

Genome-wide association study of smoking initiation and current smoking

JM Vink, AB Smit, EJC de Geus, P Sullivan, G Willemsen, JJ Hottenga, J Smit, WJ Hoogendijk, FG Zitman, L Peltonen, J Kaprio, NL Pedersen, PK Magnusson, TD Spector, K Ohm Kyvik, KI Morley, AC Heath, NG Martin, RGJ Westendorp, PE Slagboom, H Tiemeier, A Hofman, AG Uitterlinden, YS Aulchenko, N Amin, C van Duijn, BW Penninx, DI Boomsma [AJHG, 2009]

Background: Previous studies of smoking behavior or addiction vulnerability have listed the 20-50 most significant SNPs or genes while paying little attention to the remainder of the genes that might contribute to the trait.

Aim: To identify a biologically meaningful network of genes involved in smoking initiation and persistence using a novel variant of a pathway-based approach.

Method: GWA (genome wide association) using logistic regression analysis for smoking initiation and current smoking with sex and age as covariates in a discovery sample and 3 replication samples.

Samples:	n subjects	mean age	% ♀	% ever	% current
Discovery sample	3497	44	65	64	30
GenomEUtwin	1648	48	100	50	25
Rotterdam	5810	69	59	63	23
Leiden	405	60	57	72	13

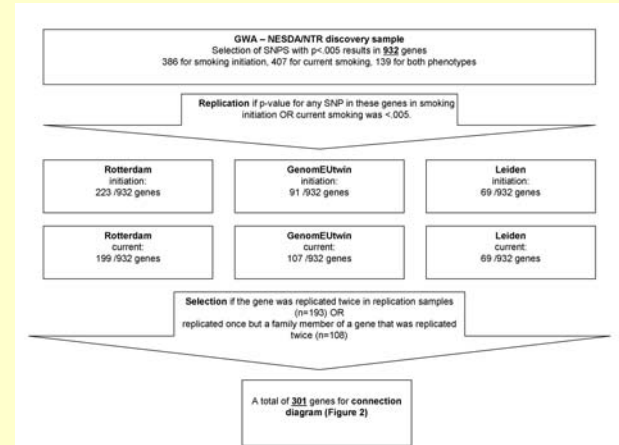


Figure 1 Selection procedure for connectivity diagram

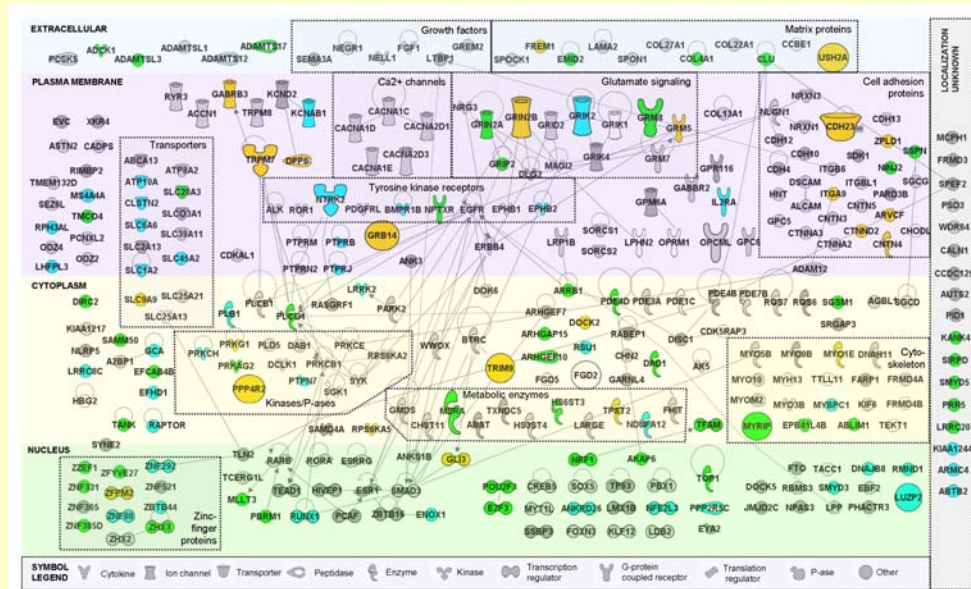


Figure 2. Connectivity diagram for replicated genes. Large symbols p -value < 0.0001 , small symbols $.0001 < p < .005$; green = smoking initiation; blue = current smoking; orange = both; light grey = empirical p -values > 0.10 ; dark grey $0.05 < \text{empirical } p < 0.10$ in discovery sample. Lines: direct connectivity i.e. protein-protein interaction / functional regulatory relationships.

Results: In total, 301 genes were replicated based on criteria in Figure 1. Those genes were grouped based on function, structure and location in cell of their encoded proteins (Figure 2).

Several interesting groups of genes were found including genes coding for glutamate receptors, tyrosine kinase receptors, transporters and cell adhesion molecules. Some members of those groups were associated with smoking or addiction in previous human studies, like GRIK2, GRM7, GRIN2A, NTRK2, SLC1A2, CDH13, NTRK2 while others were not: GRIN2B, GRB14.

Conclusion: Genes influencing smoking behavior tend to code for proteins that have similar biological functions. A network-based GWA approach offers additional insights at the level of biological interpretation. This approach could be useful for other phenotypes too.