Neuroscience Campus Amsterdam

GENOME-WIDE COMPLEX TRAIT ANALYSIS (GCTA) FOR COMPLEX TRAITS INCLUDING MAJOR DEPRESSIVE DISORDER AND SMOKING

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Background

Genome-wide association studies of psychiatric disorders have been criticized for not explaining a substantive proportion of the heritability established in twin and family studies. Here we show that SNPs typed on current platforms do contain substantial information on the additive genetic variance of MDD, and compare these results to those of other complex phenotypes.

GCTA

We used the software program Genome-wide Complex Trait Analysis (GCTA) to estimate phenotypic variance due to the genotyped SNPs (Yang, J., Lee SH, Goddard ME, Visscher PM, *Am J Hum Genet* 2011; **88**: 76-82). **The method involves calculating the genetic similarity between all pairs of subjects based on all measured SNPs, which is then used to predict the phenotype. We compare the estimated additive genetic variance to estimates of heritability obtained in twin families from the same population.**

Phenotypes

We investigated Major Depressive Disorder and 4 other phenotypes that are currently targets of large GWA projects (height, fasting glucose, smoking initiation, and current smoking).

Data originated from the Netherlands Twin Register (NTR) and the Netherlands Study of Depression and Anxiety (NESDA). Genotyping was done as part of the GAIN-MDD study, funded by the NIMH.

Results

Phenotype	Variance explained typed SNPs	Total Heritability
MDD	21.1%	36%
Smoking initiation	12.2%	44%
Current smoking	42.1%	79%
Fasting glucose	25.4%	53%
Height	48.2%	90%

Conclusions

Our analysis clearly shows that SNPs typed on currently available platforms contain substantial information on the additive genetic variance of MDD and other complex phenotypes.

The fact that conventional Genome-Wide Association Studies have so far failed to detect the majority of SNPs associated with MDD should therefore be interpreted as a shortcoming of the statistical method of analysing SNPs individually. Novel analytical approaches are clearly needed to extract the information that is present in genome-wide SNP data.

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