Amsterdam Public Health
research institute

Gene regulation of ADHD and ASD genetic variants

Refining ADHD and ASD genetic loci by integrating summary data from GWAS, eQTL and mQTL studies

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Introduction

Recent GWAS have identified the first genetic loci for attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).

Next step: understand the underlying biological mechanisms that drive these findings.

Aim: shed light on the mechanisms underlying the genetic signals and prioritize genes by integrating GWAS results with gene expression and DNA methylation levels.

Methods

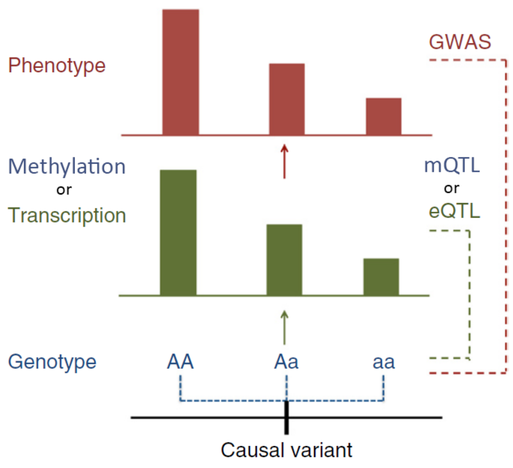
Data

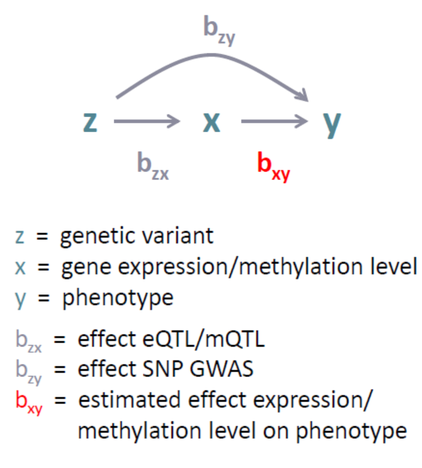
GWAS of ADHD and ASD & eQTL and mQTL datasets of fetal brain (main focus), meta-Brain and Blood.

Analysis

STEP1: SMR (summary data-based Mendelian Randomization)

Indentifies genetic variants associated with both the phenotype and gene-expression/DNA-methylation levels.

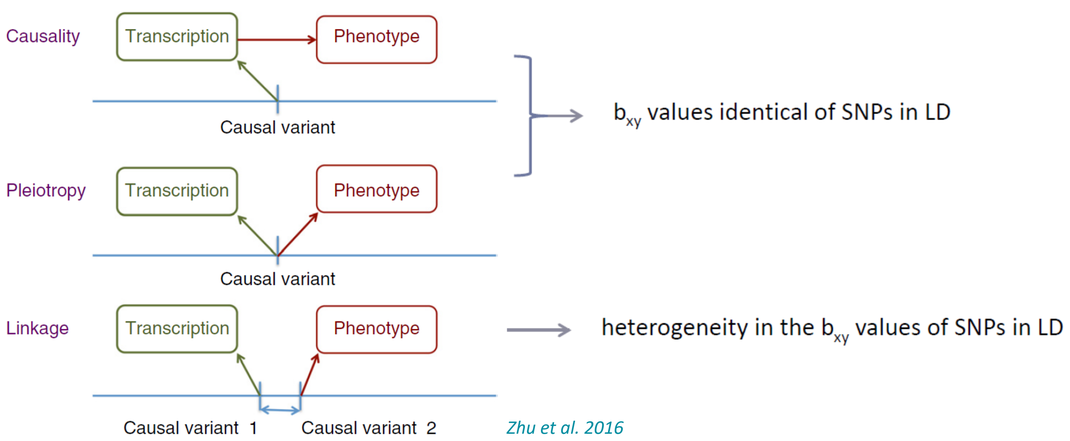




z = genetic variant
x = gene expression/methylation level
y = phenotype
b_{zx} = effect eQTL/mQTL
b_{zy} = effect SNP GWAS
b_{xy} = estimated effect expression/ methylation level on phenotype

STEP2: HEIDI (heterogeneity in dependent instruments) test

Distingueshes pleiotropic associations from linkage.



Zhu et al. 2016

Results

Trait	Locus	Tissue	QTL	Probe	Gene
ADHD	1p34.2	Fetal brain	mQTL	cg10881128	*PTPRF*
		meta-Brain	mQTL	cg06373377	*TMEM125*
		Blood	mQTL	cg08959526	*ELOVL1*
		Blood	mQTL	cg13666471	*KDM4A*
		Blood	eQTL	ENSG00000159479	*MED8*
		Blood	eQTL	ENSG00000229431	*AL139289.1*
	11p15.5	meta-Brain	eQTL	ENSG00000177236	*AP006621.1*
		Blood	eQTL	ENSG00000177236	*AP006621.1*
		Blood	eQTL	ENSG00000255284	*AP006621.5*
	12q21.33	Blood	mQTL	cg08802841	*POC1B, AC025034.1*
		Blood	mQTL	cg12414174	*POC1B, AC025034.1*
		Blood	mQTL	cg05403689	*POC1B, AC025034.1*
ASD	17q21.31	Fetal brain	eQTL	ENSG00000263503	*RP11-707O23.5*
		Fetal brain	eQTL	ENSG00000120071	*KANSL1*
		Fetal brain	eQTL	ENSG00000214401	*KANSL1-AS1*
		Fetal brain	eQTL	ENSG00000176681	*LRRC37A*
		Fetal brain	eQTL	ENSG00000238083	*LRRC37A2*

Table 1. SMR+HEIDI tests reveiled pleiotropic relationships between gene expression, DNA methylation and ADHD and ASD in four genetic loci (additional associations identified without evidence for pleiotropy).

ADHD and ASD results show modest correlations (r = 0.29-0.40).

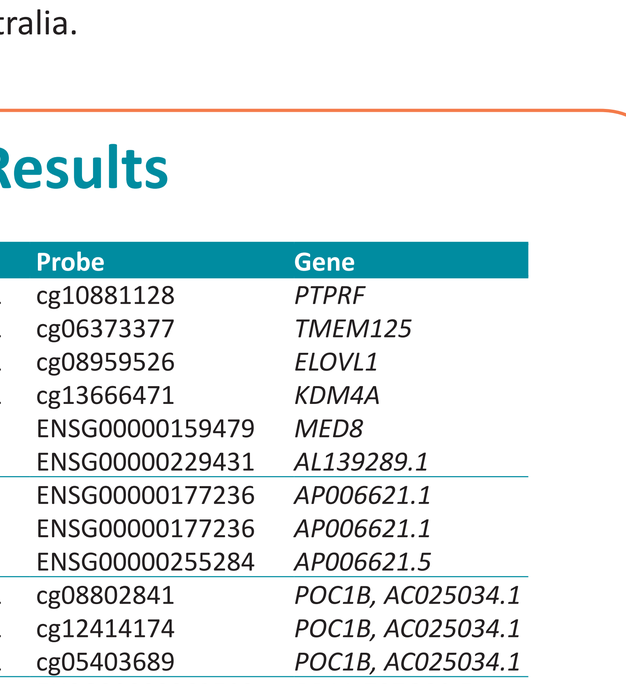


Figure 1. SMR results of ADHD and fetal brain mQTLs at 1p34.2

Conclusions

We identified genetic variants that show pleiotropic associations with ADHD or ASD and gene expression levels or DNA methylation levels. This indicates that genetic variation associated with the disorders likely acts through gene regulation.

In addition to the target tissue, a gain in statistical power of other larger tissue datasets can provide further insight. Netvertheless, comparing tissue results remains challenging.

Our results facilitate the prioritization of candidate genes implicated in disease etiology and can inform functional follow-up studies that could lead to therapeutic strategies.