Genome-wide association analyses of cotinine levels in two Dutch cohorts

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Background

Circulating levels of cotinine, one of the metabolites of nicotine, has been widely used as biomarker for assessment of exposure to cigarette smoking. Cotinine is a metabolite of nicotine. It has an average half-life of 18-20 hours (nicotine 2-3 hours). Level of cotinine is proportionational to the amount of exposure to tobacco smoke.

Aims

1. Are cotinine levels in smokers influenced by genes?
2. Which genetic variants are associated with differences in cotinine level in smokers?

Twin correlations	Rmz	Rdz	ßsex	ßage	ßncig
Model 1	.60	.10	-.225	.204	-
Model 2	.56	-.07	-.08	.10	.74

Twin correlations (aim 1)

Cotinine levels are influenced by genetic factors because Rmz > Rdz. Note: Rmz more than twice Rdz: genetic non-additivity?

Genome wide association analyses (aim 2)

See manhatten plot of Model A and Model B, with chromosome 1 to 22 on the x-axes and –log10(p) on the y-axes.

Methods

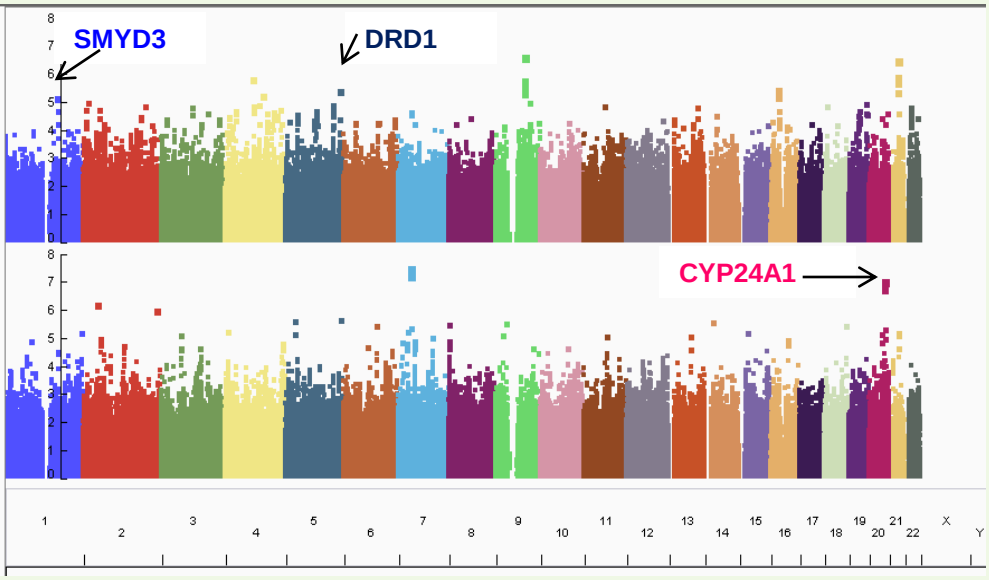
1 .Twin Study: N=888 twins (149 complete pairs) from the Netherlands Twin Register (NTR). All subjects are current smokers and cotinine levels are determined.
2 .GWA study: 781 subjects from NTR and 633 subjects from the Netherlands Study to Depression and Anxiety (NESDA). Data of 1444 smokers are available. Mean age 43.4 (SD 13.3), 61% female. Cotinine levels are measured in blood. DNA is genotyped. Non-genotyped SNPs are imputed.

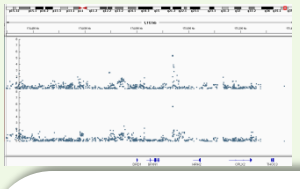
Analyses

1. Twin correlations for lnCotinine are estimated using Mx.
   A. Age and sex are modeled on the mean.
   B. Age, sex and ncig are modeled on the mean.
2. Genome wide association analyses are carried out in Plink.
   A. LnCotinine, additive model, covariates age and sex
   B. LnCotinine, additive model, covariates age, sex , ncig.

Conclusion

SMYD3= *histone lysine methyltransferase gene*, implicated in cell proliferation and carcinogenesis . Previous study: increased risk esophageal squamous cell carcinoma but in smokers only (Wang *et al*).
CYP24A1=*member of Cytochrome P450 superfamily, initiates degradation of Vitamin D3*. Previous study: assoication with lung cancer, and interaction with smoking dose (Dong et al).
DRD1= *dopamine D1 receptor gene*. In previous studies associated with addictive behavior. Two linkage studies to smoking (Duggirala et al, Vink et al). Associations with smoking abstinence across slow and normal nicotine metabolizers (Wonho Lee et al 2012). But note: our hit not in, but close to DRD1 gene.





General conclusions :

-Cotinine levels are influenced by genetic factors
-No genome-wide significant hits.
-Results model A/B different.
-Some potentially interesting results in genes previously associated with smoking.
-Next steps: increase sample size and run pathway analyses.

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