Using Functionally Annotated Polygenic Scores to Explore the Impact of Gene-Environment Interactions on Smoking Behavior

Lauren L. Schmitz, PhD, James Li, PhD, Qiongshi Lu, PhD, Jason Fletcher, PhD
University of Wisconsin-Madison

Background

Research evaluating the joint effect of tobacco control policies and polygenic risk factors for smoking behavior is needed to inform interventions that seek to reduce the persistence of cigarette smoking and nicotine addiction.[1-3] However, while the use of polygenic scores (PGSs) has increased statistical power to detect G x E interaction effects, identifying potential behavioral or pharmacotherapy interventions based on PGSs are difficult because whole-genome aggregation masks the specific genomic regions or cellular programs that are interacting with tobacco environments. Illuminating novel avenues to further tailor clinical and policy interventions will help reduce the public health toll from cigarette dependence in the U.S.

Study Aims

- Utilize data from population-based studies and a large multicenter RCT to identify sources of genetic and environmental heterogeneity that contribute to the efficacy of smoking interventions.
- Leverage genomic and epigenomic functional annotations related to smoking behavior to determine whether the use of PGSs that prioritize cell-specific regulatory pathways can improve the detection of G x E interactions and biological mechanisms for clinical intervention.

Data

Population-based studies and RCT data:

Study	N	Study Design	Phenotypes	Environment
Health and Retirement Study (HRS)	~15,000	Longitudinal, nationally representative	Smoking initiation, intensity, and cessation	State-level tobacco taxes and clean air laws
AddHealth	~9,000	Longitudinal, nationally representative	Smoking initiation, intensity, and cessation	State-level tobacco taxes and clean air laws
MIDUS	~2,000	Longitudinal, nationally representative	Smoking initiation, intensity, and cessation	State-level tobacco taxes and clean air laws
Lung Health Study	5,887	Randomized control trial (RCT)	Smoking cessation, cardiovascular, and respiratory health	Behavioral modification and nicotine replacement therapy (NRT)

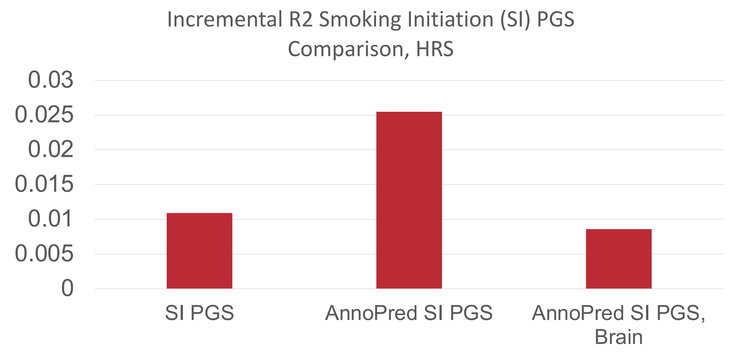
Cigarette tax data:

- Annual excise taxes per cigarette pack from The Tax Burden on Tobacco (Orzechowski & Walker, 2016) adjusted for inflation
- For HRS results on this poster, cigarette tax data span all available years the HRS cohorts were in adolescence or adulthood (1940-2016)

Clean air and youth access law data:

- State-level tobacco control polices obtained from ImpacTeen Project and the Non-Smokers' Rights Foundation (ANRF) databases
- Youth access and smoke free laws will be used both as control variables in cigarette tax G x E analysis and analyzed in separate G x E analysis

PGS Methods



We assess G x E using both traditional PGS and functionally annotated PGS

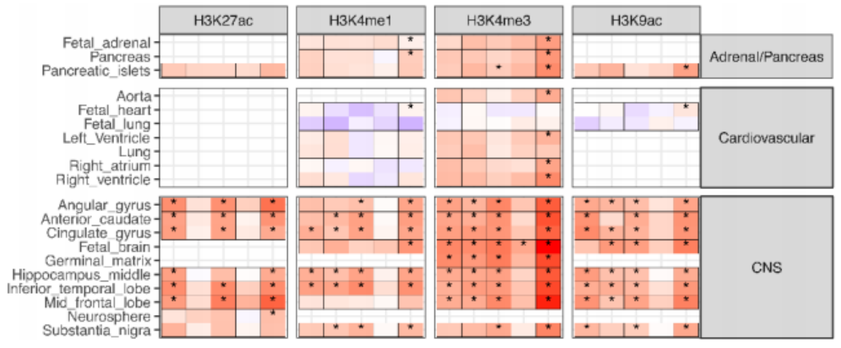
Traditional PGS: all available SNPs (p-value=1, no clumping/pruning)

Functionally annotated PGS: constructed using AnnoPred[4]

- Leverages genomic and epigenomic functional annotations
- Trained using GWAS summary statistics in an empirical Bayesian framework
- Utilizes functional annotation and LD patterns to adjust GWAS signals
- Has been shown to consistently improve genetic risk prediction

For all PGS results on this poster, we use SNP effect sizes from the GWAS of smoking initiation (SI) conducted by **GSCAN**[5] with HRS removed from the meta-analysis

Example of cell-type-specific enrichment in promoter and enhancer regions from GSCAN GWAS for various smoking phenotypes



Source: GSCAN, 2019

Empirical Model

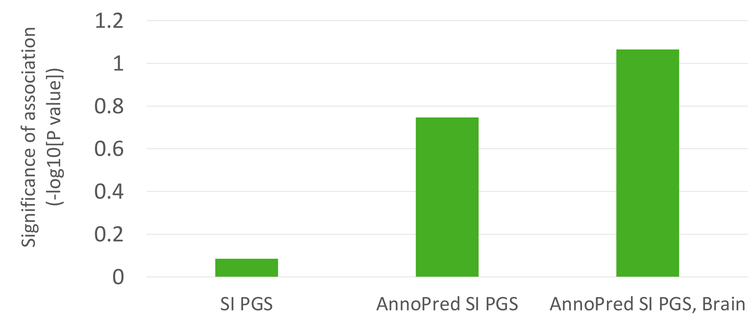
$$SmokingPhen_{isbt} = \pi_0 + \pi_1 CigTax_{st} + \pi_2 PGS_{isb} + \pi_3 CigTax_{st} * PGS_{isb} + X'_{isb}\pi_4 + S_s + B_b + P_{st} + \varepsilon_{isbt}$$

- $SmokingPhen_{isbt}$ is smoking phenotypes of interest for individual *i* in state s born in year *b* & interviewed in time *t*
- $CigTax_{st}$ is the state cigarette tax during adulthood or adolescence
- X_{isbt} is a vector of individual characteristics including sex, race, education, household wealth, and first 10 PCs of the genetic data
- S_s and B_b are fixed effects that control for time-invariant state & cohort characteristics
- P_{st} is a vector of state-level clean air and youth access laws

Preliminary G x E results: HRS

Impact of cigarette taxation in adolescence and polygenic risk on the probability of smoking initiation, Health and Retirement Study (HRS)

	SI PGS	AnnoPred SI PGS	AnnoPred SI PGS, Brain
Cigarette tax	-0.057*** (0.014)	-0.055*** (0.013)	-0.057*** (0.013)
PGS	0.054*** (0.005)	0.075*** (0.006)	0.043*** (0.005)
Cigarette tax*PGS	0.001 (0.005)	0.007 (0.005)	0.007* (0.004)
R2	0.084	0.096	0.082
N	7,776	7,776	7,776



Next Steps

- Test AnnoPred PGSs that upweight adrenal/pancreas and cardiovascular systems as well as PGSs that use functional annotation related specifically to enhancer and promoter regions
- Test GxE for smoking intensity (cigarettes per day or CPD)
- Carry-out replication analyses in AddHealth and MIDUS
- Examine RCT GxE effects on cessation and cardiovascular outcomes using the LHS
- R21 resubmission in progress to support this work

Works cited

1. Boardman, Jason D, Blalock, Casey L, & Pampel, Fred C. (2010). Trends in the genetic influences on smoking. *Journal of Health and Social Behavior, 51*(1), 108-123.
2. Boardman, Jason D, Blalock, Casey L, Pampel, Fred C, Hatemi, Peter K, Heath, Andrew C, & Eaves, Lindon J. (2011). Population composition, public policy, and the genetics of smoking. *Demography, 48*(4), 1517-1533.
3. Fletcher, J. M. (2012). Why have tobacco control policies stalled? Using genetic moderation to examine policy impacts. *PLoS One*, *7*(12).
4. Hu Y, Lu Q, et al. (2017). Leveraging functional annotations in genetic risk prediction for human complex diseases. *PLoS computational biology*.
5. Liu M et al.(2019). Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nature Genetics*. 51(2):237

Funding

This work was supported by a National Institute on Aging of the National Institutes of Health grant (**R00 AG056599**). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.