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Genetics of ADHD – risk loci and genetic overlap with other phenotypes

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iPSYCH TIMESPAN ADHD across the Lifespan ECNP Network NOVO NORDISK FOUNDATION CENTER FOR GENOMIC MECHANISMS OF DISEASE AT BROAD INSTITUTE PGC Psychiatric Genomics Consortium

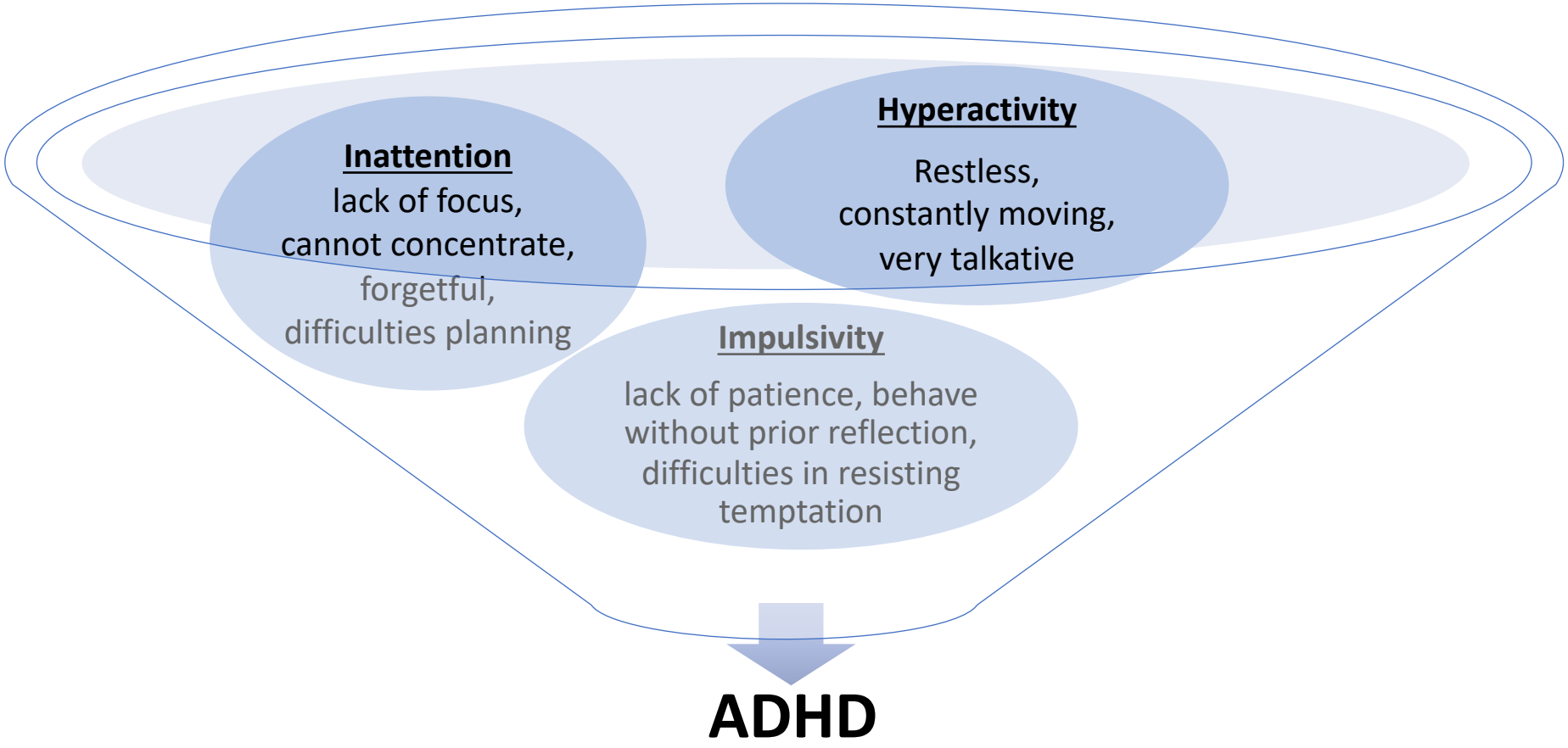
Outline

- The role of common genetic variants in ADHD
- The role of rare genetic variants in ADHD
- Genetic heterogeneity among ADHD subgroups
- Polygenic architecture of childhood maltreatment across psychiatric disorders

iPSYCH

ADHD – core symptoms

Attention-deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder affecting 5% of children and around 2.5% of adults



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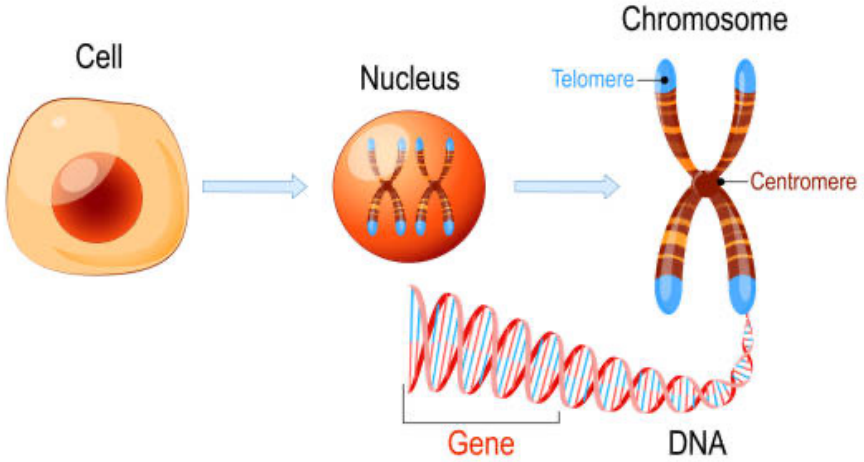
ADHD is strongly influenced by genetics

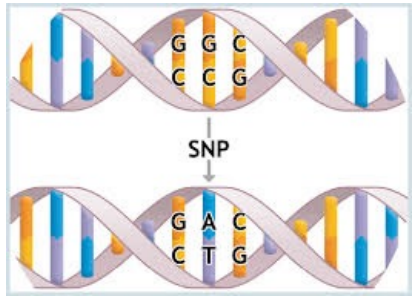
- the twin heritability has been estimated to 0.74

(Faraone and Larsson Molecular Psychiatry 2019)

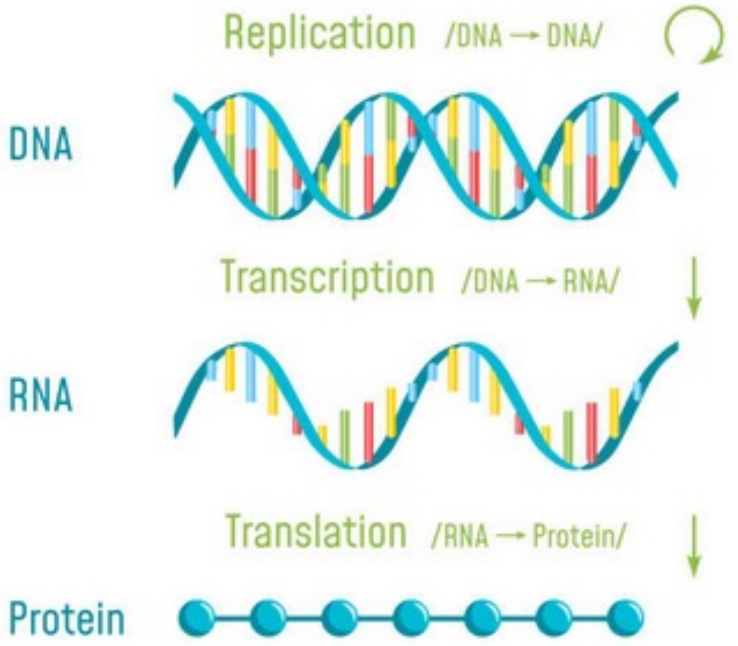
iPSYCH

From DNA to protein





An example of a genetic variant
(Single nucleotide polymorphism (SNP)
enkelt base substitution)



Genetic variants involved in ADHD

Genome-wide association studies (GWAS)

Common genetic variants
(variants with small effect on disease)

+

Whole-exome/genome sequencing

Rare genetic variants
(variants with larger effect on disease)

+

Whole-exome/genome sequencing

De novo mutations
(variants with larger effect on disease)

iPSYCH

Lundbeck Foundation Initiative for Integrative Psychiatric Research

- Nationwide population-based case-cohort with genetic information on 140,000 individuals
- Includes practically all born in Denmark from 1981-2008 that are diagnosed with at least one of 6 major psychiatric disorders
- 50,000 controls

iPSYCH PIs: Anders Børglum, Ole Mors, David Hougaard, Preben Bo Mortensen, Merete Nordentoft, Thomas Werge

Biological samples from individuals in the iPSYCH cohorts were obtained from the Newborn Screening Biobank at Statens Serum Institute

iPSYCH

The role of common genetic variants in ADHD

Genome-wide association studies (GWAS)

Common genetic variants
(variants with small effect on disease)

+

Whole-exome/genome sequencing

Rare genetic variants
(variants with larger effect on disease)

+

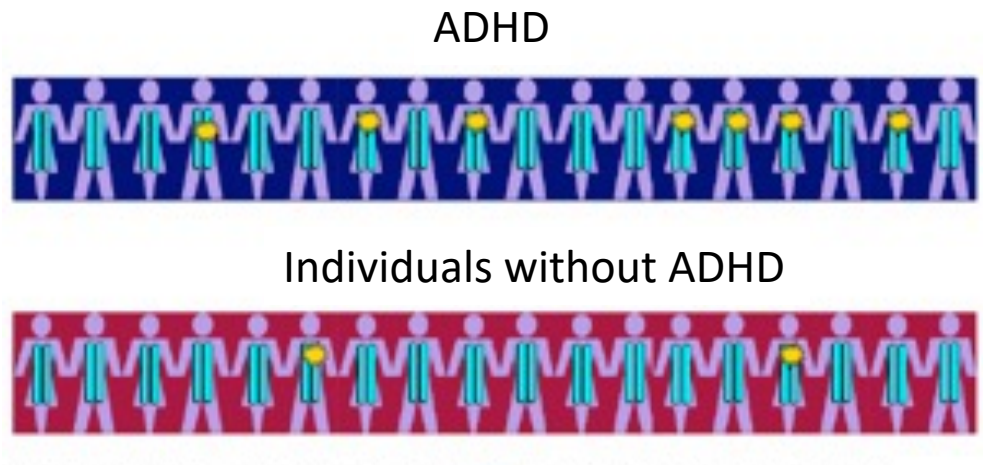
Whole-exome/genome sequencing

De novo mutations
(variants with larger effect on disease)

How do we find common genetic variants involveret i ADHD?

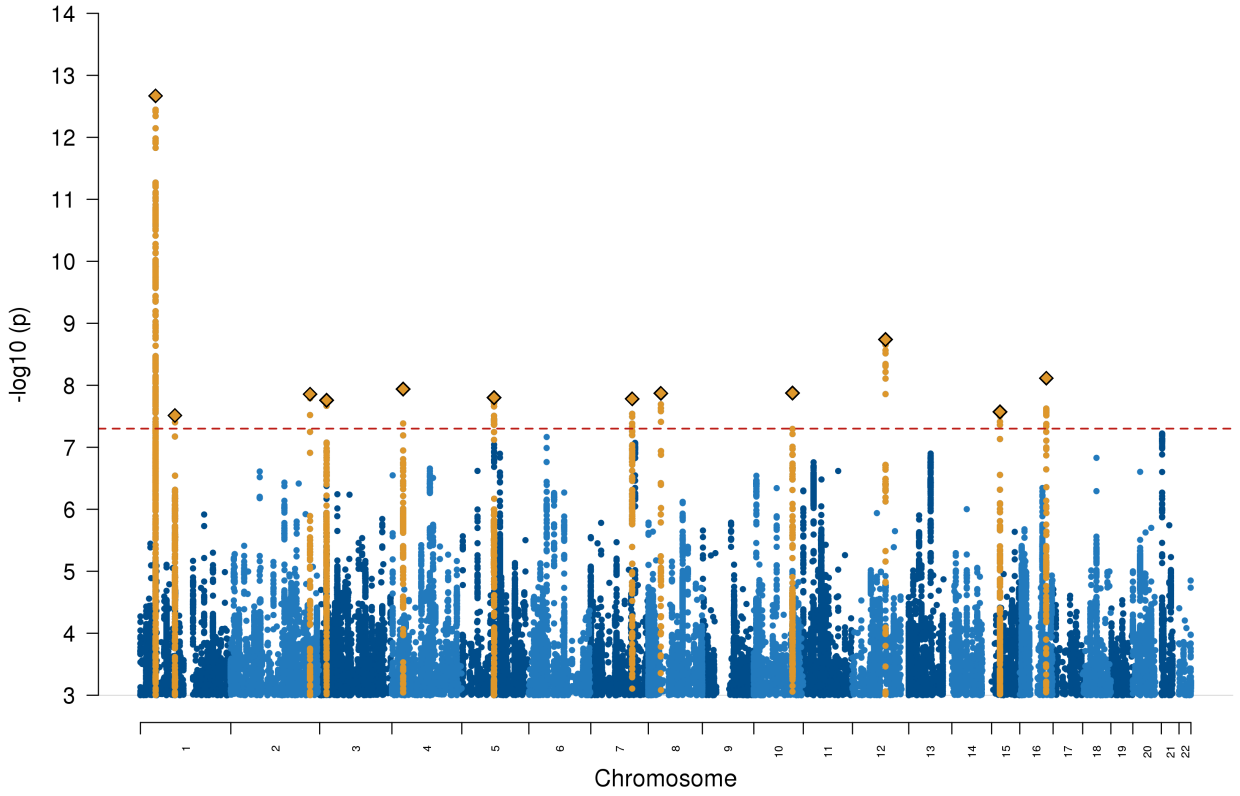
Genome-wide associations study (GWAS)

Genome-wide screening of around 8 million variants in thousands of individuals



Indentify variants that are seen more often in individuals with ADHD compared to thoses without

GWAS meta-analysis ADHD



P=5x10^{-8}

nature genetics ARTICLES
https://doi.org/10.1038/s41588-018-0269-7

Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder

Ditte Demontis[1,2,3,69], Raymond K. Walters[4,5,69], Joanna Martin[5,6,7], Manuel Mattheisen[1,2,3,8,9,10], Thomas D. Als[1,2,3], Esben Agerbo[1,11,12], Gísli Baldursson[13], Rich Belliveau[5], Jonas Bybjerg-Grauholm[1,14], Marie Bækvad-Hansen[1,14], Felecia Cerrato[5], Kimberly Chambert[5], Claire Churchhouse[4,5,15], Ashley Dumont[5], Nicholas Eriksson[16], Michael Gandal[17,18,19,20], Jacqueline I. Goldstein[4,5,15], Katrina L. Grasby[21], Jakob Grove[1,2,3,22], Olafur O. Gudmundsson[13,23,24], Christine S. Hansen[1,14,25], Mads Engel Hauberg[1,2,3], Mads V. Hollegaard[1,14], Daniel P. Howrigan[4,5], Hailiang Huang[4,5], Julian B. Maller[5,26], Alicia R. Martin[4,5,15], Nicholas G. Martin[21], Jennifer Moran[5], Jonatan Pallesen[1,2,3], Duncan S. Palmer[4,5], Carsten Bøcker Pedersen[1,11,12], Marianne Giørtz Pedersen[1,11,12], Timothy Poterba[4,5,15], Jesper Buchhave Poulsen[1,14], Stephan Ripke[4,5,27], Elise B. Robinson[4,28], F. Kyle Satterstrom[4,5,15], Hreinn Stefansson[23], Christine Stevens[5], Patrick Turley[4,5], G. Bragi Walters[23,24], Hyejung Won[17,18], Margaret J. Wright[29], ADHD Working Group of the Psychiatric Genomics Consortium (PGC)[30], Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium[30], 23andMe Research Team[30], Ole A. Andreassen[31], Philip Asherson[32], Christie L. Burton[33], Dorret I. Boomsma[34,35], Bru Cormand[36,37,38,39], Søren Dalsgaard[11], Barbara Franke[40], Joel Gelernter[41,42], Daniel Geschwind[17,18,19], Hakon Hakonarson[43], Jan Haavik[44,45], Henry R. Kranzler[46,47], Jonna Kuntsi[32], Kate Langley[7,48], Klaus-Peter Lesch[49,50,51], Christel Middeldorp[34,52,53], Andreas Reif[54], Luis Augusto Rohde[55,56], Panos Roussos[57,58,59,60], Russell Schachar[33], Pamela Sklar[57,58,59], Edmund J. S. Sonuga-Barke[61], Patrick F. Sullivan[6,62], Anita Thapar[7], Joyce Y. Tung[16], Irwin D. Waldman[63], Sarah E. Medland[21], Kari Stefansson[23,24], Merete Nordentoft[1,64], David M. Hougaard[1,14], Thomas Werge[1,25,65], Ole Mors[1,66], Preben Bo Mortensen[1,2,11,12], Mark J. Daly[4,5,15,67], Stephen V. Faraone[68,70*], Anders D. Børglum[1,2,3,70*] and Benjamin M. Neale[4,5,15,70*]

ADHD working group of the Psychiatric Genomics Consortium

12 genome-wide significant loci
20,183 individuals with ADHD and 35,191 controls,
~8 million genetic variants

Demontis et al. Nature Genetics 2019

New ADHD GWAS meta-analysis

iPSYCH1
14,584 ADHD cases,
22,492 controls

iPSYCH 2
7,880 ADHD cases
14,770 controls

Total iPSYCH1+2
22,464 ADHD cases
37,262 controls

+

deCODE Genetics
8,281 cases
137,993 controls

Bragi Walters

+

PGC
4,515 cases,
11,702 controls

Raymond Walters

=

Total
38,691 ADHD cases
186,843 controls

GWAS meta-analysis of ADHD

nature genetics

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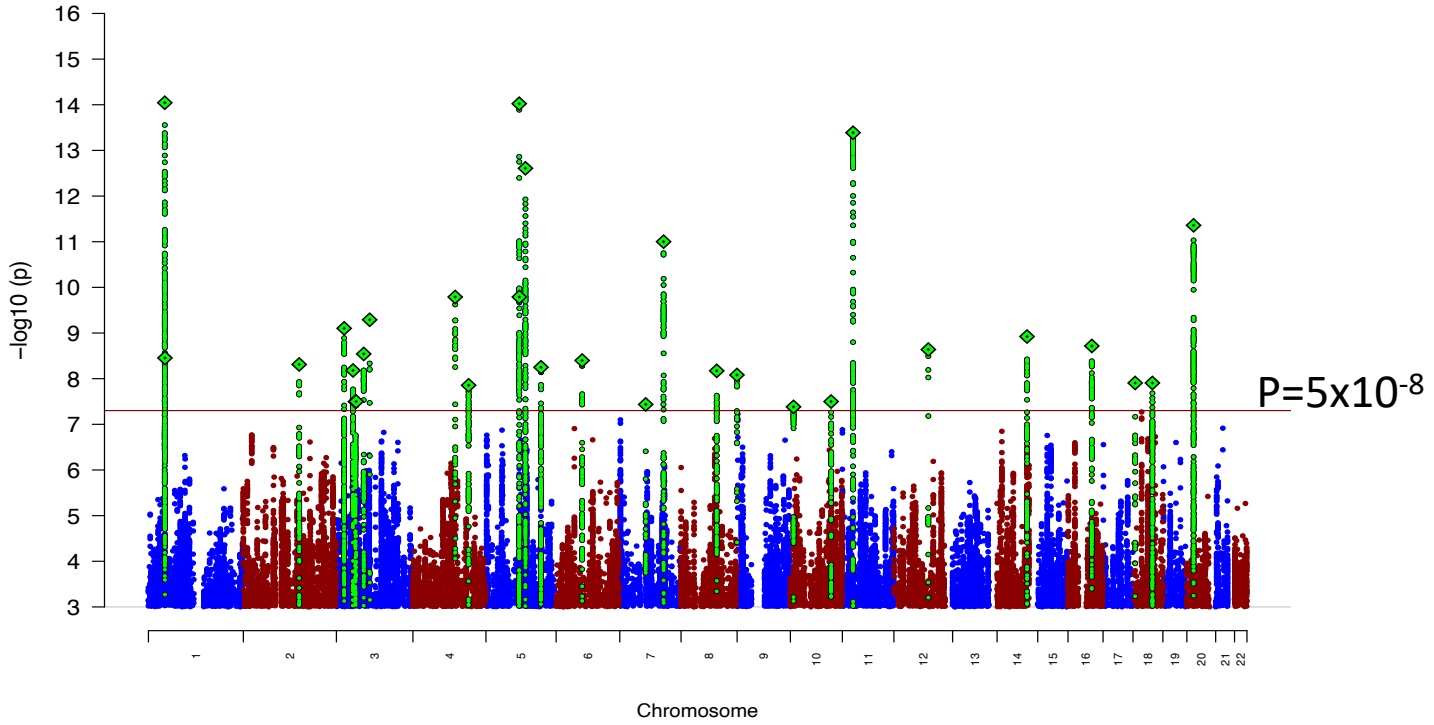
Article | Published: 26 January 2023

Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains

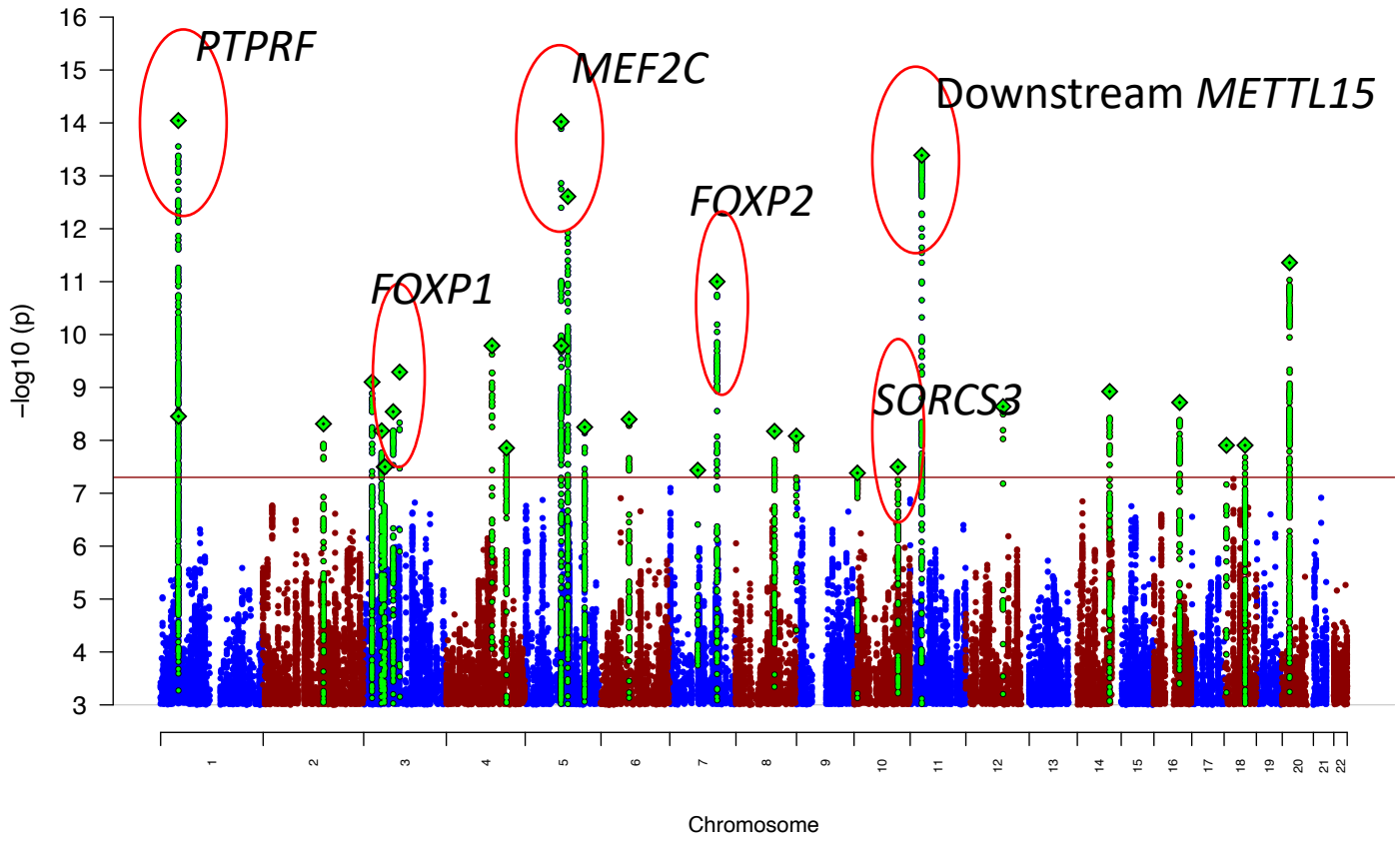
Ditte Demontis, G. Bragi Walters, Georgios Athanasiadis, Raymond Walters, Karen Therrien, Trine Tollerup Nielsen, Leila Farajzadeh, Georgios Voloudakis, Jaroslav Bendl, Biau Zeng, Wen Zhang, Jakob Grove, Thomas D. Als, Jinjie Duan, F. Kyle Satterstrom, Jonas Bybjerg-Grauholm, Marie Bækved-Hansen, Olafur O. Gudmundsson, Sigurdur H. Magnusson, Gisli Baldursson, Katrin Davidsdottir, Gyda S. Haraldsdottir, Esben Agerbo, Gabriel E. Hoffman, ADHD Working Group of the Psychiatric Genomics Consortium, iPSYCH-Broad Consortium, … Anders D. Børglum



27 independent genome-wide significant loci
38,691 ADHD cases; 186,843 controls

Demontis et al. Nature Genetics, 2023

GWAS meta-analysis of ADHD



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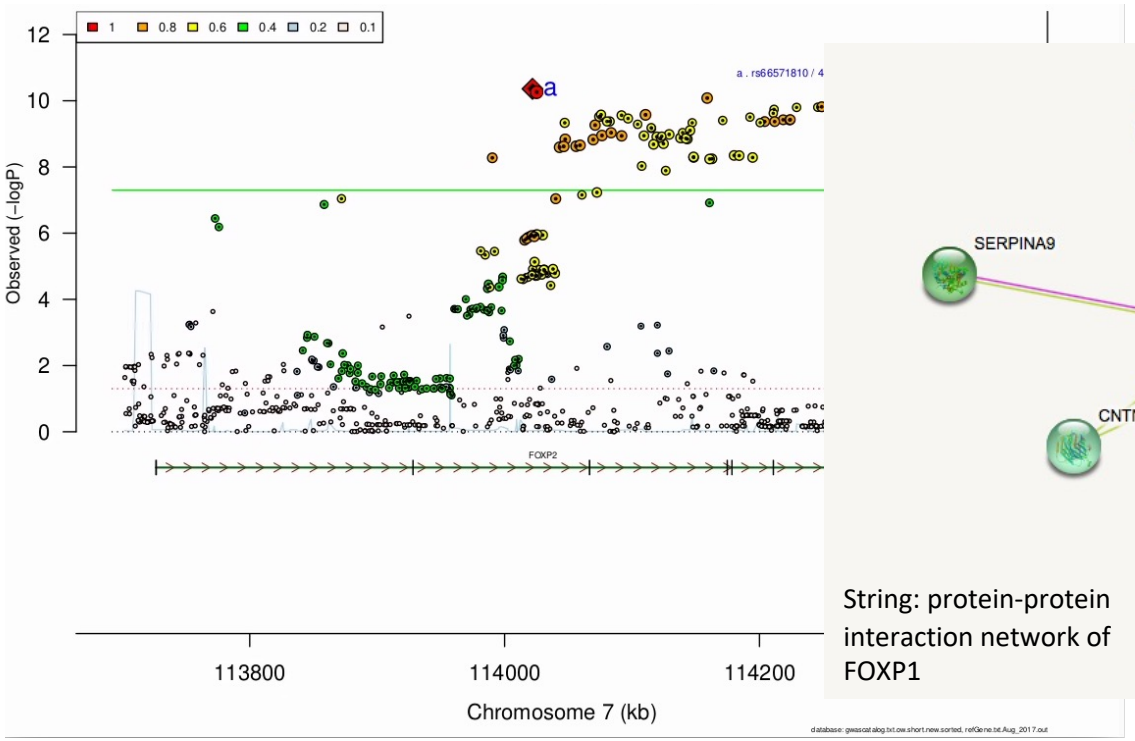
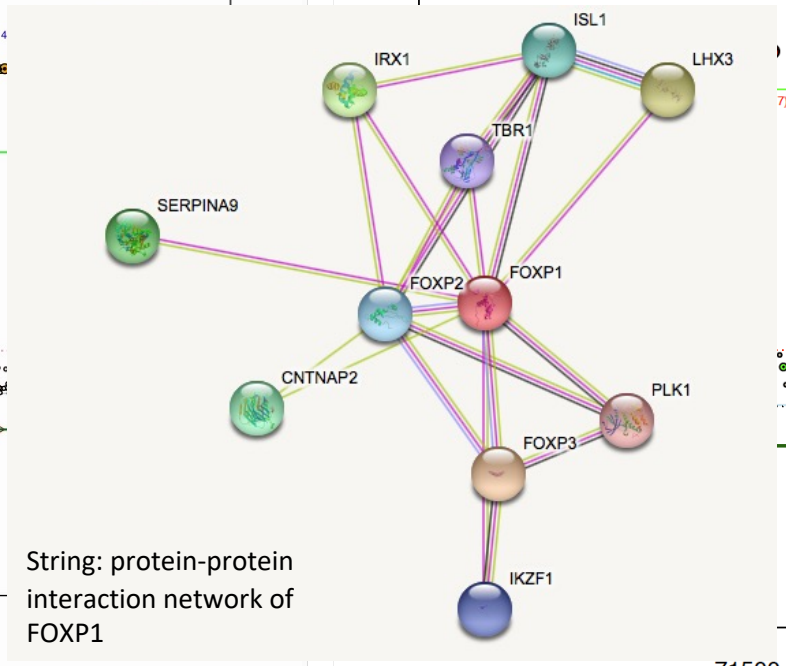
Demontis et al. Nature Genetics, 2023

ADHD risk loci

Known locus – *FOXP2* on chr 7



rs6671810; OR=1.07; P=4.37x10^{-11}



String: protein-protein interaction network of FOXP1

New locus – *FOXP1* on chr 3

rs17718444; OR=1.06; P=2.87x10^{-9}

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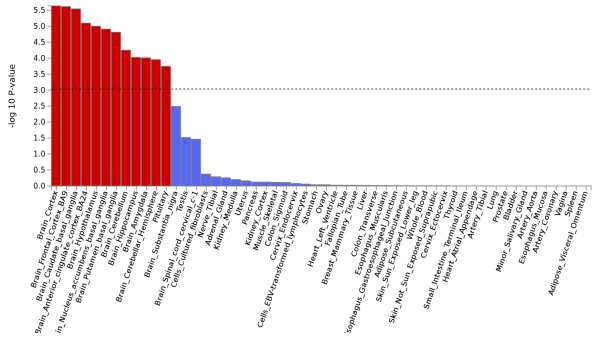
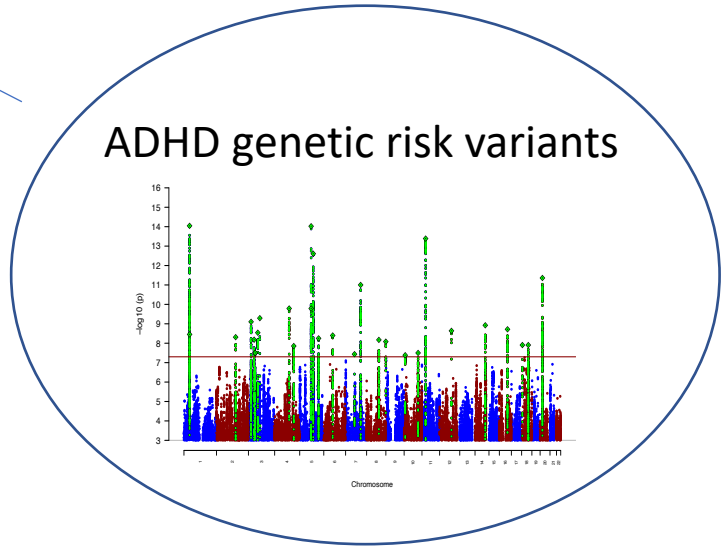
Demontis et al. (Nature Genetics, Jan 2023)

What have our analyses revealed about genes involved in ADHD?

- ADHD risk genes have high expression in almost all brain regions



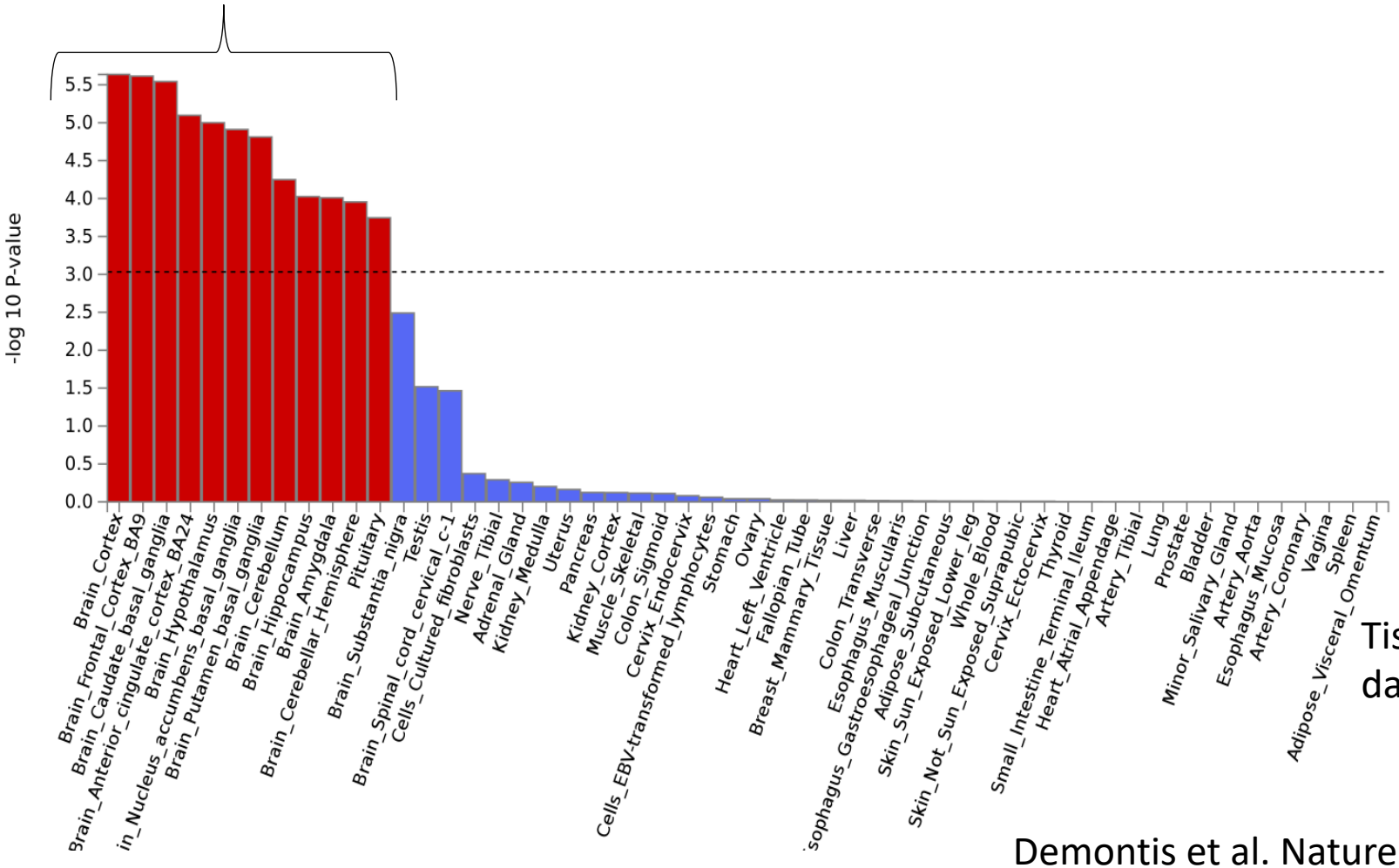


Demontis et al. Nature Genetics, 2023

- ADHD risk genes have high expression in almost all brain regions

Association of ADHD genes with tissue specific expression (-log10 P-value)

Brain tissues with significant increased expression of ADHD associated genes



Tissue specific gene expression data from GETx

Demontis et al. Nature Genetics, 2023

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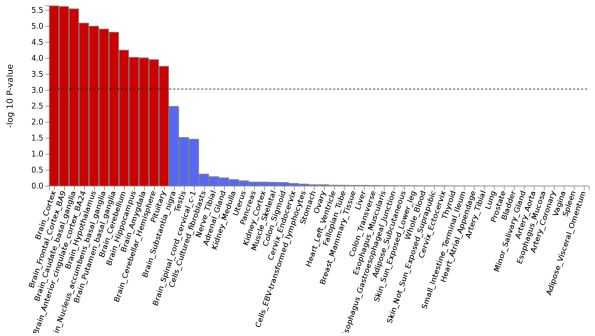
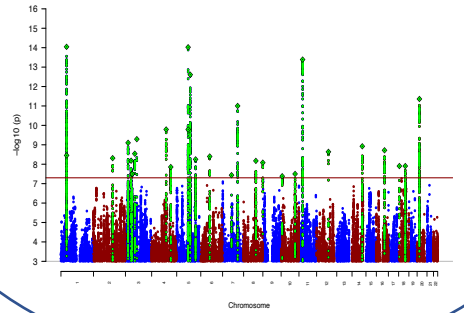
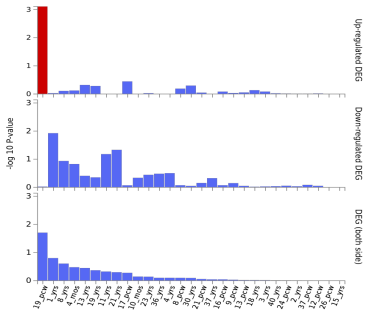


ADHD genetic risk variants



- ADHD risk genes enriched among genes expressed in early brain development
(19th postconceptional week)



Demontis et al. Nature Genetics, 2023

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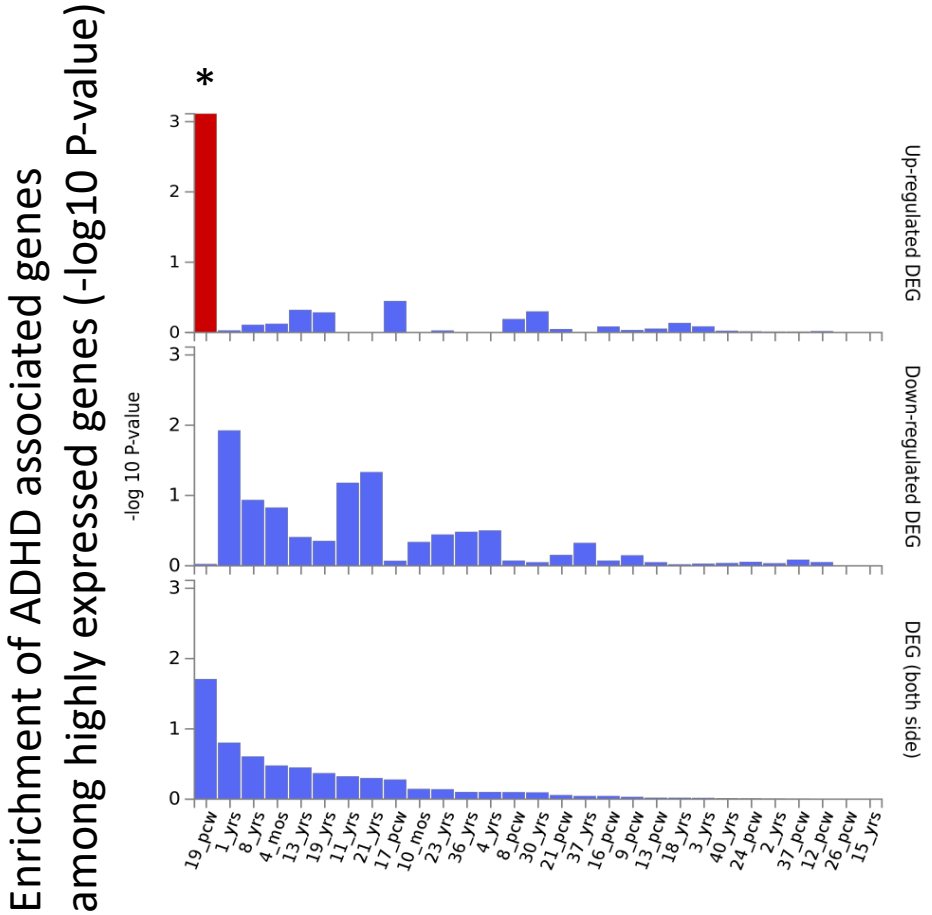

Brain developmental stages (BrainSpan data)

Demontis et al. Nature Genetics, 2023

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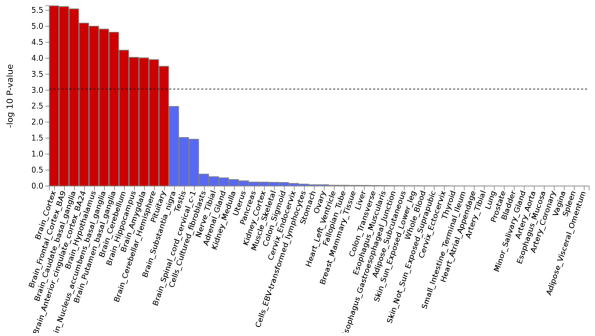
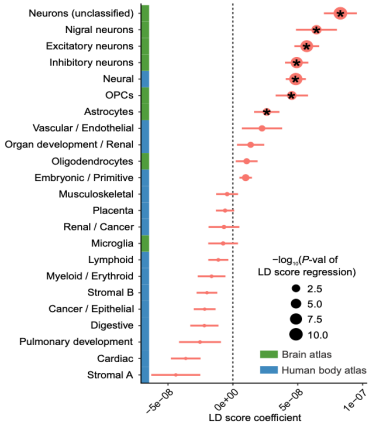
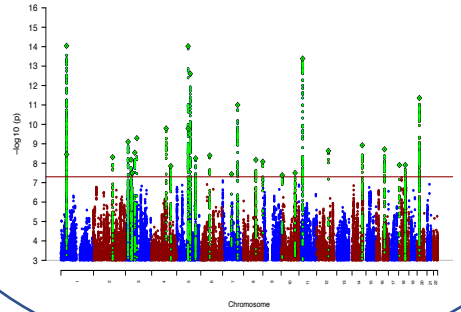


- ADHD risk variants enriched in genomic regions effecting genes with expression in neuronal cell types.



ADHD genetic risk variants



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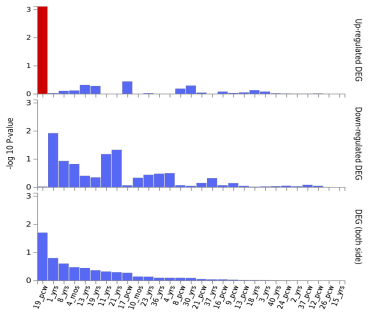
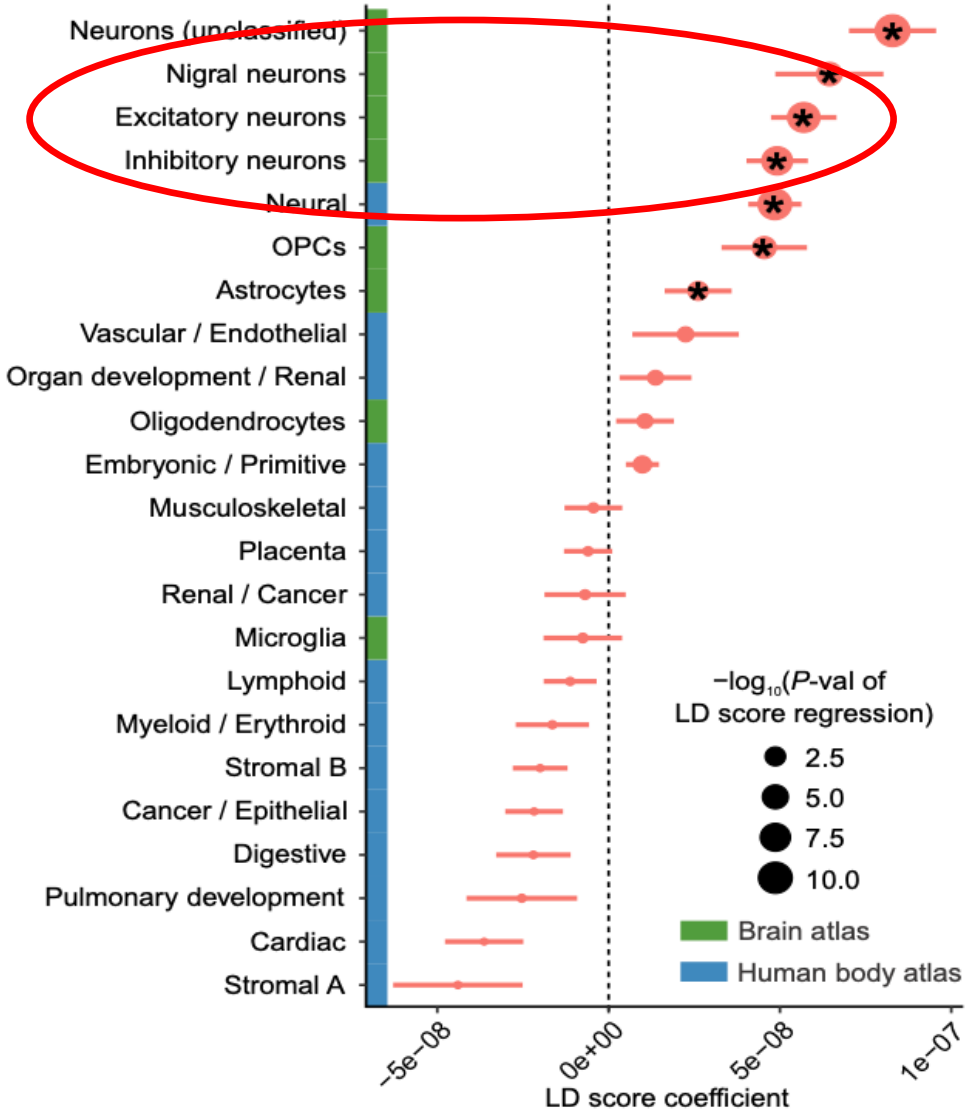


Demontis et al. Nature Genetics, 2023

Enrichment in the SNP-heritability of risk variants in cell-specific regulatory regions

- ADHD risk variants enriched in regulatory regions effecting genes with expression in neuronal cell types.



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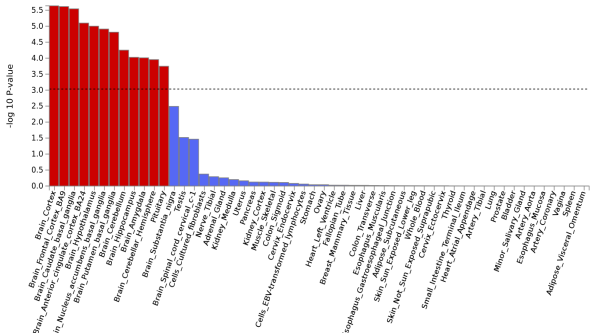
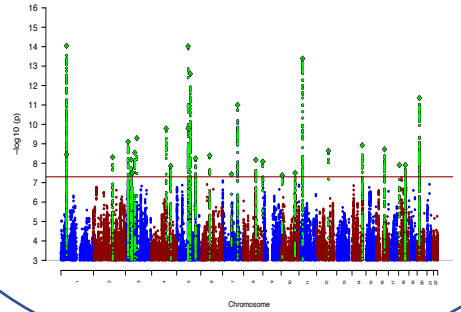


ADHD genetic risk variants



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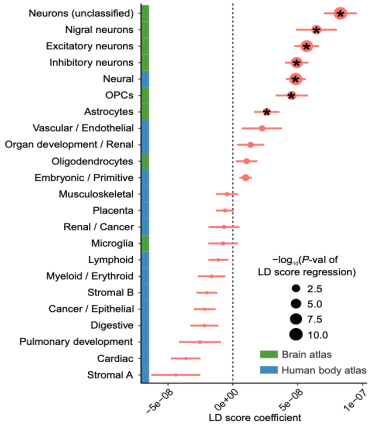
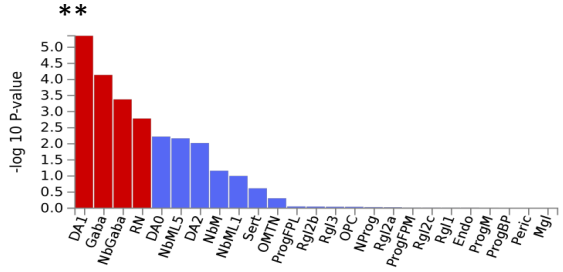
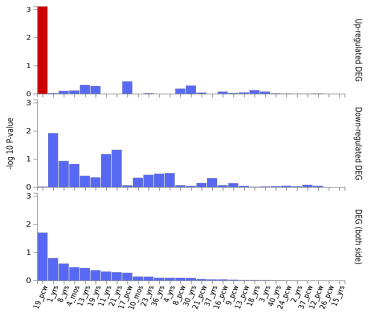


- ADHD risk genes have significant increased expression in dopaminergic neurons



- ADHD risk genes enriched among genes expressed in early brain development (19th postconceptional week)



Demontis et al. Nature Genetics, 2023

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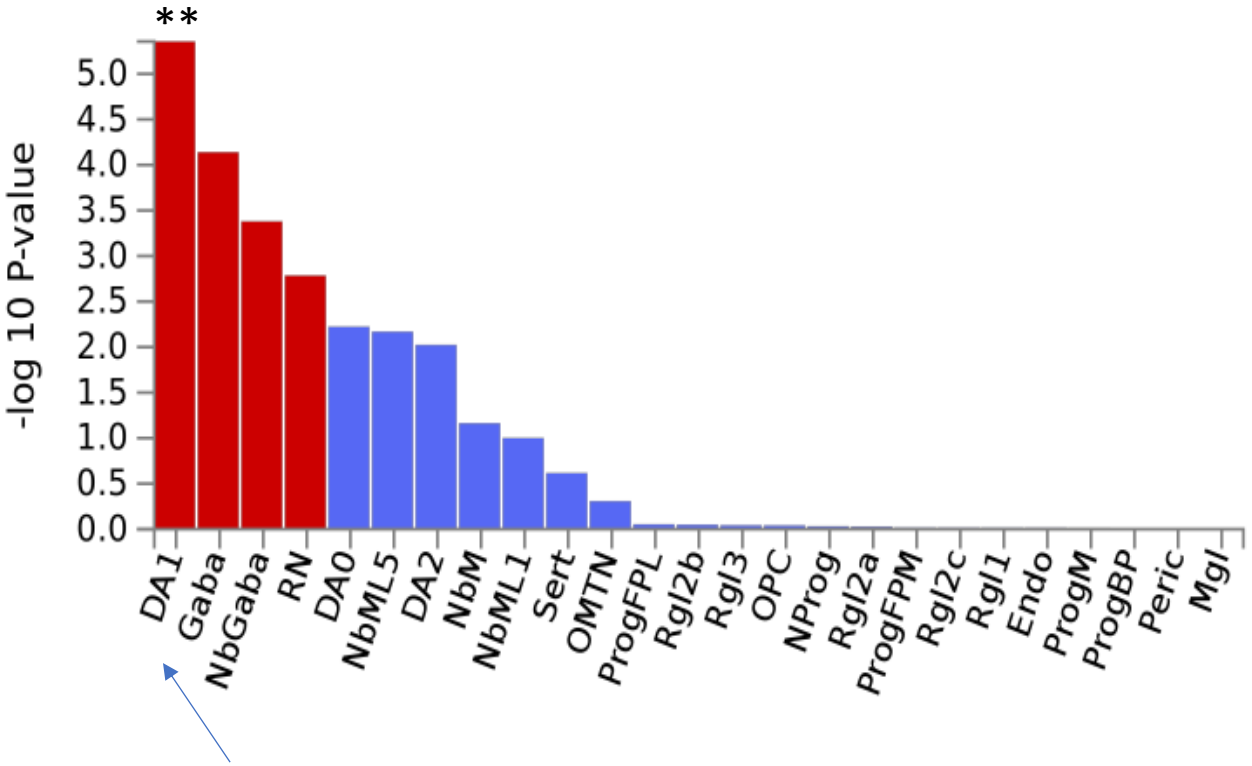
Association of ADHD risk genes with cell-type specific gene expression



Dopaminergic neurons

scRNA-sequencing data from La Manno et al. Cell 2016

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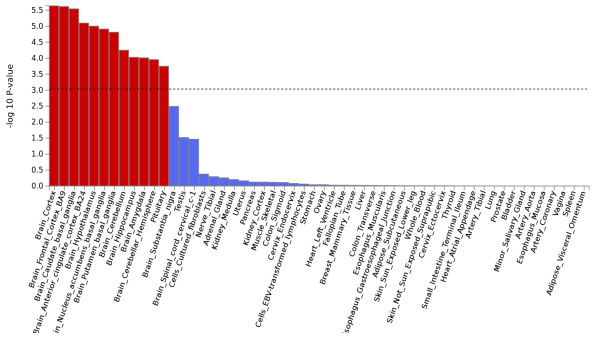
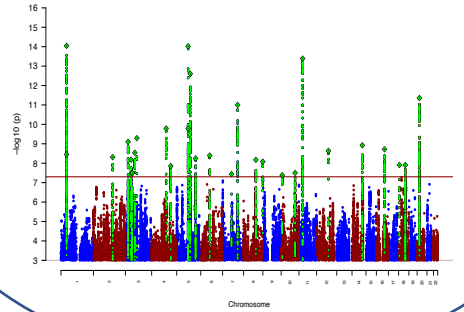


ADHD genetic risk variants



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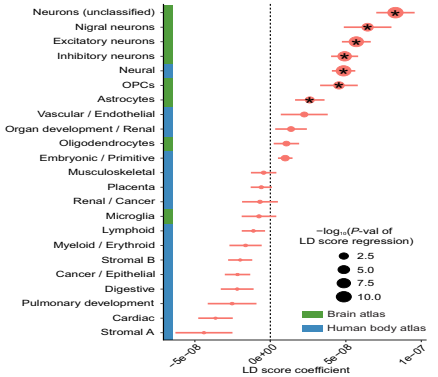

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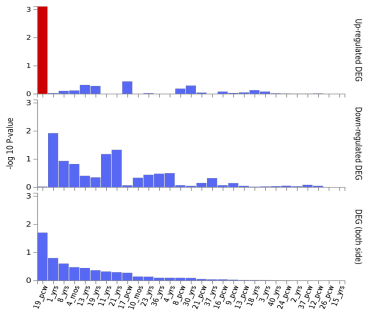

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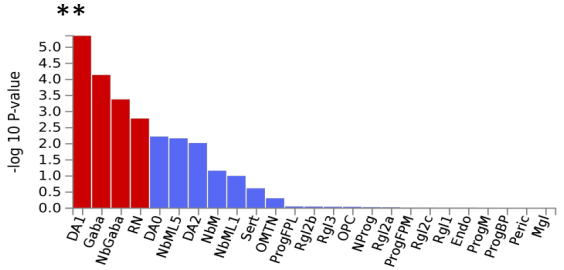
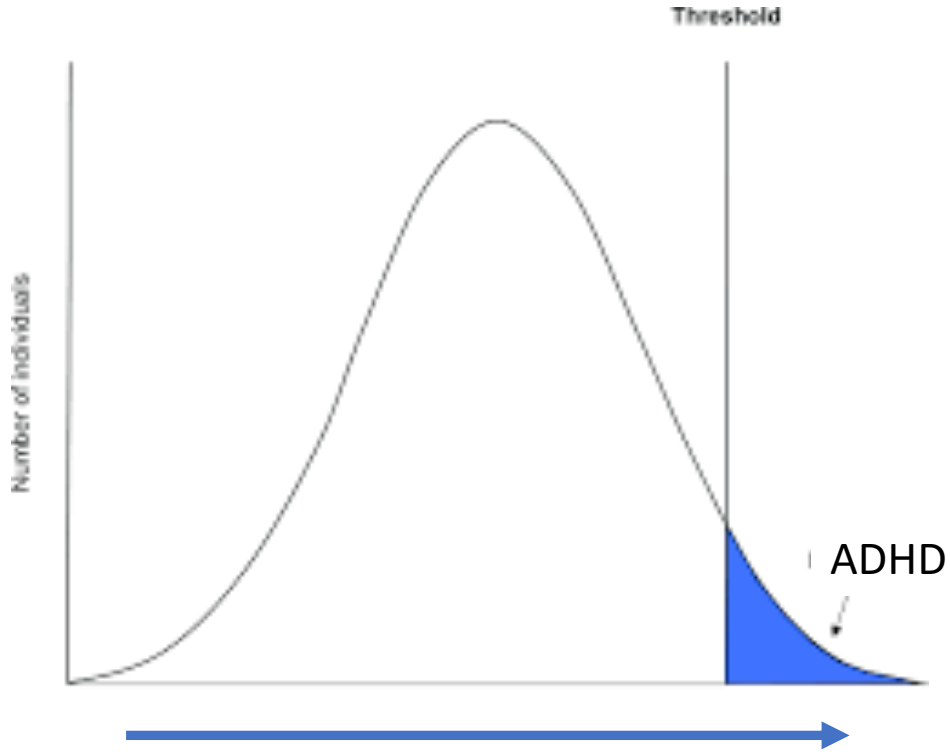


Demontis et al. Nature Genetics, 2023

Genetic overlap of ADHD with ADHD symptoms in the population

Genetic correlation of diagnosed ADHD with ADHD symptoms in the general population = 0.97

(Demontis & Walters, Nature Genetics 2019)



Genetics (e.g. number of “impulsivity” variants) + environment

Demontis et al. 2019, Nature Genetics

Genetic overlap of ADHD with other phenotypes

Genetic correlation (r_g) of ADHD with other phenotypes

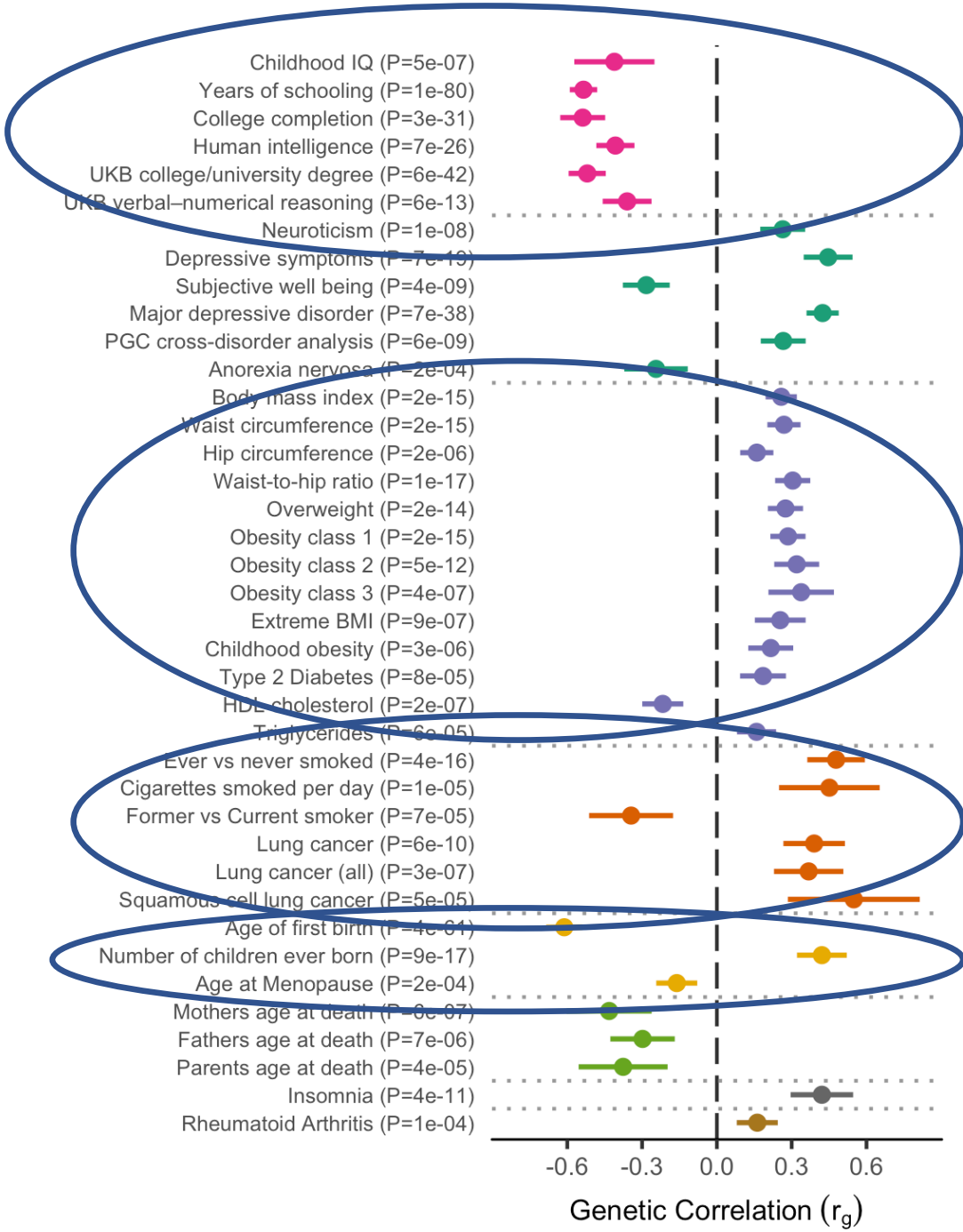
*rg = the proportion of variance that two traits share due to genetic causes

Cognition, IQ and education

Weight, BMI and obesity

Smoking

Reproduction



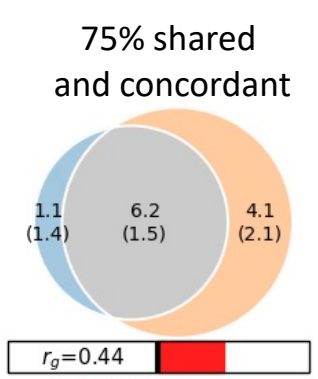
Demontis and Walters, Nature Genetics, 2019

Number of common ADHD risk variants

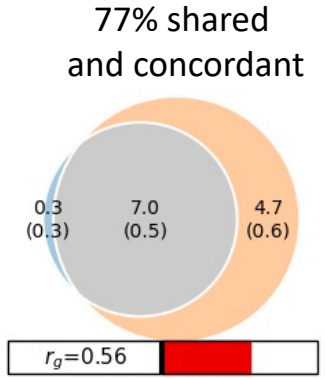
MiXeR (Frei et al. Nat. Com. 2019) uses bivariate mixture modelling to estimate total numbe of common variants that influence ADHD:

- **Around 7,300 common variants influence ADHD**

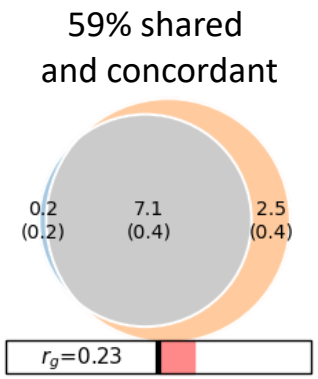
… and number of ADHD specific variants and variants shared with other disorders/phenotypes:



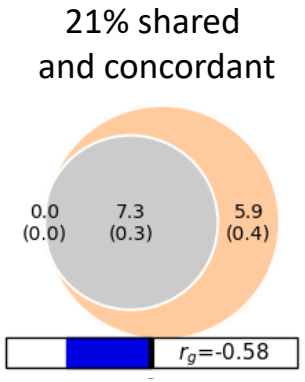
ADHD & Autism



ADHD & Depression



ADHD & Shcizophrenia



ADHD & Educational attainment


Trine Tollerup Nielsen

AARHUS UNIVERSITY

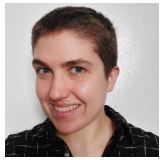
Demontis et al. Nature Genetics, 2023

Association of ADHD-polygenic score with measures of cognition

Association of ADHD-PGS with measures of cognitive abilities in the Philadelphia neurodevelopmental cohort (N=4,973).

Beta values (and standard errors) from linear regression.

Panos Roussos



Karen Therrien

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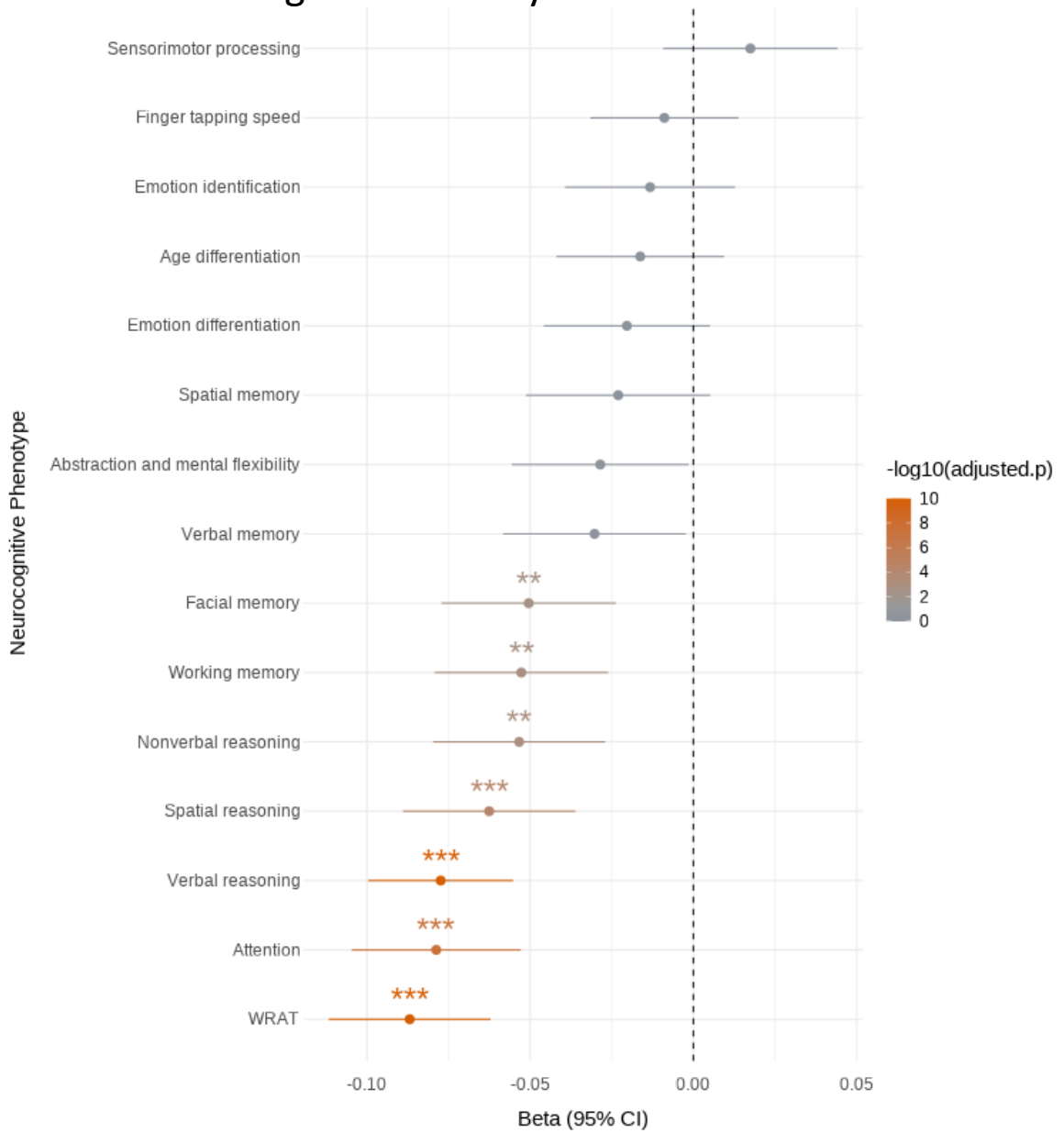
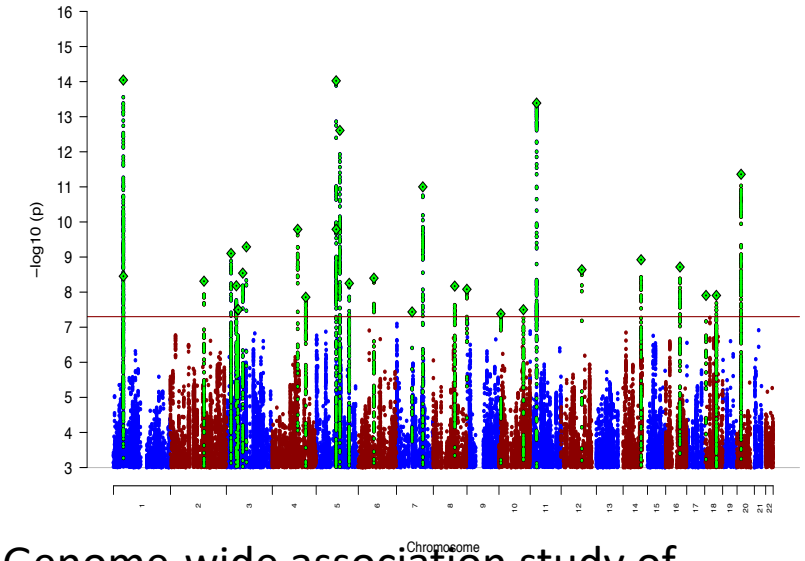
Computerized Neurocognitive Battery measures



Polygenic score (PGS) – the principle

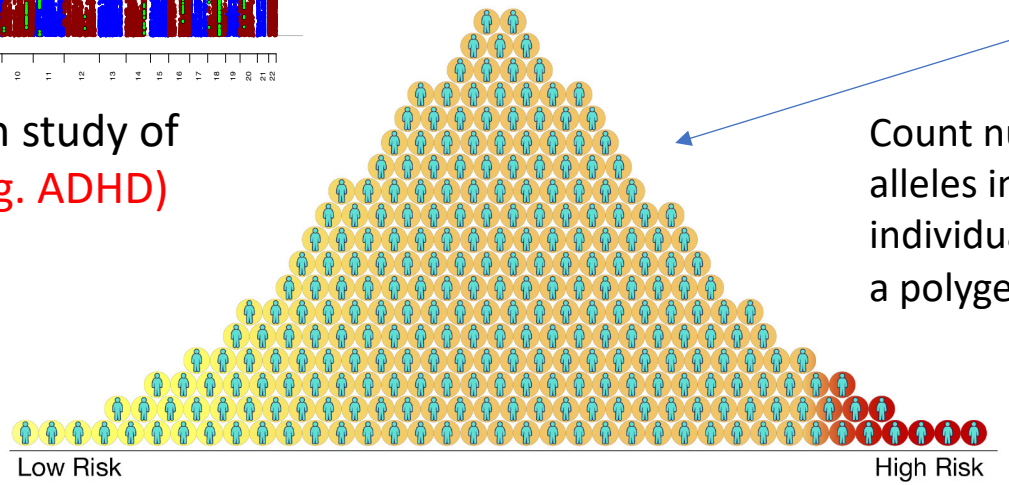


Genome-wide association study of phenotype of interest (e.g. ADHD)

Identify risk alleles
(not only those that are genome-wide significant!)

Variant 1: AT
Variant 2: GC
Varinat 3: GA
Varinat 4: AG
.
.
.
Variant x: GA

Count number of risk alleles in target individuals and sum to a polygenic risk score



Low number of common risk variants in the genome

High number of common risk variants in the genome

Association of ADHD-polygenic score with measures of cognition

Association of ADHD-PGS with measures of cognitive abilities in the Philadelphia neurodevelopmental cohort (N=4,973).

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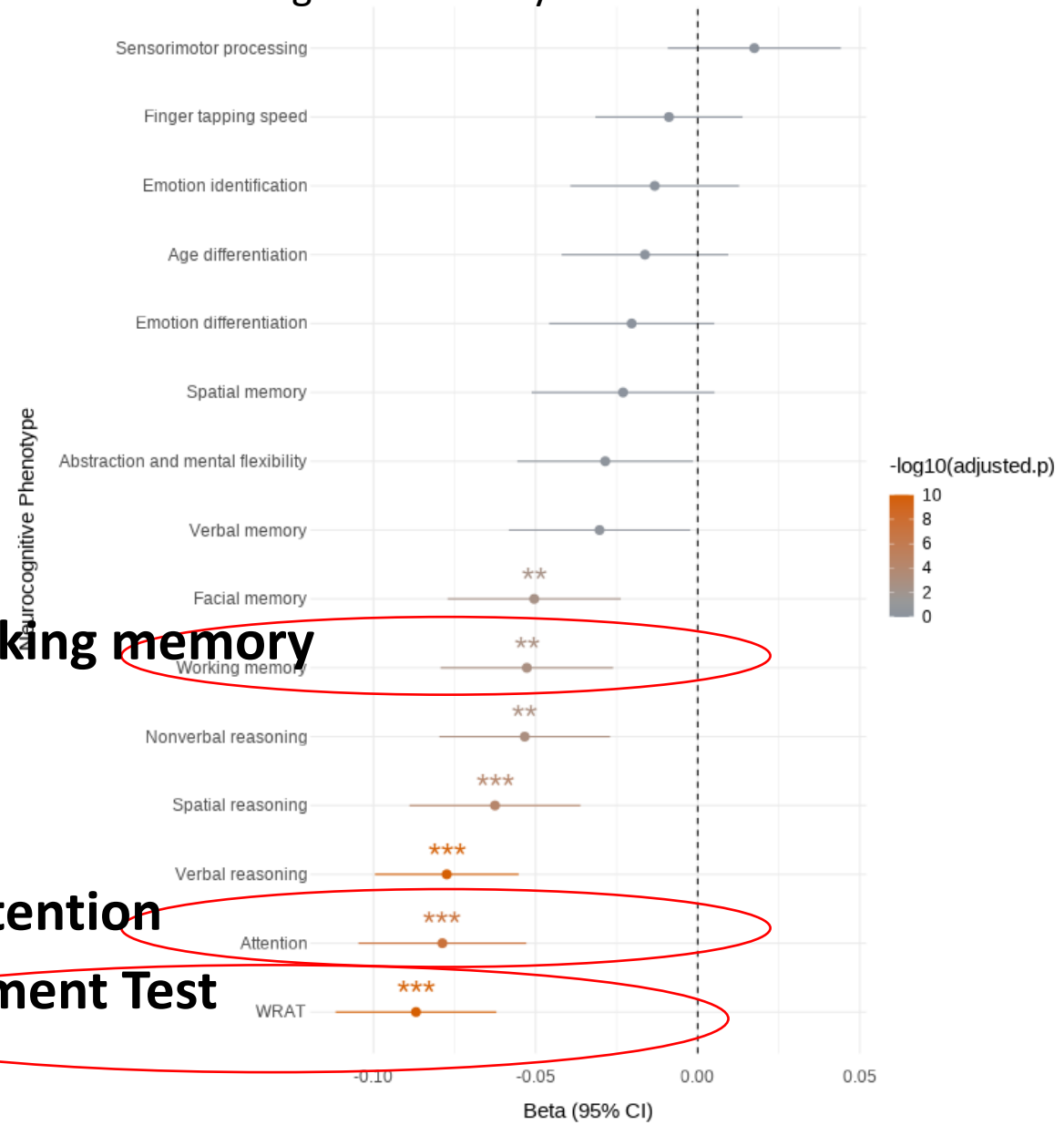


Working memory

Attention

Wide Range Achievement Test

Demontis et al. Nature Genetics, 2023

Summary – common and rare variants

- Common variants explains around 14-22% of the risk for ADHD and involves variants that affect genes with high expression in brain, in early brain development and in neurons
- Large genetic overlap with other psychiatric disorders and cognition related phenotypes

Outline

- The role of common genetic variants in ADHD
- The role of rare genetic variants in ADHD
- Genetic heterogeneity among ADHD subgroups
- Polygenic architecture of childhood maltreatment across psychiatric disorders

iPSYCH

Definition of ADHD-sub groups in iPSYCH

nature genetics

ARTICLES

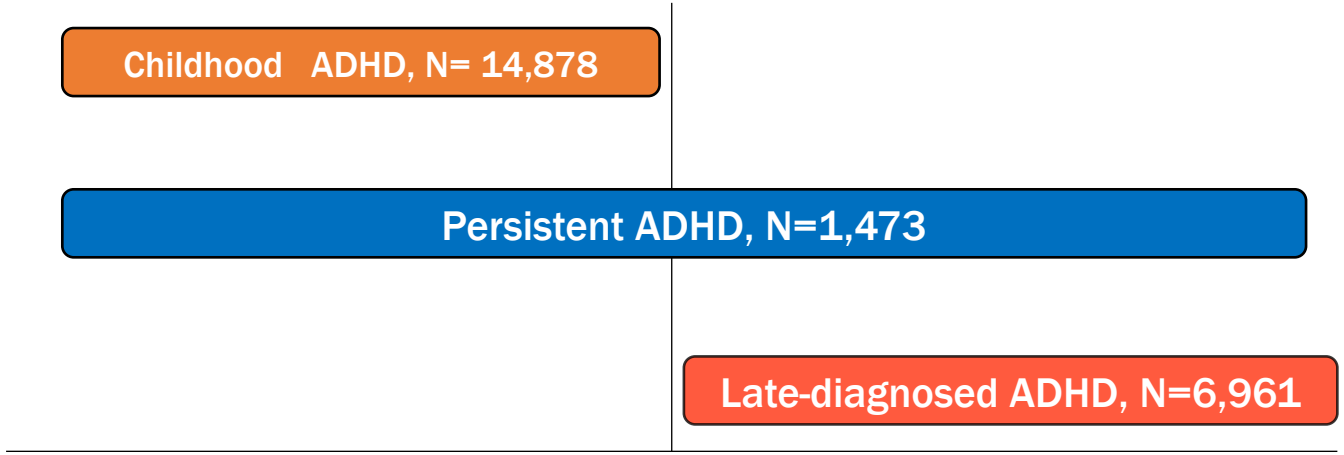
https://doi.org/10.1038/s41588-022-01143-7

Check for updates

Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention-deficit hyperactivity disorder

Veera M. Rajagopal[1,2,3], Jinjie Duan[1,2,3], Laura Vilar-Ribó[4,5,6], Jakob Grove[1,2,3,7], Tetyana Zayats[8,9,10], J. Antoni Ramos-Quiroga[4,5,6,11], F. Kyle Satterstrom[8,9], María Soler Artigas[4,5,6,11], Jonas Bybjerg-Grauholm[2,12], Marie Bækvad-Hansen[2,13], Thomas D. Als[1,2,3], Anders Rosengren[2,14], Mark J. Daly[8,9,15,16], Benjamin M. Neale[8,9], Merete Nordentoft[2,17], Thomas Werge[2,14], Ole Mors[2,18], David M. Hougaard[2,13], Preben B. Mortensen[2,19,20], Marta Ribasés[4,5,6,21], Anders D. Børglum[1,2,3] and Ditte Demontis[1,2,3]✉

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with onset in childhood (childhood ADHD); two-thirds of affected individuals continue to have ADHD in adulthood (persistent ADHD), and sometimes ADHD is diagnosed in adulthood (late-diagnosed ADHD). We evaluated genetic differences among childhood ($n = 14,878$), persistent ($n = 1,473$)



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Veera Manikandan Rajagopal

SNP-heritability and genetic correlations

SNP-heritability estimates

	H2	Prevalence
Childhood	0.24	0.05
Late diagnosed	0.27	0.03
Persistent	0.29	0.03

GCTA estimates, same controls

Genetic correlations

	Childhood	Late diagnosed
Childhood	x	
Late diagnosed	0.64 (0.03)	x
Persistent	0.82 (0.08)	0.77 (0.08)

GCTA estimate, nonoverlapping controls

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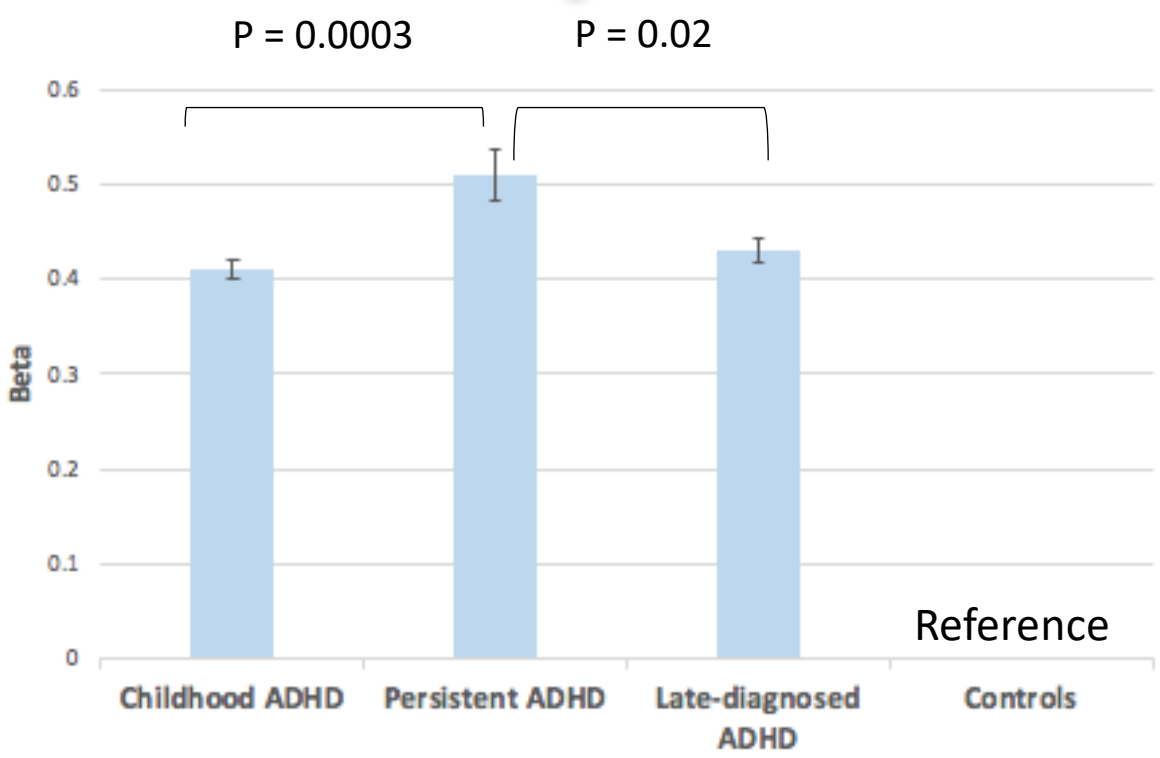
ADHD polygenic risk score analysis

Beta from multiple regression benchmarked against the controls group.



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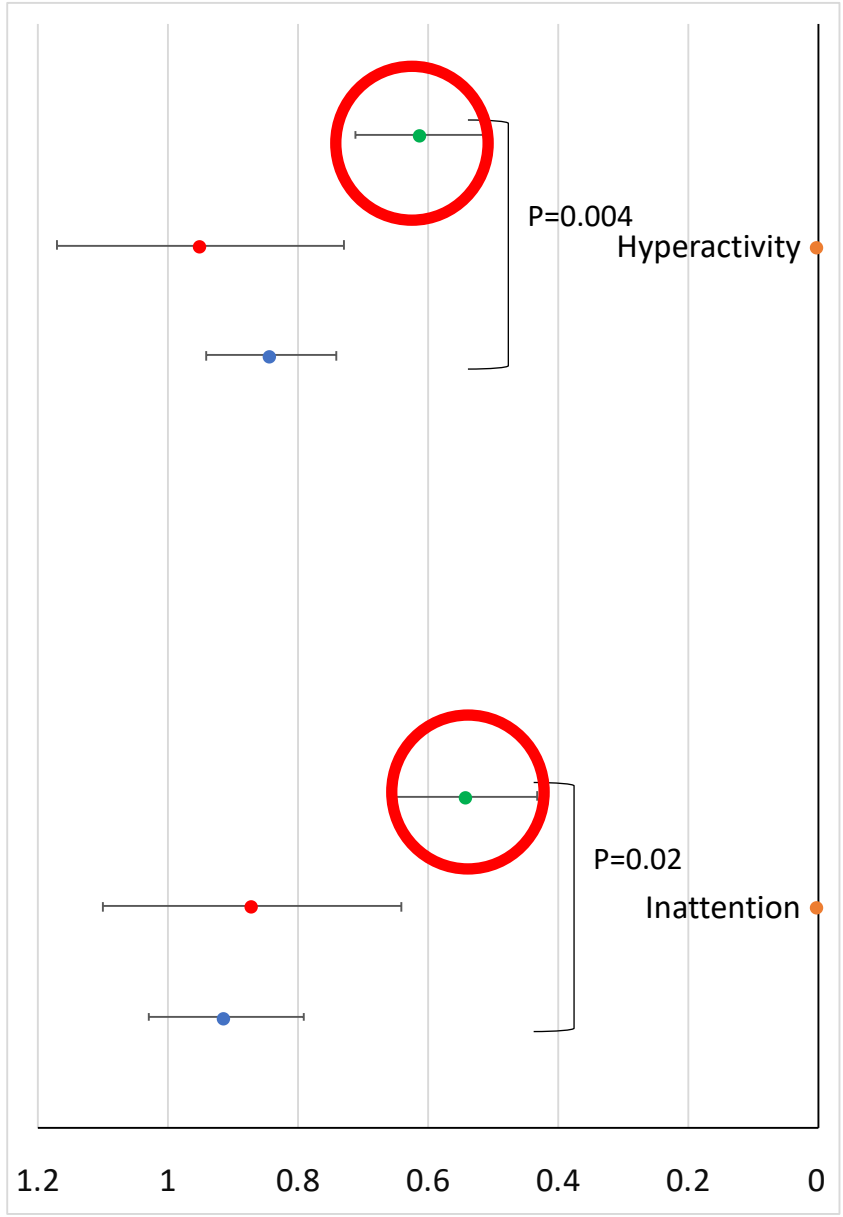
Genetic correlations of ADHD sub-groups with ADHD symptoms

GWAS meta-analysis of ADHD symptoms in the general population (N=37,000) Zayats et al. (unpublished)



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Prevalence of comorbid conditions

Comorbid Psych		Controls	Childhood ADHD	Late-diagnosed ADHD	Persistent ADHD
Autism spectrum disorder	Frq	443 (1.1%)	3466 (23.3%)	435 (6.2%)	267 (18.1%)
	Pvalue	REF	0	4.3E-176	0
Schizophrenia	Frq	171 (0.4%)	104 (0.7%)	410 (5.9%)	73 (4.9%)
	Pvalue	REF	0.0003	1.3E-300	2.7E-103
Bipolar disorder	Frq	85 (0.2%)	36 (0.2%)	325 (4.6%)	43 (2.9%)
	Pvalue	REF	0.73	4.1E-283	4E-70
Major depressive disorder	Frq	860 (2.2%)	581 (3.9%)	1909 (27.42%)	292 (19.8%)
	Pvalue	REF	4.9E-26	0	0
Cannabis use diorder	Frq	239 (0.62%)	374 (2.5%)	1313 (18.8%)	255 (17.31%)
	P value	REF	1E-74	0	0
Alcohol use disorder	Frq	104 (0.27%)	45 (0.3%)	447 (6.4%)	53 (3.5%)
	P value	REF	0.6	0	5E-87
Obssessive complusive disorder	Frq	234 (0.61%)	483 (3.2%)	363 (5.2%)	95 (6.4%)
	P value	REF	2.4E-123	7.1E-210	1.17E-128

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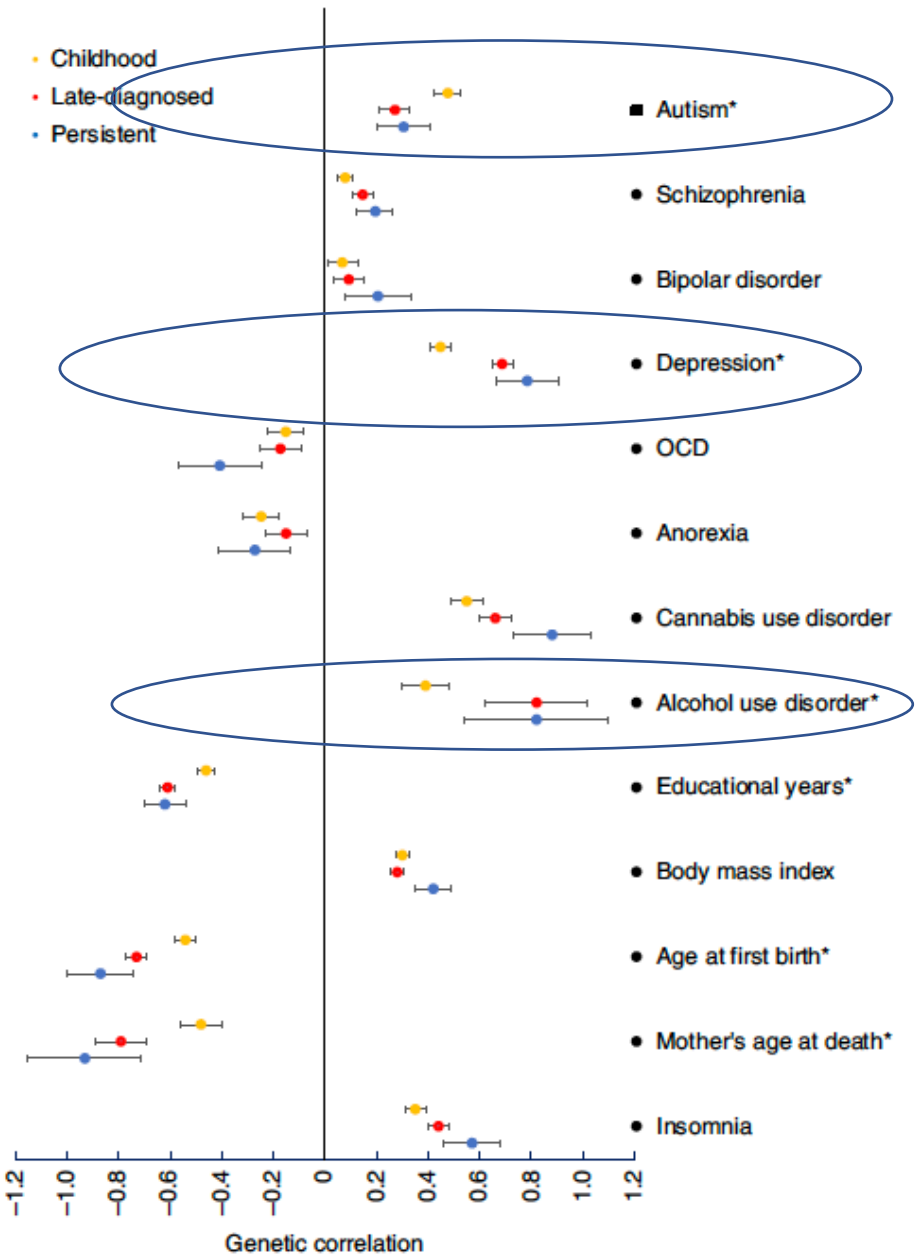
Genetic overlap of ADHD-subgroups with other phenotypes



*indicate significant genetic corelation between childhood ADHD and late diagnosed ADHD

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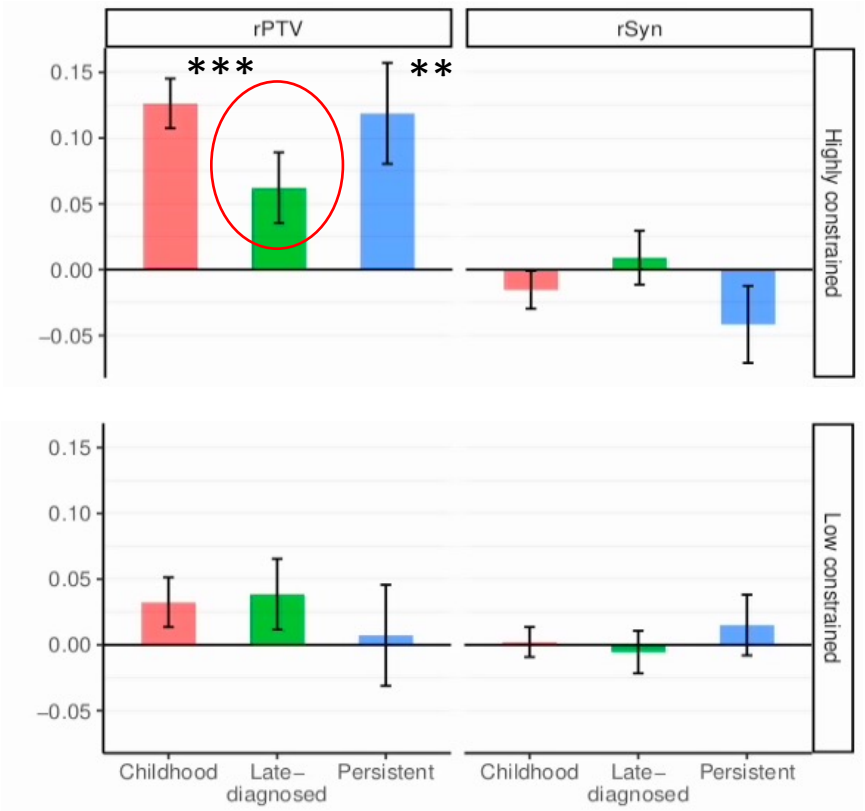
Rare variant analysis

Whole exome sequencing data:
Childhood, N=4,987
Persistent, N=748
Late-diagnosed, N=1,915
Controls, N=8,649

Rare variants = allele count < 5 in iPSYCH+gnomAD (non-Finish Europeans from the nonpsychiatric exome subset of gnomAD)

Rare protein truncating variants

Rare synonymous variants



Highly constrained
(pLI > 0.90; N=3488)

Low constrained
(pLI < 0.10; N=9662)

Results from multiple logistic regression

Significant enrichment in rPTVs in childhood and persistent ADHD in highly constrained genes compared to controls
($P_{childhood\_ADHD}=2.41x10^{-11}$, $P_{persistent\_ADHD}=1.90x10^{-3}$)

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Summary - genetic heterogeneity within ADHD

- Late-diagnosed ADHD has larger genetic overlap with depression and alcohol use disorder than childhood diagnosed ADHD
- Childhood diagnosed ADHD has higher genetic overlap with autism
- Late diagnosed ADHD is less enriched in variants associated with impulsivity and inattention and less burdend with rPTVs compared to the other two groups.

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