

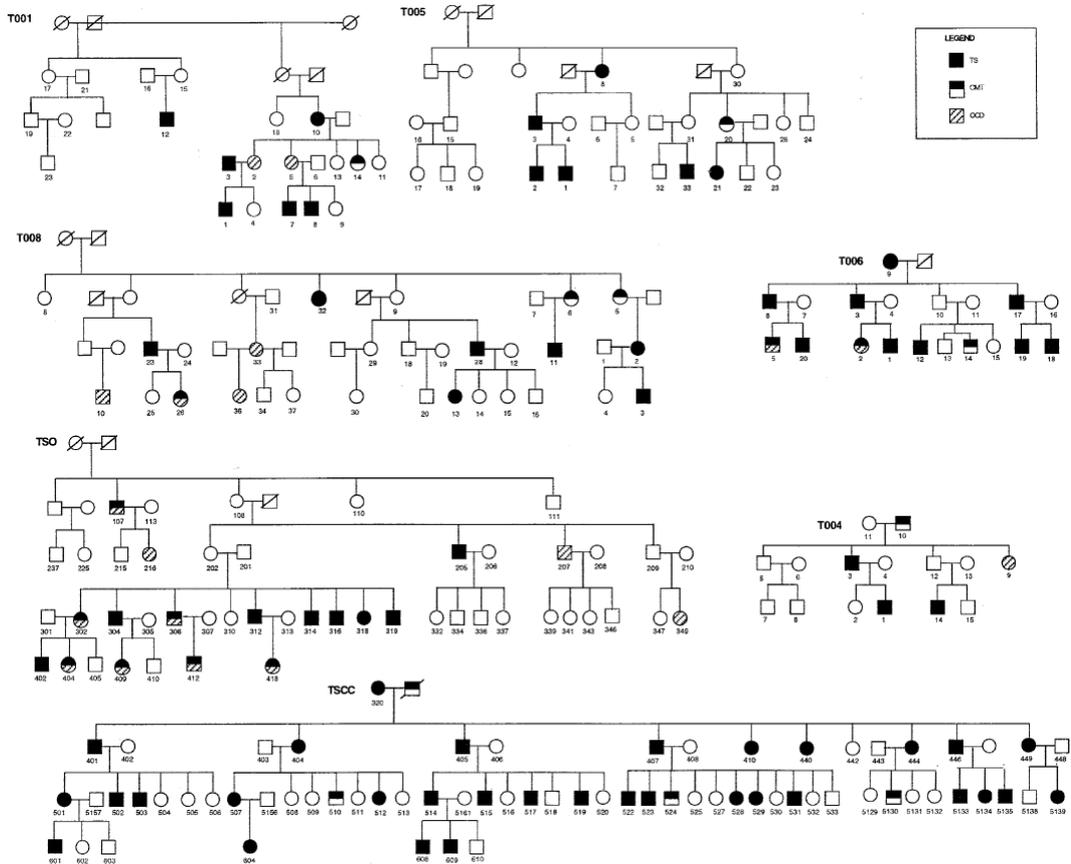
ESSTS

Brussels²⁰²³



Neuroimaging and Genetics for Tourette Syndrome

*Peristera Paschou, Professor
Purdue University, USA*

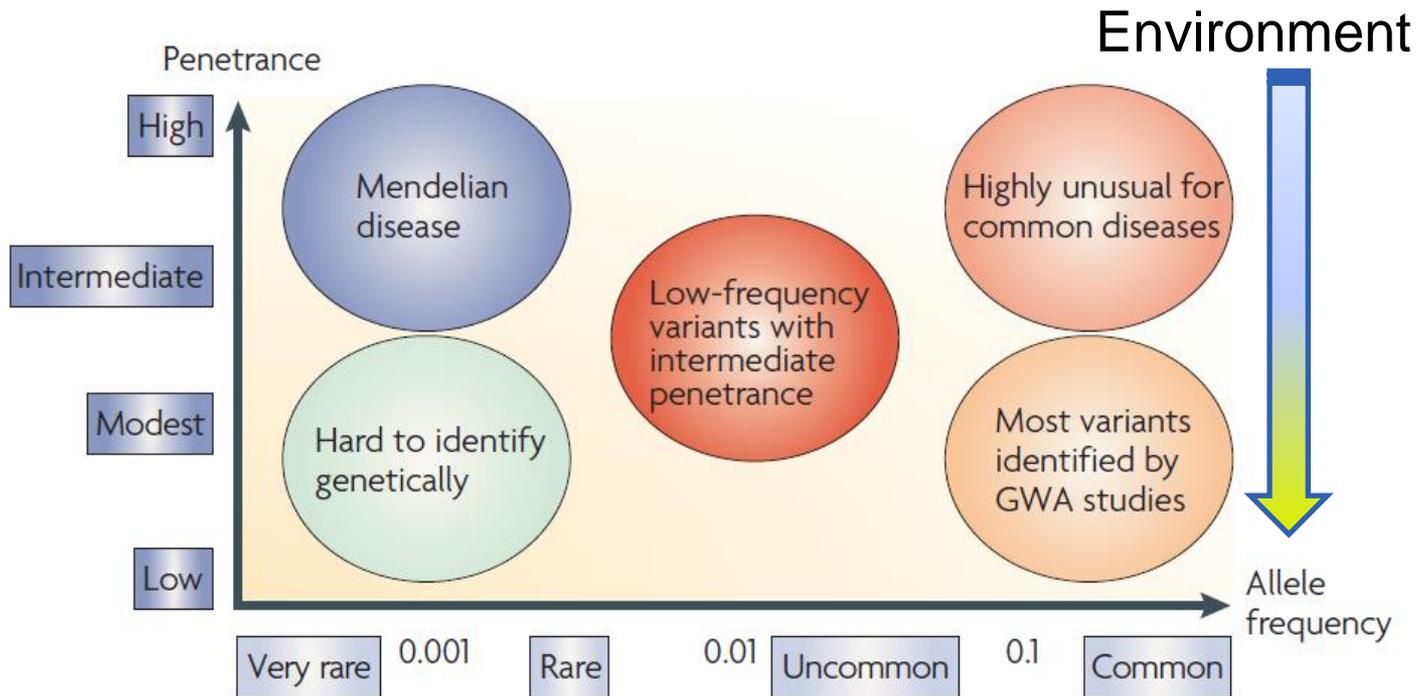


Tourette Syndrome pedigrees....

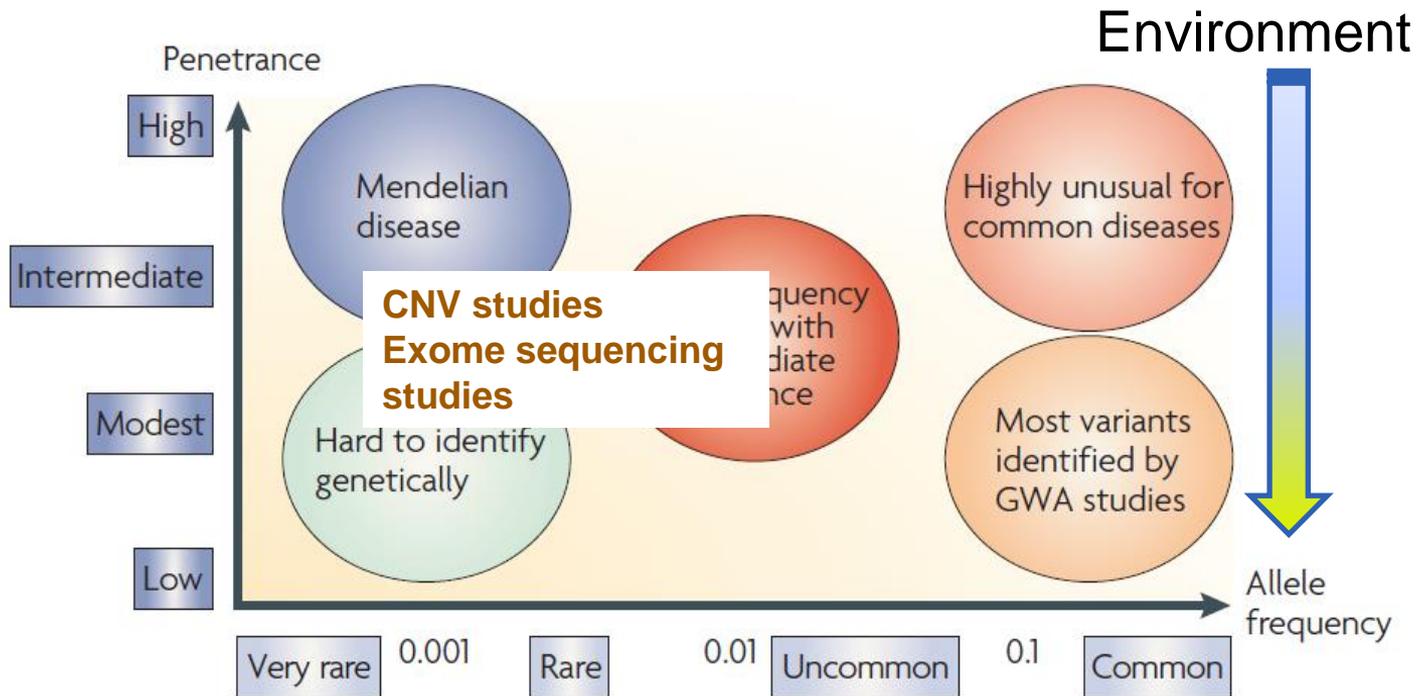
Barr et al 1999
Pauls et al 1990
Kurlan et al 1986



Tourette Syndrome is caused by multiple genes interacting with each other and the environment.



Tourette Syndrome is caused by multiple genes interacting with each other and the environment.



De Novo Sequence and Copy Number Variants are Strongly Associated with Tourette Disorder and Implicate Cell Polarity in Pathogenesis

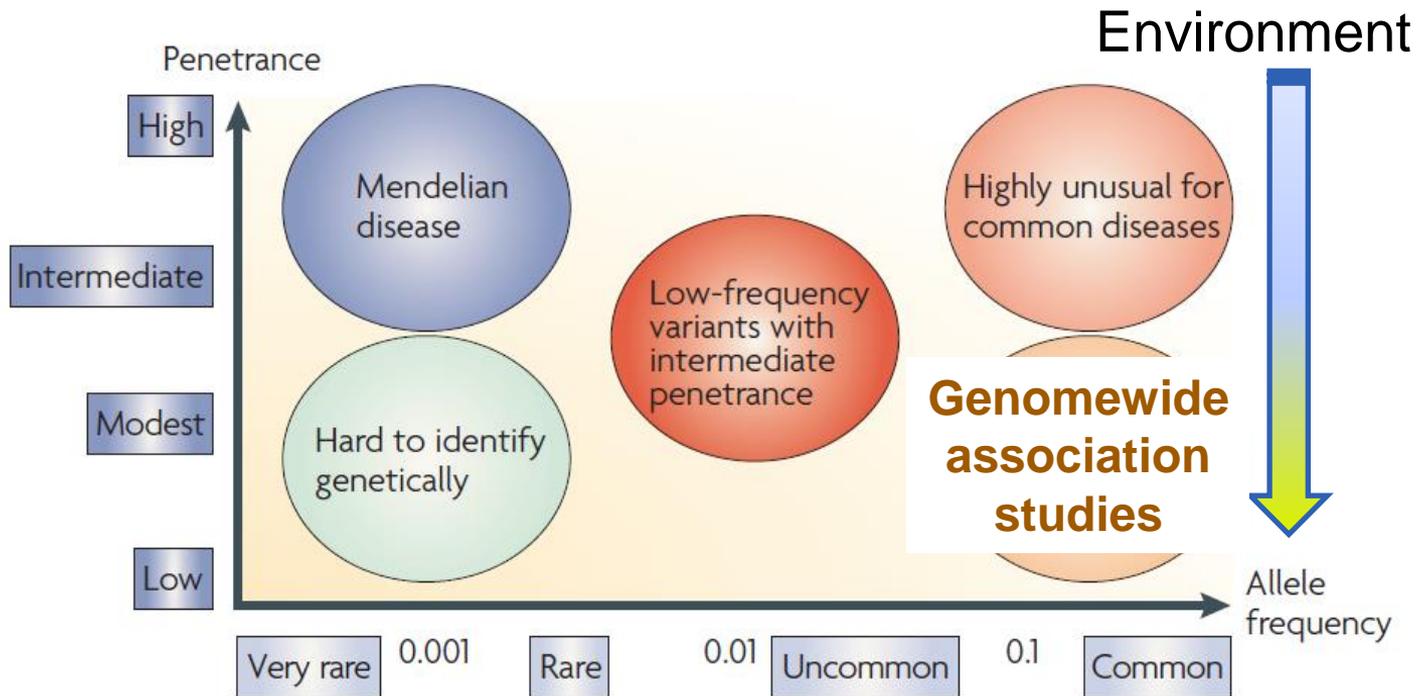
- **TSGeneSEE, TIC Genetics, TAAICG**
- Whole exome sequencing of 800 trios
- Recurrent *de novo* variants identify two new high-confidence TD risk genes: *CELSR3* & *OPA1*
- High confidence and probable TD genes suggest cell polarity as a potential pathogenic mechanism



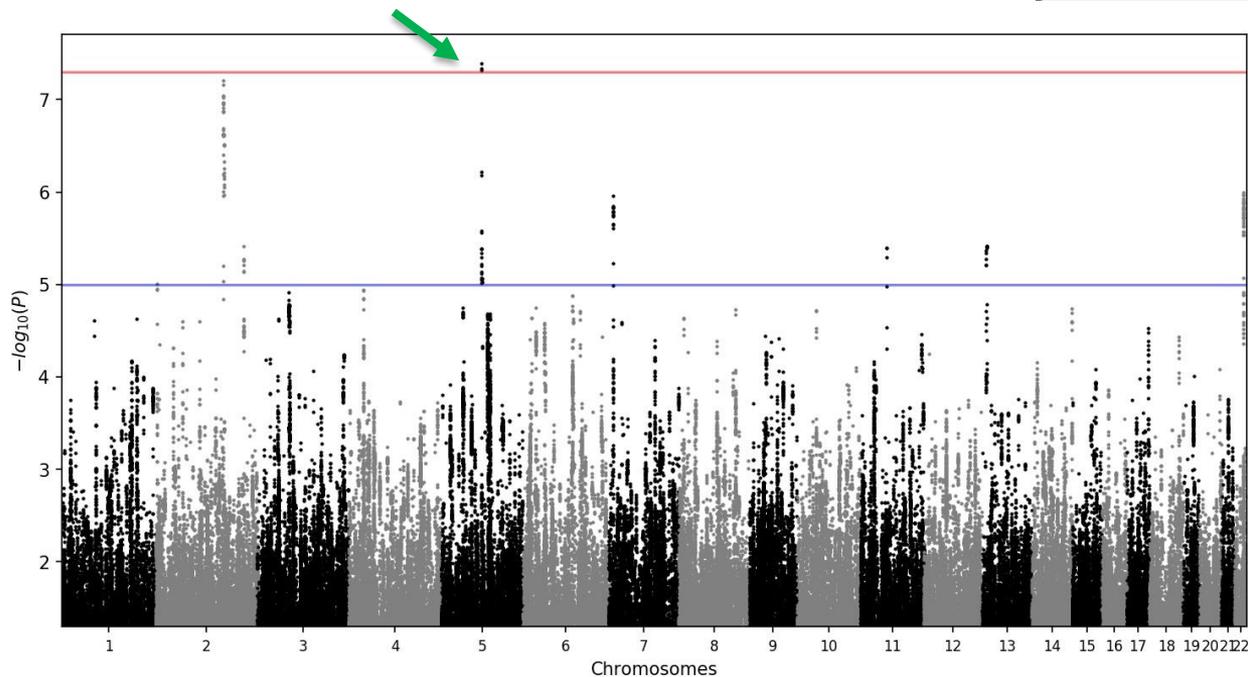
Wang et al. Cell Reports 2018

**Peristera Paschou
Jeremy Willsey
Matthew State**

Tourette Syndrome is caused by multiple genes interacting with each other and the environment.



A large-scale GWAS for Tourette Syndrome



6,133 TS cases
13,565 controls
1,955,677 SNPs
1 genome-wide
significant locus



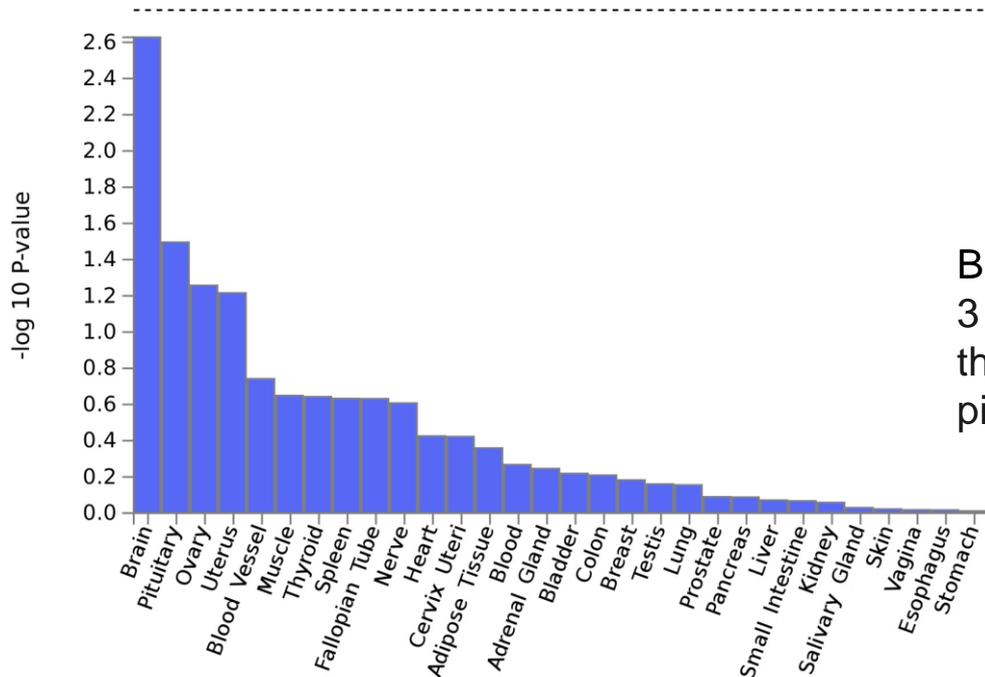
Apostolia
Topaloudi



Fotis
Tsetsos

Tsetsos et al. Biological Psychiatry 2022

A large-scale GWAS for Tourette Syndrome



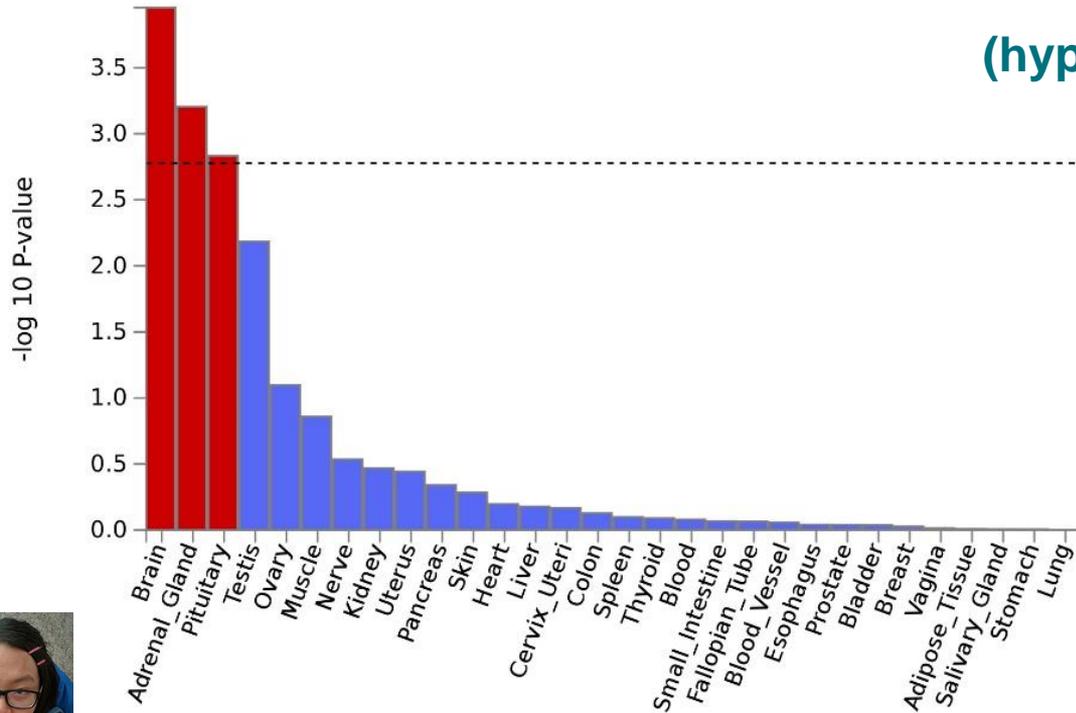
Brain, pituitary, and ovary are the top 3 GWAS enriched tissues, pointing to the involvement of hypothalamus-pituitary axis in TS pathogenesis



Apostolia
Topaloudi

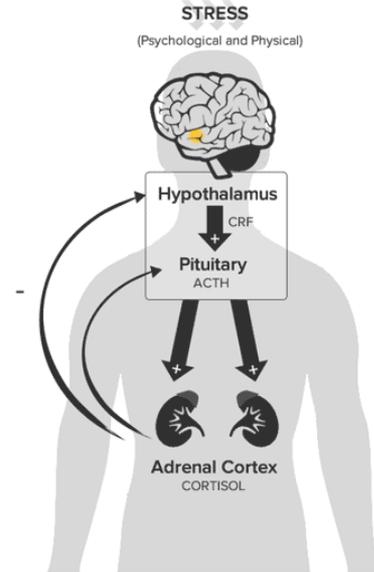
Cross-disorder GWAS

ADHD-ASD-OCD-TS tissue specificity analysis



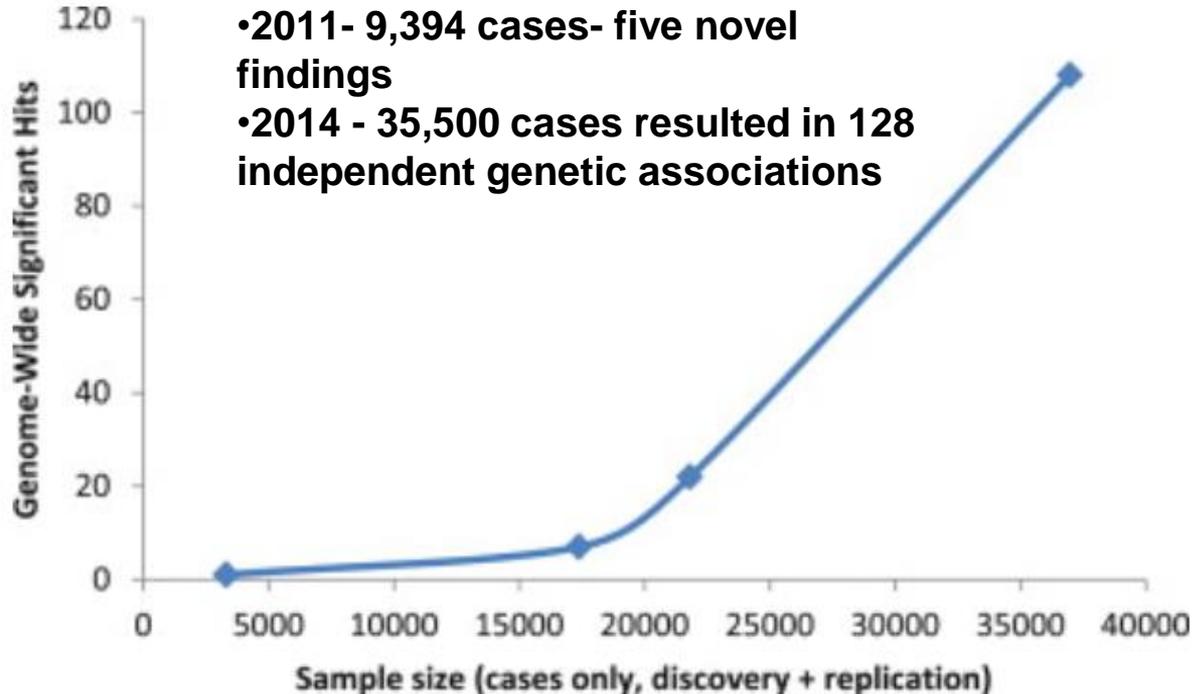
Zhiyu Yang

The HPA axis (hypothalamic-pituitary-adrenal)



Yang et al. 2021, *Biological Psychiatry*

PGC - Genome-Wide Association Studies of Schizophrenia



After the point of 13,000 cases the rate of new findings increased rapidly by about four independent associations per 1,000 new cases.

Bringing together all TS genetics consortia!

NINDS R01 (MPIs: Paschou, Scharf, Mathews)



**Tourette Association of America
International Consortium for Genetics**



**Tourette Syndrome Genetics
The Southern and Eastern Europe Initiative
TSGeneSEE**



**COST ACTION BM0905
European Network for the
Study of Gilles de la Tourette
Syndrome**



**Nordic
OCD &
Related
Disorders
Consortium**



**Danish
OCD &
Tic
Study**

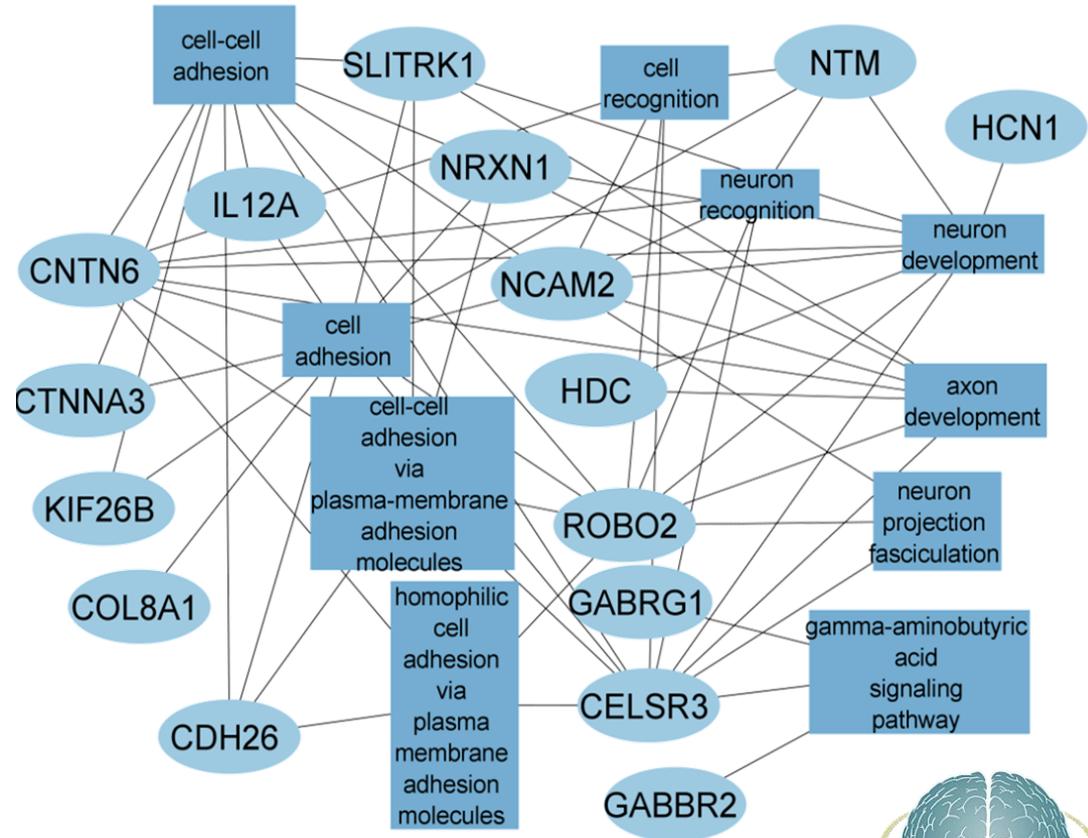


**TS+EUROTRAIN
Marie Curie
Initial Training Network**



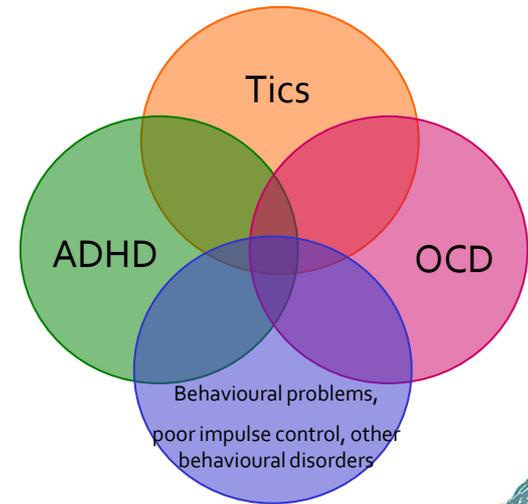
TS genes implicated through large-scale genomic analysis

- Huang et al 2017 Neuron
 - CNV analysis - 2,434 TS cases/4,093 controls
- Yu et al 2019 Am J Psychiatry
 - GWAS 4,232 cases - 8,411 controls
- Tsetsos et al 2021 Translational Psychiatry
 - gene set analysis on Yu et al.
- Wang et al 2018 Cell Reports
 - Whole exome sequencing 800 trios
- Tsetsos et al Biol Psychiatry
 - GWAS 6,133 TS cases - 13,565 controls
- Scharf, Paschou, Mathews – GWAS >12,000 cases – to be completed 2023

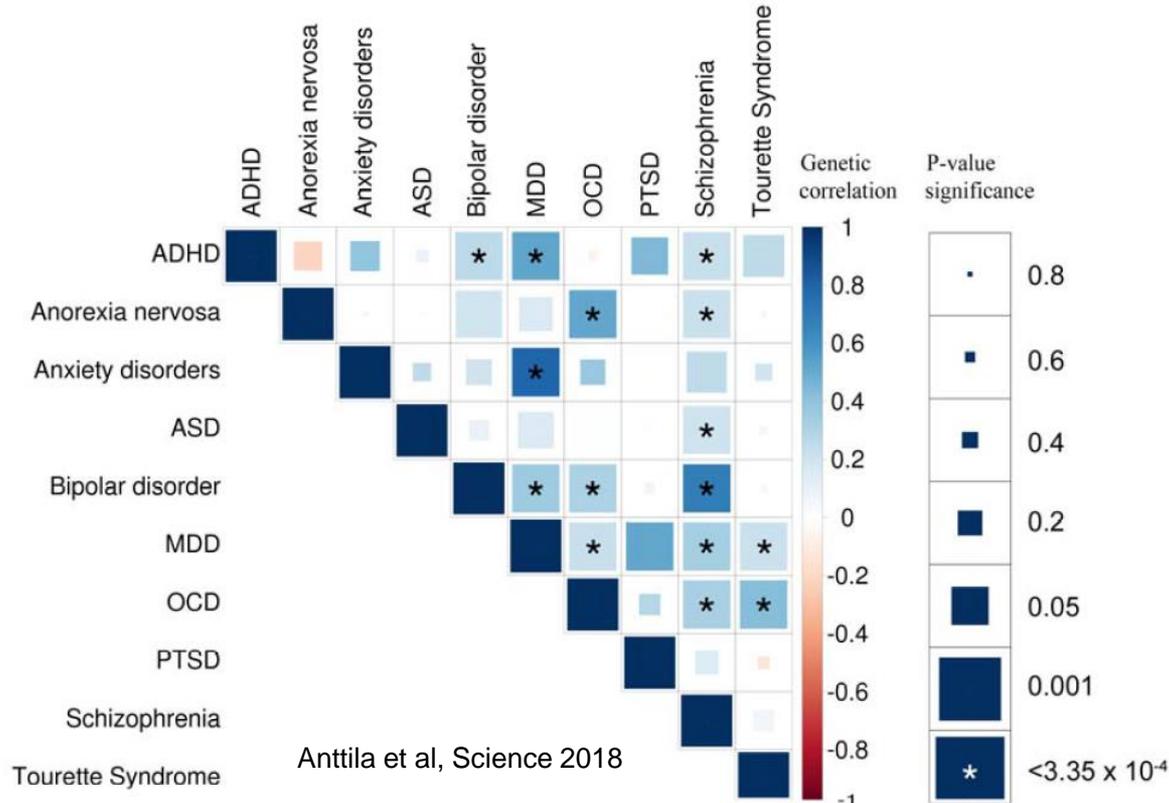


TS is more than just tics...

- 90% of TS patients present with comorbid neuropsychiatric disorders
- Obsessive Compulsive Disorder (OCD up to 50% of TS patients)
- Attention Deficit Hyperactivity Disorder (ADHD up to 54.3%)
- Autism Spectrum Disorders (ASD up to 20%)
- Major Depressive Disorder (MDD up to 26%)
- Anxiety Disorders (AXD up to 36%)

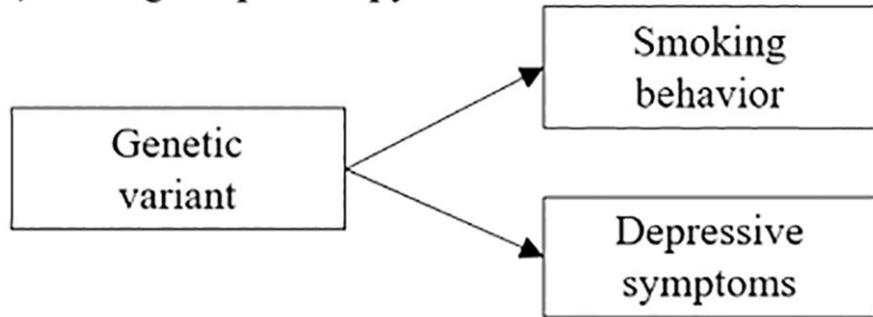


TS genetics correlate with other neuropsychiatric disorders.

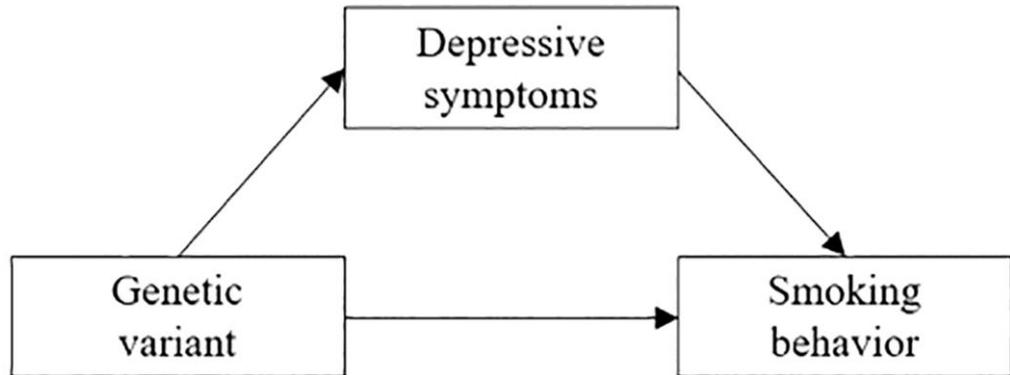


Examining pleiotropy

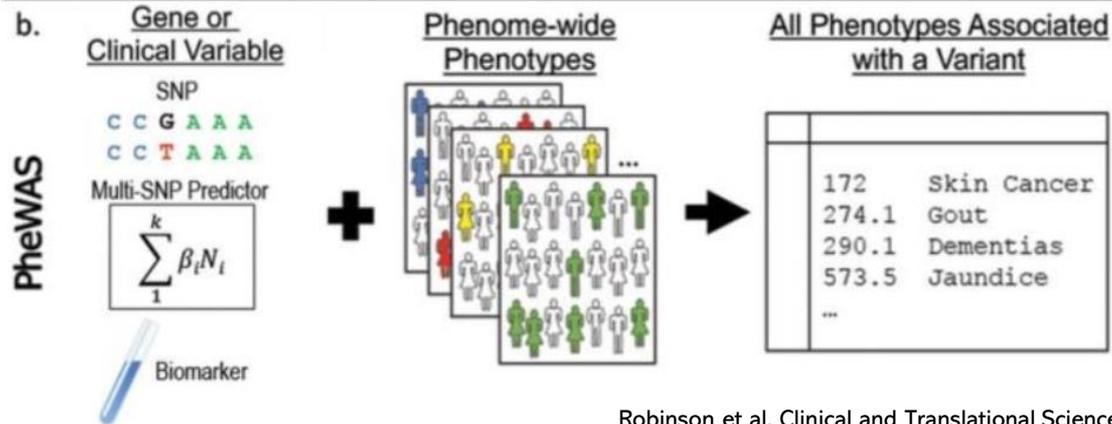
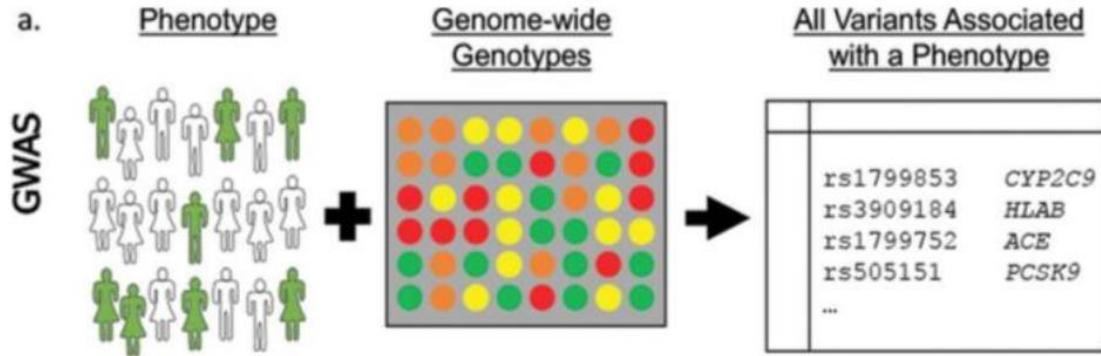
(a) Biological pleiotropy



(b) Mediated pleiotropy



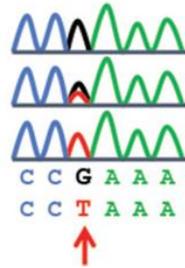
GWAS vs PheWAS



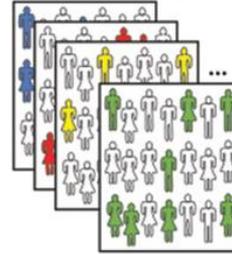
Phenome Wide Association Study of Tourette Syndrome

SNP based PheWAS

Variant Genotype



Phenome-wide Phenotypes



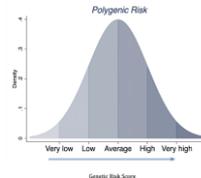
All Phenotypes Associated with a Variant

172	Skin Cancer
274.1	Gout
290.1	Dementias
573.5	Jaundice
...	

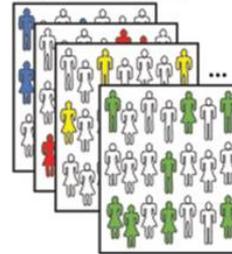
Polygenic Risk Score based PheWAS

Multi-SNP Predictor

$$\sum_{1}^{k} \beta_i N_i$$



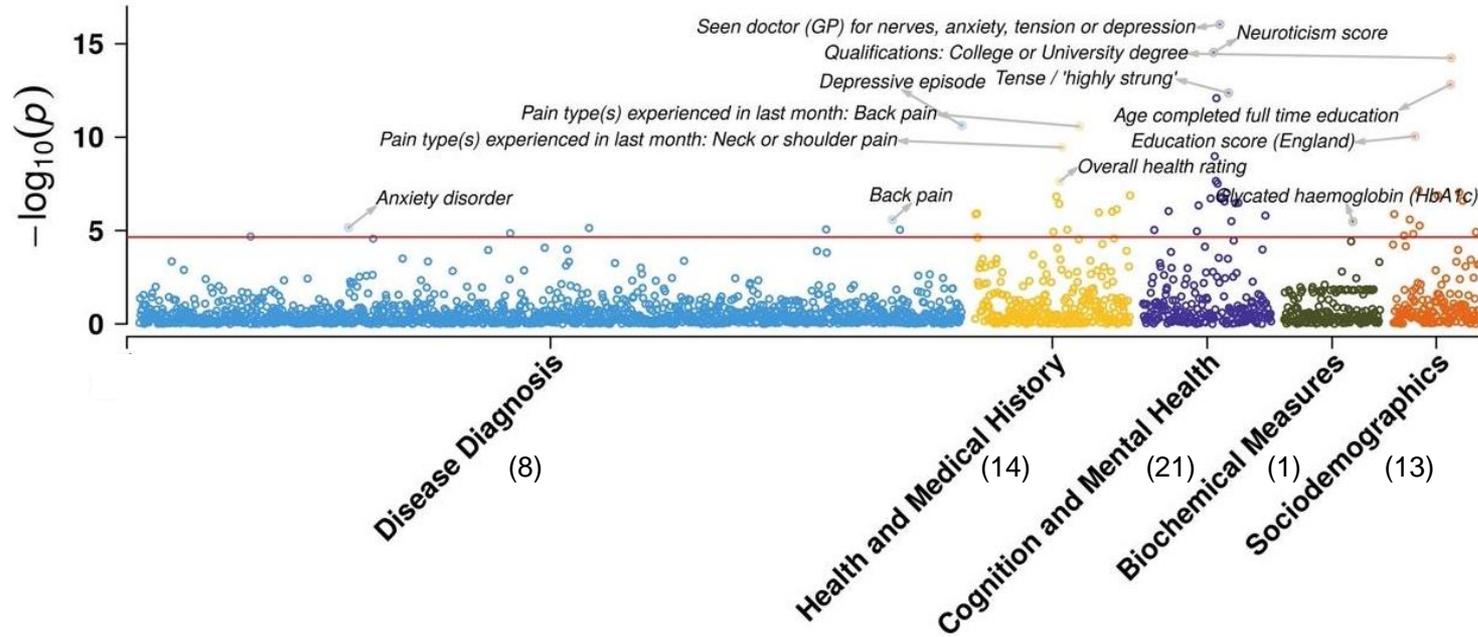
Phenome-wide Phenotypes



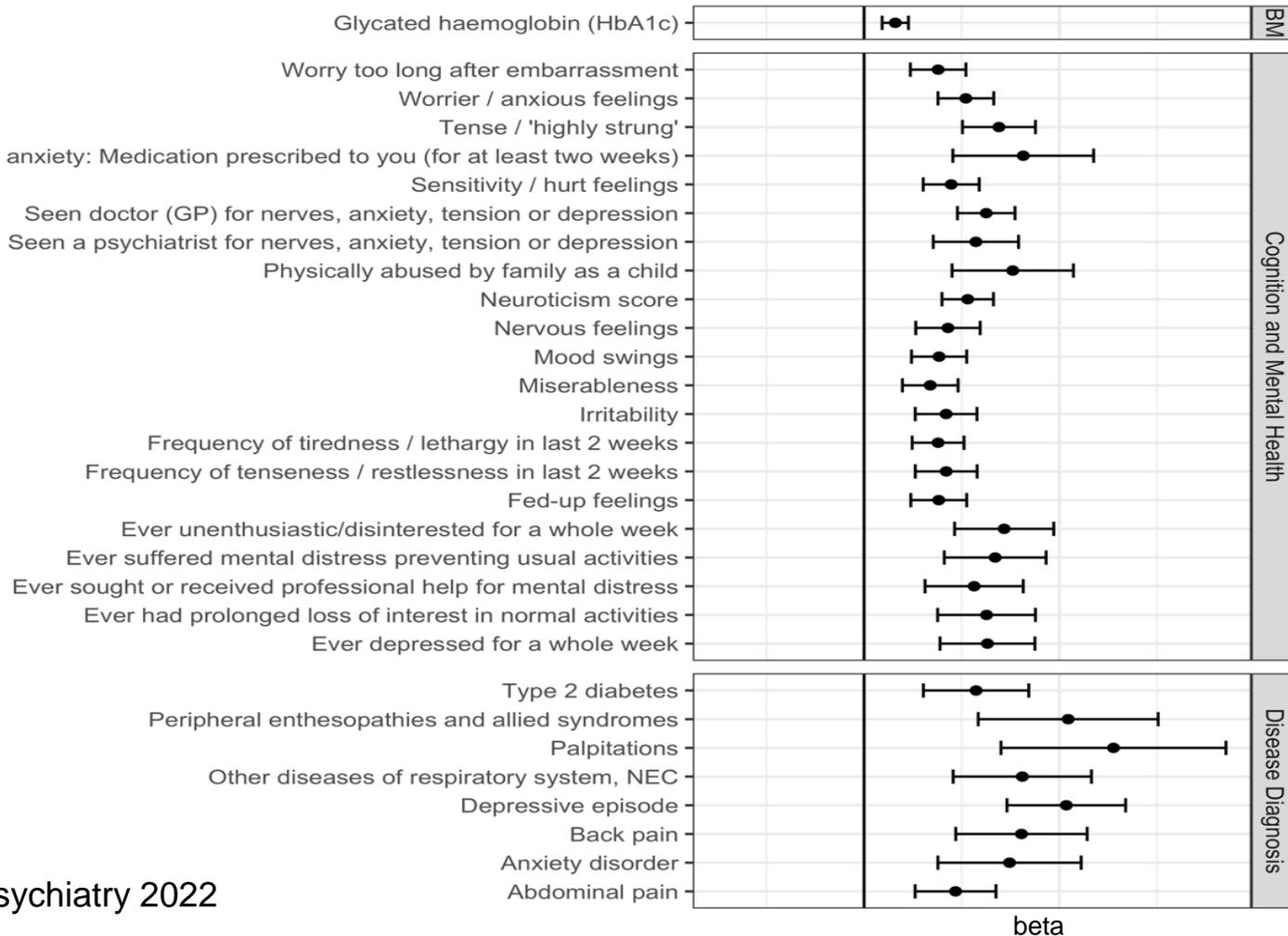
All Phenotypes Associated with the Risk Score

172	Skin Cancer
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...	

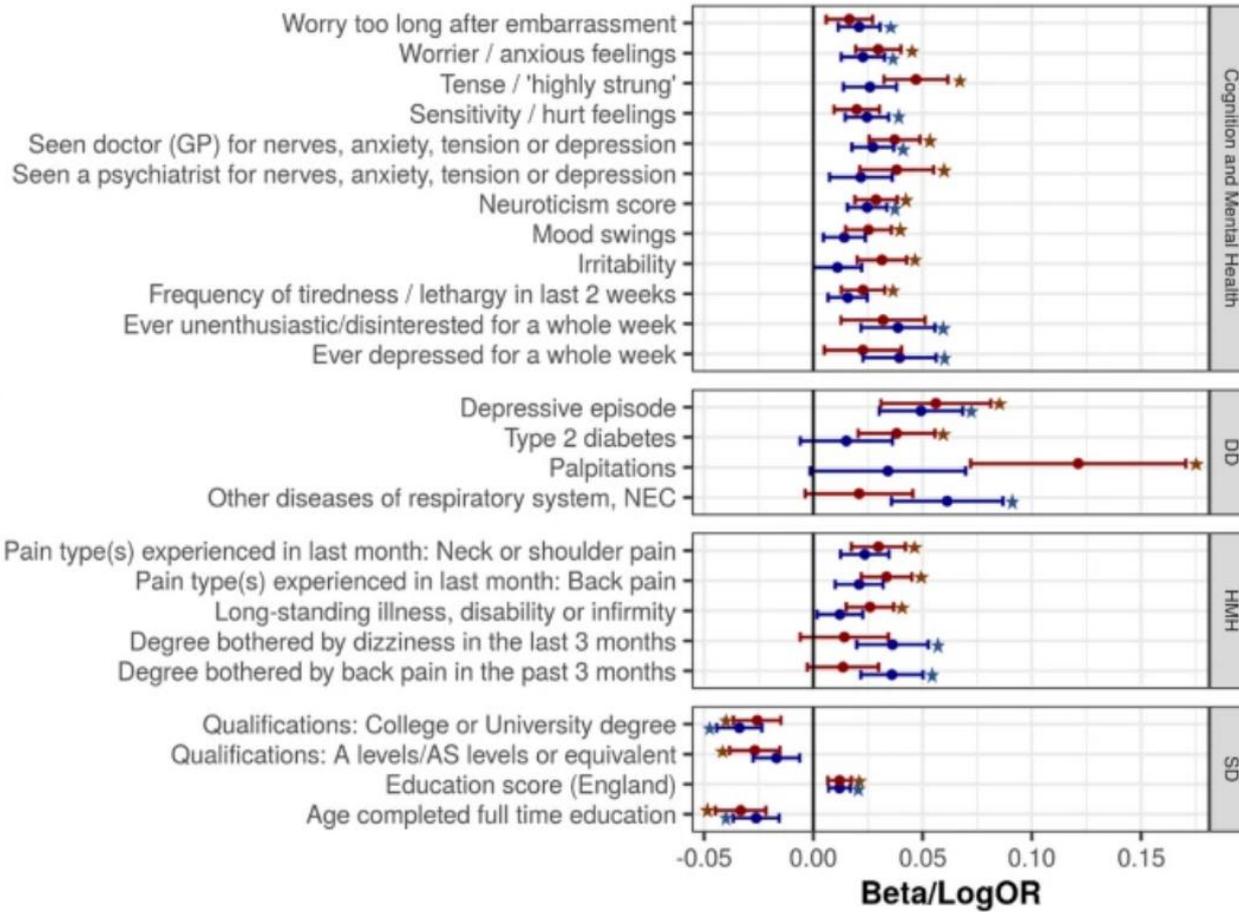
Associations between TS PRS and the Phenome



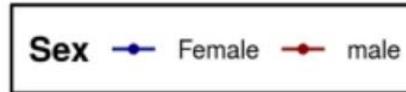
Significant associations – Biochemical measures, Cognition and Mental Health and disease diagnosis



Phenotypes



Male vs Female
PheWAS
comparisons



PheWAS Cross-disorder Comparisons

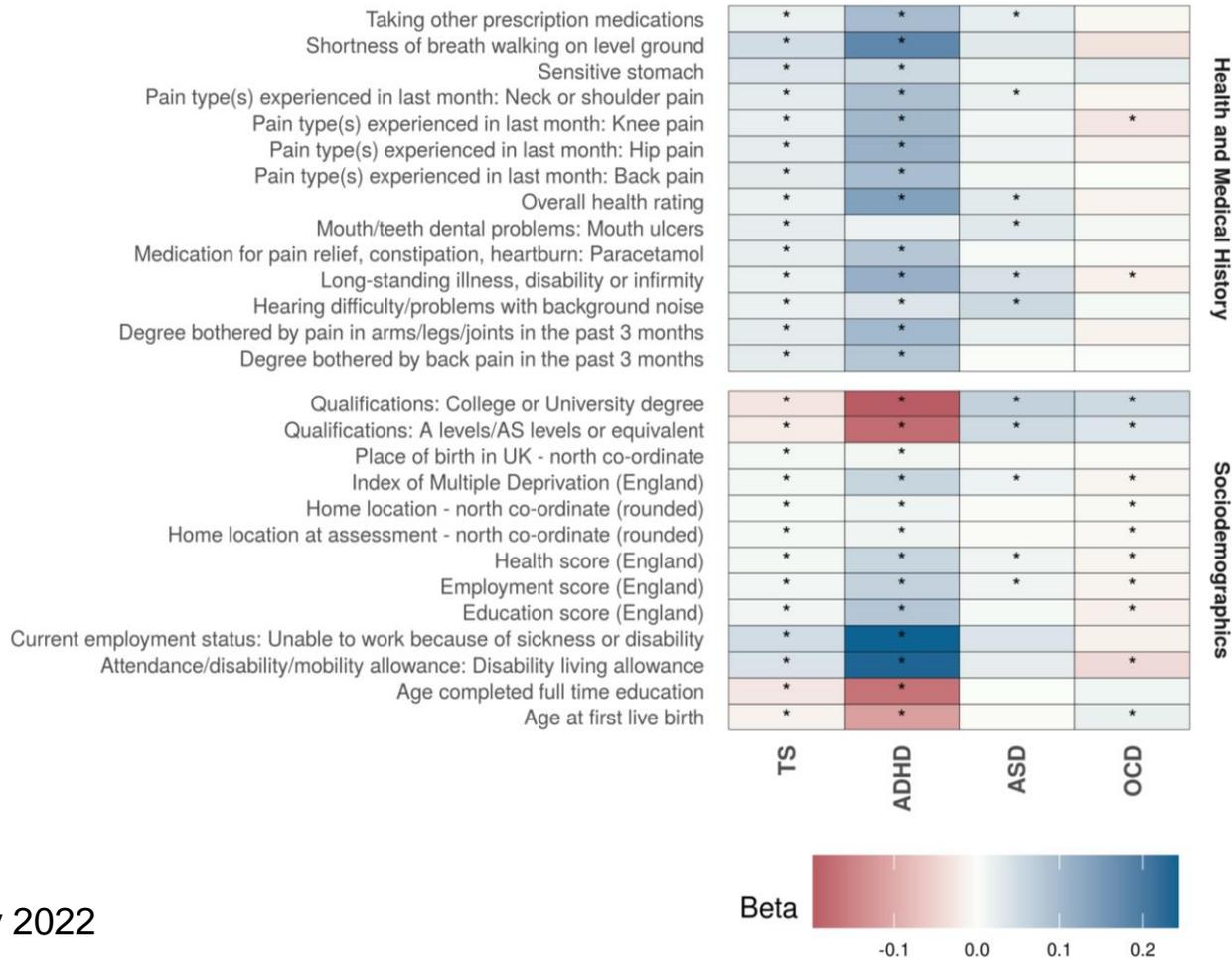


	TS	ADHD	ASD	OCD
Glycated haemoglobin (HbA1c)	*	*		
Worry too long after embarrassment	*		*	*
Worrier / anxious feelings	*		*	*
Tense / 'highly strung'	*	*	*	*
Substances taken for anxiety: Medication prescribed to you (for at least two weeks)	*	*	*	*
Sensitivity / hurt feelings	*	*	*	*
Seen doctor (GP) for nerves, anxiety, tension or depression	*	*	*	*
Seen a psychiatrist for nerves, anxiety, tension or depression	*	*	*	*
Physically abused by family as a child	*	*	*	
Neuroticism score	*	*	*	*
Nervous feelings	*		*	*
Mood swings	*	*	*	
Miserableness	*	*	*	
Irritability	*	*	*	*
Frequency of tiredness / lethargy in last 2 weeks	*	*	*	
Frequency of tenseness / restlessness in last 2 weeks	*	*	*	*
Fed-up feelings	*	*	*	
Ever unenthusiastic/disinterested for a whole week	*	*	*	
Ever suffered mental distress preventing usual activities	*	*	*	
Ever sought or received professional help for mental distress	*	*	*	*
Ever had prolonged loss of interest in normal activities	*	*	*	
Ever depressed for a whole week	*	*	*	

Depressive episode	*	*	*	
Type 2 diabetes	*	*	*	*
Peripheral enthesopathies and allied syndromes	*	*		
Palpitations	*	*		
Other diseases of respiratory system, NEC	*	*		
Back pain	*	*		
Anxiety disorder	*	*		*
Abdominal pain	*	*		

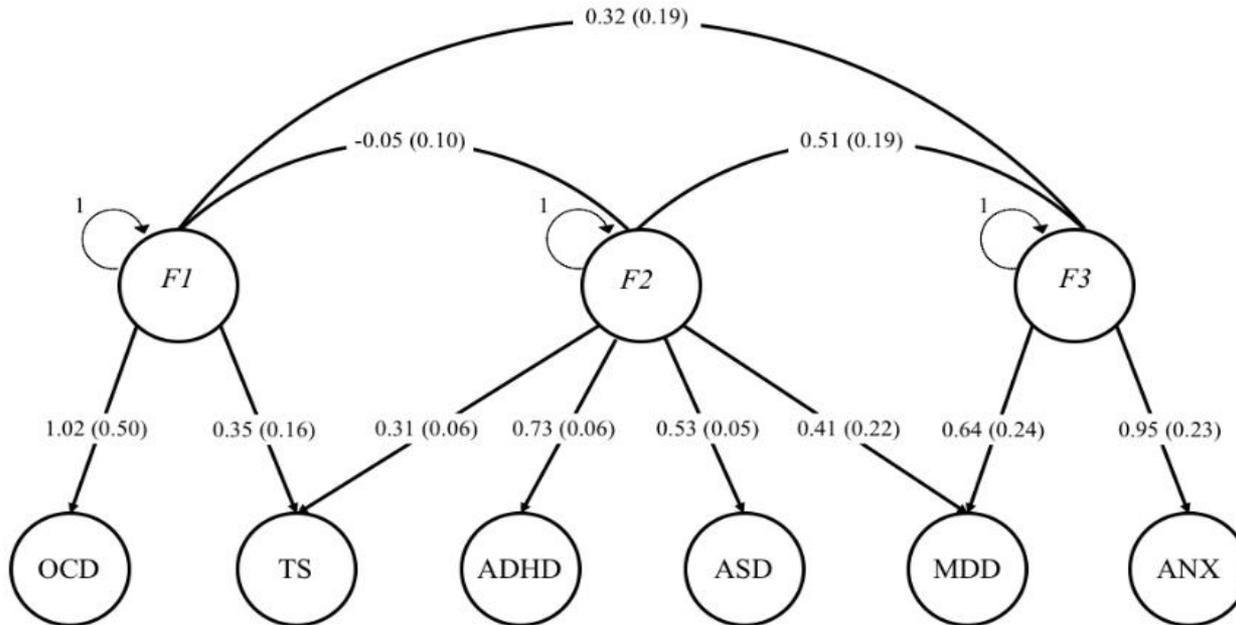
	TS	ADHD	ASD	OCD		
	*	*			BM	
	*		*	*	Cognition and Mental Health	
	*		*	*		
	*	*	*	*		
	*	*	*	*		
	*	*	*	*		
	*	*	*	*		
	*	*	*	*		
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	*	*	*	*		
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	*	*	*	*		
	*	*	*	*		Disease Diagnosis
	*	*	*	*		
	*	*				
	*	*				
	*	*		*		
	*	*				

PheWAS Cross-disorder Comparisons



Genetic architecture of TS correlated disorders

Cross-disorder genetic architecture based on exploratory factor analysis.



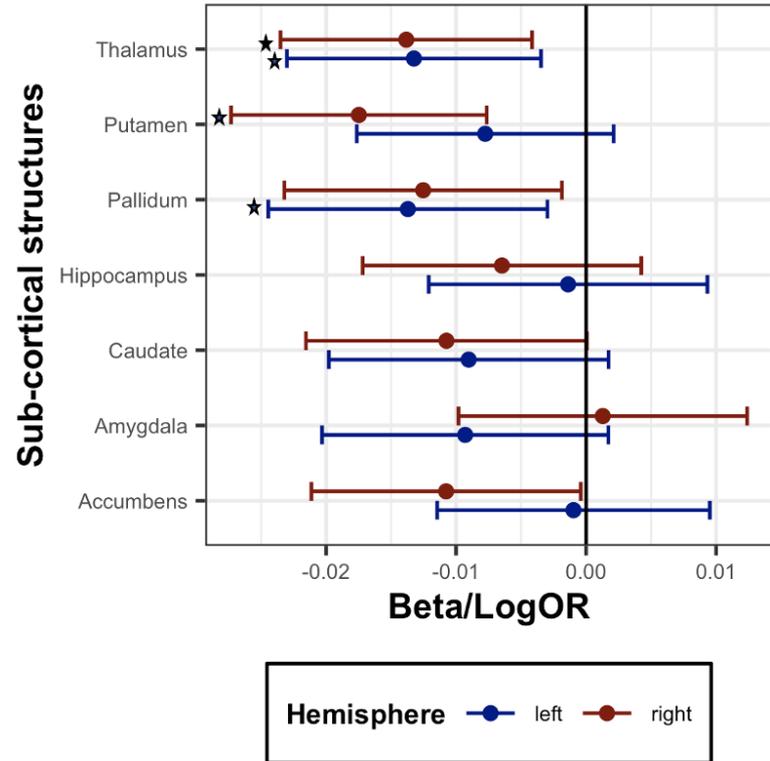
Zhiyu Yang

TS genetic risk vs brain volumes in UK Biobank (30,000 individuals)

- We observed that increase in the genetic risk of TS was associated with decrease in right putamen and left pallidum volumes.
- Significant associations were also observed between PRS_{TS} and bilateral thalamic volume

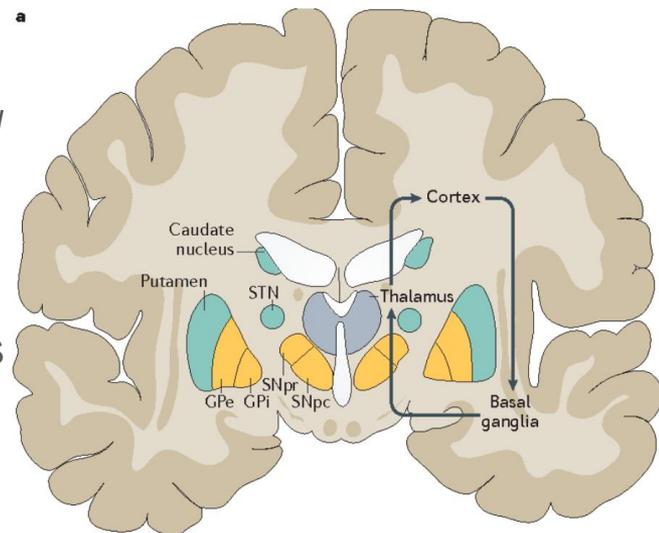


Pritesh Jain

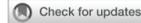


TS neuroimaging studies to date

- TS neuroimaging studies to date: on average 30 patients/30 controls
- Reduced prefrontal cortical thickness in patients with TS (eg Draganski et al 2010, Fahim et al 2010, Müller-Vahl et al 2009, Sowell et al 2008, Worbe et al 2010)
- Structural alterations involving most brain structures associated with sensorimotor processing (reviewed in Worbe et al. 2015)
- Largest study to date: 103 TS patients and 103 controls (Greene et al 2017):
 - smaller white matter volume bilaterally in orbital and medial prefrontal cortex
 - larger gray matter volume in posterior thalamus, hypothalamus, and midbrain in TS patients
- TS rsfMRI studies: reduced long-range connectivity and increased short distance connectivity associated with motor processing (Church et al 2008, Worbe et al 2012)



Robertson et al. 2017



OPEN ACCESS

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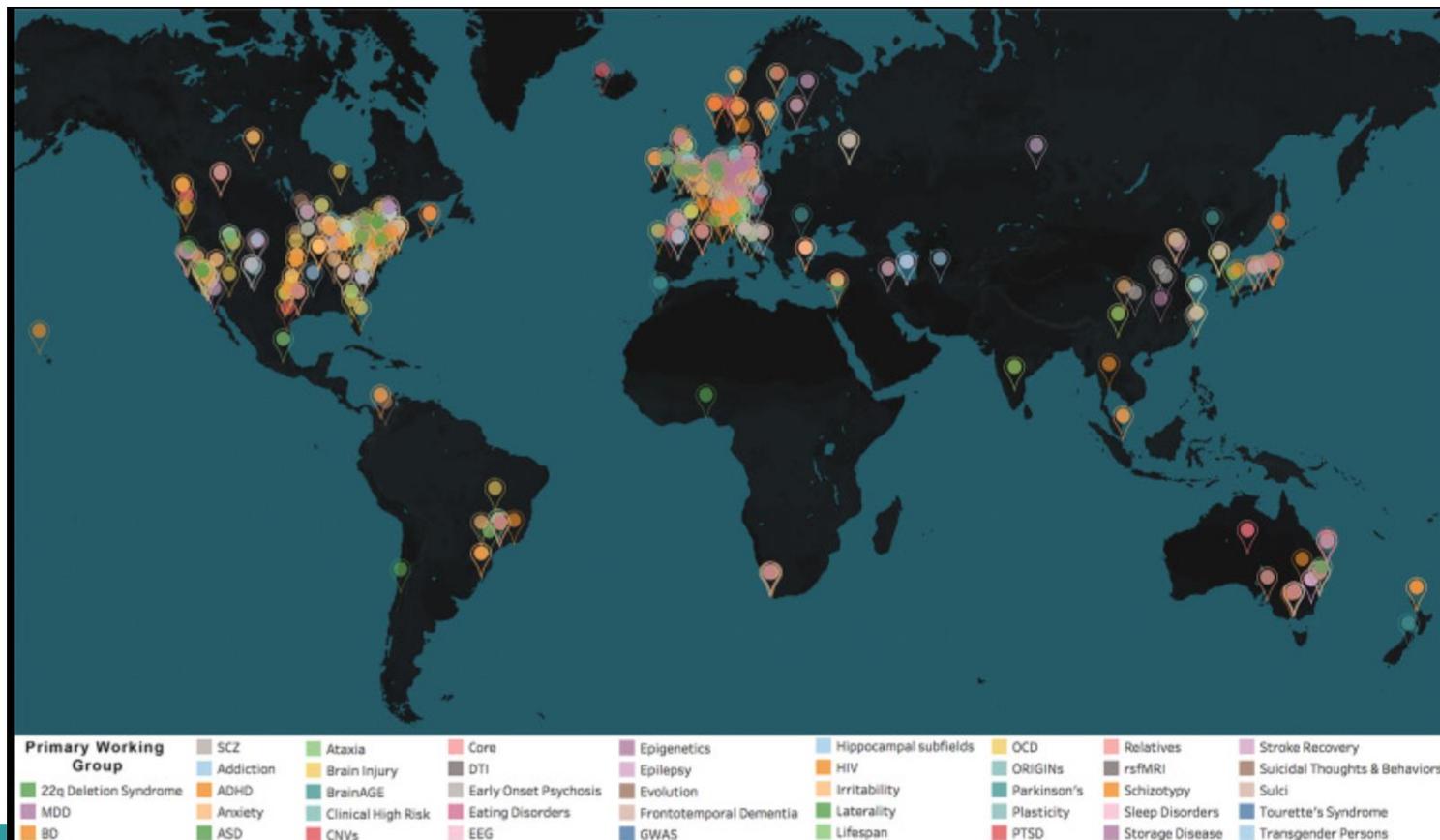
Enhancing neuroimaging genetics through meta-analysis for Tourette syndrome (ENIGMA-TS): A worldwide platform for collaboration

Peristera Paschou^{1*}, Yin Jin¹, Kirsten Müller-Vahl²,
Harald E. Möller³, Renata Rizzo⁴, Pieter J. Hoekstra⁵,
Veit Roessner⁶, Nanette Mol Debes⁷, Yulia Worbe⁸,
Andreas Hartmann⁹, Pablo Mir^{10,11}, Danielle Cath⁵,
Irene Neuner^{12,13,14}, Heike Eichele¹⁵, Chencheng Zhang¹⁶,
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Federica Saia²⁹, Natalia Szejko²⁷, Renzo Torrecuso³,
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Tomasz Wolańczyk³², Jade-Jocelyne Zouki²⁰, Pritesh Jain¹,
Apostolia Topaloudi¹, Mary Kaka¹, Zhiyu Yang¹,
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Jan Buitelaar²⁴, Barbara Franke²⁴, Odile van den Heuvel³⁹,
Neda Jahanshad³⁴, Paul M. Thompson³⁴ and Kevin J. Black²²
on behalf of the ENIGMA-TS Working Group



ENIGMA – Enhancing Neuroimaging Genetics through meta-analysis

1,400 investigators across 43 countries – 50 WGs – 26 brain disorders



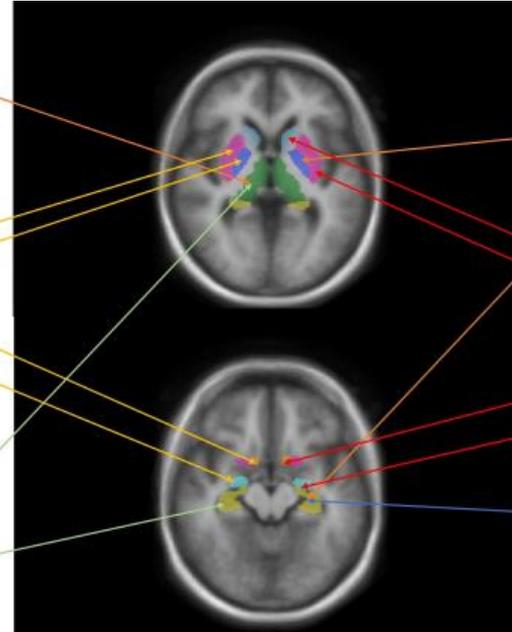
ENIGMA Working Groups related to TS

- **ENIGMA-OCD:**
 - 5,423 individuals - 30 sites
- **ENIGMA-ADHD:**
 - 4,180 individuals - 36 sites.
- **ENIGMA-ASD:**
 - 3,222 individuals - 51 sites
- **ENIGMA-MDD:**
 - 10,327 individuals – 35 sites
- **ENIGMA-AXD:**
 - analysis launching - more than 100 unique datasets from 16 countries

Children with OCD
Thalamus ↑
(Boedhoe et al. 2017)

ASD
Putamen ↓
Pallidum ↓
Accumbens ↓
Amygdala ↓
(Van Rooij et al. 2019)

Children with TS
Thalamus ↑
Hypothalamus ↑
Hippocampus ↑
(Greene et al. 2016
Kim et al. 2020)



Adults with OCD
Pallidum ↑
Hippocampus ↓
(Boedhoe et al. 2017)

Children with ADHD
Caudate ↓
Putamen ↓
Accumbens ↓
Amygdala ↓
(Hoogman et al. 2017)

MDD
Hippocampus ↓
(Schmaal et al. 2016)



ENIGMA-TS

- Bring together TS research groups to share neuroimaging and genetic databases
- Identify brain regions and brain circuits that are involved in the neurobiology of TS and investigate how these relate to genomic background.
 - Identify predictive biomarkers
 - Define heritable sub-phenotypes
 - Perform cross-disorder comparisons
- So far – 23 sites, 12 countries (USA, France, Germany, Netherlands, Norway, Poland, Spain, Denmark, Italy, UK, Australia, China)
- T1 datasets from ~1000 patients and ~1000 controls

*Yin
Jin*



ENIGMA-TS: Building our database

Different options for participation/data sharing

- Perform FreeSurfer processing/QC and run statistical analyses at your home site. Then transfer meta-data for centralized meta-analysis.
- Perform FreeSurfer processing/QC then transfer individual level summary data (cortical/subcortical ROI .csv's) to data analysis site for a mega-analysis
- Send raw MRI data via a secure FTP protocol and receive FreeSurfer output and visual quality control back for your own future projects



Site Name	Cases contributed	Controls contributed	Cases expected	Controls expected	Total
Deakin University	10	12	10	12	34
Department of pediatrics, Herlev University Hospital, Denmark					
Instituto de Biomedicina de Sevilla	19	93	19	93	205
Ludwig-Maximilians-University of Munich					
University Lübeck	22	36	22	36	58
Hannover University					
Max Planck Institute for Human Cognitive and Brain Sciences			200	200	400
Medical University of Warsaw					
Medical University of Warsaw					
Pitié-Salpêtrière Hospital			60	60	120
RWTH Aachen University	48	36	48	36	120
Shanghai Research Center for Brain Science	20	40	20	40	60
University of Southampton	11	11			22
University of Bergen, Norway			57	35	92
University of Catania, Italy	30	30	30	30	60
University Hospital Dresden (Scanned in Göttingen)(3D T1-weighted MRI only)	44	44	44	44	88
University Hospital Dresden	20	27	20	27	47
University Medical Center Groningen, Groningen, Netherlands	57	57	57	57	114
VU University medical center (VUmc) Amsterdam	25	22	25	22	47
Wake Forest School of Medicine					
Washington University in St. Louis	17	170	500	500	1000
University of Toronto					
University of Rome	15	15	15	15	30
	338	593	1127	1207	2497

ENIGMA-TS: 23 sites – 12 countries

K. Müller-Vahl; Hannover Medical School, Germany
R. Rizzo, F. Saia, S. Palmucci, A. Prato; University of Catania, Italy

N. Mol Debes; Herlev University Hospital, Denmark

V. Roessner, A. Uhlmann; TU Dresden, Germany

J. Verrel, T. Paulus, Alexander Münchau; University of Lübeck, Germany

Y. Worbe, A. Hartmann; Pitié-Salpêtrière, France

R. Musil, Eva Hoffer; Ludwig-Maximilians-University of Munich, Germany

I. Neuner; S. Ramkiran; RWTH Aachen University, Germany

V. Brandt; University of Southampton, UK

C. Ganos; Charité University Clinic Berlin, Germany

T. Silk, J. Zouki; Deakin University, Australia

H. Eichele; University of Bergen, Norway

H. Möller, R. Torrecuso, K. Müller; Max Planck Institute for Human Cognitive and Brain Sciences, Germany

O. van den Heuvel; VU University, Netherlands

P. Hoekstra, A. Dietrich; University of Groningen, Netherlands

S. Tommasin, G. Conte, F. Cardona; University of Rome

P. Mir, J. Martin-Rodriguez, M. Grothe; Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, University of Seville, Spain

K. Lewandowska, T. Wolanczyk, P. Janik, N. Szejko; Medical University of Warsaw, Poland

C. Hanlon; Wake Forest University Medical School, USA

C. Zhang, C. Chunguang; Shanghai Research Center for Brain Science and Brain-Inspired Intelligence, China

J. Buitelaar, B. Franke, N. Forde; Radboud University, Netherlands

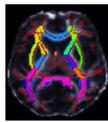
P. Thompson, N. Jahanshad, S. Thomopoulos; USC, USA

K. Black, E. Bihun, J. Koller; WUSTL, USA

Y. Jin, P. Jain, P. Drineas,

P. Paschou; Purdue University, USA





DIFFUSION MRI ANALYSES



FUNCTIONAL MRI PIPELINE: HALFPIPE

Facilitates reproducible analysis, preprocessing, single-subject & group analysis

<https://github.com/HALFPipe>

Developed by Lea Waller, Ilya Veer, Susanne Erk, Henrik Walter

MEG PIPELINE

https://github.com/jstout211/enigma_MEG

Developed by Jeff Stout, Anna Namyst, Allison Nugent

EEG PROTOCOLS

<http://enigma.ini.usc.edu/ongoing/enigma-eeeg-working-group/>

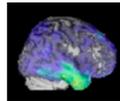
Developed by Dirk Smit & ENIGMA-EEG

CAT12

voxel- and surface-based morphometry, region-based measures

<http://neuro-jena.github.io/enigma-cat12>

Developed by Christian Gaser



VOXEL BASED MORPHOMETRY (VBM)

Automated pipeline to perform DARTEL VBM, QC steps and sensitivity analyses

<https://sites.google.com/view/enigmavbm>

Developed by Matthew Kempton

FREESURFER CORTICAL & SUBCORTICAL ANALYSES

+ Hippocampal, Amygdalar and Thalamic Subfields

FREESURFER LONGITUDINAL ANALYSES

Developed by ENIGMA-Plasticity WG

SULCAL SEGMENTATION

Segmentation and QC pipeline using FreeSurfer, BrainVISA, R and ImageMagick

Developed by Fabrizio Pizzagalli



CEREBELLAR & SPINAL CORD PIPELINES

Developed by ENIGMA-Ataxia WG



VERTEX WISE / SHAPE ANALYSES

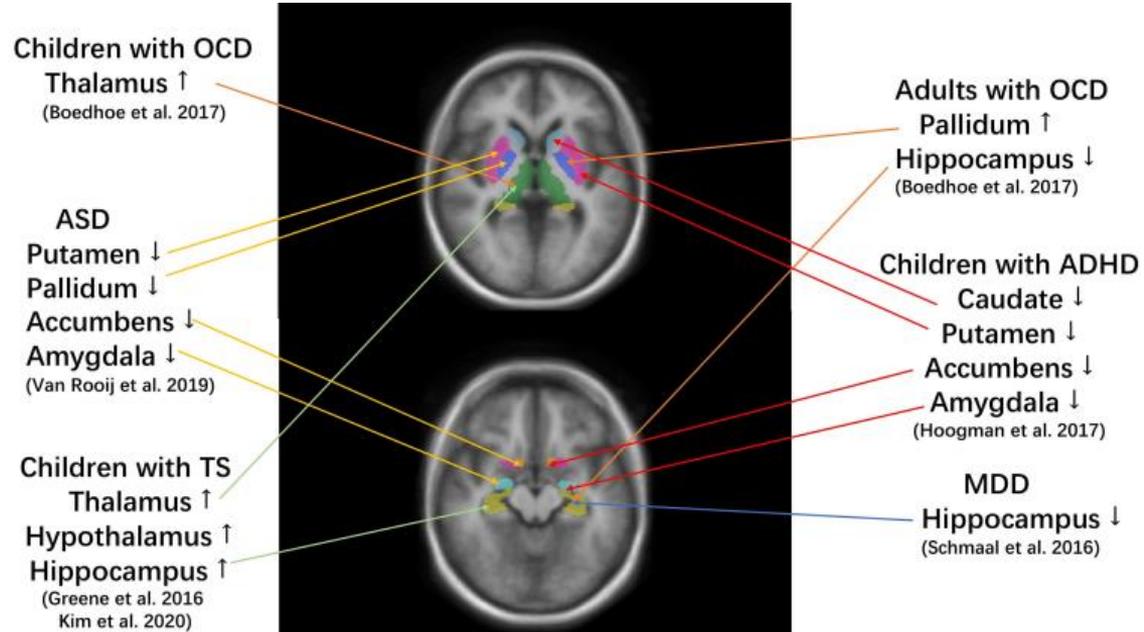
<http://enigma.ini.usc.edu/ongoing/enigma-shape-analysis>

Methods
used across
ENIGMA

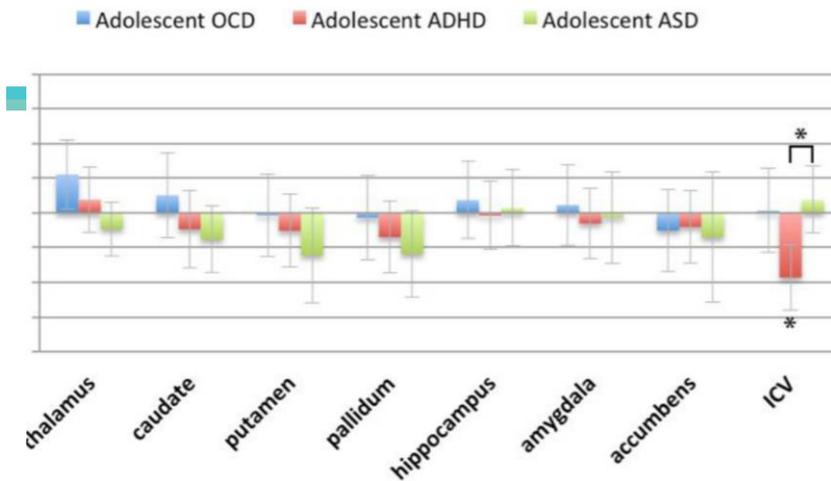
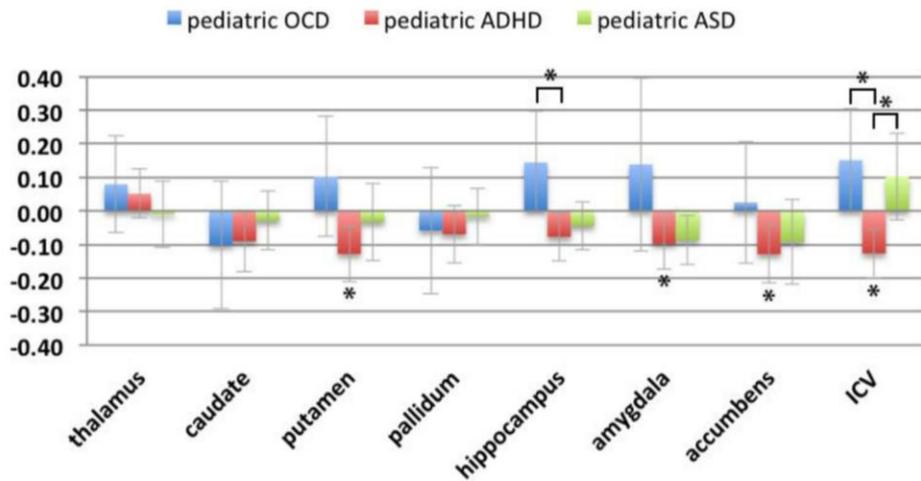


ENIGMA Working Groups related to TS

- **ENIGMA-OCD:**
 - 5,423 individuals - 30 sites
- **ENIGMA-ADHD:**
 - 4,180 individuals - 36 sites.
- **ENIGMA-ASD:**
 - 3,222 individuals - 51 sites
- **ENIGMA-MDD:**
 - 10,327 individuals – 35 sites
- **ENIGMA-AXD:**
 - analysis launching - more than 100 unique datasets from 16 countries



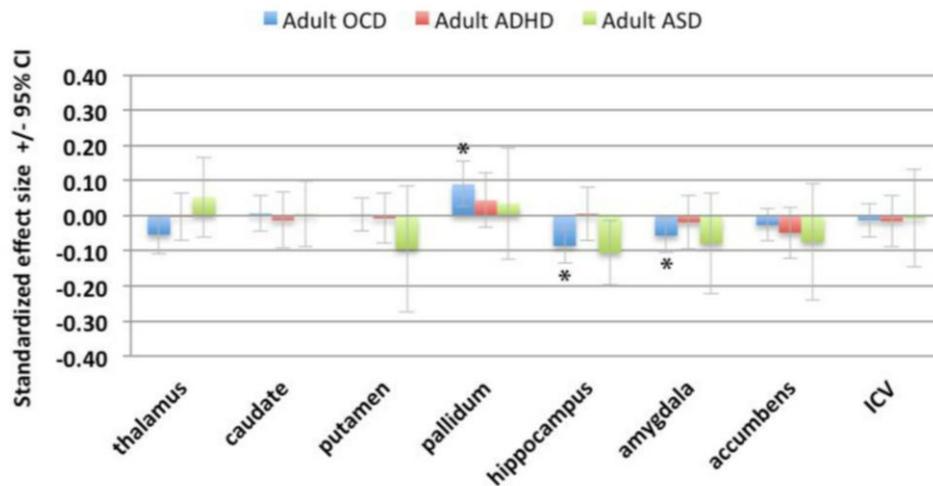
Standardized effect size +/- 95% CI



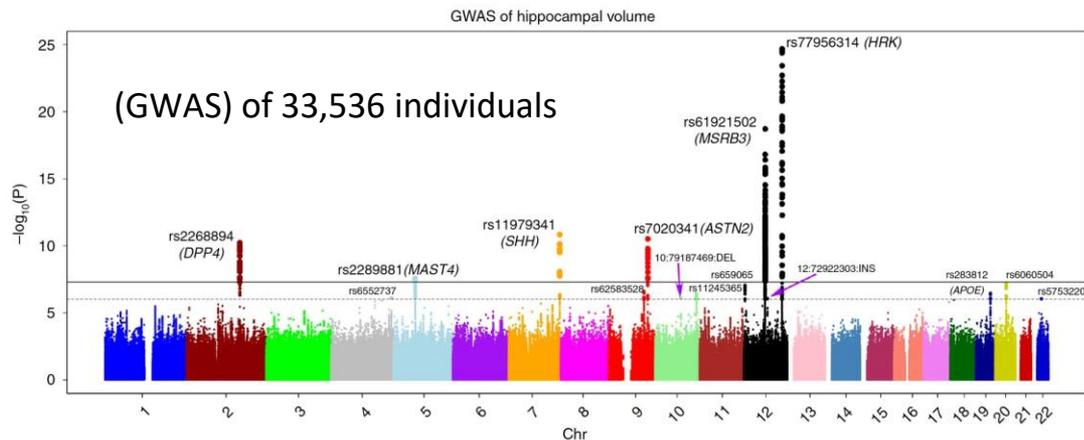
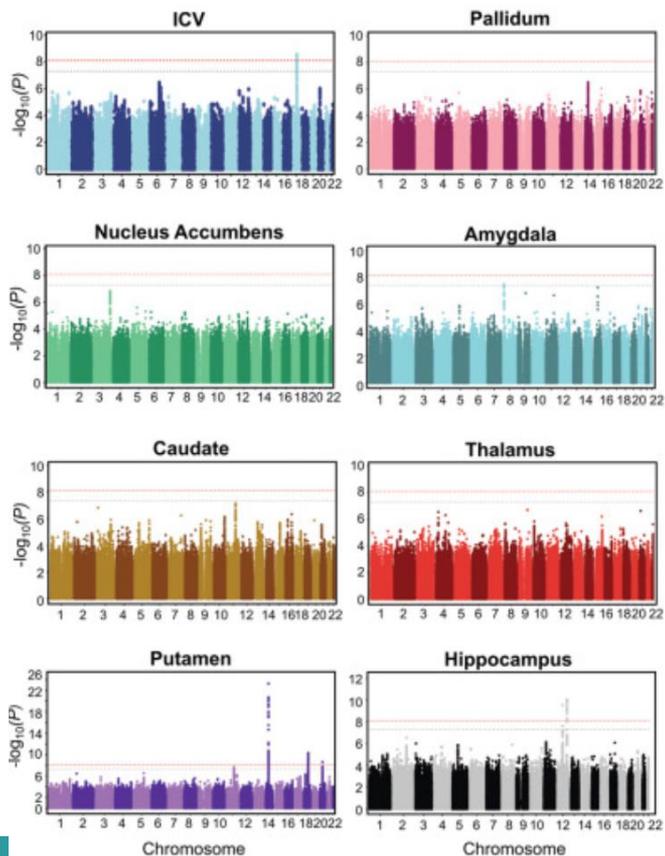
ENIGMA ADHD-ASD-OCD

Cross-disorder comparisons

Boedhe et al. Am J Psychiatry 2020



Genetic background of brain structure



Over 45 genetic loci associated with subcortical structure volumes (Hibar et al., Satizabal et al.) and over 200 genetic loci associated with cortical thickness and surface area (Grasby et al.).



CONCORDANCE OF GENETIC VARIATION THAT INCREASES RISK FOR TOURETTE'S DISORDER AND INFLUENCES ITS UNDERLYING NEUROCIRCUITRY

- Summary statistics for genome-wide association studies (GWASs) of TS from the PGC-TS and of subcortical volumes from the ENIGMA consortium.
- SECA revealed significant pleiotropy between TS, putamen, and caudate volumes, independent of direction of effect, and significant concordance between TS and lower thalamic volume.
- LDSR showed association between TS and thalamus volume.



*Dan Stein
University of Cape Town*

Mufford et al. 2019, Translational Psychiatry



Exploring effect of TS SNPs on brain volume

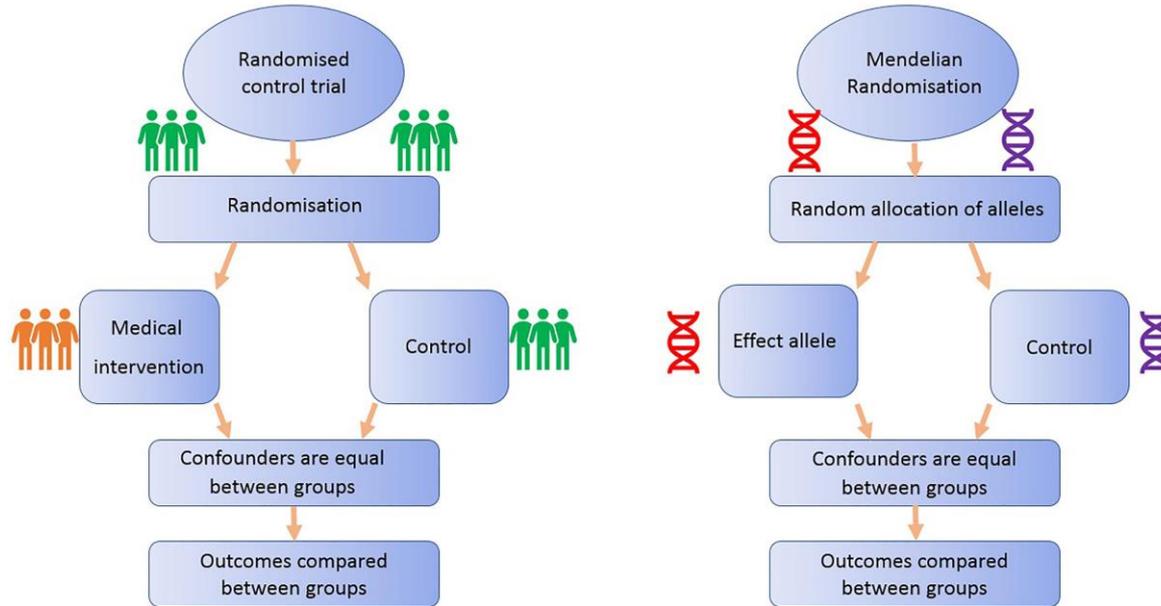
Brain regions	Pleiotropy P value	Concordance P value	Direction
Accumbens	0.004*	1	NEGATIVELY
Brainstem	0.012 *	0.16	NEGATIVELY
Caudate	0.004 *	1	NEGATIVELY
Putamen	0.00999*	1	NEGATIVELY

SNP effect and concordance
analysis – Most recent
TSGWAS 3



*Yin
Jin*

Mendelian randomization can help reveal causality of association.



Multiomic approach and Mendelian randomization analysis identify causal associations between blood biomarkers and subcortical brain structure volumes

Data type	Dataset	N
Exposures	Plasma Proteome (3301 Europeans)	2994
	Metabolome (7824 Europeans)	237
	Microbiome (18340 Trans-ancestry)	104
Outcomes	Brain volume (30717 Europeans)	7

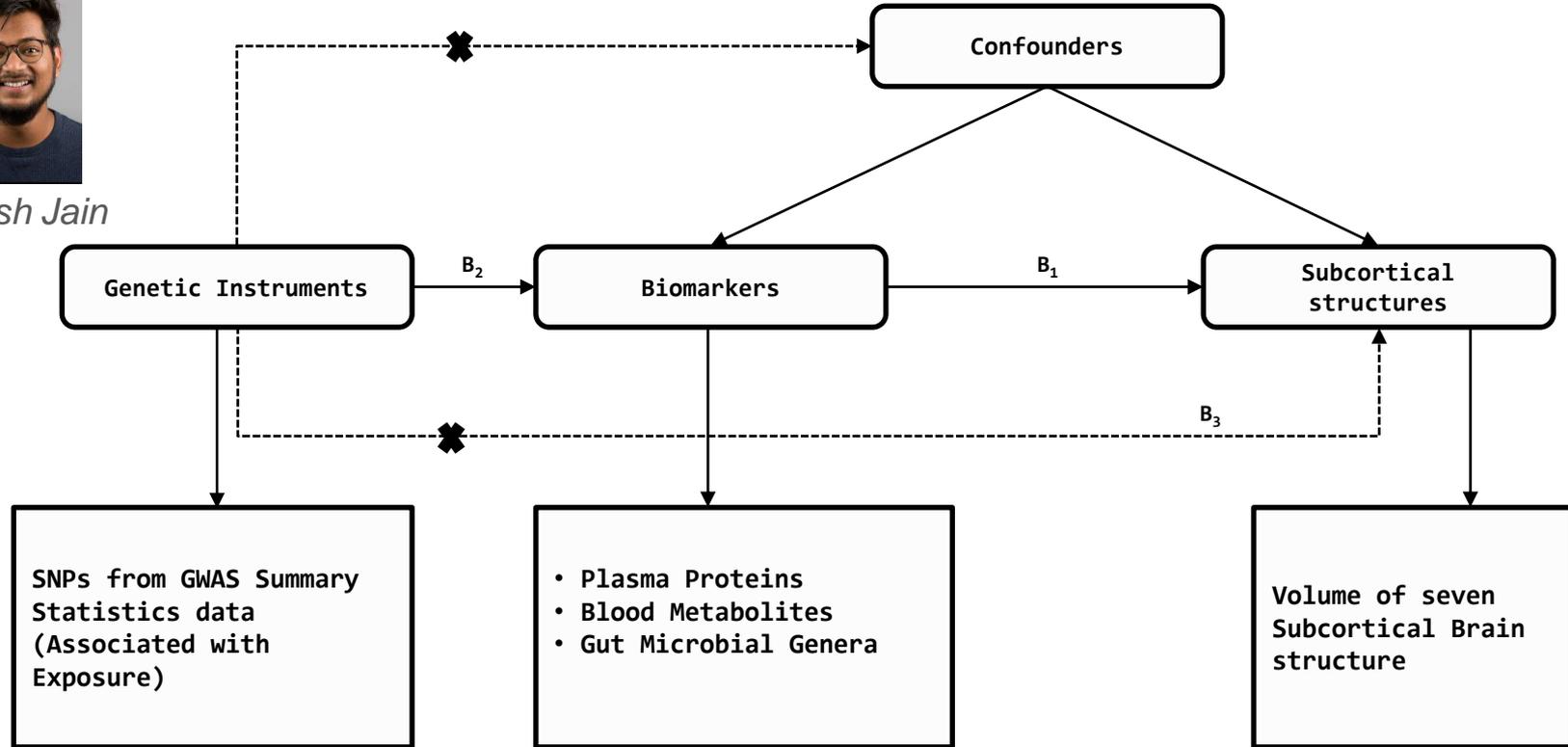


Pritesh Jain

Mendelian Randomization using Summary Statistics



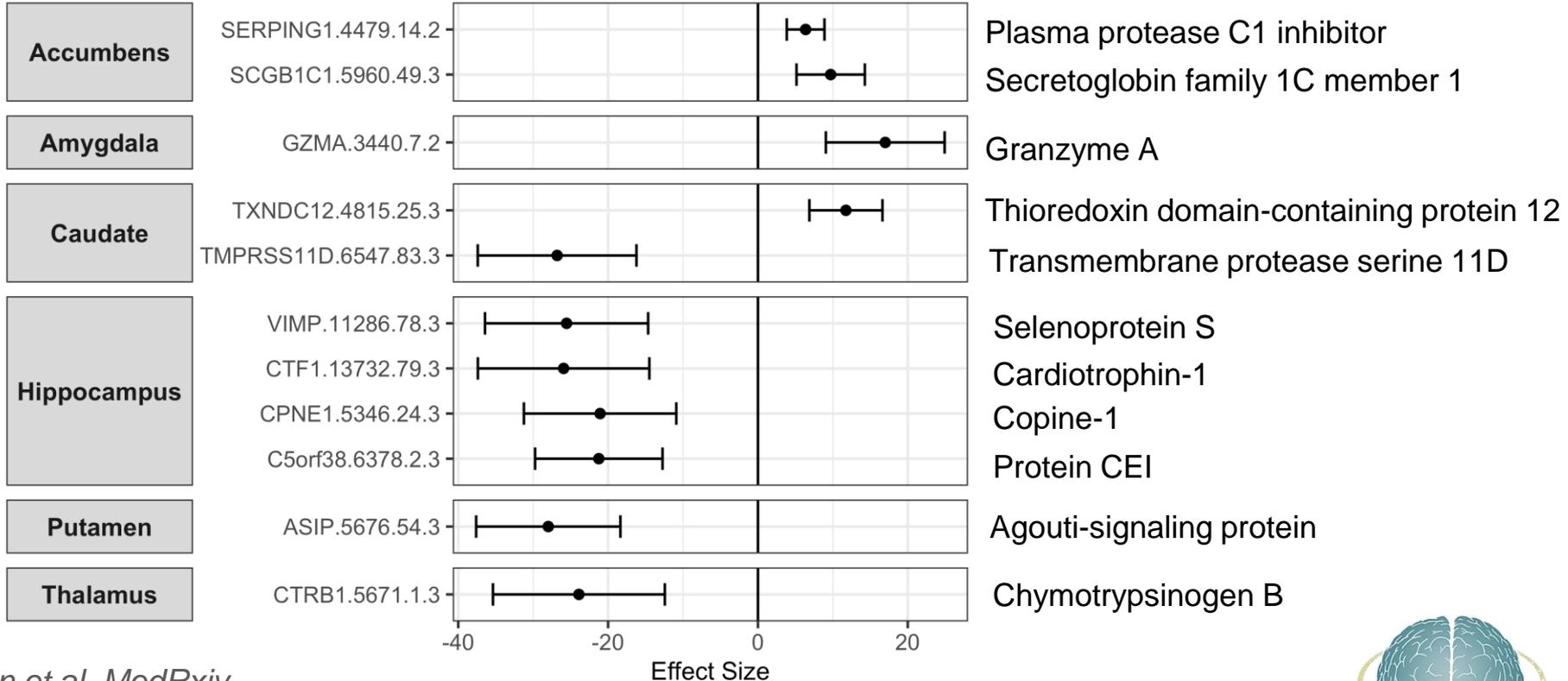
Pritesh Jain



$$B_1 = B_3 / B_2 \quad (B_2 \text{ and } B_3 \text{ obtained from GWAS Sumstats})$$



Proteome and Brain Volume



Proteome and Brain Volume

SERPING1

- previously found to be associated with influencing frontal cortical thickness.
- The nucleus accumbens has been an important brain region for regulating behaviors related to schizophrenia, depression

GZMA,

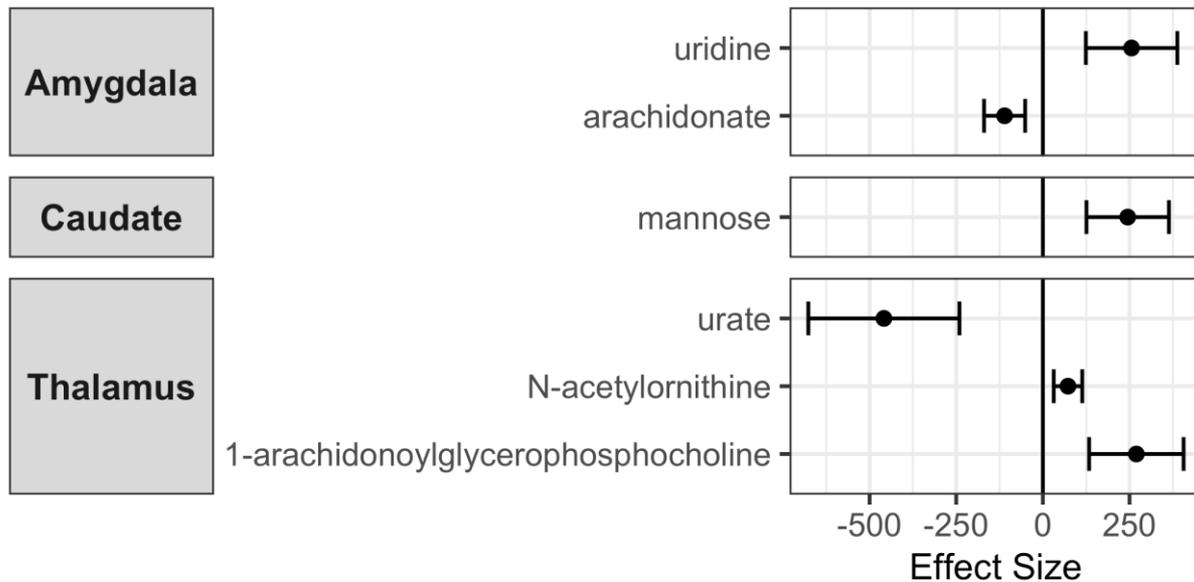
- lower expression in patients with major depressive disorder (MDD) compared to healthy controls.
- Patients with MDD also tend to have decreased amygdala volume

TXNDC12

- role of Trx-mediated oxidative stress in Parkinson's disease-associated dopaminergic neuron degeneration (caudate).
- Changes in caudate volume have been found to be associated with disorders such as anorexia and Parkinson's disease
- Copine-1: neuronal progenitor cell differentiation and induces neurite outgrowth
- Cardiotrophin-1: differentiation of neuronal stem cells
- Selenoprotein: mammalian brain development and other functions such as antioxidant protection and synaptic signaling.



Metabolome and Brain Volume



Identifying the potential mediators of brain structure changes in neuropsychiatric disease

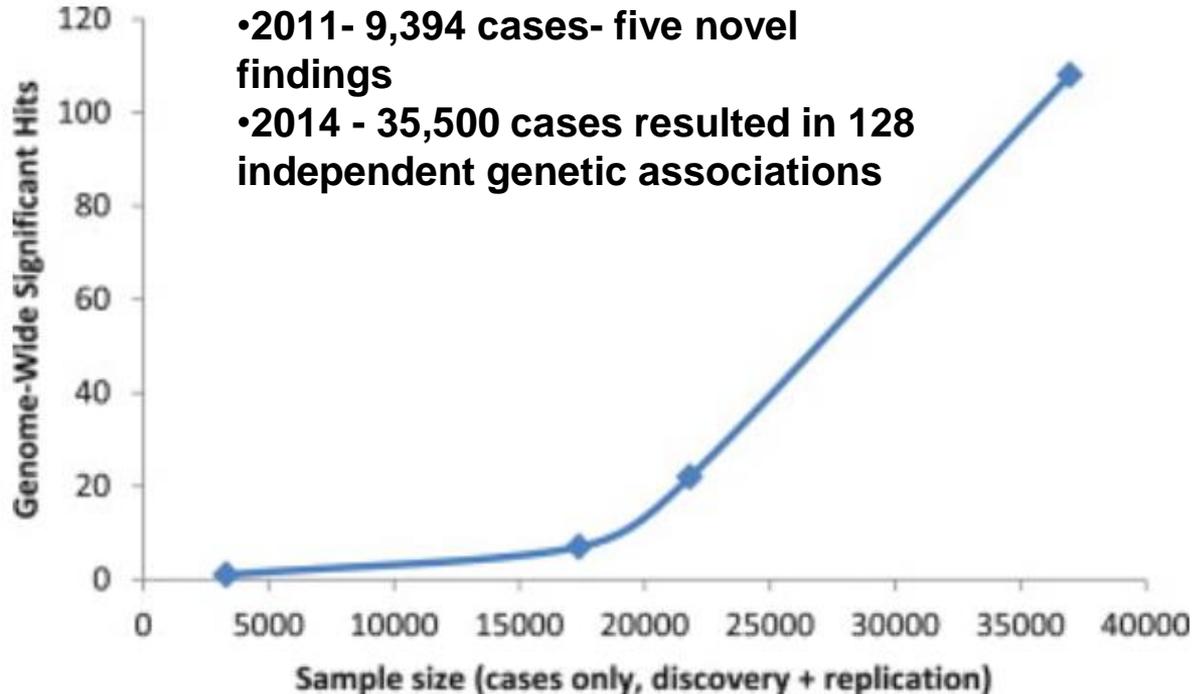
- Two Sample MR analysis identified eleven plasma proteins and six metabolites having a putative causal association with sub-cortical brain structure volumes.
- Many of these biomarkers have been found to be associated with neurological disorders and can explain how the brain volume is influenced in these conditions
- These biomarkers should be validated using animal model studies and can potentially be used as diagnostic markers or novel treatment targets.
- The study can be extended to look at epigenomic data such as methylation and acetylation as well.

ENIGMA-TS: Current status and next steps

- Building ENIGMA-TS database for meta and mega-analysis
- ENIGMA-TS pipelines available at the Paschou lab GitHub (https://github.com/Paschou-Lab/ENIGMA_TS_T1_pipeline).
- As a first goal, the group is pursuing joint analysis for cortical and subcortical volumes. Sharing of csv's with subject level summary values (but no images) is the fastest way to proceed in most cases.
- Initial analyses plan
 - Structural data – cortical and subcortical structures in TS patients
 - Comparison to ADHD, OCD, ASD, MDD, AXD findings
 - Genetic correlation
 - Analysis in Generation R and ABCD cohorts



PGC - Genome-Wide Association Studies of Schizophrenia



After the point of 13,000 cases the rate of new findings increased rapidly by about four independent associations per 1,000 new cases.

Bringing together all TS genetics consortia!

NINDS R01 (MPIs: Paschou, Scharf, Mathews)



**Tourette Association of America
International Consortium for Genetics**



**Tourette Syndrome Genetics
The Southern and Eastern Europe Initiative
TSGeneSEE**



**COST ACTION BM0905
European Network for the
Study of Gilles de la Tourette
Syndrome**



**Nordic
OCD &
Related
Disorders
Consortium**



**Danish
OCD &
Tic
Study**



**TS+EUROTRAIN
Marie Curie
Initial Training Network**





**Tourette Syndrome
Association International
Consortium for Genetics**



TSGeneSEE



EUNetGTS

**European Network for the Study of
Gilles de la Tourette Syndrome**



**European Cooperation in
Science and Technology**



**European Society for the
Study of Tourette Syndrome**



**European Union
European Social Fund**



**MINISTRY OF EDUCATION & RELIGIOUS AFFAIRS, CULTURE & SPORTS
MANAGING AUTHORITY**

Co-financed by Greece and the European Union



**Tourette Association of
America**



Thank you!



ENIGMA-TS



PGC



EMTICS

TS-EUROTRAIN



Genetic architecture of TS correlated disorders

Pairwise genetic correlation across
TS, OCD, ADHD, ASD, ANX, MDD
(LD score regression, *statistically significant).

	ADHD	ASD	OCD	TS	ANX	MDD
ADHD	1	* 0.35	-0.17	* 0.26	0.33	* 0.54
ASD		1	0.12	0.18	0.28	* 0.41
OCD			1	* 0.38	0.35	* 0.22
TS				1	0.19	* 0.25
ANX					1	* 0.83
MDD						1



Zhiyu Yang

Significant associations – Health and medical history, Socio-demographics

