Genetics of Tourette Syndrome

Starting with linkage and sib pair studies, and changing with the times. Turns out that TS is much more complex than we originally thought…

Genetics of Tourette Syndrome

TS is highly heritable

- 1st degree relatives of TS patients have increased risk:
  - TS: 10-20%
  - Chronic Tics (CT): additional 10-20%
  - OCD: 10-20%
- Small twin studies suggest high heritability (h^2~0.6-0.8)
- Recent population-based estimates:
  - TS/CT Sib recurrence risk: 18.6 (15.3-22.6)
  - TS/CT Child recurrence risk: 61.0 (44.4-83.8)
  - TS/CT Heritability: 0.77 (0.70-0.85)
- TS is heritable, but also complex—

Mataix-Cols et al. *JAMA Psych* 2015; Browne et al., *JAMA Psych* 2015;

Familial relative risk (RR) for various neuropsychiatric disorders

Disease	Population prevalence per 100,000	Morbid risk in first-degree relatives (%)	Relative risk
Narcolepsy	10–100	30–50	5,000
Huntington's disease	19	50	2,630
Wilson's disease	10	25	2,500
Parkinson's disease (SNCA, Parkin, Etc)	133	8.3	62.4
Autism	50–100	2–4	45–90
Bipolar disorder	500–1,500	8	16
Schizophrenia	900	12.8	14.2
Panic disorder	2,700	31	10
Obsessive-compulsive disorder	1,000–2,000	10	4.5
Alzheimer's disease (APP, PS1, PS2)	7,700	14.4	1.9
Prion diseases	<0.1	?	?
Tourette Syndrome	600	10-20%	19-61

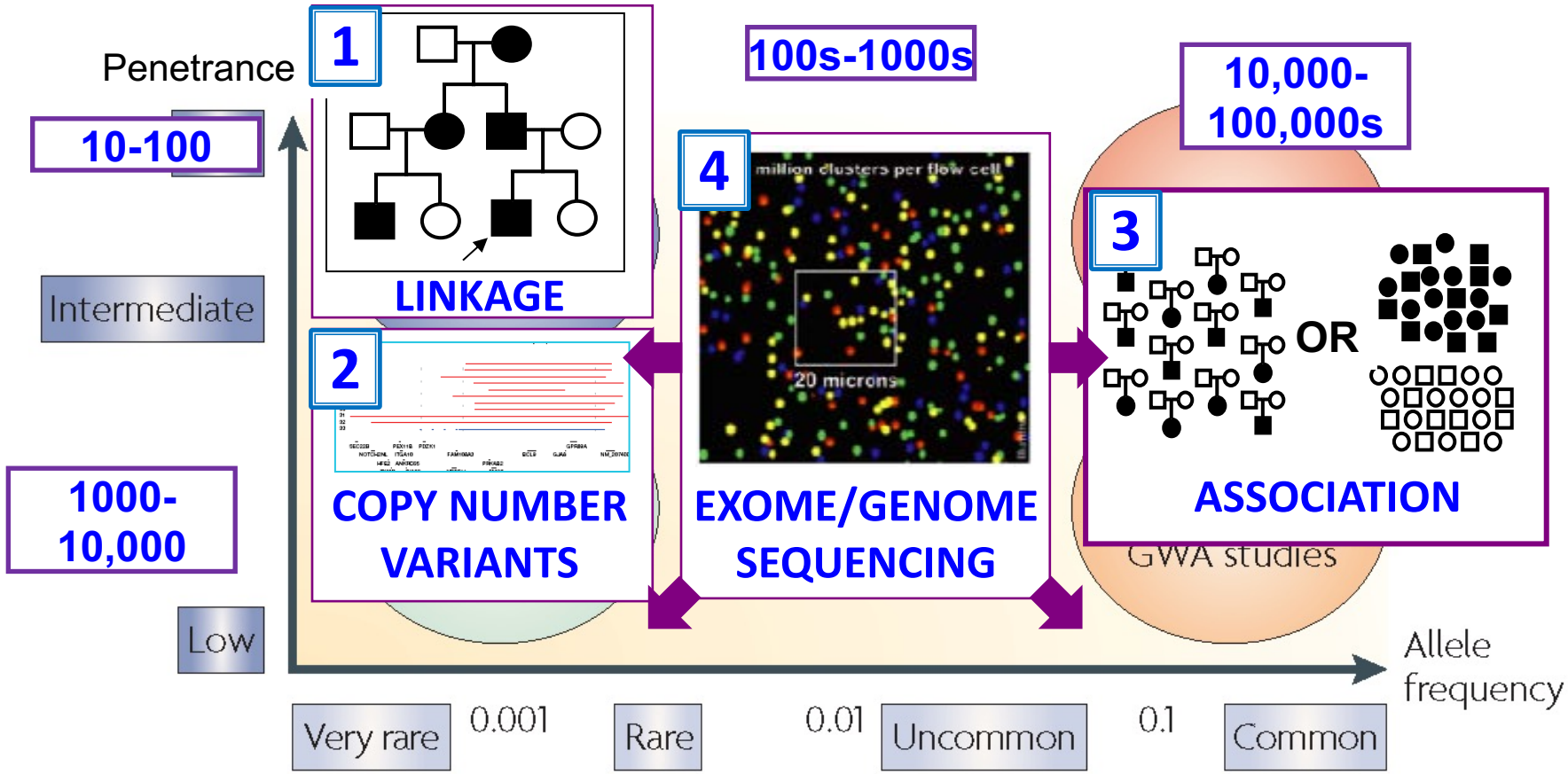
Mendelian (monogenic) — "Deterministic"

Complex Inheritance genetic + non-genetic ("environmental") — "Probabilistic"

Textbook of Neuropsychiatry and Behavioral Neurosciences, 5th Edition. Eds, Yudofsky SC, Hales RE.© 2008

Genetics of Tourette Syndrome

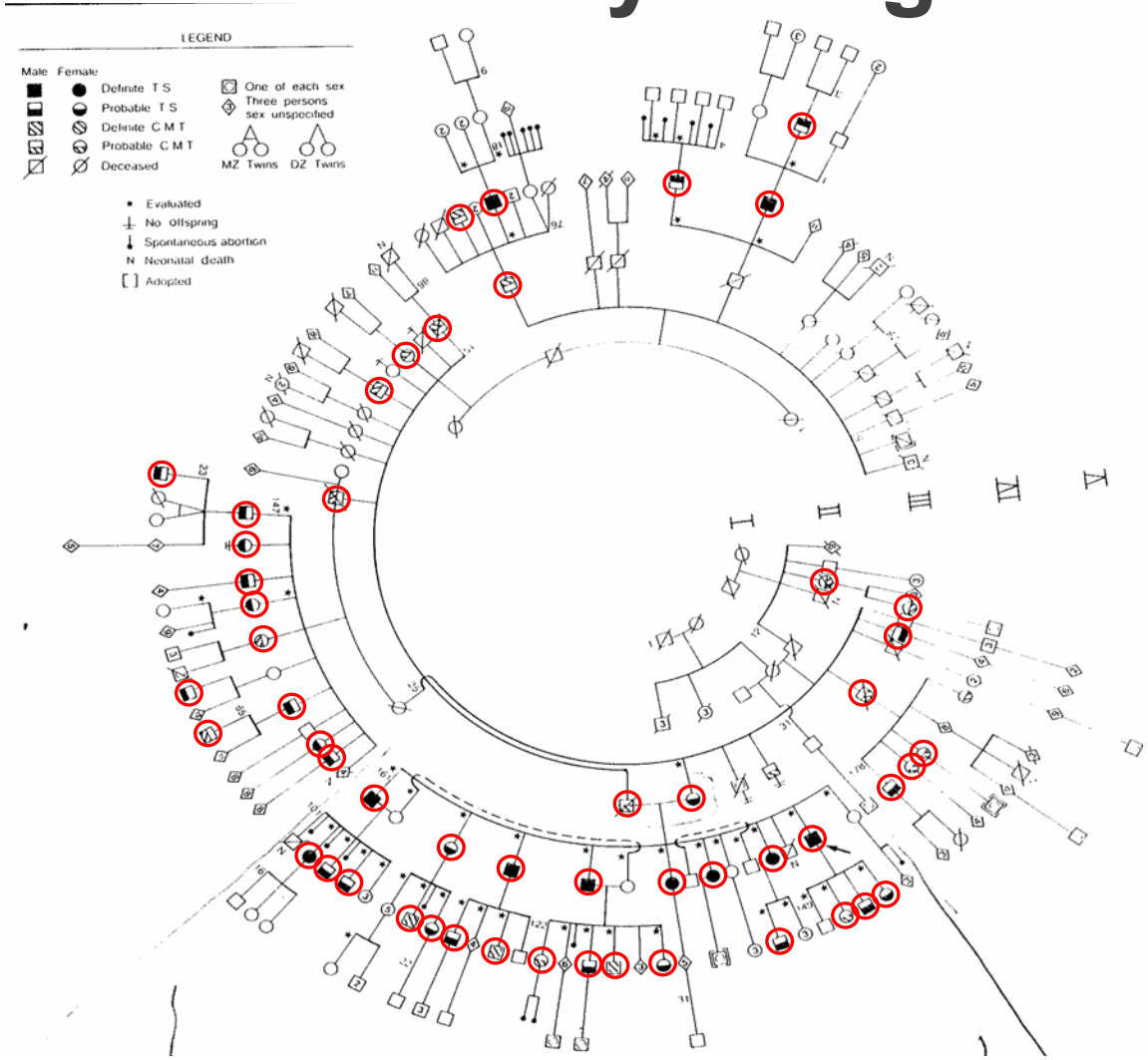
For complex disorders, multiple approaches are needed



McCarthy et al., 2008; Sullivan et al., 2012

Genetics of Tourette Syndrome

Large, multigenerational families were traditionally how genes are identified



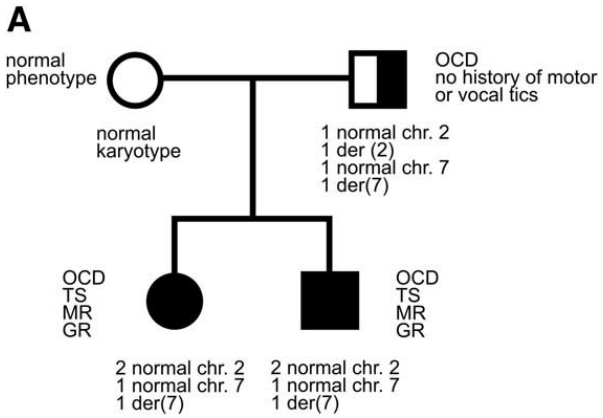
- 503 members + spouses
- 94 affected with TS/CT in 4 generations
- May be enriched for highly penetrant TS variants
- Exome and chr 2 targeted sequencing non-informative

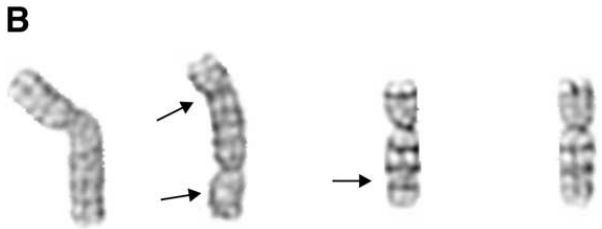

Giovanni Coppola

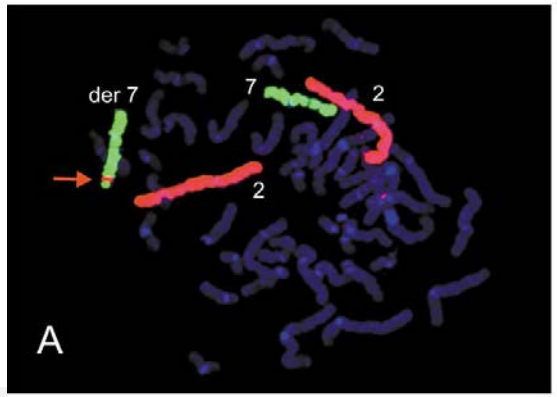

Jae-Hoon Sul


Dongmei Yu

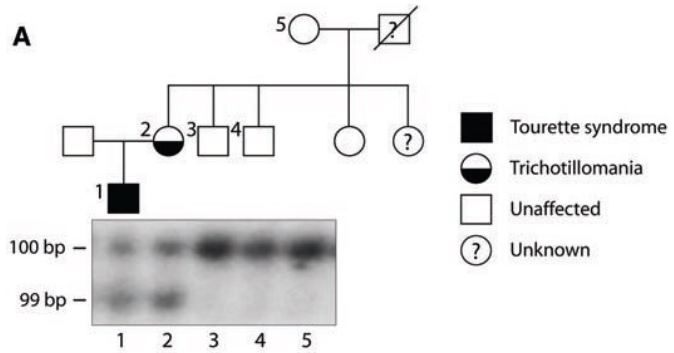
Family studies and chromosomal rearrangements



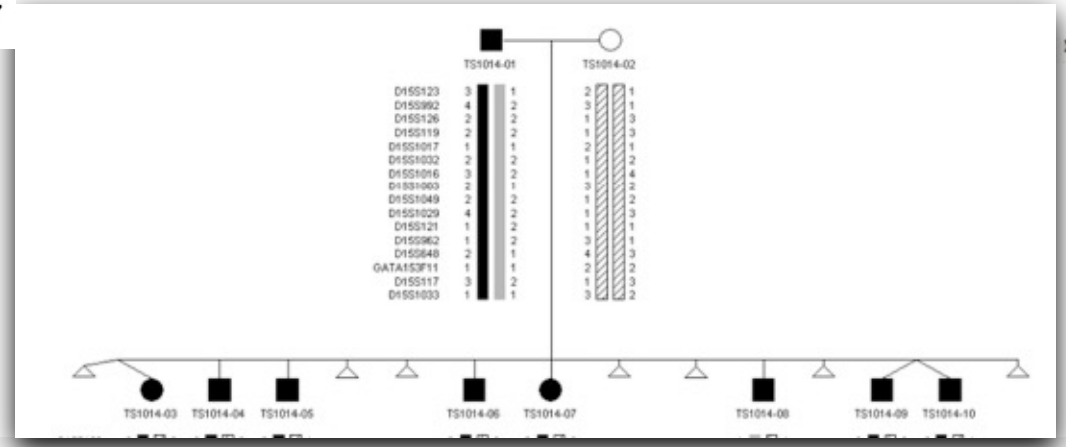


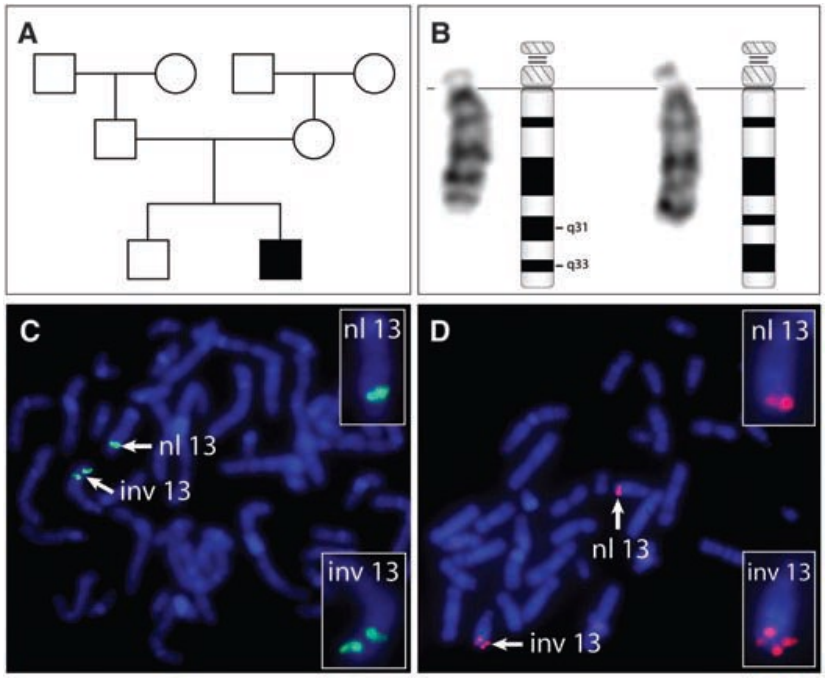


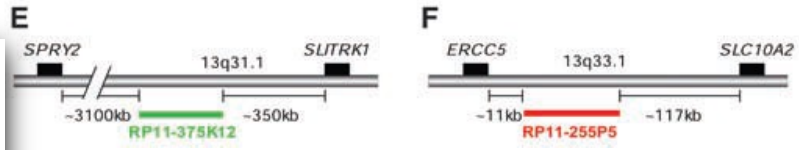
SLITRK-1



CNTNAP2







HDC

Abelson Science I 2005

Verkerk Genomics 2003

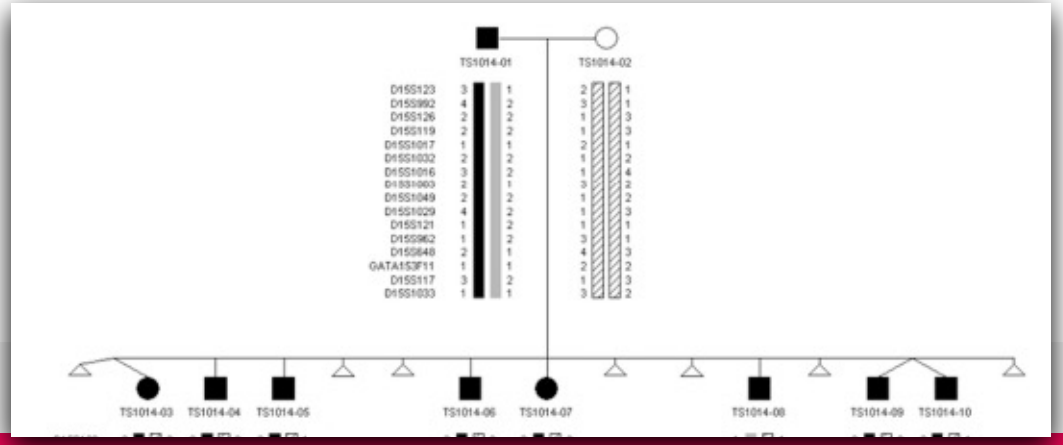
Ercan-Sencicek et al., NEJM 2010

Castellan Baldan et al., Neuron 2014

Genetics of Tourette Syndrome

L-Histidine Decarboxylase (HDC) & TS

- Single family, 8 affected offspring; 8 previous miscarriages
- Parametric linkage to an 8Mb chr 15 region (LOD 2.05)
- Sequenced 51 genes under peak
- Nonsense mutation (W318X) in HDC in all affecteds
  - W318X not found in 1500 matched controls
  - No additional nonsense mutations in 720 TS cases & 360 controls
- In-vitro enzymatic assay demonstrated mutant protein could not convert histidine to histamine
- Known interaction in basal ganglia between H3R and D2R

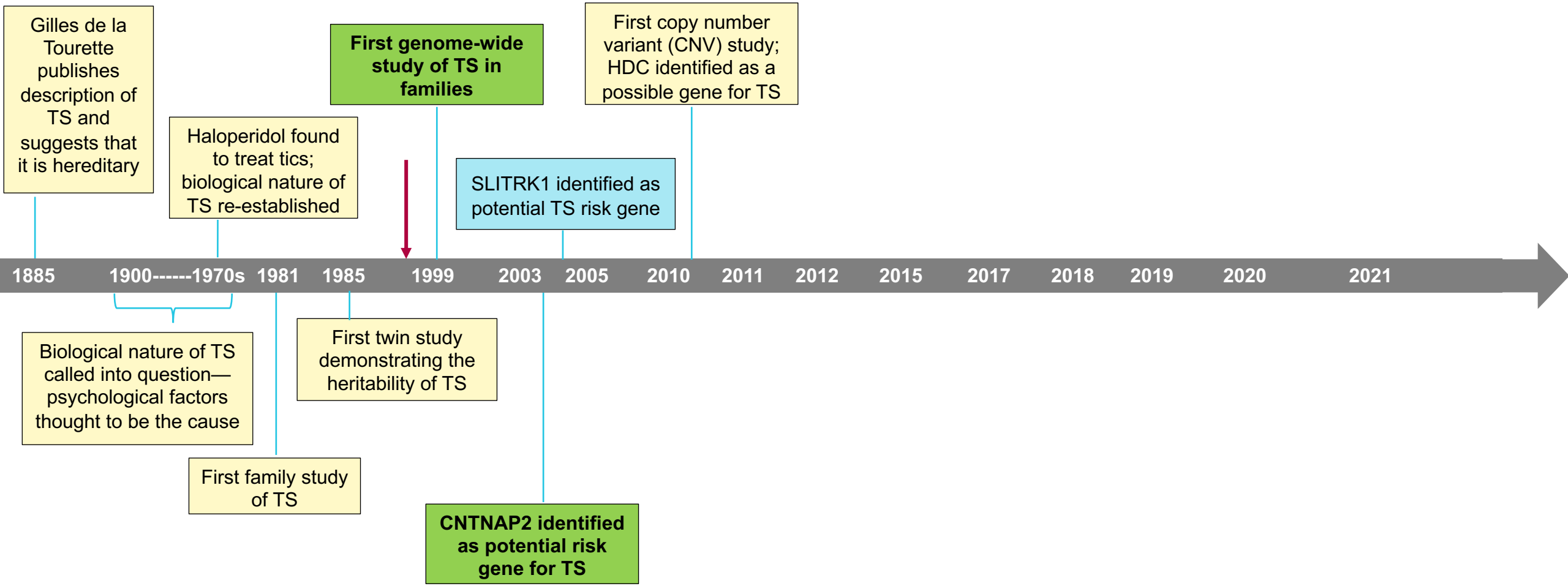


Ercan-Sencicek et al., NEJM 2010

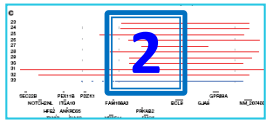
Castellan Baldan et al., Neuron 2014

Genetics of Tourette Syndrome

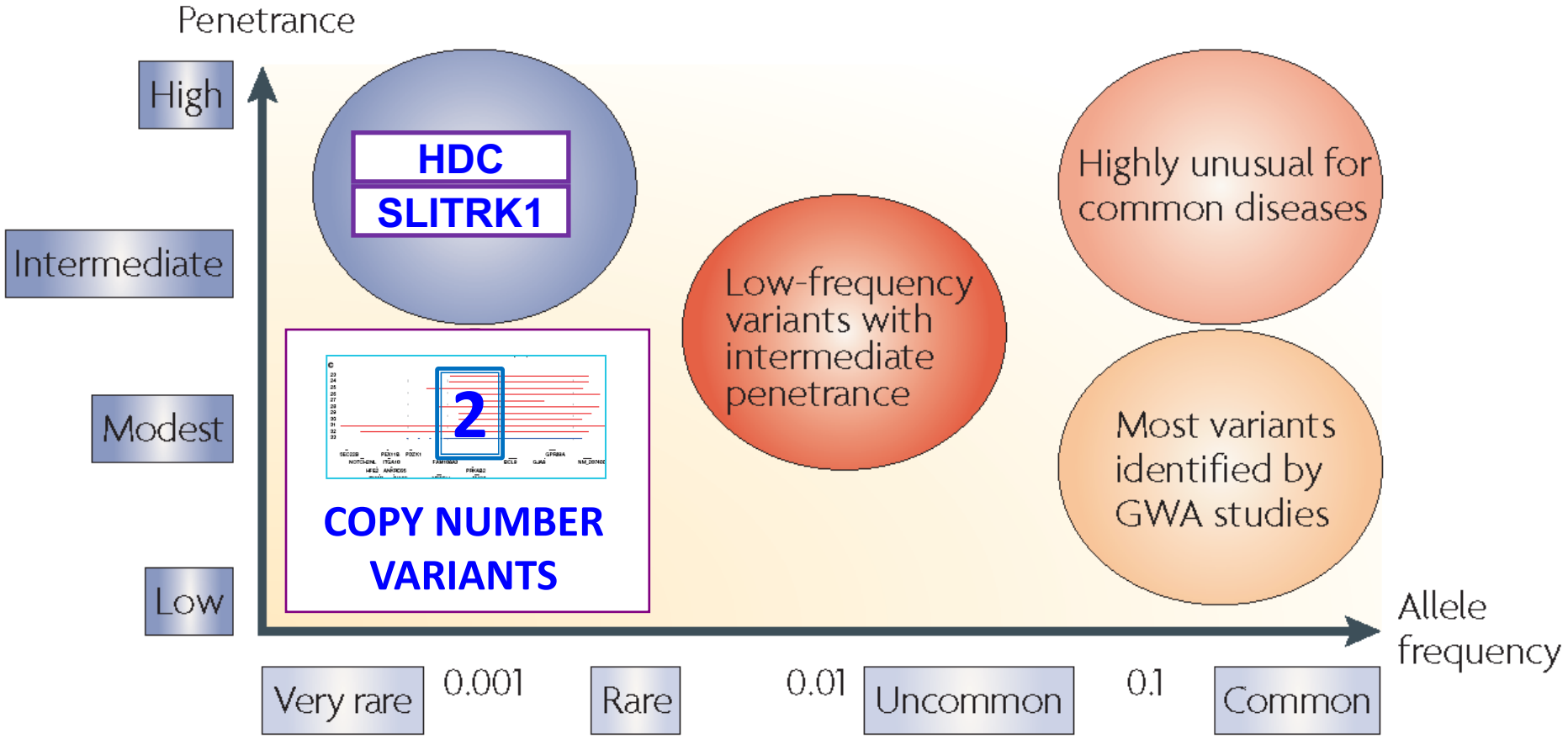
Progress in understanding the causes of TS



Genetics of Tourette Syndrome



COPY NUMBER VARIANTS



McCarthy et al., 2008; Sullivan et al., 2012

Genetics of Tourette Syndrome

Large, rare, recurrent CNVs are found across neurodevelopmental disorders

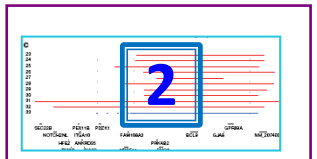
TABLE 1 Representative Recurrent Copy Number Variants (CNV)

CNV Locus	Size (kb)	Del/Dup	Classic Genomic Disorder?	ID	Autism Symptoms	Schizophrenia	Epilepsy
1q21.1	1,350	del		Mild to moderate	Yes	Yes	Yes
	1,350	dup		Mild to moderate	Yes	ND	ND
3q29	1,500	del		Mild to moderate	ND	Yes	ND
	453-1,760	dup		Mild to moderate	Yes	ND	ND
7q11.23	2,284	del	Williams-Beuren syndrome	Mild to severe	No	ND	ND
	2,284	dup		Mild to severe	Yes	ND	Yes
15q11-q13	4,770-8,147	del-maternal	Prader-Willi syndrome	Mild to severe	No	ND	Yes
	4,700-8,147	del-paternal	Angelman syndrome	Mild to severe	Yes	ND	Yes
		dup		Mild to severe	Yes	ND	Yes
15q13.3	1,930	del		Mild to severe	Yes	Yes	Yes
	1,930	dup		Mild to moderate	Yes	Yes	No
16p11.2	700	del		Mild to moderate	Yes	ND	Yes
	700	dup		Mild to moderate	Yes	Yes	ND
17p11.2	3,775	del	Smith-Magenis syndrome	Moderate to severe	No	No	Yes
	3,775	dup	Potocki-Lupski syndrome	Mild to moderate	Yes	ND	ND
22q11.2	1,500-3,000	del	Velocardiofacial syndrome	Mild to severe	Yes	Yes	Yes
	1,500-3,000	dup		None to mild	Yes	ND	ND

Currently in clinical practice for Intellectual Disability & Autism (chromosomal micro-array)

From Morrow, JAACAP 2010

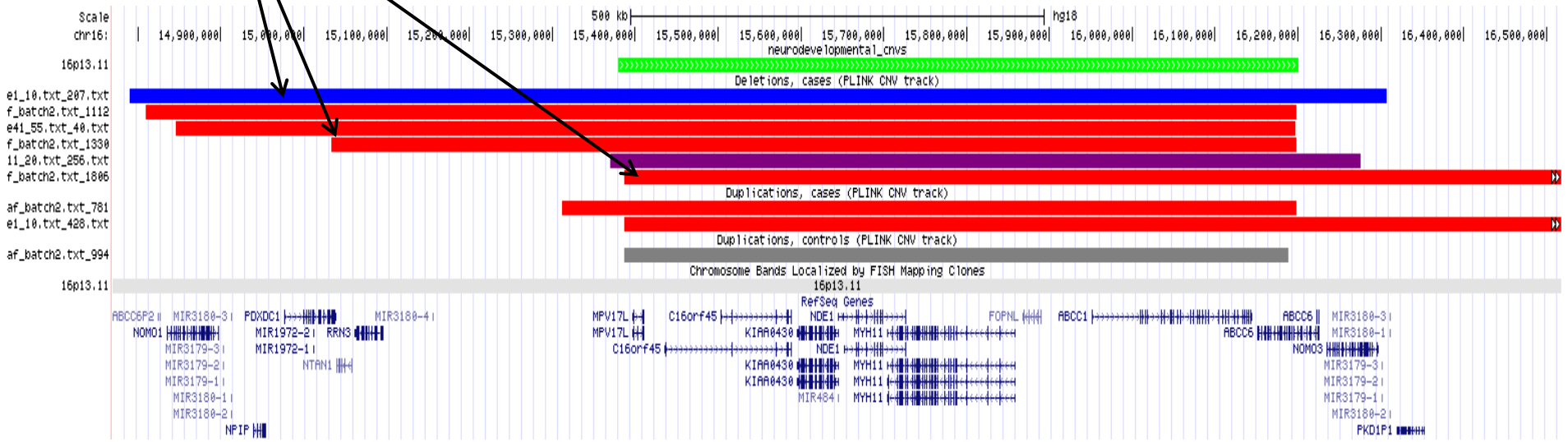
Genetics of Tourette Syndrome



COPY NUMBER VARIANTS

Recurrent Genomic Deletions in TS & OCD

Also de novo (n=3)



16p13.11

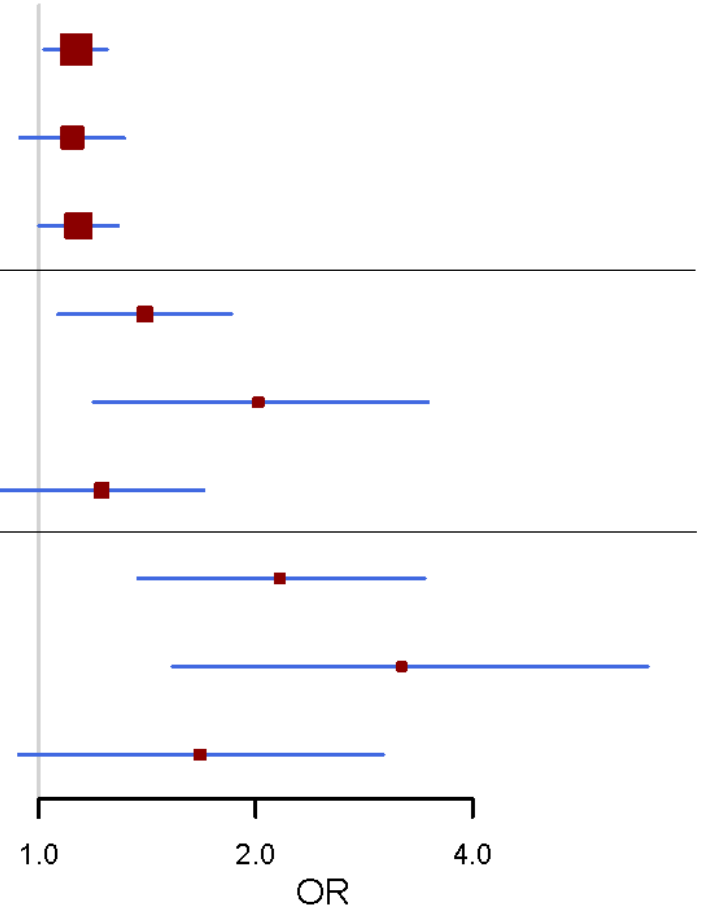
2724 total cases
(1086 TS, 1286 OCD)
1789 controls

McGrath et al. JAACAP, 2013

Genetics of Tourette Syndrome

Increased burden of large, rare genic CNVs in 2435 TS cases vs 4100 controls

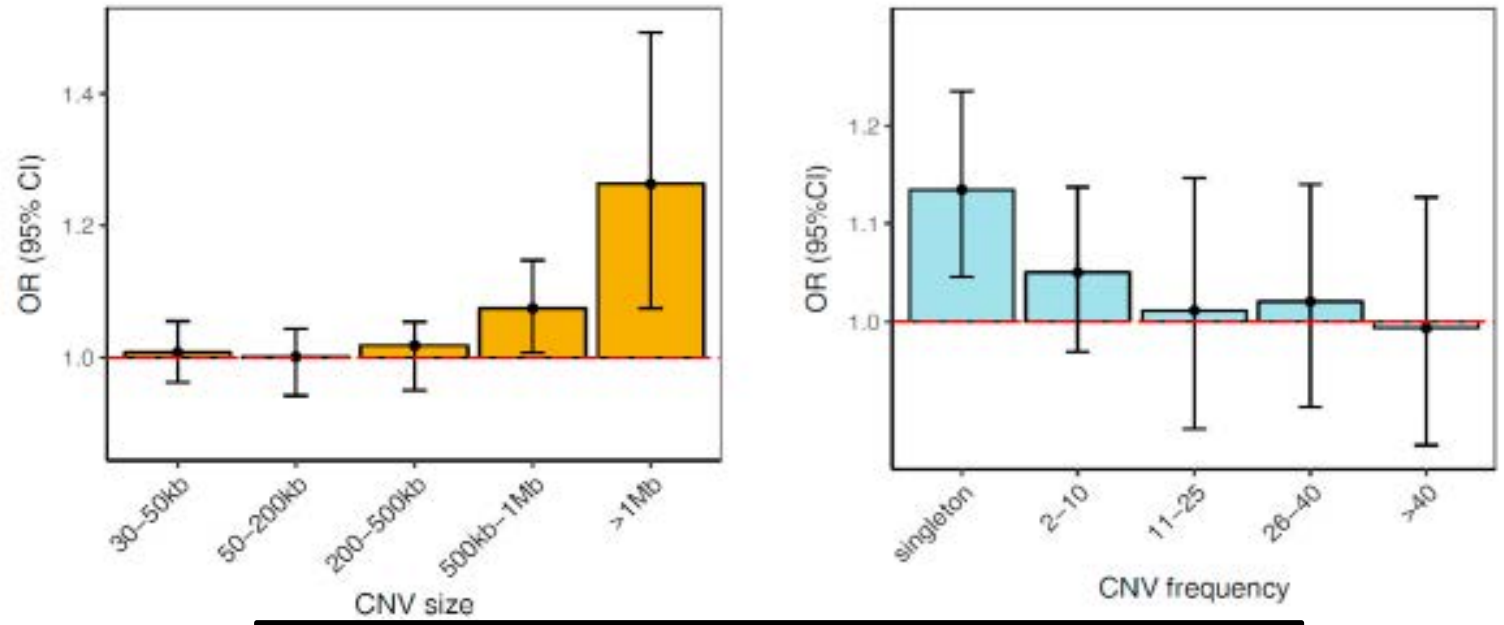
SIZE	TYPE	OR	p-val
>50kb	DEL+DUP	1.13	0.02
	DEL	1.11	0.21
	DUP	1.14	0.05
>500kb	BOTH	1.4	0.02
	DEL	2.02	0.01
	DUP	1.22	0.23
>1MB	BOTH	2.16	9×10^{-4}
	DEL	3.19	3×10^{-3}
	DUP	1.67	0.08



Huang et al. *Neuron* 2017

Genetics of Tourette Syndrome

Additional TS case enrichment for large (> 1Mb), ultra-rare (singleton) CNVs



~1% of TS cases carry a large (> 1 Mb) rare CNV

Huang et al. *Neuron* 2017

Genetics of Tourette Syndrome

1% of TS cases also carry one of these 2 CNVs

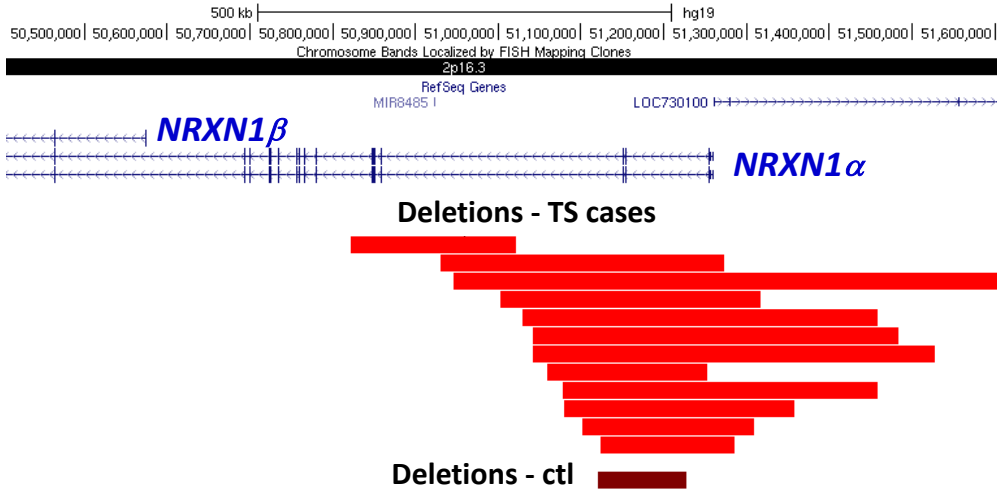
NRXN1 Deletions:

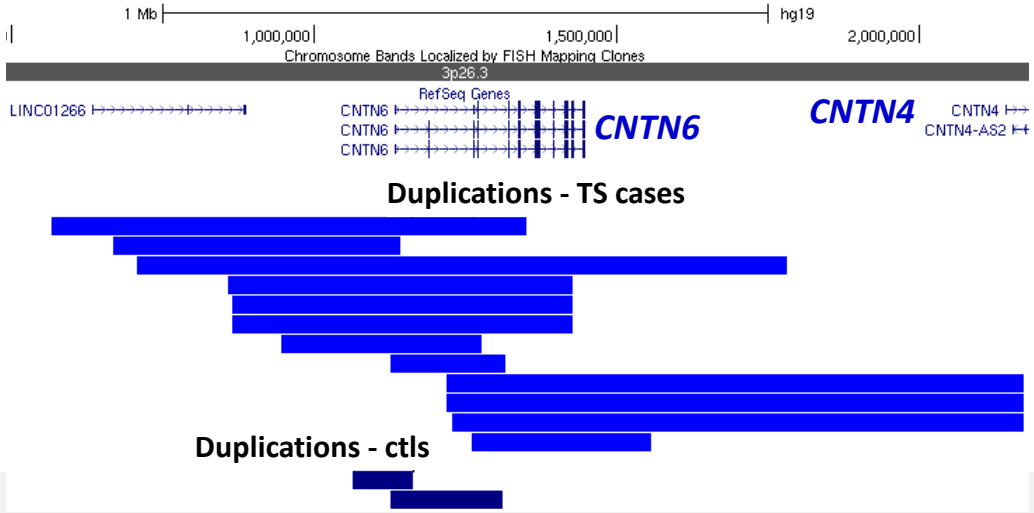
0.49% of TS cases

OR=20.3 (2.6-156.2)

$p_{locus} = 6 \times 10^{-6}$

$p_{corr} = 9 \times 10^{-4}$





CNTN6 Duplications:

0.49% of TS cases

OR=10.1 (2.3-45.4)

$p_{locus} = 4 \times 10^{-5}$

$p_{corr} = 7 \times 10^{-3}$

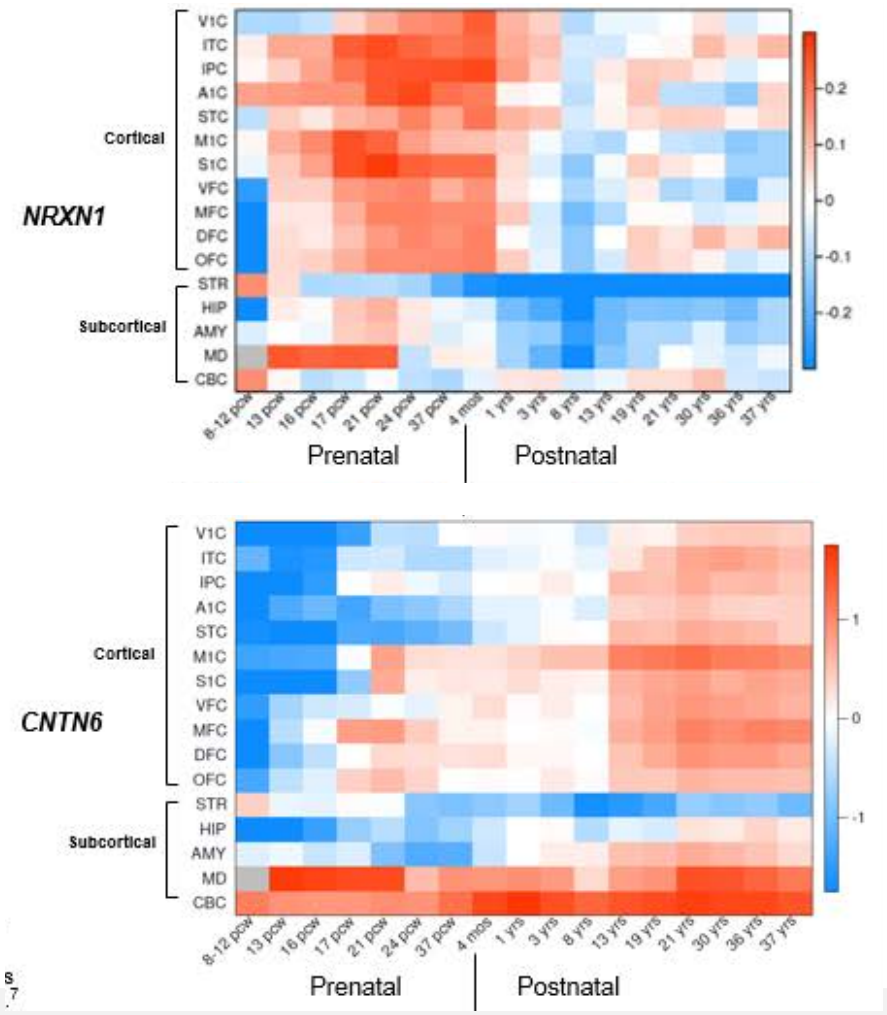
Huang et al. *Neuron* 2017

Genetics of Tourette Syndrome

Phenotypes of *NRXN1/CNTN6* carriers

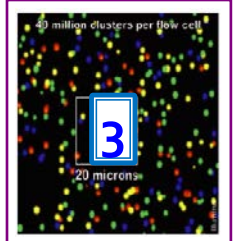
INDIV_ID	TYPE	GENE	TS	OCD	ADHD	ATYPICAL FEATURES
TS1_0776	DEL	*NRXN1*	Y	N	Y	Sibling w/ ASD
TS1_0180	DEL	*NRXN1*	Y	N	N	ASD
TS1_0630	DEL	*NRXN1*	Y	N	N	Developmental Delay unspecified
TS1_0446	DEL	*NRXN1*	Y	Y	Y	None
TS1_0105	DEL	*NRXN1*	Y	N	Y	None
TS2_1256	DEL	*NRXN1*	Y	N	Y	Other dev. speech/language disorder
TS2_0924	DEL	*NRXN1*	Y	N	Y	None
TS2_0750	DEL	*NRXN1*	Y	Y	Y	ASD
TS2_1238	DEL	*NRXN1*	Y	Y	N	Paranoid personality disorder
TS1_0573	DEL	*NRXN1*	Y	NA	NA	NA
TS1_0698	DEL	*NRXN1*	Y	Y	Y	None
TS2_0026	DEL	*NRXN1*	Y	N	N	None
TS2_1805	DUP	*CNTN6*	Y	Y	NA	None
TS2_1405	DUP	*CNTN6*	Y	Y	Y	None
TS2_1624	DUP	*CNTN6*	Y	N	N	None
TS2_1525	DUP	*CNTN6*	Y	Y	Y	None
TS2_1545	DUP	*CNTN6*	Y	N	Y	None
TS2_1568	DUP	*CNTN6*	Y	Y	Y	None
TS1_0558	DUP	*CNTN6*	Y	N	Y	None
TS2_1320	DUP	*CNTN6*	Y	Y	N	None
TS1_0618	DUP	*CNTN6*	Y	N	N	None
TS2_1156	DUP	*CNTN6*	Y	N	Y	None
TS2_0452	DUP	*CNTN6*	Y	N	N	None
TS2_0827	DUP	*CNTN6*	Y	N	N	None

Expression of *NRXN1* and *CNTN6* across human neurodevelopment

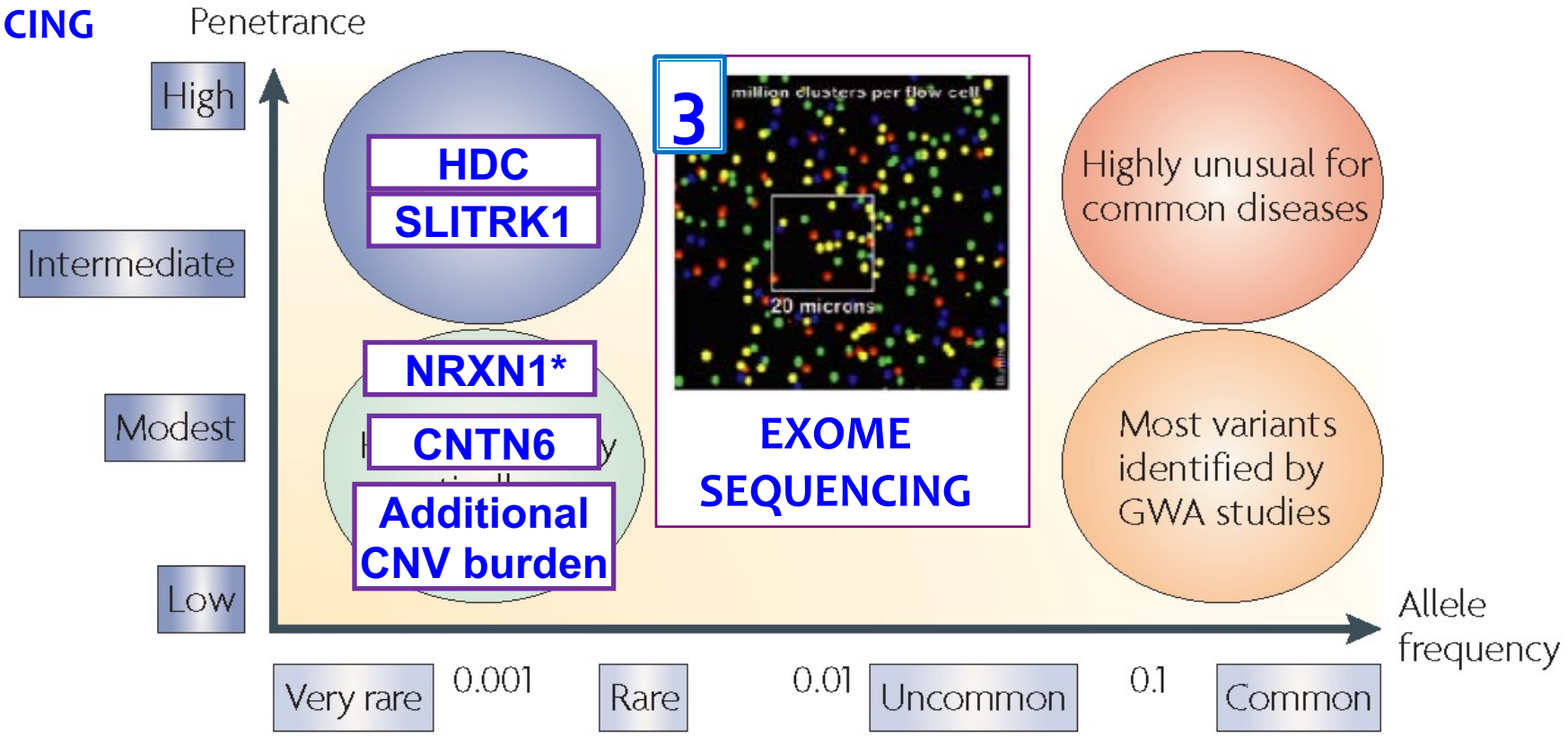


www.brainspan.org

Genetics of Tourette Syndrome



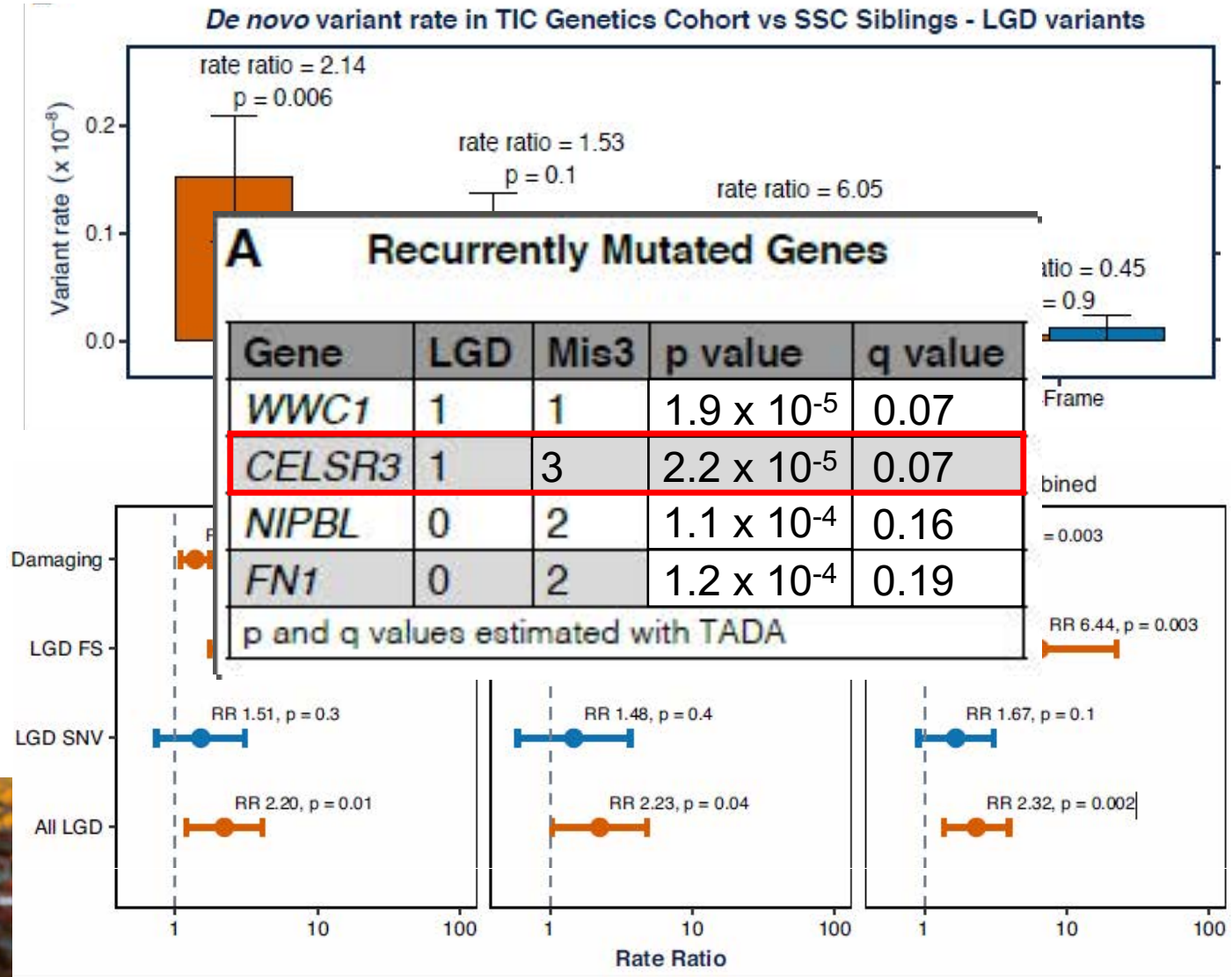
NEXT-GEN SEQUENCING



McCarthy et al., 2008; Sullivan et al., 2012

Genetics of Tourette Syndrome

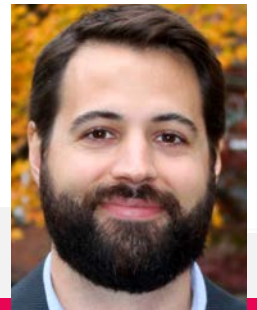
TS cases are enriched for *de novo* "likely gene damaging" (LGD) variants



A **Recurrently Mutated Genes**

Gene	LGD	Mis3	p value	q value
WWC1	1	1	1.9×10^{-5}	0.07
CELSR3	1	3	2.2×10^{-5}	0.07
NIPBL	0	2	1.1×10^{-4}	0.16
FN1	0	2	1.2×10^{-4}	0.19

p and q values estimated with TADA

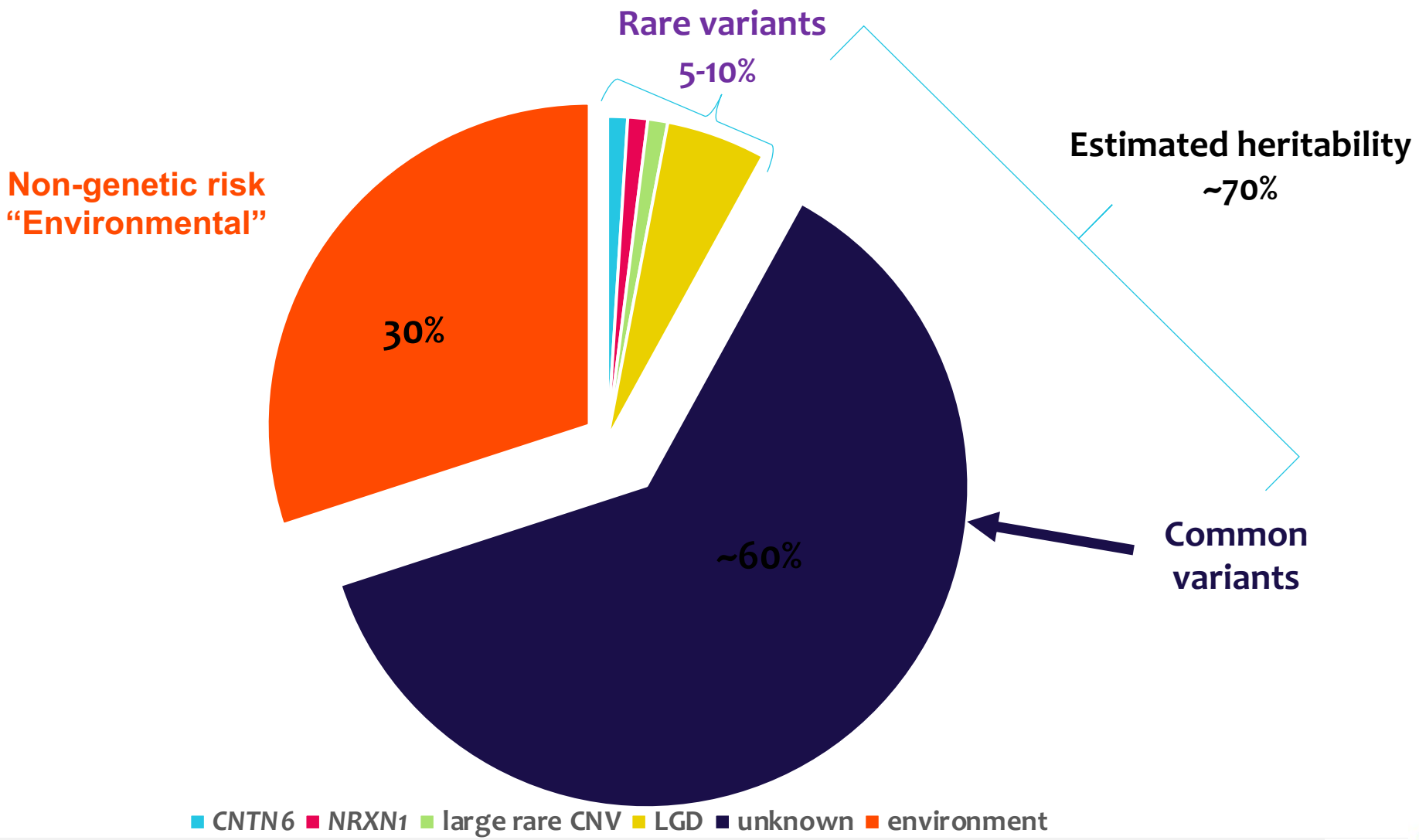


TIC Genetics/TAAICG/ TSGeneSEE

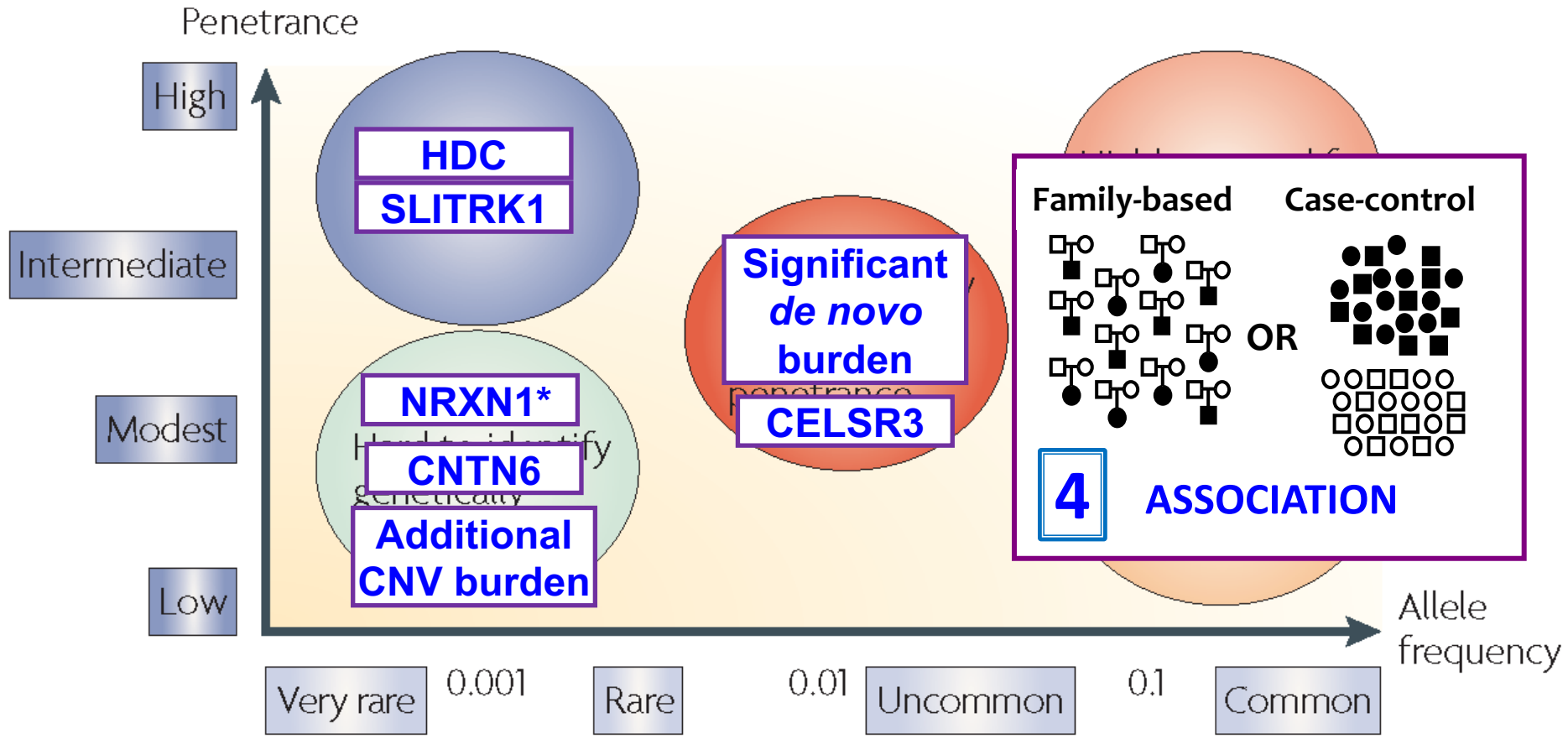
Willsey et al., Neuron, 2017

Wang et al., Cell Reports, 2018

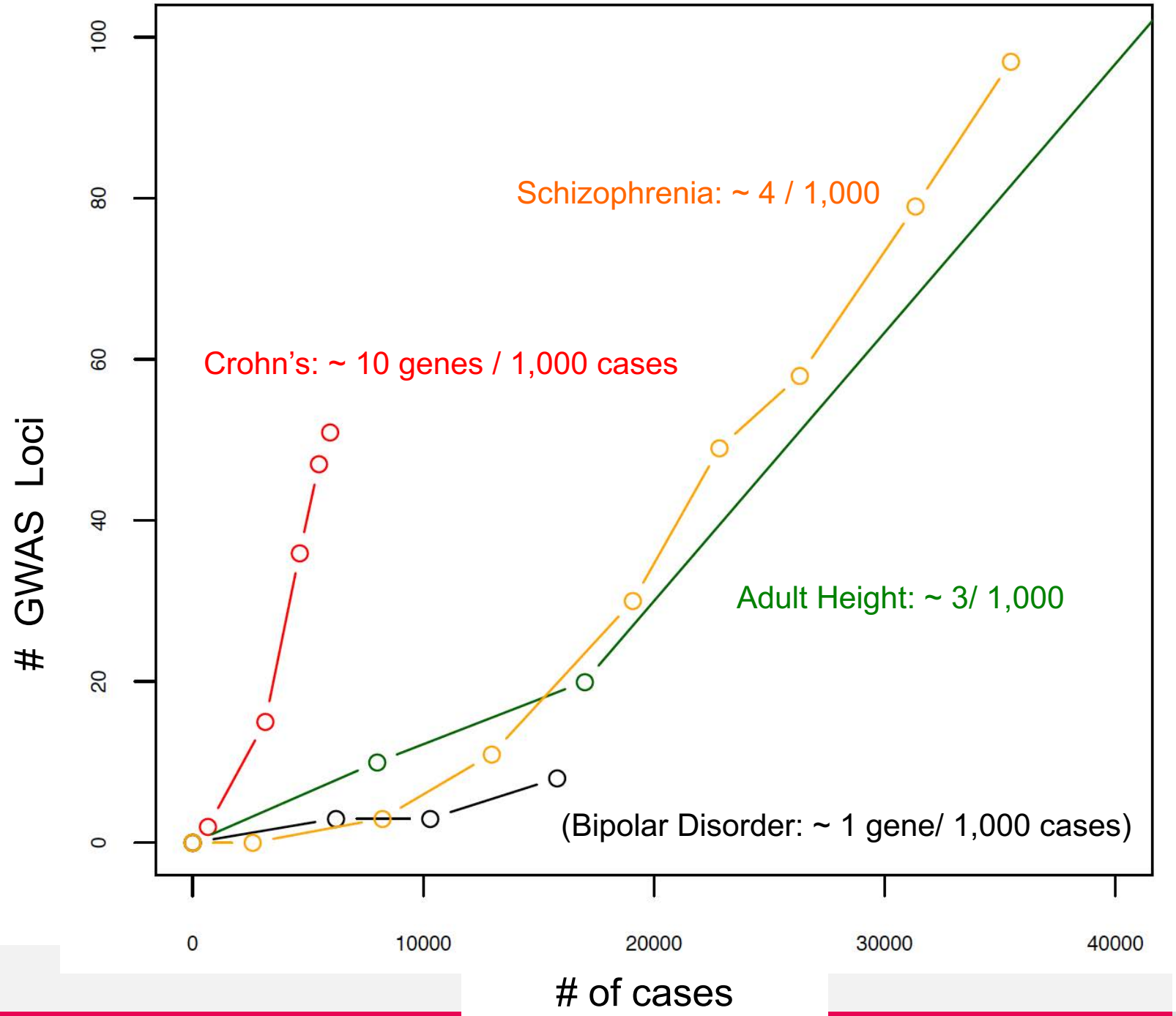
Progress in understanding TS genetic risk



Genetics of Tourette Syndrome



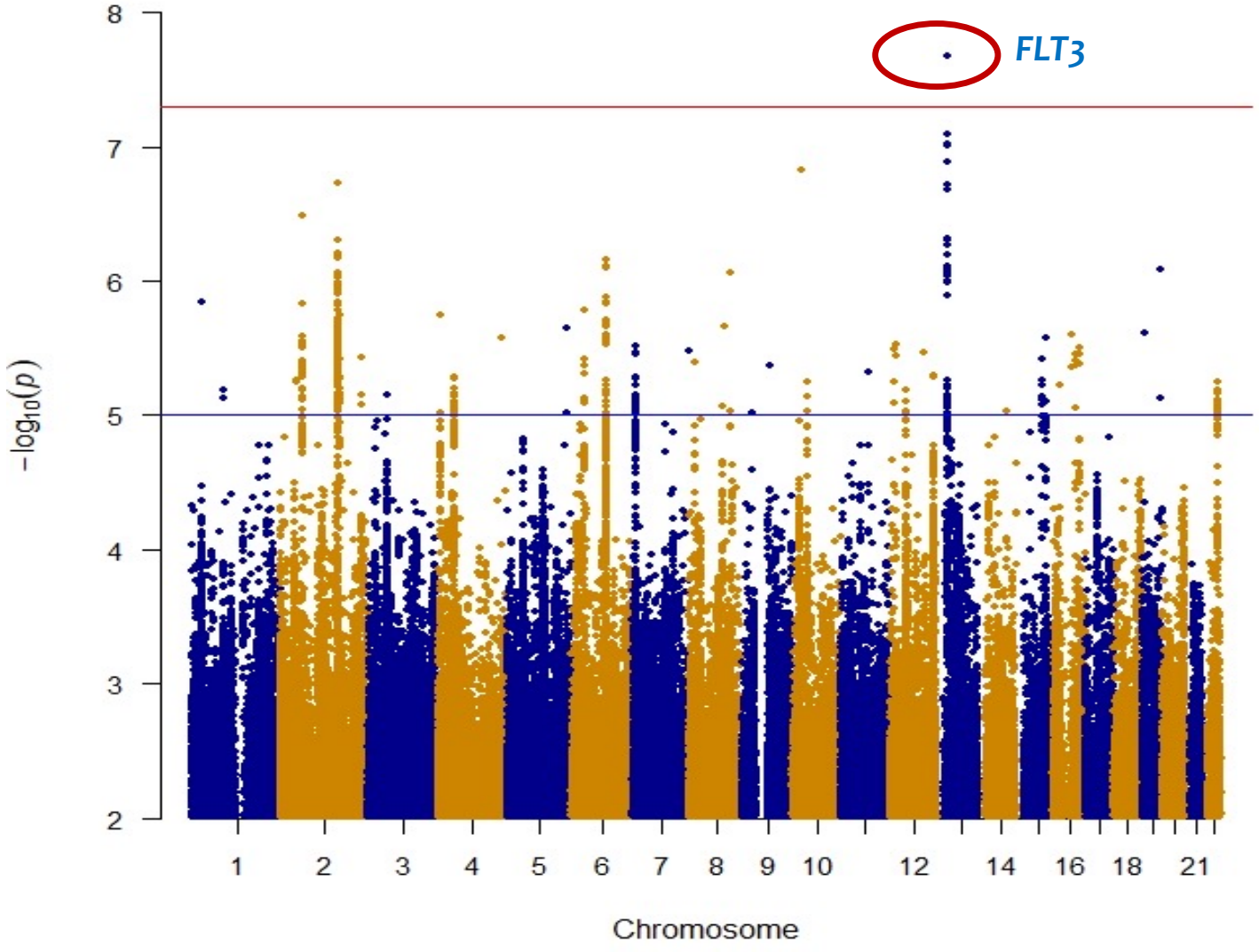
McCarthy et al., 2008; Sullivan et al., 2012



Genetics of Tourette Syndrome

ASSOCIATION

PGC TS GWAS2 meta-analysis - 2019



4819 cases
9488 controls
λ_{1000} = 1.010

Replication
DeCODE
706 cases
9784 controls

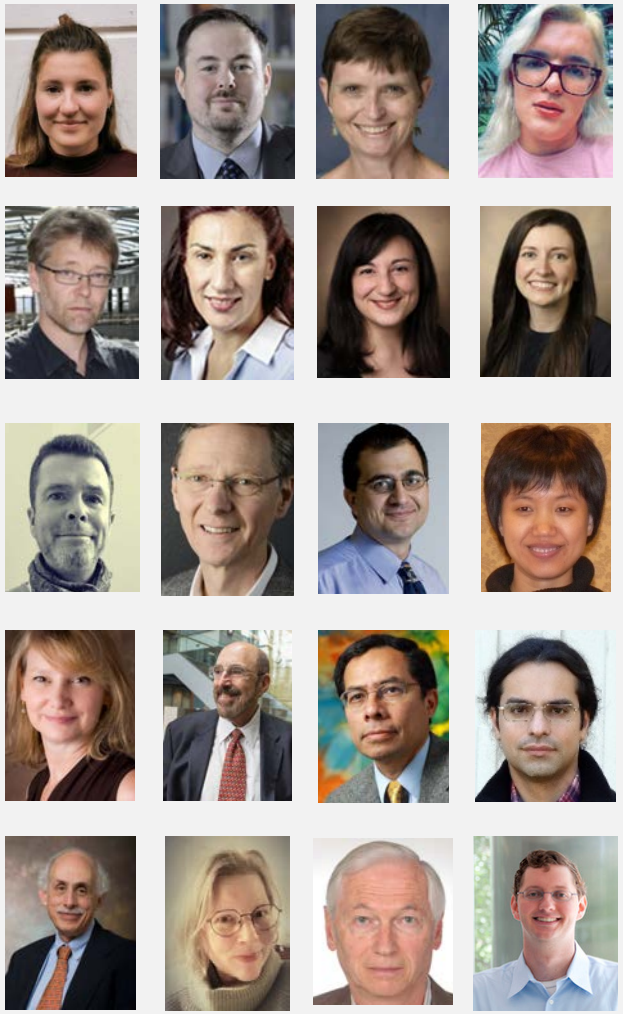
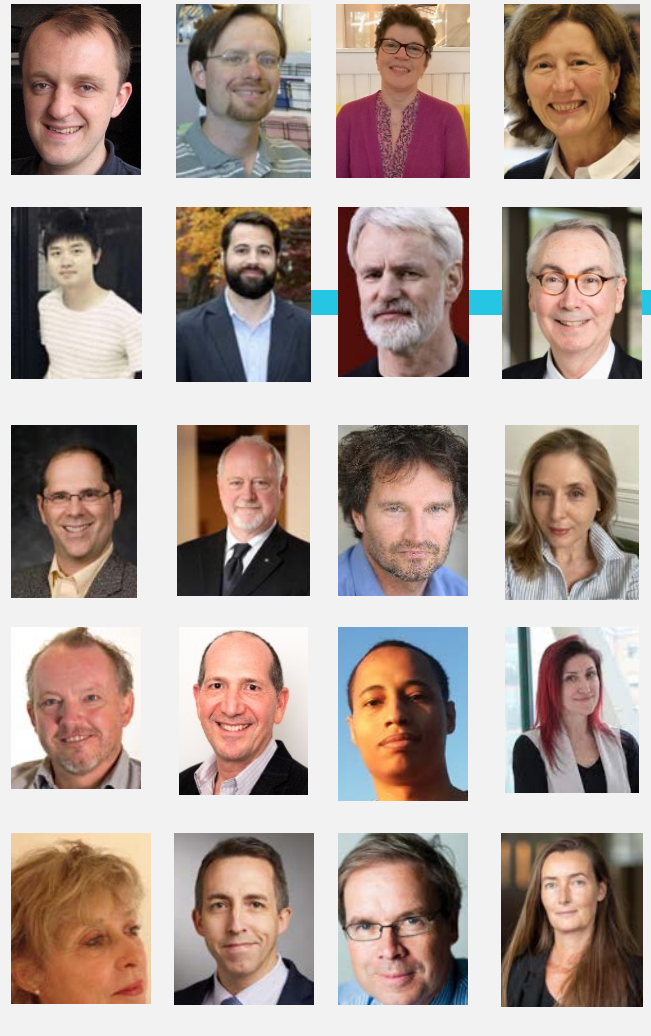
Yu*, Sul*, Tsetsos*, et al., *Am J Psychiatry*, 2019

TS GWAS3 meta-analysis

2022-2023, and beyond….


PGC TS GWAS3 meta-analysis- 2022

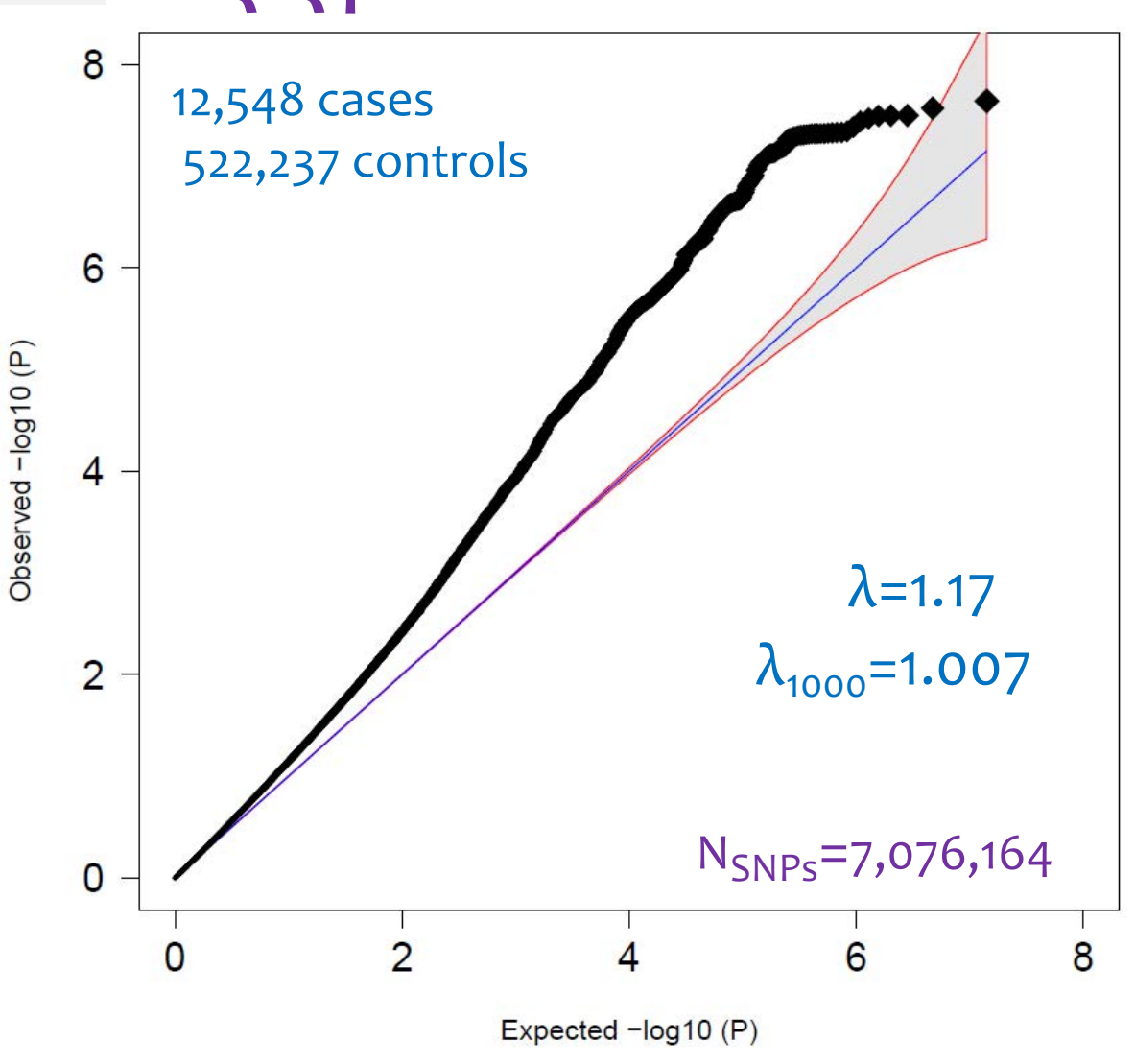
Data Set	# Cases	# Controls
iPSYCH	3,041	29,808
TS GWAS2	2,748	3,137
deCODE (TS+CT)	1,998	134,508
EMTICS	1,225	3,341
TAAICG_GWAS1	857	2,256
TAAICG_Fam	818	1,762
TIC Genetics	532	1,448
BioVU	319	1,585
FinnGen	293	342,206
Sweden	284	1,136
PGC TS_GSA	209	458
NORDiC_SWE	188	414
PGC PsychChip	36	178
Meta-analysis	**12,548**	**522,237**
23andMe replication	1,571	941,405
Total	**14,119**	**1,463,642**

PGC TS GWAS3 meta-analysis - 2022

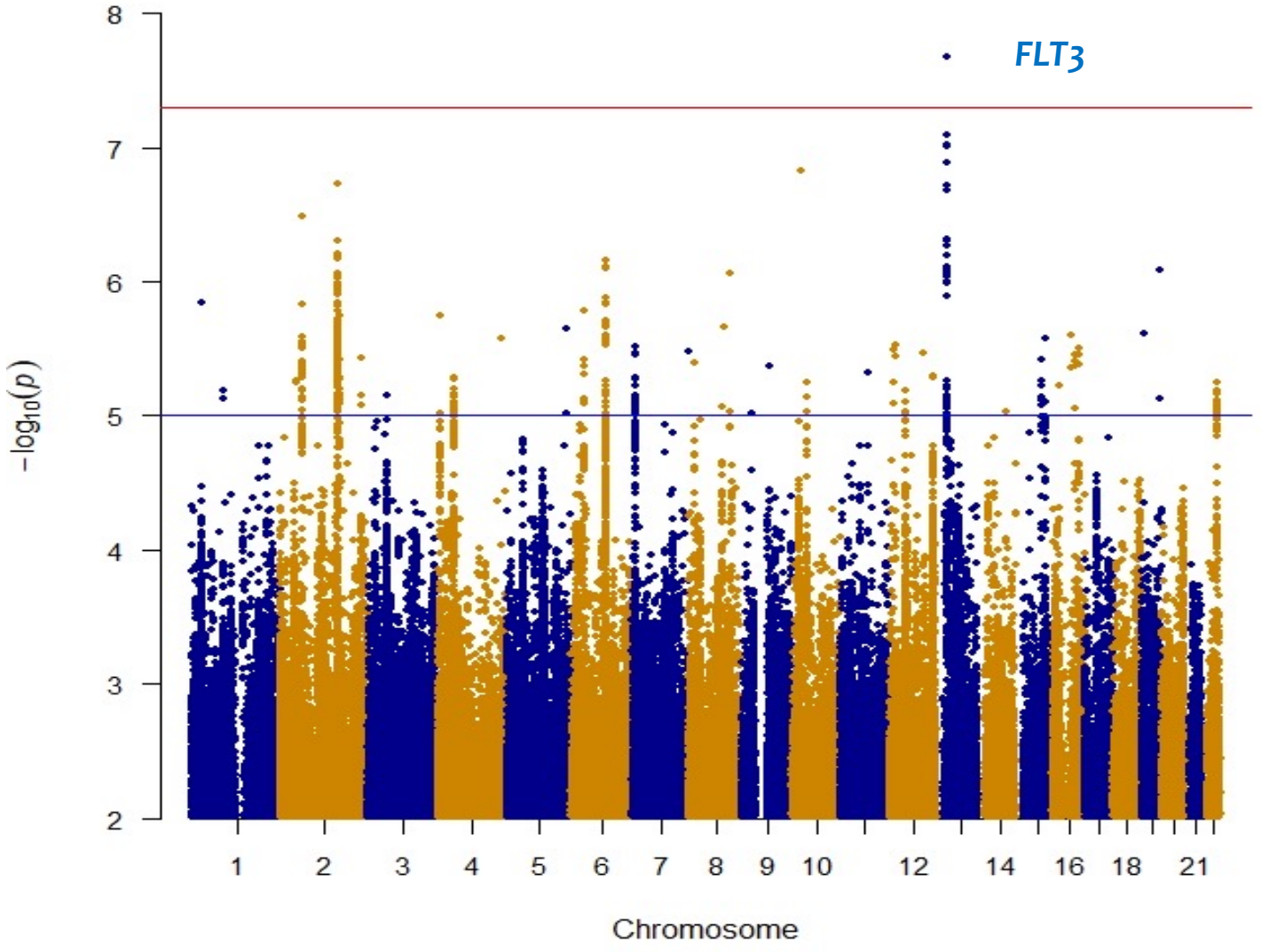
- 13 independent datasets
  - Individual level data: 7 datasets
  - Summary statistics: 6 datasets
- Non-isolate data were imputed with HRC reference panel
- Association tests
  - Logistic regression for unrelated samples with balanced case/control ratios
  - LMM for datasets with related samples (deCODE, FinnGen, TAAICG_Fam)
- Meta-analysis
  - SE-weighted, fixed-effect model in METAL
  - SNPs retained w/ INFO>0.8 & MAF>1%

Q-Q plot - Association tests



ASSOCIATION

PGC TS GWAS2 meta-analysis - 2019



4819 cases
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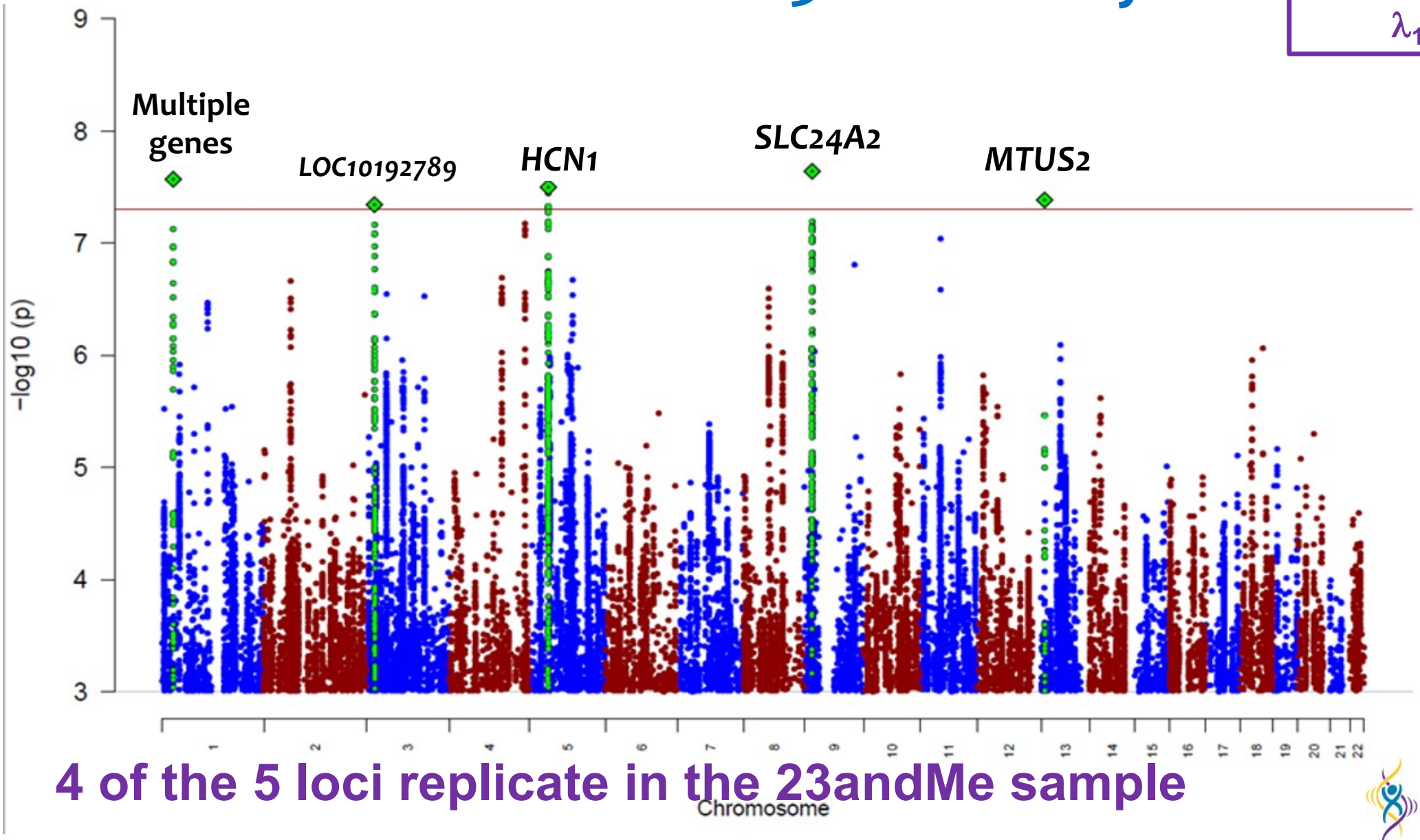
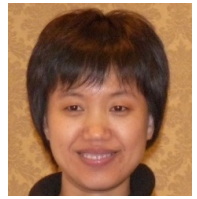



Matt Halvorsen


Nora Strom


Dongmei Yu


Apostolia Topalaudi

4 of the 5 loci replicate in the 23andMe sample

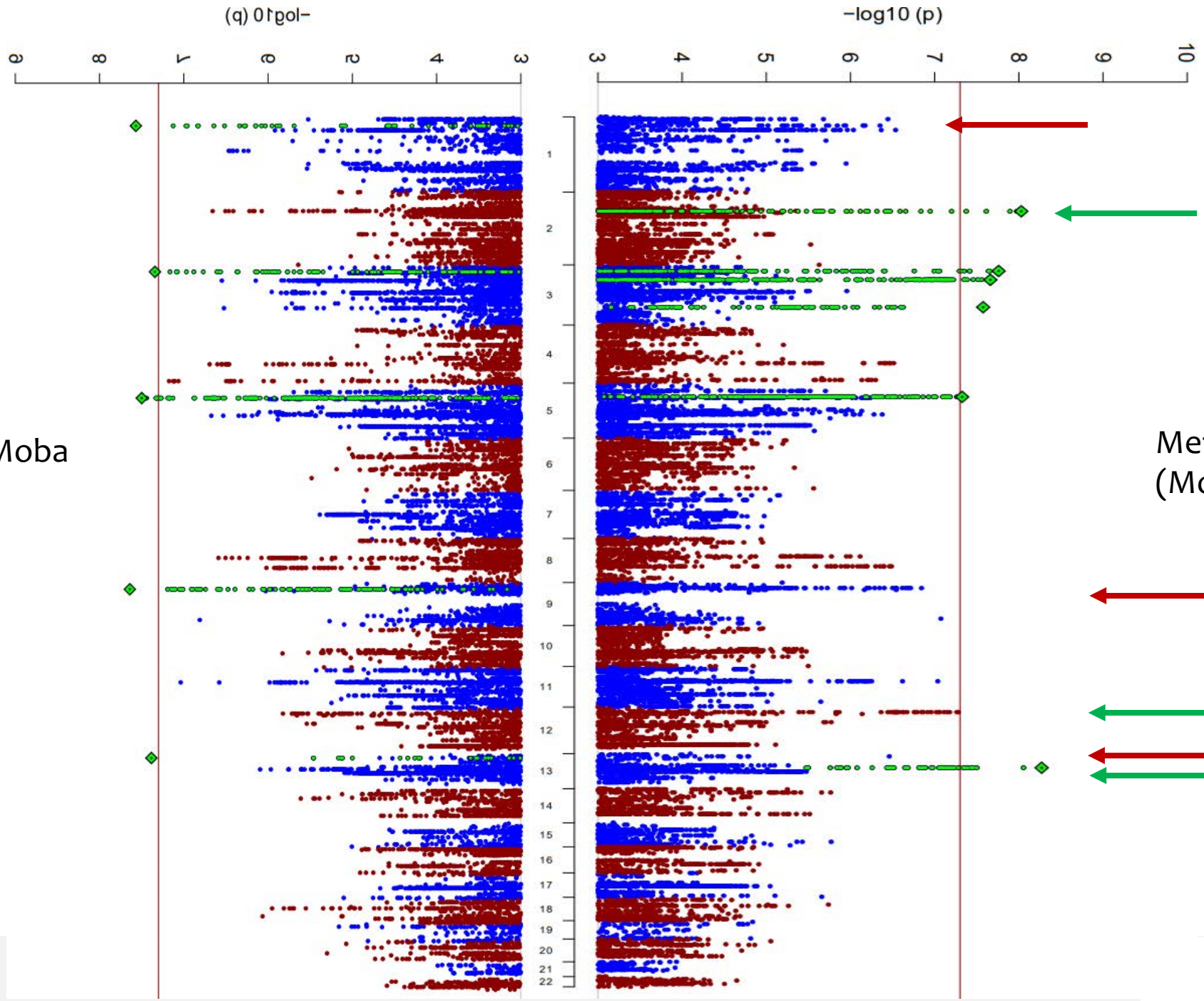
Genetics of Tourette Syndrome

TS GWAS3 meta-analysis 2023

Data Set	N_cases	N_controls	N_eff	N
iPSYCH	3,041	29,808	11,038	32,849
GWAS2	2,748	3,137	5,859	5,885
deCODE (TS+CT)	1,998	134,508	7,875	136,506
EMTICS	1,225	3,341	3,585	4,566
TAAICG_GWAS1	857	2,256	2,484	3,113
TAAICG_fam	818	1,762	1,790	2,580
TICGen	532	1,448	1,556	1,980
BioVU	319	1,585	1,062	1,904
FinnGen	293	342,206	1,171	342,499
Sweden	284	1,136	909	1,420
TS_GSA	209	458	574	667
NORDiC_SWE	188	414	517	602
PsychChip	36	178	120	214
Meta_202112	**12,548**	**522,237**	**38,541**	**534,785**
Moba (Norway)	699	13,980	2,663	14,679
Meta_2023	**13,247**	**536,217**	**41,204**	**549,464**

Genetics of Tourette Syndrome

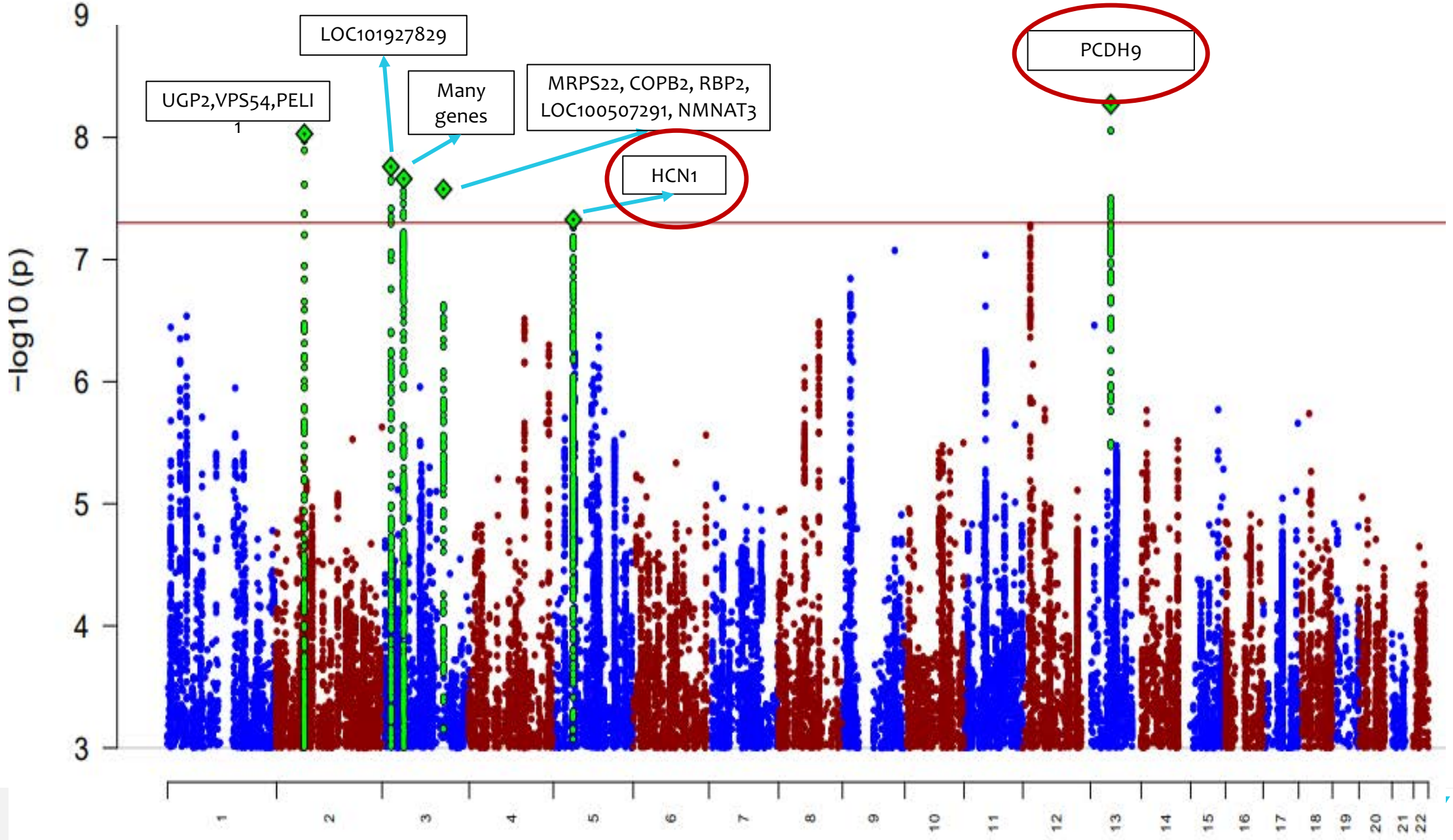
Meta_202112 (Moba NOT included)



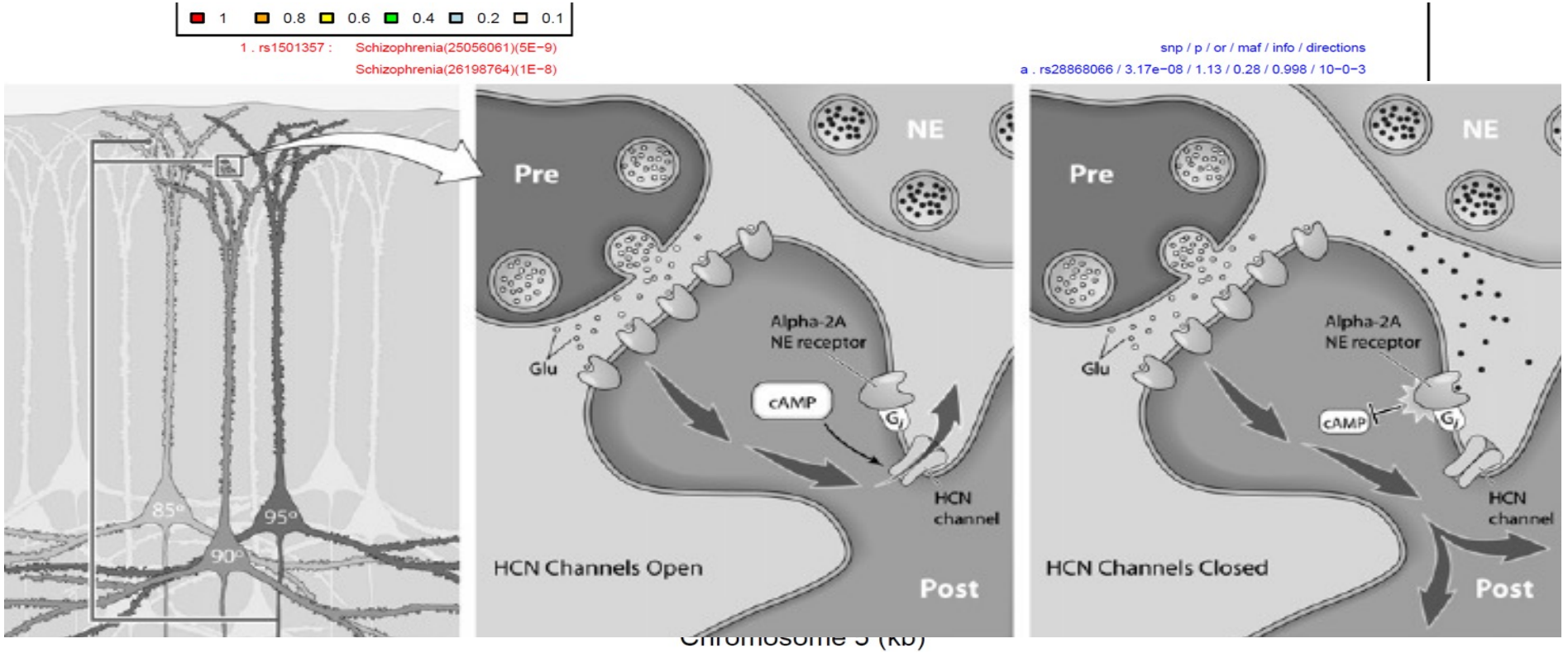
Meta_2023 (Moba included)

Genetics of Tourette Syndrome

Manhattan Plot



HCN1 locus

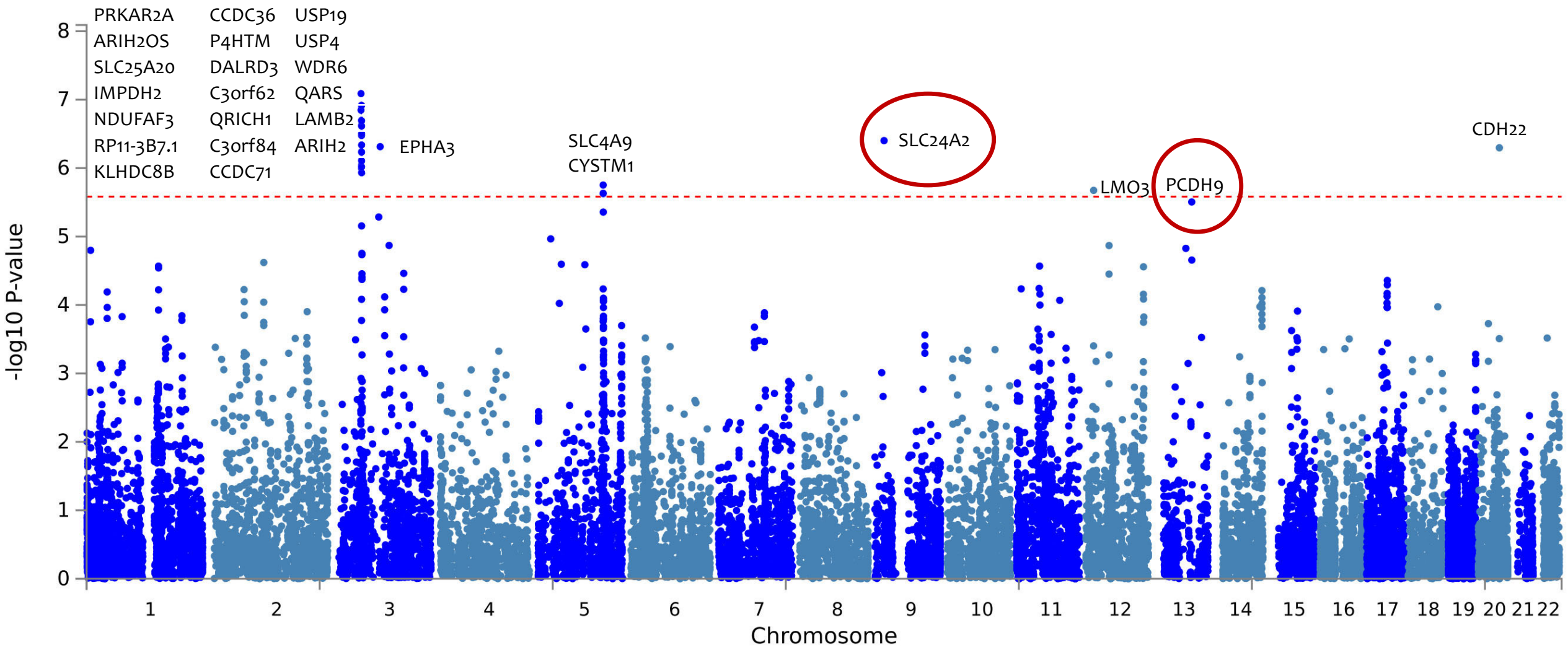


HCN1 forms a cAMP-dependent ion channel that regulates post-synaptic cell excitability

In frontal cortex, the HCN channel is regulated by the alpha-2A NE receptor which is the drug target of the alpha-2 agonists clonidine & guanfacine

Genetics of Tourette Syndrome

Gene-based GWAS in MAGMA

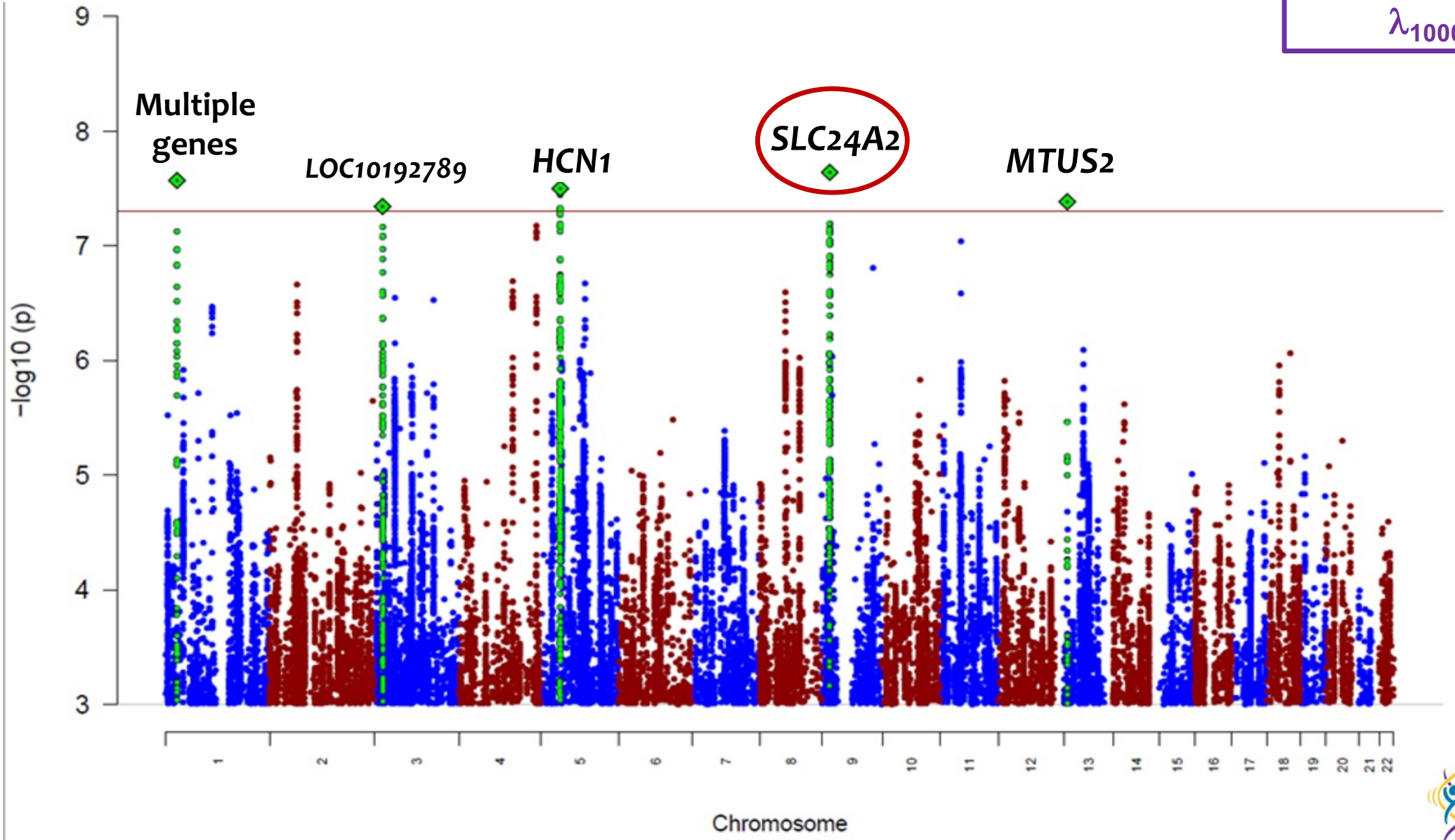


Manhattan plot of gene-based analysis. The genome-wide significance (red dashed line) is P<2.6e-6 for Bonferroni correction of 19,172 genes.

Genetics of Tourette Syndrome

PGC TS GWAS3 meta-analysis

12,548 cases
522,237 controls
λ_{1000} = 1.010

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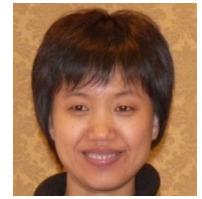
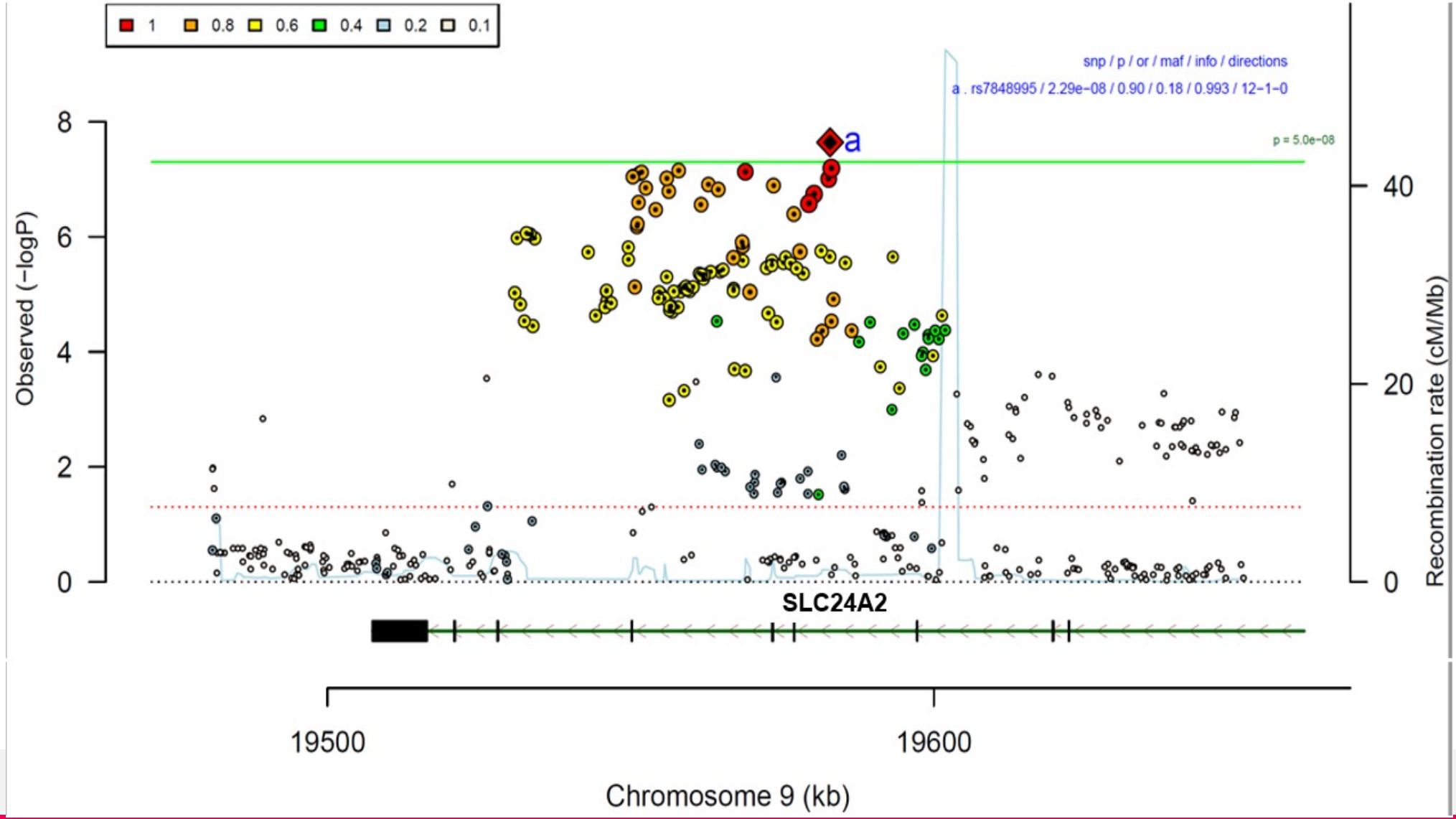
Nora Strom


Dongmei Yu


Apostolia Topalaudi

Genetics of Tourette Syndrome

SLC24A2 locus

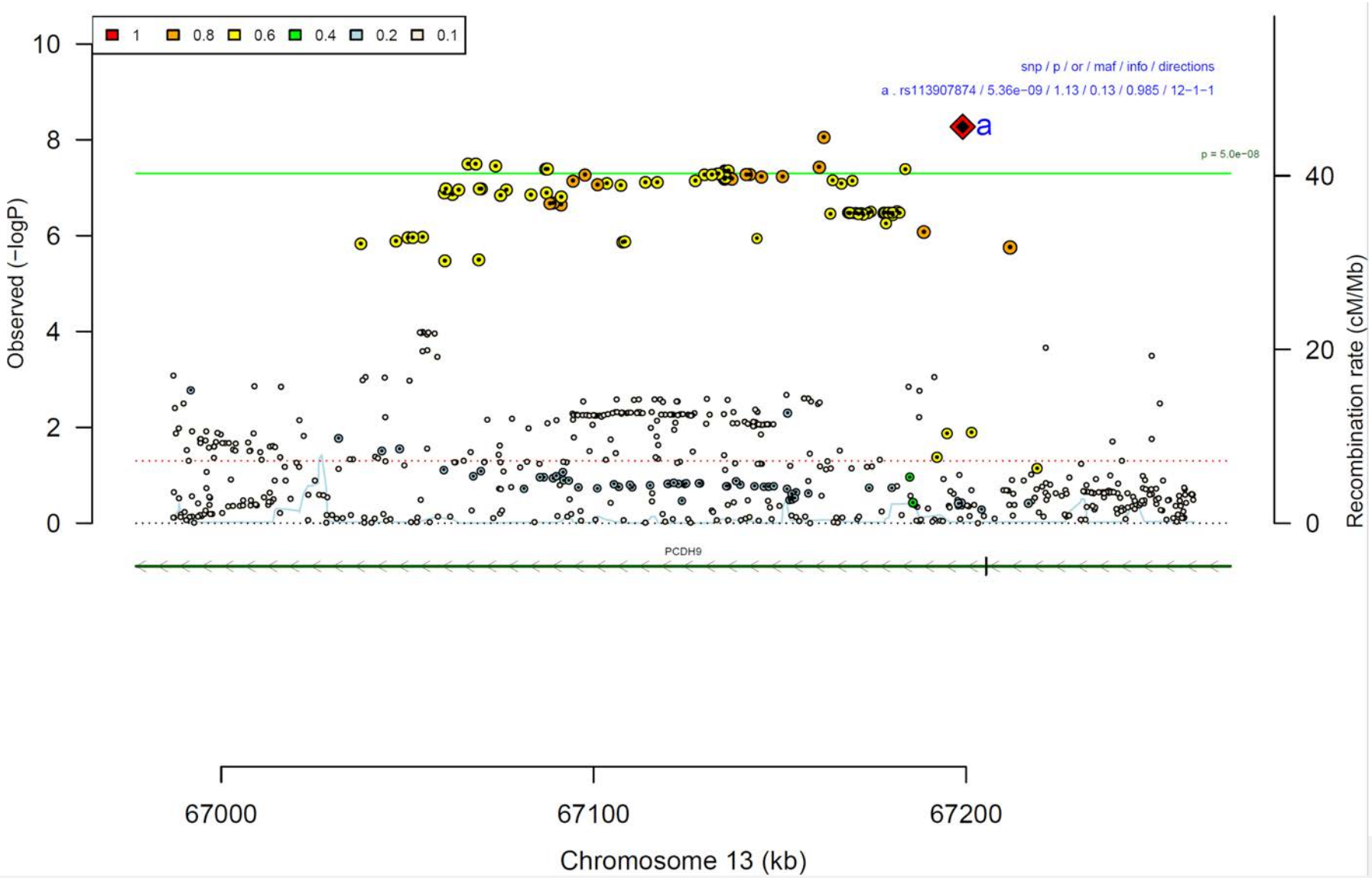


SLC24A2:
Calcium/cation antiporter super-family member;

strongly expressed in brain

Genetics of Tourette Syndrome

PCDH9 locus

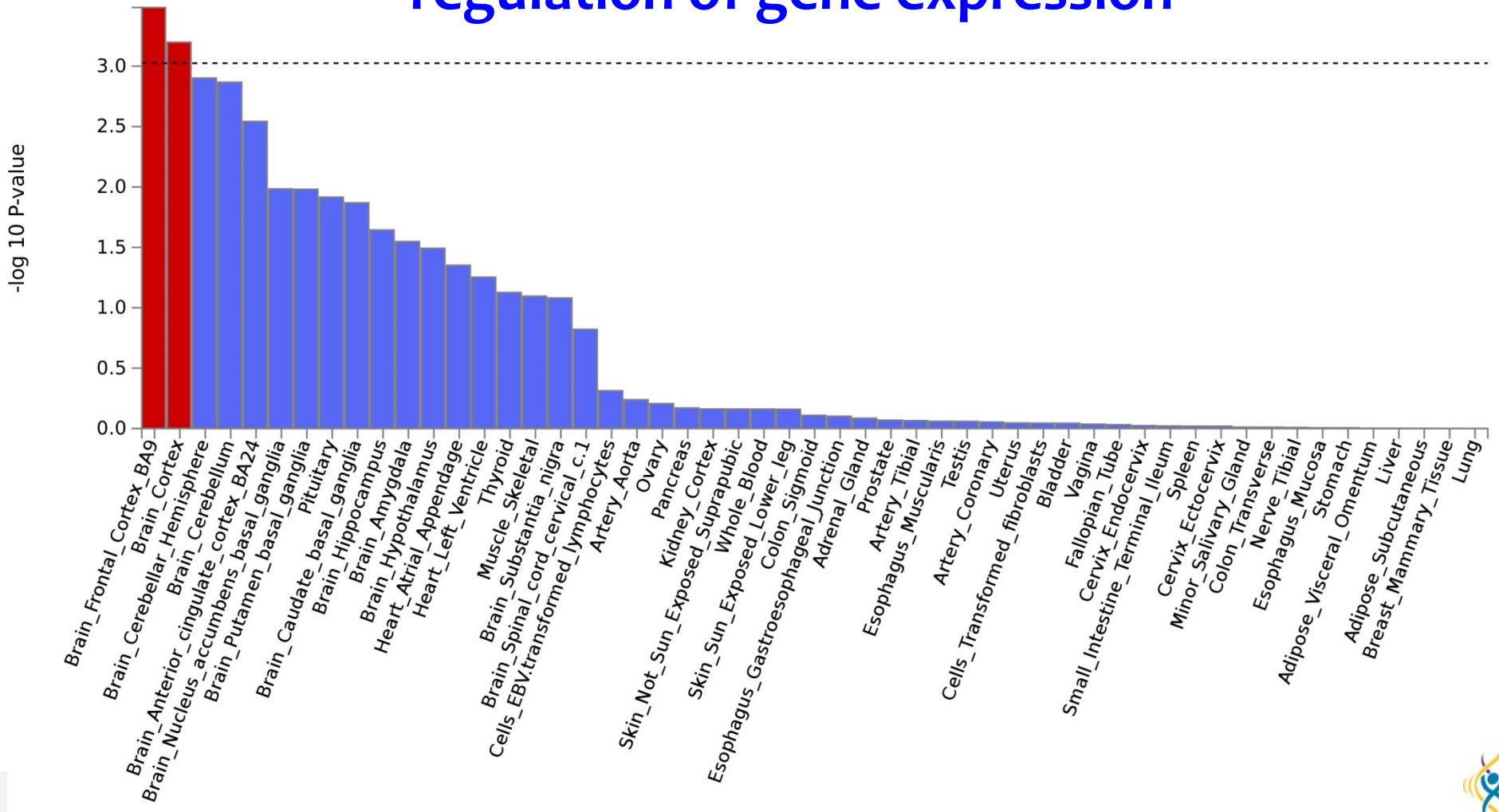


PCDH9: protocadherin 9; strongly expressed in brain

Mediates cell adhesion in neural tissues in the presence of calcium

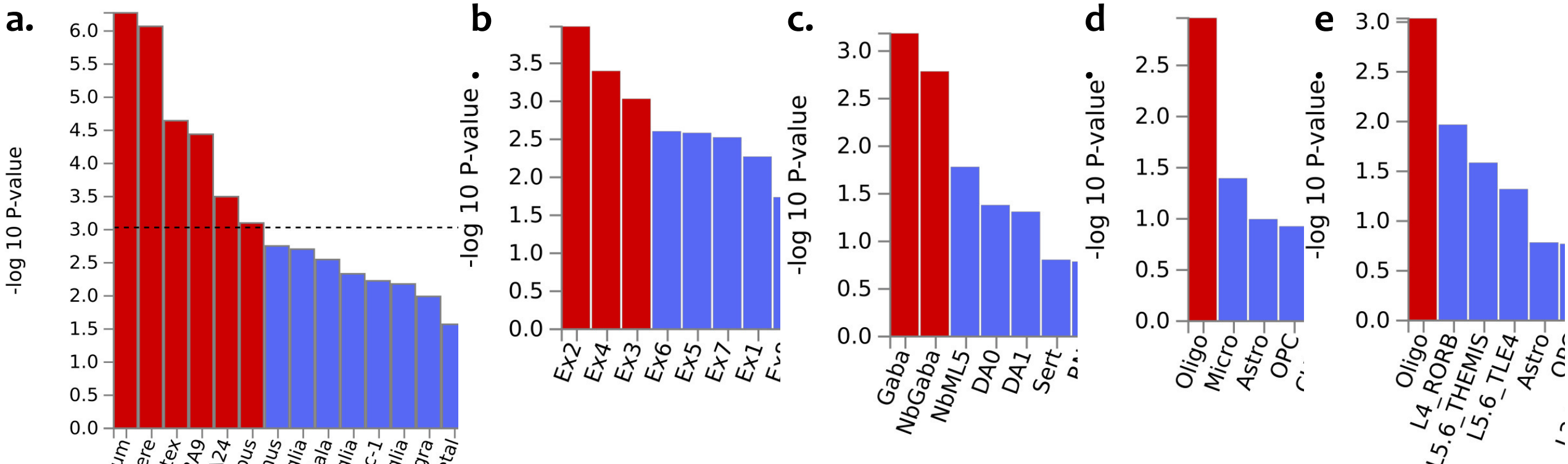
Genetics of Tourette Syndrome

Polygenic risk scores can be used to calculate a genome-wide "fingerprint" of disease-specific regulation of gene expression



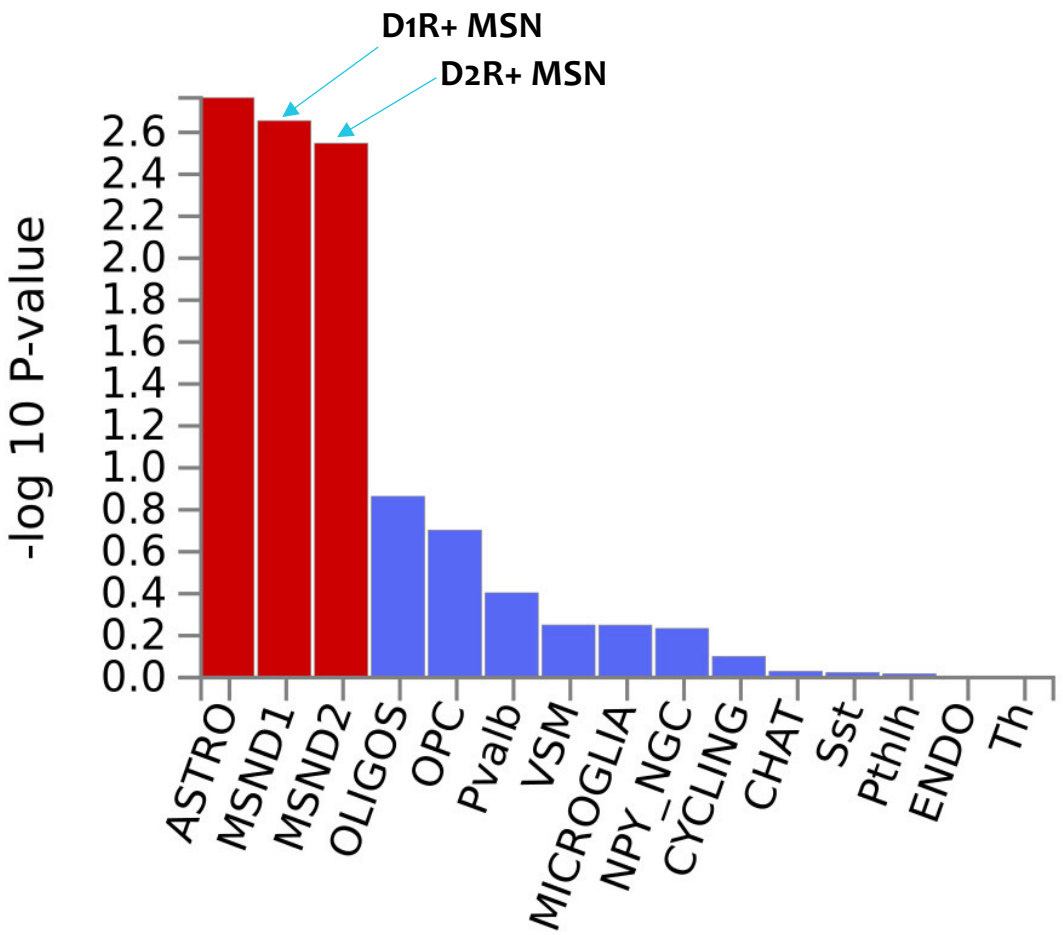
Genetics of Tourette Syndrome

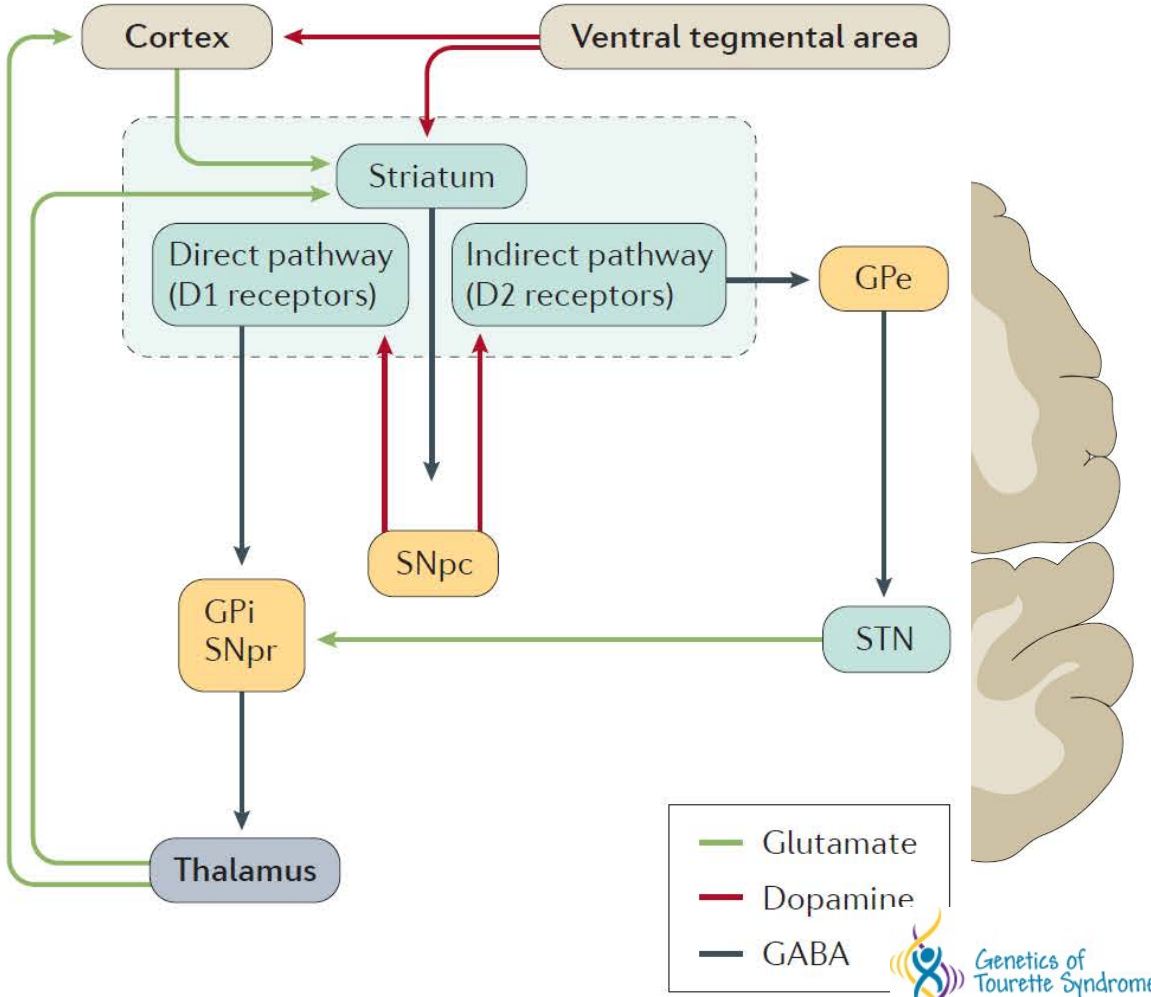
Tissue/Cell Type Specific Analyses



a) Tissue expression analysis using 53 tissue types from GTEx v8; **b-c** are cell type specific analyses using single cell RNA (scRNA) data. **b** is based on human 4,249 cells from developmental stage from PsychENCODE (Wang et al. 2018); **c** is based on 1,977 human ventral midbrain from 6-11 weeks embryos (La Manno et al. 2016); **d and e** are based on fetal and infancy postmortem prefrontal cortex samples, respectively (Herring et al. 2022). All P-values are after Bonferroni correction.

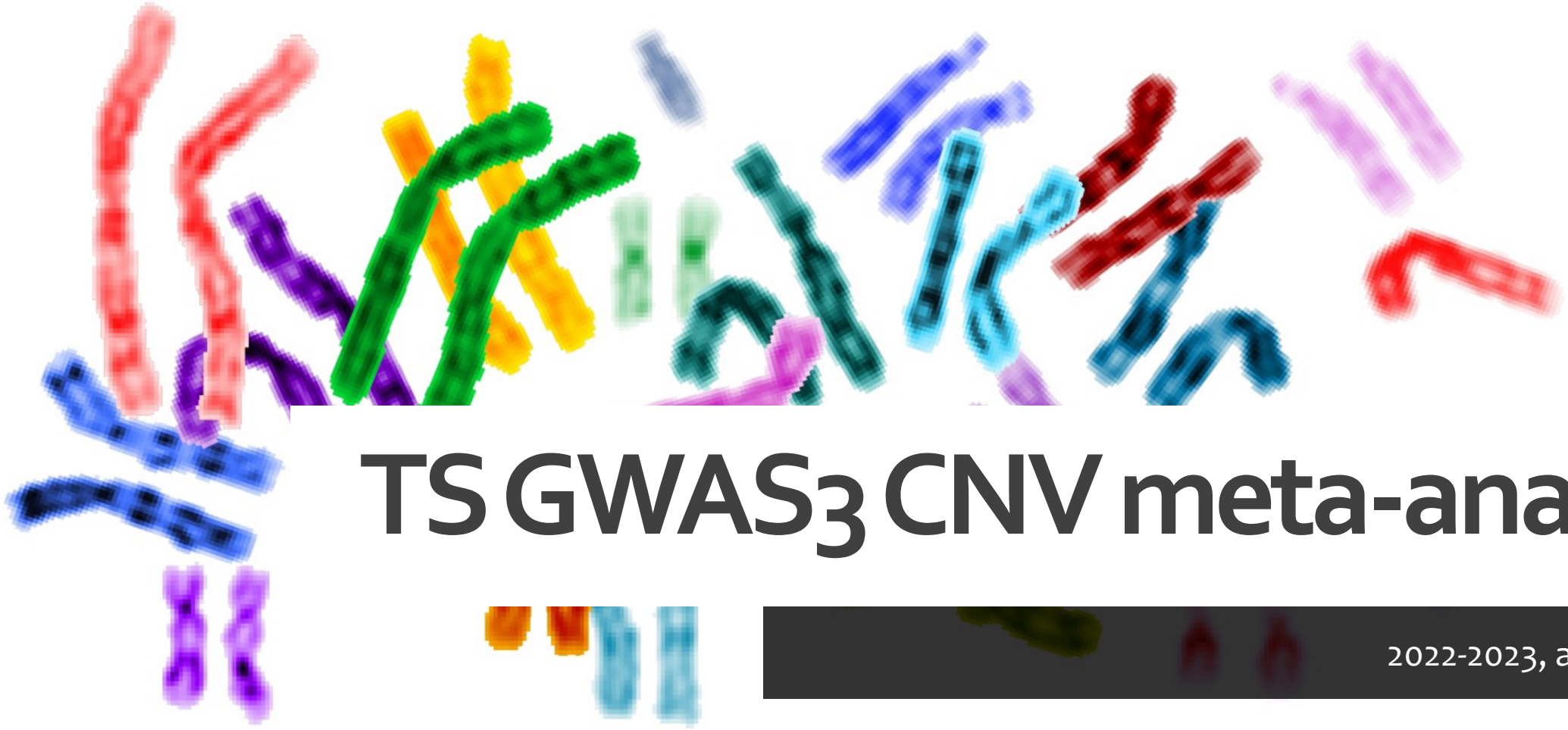
TS GWAS3 Genes Are Preferentially Expressed in Dopamine D1R+ & D2R+ Medium Spiny Neurons





Mouse Striatum

Genetics of Tourette Syndrome



TS GWAS3 CNV meta-analysis

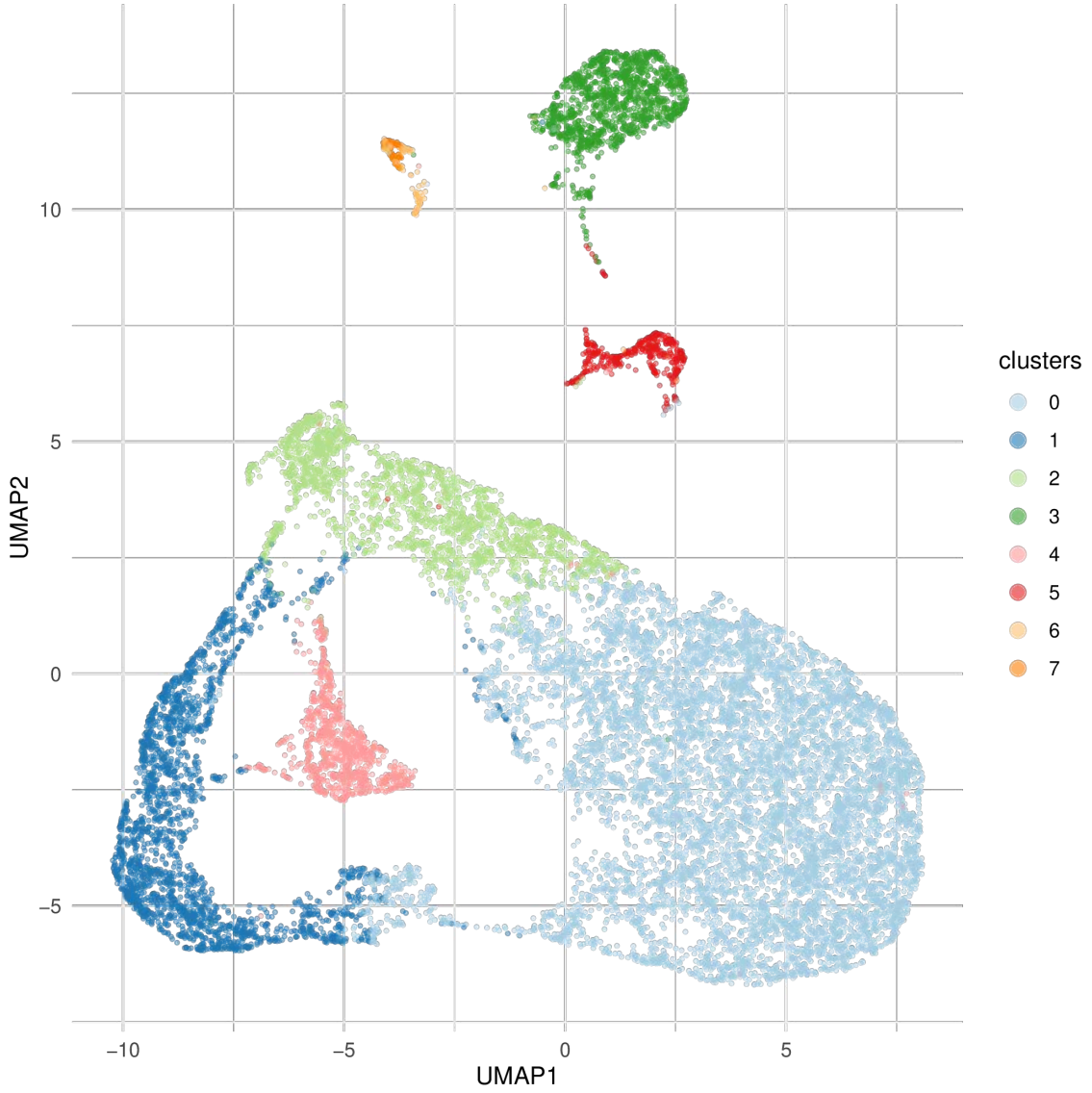
2022-2023, and beyond….

Case/control groups

- ~12,000 TS cases and 530,000 controls in the TS GWAS3
- Not all of these are available for individual CNV analyses

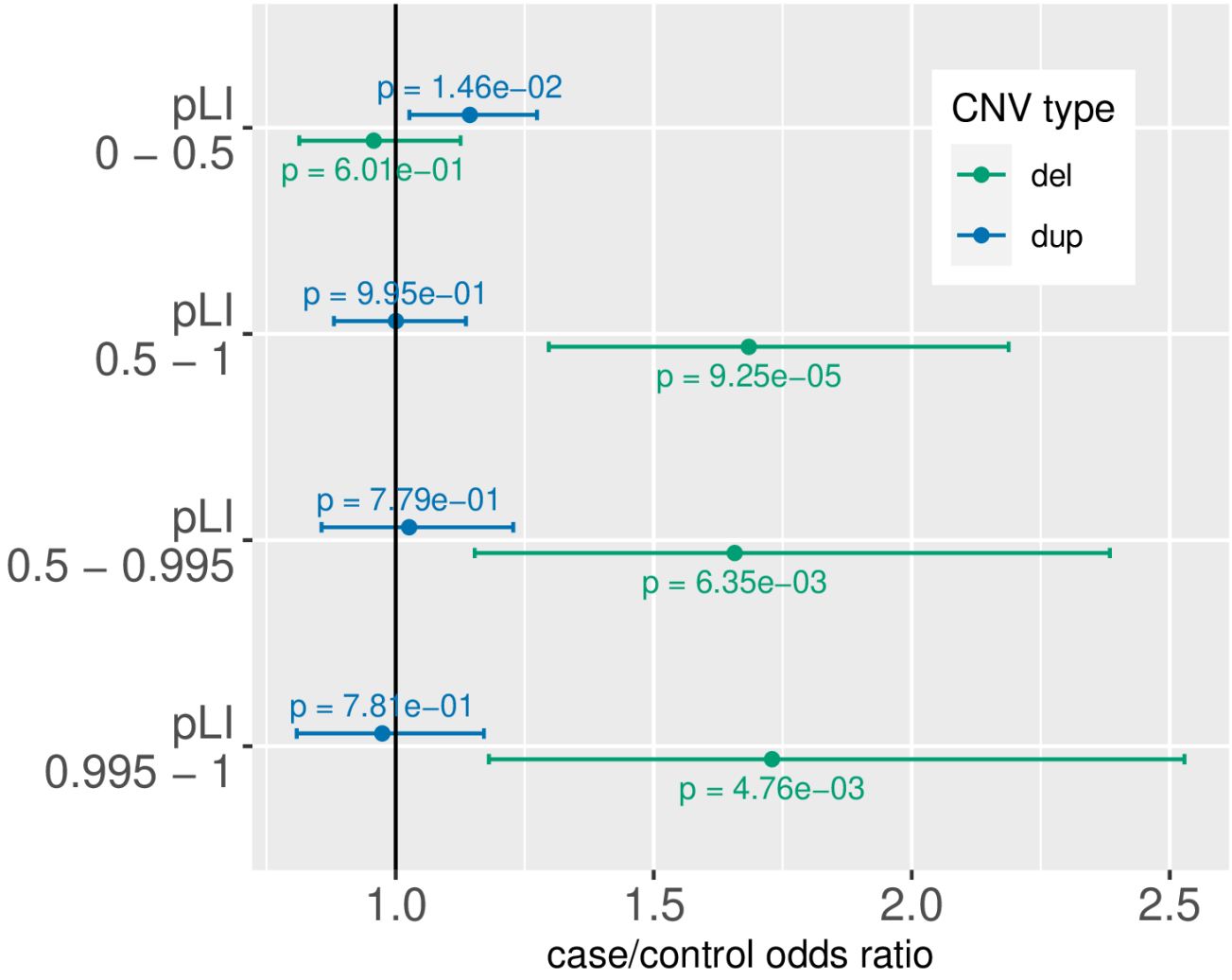
- Defined by unique combination of array group (3 total), ancestry cluster (8 total) and biological sex (2 total) = 48 combinations
- Require that group has at least 5 cases, 5 controls, and case/control ratio between 10%-90%
  - Total of 31 groups

- 5202 TS cases, 8667 controls
  - Double the sample size of Huang et al (N=2435 & 4100)



Genetics of Tourette Syndrome

Increased CNV burden (deletions) in TS in constrained protein-coding genes



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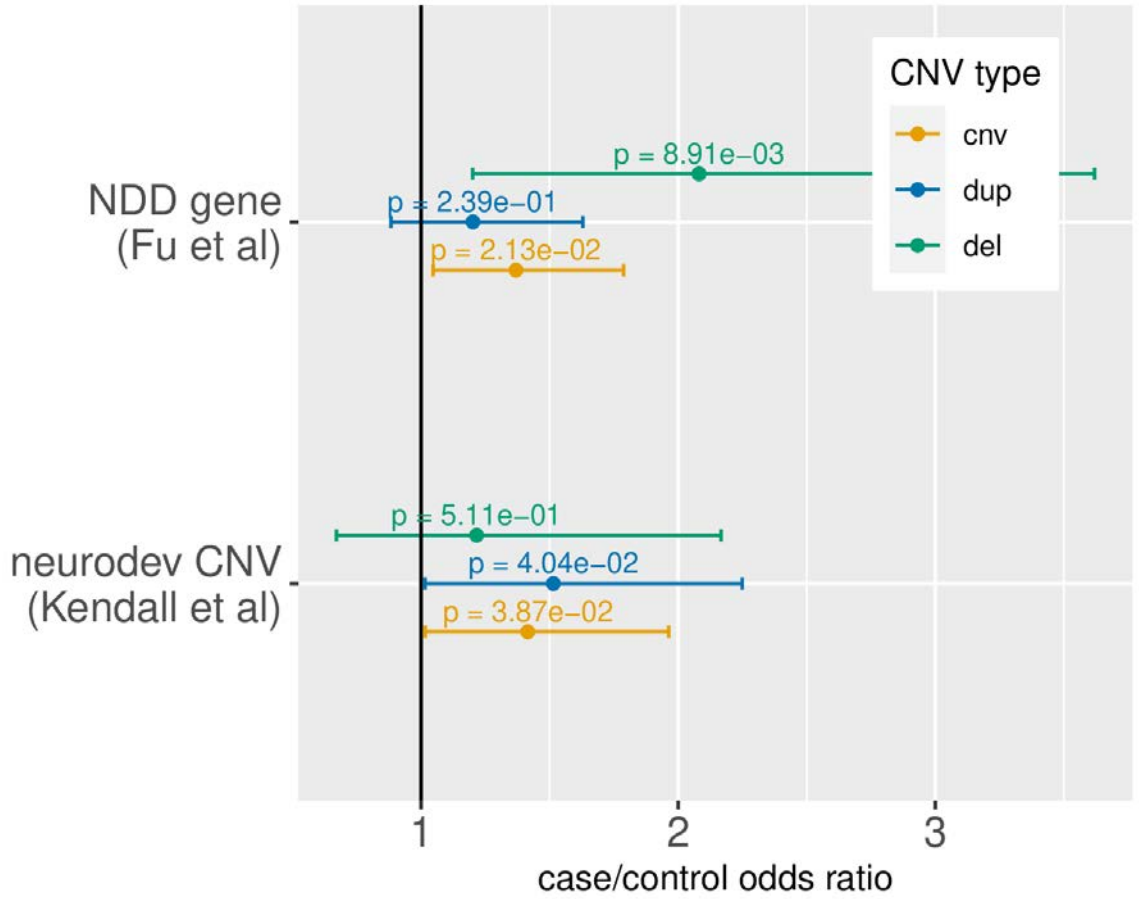
Genetics of Tourette Syndrome

Increased CNV burden in TS in previously identified neurodevelopmental genes



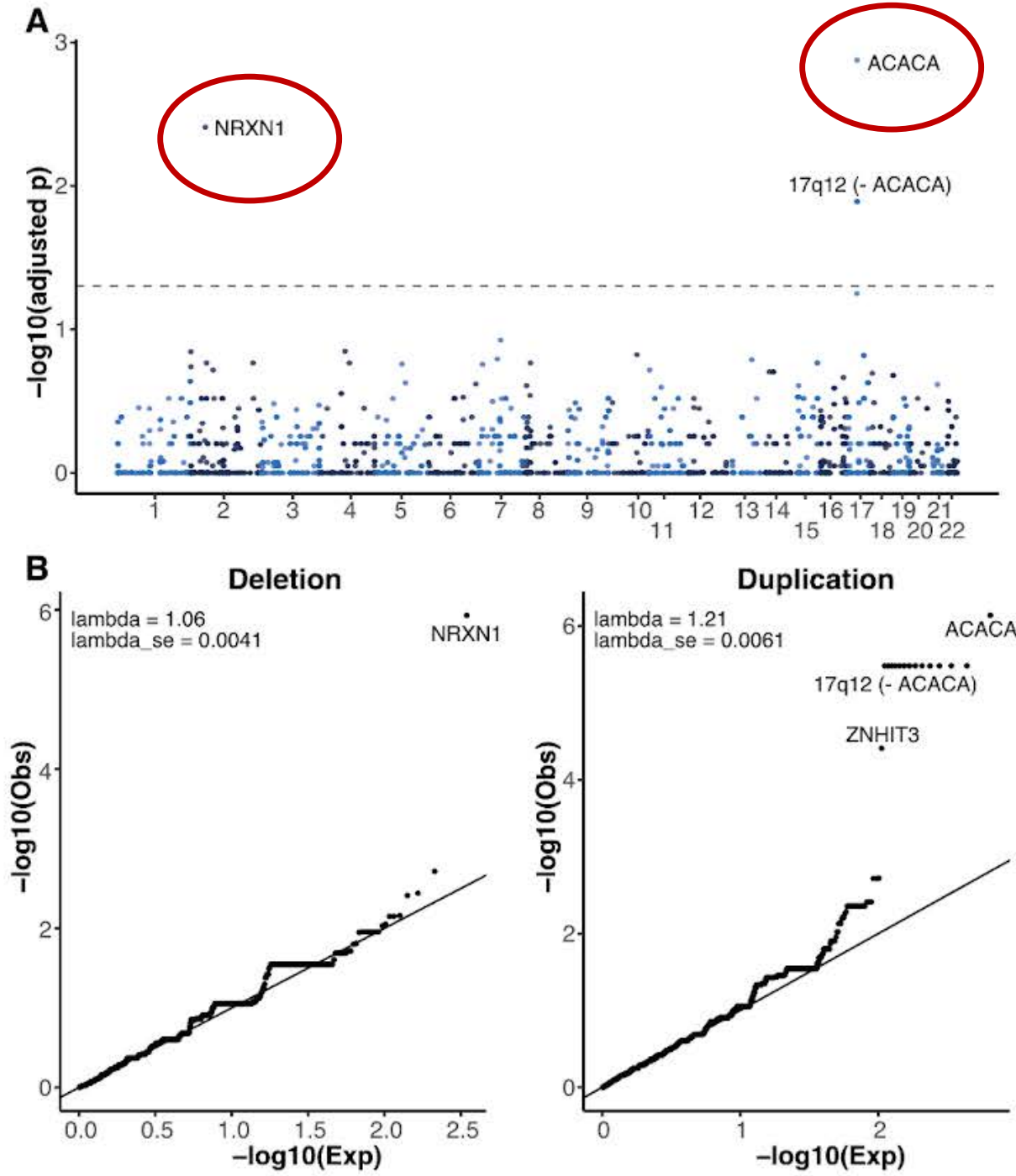
- Fu et al. : 664 neurodevelopmental genes implicated at Q<0.1 in a large exome seq study
- Kendall et al. : manually curated list of 53 CNVs associated with neurodev phenotype

Genetics of Tourette Syndrome

Association test results

- Bring in count-based data from datasets for which we don't have access to individual data
- 524 cases, 2315 controls
  - NORDiC
  - EGOS
  - BioVU
- New sample size: 5726 cases and 10,982 controls

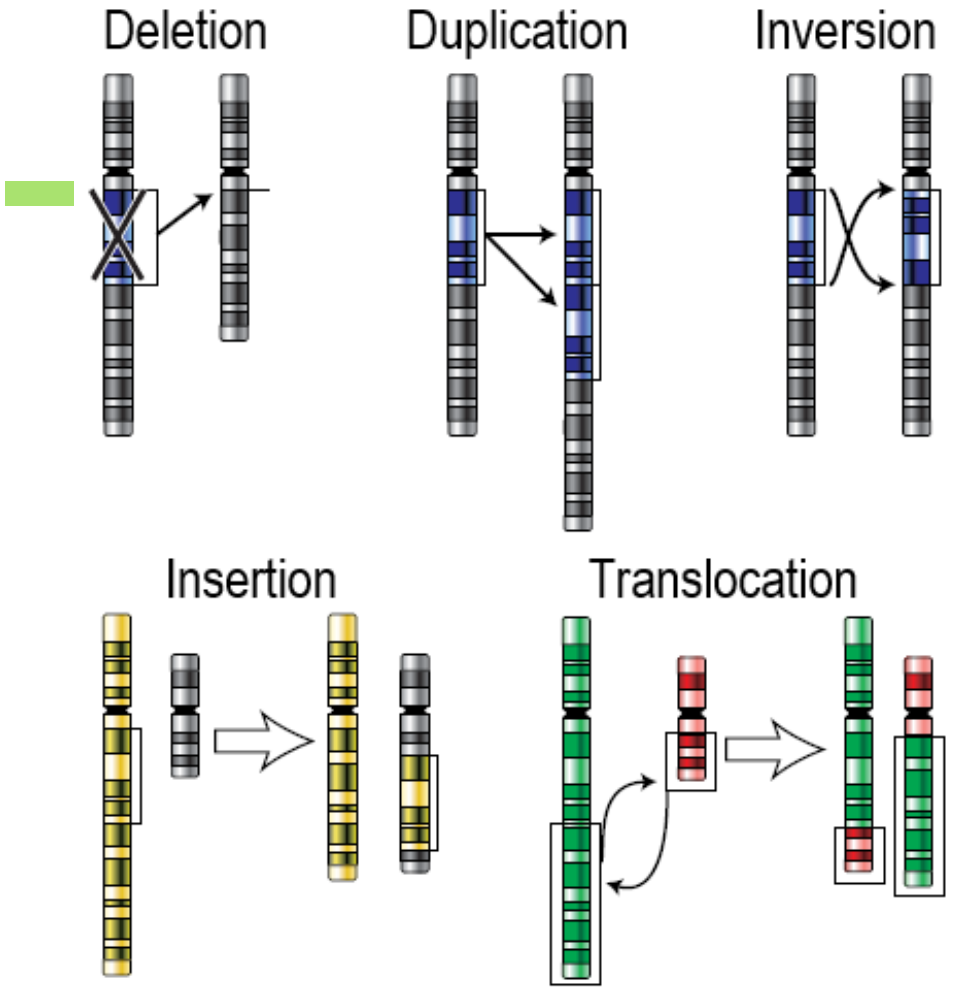
- Genome-wide significant:
  - NRXN1 deletions
    - Replication of Huang et al. 2017 result
  - 17q12 duplications
    - Novel result



ACACA gene

Chromosome 17q12

- acetyl-Co-A carboxylase alpha
- expressed in brain
- Involved in fatty acid synthesis
- Implicated in multiple studies of BMI
- Has been implicated in one study of NDD



TS Genetic architecture is becoming known

Rare variants

Estimated heritability ~70%

Non-genetic risk "Environmental"

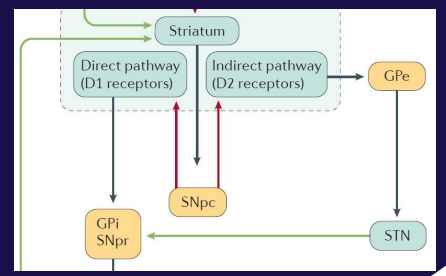
HCN1

SLC24A2

FLT3

PCDH9

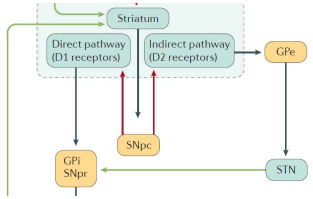
Common variants



■ *CNTN6* ■ *NRXN1* ■ large rare CNV ■ LGD ■ unknown ■ environment

Genetics of Tourette Syndrome

Progress in understanding the causes of TS



1885 — Gilles de la Tourette publishes description of TS and suggests that it is hereditary

1900------1970s — Haloperidol found to treat tics; biological nature of TS re-established

1900------1970s — Biological nature of TS called into question—psychological factors thought to be the cause

1981 — First family study of TS

1985 — First twin study demonstrating the heritability of TS

1999 — **First genome-wide study of TS in families**

2003 — **CNTNAP2 identified as potential risk gene for TS**

2005 — SLITRK1 identified as potential TS risk gene

2010 — First copy number variant (CNV) study; HDC identified as a possible gene for TS

2010 — First whole exome sequencing (WES) study (Sundaram); CNVs found to be relevant to TS genetics

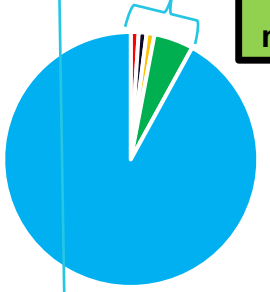
2011 — **First genome-wide association (GWAS) study**

2012 — **NRXN1 & CNTN6 confirmed as risk genes for TS via CNV**

2015 — CELSR3 identified as risk gene for TS via WES

2017 — **FLT3 identified as possible risk gene for TS via GWAS; TS genetic risk also found to influence other tic disorders**

2018 — **8% of genetic risk for TS identified**



2019 — **~5 new TS genes identified in multi-consortia GWAS**

2021 — **NRXN1 confirmed as a risk gene for TS Additional CNV on 17q12 identified**

Genetics of Tourette Syndrome

Spectrum of Developmental Tic Disorders

- Transient Tic Disorder (TTD)
  - Single or multiple tics lasting > 4 weeks, < 1 year
  - Now "Provisional Tic Disorder" in DSM-5

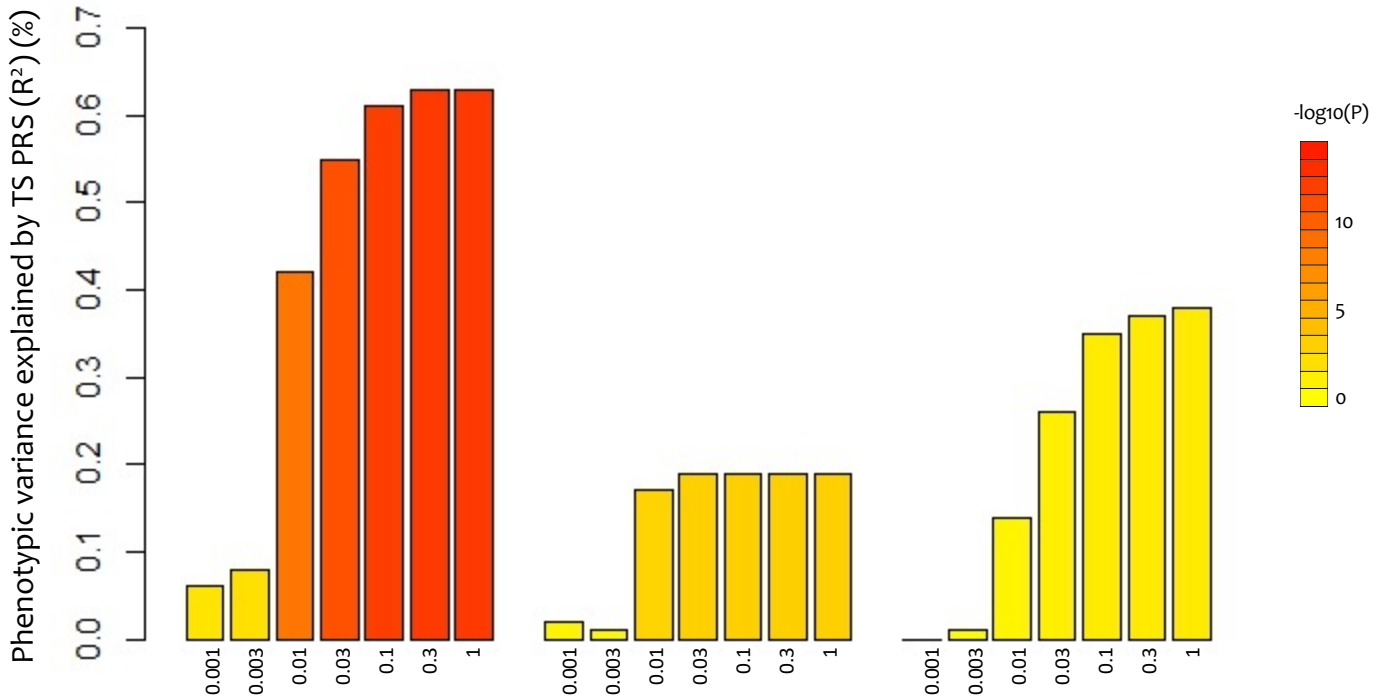
- Chronic (Persistent) Tic Disorder (CTD/PTD)
  - Multiple motor OR vocal tics lasting > 1 year

- Gilles de la Tourette Syndrome (GTS/TS)
  - Multiple motor AND one vocal tic lasting > 1 year
  - Onset before age 18
  - DSM-5 removed "no 3 month period w/o tics"

Continuous biologic... spectrum

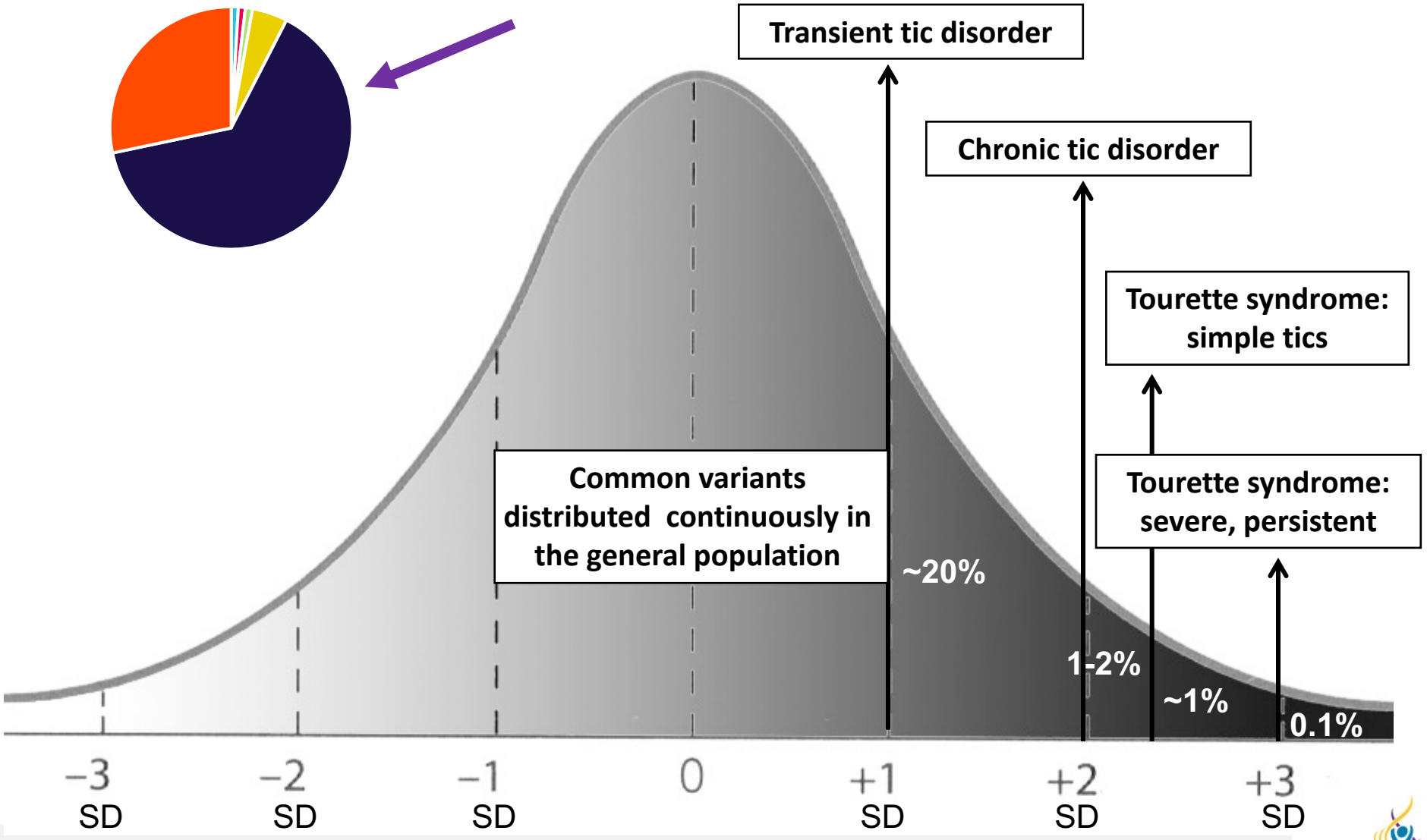
Genetics of Tourette Syndrome

TS genetic risk score analysis confirms shared genetic susceptibility between TS and tic spectrum disorders

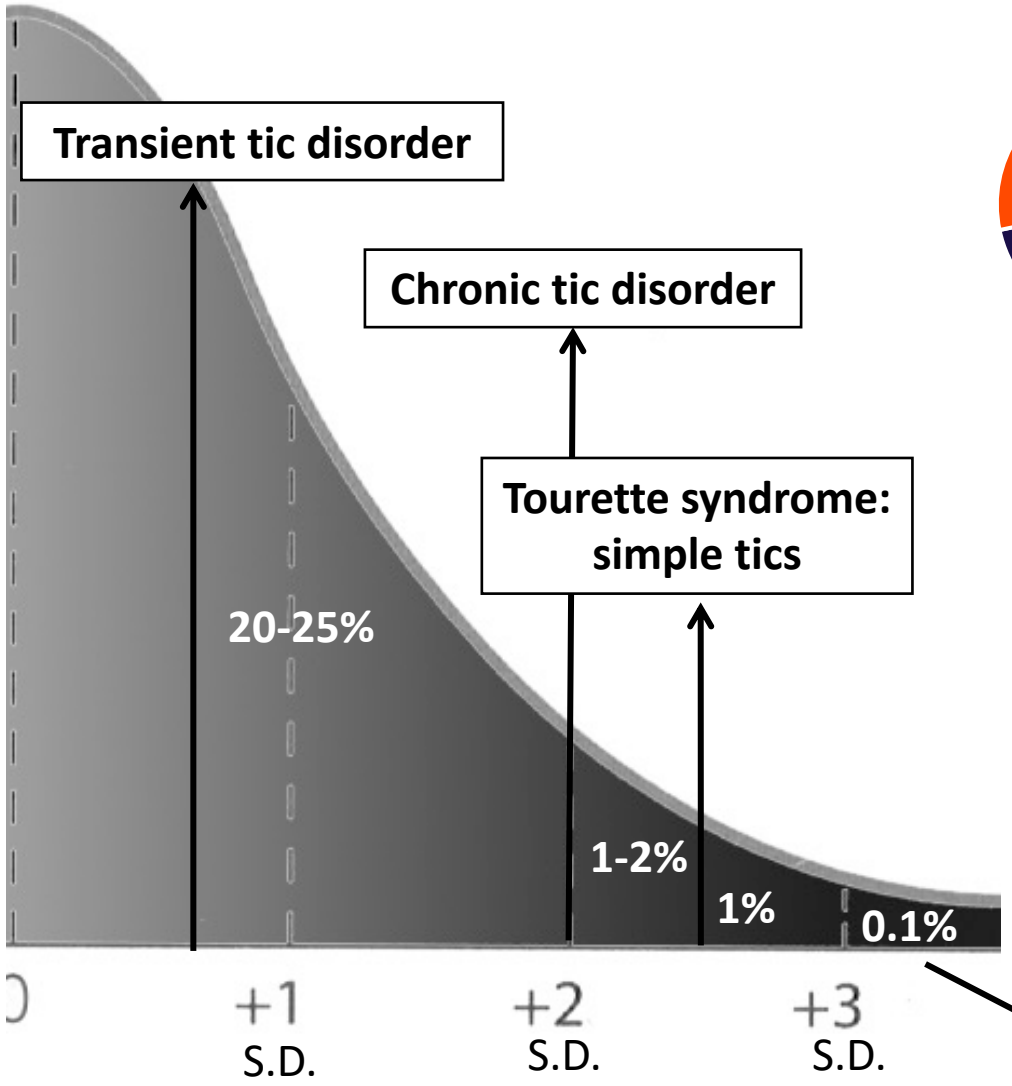


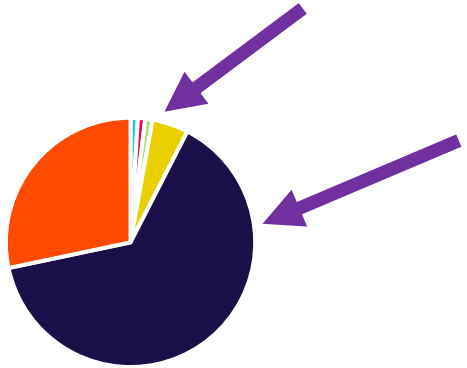
Genetics of Tourette Syndrome

Genetic model for heritability of developmental tic disorders



Genetics of Tourette Syndrome



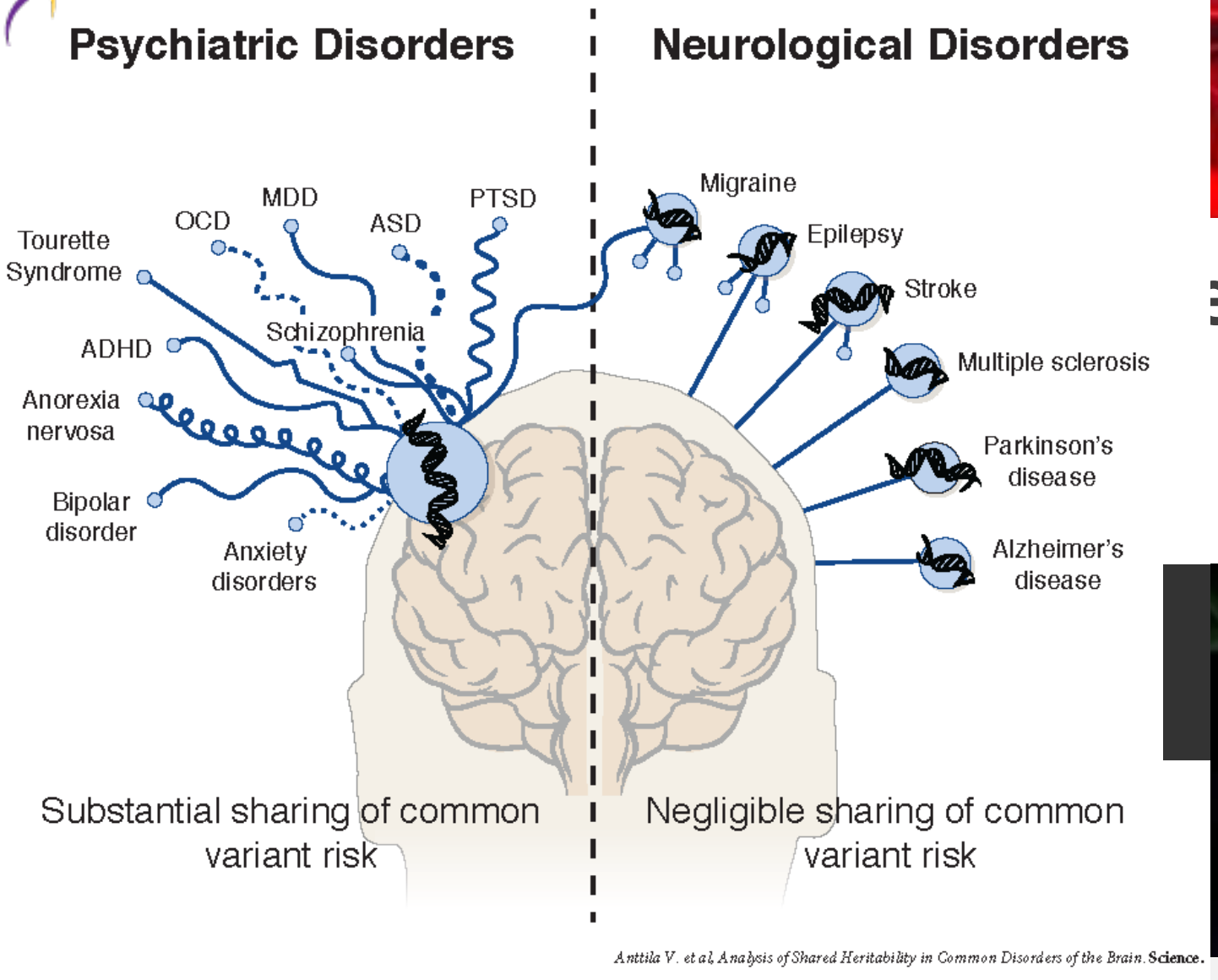


Severe TS:

- High TS polygenic burden >99.9%ile
- Moderate polygenic burden plus large, rare CNV (e.g., *CNTN6)*
- Lower polygenic burden plus non-genetic risk factor(s)
- Combination of all 3 above

Tourette syndrome: severe, persistent

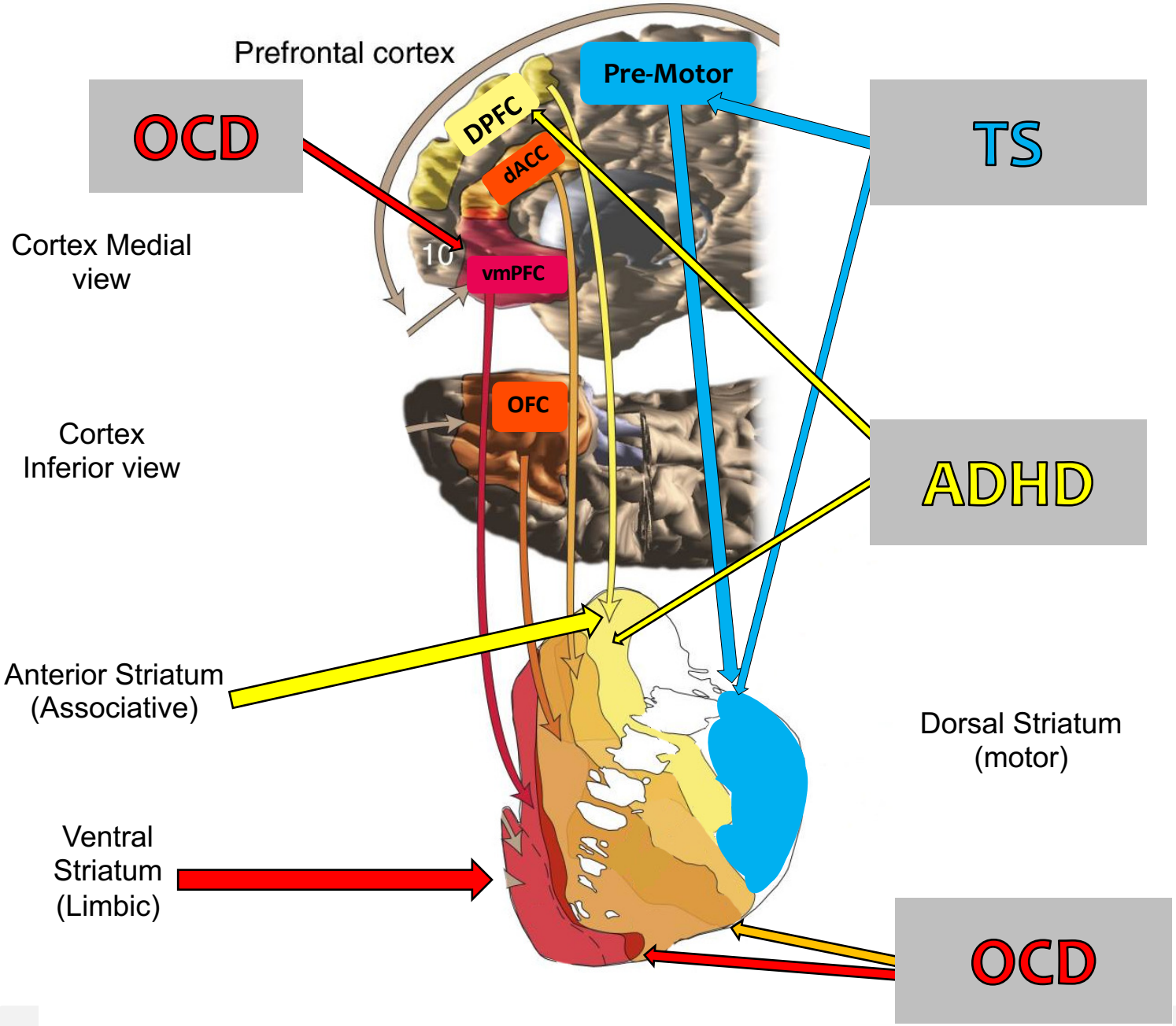
Genetics of Tourette Syndrome



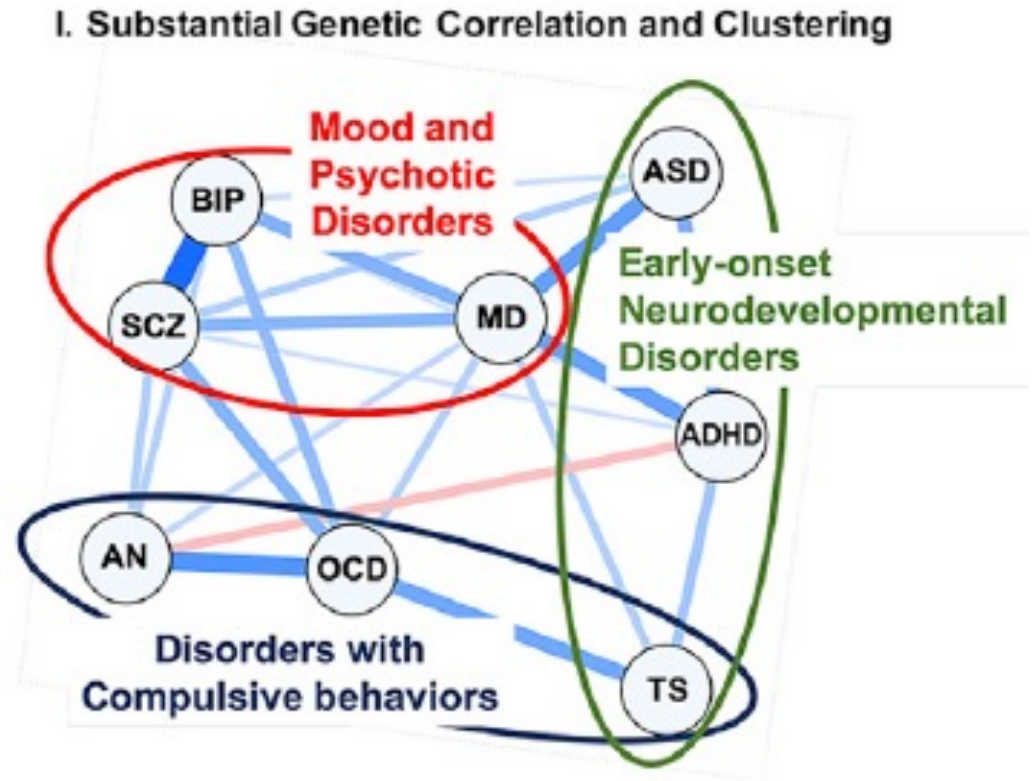
Anttila V. et al, Analysis of Shared Heritability in Common Disorders of the Brain. **Science**.

enetics helps shape how we think about TS biologically and phenotypically

From a genetic standpoint, Tourette Syndrome is a neuropsychiatric disorder, with more in common with psychiatric than neurological illnesses



Modified from Haber & Knutson, Neuropsychopharmacology, 2010



Lee, et el, & Cross Disorders Group of the PGC, Cell, 2019

Neurocircuitry and genetics tell the same story

- Psychiatric illnesses are disorders of circuitry rather than brain regions, and there is substantial overlap between them

Acknowledgments

- **Funding:**
  - NIH: R01 NS105746
  - Tourette Association of America
- **Thanks to all the TS patients and families for their participation in TS research**