

Elucidating the genetic architecture of psychiatric disorders by Genome-Wide Gene-Environment interaction in ADHD, Depression, BMI and Height.



Background: Gene by environment interaction (GxE) can be studied in genome-wide SNP data using the genetic relationship matrix (GRM) estimated in GCTA (Yang, et al. 2011). In GCTA, GxE is limited to a binary moderator. We extended this approach to include continuous moderators (*moderation model*). We applied this to study GxAge in anxious-depression symptoms (AnxDep), attention problems (AP), height, and BMI.

We also considered a second model (*mediation model*) included a GRM based on all SNPs and a Gene Expression Relationship Matrix (ExRM), based on expression probes. In this model, we estimated simultaneously the direct effects on the phenotypes of the SNPs and the gene expression.

Methods and subjects: We based our approach on Zaitlen et al. (2013), which allows the inclusion of family members. The moderation model is fitted to Height and BMI data, AnxDep data on 5809 and AP data on 6217 individuals from a sample of 10802 genotyped individuals in 5965 families. The extended GRMxE model is fitted to 2307 individuals for which AP, expression and SNP data was available.

For the inclusion of gene expression data (from peripheral blood), the expression relationship matrix, ExRM, was created containing the correlation between individuals across expression probes.

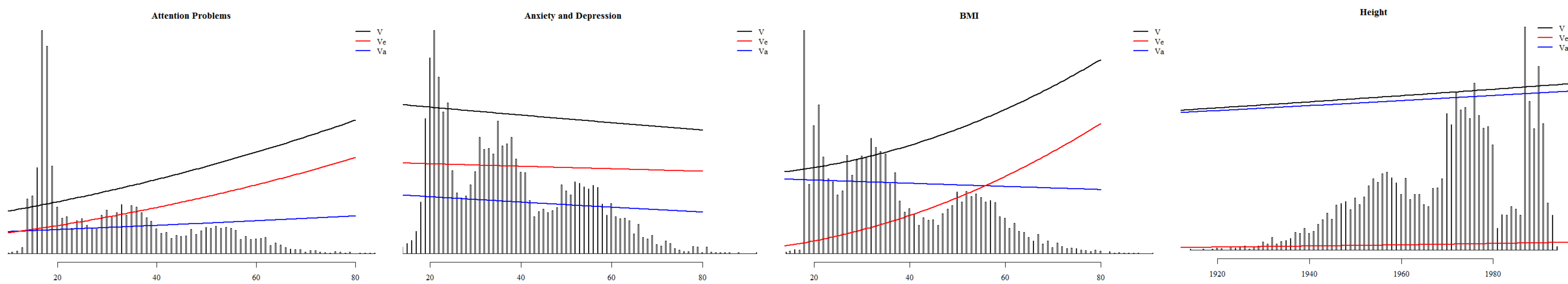
We include the ExRM and the GRM (obtained from GCTA) in model, with a matrix identifying the covariance between the gene effects and expression effects (c_{ge}), this matrix is labeled rRM in the mediation model below.

Moderation model:

$$\text{Var}(Y) = \text{GRM} \otimes (g + B_g * \text{Age})^2 + \text{I} \otimes (e + B_e * \text{Age})^2$$

Mediation model:

$$\text{Var}(Y) = \text{GRM} \otimes g^2 + \text{ExRM} \otimes \text{Ex}^2 + \text{rRM} \otimes c_{ge} + \text{I} \otimes e^2$$



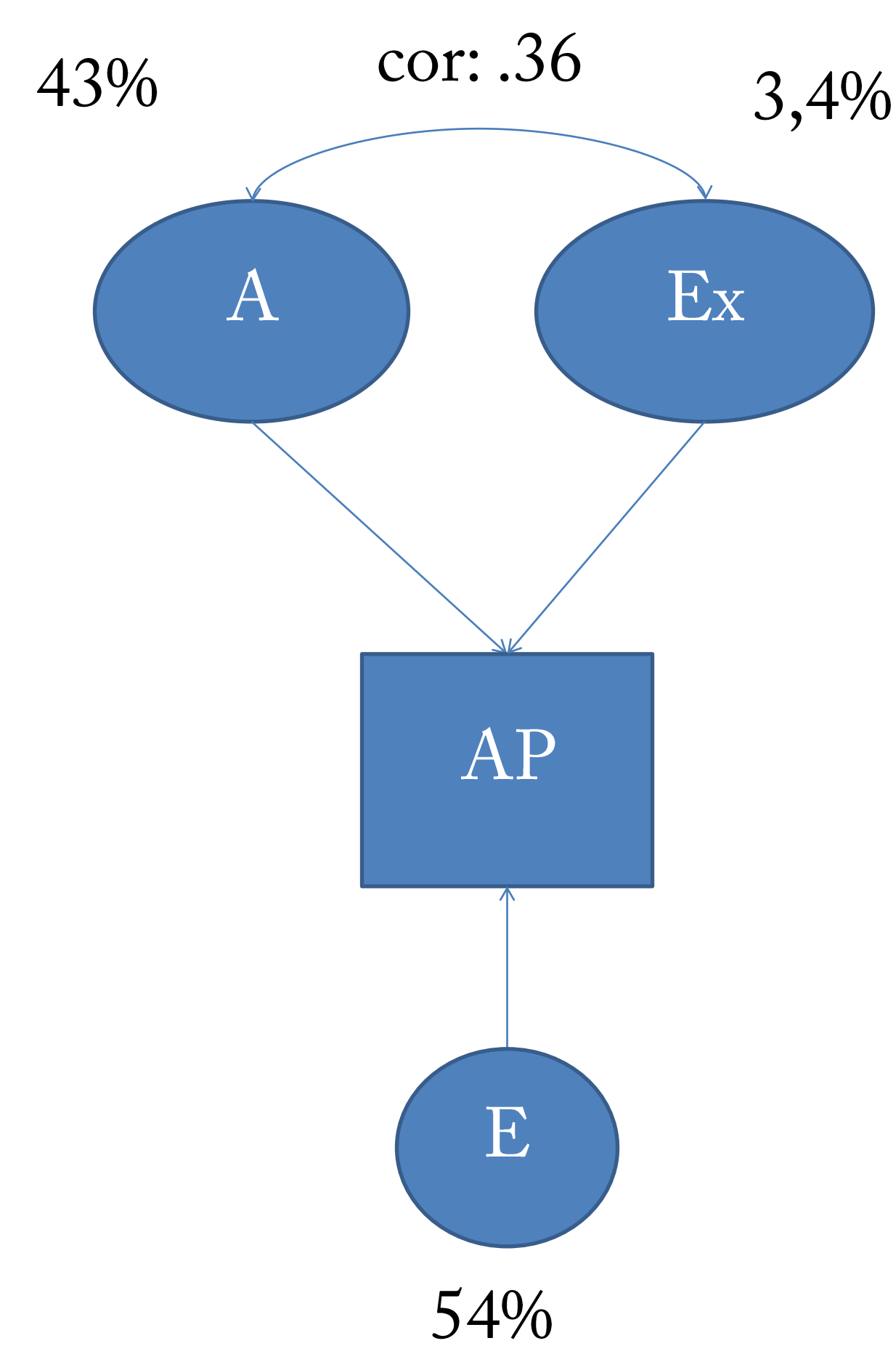
Attention problems' h² is 43.7%. 20% of phenotypic variance is captured by the SNPs. Moderation of the genetic and environmental effects on AP by age results in a small increase in genetic variance (p<0.05), but a larger increase in environmental variance (p<0.001). Consequently, the heritability of AP decreases with age.

Anxiety & Depression's h² is 40%. 6% of the phenotypic variance is captured by the SNPs. Moderation of the genetic and environmental variance was not significant.

BMI's h² is 78%. 34.8% of the phenotypic variance is captured by the SNPs is also substantial (34.8%). The environmental variance increases with age (p<0.001), but the genetic variance remains constant. This results in a decrease of the h² with age.

Height's h² is 96%. 35% of the phenotypic variance is attributable to SNPs. The environmental variance increases with birth year (p <0.001), but the genetic variance is constant. This results in a slight decrease h² of height between the 1930's and 1990's.

Mediation of gene effect by gene expression:



Preliminary simulations showed the Mediation model was able to correctly retrieve simulated covariance, genetic and expression effects.

On a subset of 2307 related individuals genotype data, gene expression data, and attention problem data were available. On this subsample the mediation model was fitted as a proof of principle. The effects by gene expression in peripheral blood were small and did not reach significance in this subsample. We aim too boost this subsample, and take steps to increase power for future analysis.

Conclusion: This method allows for:

1. The inclusion of related individuals in GCTA, dichotomous and continuous moderation.
2. The inclusion of relatedness matrices based on different biomarkers (including but not limited to gene expression).
3. The modeling of covariance between the effects of different biomarkers on a phenotype.