Epigenetic Variation in Twins and Trios

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Introduction: Genetic factors are important in the etiology of psychiatric disorders, but the relatively high discordance in monozygotic (MZ) twins for disorders such as major depression indicates that other factors also contribute to disease etiology. MZ discordancy may be due in part to epigenetic mechanisms, though variation in epigenetic marks is also regulated by the genome, the extent of the regulation is unknown.

Methods

In a large cohort of well-characterized adult twins (mean age at sample collection 35 years, SD = 12), who participate in survey and longitudinal studies of the Netherlands Twin Register, we assessed the epigenome (DNA methylation) using the Illumina 450K array in DNA from peripheral blood. The study included 839 MZ, 493 DZ twin pairs, and 269 single twins. The parents of a subset of twins were also included (65 trios of 2 parents and one offspring; and 30/5 families with 2 parents and 2/3 offspring).

Analyses

Prior to analysis, the normalized methylation data were corrected for sex, age, array row, 96-wells plate and percentages of white blood cells (assessed at sample collection). Analyses were done at 411169 autosomal CpG sites (excluding probes with SNPs within the C or G). A genetic relatedness matrix (GRM), which summarizes measured genetic relatedness between all subjects (N=2239), was based on genotyped autosomal SNPs (Affymetrix6, MAF > 0.01).

Heritability

The proportion of variance in DNA methylation attributable to genetic effects (h^2), and moderation of additive genetic effects (A) and unique environment (E) by age and sex were assessed by the following models:

1) Classical twin model

$h^2 = 2 * (rMZ-rDZ)$, where rMZ and rDZ are the correlations between the MZ (N=713), and between the DZ twins (N=422), respectively.

2) Total heritability and heritability explained by SNPs:

See poster Nivard et al. (45; Thursday)

3) Sex differences in total heritability

Var(Methylation)=

$$Var(Y) = \mathbf{GRM} \otimes (a+B_a*Sex)^2 + \mathbf{I} \otimes (e+B_e*Sex)^2$$

4) Age moderation of total heritability

Var(Methylation) =

$$Var(Y) = \mathbf{GRM} \otimes (a+B_a*Age)^2 + \mathbf{I} \otimes (e+B_e*Age)^2$$

Results

Table 1: Good agreement (r=0.84) between h^2 based on twin correlations and h^2_{total} based on GRM.

Figure 1: Measured SNPs on average explained 46% of the total heritability. SNPs explained > 99% of total heritability in 25% of CpGs, and < 1% in 32% of CpGs.

Figure 2: 2717 CpGs showed significant (p <1.3e-07) interaction of genes or environment with sex and 28862 CpGs showed significant (p <1.3e-07) interaction of genes or environment with age.

Figure 3: In 62% of significantly sex-moderated sites, heritability was smaller in females.

Figure 4: In 89% of significantly age-moderated sites, heritability dropped between age 25 and 50.

Table 1

Classical twin heritability				
Parameter	**Min**	**Median**	**Mean**	**Max**
rMZ	-0.13	0.13	0.20	0.99
rDZ	-0.25	0.07	0.09	0.89
h^2	-1.56	0.17	0.22	1.65
Heritability based on GRM				
Parameter	**Min**	**Median**	**Mean**	**Max**
h^2_{total}	0.00	0.13	0.21	0.99
h^2_{SNPs}	0.00	0.03	0.09	0.99
h^2_{SNPs} / h^2_{total}	0.00	0.42	0.46	1.00

Figure 1

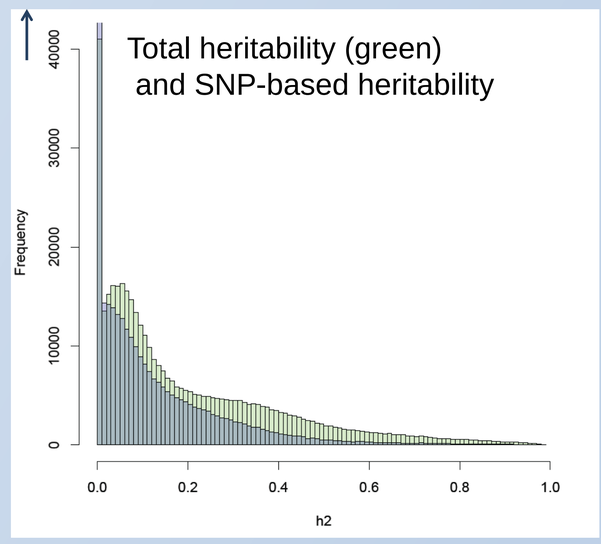


Figure 2

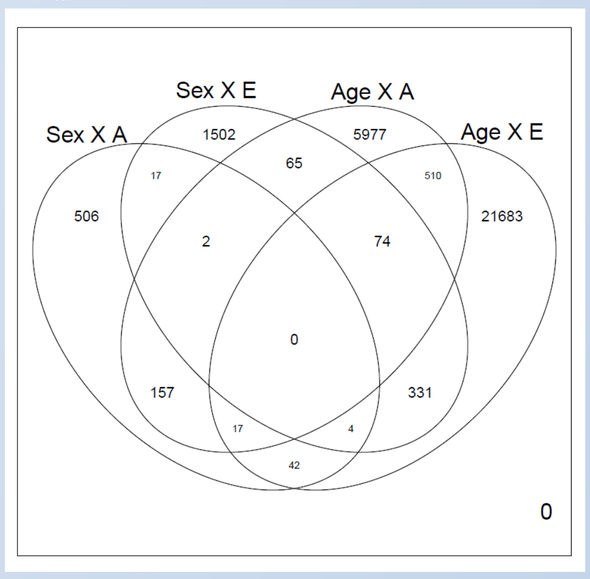


Figure 1: cont

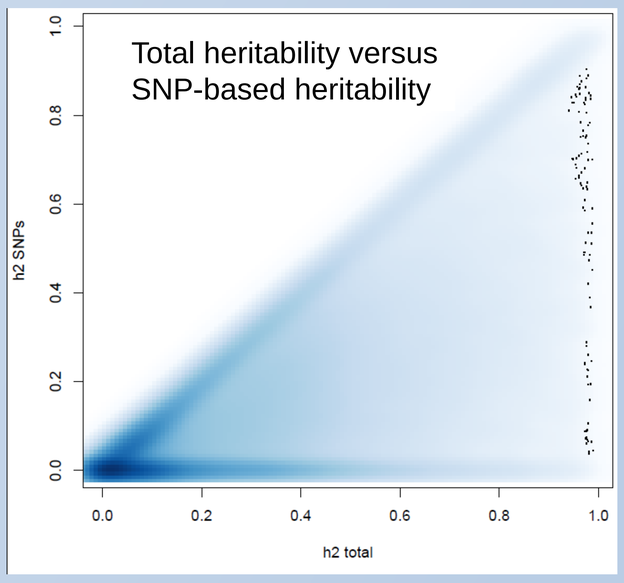


Figure 3

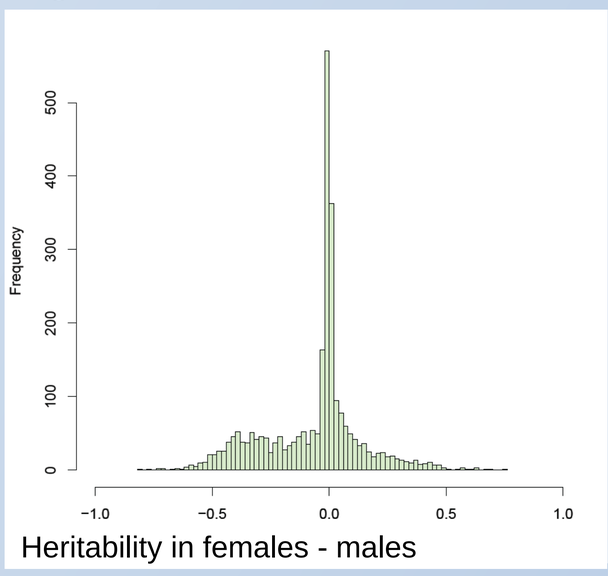
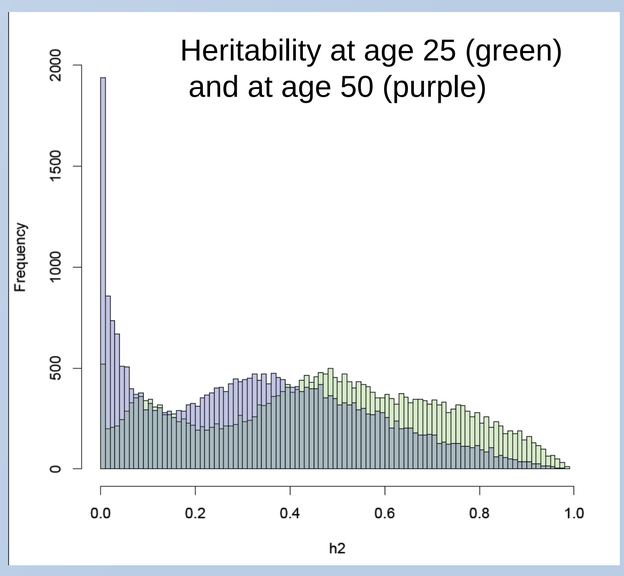
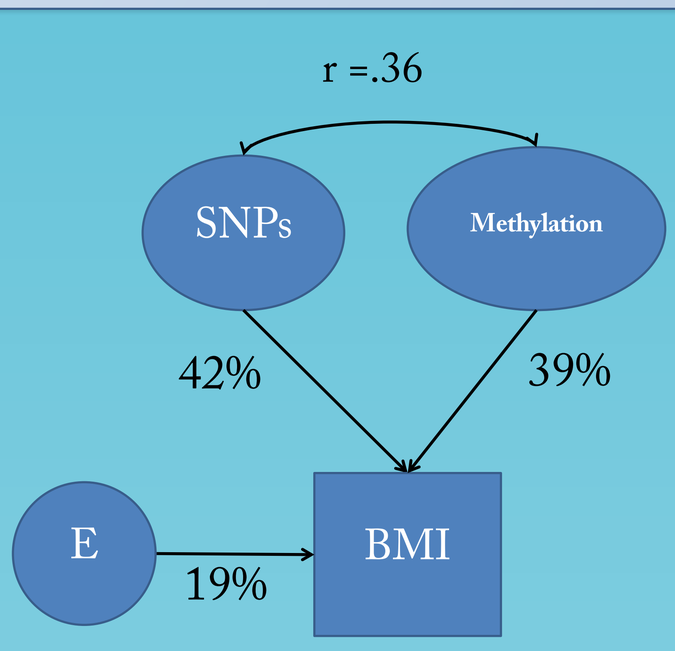


Figure 4





Results 2

Two GRMs were computed in unrelated individuals (N=1252): one based on SNPs and one based on methylation probes. A third GRM was derived mathematically to allow for the effects of the correlation between the two GRMs.

Both SNPs and genome wide methylation influence BMI, these effects on BMI are significantly correlated.

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