

TRENDS IN GENOME WIDE ASSOCIATION RESULTS OF MULTIPLE PHENOTYPES

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Study sample

The sample consisted of 3540 GWAS of unrelated Dutch adults from the Netherlands Twin Registry and Netherlands Study of Anxiety and Depression. Originally the sample was selected for a case-control study of major depression. The mean age at time of sampling was 43.8 (sd = 13.4) and 65% were women.

Phenotypes

For this study, data were available for 40 phenotypes (in 19 cases for only one of the centers). Phenotypes included among others lipid & glucose metabolism, body composition, liver enzymes, and psychometric scales.

Genotyping, quality Control and imputation

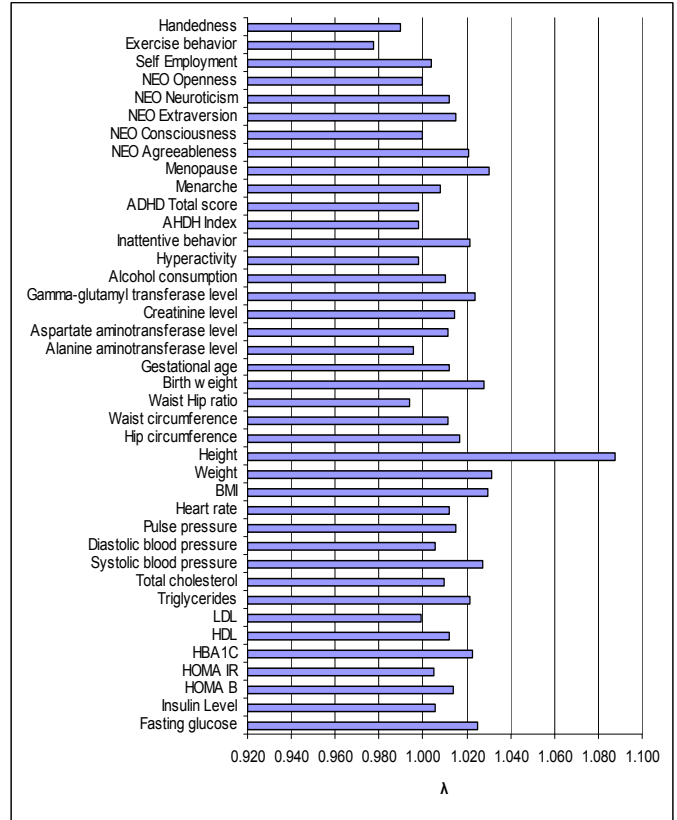
Perlegen 600k SNP chip, MAF > 0.01, Missing genotypes < 0.05 in SNPs and individuals, HWE > 0.00001, PCA for relatedness. Imputation was done with IMPUTE to ~2.5 million SNPs of Hapmap build 36. Subsequently SNPs with MAF > 0.05 were selected for this study.

Genome-wide association tests

Linear - or logistic regression was done using an additive model to test for association for each phenotype (SNPTEST). Sex and age were included as covariates (center if required). From the resulting p-values the genomic inflation factor λ was calculated. A fractional rank score was given to each p-value. Over the 40 phenotypes the number of times a SNP belonged to the top 10% in rank was calculated. The SNPs, being ≥ 18 times in the rank top 10%, were subsequently annotated with the Ensembl genome browser.

Aim 1

Population stratification tested with the genomic control λ value for all phenotypes



Aim 2 Genes associated with the phenotype at p < 0.05 level and being at least 18 times in the top 10% of p-values over all 40 phenotypes

Gene cluster / Region	N SNPs*	Fasting glucose (2)	Insulin Level (1)	HOMA B (1)	HOMA IR (1)	HBA1C (1)	LDL (2)	Triglycerides (2)	Total cholesterol (2)	Systolic blood pressure (2)	Diastolic blood pressure (2)	Pulse pressure (2)	Heart rate (1)	BMI (2)	Weight (2)	Height (2)	Hip circumference (2)	Waist circumference (2)	Waist Hip ratio (2)	Birthweight (1)	Gestational age (1)	Alanine aminotransferase level (1)	Aspartate aminotransferase level (1)	Creatinine level (1)	Gamma-glutamyl transferase level (1)	Alcohol consumption (2)	Hyperactivity (1)	Inattentive behavior (1)	ADHD Total score (1)	Menarche (1)	NEO Agreeableness (2)	NEO Conscientiousness (2)	NEO Extraversion (2)	NEO Neuroticism (2)	NEO Openness (2)	Self Employment (1)	Exercise behavior (1)	Handedness (2)						
Gene Desert chromosome 15	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Gene Desert chromosome 2	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gene Desert chromosome 12	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gene Desert chromosome 4	2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gene Desert chromosome 18	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AIG1, HIVEP2, ADAT2, PEX3	4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AHR, SNX13, PRPS1L1, HD9	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CD200R1L, CCDC80, SLC35A5, ATG3, BTLA, CD200R1, GTPBP9, SLC9A10	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CBLN4, MCSR	14	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCDC26	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CHCHD2, PHKG1, SUMF2, CCT6A, PSPH, GBAS, ZNF13, SEPT14	4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
COL6A1, COL6A2, FTCD, LSS, MCM3AP, PCNT, DIP2A, S100B, PRMT2	3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PARK2, PACRG	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
GFRA2, DOK2, XPO7, NPM2, FGF17	3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ATP10B, SLU7, C10orf2	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protein EFR3 homolog A	2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSHD4, LRR49, THAP10, NR2E3, MYO9A	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
STFA3, IF3MT, LNX2, RP11A	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TMEM195, DGKB	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*Multiple SNPs in the region showed similar results due to linkage disequilibrium

• (L-2) Data available in 1 or 2 cohorts

Conclusions

- In general there is little to no effect of population stratification over various phenotypes once initial checks on the genotype data have been made. The only exception in our sample is height.

- Some genes seem related to multiple correlated phenotypes. Of particular interest are the genes related to glucose, lipid metabolism and body stature: DGKB & SLC35A5 & MCR3, and also the muscle gene PHKG1.

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