



Genome-wide association study for leisure-time exercise behavior



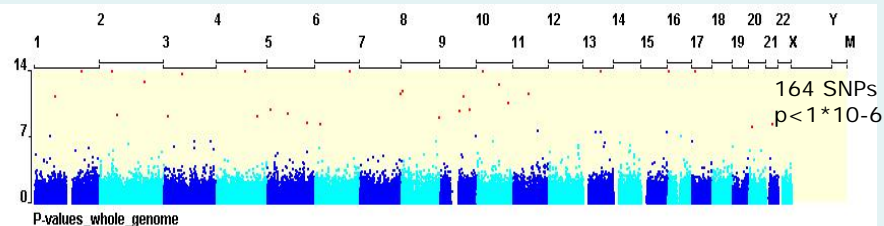
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Aim 1: Test association with candidate genes (confirmatory)

SNP	P-value	Gene	Chrom	Lowest p in gene	Rs number	#SNPs in gene
na	na	ACE	17q23	0.0713	rs4267385	20
rs1801725	0.7600	CASR	3q21	0.0209	rs3804588#	178
na	na	CYP19A1	15q21	0.00604	rs8029807#	114
rs6275#	0.2948	DRD2	11q23	0.1672	rs4587762#	76
rs1137101	0.5665	LEPR	1p31	0.0463	rs11808888#	239
rs7242169	na	MC4R	18q21	na	na	0

= imputed

Aim 2: Identify new genetic variants (exploratory)



P-value	Gene	Chromosome	Region in gene
2.2×10^{-10}	BCDIN3D	12q13	synonymous coding
6.1×10^{-7}	RYR1	19q13	synonymous coding
9.4×10^{-7}	NFATc1	18q23	3prime UTR

Sample:

- 1,680 unrelated Dutch adults
- from the Netherlands Twin Registry
- Mean age 44 (SD=14.6), 63% women

Phenotype:

- Survey data mainly from 2004
- Questions on type, frequency and duration of exercise
- Classification METHours:

Sedentary	0-3	51.6%
	4-12	22.5%
	13-21	13.2%
	22-30	5.7%
	31-39	2.5%
Vigorous	>=40	4.5%

Genotyping:

- Perlegen 600k SNP chip

Quality control:

- mapping, duplicate and mendelian errors
- maf > 0.01
- missing genotypes > 0.05
- 427,024 autosomal SNPs remain

Imputation:

- Software IMPUTE
- Based on HAPMAP Phase 2
- 2,135,543 imputed SNPs
- All SNPs maf < 0.05 excluded
- 413,568 observed
- 1,711,974 imputed SNPs

Genome-wide association test:

- Software SNPtest
- Taking genotype uncertainty into account
- Genotypic test (2 df)
- Sex and age included as covariates

Conclusions:

- No replication of candidate genes
- All associated variants are new variants
- Some of these genes (e.g. RYR1 and NFATc1) are expressed in the skeletal muscle, suggesting that exercise ability is related to the drive to exercise
- Replication samples are needed to confirm these results