Large scale studies of CNV across the major psychiatric disorders

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on behalf of the
PGC CNV group
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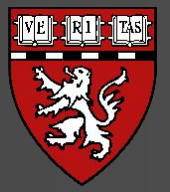
Benjamin M Neale

And the

Psychiatric Genomics Consortium



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CARDIFF UNIVERSITY
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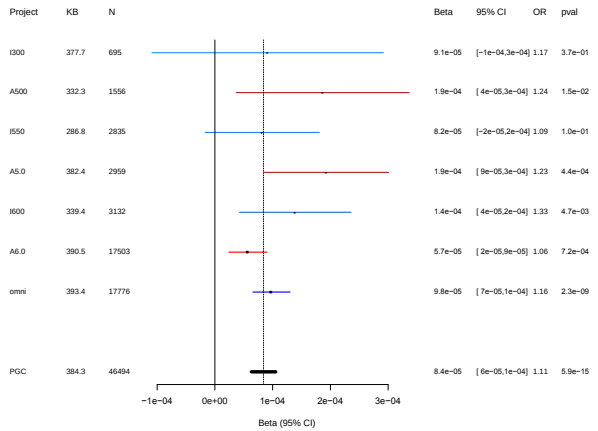
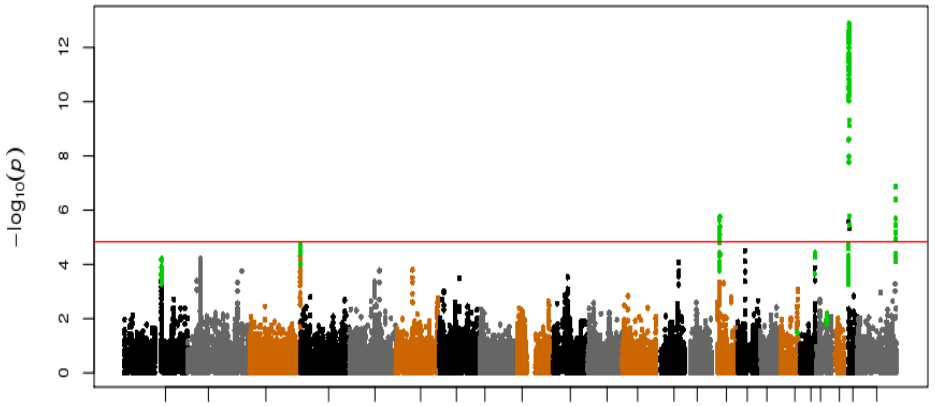
UCSD

Four primary goals of the analysis

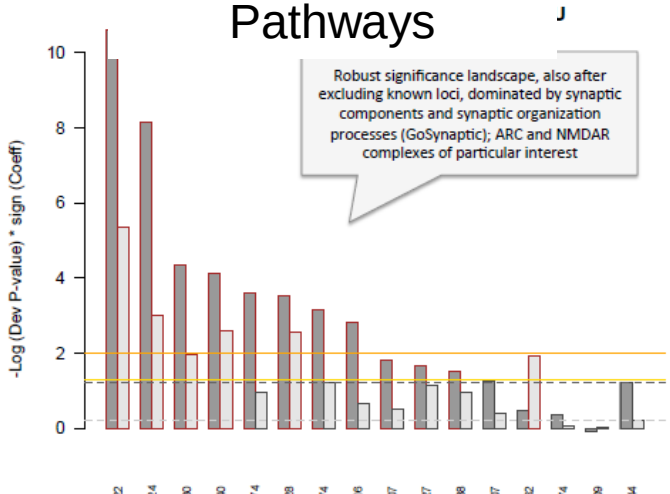
CNV burden



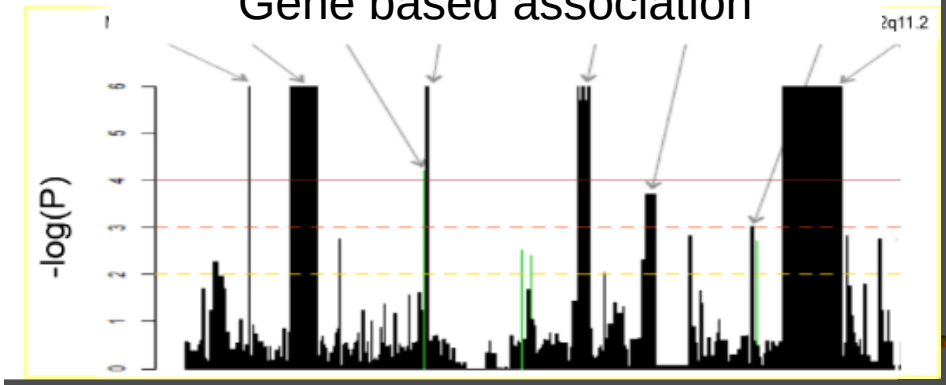
Breakpoint association



Pathways



Gene based association



CNV association testing

Controlling for potential confounds across datasets

- Genotyping platform
- Ancestry
- CNV calling metrics

CNV Burden: Linear regression model

CNV ~ SCZ status + covariates

Pathway and gene association: Deviance test of nested models

[*SCZ status ~ CNV + covariates*] ***vs.*** **[*SCZ status ~ covariates*]**

Pathways - Controlling for CNV size + large gene bias

Total genes covered by CNV added as a covariate

PGC SCZ CNV dataset

- N = 41,321
  - 21,094 cases
  - 20,227 controls

Genotyping Platform	Datasets	Percent of full sample	Cases	Controls	percent cases	total samples
Affymetrix 5.0	4	6.2%	1572	1001	61.1%	2573
Affymetrix 500	1	1.2%	314	201	61%	515
Affymetrix 6.0	12	37.4%	7027	8422	45.5%	15449
Illumina 300	1	1.7%	410	285	59%	695
Illumina 550	2	6.9%	1130	1705	39.9%	2835
Illumina 610	2	3.5%	818	623	56.8%	1441
Illumina OmniExpress	11	43%	9795	7980	55.1%	17775
Illumina Omni 2.5	1	0.1%	28	10	73.7%	38
Affymetrix	17	44.9%	8913	9624	48.1%	18537
Illumina	16	55.1%	12181	10603	53.5%	22784
Total	33	---	21094	20227	51%	41321

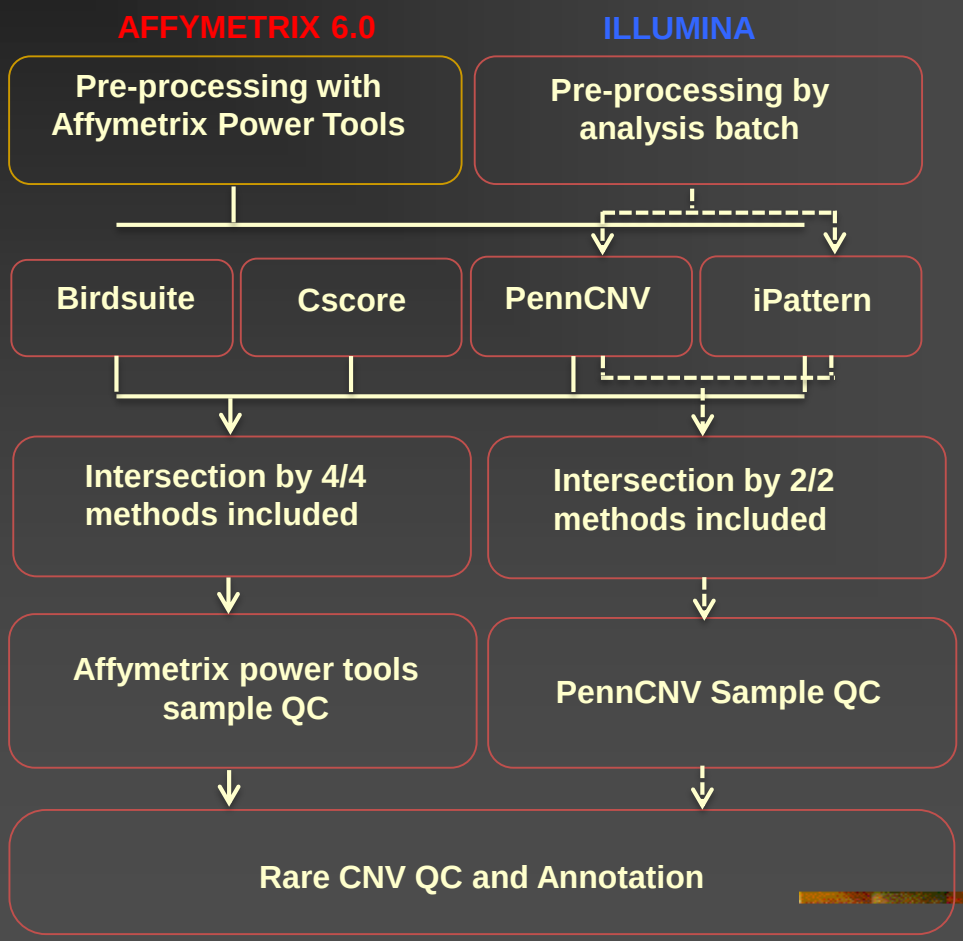
Wenting Wu

Doug Greer

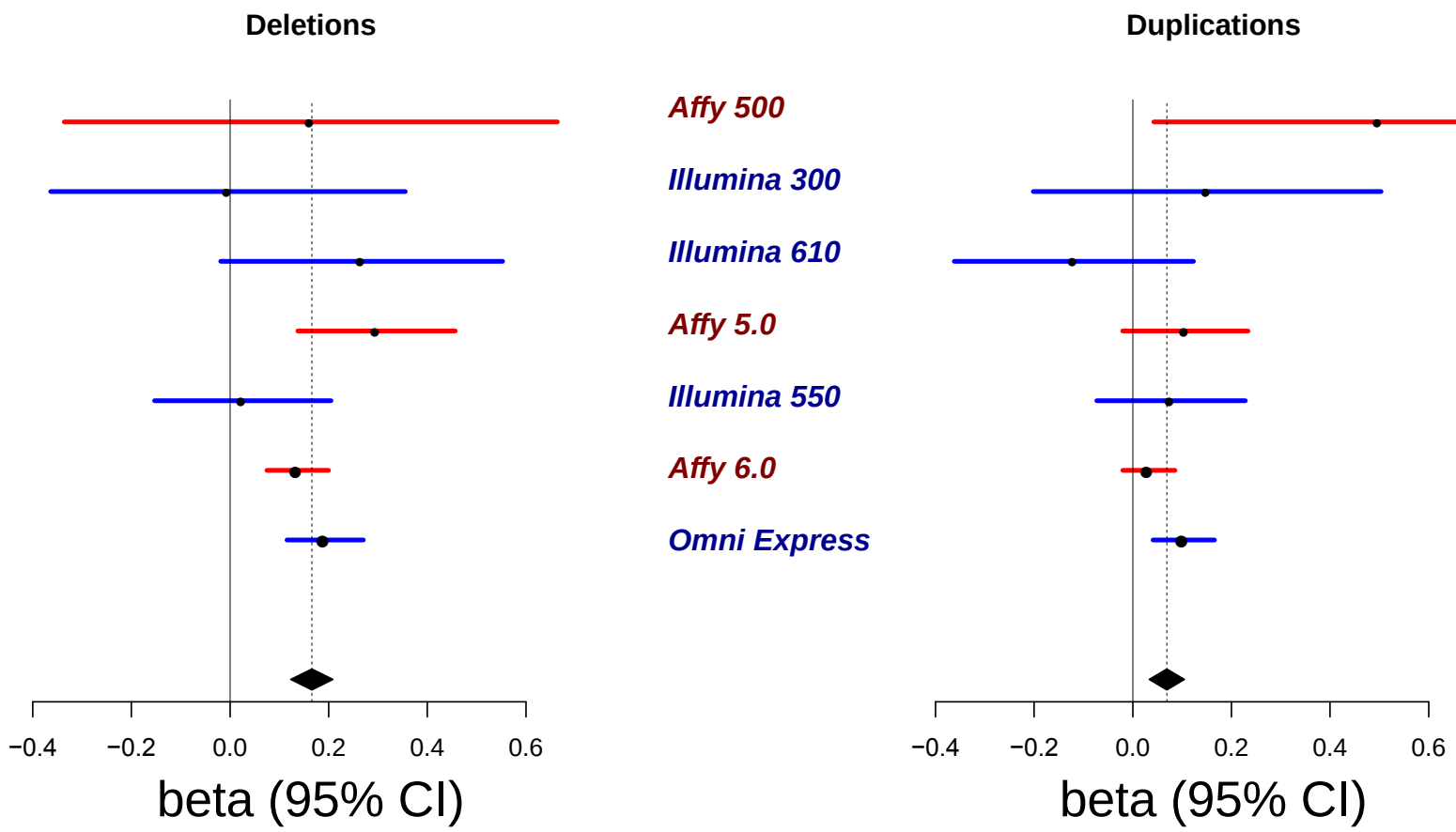
PGC CNV Pipeline

Christian Marshall

Bhooma Thiruvahindrapuram



Robust Enrichment of CNV Burden in Schizophrenia



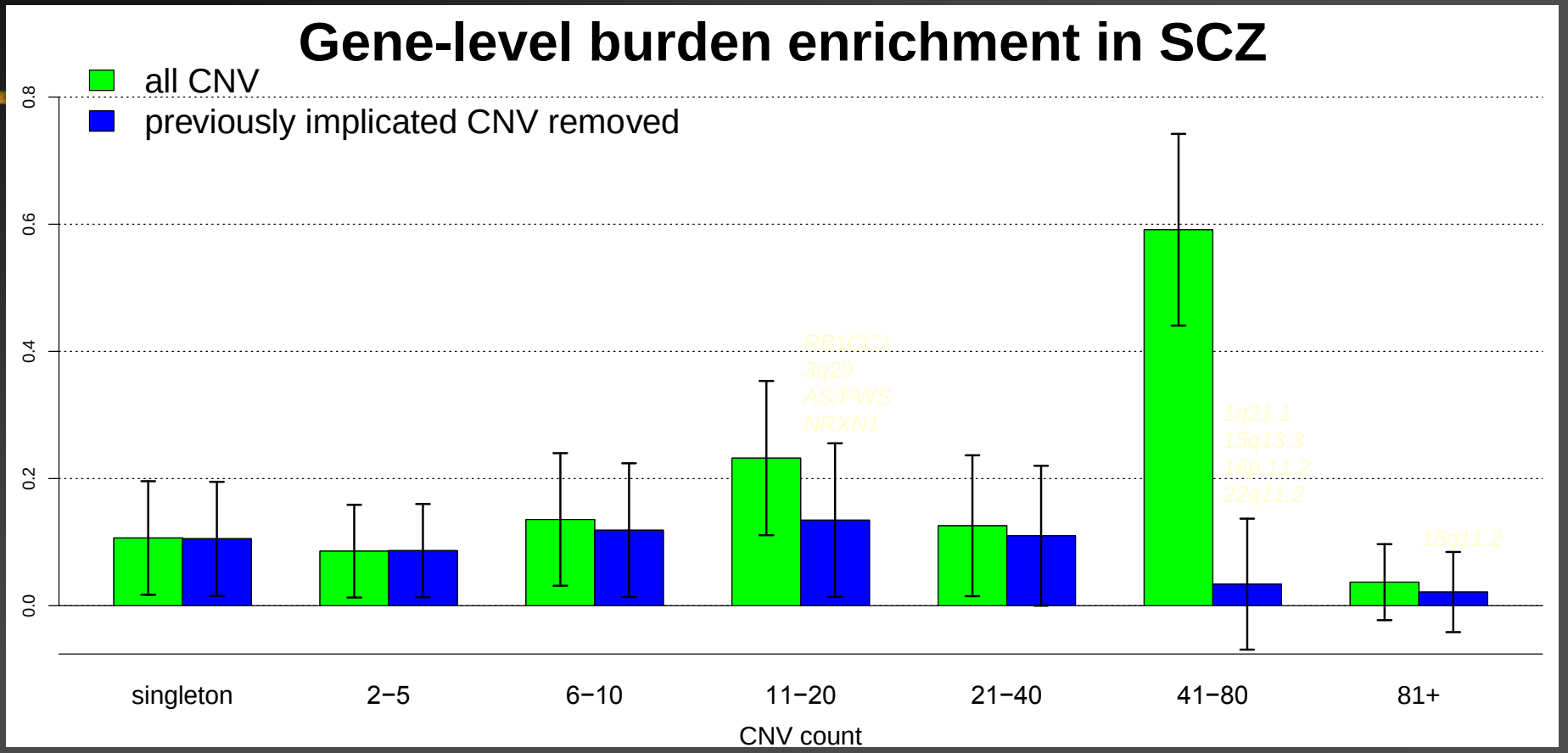
Case/control ratio = **1.17**
p-value = **8.8e-14**

Case/control ratio = **1.06**
p-value = **1.5e-4**

Ben Neale
Dan Howrigan

Undiscovered CNV risk coming from the rarest events

1% MAF = 413 CNV
0.1% MAF = 41 CNV
0.01% MAF = 4 CNV



CNV burden *outside previously implicated CNV*

Case/control ratio = **1.1**

p-value = **1.9e-7**

Enrichment in neuronal pathways

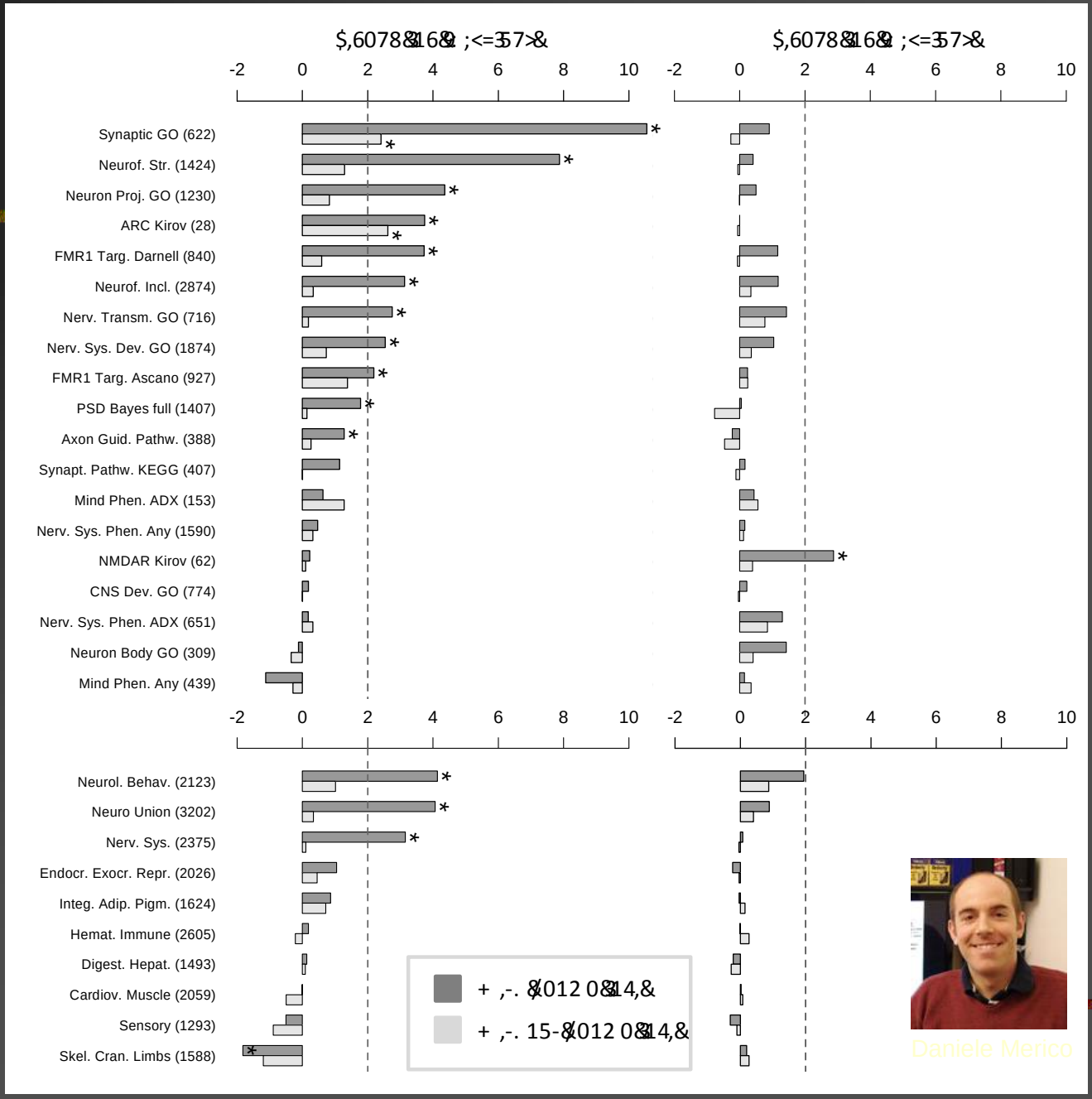
Deletions

37 neuronal gene-sets analyzed

Deletions
- GO synaptic
- GO neuronal function
- FMRP targets
- ARC network

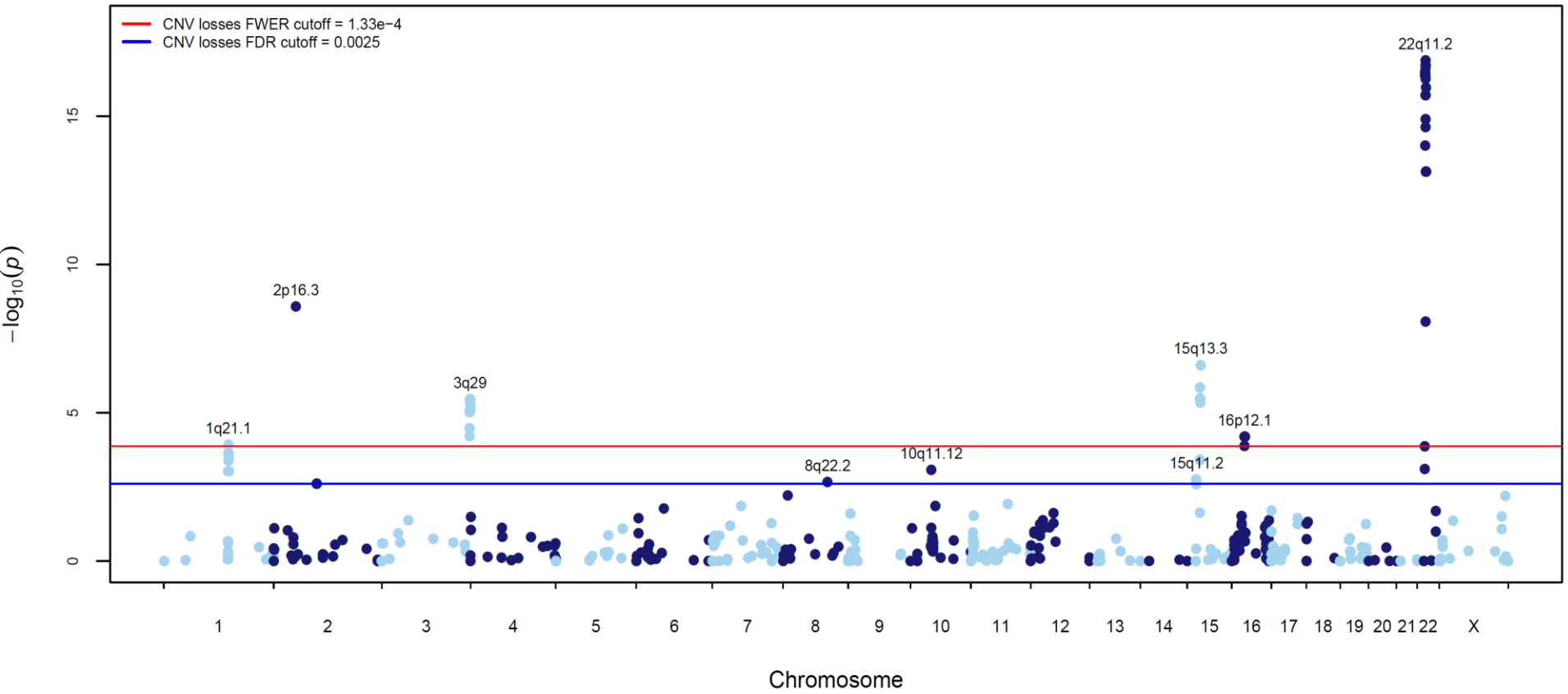
Duplications
- NMDAR network

Mouse organ systems
No enrichment in non-neuronal sets



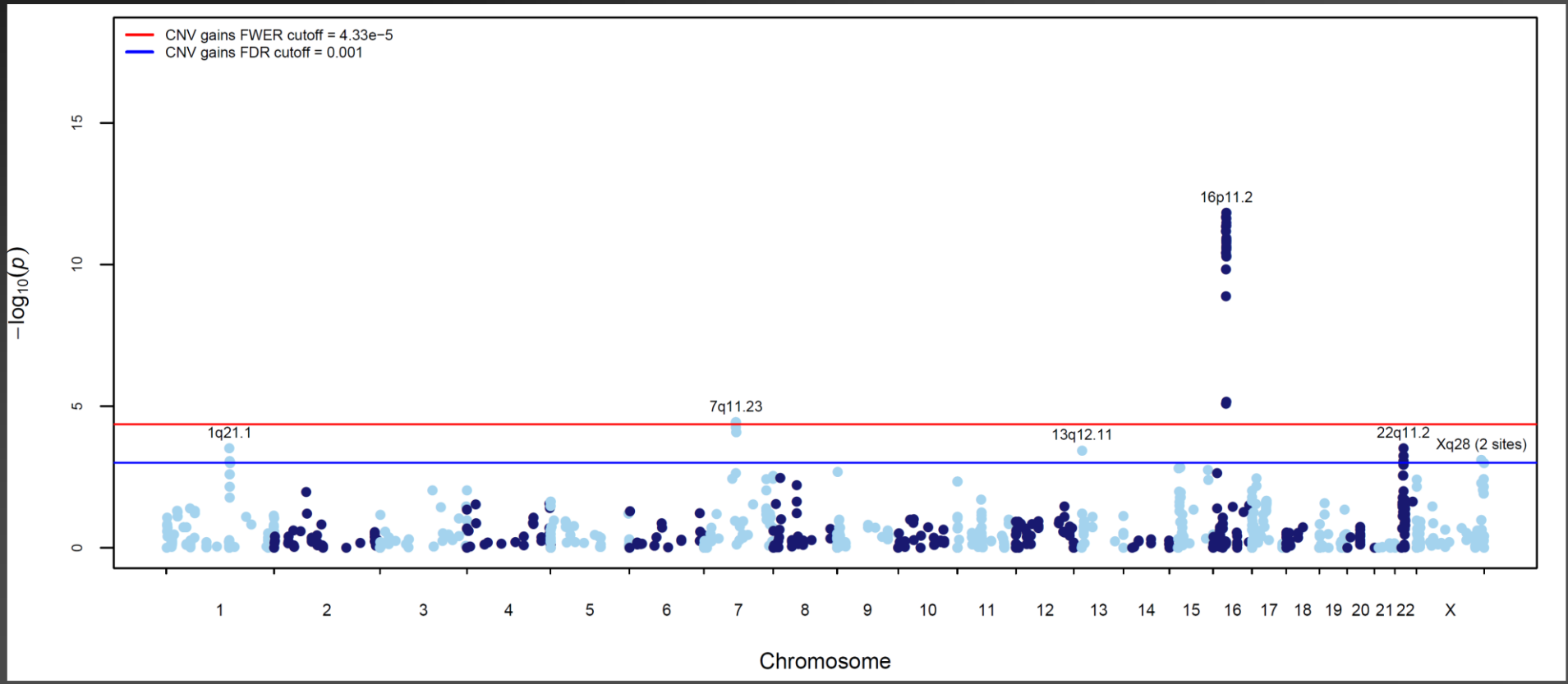
Daniele Merico

Gene based association (deletions)



6 CNVs genome wide significant

Gene based association (duplications)

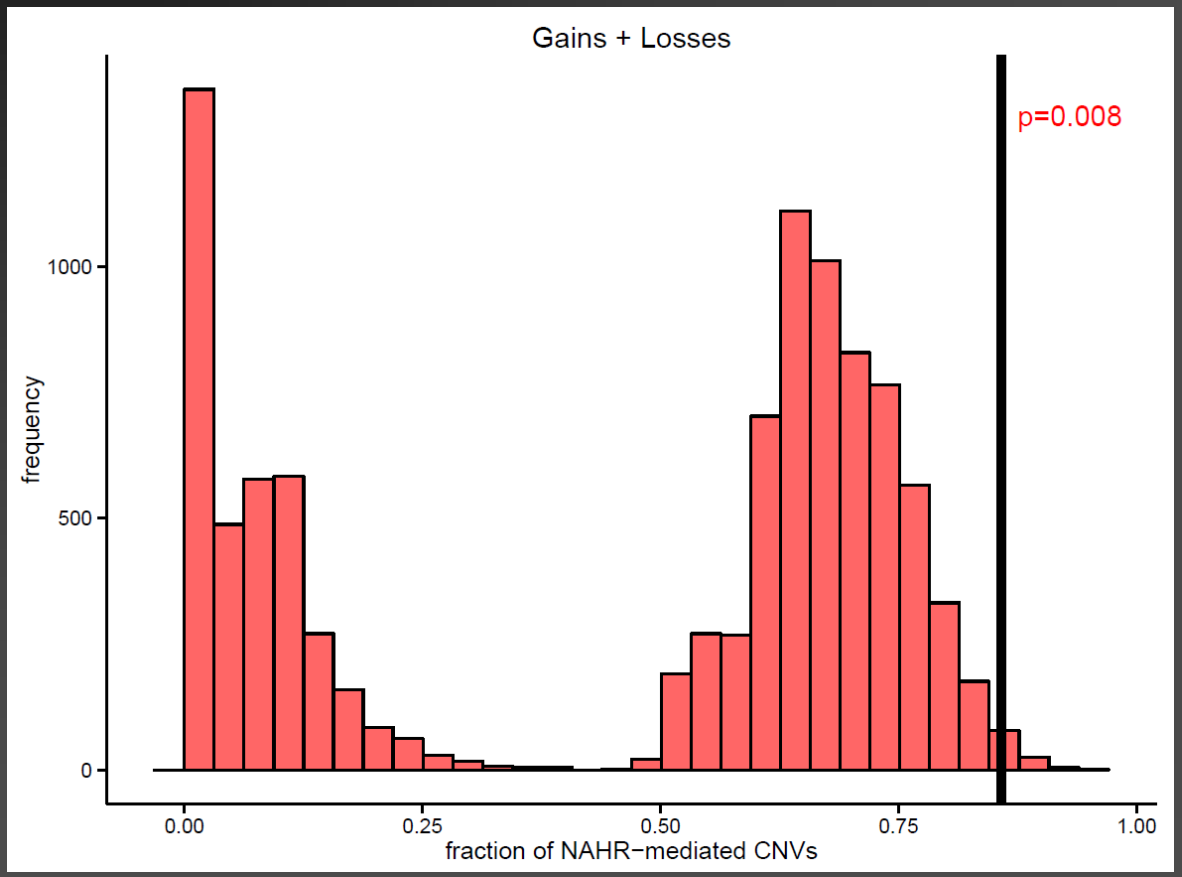


2 CNVs genome wide significant

8 loci survive genome-wide correction

CHR	BP1	BP2	locus GENE	Putative Mechanism	CNV test	direction	FWER	BH-FDR	Cases	Controls	Regional P-value	CMH OR
22	17400000	19750000	22q11.21	NAHR	del	risk	yes	3.54E-15	64	1	5.70E-18	67.7
16	29560000	30110000	16p11.2 (proximal)	NAHR	dup	risk	yes	5.82E-10	70	7	2.52E-12	9.4
2	50000992	51113178	2p16.3 **NRXN1**	NHEJ	del	risk	yes	3.52E-07	35	3	4.92E-09	11.0
15	28920000	30270000	15q13.3	NAHR	del	risk	yes	2.22E-05	28	2	2.13E-07	13.8
1	144646000	146176000	1q21.1	NAHR	del_dup	risk	yes	0.00011	60	14	1.50E-06	4.1
3	197230000	198840000	3q29	NAHR	del	risk	yes	0.00024	16	0	1.86E-06	INF
16	28730000	28960000	16p11.2 (distal)	NAHR	del	risk	yes	0.0029	11	1	5.52E-05	12.7
7	72380000	73780000	7q11.23	NAHR	dup	risk	yes	0.0048	16	1	1.68E-04	16.6
23	153800000	154225000	Xq28 (distal)	NAHR	dup	risk	no	0.049	18	2	3.61E-04	8.4
22	17400000	19750000	22q11.21	NAHR	dup	protective	no	0.024	3	16	4.54E-04	0.19
7	64476203	64503433	7q11.21 **ZNF92**	NAHR	del_dup	protective	no	0.033	131	180	6.71E-04	0.69
13	19309593	19335773	13q12.11 **ZMYM5**	NHEJ	dup	protective	no	0.024	15	38	7.91E-04	0.39
23	148575477	148580720	Xq28 **MAGEA11**	NAHR	dup	protective	no	0.044	12	36	1.06E-03	0.30
9	831690	959090	9p24.3 **DMRT1**	NHEJ	del_dup	risk	no	0.049	13	1	1.35E-03	13.4
8	100094670	100958984	8q22.2 **VPS13B**	NHEJ	del	risk	no	0.048	7	1	1.74E-03	7.1
7	158145959	158664998	7p36.3 **VIPR2 WDR60**	NAHR & NHEJ	del_dup	risk	no	0.046	20	6	5.79E-03	3.2

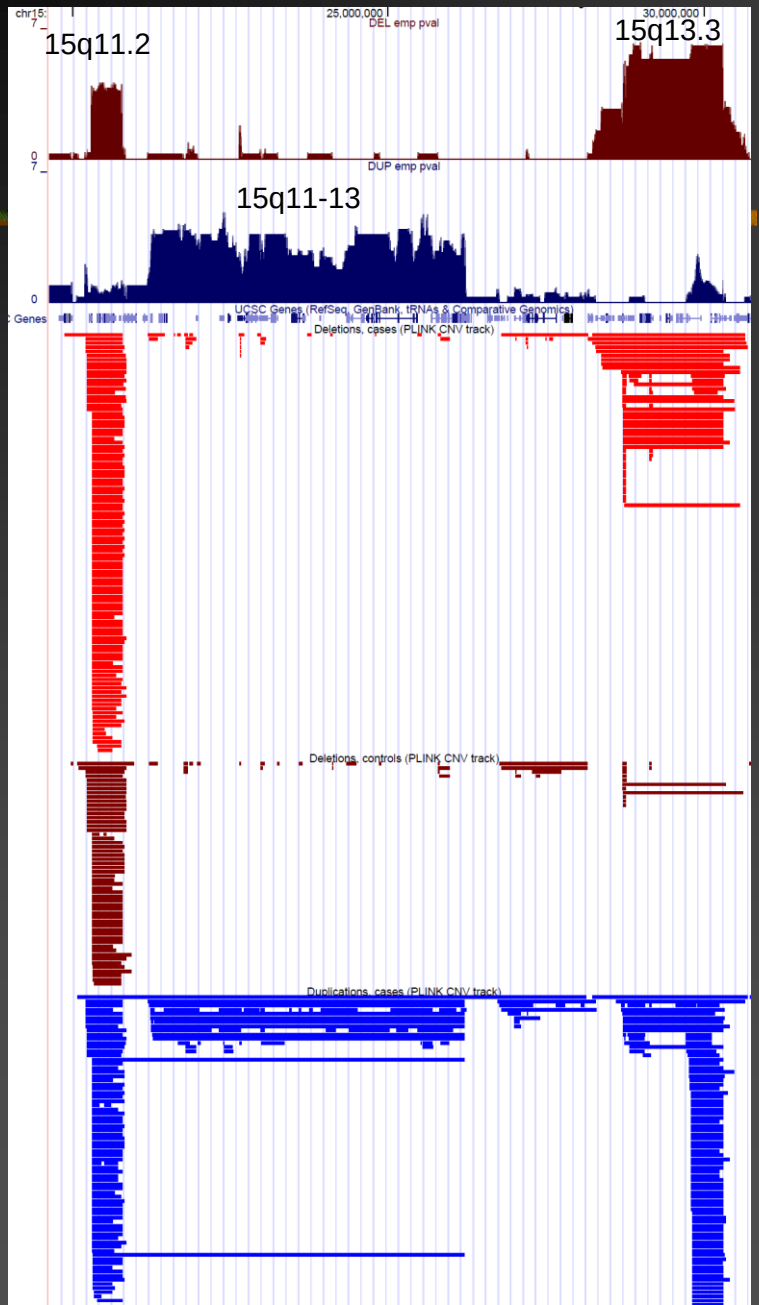
Novel loci that meet suggestive criteria are enriched for CNVs mediated by NAHR

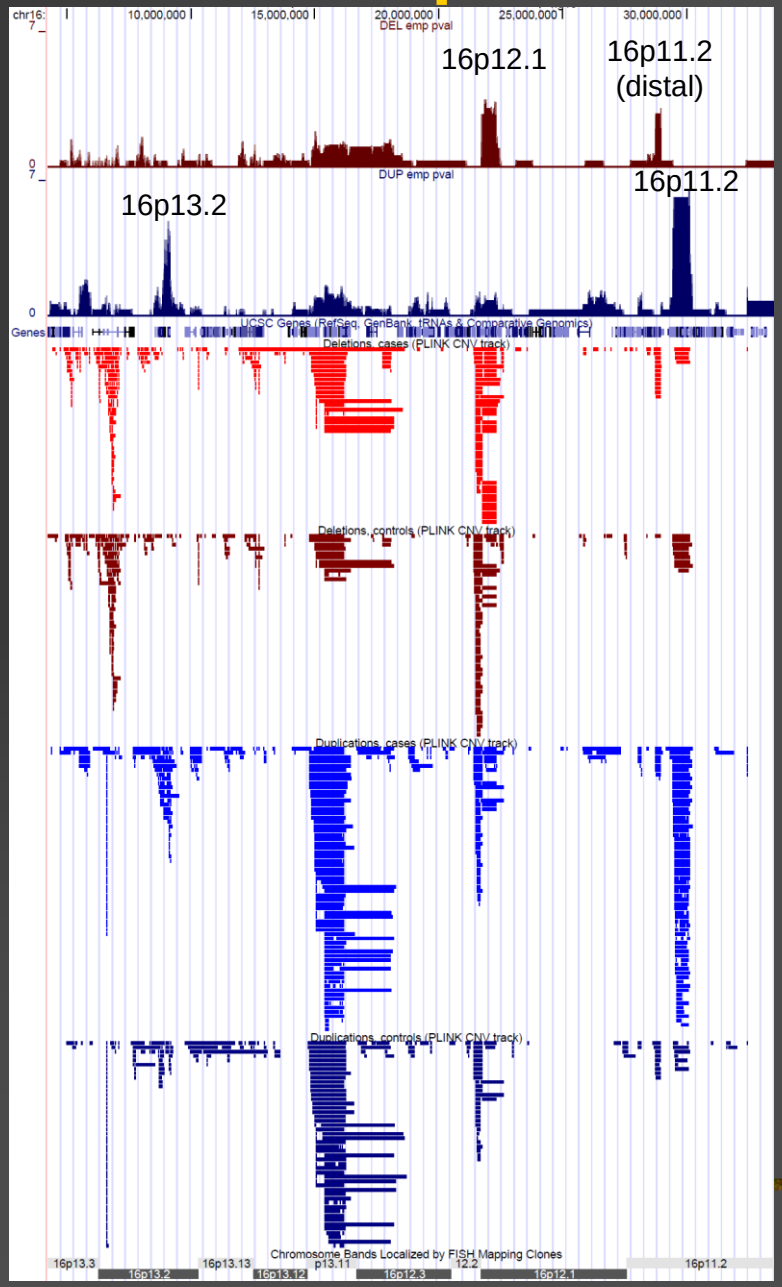


Hotspots and more hotspots

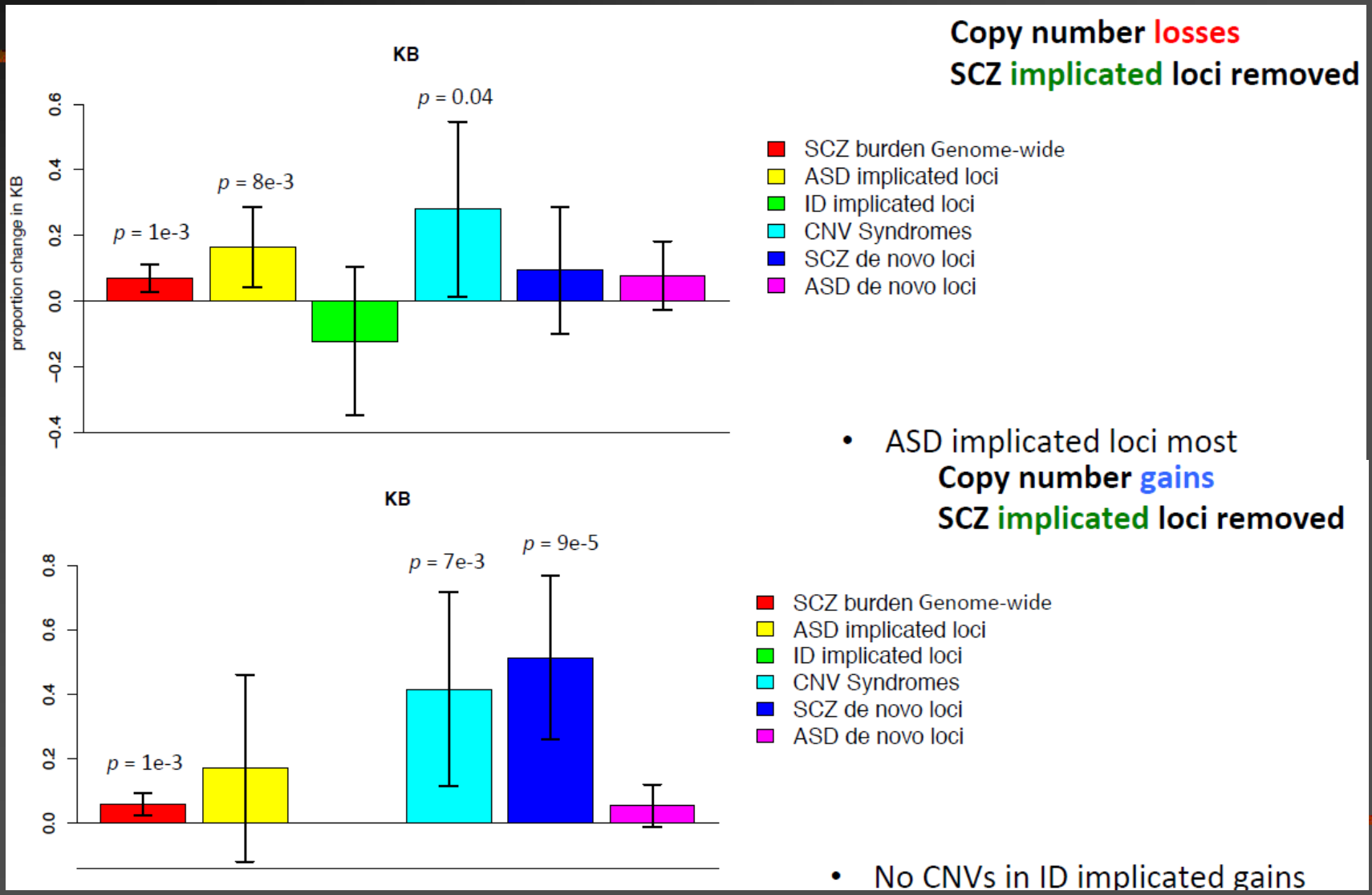
Del

Dup





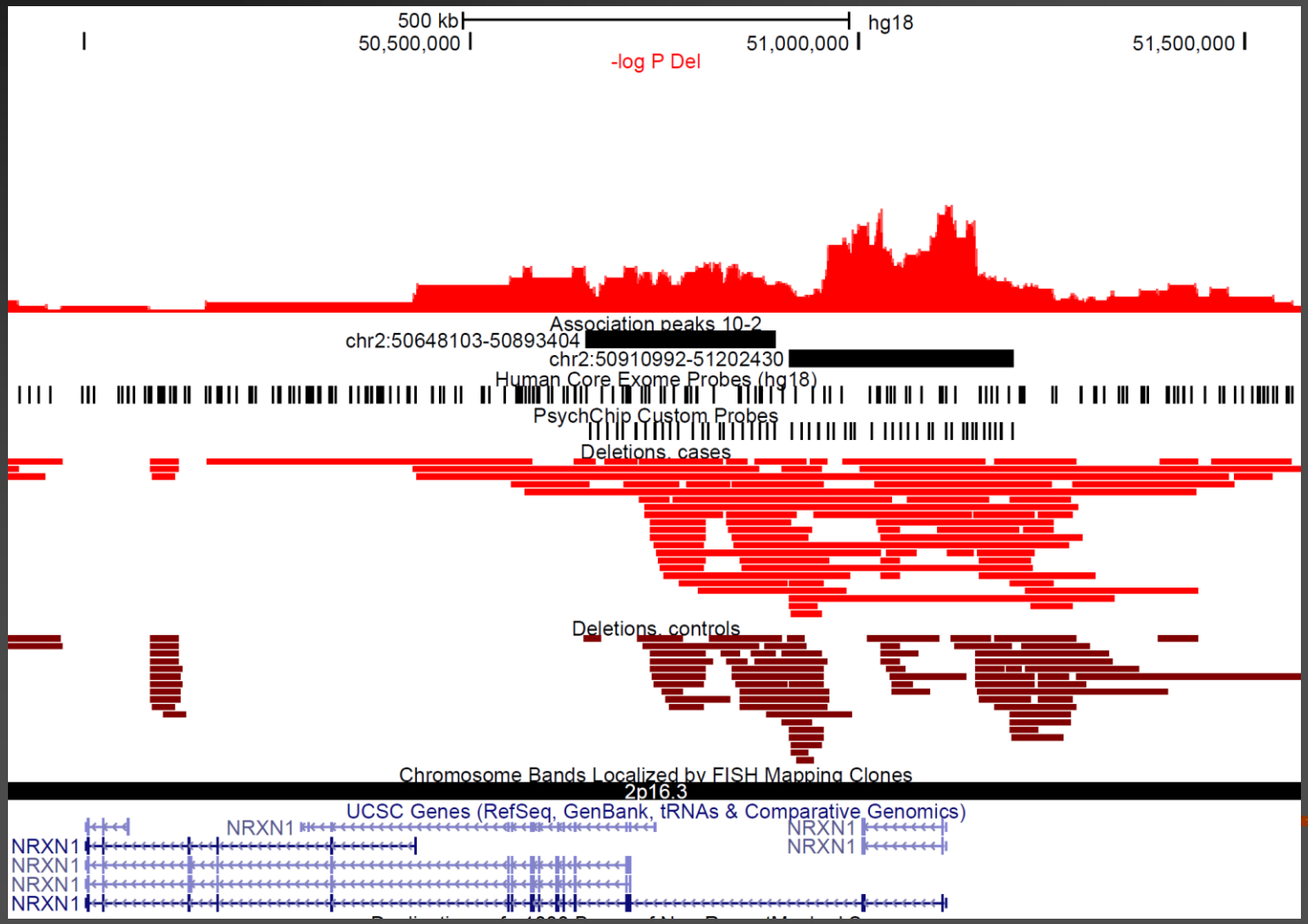
An enriched CNV burden of genomic disorders and de novo loci



- ASD implicated loci most
  Copy number gains
  SCZ implicated loci removed

- No CNVs in ID implicated gains

Frequent non-recurrent CNVs enable fine scale delineation of a locus



Summary

- Technical challenges to massive CNV studies across studies and platforms are readily addressable using meta-analytic approaches
- Enriched CNV burden in SCZ is robust. Following removal of Published CNV loci, remaining signal is concentrated among singleton variants.
- Several loci of major effect are evident as genome-wide significant associations
- Neuro gene set analysis

Applying the PGC CNV pipeline to other disorders

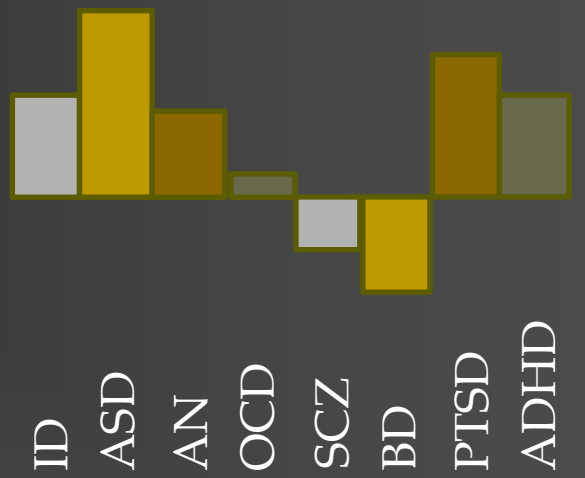
- Data aggregation and processing is under way for 4/5 PGC2 disorders
  - ADHD (90% complete)
  - Bipolar Disorder (50% complete)
  - PsychChip (5% complete)
  - Autism (initiated, awaiting update)
  - PTSD (initiated, awaiting update)
  - MDD (not started)

Additional disorders proposed for PGC phase 3

- Anorexia
- OCD/TS
- Substance Abuse

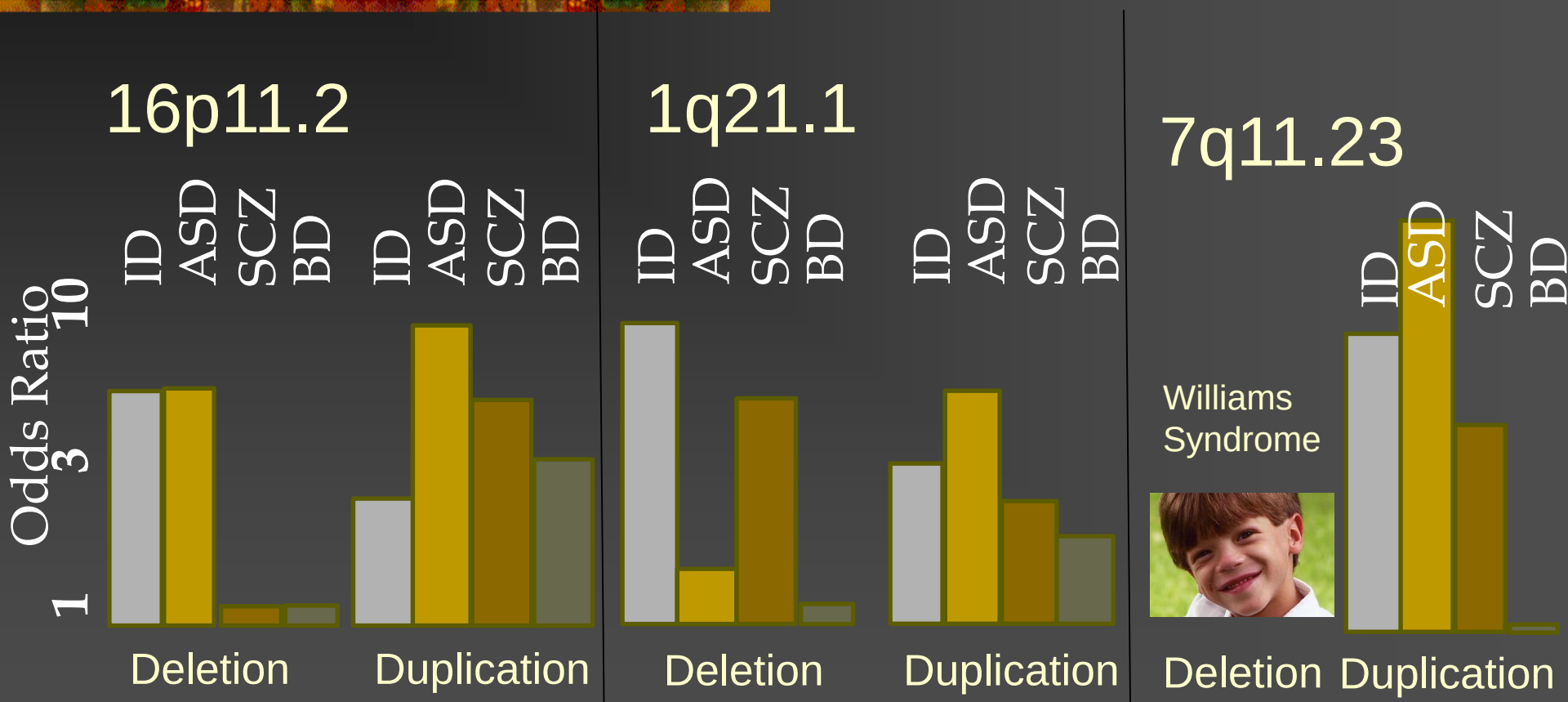
Future directions
Exploring shared risk across all major psychiatric disorders

- ASD
- ADHD
- Anorexia Nervosa
- Bipolar Disorder
- PTSD
- OCD/Tourettes
- Major Depression
- Schizophrenia
- Substance Abuse



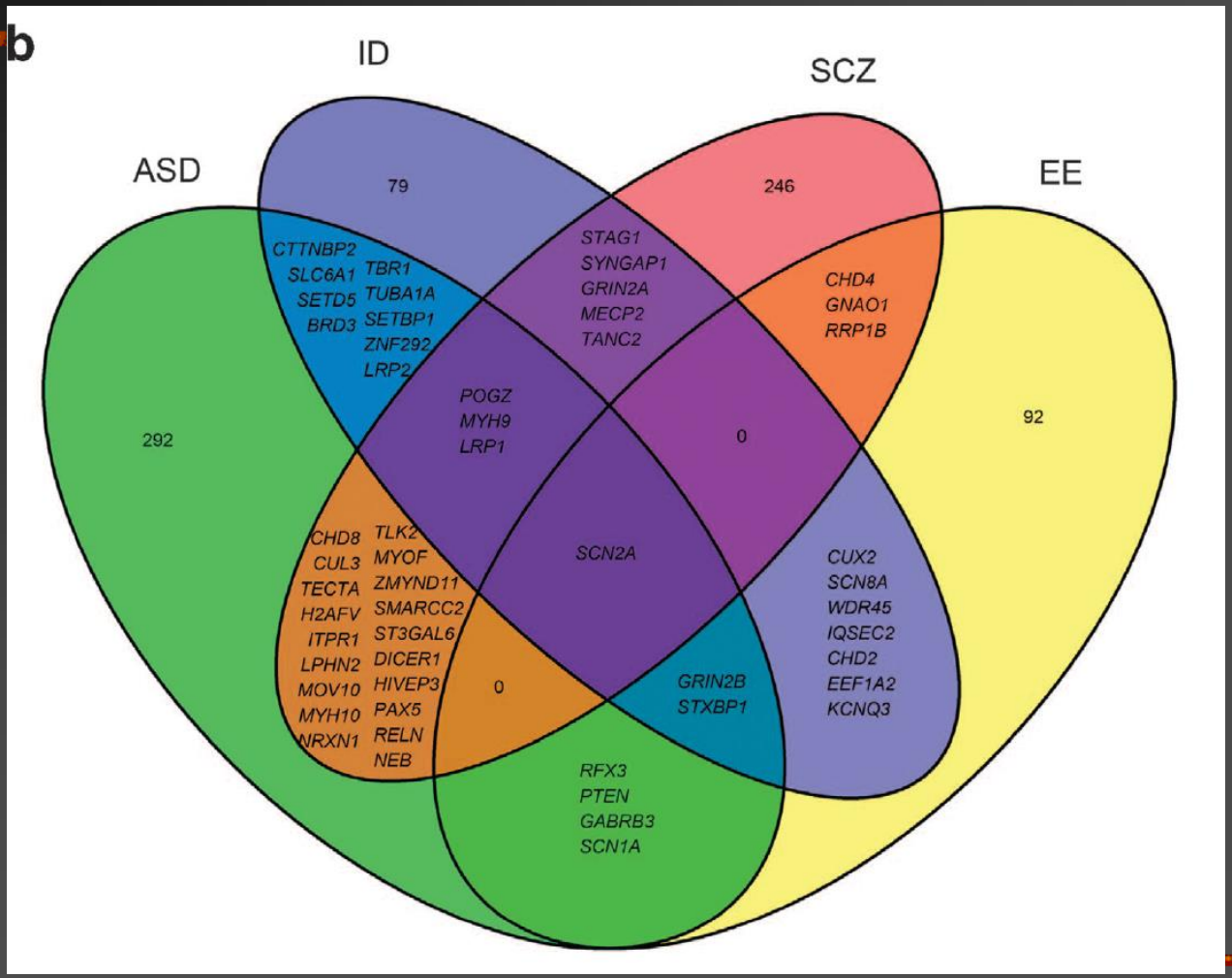
Current PGC efforts projected to reach >30,000 of each disorder

Most CNVs that contribute to SCZ also contribute to ASD



Malhotra et al, Cell 2012

Rare de novo mutations implicate overlapping genes in ASD and SCZ



Li et al Mol Psychiatry. 2015 Apr 7.

How does one mutation give rise to 2 disorders?

Hypothesis 1: Features of autism are the pediatric symptoms of an adult psychiatric disorder

ASD

SCZ

Hypothesis 1: Features of autism are the pediatric symptoms of an adult psychiatric disorder

- This model is not strongly supported
- Features of autism are NOT predictive of the development of psychosis
  - In the population

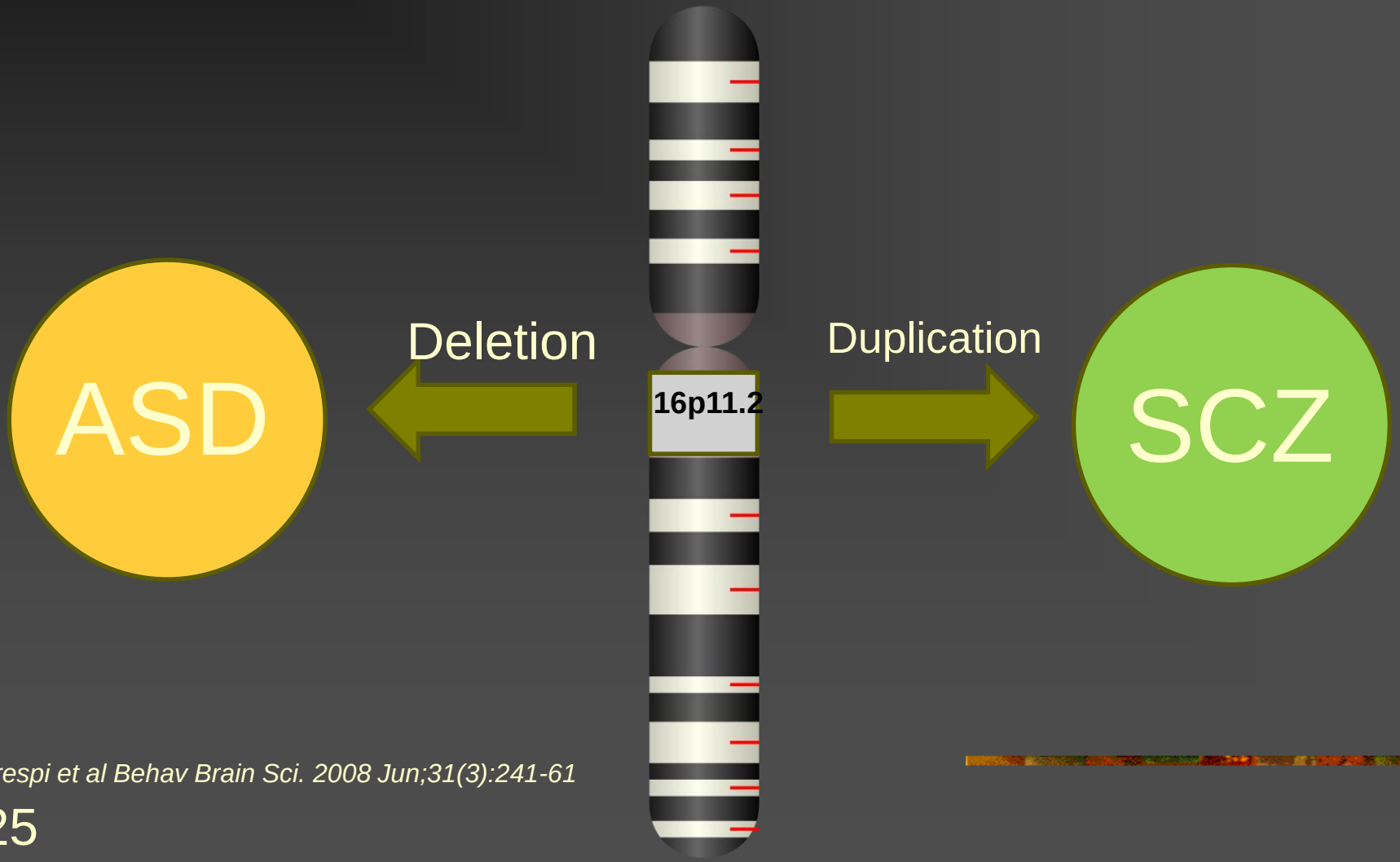
Esterberg et al. Schizophr. Res. 104 (1), 265–273. 2008.

-or-

  - In a specific genetic disorder (22q11.2 microdeletion)

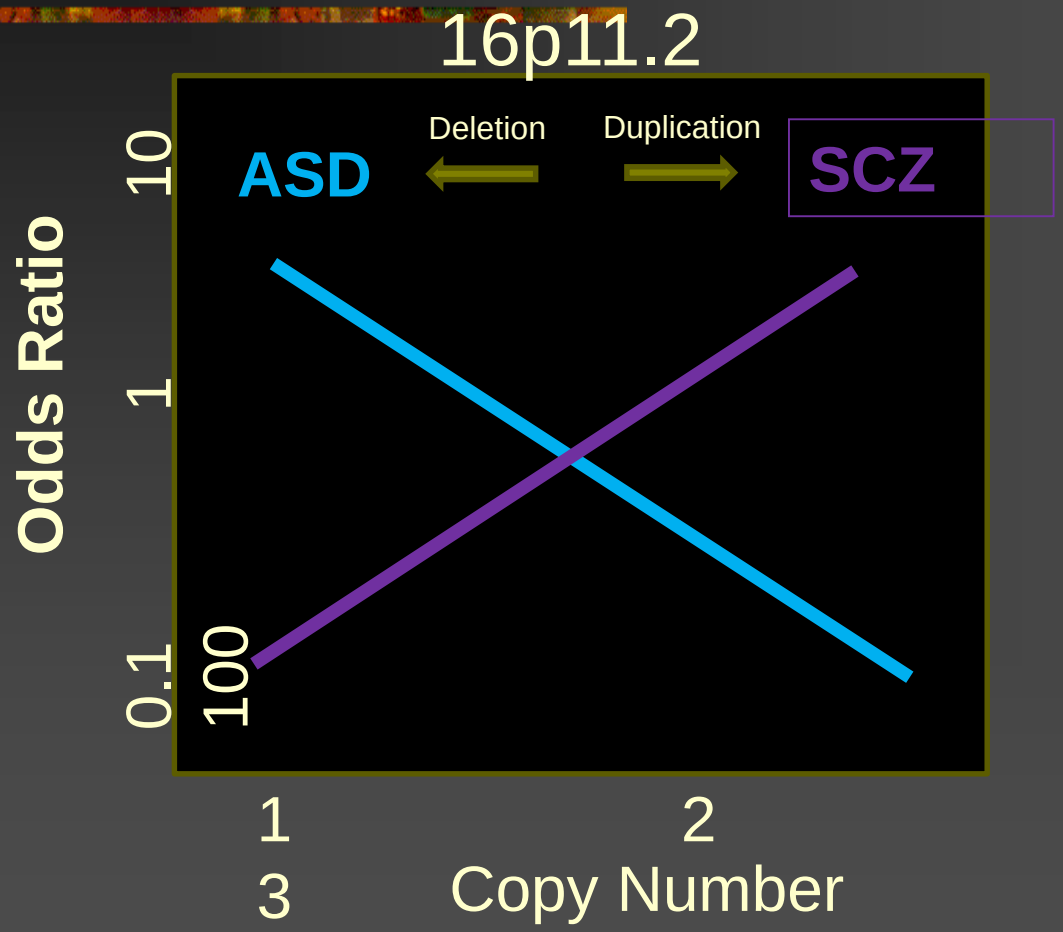
Vorstman et al Schizophr. Res. 143 (1), 55–59, 2013

Hypothesis 2: ASD and SCZ are diametric opposites

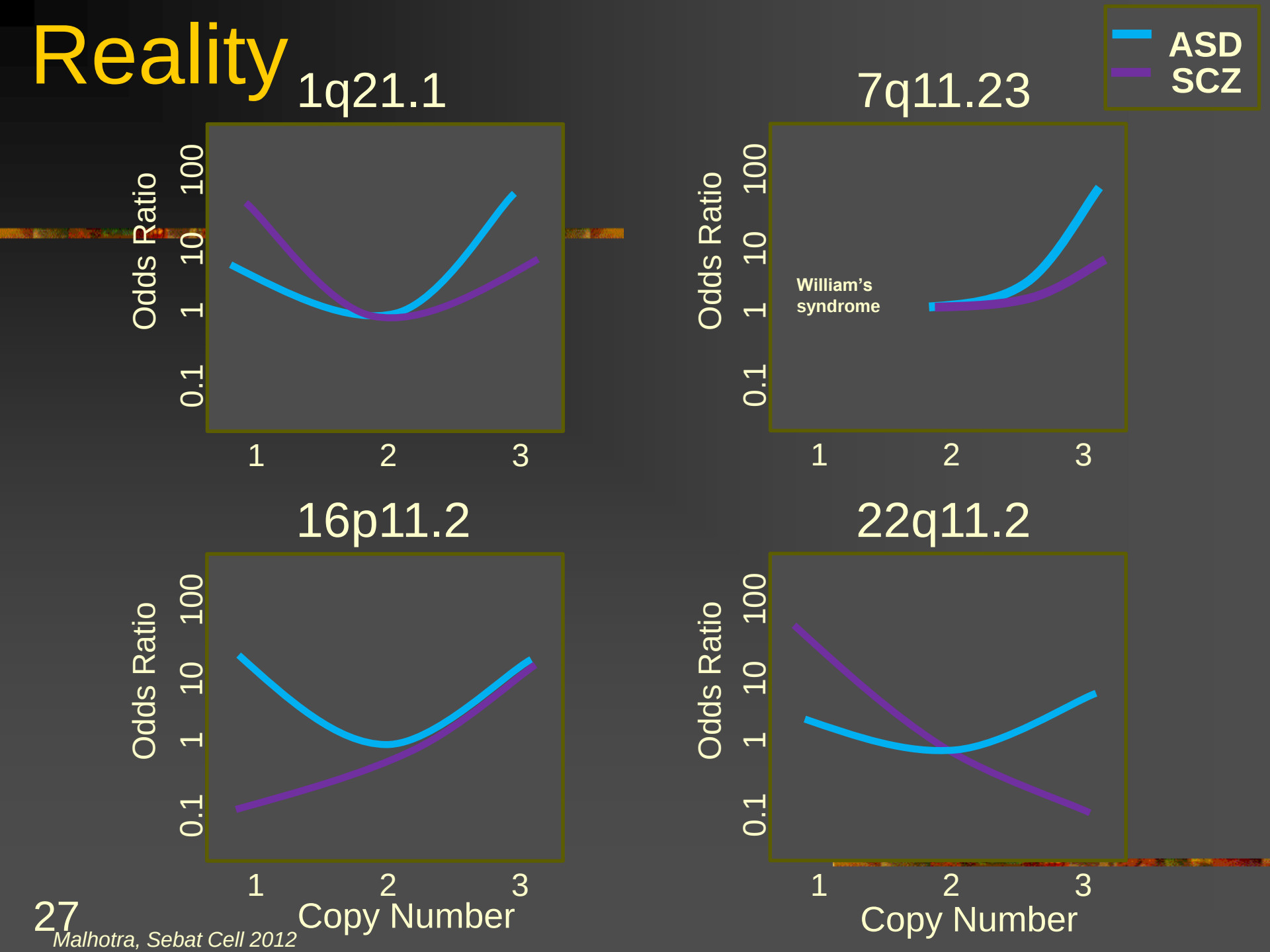


Crespi et al Behav Brain Sci. 2008 Jun;31(3):241-61

Theory

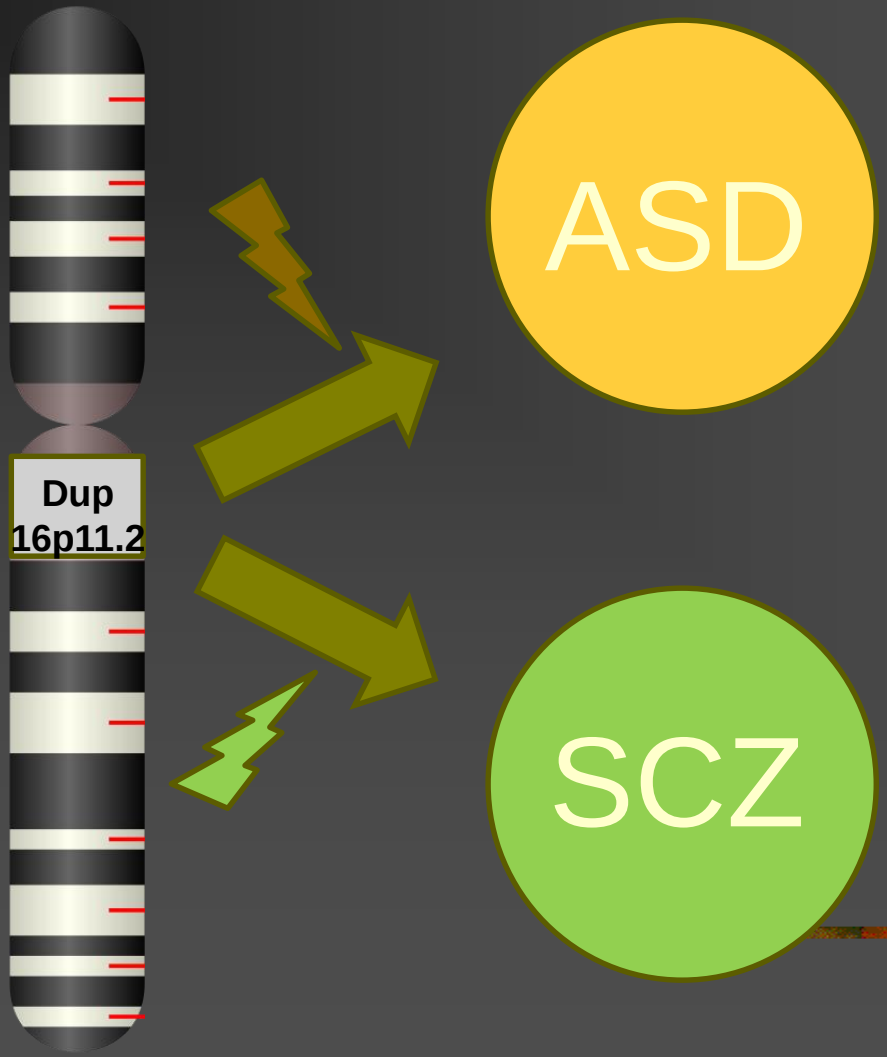

16p11.2
Deletion
Duplication
ASD
SCZ
Odds Ratio
10
1
0.1
100
1
2
3
Copy Number

Reality



Malhotra, Sebat Cell 2012

Hypothesis 3: ASD and SCZ are divergent outcomes (determined by modifiers)



Outcome is influenced by Genetic background

Original Investigation

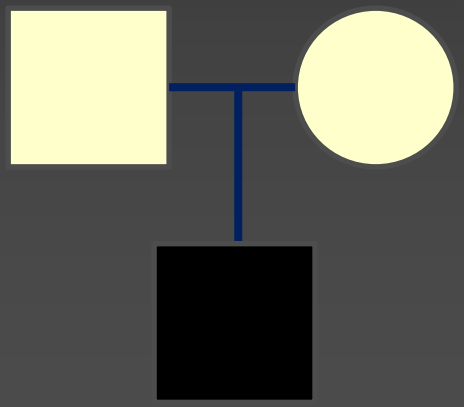
The Role of Parental Cognitive, Behavioral, and Motor Profiles in Clinical Variability in Individuals With Chromosome 16p11.2 Deletions

Andres Moreno-De-Luca, MD; David W. Evans, PhD; K. B. Boomer, PhD; Ellen Hanson, PhD; Raphael Bernier, PhD; Robin P. Goin-Kochel, PhD; Scott M. Myers, MD; Thomas D. Challman, MD; Daniel Moreno-De-Luca, MD; Mylissa M. Slane, MS; Abby E. Hare, PhD; Wendy K. Chung, MD; John E. Spiro, PhD; W. Andrew Faucett, MS; Christa L. Martin, PhD; David H. Ledbetter, PhD

In all cases the child carried a deletion

Parents did not

Relative the parental average, the child has significant impairments in social, cognitive and motor skills



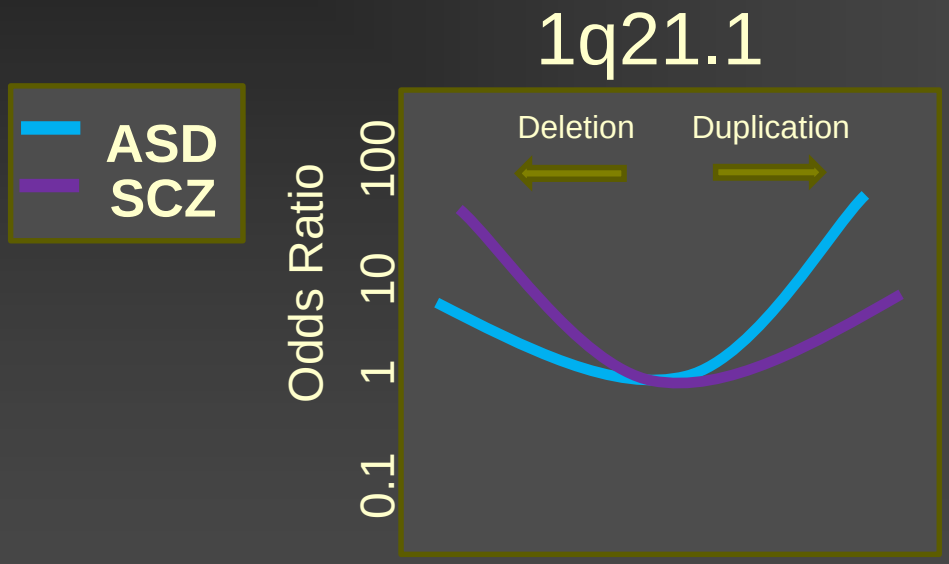
However,
variation in clinical outcome of the child in different families was significantly correlated with the parent's -
average
-IQ
-Social responsiveness
-Motor performance

What could the genetic background consist of?

- Other rare variants (oligogenic model)
- Cumulative load of autism polygenic risk vs schizophrenia polygenic risk
  - Since polygenic risk is largely not shared, these modifiers could be a key factor in determining clinical diagnosis

Support for models #2 & #3

- A shift in gene dosage can produce a shift from ASD risk toward SCZ risk

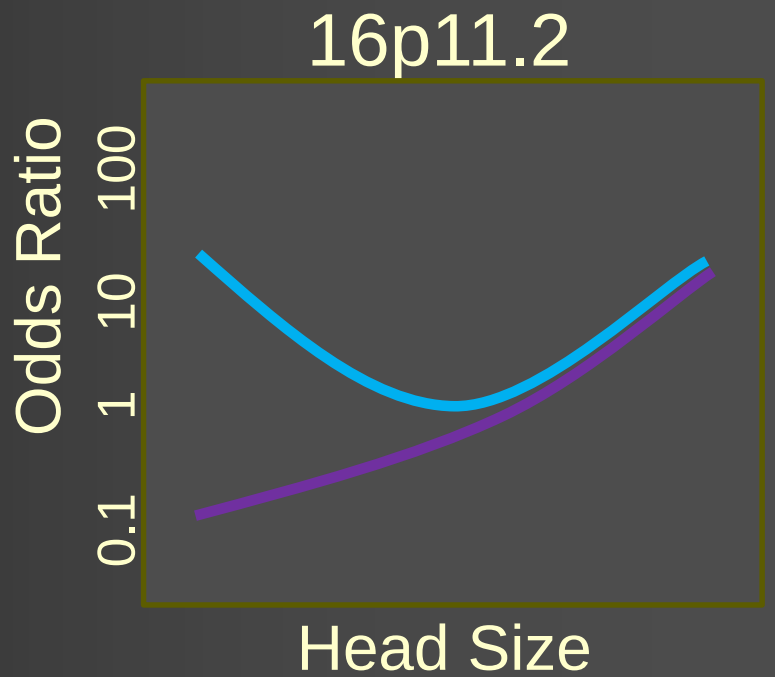


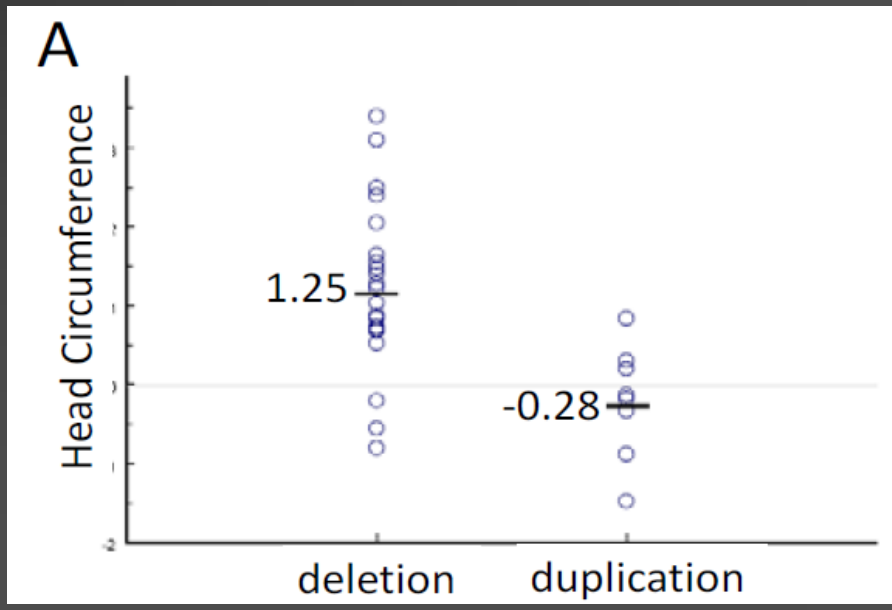
- But it's not so simple
- Each CNV has a different profile of dosage vs. risk
- Outcome is also influenced by genetic background and environment

What is the underlying neurobiological basis of risk?

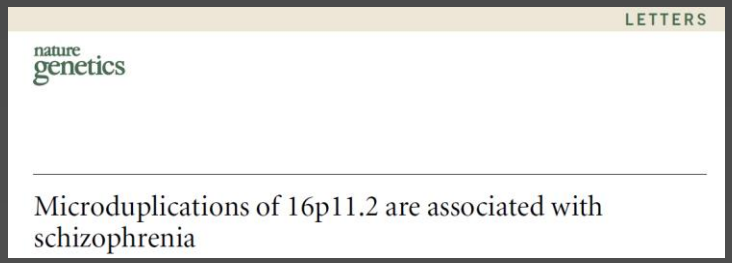
16p11.2 is associated with alterations in head size

- Deletion is associated with ASD and enlarged head (+1.25 SD)
- Duplication is associated with reduced head size, ASD and SCZ





McCarthy et al, Nature Genetics 2009


LETTERS

nature genetics

Microduplications of 16p11.2 are associated with schizophrenia

16p11.2 may contribute in part to increased brain volume in autism

Evidence of Brain Overgrowth in the First Year of Life in Autism

Eric Courchesne, PhD
Ruth Carper, PhD
Natacha Akshoomoff, PhD

Context Autism most commonly appears by 2 to 3 years of life, at which time the brain is already abnormally large. This raises the possibility that brain overgrowth begins much earlier, perhaps before the first clinically noticeable behavioral symptoms.

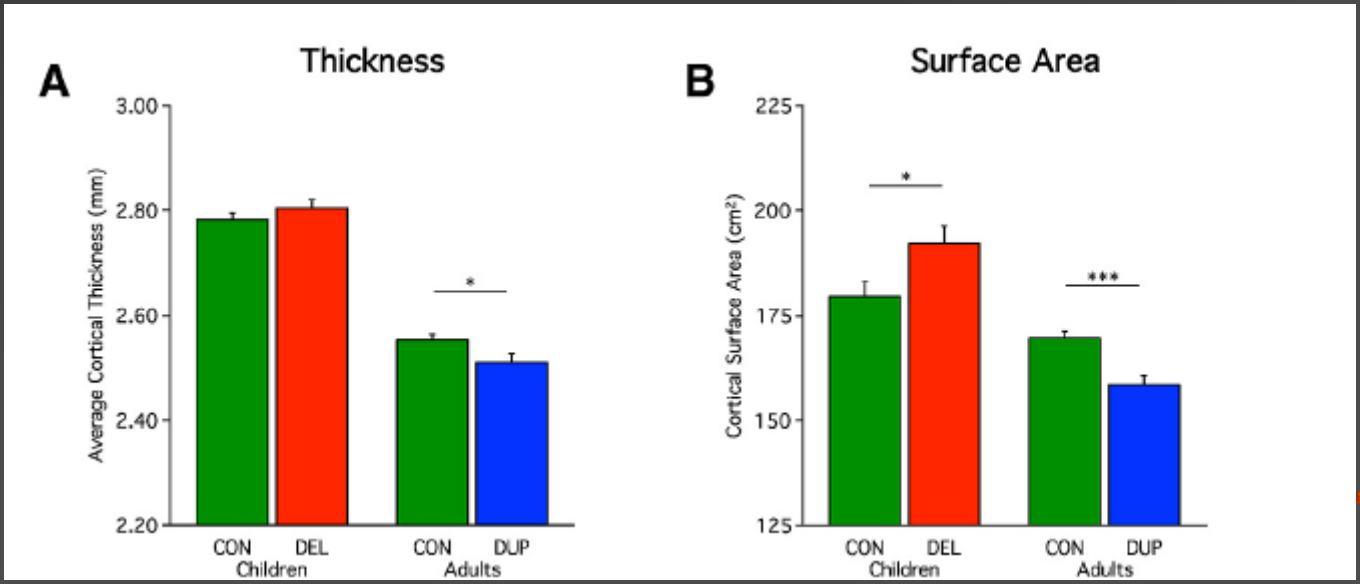
Objectives To determine whether pathological brain overgrowth precedes the first

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,[3] Timothy P.L. Roberts,[3] Srikantan S. Nagarajan,[7] John E. Spiro,[10] Wendy K. Chung,[11] Elliott H. Sherr,[8] and Randy L. Buckner[1,3,6] on behalf of the Simons VIP Consortium

[1]Harvard University, Department of Psychology and Center for Brain Science, Cambridge, Massachusetts 02138, Departments of [2]Neurology and [3]Psychiatry, Massachusetts General Hospital, Boston, Massachusetts 02114, [4]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, Massachusetts 02129, [5]Ludwig Maximilians University Munich, Institute of Clinical Radiology, Munich 81377, Germany, [6]Departments of Neurology and Radiology, Washington University School of Medicine in St. Louis, St. Louis, Missouri 63110, Departments of [7]Radiology and Biomedical Imaging, and [8]Neurology, University of California, San Francisco, California 94158, [9]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104, [10]Simons Foundation, New York, New York 10010, and [11]Department of Pediatrics and Medicine, Columbia University Medical Center, New York, New York 10032

Simons VIP study finds that brains are uniformly larger in the patients with deletion of 16p11.2 (no one region disproportionately affected).
Effect is stronger on cortical surface area than on cortical thickness



Genetic effect on brain development is recapitulated in mouse

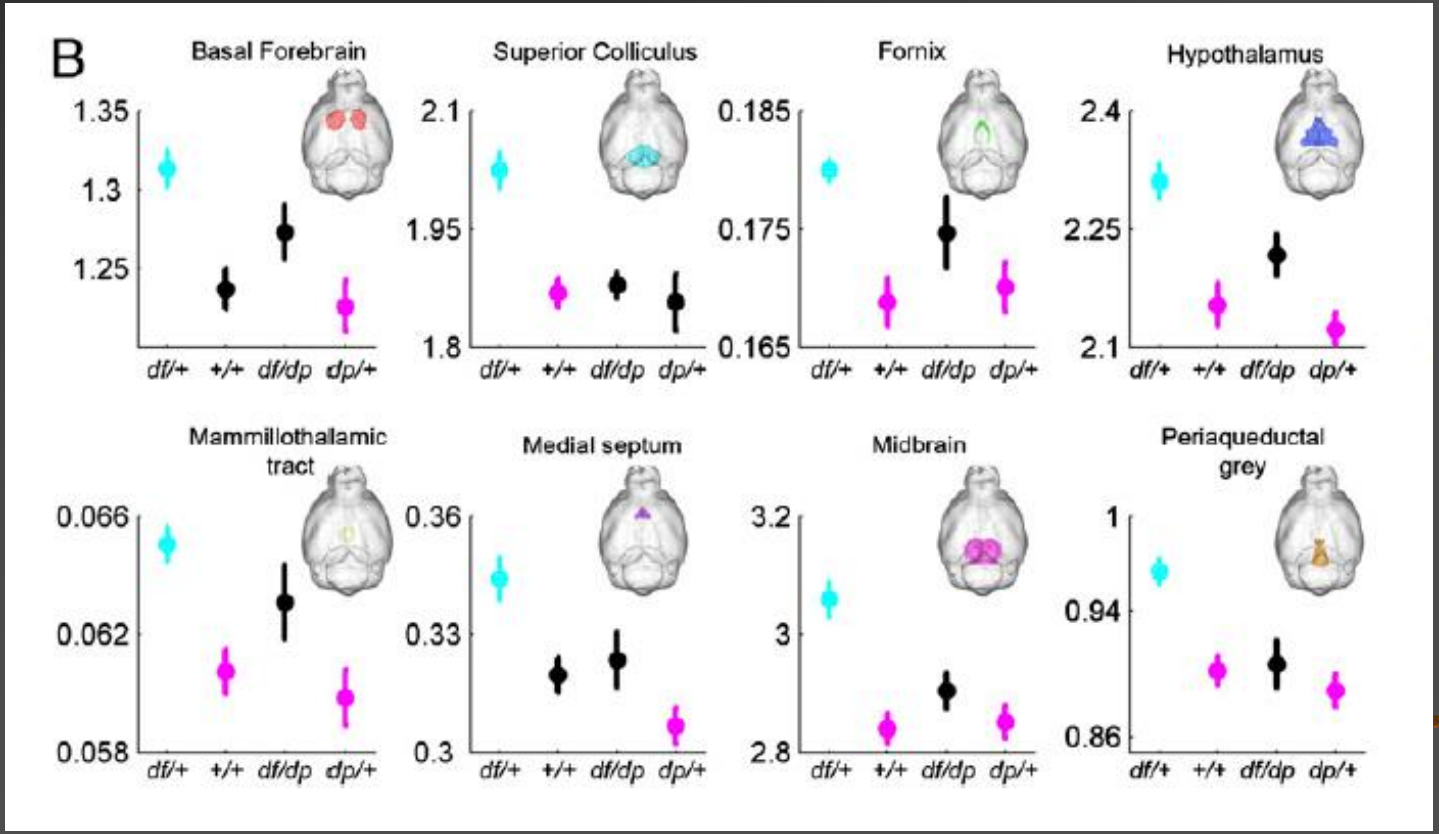
Dosage-dependent phenotypes in models of 16p11.2 lesions found in autism

Guy Horev[a], Jacob Ellegood[b], Jason P. Lerch[b], Young-Eun E. Son[a], Lakshmi Muthuswamy[a,1], Hannes Vogel[c], Abba M. Krieger[d], Andreas Buja[d], R. Mark Henkelman[b], Michael Wigler[a,2], and Alea A. Mills[a,2]

[a]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724; [b]Mouse Imaging Centre, Hospital for Sick Children, Toronto, ON, Canada M5T 3H7; [c]Department of Pathology, Stanford University, Stanford, CA 94305; and [d]Wharton School, University of Pennsylvania, Philadelphia, PA 19104

Contributed by Michael Wigler, August 31, 2011 (sent for review July 18, 2011)

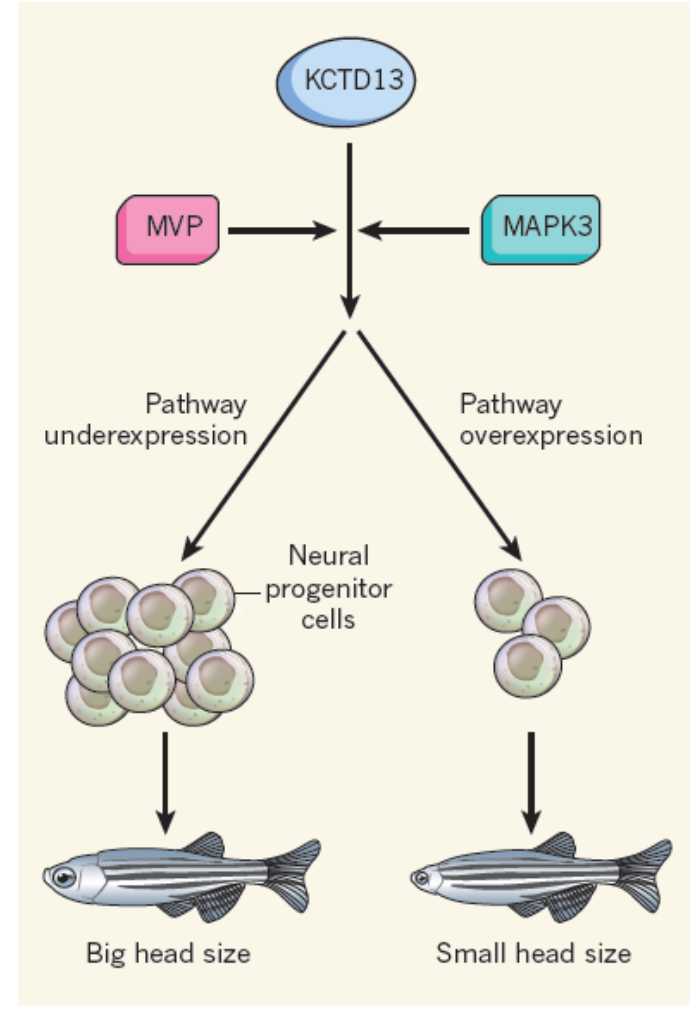
Mouse Model of 16p11.2: gene dosage in correlates with brain volume



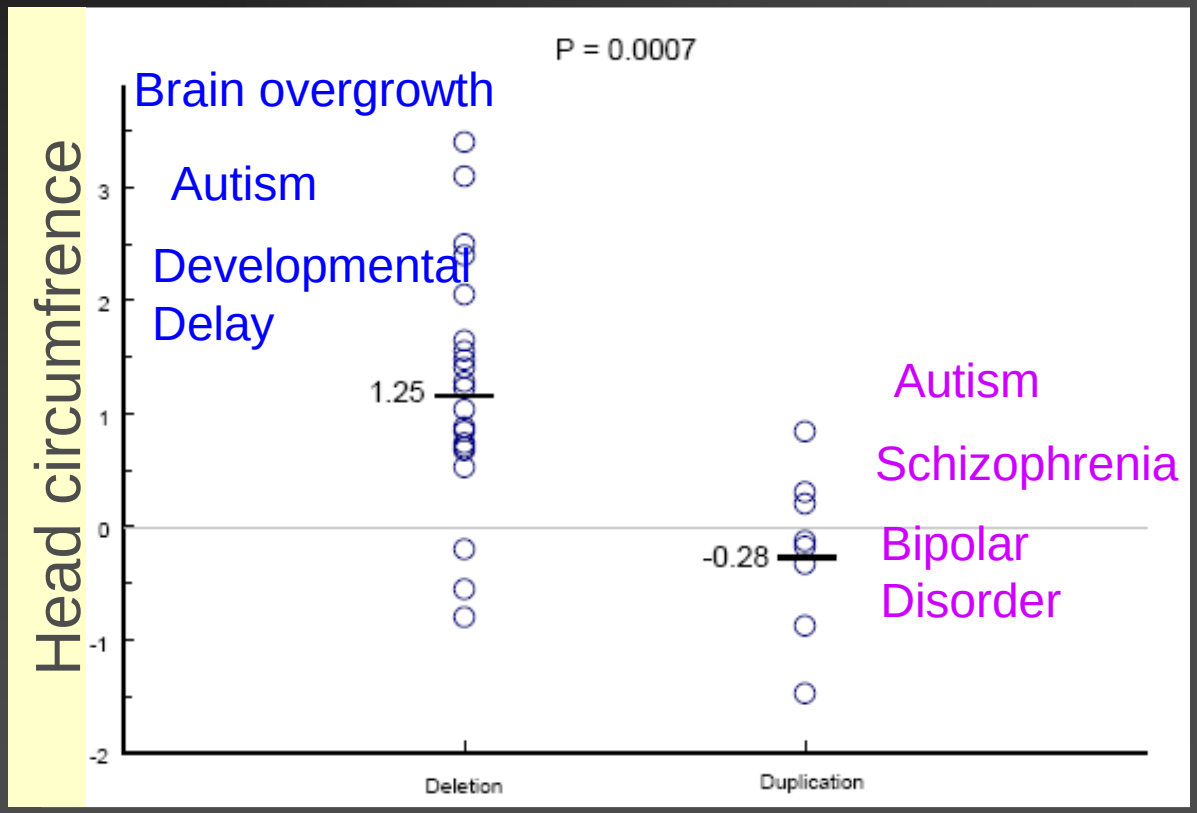
And fish…

Golzio, Katsanis et. Al, Nature, 2012

- 16p11.2 CNV effect on brain growth can also be recapitulated in zebrafish
- The gene KCTD13 has been identified as a key driver of brain growth abnormalities



Psychiatric traits are linked to genetic effects on brain development



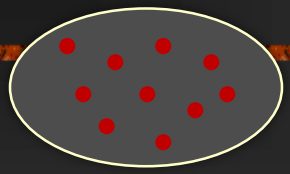
And the molecular basis?

Lilia
Iakoucheva
UCSD

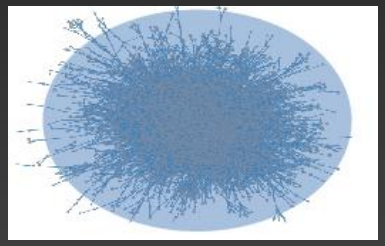
Guan Ning Lin
Iakoucheva Lab
Department of Psychiatry
University of California San Diego

Protein networks within brain context

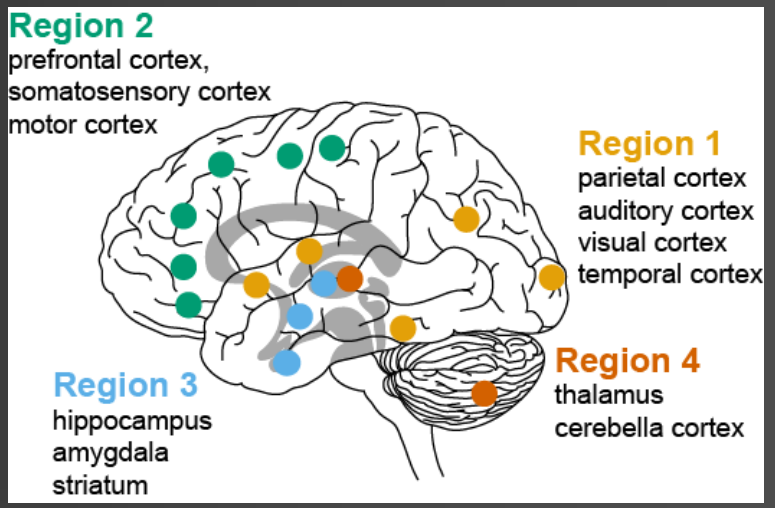
Map all genes within a single CNV to biological networks



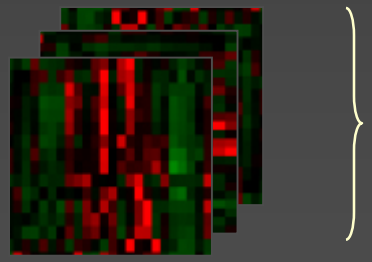
PPI datasets

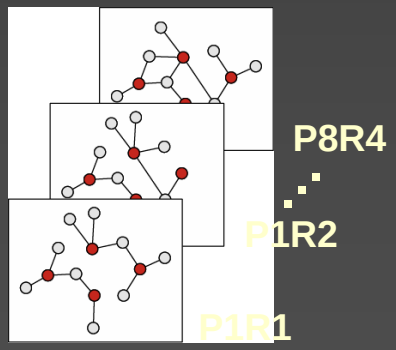


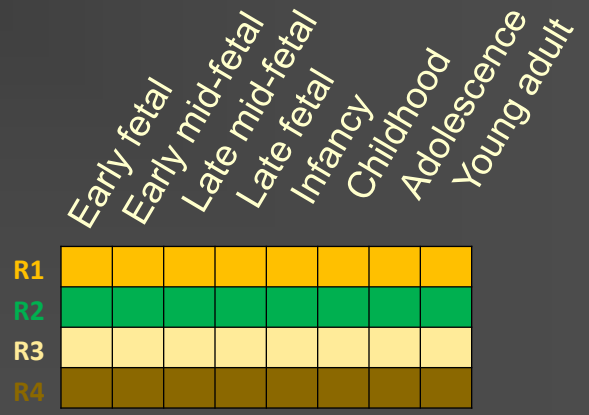
Spatio-temporal brain transcriptome (Brainspan)



Spatio-temporal PPI networks

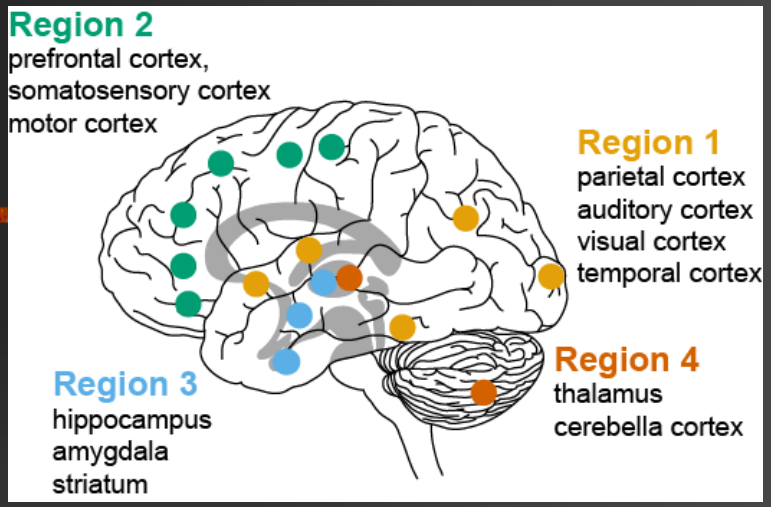






32 P_xR_y spatio-temporal intervals

CNVs have distinct spatio-temporal signatures

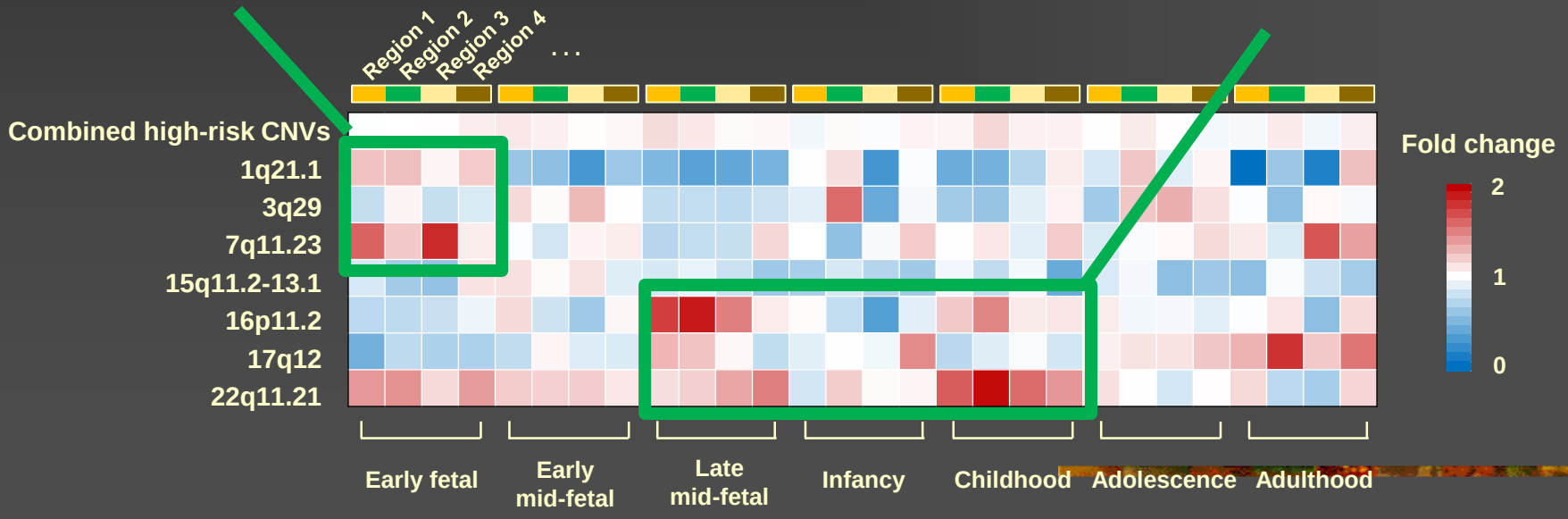


Lilia Iakoucheva

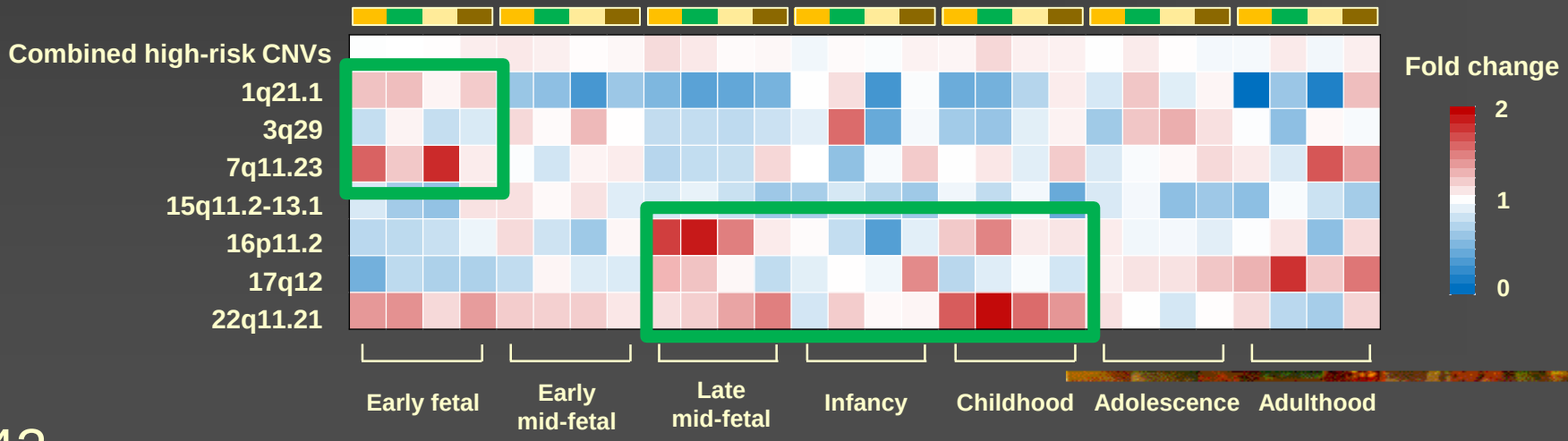
CNV genes are coexpressed during….

Early Fetal Period

Late fetal – early childhood

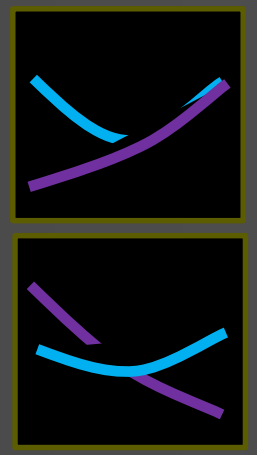


Do CNVs with similar brain expression profiles have similar Risk profiles?



Summary

- Autism, Schizophrenia and related disorders have a shared genetic basis
- A shift in gene dosage can produce a shift in the probability of ASD vs SCZ diagnosis
- However each CNV has a different risk profile
- Understanding the impact of gene dosage on neural circuits could shed light on how these different aspects of cognition develop



Special Thanks

UCSD

Wenting Wu

Doug Greer

Madhu Gujral

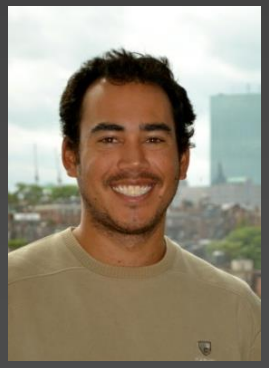
Dheeraj Malhotra

Cardiff

Mick O'Donovan

Broad Institute

Ben Neale



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