4], Bernt Popp [2 5], Linda K Rey [1], Jörg Schaper [6], Harald Surowy [1], Martin Zenker [4], Christiane Zweier [5], Dagmar Wieczorek [1], Silke Redler [1]

Affiliations + expand

PMID: 33009816 DOI: 10.1111/cge.13853

Abstract

Ververi-Brady syndrome (VBS, # 617982) is a rare developmental disorder, and loss-of-function variants in QRICH1 were implicated in its etiology. Furthermore, a recognizable phenotype was proposed comprising delayed speech, learning difficulties and dysmorphic signs. Here, we present four unrelated individuals with one known nonsense variant (c.1954C > T; p.[Arg652*]) and three novel de novo QRICH1 variants, respectively. These included two frameshift mutations (c.832_833del; p.(Ser278Leufs*25), c.1812_1813delTG; p.(Glu605Glyfs*25)) and interestingly one missense mutation (c.2207G > A; p.[Ser736Asn]), expanding the mutational spectrum. Enlargement of the cohort by these four individuals contributes to the delineation of the VBS phenotype and suggests expressive speech delay, moderate motor delay, learning difficulties/mild ID, mild microcephaly, short stature and notable social behavior deficits as clinical hallmarks. In addition, one patient presented with nephroblastoma. The possible involvement of QRICH1 in pediatric cancer assumes careful surveillance a key priority for outcome of these patients. Further research and enlargement of cohorts are warranted to learn about the genetic architecture and the phenotypic spectrum in more detail.

Keywords: QRICH1; Ververi-Brady syndrome; autism spectrum disorder; language development disorders.

40179 paternally inherited *PRODH* loss

Del: PRODH, DGCR5... +2 genes
94kb | chr22:18,932,000-19,026,000 | 22q11.21 | Exonic | UCSC

Franklin ACMG Classification | Variant Assessment | Genes and Regions | Associated Conditions | Publications | My Organization Ass

Clinical Summary | Region Viewer | Confidence | Occurrences | Internal Occurrence | Family Zygosity | Sequence Browser | References

Clinical Summary

Agree | Suggest a change

FRANKLIN AUTOMATED CLASSIFICATION See details

0.95 | Likely Pathogenic

-0.99 -0.90 0.00 0.90 0.99

RELEVANT GENES AND REGIONS See all genes and regions

22q11.21, 22q11.21, PRODH
Found to be **Haploinsufficient** by Clingen and Franklin, and are related to **Autosomal dominant** inherited conditions that fit the variant zygosity.

PATIENT IS SUSPECTED TO BE **AFFECTED** WITH:

Schizophrenia 4
PRODH | AUTOSOMAL_DOMINANT | Matching case phenotypes 1/1: **Abnormality of the nervous system**

Hyperprolinemia type 1
PRODH | AUTOSOMAL_RECESSIVE | Matching case phenotypes 0/1:

PLoS Genet. 2008 Nov 7;4(11):e1000252. doi: 10.1371/journal.pgen.1000252

Functional Polymorphisms in *PRODH* Are Associated with Risk and Protection for Schizophrenia and Fronto-Striatal Structure and Function

Lucas Kempf [1,2], Kristin K Nicodemus [2,¤a], Bhaskar Kolachana [2], Radhakrishna Vakkalanka [2], Beth A Verchinski [2,3], Michael F Egan [2,¤b], Richard E Straub [2], Venkata A Mattay [2,3], Joseph H Callicott [2], Daniel R Weinberger [2,*], Andreas Meyer-Lindenberg [1,2,3,4,*]

Editor: Nicholas Katsanis[5]

Author information | Article notes | Copyright and License information

PMCID: PMC2573019 PMID: 18989458

PRODH (exonic 1)
NM_016335 | Inheritance: **AD, AR**

3 Associated conditions See all | 15/222 Publicat with ph See all

ClinGen Haploinsufficiency: AR
ClinGen Triplosensitivity: 0
Calculated LOF score: 3
Decipher HI score: 45.38
pLI: 0
o\e LOF (upper): 1.1

Schizophrenia 4 AD
OMIM

Hyperprolinemia Type 1 AR
CLINGEN | OMIM | Monarch | Orphanet | GENCC

Matching case phenotypes 1/1
Psychosis

Mol Psychiatry. 2003 Jul;8(7):644-5. doi: 10.1038/sj.mp.4001276.

Association between PRODH and schizophrenia is not confirmed

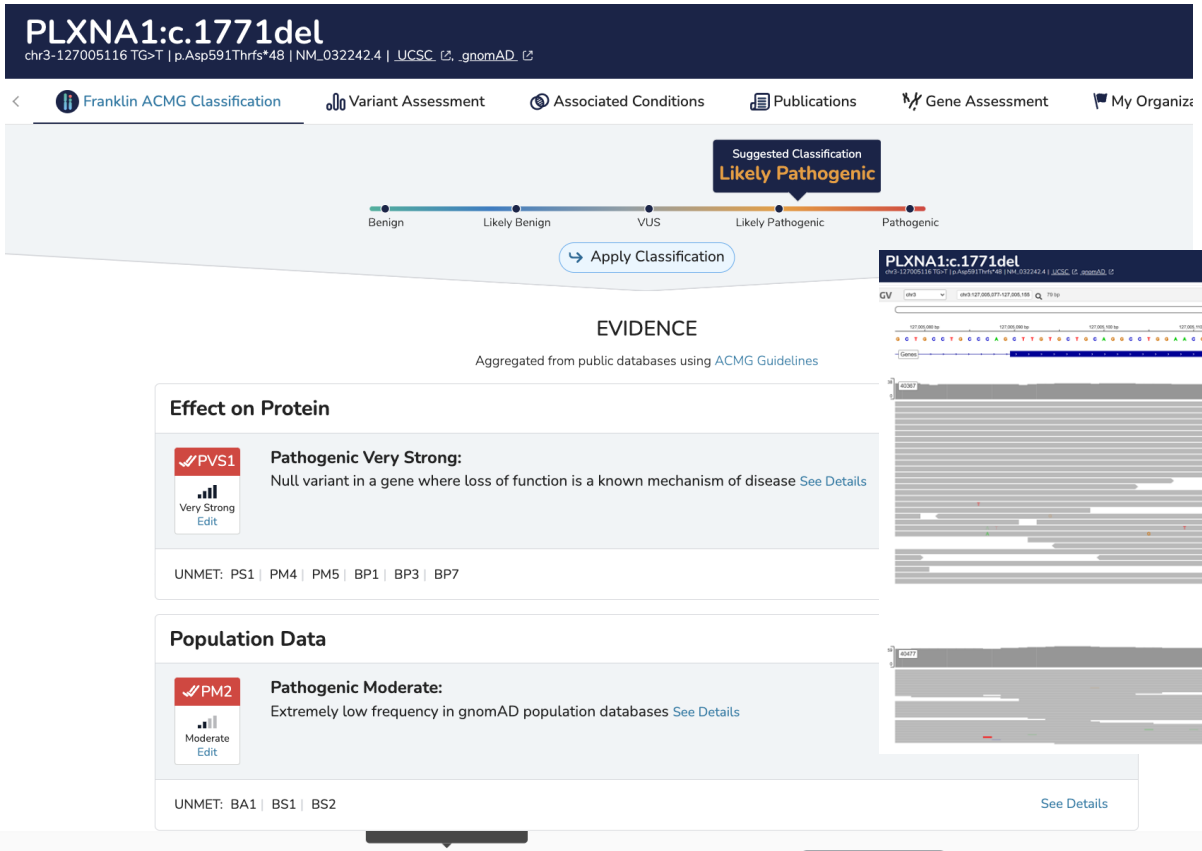
H J Williams, N Williams, G Spurlock, N Norton, D Ivanov, R G McCreadie, A Preece, V Sharkey, S Jones, S Zammit, I Nikolov, I Kehaiov, A Thapar, K C Murphy, G Kirov, M J Owen, M C O'Donovan

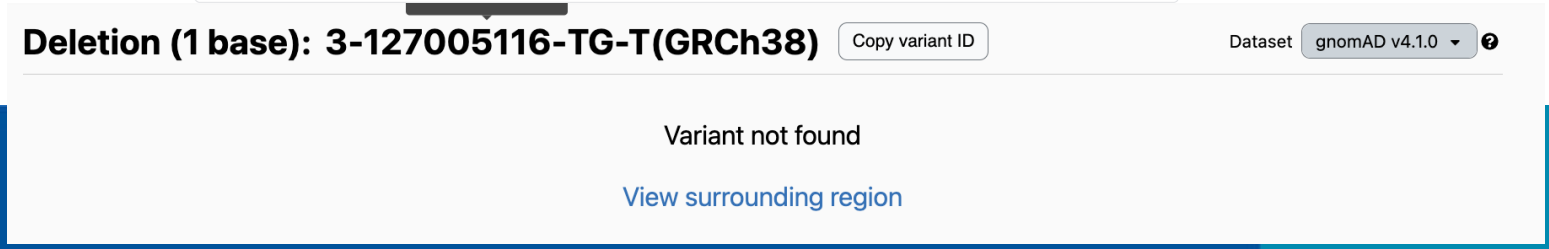
PMID: 12874599 DOI: 10.1038/sj.mp.4001276

No abstract available

PubMed Disclaimer

Family 40367- *PLXNA1* paternally inherited or *de novo*





Article | Published: 22 January 2014

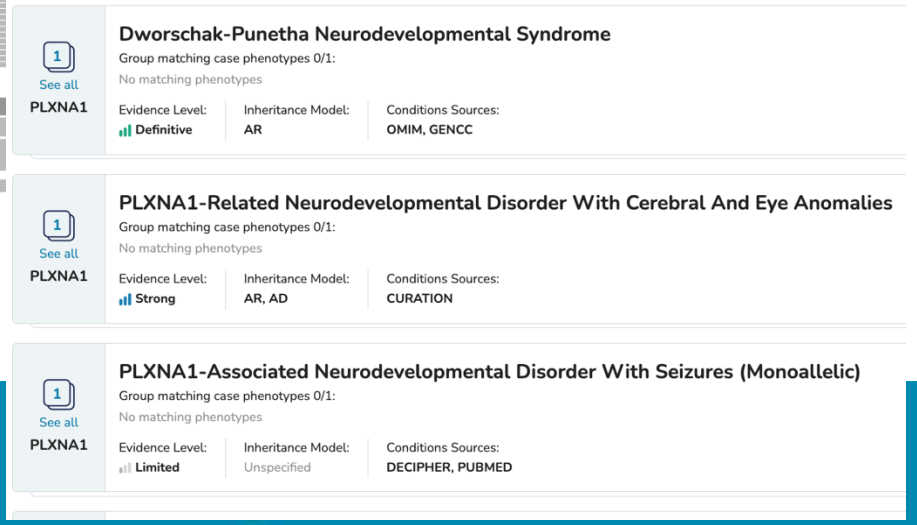
De novo mutations in schizophrenia implicate synaptic networks

Menachem Fromer, Andrew J. Pocklington, David H. Kavanagh, Hywel J. Williams, Sarah Dwyer, Padhraig Gormley, Lyudmila Georgieva, Elliott Rees, Priit Palta, Douglas M. Ruderfer, Noa Carrera, Isla Humphreys, Jessica S. Johnson, Panos Roussos, Douglas D. Barker, Eric Banks, Vihra Milanova, Seth G. Grant, Eilis Hannon, Samuel A. Rose, Kimberly Chambert, Milind Mahajan, Edward M. Scolnick, Jennifer L. Moran, ... Michael C. O'Donovan + Show authors

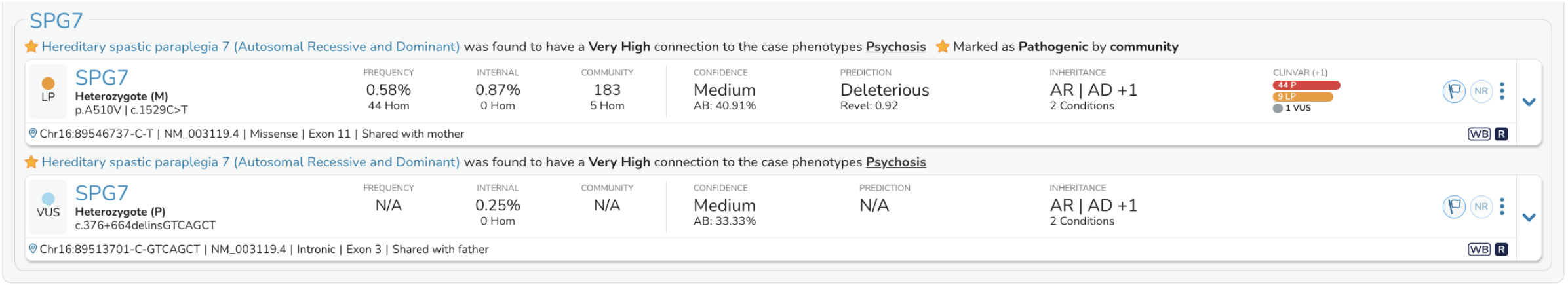
Nature **506**, 179–184 (2014) | Cite this article

50k Accesses | **1185** Citations | **327** Altmetric | Metrics

This article has been updated



Family 40852- compound het in SPG7



ICD+

607259

SPASTIC PARAPLEGIA 7, AUTOSOMAL RECESSIVE; SPG7

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
16q24.3	Spastic paraplegia 7, autosomal recessive	607259	AD, AR	3	PGN	602783

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

TEXT

A number sign (#) is used with this entry because spastic paraplegia-7 (SPG7) is caused by homozygous or compound heterozygous mutation in the paraplegin gene (SPG7; 602783) on chromosome 16q24. Some patients with the disorder carry heterozygous SPG7 mutations.

Description

Hereditary spastic paraplegia (SPG) is characterized by progressive weakness and spasticity of the lower limbs due to degeneration of corticospinal axons. There is considerable genetic heterogeneity. Inheritance is most often autosomal dominant (see 182600), but X-linked (see 312920) and autosomal recessive (see 270800) forms occur.

SPG7 shows phenotypic variability between families. Some cases are pure, whereas other are complicated with additional neurologic features (Warnecke et al., 2007).

Gene Scope | Genoox NLP | BMC Neurol | 2022 | PMID:35637455

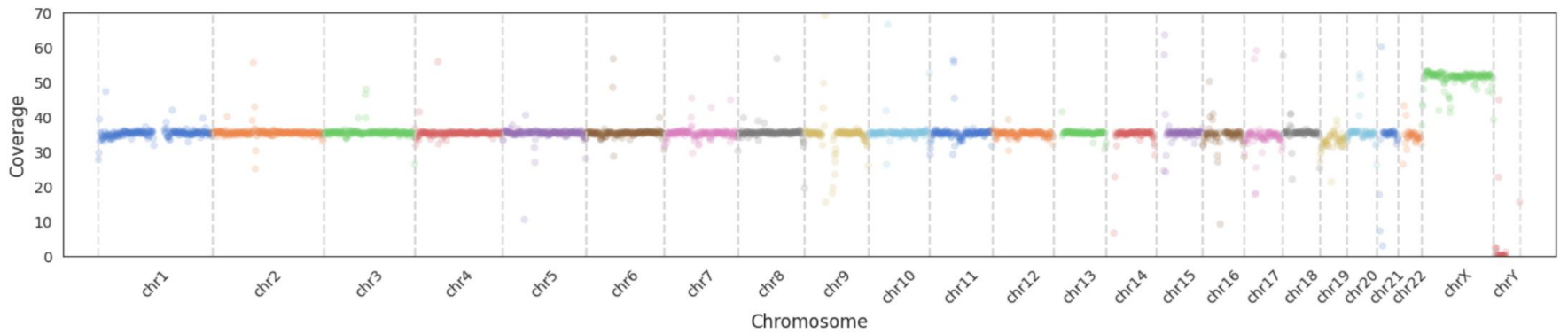
A novel compound heterozygous SPG7 variant is associated with progressive spastic ataxia and persecutory delusions found in Chinese patients: two case reports.

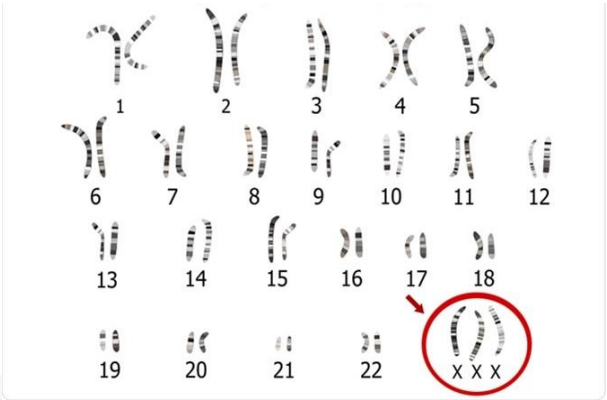
Wang S, Wang Y, Wu Y, Zhang J, Zhang W, Li C, Song X

BACKGROUND: Hereditary spastic paraplegia 7 (SPG7) is one of the subtypes of autosomal-recessive hereditary spastic paraplegia, which is a clinically heterogeneous neurodegenerative disorder. SPG7 often displays a complicated phenotype, including optic atrophy, ophthalmoparesis, and impaired emotional communication. In the Chinese population, sporadic cases of SPG7 variant-associated spastic ataxia are rarely reported. CASE PRESENTATION: We carefully analysed the clinical features, imaging and genetic tests of two sporadic patients with SPG7, both from the Hebei region of China. One patient presented with progressive bilateral lower limb weakness, spastic-ataxia and no cognitive impairment. Brain MRI revealed mild cerebellar atrophy. Genetic analysis revealed c.1150_1151insCTAC (p.G384Afs*13) frameshift variant and exon1-3 heterozygous deletion. The other patient presented with progressive bilateral lower limb weakness, ataxia, dysarthria and a mild psychosis associated with persecutory delusions, which drew almost no attention, in addition to mild cognitive impairments characterized by a decrease in verbal memory and executive function. Genetic analysis identified two heterozygous variants in the SPG7 gene: c.1150_1151insCTAC (p.G384Afs*13) and c.1496delC (p.Q500Sfs*13). CONCLUSIONS: The c.1496delC (p.Q500Sfs*13) variant in exon 11 has not been reported before. The c.1150_1151insCTAC variant is speculated to be a hotspot variant in the Chinese population. Patients with SPG7 may have cognitive impairments and psychosis, displaying specific characteristics, which should be of concern.

Detailed View

40331 (control) - Triple X Syndrome





Triple X syndrome

Suggest an update

Disease definition

A rare sex-chromosome anomaly characterized by a variable phenotype, including various degree of global developmental delay, tall stature, epicanthal folds, hypotonia, and clinodactyly in association with seizures, renal and genitourinary abnormalities, and premature ovarian failure (POF).

ORPHA:3375

Classification level: Disorder

Synonym(s):

47,XXX syndrome

Triplo-X syndrome

XXX syndrome

Source: PubMed ID 32489015 32506765 19568271

Prevalence: 1-5 / 10 000

Inheritance: Not applicable

Age of onset: Childhood, Infancy

ICD-10: Q97.0

ICD-11: LD50.1

UMLS: C0221033

MeSH: C535318

GARD: 5672

MedDRA: 10076910

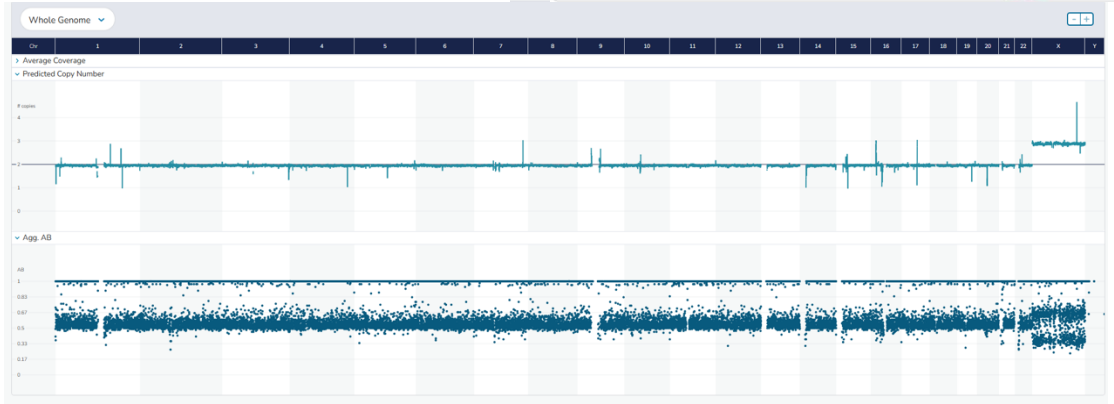
Summary

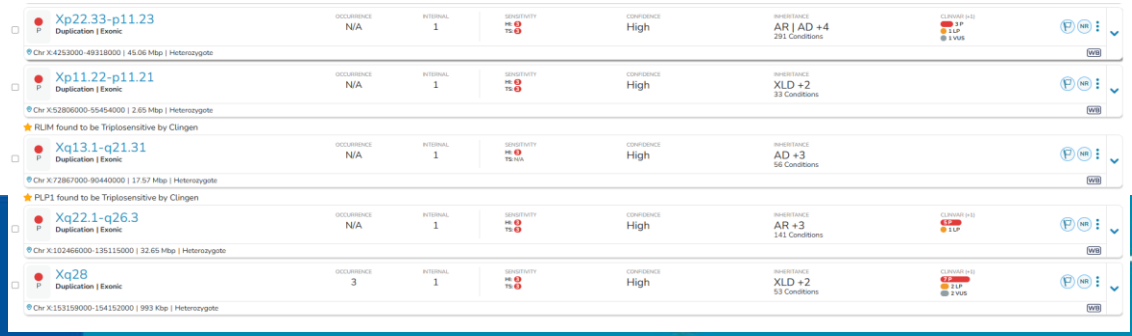
Epidemiology

It is the most common chromosomal abnormality in females, occurring in approximately 1 in 1,000 female births. However, since most individuals are only mildly affected or asymptomatic, it is estimated that only 10% of individuals with trisomy X are actually diagnosed with the syndrome.

Clinical description

The most common physical features include tall stature (height typically increases in early childhood and often remains above the 75th percentile during adolescence), long legs, short sitting height, average head circumference below the 50th percentile, epicanthal folds, hypotonia, and clinodactyly. Seizures, renal and genitourinary abnormalities (kidney and renal dysplasia, ovarian malformations), and POF are also associated findings. Congenital heart defects, constipation and abdominal pain have also been described. Children with triple X syndrome have higher rates of motor and speech delays compared to the general population, with an increased risk of cognitive deficits and learning disabilities emerging during the school-age years. Psychiatric disorders including attention deficit, mood disorders (such as anxiety and depression), and adjustment disorders are also more prevalent than in the general population. A susceptibility to autoimmune diseases such as systemic lupus erythematosus and glaucoma was also reported in adulthood.





Hospital

Next steps

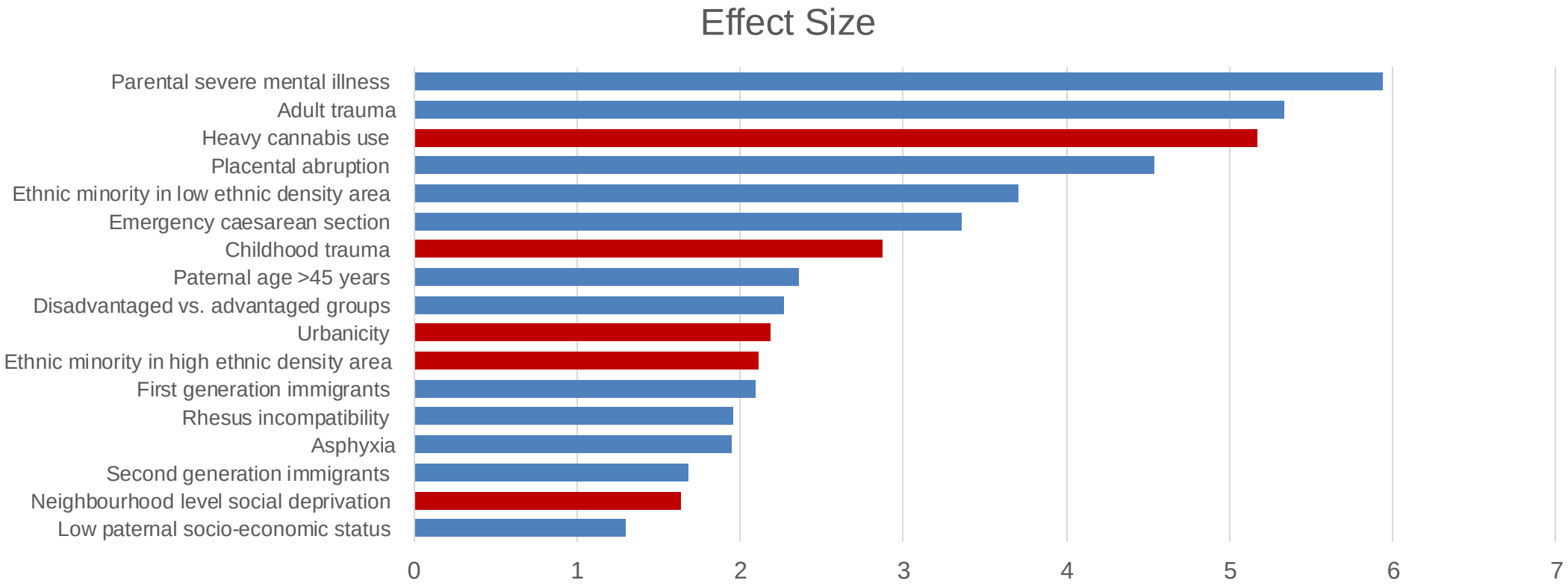
- Continuing Analyses
  - Mendelian
  - Cohort analyses
    - Psychiatric diagnoses in controls
    - Non-psychiatric patient controls
  - Comorbidities
  - Suicidal ideation

- Continuing to enroll
  - Imaging studies
  - Transcriptome analyses
  - Proteomics

Environmental influences on early onset psychosis

Learning Objective 3. To review the impact of early life adversity, including trauma and social disparities, on early onset psychosis

Select psychosis risk factors



What causes psychosis? An umbrella review of risk and protective factors

Joaquim Radua[1-3], Valentina Ramella-Cravaro[1,4], John P.A. Ioannidis[5-8], Abraham Reichenberg[9-12], Nacharin Phiphopthatsanee[1], Taha Amir[1], Hyi Yenn Thoo[1], Dominic Oliver[1], Cathy Davies[1], Craig Morgan[9,13], Philip McGuire[9,13], Robin M. Murray[9,13], Paolo Fusar-Poli[1,13,14]

(World Psychiatry 2018;17:49–66)

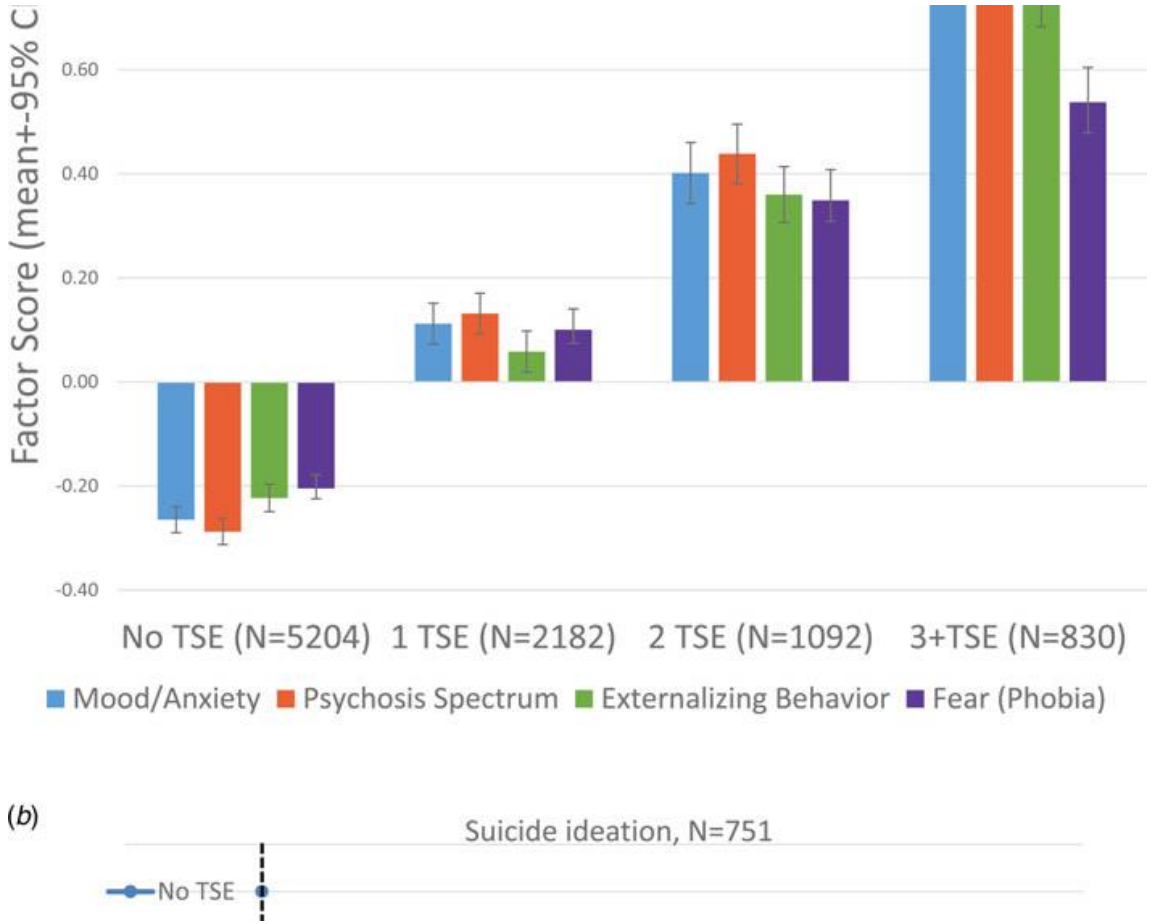
Early life adversity (trauma) & psychopathology

Association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort

Ran Barzilay[1,2], Monica E. Calkins[1], Tyler M. Moore[1], Daniel H. Wolf[1], Theodore D. Satterthwaite[1], J. Cobb Scott[1], Jason D. Jones[2], Tami D. Benton[2], Ruben C. Gur[1,2] and Raquel E. Gur[1,2]

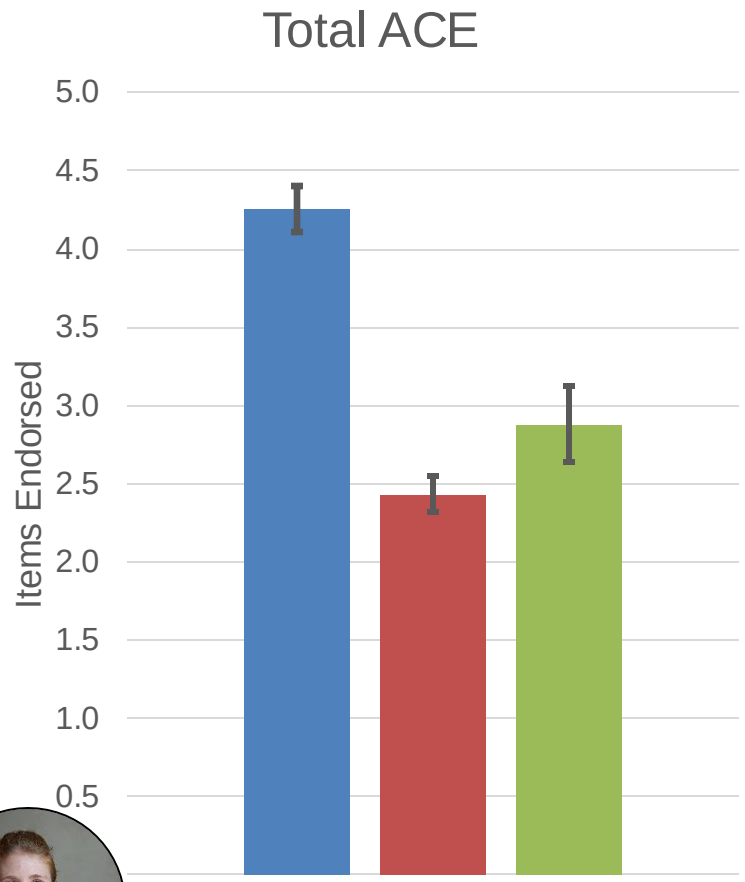
Psychological Medicine

- Higher stress load was associated: mood/anxiety (β=0.38); psychosis (β=0.36); externalizing (β= 0.31); and fear (β=0.26)
- Exposure to high-stress load was robustly associated with suicidal ideation (OR=5.3) and cannabis use (OR=3.2)

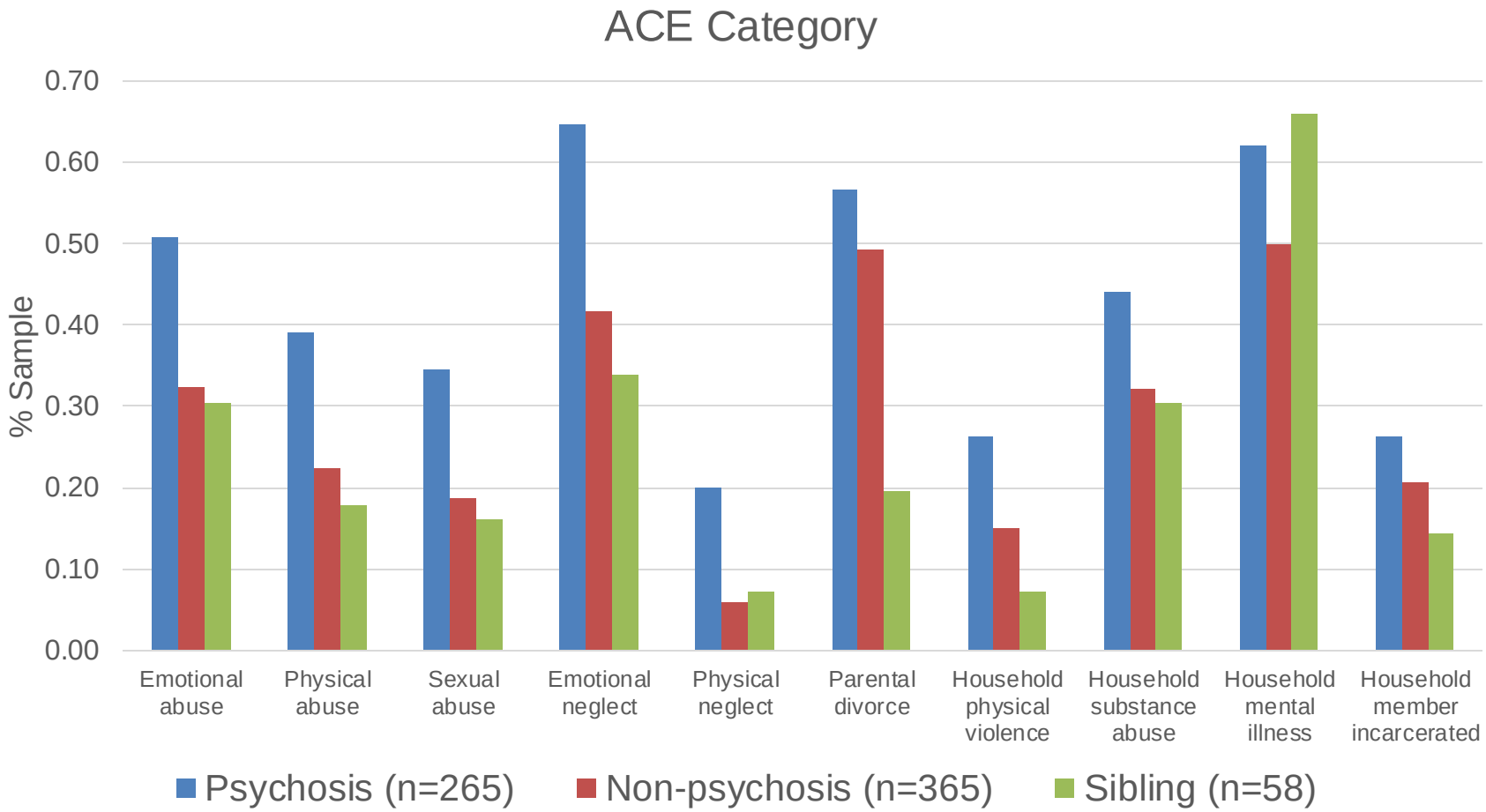


Traumatic Stressful Event (TSE)

EPIMex: Early life adversity in EOP & siblings



n=801



EOP & social disparities

From Womb to Neighborhood: A Racial Analysis of Social Determinants of Psychosis in the United States

Deidre M. Anglin, Ph.D., Sabrina Ereshefsky, Ph.D., Mallory J. Klaunig, Ph.D., Miranda A. Bridgwater, B.S., Tara A. Niendam, Ph.D., Lauren M. Ellman, Ph.D., Jordan DeVylder, Ph.D., Griffin Thayer, M.A., Khalima Bolden, Ph.D., Christie W. Musket, M.S., Rebecca E. Grattan, Ph.D., Sarah Hope Lincoln, Ph.D., Jason Schiffman, Ph.D., Emily Lipner, M.A., Peter Bachman, Ph.D., Cheryl M. Corcoran, M.D., Natália B. Mota, M.D., Els van der Ven, Ph.D.

Am J Psychiatry 2021; 0:1–12; doi: 10.1176/appi.ajp.2020.20071091

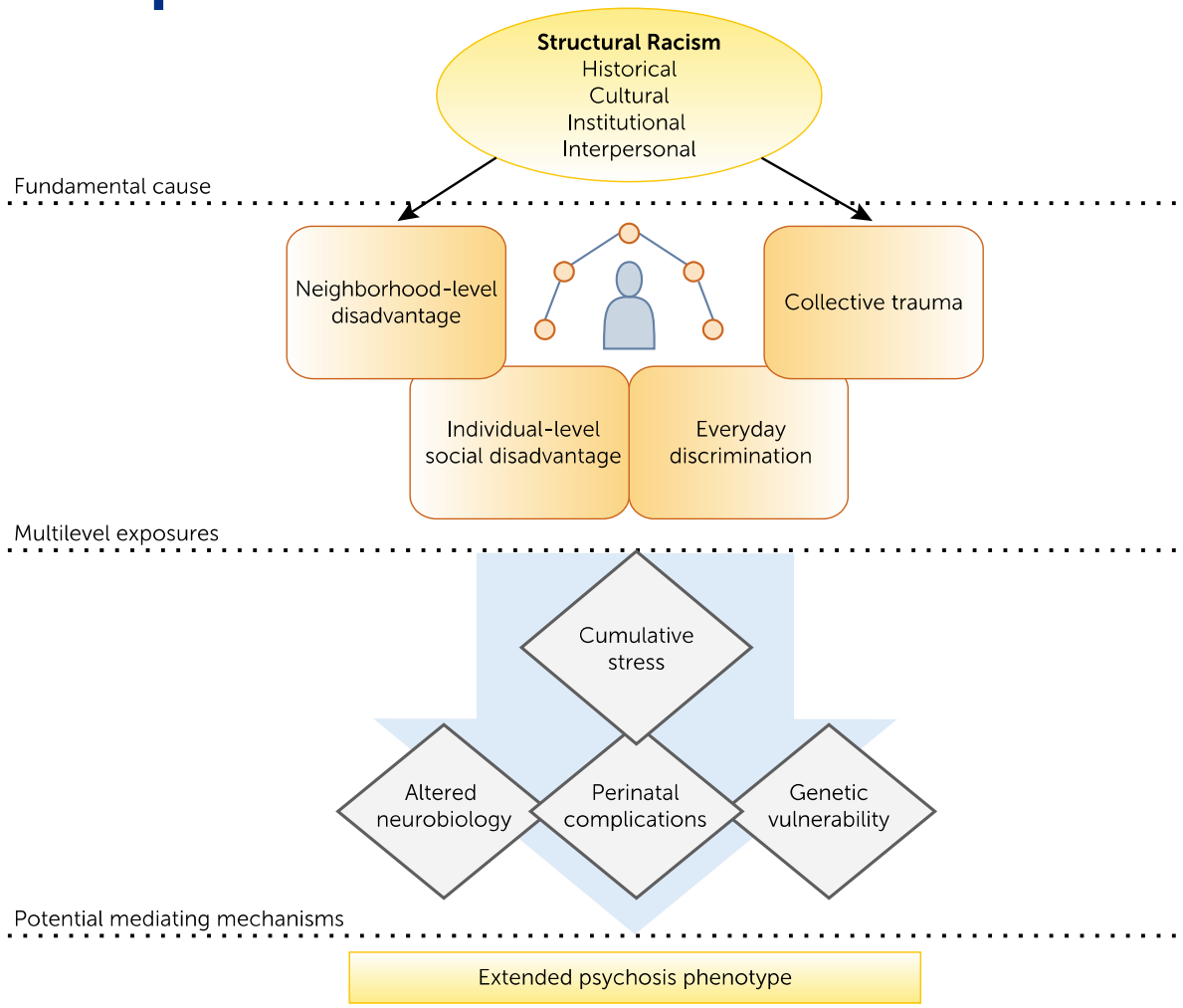
Ethnicity and long-term course and outcome of psychotic disorders in a UK sample: the ÆSOP-10 study

Craig Morgan, Paul Fearon, Julia Lappin, Margaret Heslin, Kim Donoghue, Ben Lomas, Ulrich Reininghaus, Adanna Onyejiaka, Tim Croudace, Peter B. Jones, Robin M. Murray, Gillian A. Doody and Paola Dazzan

BJPsych | The British Journal of Psychiatry (2017) 211, 88–94. doi: 10.1192/bjp.bp.116.193342

Going Upstream to Advance Psychosis Prevention and Improve Public Health

JAMA Psychiatry July 2020 Volume 77, Number 7



Cannabis use increases EOP risk

Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort

E. Manrique-Garcia[1]*, S. Zammit[2], C. Dalman[3], T. Hemmingsson[4], S. Andreasson[5] and P. Allebeck[1]

Psychological Medicine (2012), **42**, 1321–1328.

Cannabis Use Is Associated With Increased Psychotic Symptoms and Poorer Psychosocial Functioning in First-Episode Psychosis: A Report From the UK National EDEN Study

Jennifer L. Seddon[*,1], Max Birchwood[2], Alex Copello[3,4], Linda Everard[4], Peter B. Jones[5], David Fowler[6], Tim Amos[7], Nick Freemantle[8], Vimal Sharma[9,10], Max Marshall[11], and Swaran P. Singh[2]

Schizophrenia Bulletin vol. 42 no. 3 pp. 619–625, 2016

Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people

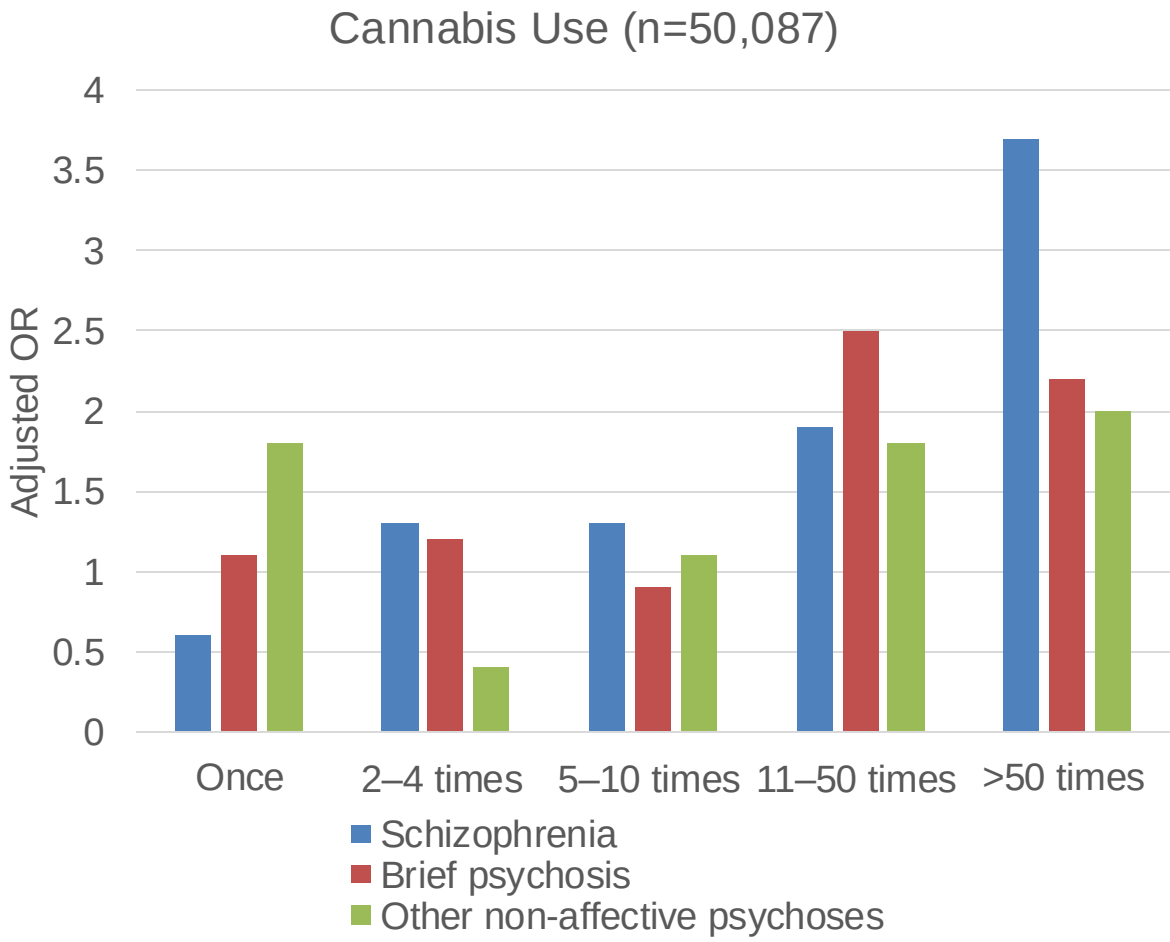
Cécile Henquet, Lydia Krabbendam, Janneke Spauwen, Charles Kaplan, Roselind Lieb, Hans-Ulrich Wittchen, Jim van Os

BMJ Online First bmj.com

Causal association between cannabis and psychosis: examination of the evidence

LOUISE ARSENEAULT, MARY CANNON, JOHN WITTON and ROBIN M. MURRAY

BRITISH JOURNAL OF PSYCHIATRY **(2004), 184, 110–117**



Conclusions

- Symptoms and impairments in EOP youth are similar to those seen in the adult-onset psychosis
- Cognitive and neuroanatomic deficits are common
- CNVs influence liability
- Childhood trauma and heavy cannabis use are risk factors
- Outcomes are highly variable
- Better treatments are needed

Collaborators & Colleagues

Boston Children's/Harvard
- David Glahn
- Alan Beggs
- Emma Deaso
- Casie Genetti
- Joseph Gonzalez-Heydrich
- Emma Knowles
- Sam Mathias
- Josephine Mollon
- Amanda Rodrigue
- Mustafa Sahin
- Chris Walsh

UCLA
- Carrie Bearden
- Katie Karlsgodt

Yale
- Marinka Koenis
- Godfrey Pearlson

U Penn/CHOP
- Aaron Alexander-Bloch
- Laura Almasy
- Raquel Gur
- Ruben Gur
- Laura Schultz

Oxford University
- Tom Nichols
- Steve Smith

U Texas Rio Grande
- Marcio de Almedia
- John Blangero
- Joanne Curran
- Ravi Duggirala
- Juan Peralta
- Anderson Winkler

Northwestern University
- Richard Smith

Stanford University
- Russ Poldrack

UT Health San Antonio
- Peter Fox
- Rene Olvera

Mexico
- Nuria Lanzagorta
- Humberto Nicolini

Université de Montréal
- Elise Douard
- Guillaume Huguet
- Sébastien Jacquemont

University of Edinburgh
- Andrew McIntosh
- Pippa Thomson

Alumni & Others
- Jen Barrett
- Christian Beckmann
- Alan Evans
- Sophia Frangou
- Karen Hodgson
- Peter Kochunov
- Angie Laird
- D Reese McKay
- Armin Raznahan
- Emma Sprooten
- Paul Thompson

Galatea Bio/Stanford
- Carlos Bustamante
- Alex Ioannidis

U Costa Rica
- Gabriela Chavarria
- Henriette Raventos

And many more!!!

THE TOMMY FUSS CENTER
for Neuropsychiatric Disease Research

Financial support from the Fuss Center, NIMH and others

Boston Children's Hospital
Until every child is well™

EPICenter and Manton Center information

- EPICenter Email: epicenter@childrens.harvard.edu
- EPICenter website:

https://www.childrenshospital.org/research/centers/epicenter-research

- Manton Center Email:

gdc@childrens.harvard.edu.

Manton Center website:

https://www.childrenshospital.org/research/centers/manton-center-orphan-disease-research/about-center

Thank you!