A Genetics-First Approach to Autism and Psychosis Spectrum Disorders: The 22q11.2 Deletion Syndrome

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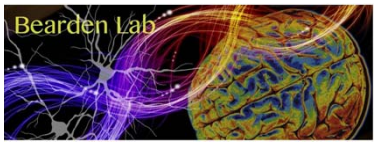

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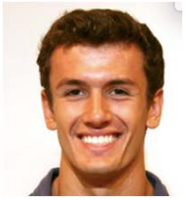

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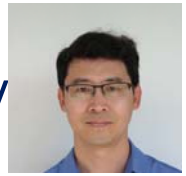

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22q11.2 International Brain Behavior Consortium

22q IBBC
International 22q11.2 Brain Behavior Consortium

22q11 ENIGMA Working Group

ENIGMA

IGC

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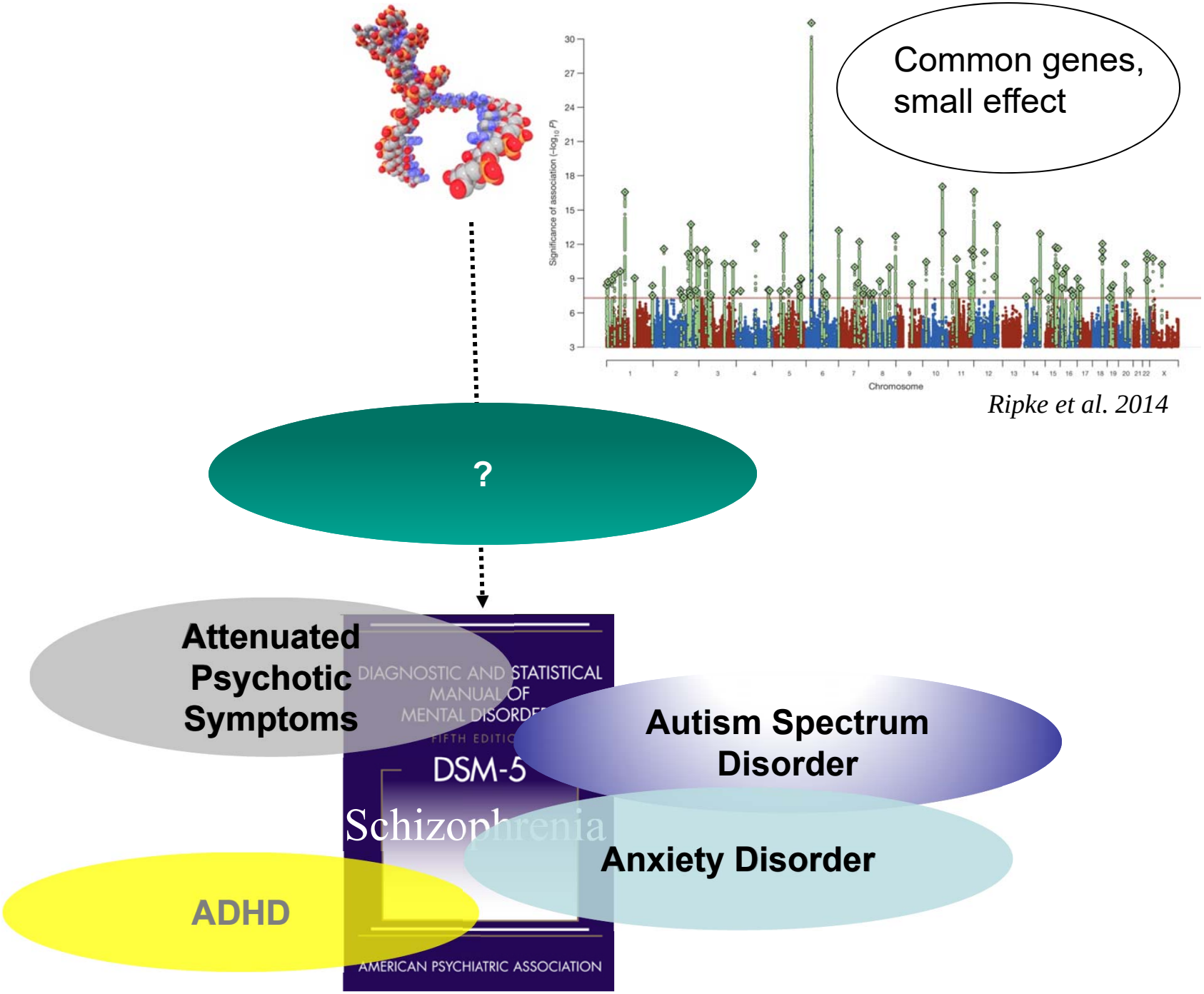
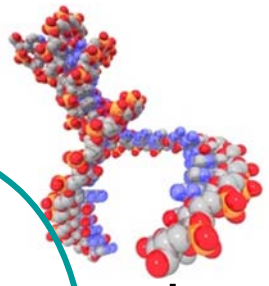

Common genes, small effect
Significance of association (-log10 P)
Chromosome
Ripke et al. 2014
?
Attenuated Psychotic Symptoms
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
FIFTH EDITION
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION
Autism Spectrum Disorder
Schizophrenia
Anxiety Disorder
ADHD

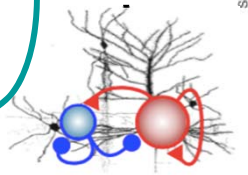
High Penetrance (rare) Genes

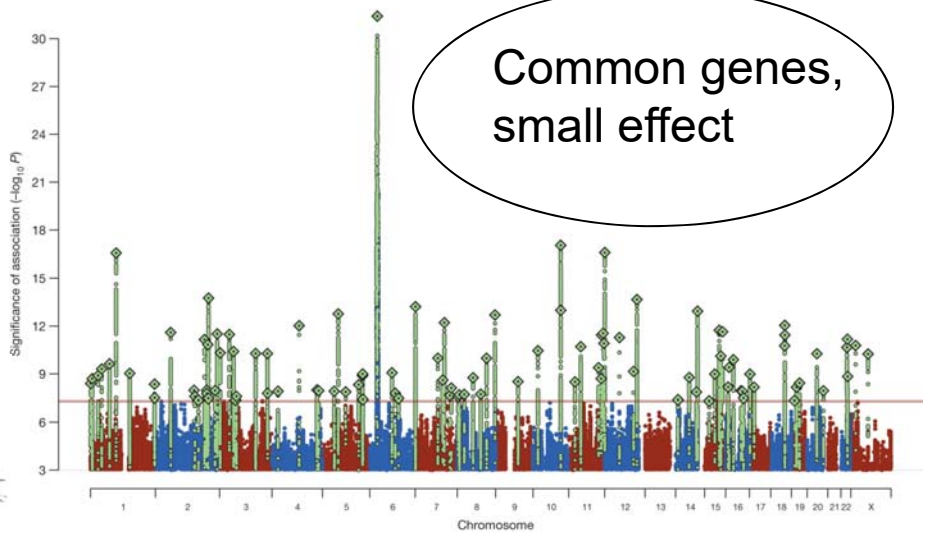
15q13.3 del

3q29 del

22q11.2 microdeletion



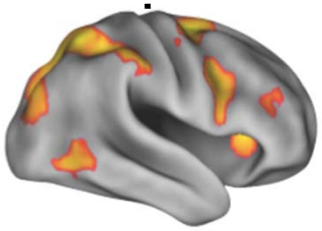




Common genes, small effect

Ripke et al. 2014

- Allows development of animal models with strong construct validity
- Ideal systems to dissect circuitry mediating behaviors
- Identified very early in development



Attenuated Psychotic Symptoms

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
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AMERICAN PSYCHIATRIC ASSOCIATION

Autism Spectrum Disorder

Schizophrenia

Anxiety Disorder

ADHD

Adapted from Bearden et al. Dev&Psychopathology 2016

Schizophrenia: Genome, Interrupted

Rita M. Cantor[1,2,*] and Daniel H. Geschwind[1,2,3,*]

Rare de novo variants associated with autism implicate a large functional network of genes involved in formation and function of synapses

Sarah R. Gilman[1,*], Ivan Iossifov[2,#,*], Dan Levy[2], Michael Ronemus[2], Michael Wigler[2], and Dennis Vitkup[1,#]

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

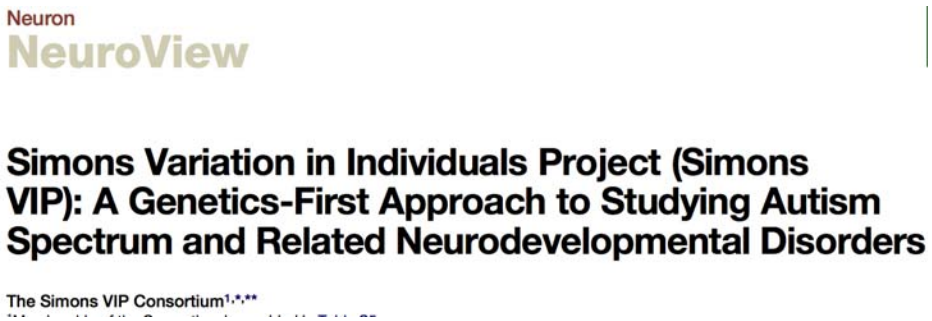
Jonathan Sebat[1], Deborah L. Levy[2] and Shane E. McCarthy[1]

CNVs: Harbinger of a Rare Variant Revolution in Psychiatric Genetics

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

- Majority of cases of developmental neuropsychiatric dx of unknown etiology; But- rare genomic copy number variants (CNVs) may account for a larger proportion of cases than previously believed
  - ~2% of schizophrenia cases (Levinson et al. 2011; Bassett et al. 2010; Rees et al 2014); 25% of cases of simplex ASD (Geschwind 2015, Devlin & Scherer 2012)
- Also provide strong evidence for genetic pleiotropy, challenging widely held views of diagnostic 'categories'

Genetics First Approach


Neuron
NeuroView

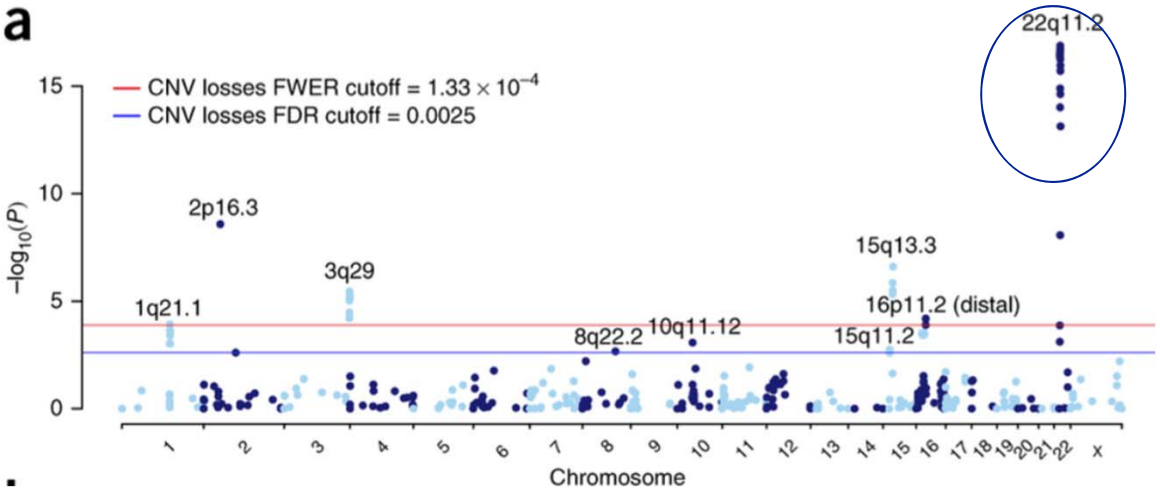
Simons Variation in Individuals Project (Simons VIP): A Genetics-First Approach to Studying Autism Spectrum and Related Neurodevelopmental Disorders

The Simons VIP Consortium[1,*,**]

- Sample heterogeneity has been a major barrier to scientific discovery.
- Are there characteristics specific to certain subsets of patients with distinct genetic etiology?
- Treatment implications- Are treatments best tailored to a specific genetic event, or generalizable to those with neurodevelopmental/psychiatric illness of other or unknown etiology?

22q11.2 Microdeletion Syndrome

- Velocardiofacial/DiGeorge Syndrome
- Estimated incidence ~ 1/4000 live births (Grati et al 2015)
- Results from hemizygous deletion of chromosome 22q11 (~2.6 Mb)
- Cardiac defects, immune deficiency, craniofacial anomalies, intellectual disability
- Risk of schizophrenia ~ 25x the general population risk (O'Rourke & Murphy 2019; Bassett et al. 2010); account for ~1% of sporadic SZ cases (Stefansson et al., 2008; Karayiorgou et al. 2010)
- Elevated rates of Autistic Spectrum Disorder (12-50%), ADHD (33-40%) and anxiety disorder (40-50%) in childhood (Schneider et al. 2014; Richards et al. 2014)



CNV and SCZ Working Group of PGC, Nat Gen 2016

Kobrynski Lancet 2007; Kapadia & Bassett, CMAJ 2008

Key Questions

- Limited data on individuals carrying the same highly penetrant CNV

- What are risk factors for psychosis in a highly penetrant CNV like 22q11DS ? Do these overlap with idiopathic illness?

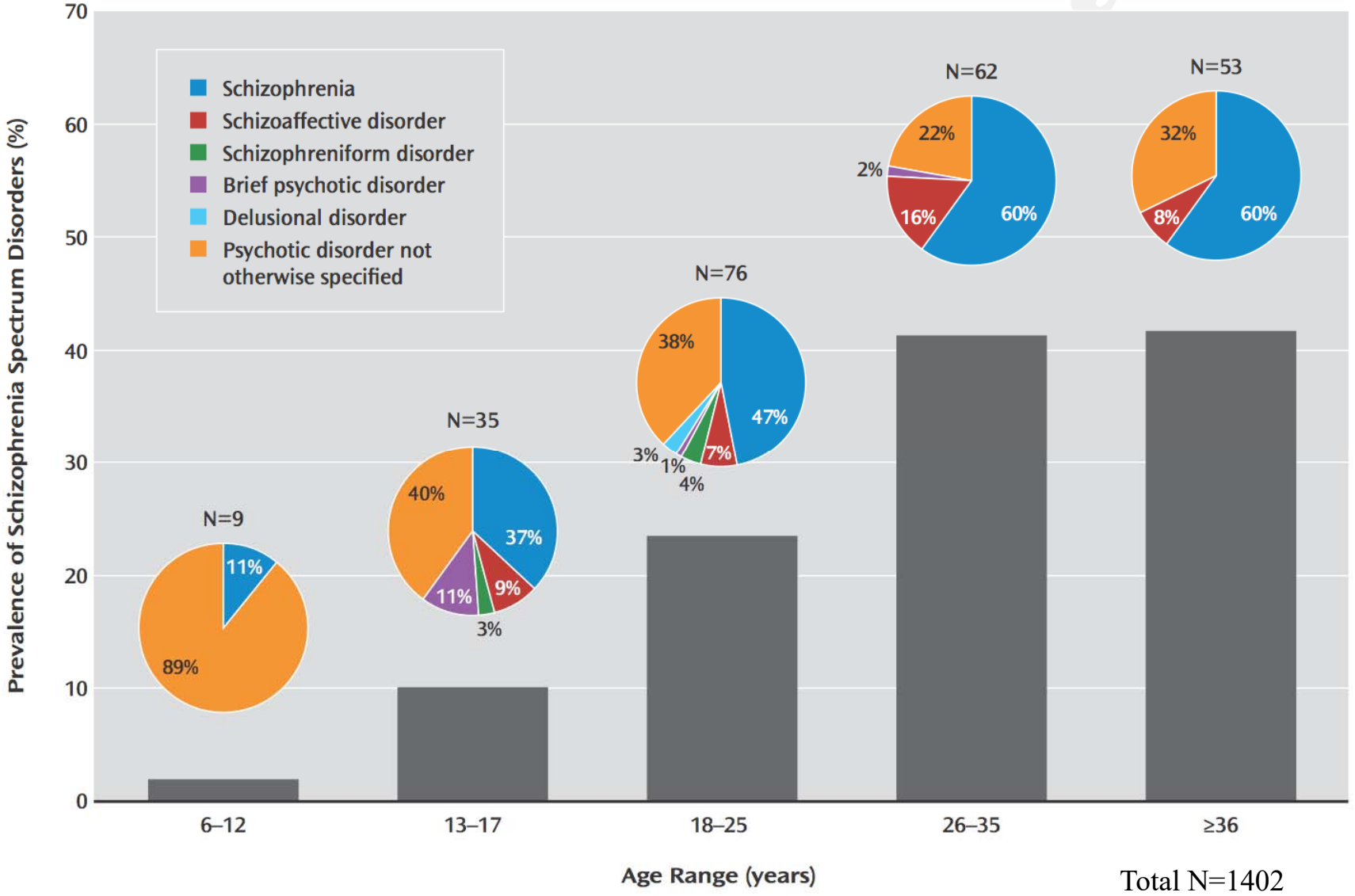
- Are there consistent and reproducible effects of the 22q11.2 deletion on brain structure? Do these effects converge with those observed in idiopathic psychosis?

- What are mechanisms underlying diverse phenotypic presentations in 22q11DS?

- **Gene dosage effects may provide clues into disease biology; What are neurofunctional consequences of reciprocal imbalances?**

- Premise: Copy number variation may have a more powerful effect on intermediate phenotype than common genetic variation.

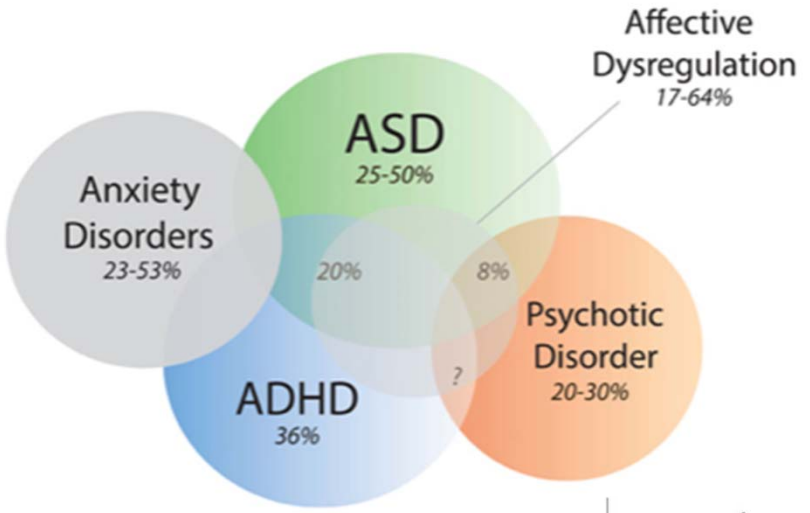
Prevalence of Schizophrenia Spectrum Disorders by Age in 22q11DS (n=1402); 41% of adults age 25+



Total N=1402

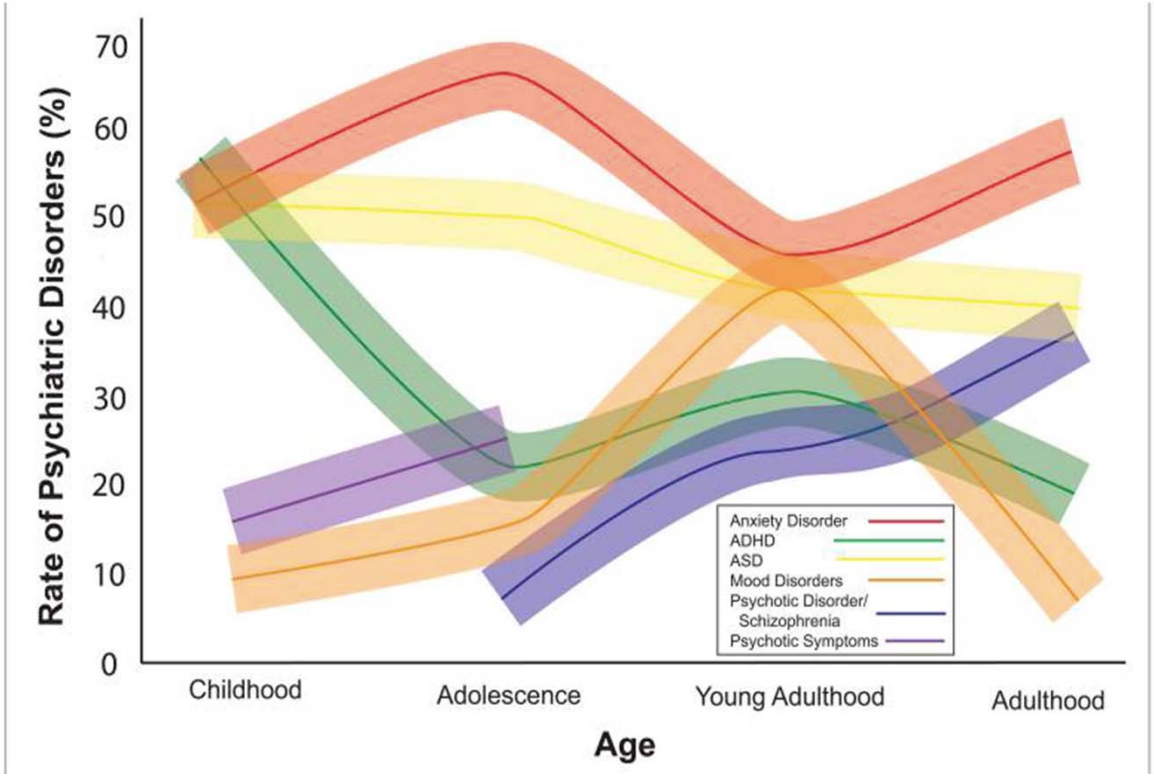
Schneider , iBBC et al AJP 2014

Overlapping and Distinct Neuropsychiatric Traits in 22q11DS



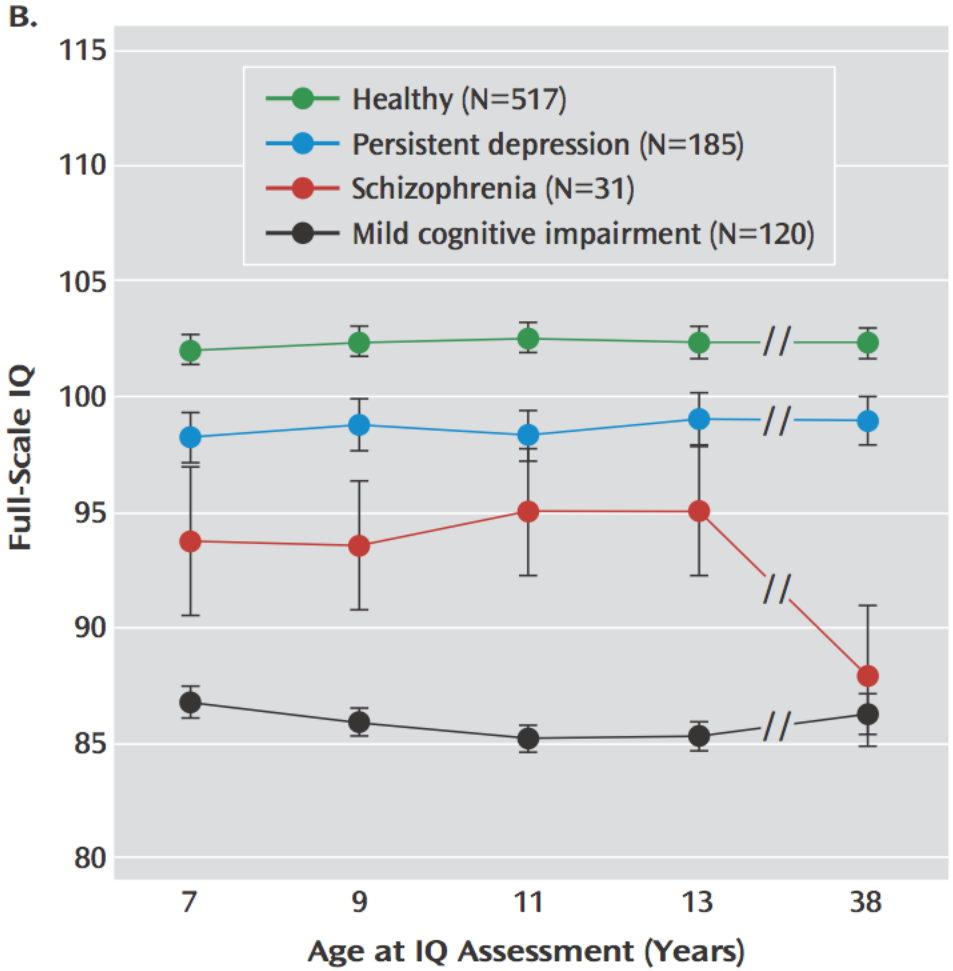
-Comorbidity rates are not frequently reported; but is the rule rather than exception.

-Affective dysregulation present in a substantial proportion of 22q11DS patients, across diagnoses



Jonas et al Biol Psych 2014

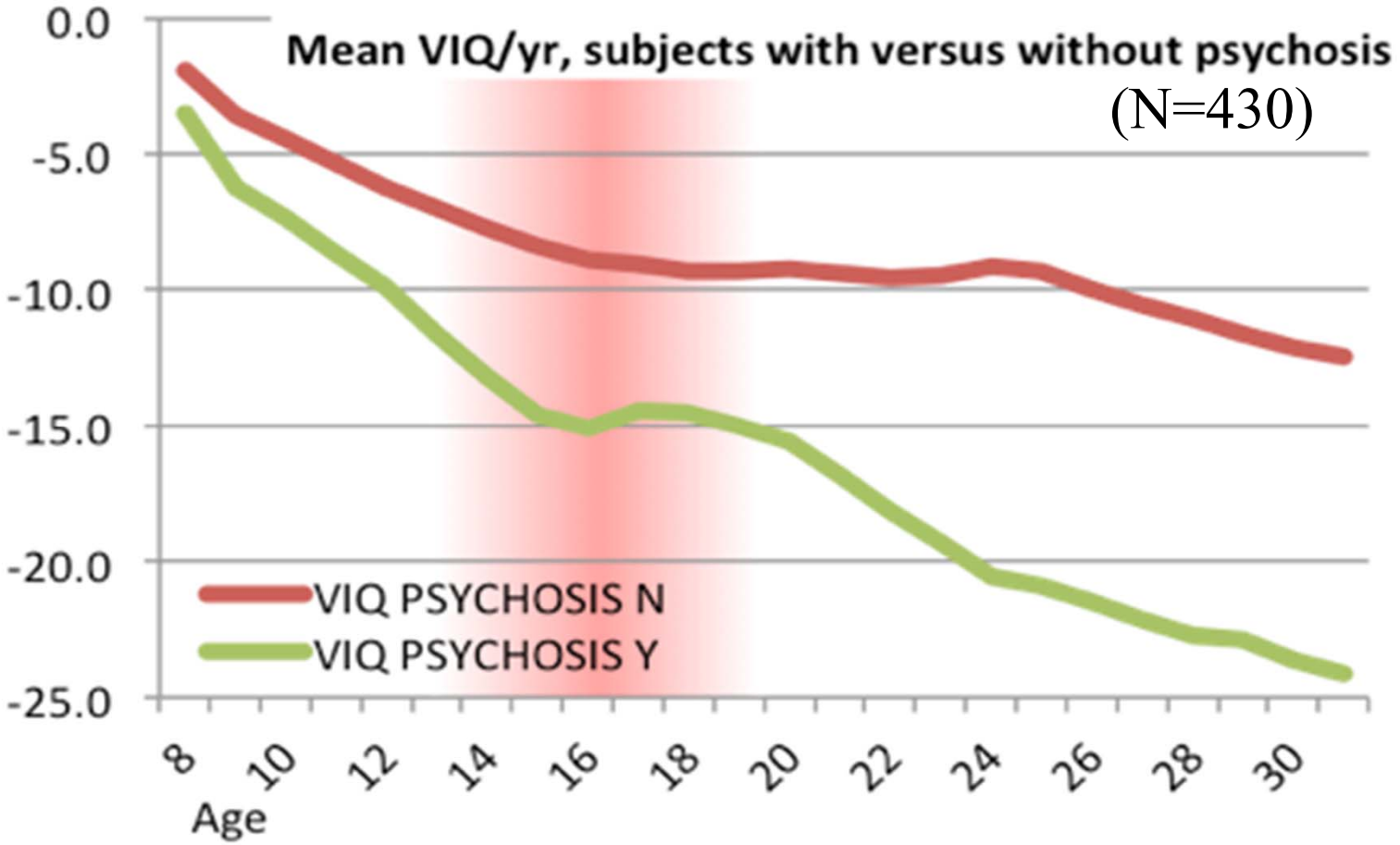
Cognitive Decline as a Predictor of Psychosis in the General Population; Dunedin Birth Cohort



IQ was stable across childhood for all groups but declined for the schizophrenia group between ages 13 and 38 (0.39 SD)

Meier et al. AJP 2014

Does Cognitive Decline Predict Psychosis in 22q11DS?



Verbal IQ decline significantly increased risk for psychosis (OR 3.5; 95% CI=1.77-9.04, p=0.001)

Vorstman et al JAMA Psychiatry, 2015

Other Risk Factors for Psychosis in 22q11DS

- Inattention symptoms (OR 1.51(1.05–2.22), p=.03) and ADHD diagnosis, esp. at 2 timepoints (OR=9.79(3.59–30.52), p<.001) predicted development of psychotic symptoms; ADHD diagnosis at both timepoints associated with psychotic disorder (4.76(1.37–18.91), p<.01) (Niarchou, iBBC, et al, 2019)

- Negative symptoms and functional impairment predicted emergence of positive psychosis-spectrum symptoms (Tang et al. 2017)

- Impairment in odor discrimination correlated with higher negative and overall psychosis-spectrum symptoms (Tang et al. 2018)

- Inflammation - higher serum levels of IL-6 and higher IL6:IL10 ratio (indicator of proinflammatory activation), inflammatory T-helper cells in psychotic 22q11DS (Domachevsky et al 2017, Vergaelen et al 2018)

- Prospective longitudinal study found no association between childhood ASD diagnosis and subsequent psychotic disorder (Fiksinski et al. 2017)

Why is rate of ASD so variable in 22q11DS studies?

-Rate of categorical ASD diagnosis ranges from 12-50% across studies

-Core autism behaviors (impairments in joint attention, gestural communication, initiating conversation, restricted interests + language delay) characteristic of 22q11DS

-Are distinct biological substrates associated with categorical ASD diagnosis in 22q11DS or does a dimensional approach better fit the findings?

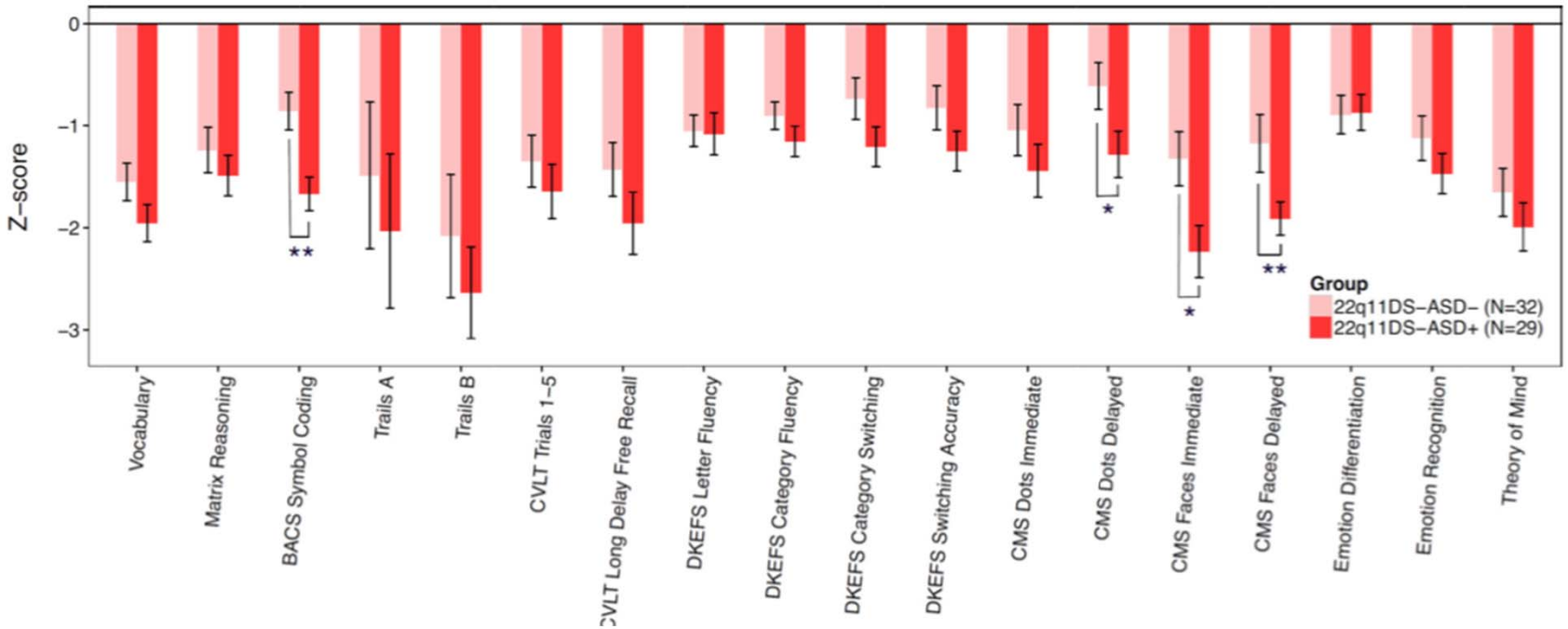
Demographic and clinical characteristics of study participants

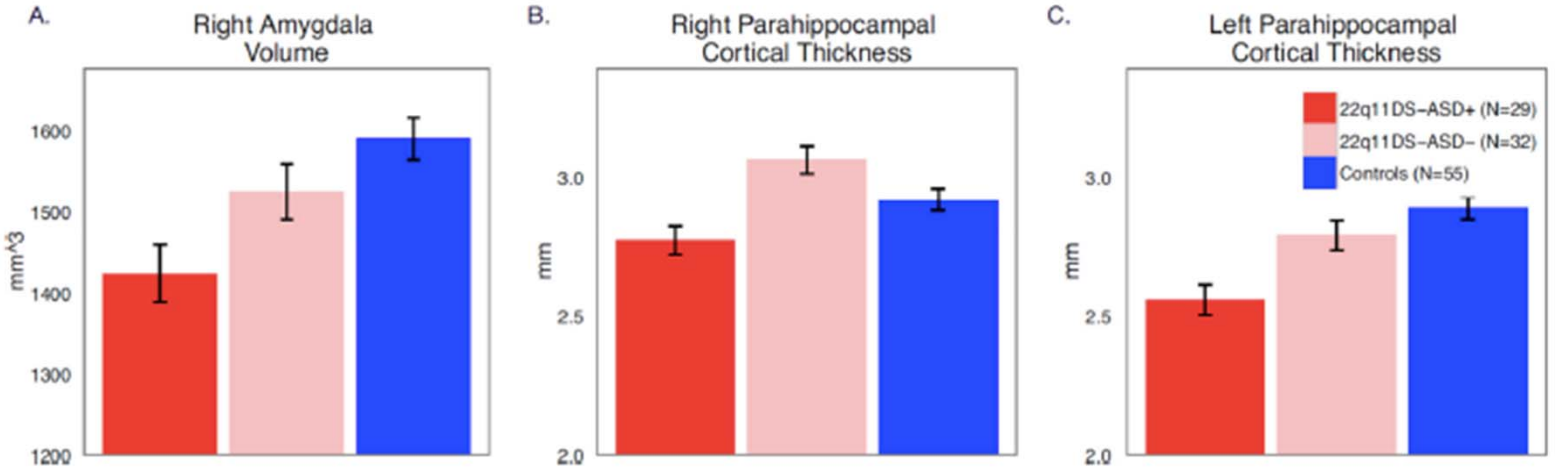
	22q11DS-ASD+ Participants (n=29)	22q11DS-ASD– Participants (n=32)	Typically Developing Controls (n=55)	
Age (years, +/– SD) [Age range, years]	14.34 (5.70) [6–26]	13.78 (5.35) [6–25]	12.87 (4.93) [6–26]	p=.45
Participant Education (years,+/– SD)	6.72 (4.41)	6.47 (4.72)	7.15 (5.16)	p=.81
Gender (N, % female)	11 (38%)	18 (56%)	26 (47%)	p=.36
Mean WASI IQ (+/– SD)	76.7 (11.8)	81.5 (14.0)	110.2 (20.4)	p= 9.0121e-15[a]

[a] 22q-ASD+ and 22q11DS-ASD– did not significantly differ on measures of WASI IQ (t=1.5, p=.2).

Jalbrzikowski et al Biol Psych CNNI 2017

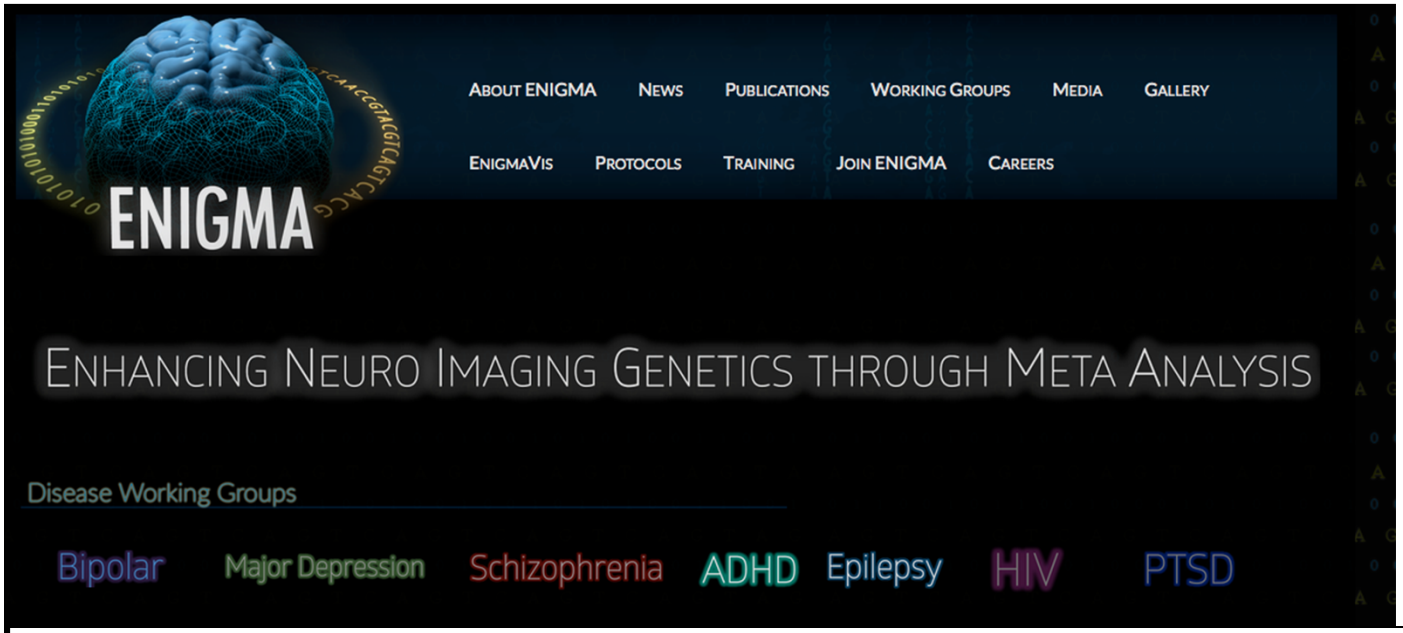
Categorical Differences: 22q11DS with and without ASD





-Dimensional model best fit for cognitive measures and amygdala volume

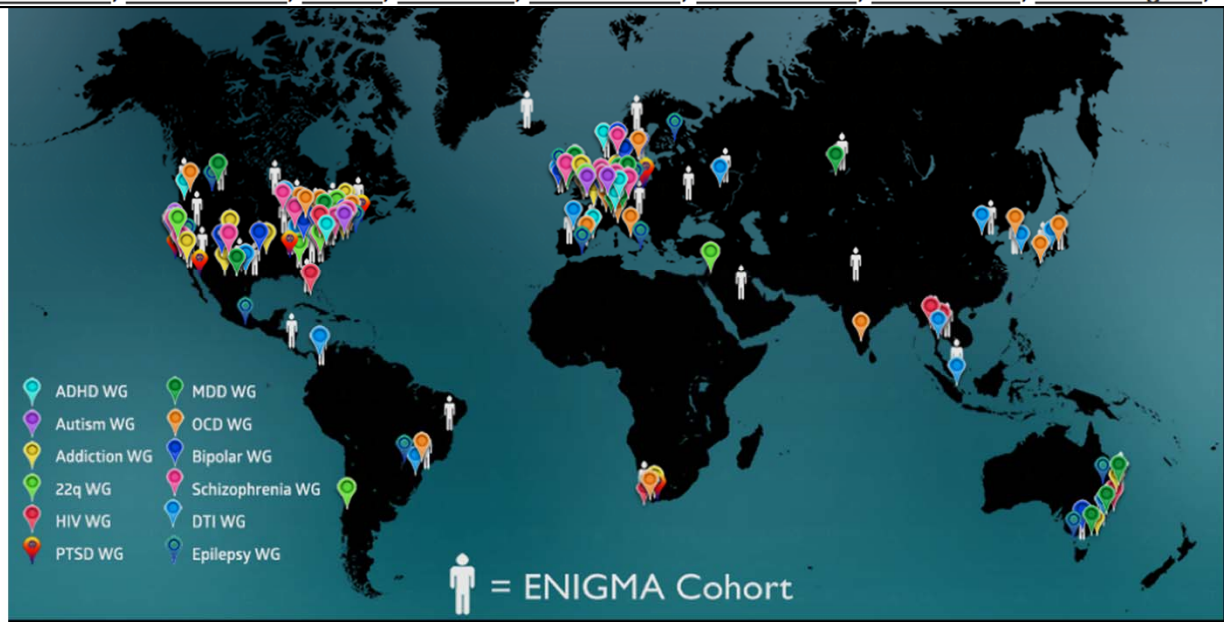
-Categorical model best fit for parahippocampal thickness



Nature. 2015 Apr 9;520(7546):224-9. doi: 10.1038/nature14101. Epub 2015 Jan 21.

Common genetic variants influence human subcortical brain structures.

Hibar DP, Stein JL, Renteria ME, Arias-Vasquez A, Desrivières S, Jahanshad N, Toro R, Wittfeld K, Abramovic L, Andersson M, Aribisala BS, Armstrong NJ,



Bearden & Thompson, Neuron, 2017

ENIGMA 22q11.2 Group Demographics

Site	N	Age ± SD	Sex (M/F)	22q11DS	22q11Dup	HC
UCLA	152	14.6±8.1	79/73	75	40	42
Davis	213	10.8±2.3	112/101	123	-	90
IOP	65	17.2±8.4	31/34	38	-	27
Newcastle	39	17.3±2.9	17/22	20	-	19
SUNY	75	20.8±2.0	43/32	55	-	20
Maastricht	74	29.6±8.8	44/30	28	-	46
Utrecht	58	18.2±3.8	19/39	58	-	-
Toronto	65	41.9±7.9	31/34	53	-	12
Penn	100	17.3±3.2	60/40	50	-	50
Cardiff	36	15.8±7.3	18/18	23	-	13
Santiago	26	21.2±5.6	9/17	14	-	12

22q11DS N= 537, *22q11Dup* N= 40 (UCLA)

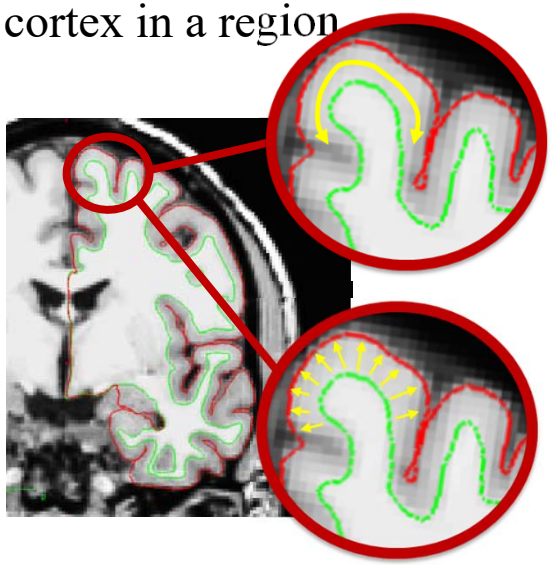
Healthy Controls N= 331

http://enigma.ini.usc.edu/?p=4900

Determinants of Neuroanatomic Features: Cortical Thickness vs. Surface Area

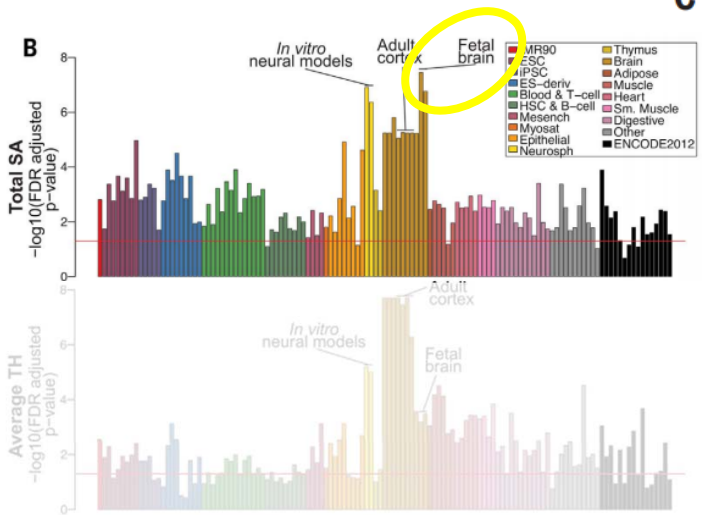
- Volume measures derived from indices of both CT and SA
- Driven by distinct genetic mechanisms[1,2]; Different underlying neurobiology/ developmental trajectory[3,4]

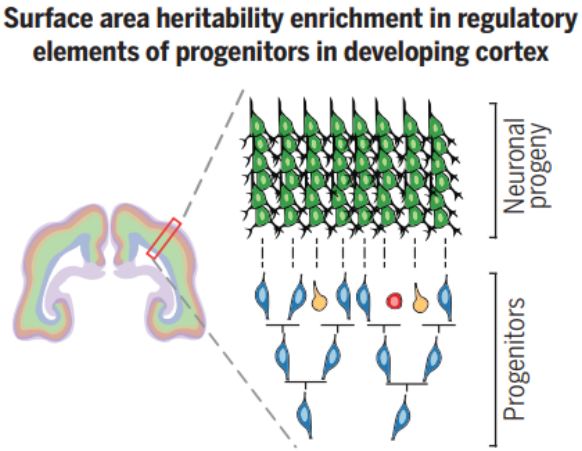
Surface Area (SA): total area covered by cortex in a region



Cortical Thickness (CT): average thickness of 6 cortical layers in region

SA impacted by regulation of neural progenitor proliferation/cell-cycle in developing cortex



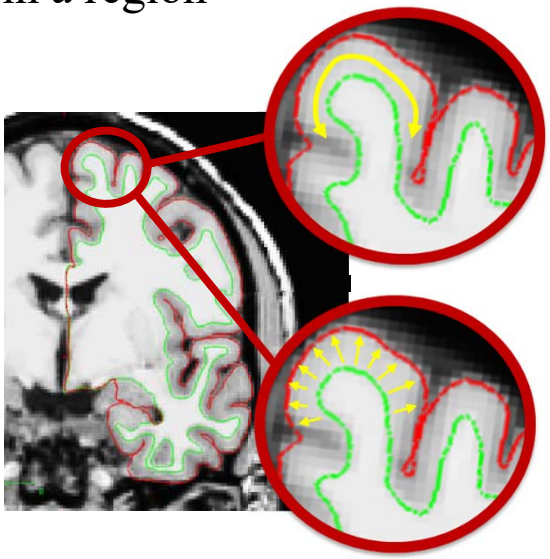


Grasby et al., 2020, *Science*

[1]Winkler et al., 2009; [2]Panizzon et al., 2009;
[3] Raznahan et al. 2011; [4]Tamnes et al 2017

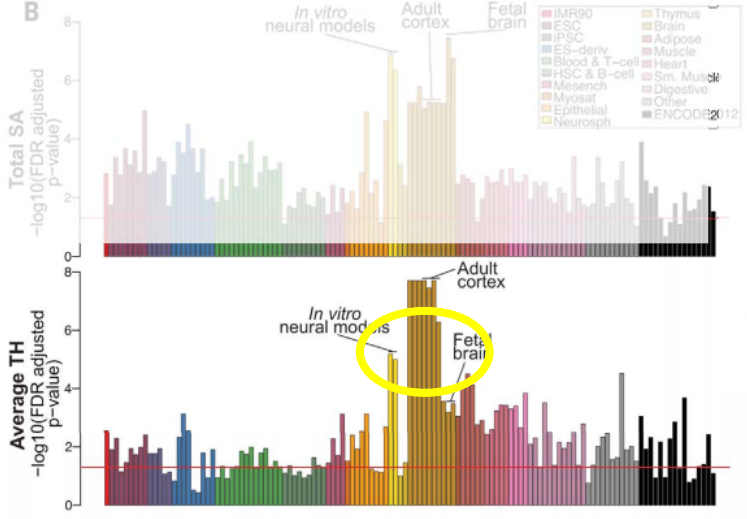
Determinants of Neuroanatomic Features: Cortical Thickness vs. Surface Area

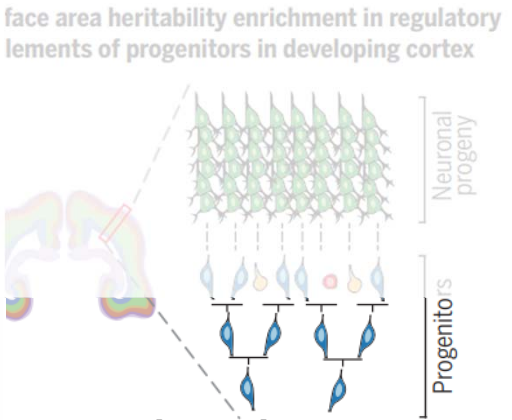
Surface Area (SA): total area covered by cortex in a region



Cortical Thickness (CT): average thickness of 6 cortical layers in region

CT shaped by later developmental processes, possibly synaptic density + myelination



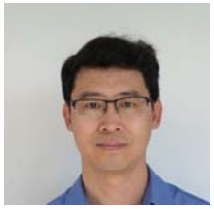


Grasby et al., 2020, *Science*

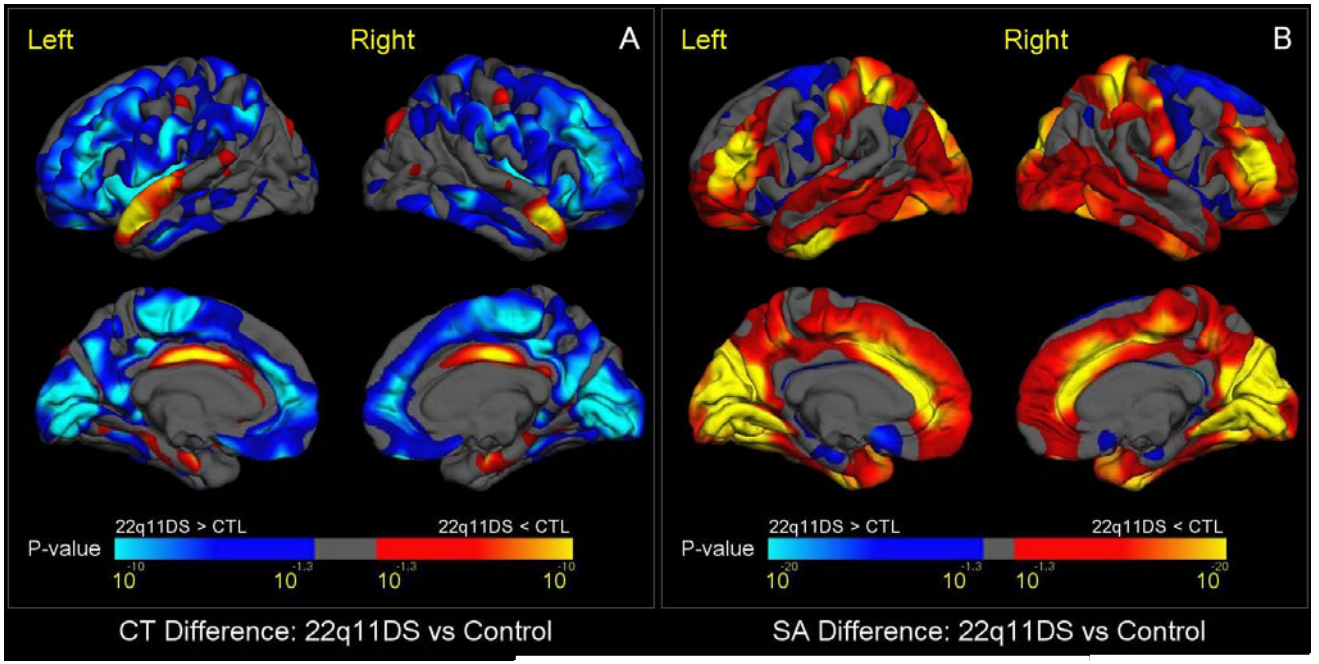
Methods

-Freesurfer 5.3.0 processing pipeline (http://enigma.ini.usc.edu/protocols/)

-Covary for age, age2, sex, site

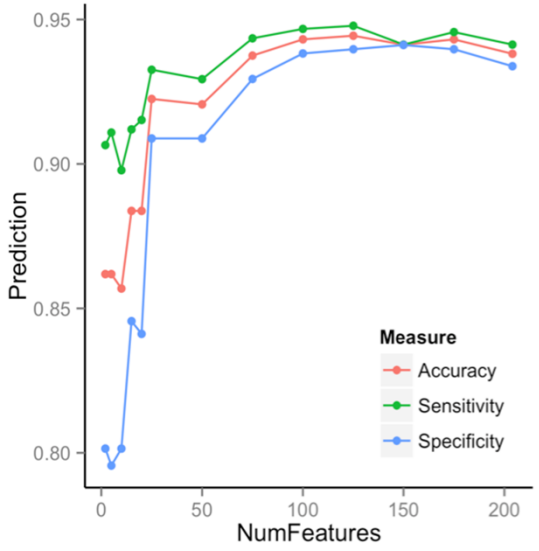


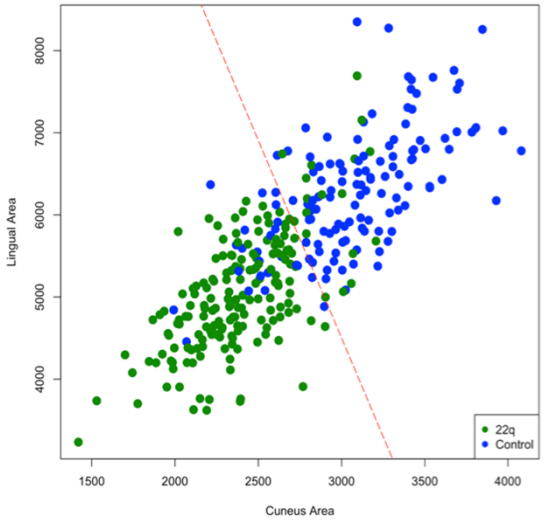
Cortical Maps: Widespread SA reductions in 22q11DS and increased CT in majority of regions



Sun et al, Molecular Psychiatry 2018

- Accuracy peaks at 94.44% (125 features) – vs. ~65% for 'idiopathic' Bipolar Disorder *(Nunes et al Molec Psych 2018)*
- 86.36% accuracy using bilateral cuneus and lingual SA

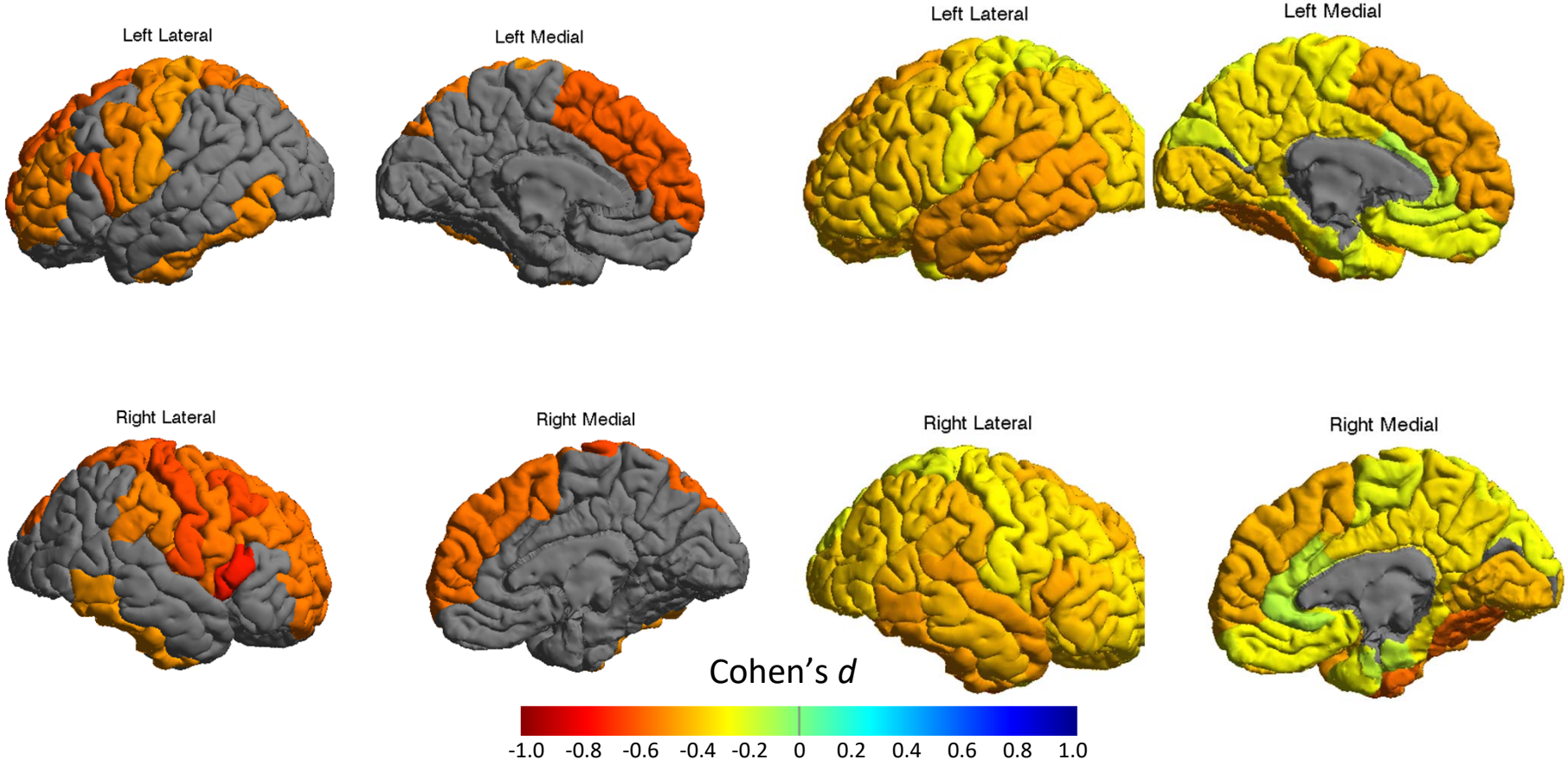




Significant Cortical Thinning in Fronto –Temporal, Heteromo Association Regions in 22q11DS-Psychosis

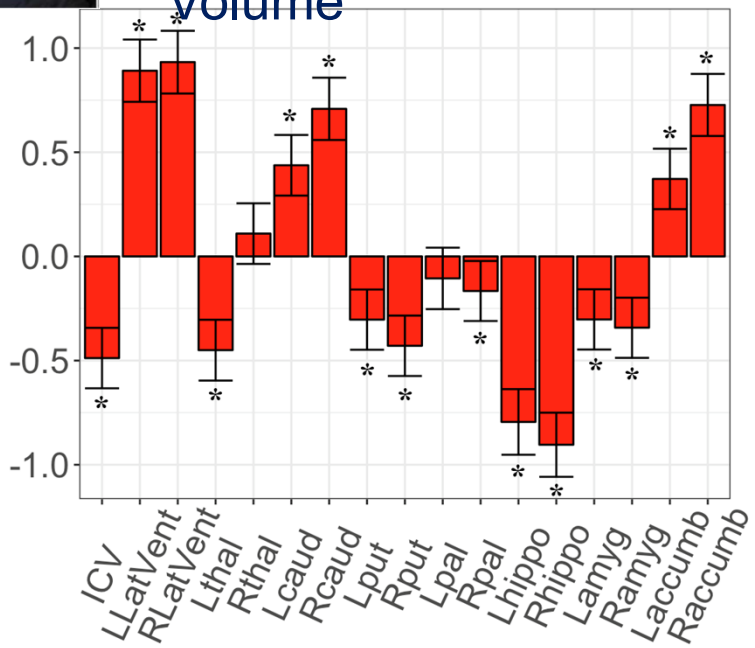
Cortical Thickness-22q Psychosis (n=60) vs. 22q-No Psychosis (n=60)

Cortical Thickness- Schizophrenia (n=4474) vs. Control (n=5098)



Cross-diagnosis correlation indicates significant convergence with cortical brain regions affected in idiopathic schizophrenia (r=0.45, p<.0001; van Erp et al, Biol Psych 2018) but not major depression (r=.06; p=0.62; Schmaal et al, Molec Psych 2017)

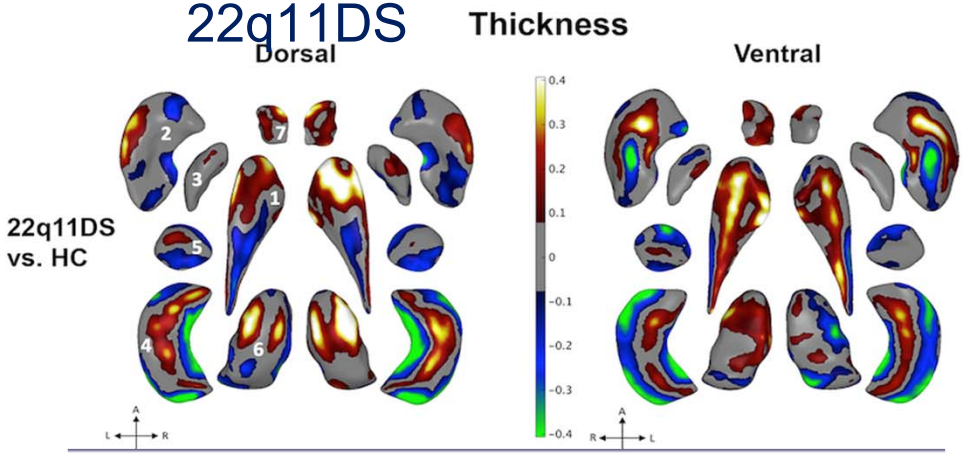
Global Volume

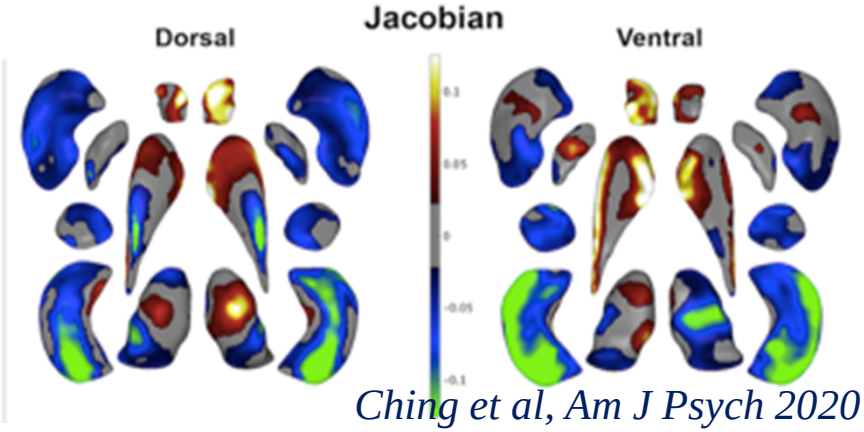


Blue/Green regions of lower thickness or SA;
Red/Yellow regions of higher thickness or SA

1. Caudate 2. Putamen 3. Globus Pallidus 4. Hippocampus 5. Amygdala 6. Thalamus 7. Nucleus Accumbens

"Masks" Complex Pattern of Subcortical Alterations in 22q11DS

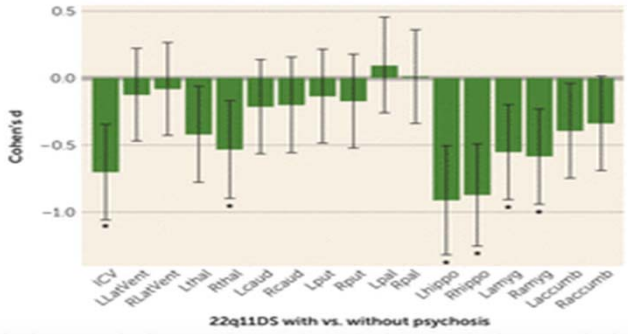




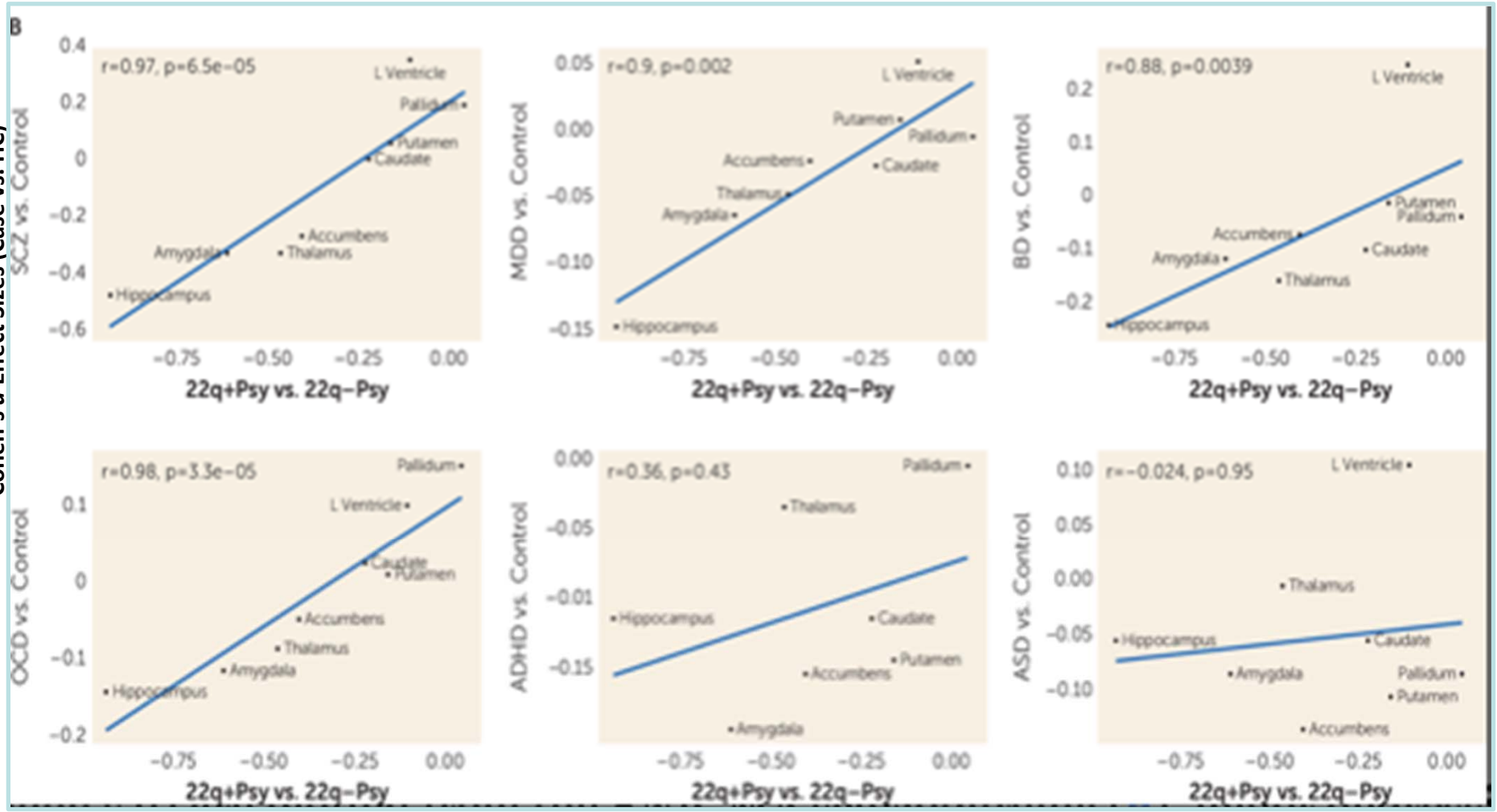
Ching et al, Am J Psych 2020

- -Predominantly affects subregions with projections
- to frontal, cingulate, and association cortices

- -Prominent Reductions in Hippocampus, Amygdala, Ventral Thalamus in 22q11DS Cases with Psychosis vs. 22q11DS-No Psychosis



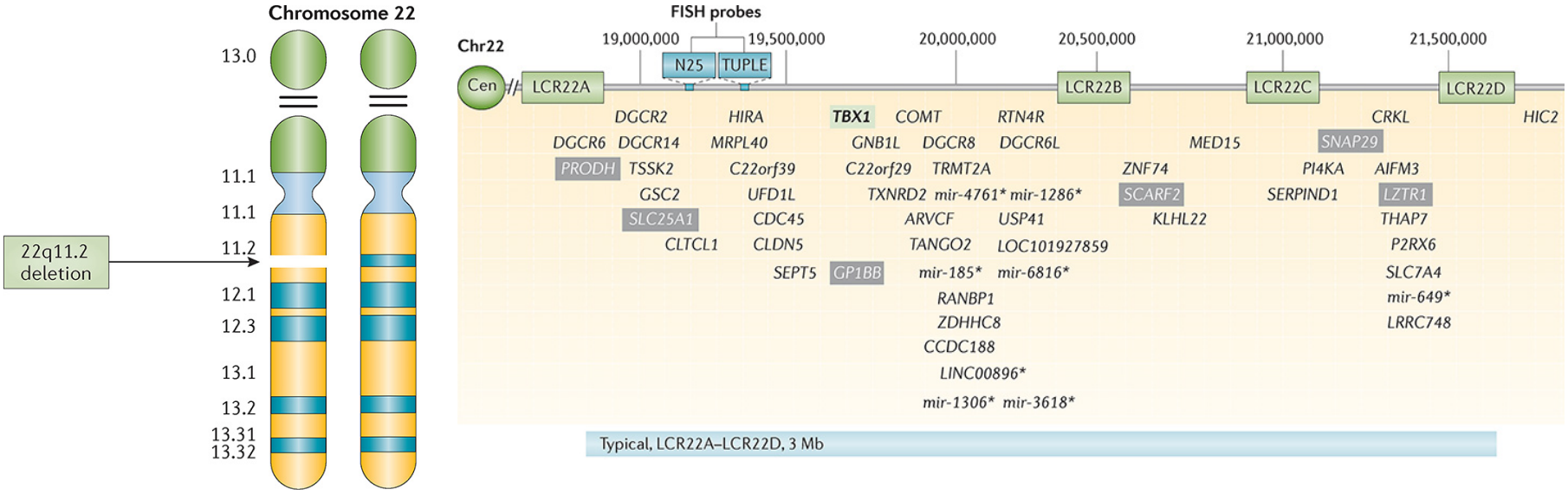
Cross-Disorder Analysis: Convergence of Subcortical Alterations in 22q+Psychosis with SCZ, MDD, Bipolar Disorder and OCD (NOT ASD, ADHD)



Ching et al, Am J Psych 2020

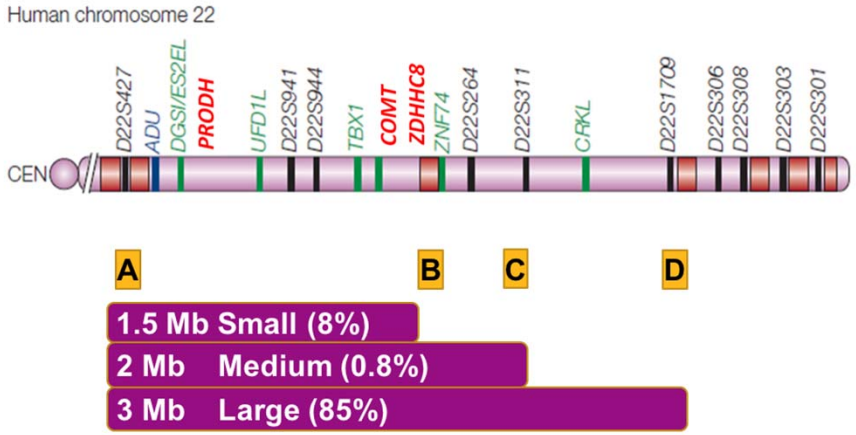
Which 22q11.2 Genes Drive Brain Phenotypes?

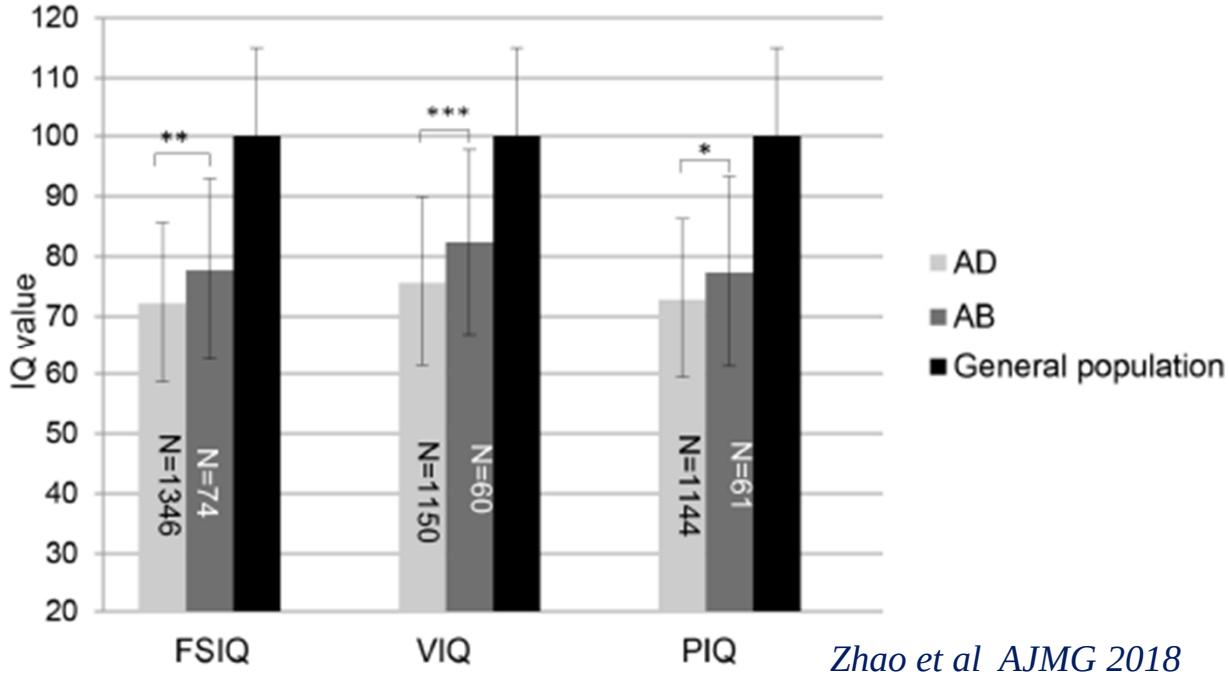
- 'Genomic hotspot' region (ISC, Nature 2008; Marshall et al. AJHG 2008; PGC 2016)
- Typical A-D 22q11.2 deletion spans 46 protein-coding genes
- Several highly expressed in brain & involved in early neuronal migration, cell fate decision in cortex, microRNAs



McDonald-McGinn et al., 2015, *Nat Rev Dis Primers*

Effects of Deletion Size on Cognition (n=1420)

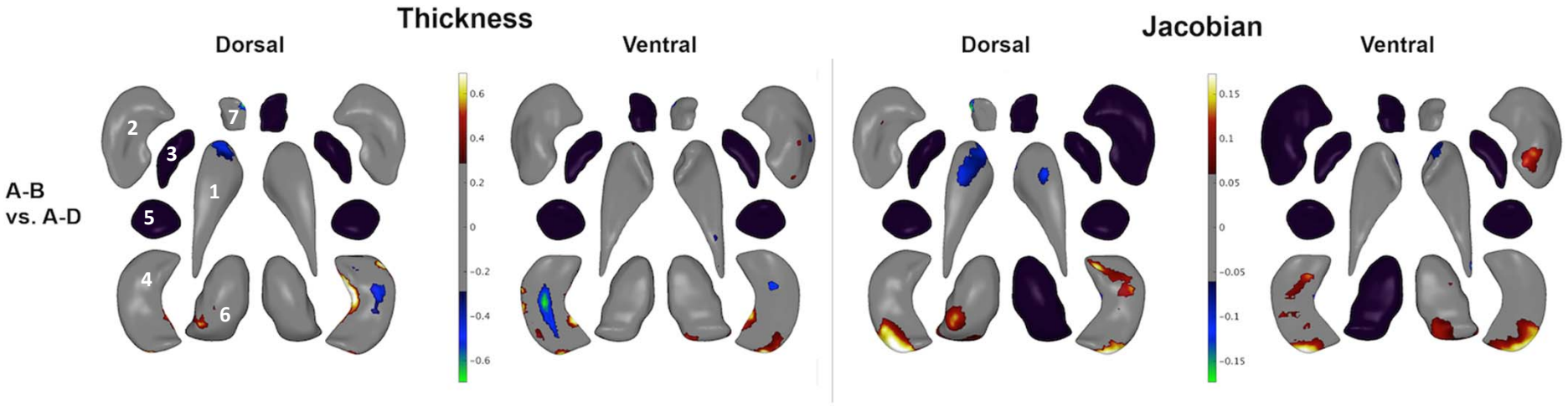




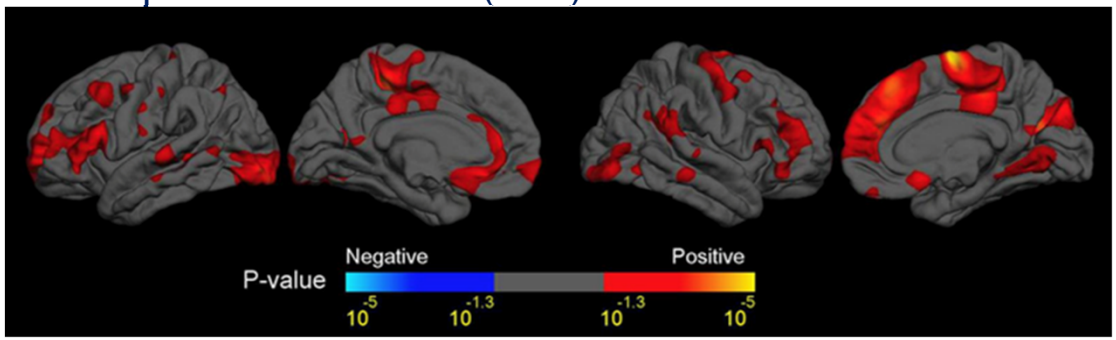
Zhao et al AJMG 2018

Full Scale, Verbal and Performance IQ decreased by 0.3-0.5 SD in AD vs. AB deletions

Might brain structural differences underlie effect of deletion size on IQ ?



- Shape analysis reveals localized differences as a function of deletion size (not detected by gross volume analysis)
- Increased SA in hippocampus, thalamus and putamen in small (A-B) deletion
- Consistent with higher cortical SA in A-B Deletion carriers (p=.003)



Mol Psychiatry 2018

Blue/Green indicate regions of lower thickness or surface area
Red/Yellow indicate regions of higher thickness or surface area

1. Caudate 2. Putamen 3. Globus Pallidus 4. Hippocampus 5. Amygdala 6. Thalamus 7. Nucleus Accumbens

ENIGMA

IMMEDIATE COMMUNICATION

Evidence that duplications of 22q11.2 protect against schizophrenia

E Rees[1], G Kirov[1], A Sanders[2,3], JTR Walters[1], KD Chambert[4], J Shi[5], J Szatkiewicz[6], C O'Dushlaine[4], AL Richards[1], EK Green[1,7], I Jones[1], G Davies[1], SE Legge[1], JL Moran[4], C Pato[8], M Pato[8], G Genovese[4], D Levinson[9], J Duan[2,3], W Moy[2], HHH Göring[10], D Morris[11], P Cormican[11], KS Kendler[12], FA O'Neill[13], B Riley[12], M Gill[11], A Corvin[11], Wellcome Trust Case Control Consortium[19], N Craddock[1], P Sklar[14], C Hultman[15], PF Sullivan[16,17,18], PV Gejman[2,3], SA McCarroll[4], MC O'Donovan[1] and MJ Owen[1]

A number of large, rare copy number variants (CNVs) are deleterious for neurodevelopmental disorders, but large, rare, protective CNVs have not been reported for such phenotypes. Here we show in a CNV analysis of 47 005 individuals, the largest CNV analysis of schizophrenia to date, that large duplications (1.5–3.0 Mb) at 22q11.2—the reciprocal of the well-known, risk-inducing deletion of this locus—are substantially less common in schizophrenia cases than in the general population (0.014% vs 0.085%, OR = 0.17, $P = 0.00086$). 22q11.2 duplications represent the first putative protective mutation for schizophrenia.

Molecular Psychiatry (2014) **19,** 37–40; doi:10.1038/mp.2013.156; published online 12 November 2013

Keywords: 22q11.2; CNV; duplication; protective; schizophrenia

Table 1. Frequencies of 22q11.2 duplications in cases and controls

Study	*Case 22q11.2dup frequency (N CNVs/N samples)*	*Control 22q11.2dup frequency (N CNVs/N samples)*	P *value (Fisher's exact test)*	*OR (95% CI)*
Discovery	0% (0/6 882)	0.089% (10/11 255)	0.017 (2-Tail)	
Replication				
MGS EA	0.090% (2/2 215)	0.16% (4/2 556)		
MGS AA	0% (0/977)	0.23% (2/881)		
ISC	0% (0/3 395)	0.031% (1/3 185)		
Irish/WTCCC2	0% (0/1 377)	0.10% (1/992)		
African American	0.061% (1/1 637)	0% (0/960)		
Swedish	0% (0/4 655)	0.066% (4/6 038)		
Total replication	0.021% (3/14 256)	0.082% (12/14 612)	0.020 (1-Tail)	
Total discovery + replication	0.014% (3/21 138)	0.085% (22/25 867)	0.00086 (2-Tail)	0.17 (0.050–0.56)
Other disorders				
ID/DD/CM				
ASD				

				Data Set 1 (2992 Cases vs. 5176 Controls)		Data Set 2 (3596 Cases vs. 2636 Controls)		Data Set 3 (4092 Controls)		
Region/Gene	CHR	BP (Mb)	Type	Cases	Controls	Cases	Controls	Controls	OR (95% CI)	p^a
Reported Loci										
22q11.2	22	18.6–21.8	DEL	1	1	5	0	0	11.01 (1.33–505.04)	.0094[b]
22q11.2	22	18.6–21.8	DUP	0	1	0	1	1	0 (0–4.44)	.5567

Li et al Biol Psych 201

Published in final edited form as:
Nat Genet. 2008 December ; 40(12): 1466–1471. doi:10.1038/ng.279.

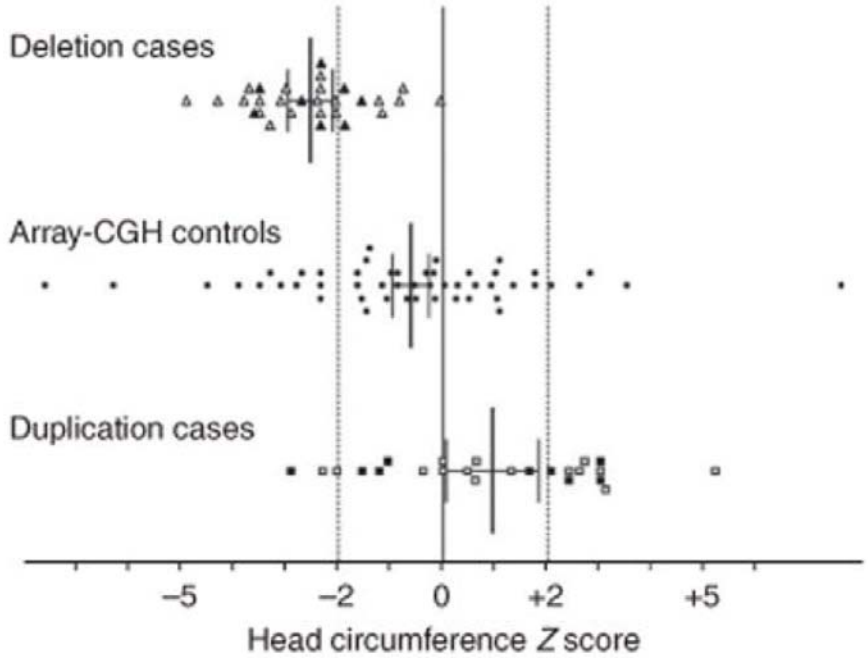
Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities

Europe PMC Funders Group
Author Manuscript
Nature. Author manuscript; available in PMC 2010 August 04.

Published in final edited form as:
Nature. 2010 February 4; 463(7281): 671–675. doi:10.1038/nature08727.

A novel highly-penetrant form of obesity due to microdeletions on chromosome 16p11.2

R. G. Walters[1,2,*], S. Jacquemont[3,*], A. Valsesia[4,6], A. J. de Smith[1], D. Martinet[3], J.



Brunetti-Pierri et al. *Nature* 2008

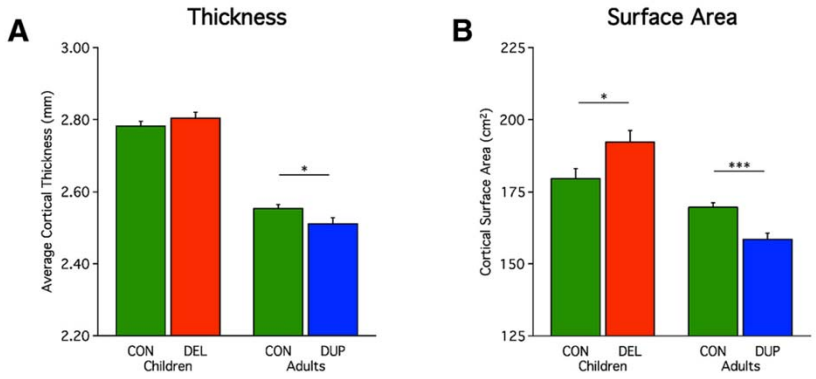
Mirror extreme BMI phenotypes associated with gene dosage at the chromosome 16p11.2 locus

Sébastien Jacquemont[1], Alexandre Reymond[2], Flore Zufferey[1], Louise Harewood[2], Robin G. Walters[3], Zoltán Kutalik[45], Danielle Martinet[1], Yiping Shen[67], Armand Valsesia[458], Noam D. Beckmann[1], Gudmar Thorleifsson[9], Marco Belfiore[1], Sonia

Neurobiology of Disease

Opposing Brain Differences in 16p11.2 Deletion and Duplication Carriers

Abid Y. Qureshi,[1,2] Sophia Mueller,[4,5] Abraham Z. Snyder,[6] Pratik Mukherjee,[7] Jeffrey I. Berman,[9] Timothy P.L. Roberts,[9] Srikantan S. Nagarajan,[7] John E. Spiro,[10] Wendy K. Chung,[11] Elliott H. Sherr,[8] and Randy L. Buckner[1,3,4] on behalf of the Simons VIP Consortium



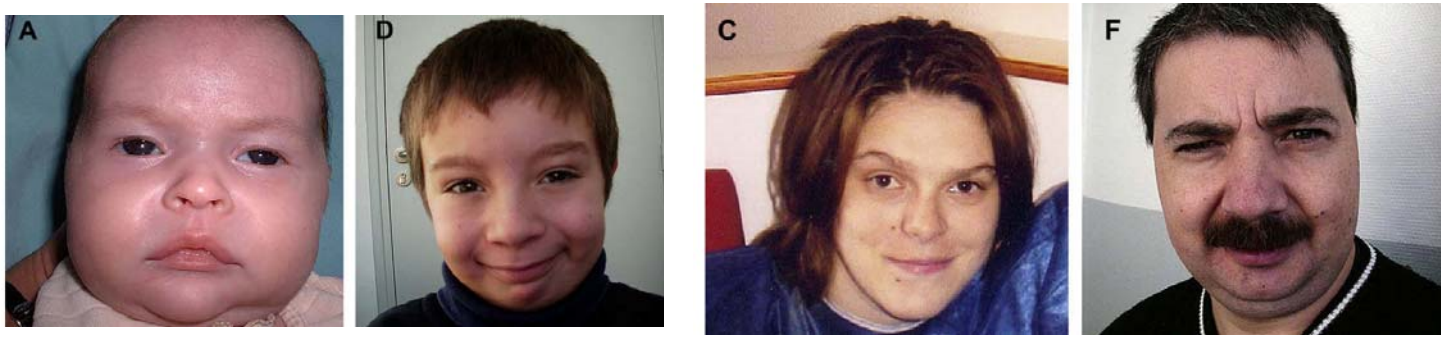
Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Microduplication 22q11.2: A new chromosomal syndrome

Marie-France Portnoï



Type	Band	Location (NCBI 36/hg18)	Size (kb)	Recurrence (del/dup)	Frequency (n = 3,816)	p value (C = 232)[a]	Studies[b]	Genes[c] (RefSeq)
	16q22.3	chr16:69,987,425–70,647,241	660	2 (1/1)	0.05%	1.00	1,2	13
	20q13.33	chr20:61,056,624–61,076,763	20	3 (1/2)	0.08%	0.53	2,4	*SLC17A9*
	22q11.21	chr22:17,265,500–19,786,200	2,521	5 (3/2)	0.13%	**0.002**	1,2,3,4	56

Sanders et al. Neuron 2011, 2015

-Frequency of 0.05% in non-syndromic simplex ASD

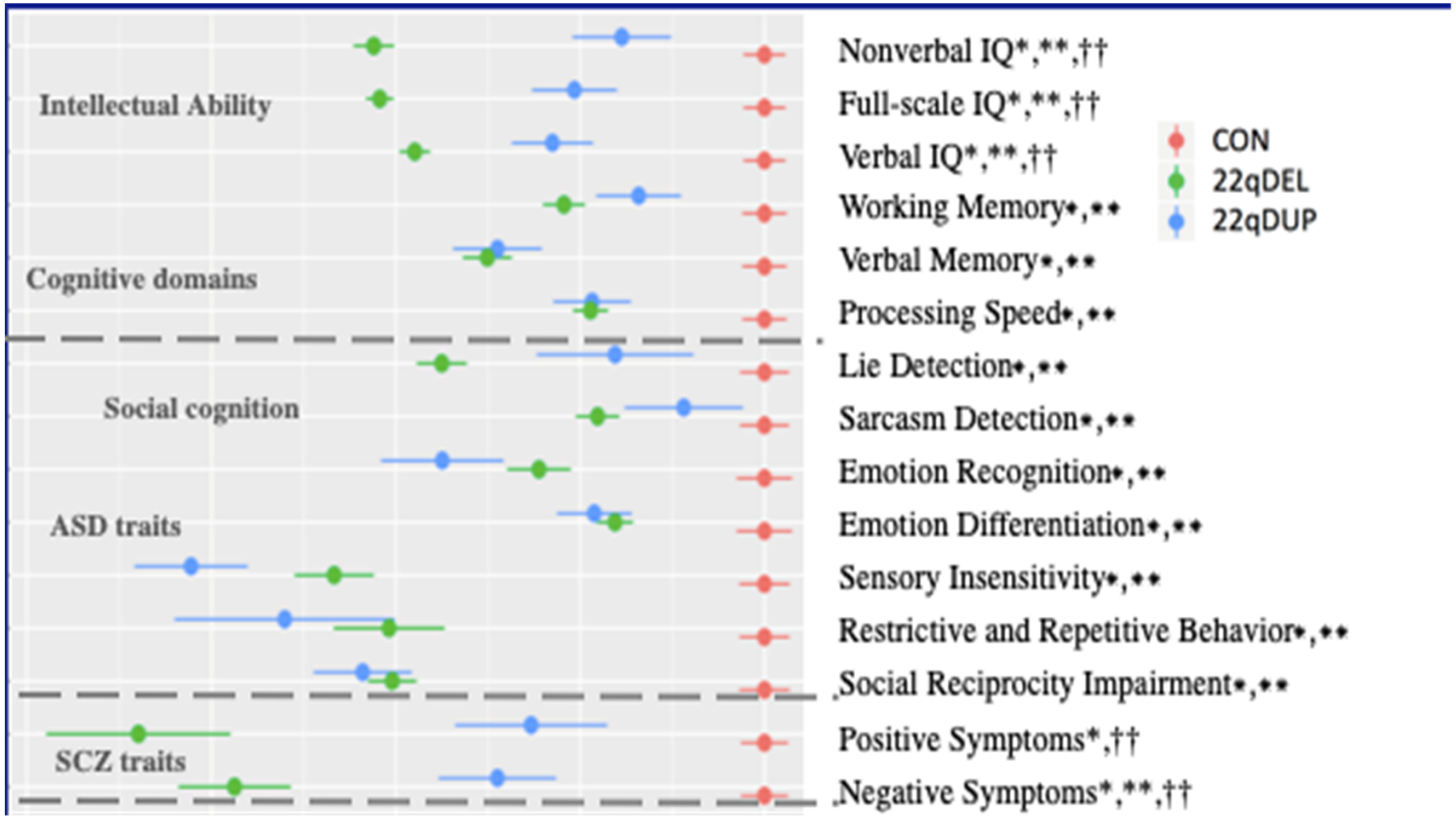
UCLA Study Participant Demographics

	22q11.2 Deletion Carriers	Typically-developing Controls	22q11.2 Duplication Carriers
N	107	82	38
Age (SD)	16.03 (10.3)	14.47 (7.5)	15.87 (12.4)
Age Range	6 to 61	6 to 45	5 to 49
N males (%)	52 (48.6%)	42 (50.6%)	22 (57.9%)
N White (%) *,, ††**	93 (86.9%)	51 (62.2%)	37 (97.4%)
N Other (%) *,,**	2 (1.9%)	18 (16.8%)	1 (2.7%)
N Multi-racial (%) **, ††	12 (11.2%)	12 (14.6%)	0 (0%)
Highest Parental Education in years (SD)	16.1 (2.7)	16.0 (3.3)	15.8 (2.5)
N ASD (%) *,**	49 (45.8%)	0 (0%)	17 (44.7%)
N Psychosis (%) *,††	13 (12.1%)	0 (0%)	0 (0%)
N ADHD (%) *,**	47 (43.9%)	5 (6.1%)	15 (39.4%)

* indicates corrected 22qDEL-22qCON difference. ** indicates corrected 22qDUP-22qCON differences. †† indicates corrected 22qDEL-22qDUP difference.

Lin et al, Biological Psych 2020

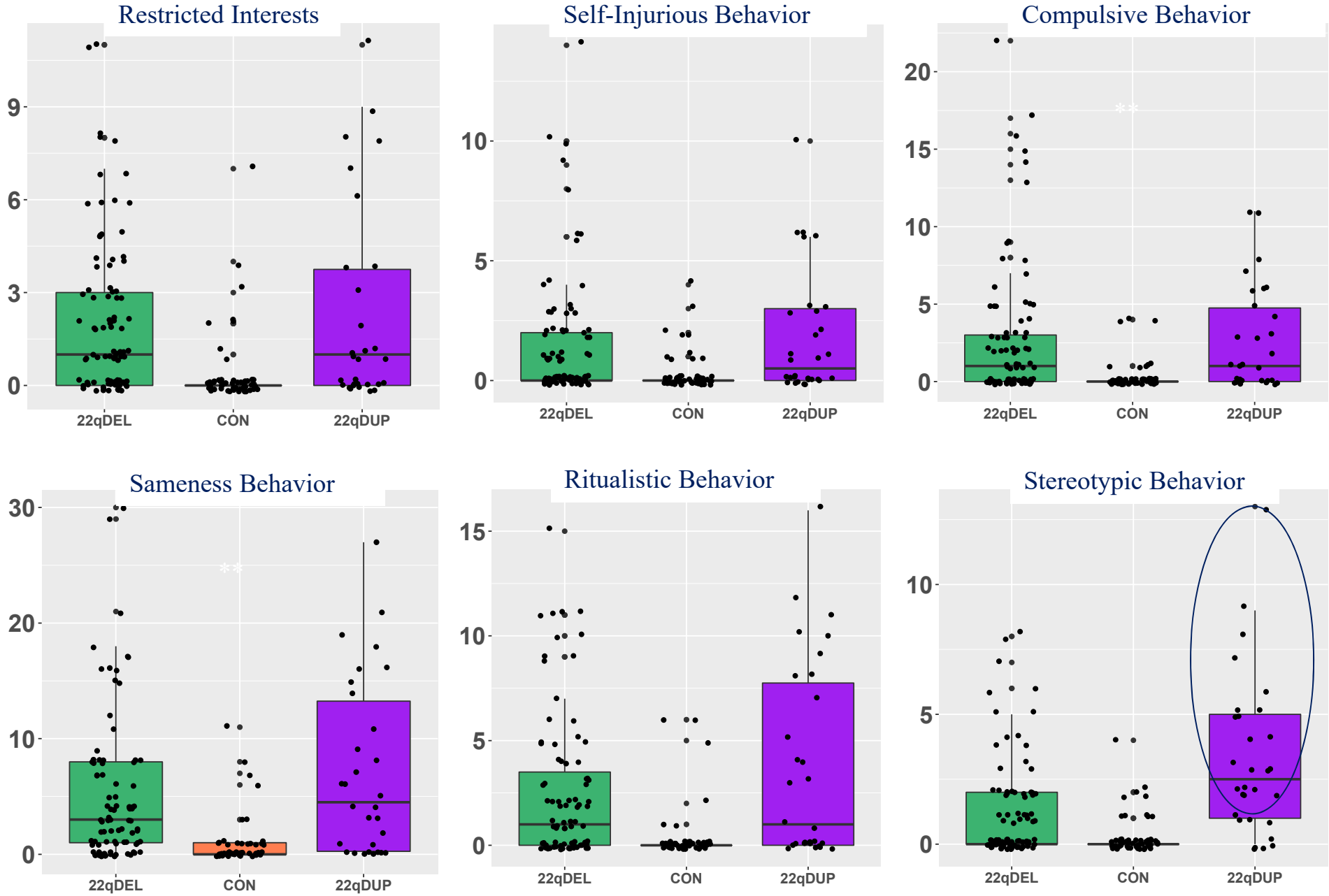
Gene Dosage Effect on 22q11.2 Behavioral Phenotype



z-score

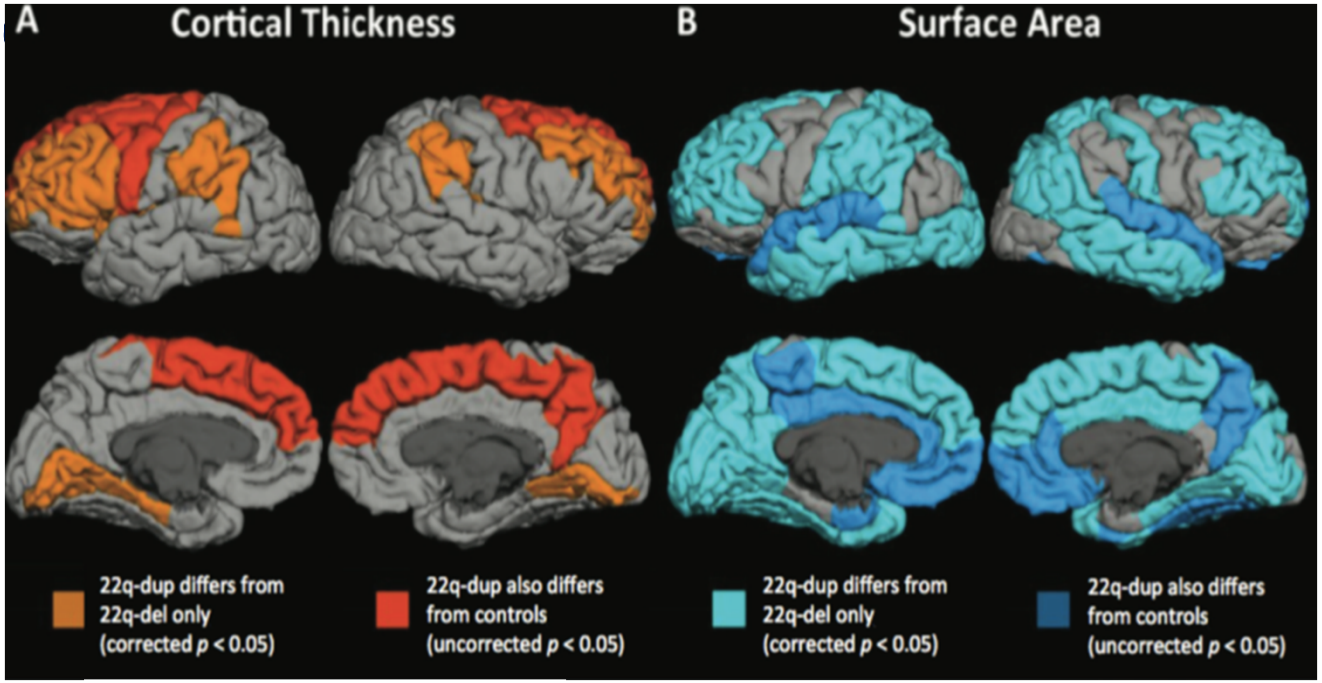
Lin et al, Biological Psych 2020

Gene Dosage Effect on Repetitive Behavior Phenotypes



Lin et al, Biological Psych 2020

Opposing Effects on Cortical Surface Area and Thickness in Deletion vs. Dupli



dup < CTL < del

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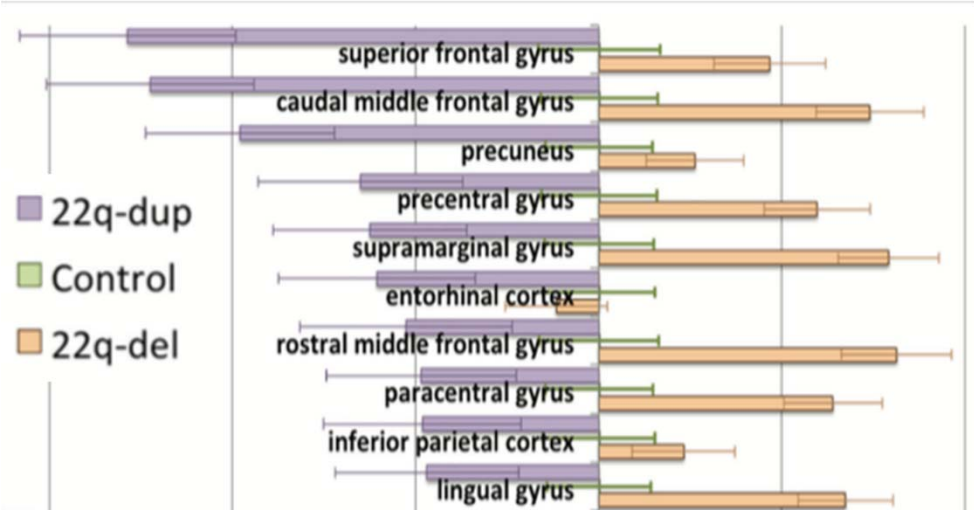
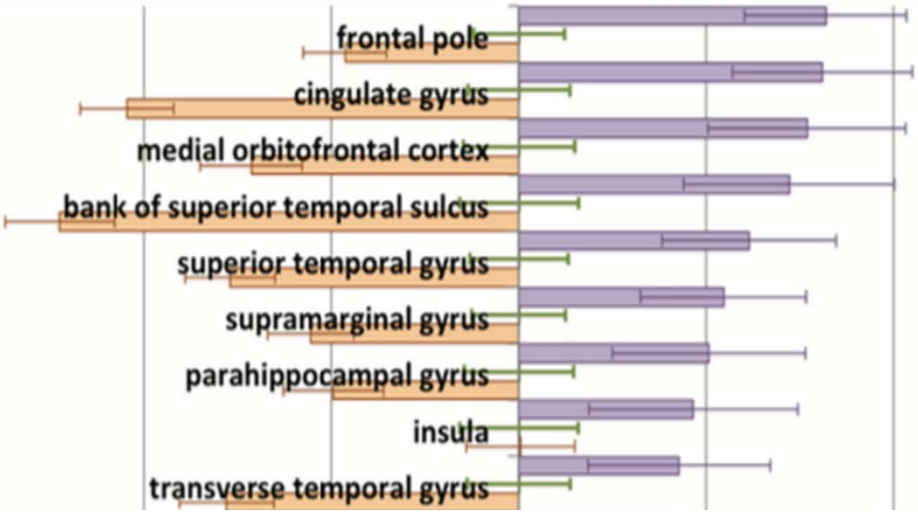
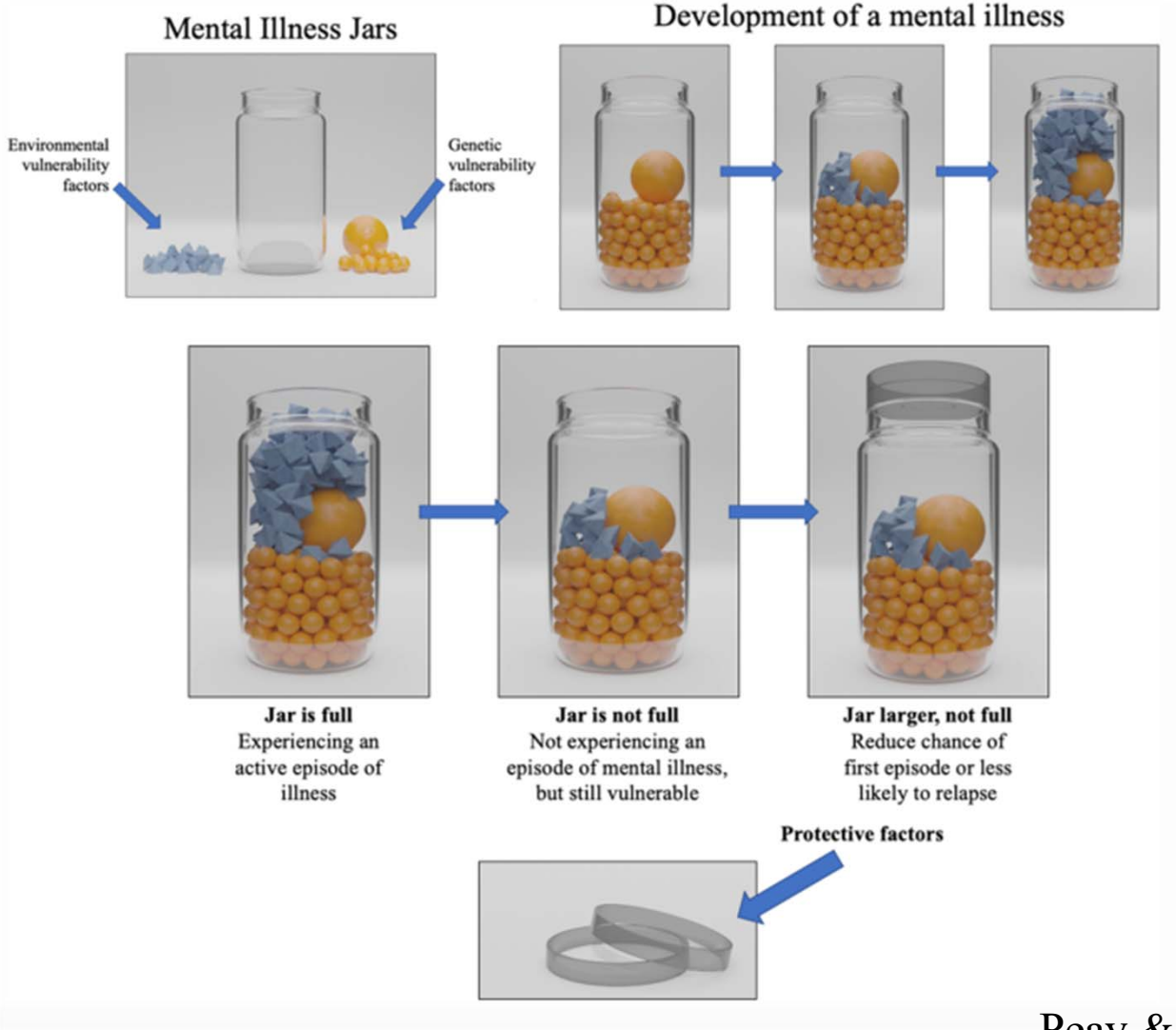
Lin et al J Neurosci 2017





Genetic Counseling Considerations

-For many parents of children with 22q11DS, risk of psychiatric illness is main concern regarding their child's health (Hercher and Bruenner 2008, Martin et al. 2012).



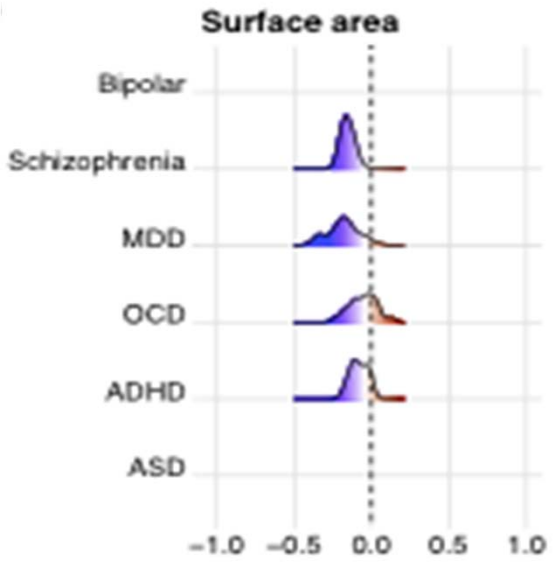
Peay & Austin 2011, 2021

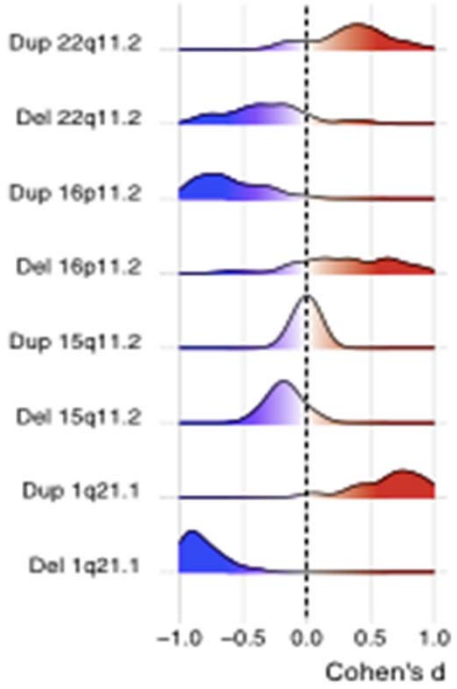
Cross – Disorder Analyses

-Fundamental principles of how genomic CNVS affect brain architecture

-May be distinguishable 'neuropsychiatric' profiles in subgroups based on genetic etiology

-Substantially larger effect sizes on phenotype





HUMAN BRAIN MAPPING Open Access

REVIEW ARTICLE | Open Access

Effects of copy number variations on brain structure and risk for psychiatric illness: Large-scale studies from the ENIGMA working groups on CNVs

Ida E. Sønderby, Christopher R. K. Ching, Sophia I. Thomopoulos, Dennis van der Meer, Daqiang Sun, Julio E. Villalon-Reina, Ingrid Agartz, Katrin Amunts, Celso Arango ... See all authors

nature COMMUNICATIONS

Nat Commun. 2020; 11: 5272.
Published online 2020 Oct 19. doi: 10.1038/s41467-020-18997-2

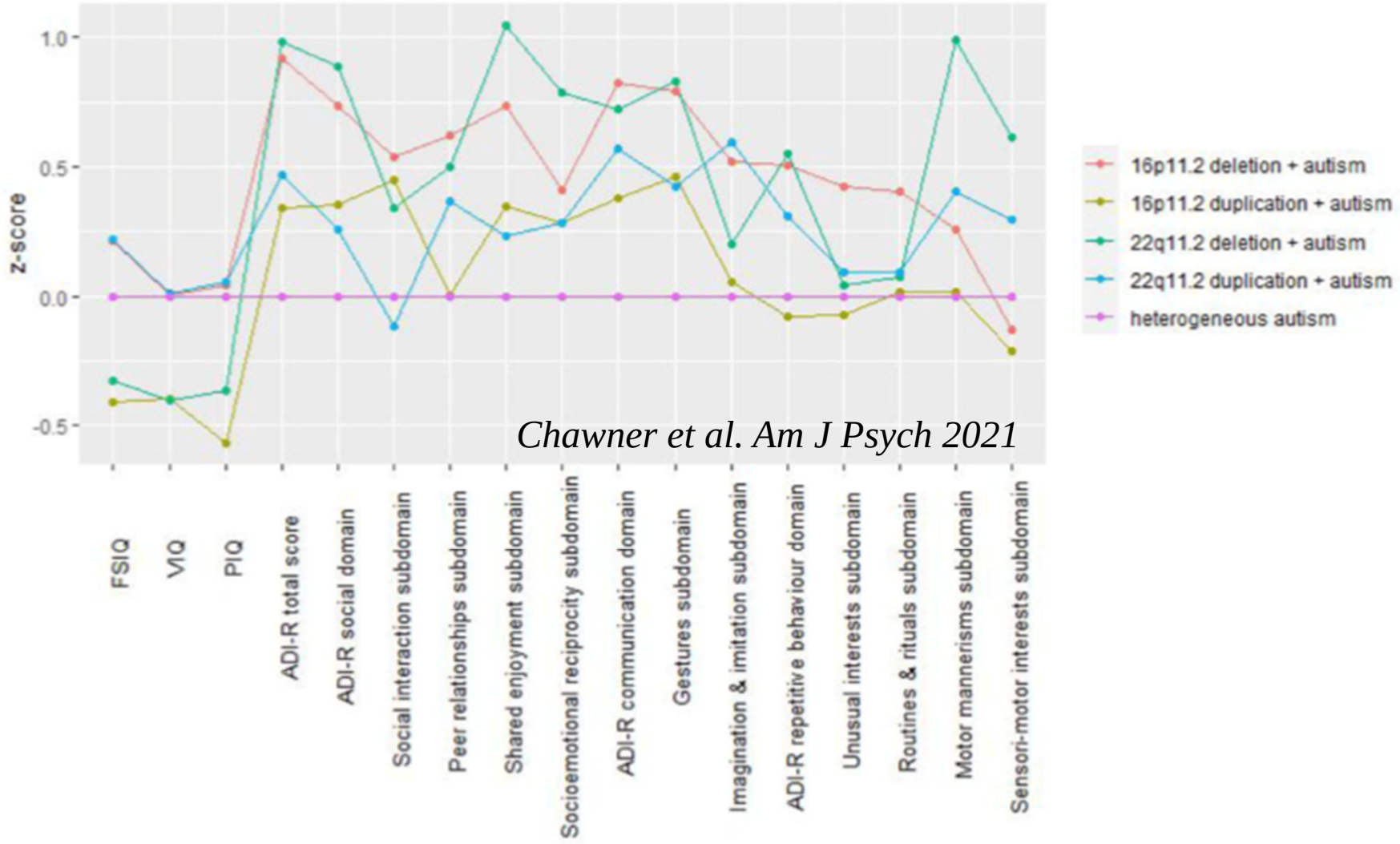
PMCID: PMC7573583
PMID: 33077750

Mutations associated with neuropsychiatric conditions delineate functional brain connectivity dimensions contributing to autism and schizophrenia

Clara A. Moreau,[#1,2] Sebastian G. W. Urchs,[#2,3] Kumar Kuldeep,[1] Pierre Orban,[4,5] Catherine Schramm,[1,6] Guillaume Dumas,[1,7] Aurélie Labbe,[8] Guillaume Huguet,[1] Elise Douard,[1] Pierre-Olivier Quirion,[2,9] Amy Lin,[10] Leila Kushan,[10] Stephanie Grot,[4,5] David Luck,[1] Adrianna Mendrek,[11] Stephane Potvin,[5] Emmanuel Stip,[5,12] Thomas Bourgeron,[7] Alan C. Evans,[3] Carrie E. Bearden,[10] Pierre Bellec,[2] and Sebastien Jacquemont[1,13]

Moreau et al Curr Opinion Gen & Development

Neurobehavioral Profile of ASD-Associated CNVs



-Profile differences between genetic variant groups

-54% of CNV carriers who did not meet full ASD diagnostic criteria had elevated levels of autistic traits.

Areas needing (lots) more attention

- Effectiveness of interventions used in idiopathic disorders (cognitive-behavioral therapy, social skills training)
- 3 small studies of computerized cognitive training, 1 of small-group social cognitive training; preliminary evidence for feasibility/ effectiveness (Buijs et al. 2019)

- Environmental risk factors (family environment, social support, SES)

- 22q11.2-associated disorders in diverse, non-European populations extremely understudied

Genes to Mental Health NETWORK

The "Genes to Mental Health" (G2MH) consortium is an initiative funded ($6 Million) under the RFA 'Rare Genetic Disorders as a Window into the Genetic Architecture of Mental Disorders' by the National Institute of Mental Health? (NIMH) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). It includes researchers from 14 institutions and seven countries from North America, Europe, and Africa. Learn more.

Why G2MH?

Rare genomic disorders affect less than 1/2000 people in the general population, but collectively, they are a major cause of developmental and psychiatric conditions, such as autism spectrum disorder, schizophrenia, attention deficit hyperactivity disorder, and intellectual disability. Recent advances in genomic technologies and data sharing have revolutionized the identification and diagnosis of these rare variants. Rare genomic disorders have large impacts, which allow researchers to interrogate the link between molecular function and psychiatric symptoms. However, more detailed studies are needed to fully characterize clinical presentation and risk for particular developmental and psychiatric conditions in individuals with a rare genomic variant. The G2MH consortium was initiated to address this challenge.

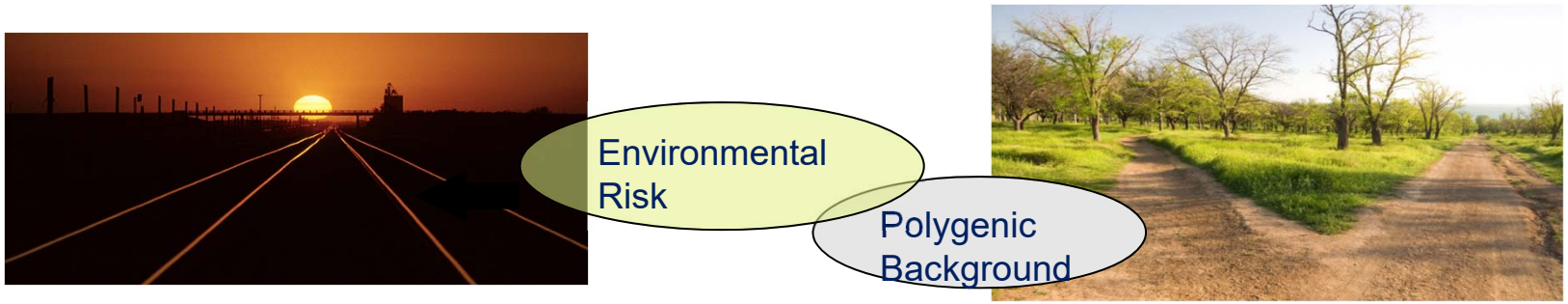
How can G2MH further our understanding of mental health consequences of rare genomic disorders?

Most rare variants have been studied in isolation. As a result, essential information is sprinkled across many small studies that are difficult to compare. To accelerate discovery, the G2MH consortium will collate and harmonize genetic data with quantitative measures of cognition and behavior across multiple genomic variants associated with increased risk of developmental and psychiatric outcomes. This coordinated effort across patients, families, researchers, clinicians and institutions, including rapid sharing of data, is required to translate discoveries into therapeutic potential.

https://genes2mentalhealth.com

Summary and Future Directions

- Rare genomic disorders like 22q11 collectively a major cause of developmental neuropsychiatric disorders
- 22q11DS is one of greatest known risk factors for psychosis; prognostic markers (cognitive decline, inattention) appear similar to idiopathic psychosis
- Reductions in heteromodal association cortex /hippocampus converge with regions affected in idiopathic schizophrenia - suggests highly penetrant CNV's can inform understanding of broader psychiatric disease risk
- More severe brain and cognitive impact in those with larger deletion extent
- New evidence that 22q11 is a genomic region associated with mirrored anatomic phenotypes
- Ongoing work in longitudinal, global cohorts of reciprocal 22q11 variants and other RGDs, and in animal and in vitro models can guide translation of neurobiologically-informed therapeutic targets.



Acknowledgements

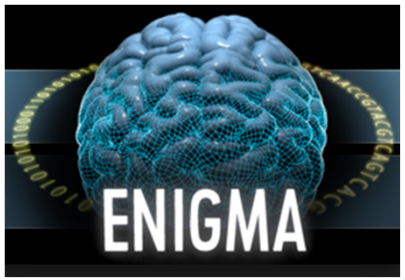
This work supported by: The National Institute of Mental Health (NIMH), Brain-Behavior Research Foundation (NARSAD), Simons Foundation, and all the patients and their families who participated.

UCLA CART
Center for Autism Research and Treatment

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

NIH National Institute of Mental Health

BRAIN & BEHAVIOR RESEARCH FOUNDATION



Carrie@winkytheelf