GENETIC ASSOCIATIONS WITH REGULAR SMOKING AMONG ADOLESCENTS: THE SOCIAL ENVIRONMENT AS A FUNDAMENTAL CAUSE*

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Abstract

This paper examines the interactive relationship between genetic characteristics and the social environment as a predictor of regular smoking among adolescents. Using a subset of the genetic sample of the National Longitudinal Study of Adolescent Health (n = 1,599) in conjunction with information regarding adolescents' friends, families, schoolmates, we find an association between the number of long alleles from the dopamine transporter gene DAT1 and the likelihood that adolescents will begin smoking regularly between Wave I and Wave II of the study. Our findings suggest that the effect of DAT1 on the risk of smoking is comparable in magnitude to the effects associated with three known risk factors: a) smoke in the household; 2) smoking among friends; and 3) smoking prevalence at respondent's schools. Equally important, preliminary results suggest that the effects of DAT1 on regular smoking are the strongest among adolescents from non-smoking environments.

Introduction

Social demographers and sociologists concerned with health-related behaviors of adolescents and young adults have made great efforts to operationalize and measure the normative environment of adolescent's schools, neighborhoods, and families; the social contexts in which youth primarily interact with one another (Berkman and Kawachi 2003). Given this interest, it is important for social scientists to be active participants in the growing field of behavioral genetics. Although social demographers have contributed to discussions regarding the role of genetic characteristics as potential determinants of health and well-being (Van den Oord & Rowe 2000), few have incorporated genetic information in their models--even those that are considered standard measures used in behavioral genetics. With an increasing number of data sets including genetic information of respondents, sociologists are poised to make important contributions to this growing and important body of work. The issues of structure, agency, and structuration (Giddens 1979) remain the guiding principles of our work and yet these important theoretical considerations have made little progress into the work of behavioral geneticists.

For example, in a recent and widely cited paper, Caspi and colleagues (Caspi et al. 2003) report that the presence of one or two copies of the short allele of the 5-HTT serotonin transporter significantly increased the risk of depression among adults, but only among those with an elevated number of stressful life events. Among those with stressful profiles (e.g., death of a loved one, divorce, criminal victimization, etc.), the authors found that those with this allele (π=.33) were twice as likely as those without the allele (π =.17) to be diagnosed with depression. However, absent these stressors, the presence of the short allele of 5-HTT had no bearing on adult's mental health. Thus, in their study,

the social environment was a critical determinant of genetic expression; the proximate cause of this particular aspect of health may have some genetic orientations, but the social context remains the fundamental cause (Link and Phelan 1995).

In this paper, we develop and test four hypotheses regarding the ways in which a particular genotype-phenotype relationship is structured by the social environment within which individuals interact with one another. We examine the association between the dopamine transporter gene polymorphism (DAT1) and the risk of smoking regularly among a nationally representative sample of adolescents in the U.S.. Importantly, we compare the association between DAT1 and this health-related behavior across the adolescent's primary social environments: a) family; b) friends; and c) schools.

Although previous researchers have demonstrated an association between genotype and tobacco use, none have carefully considered the moderating role of the social environment. For example, using data from the Add Health study Timberlake et al. (2005) find that both smoking initiation and subsequent frequency of smoking to be negatively associated with the presence of the 9-repeat allele of DAT1. Although there is some dispute regarding the nature of the samples involved, the study design, and the modeling techniques (see Jorm et al. 2000), these findings have been supported by several other important studies (Sabol et al. 1999).

[TABLE 1 ABOUT HERE]

In this paper, we examine three distinct but interrelated hypotheses (these hypotheses are summarized in Table 1): 1) the *direct genetic effect hypothesis* states that genetic characteristics are associated with the risk of smoking regularly among adolescents regardless of the smoking environment of adolescents; 2) the *social*

expression hypothesis states that genetic influences on regular smoking will only manifest among adolescents from environments in which a smoking is *relatively common*; and 3) the *genetic distinction and novelty seeking hypotheses* state that genetic influences will only manifest among adolescents whose social environments contain *few* smokers.

Data

Data for this study come from the genetically informative supplement of the National Longitudinal Study of Adolescent Health (Add Health). In total, genetic information on 2,612 subjects was collected and complete genotypes (for DAT1 polymorphisms) were available for 2,521 adolescents. Bucal cells were collected at Wave III –year 2003- of the study and DAT1 VNTR was genotyped as described elsewhere (Anchordoquy et. al, 2003). Allele frequencies for the 9-repeat (9R) and the 10-repeat (10R) for this polymorphism were .21 and .77, respectively. Those with neither of these two alleles (n=99) were deleted from the sample.

In the present analyses, regular smoking is assessed at Waves I and II. Adolescents were asked if they have "ever smoked cigarettes regularly, that is, at least 1 cigarette every day for 30 days?" At Wave II, respondents were asked to report the month and year that they began smoking regularly. In this paper, we chose to employ relatively strict selection criteria; specifically, we deleted those who reported regular smoking at Wave I of the study. In this way, we model the duration to smoking onset among previous non-smokers. We use characteristics measured at Wave I to predict the timing of smoking onset adjusting for differences in exposure between the respondents. A traditional Cox Proportional Hazards model deals with data such as these quite nicely.

The survey commands available in Stata 9.0 enable us to further adjust for design effects and oversampling in the complex Add Health Survey design.

We focus my analyses on three measures of the smoking environment: 1) home; 2) friends; and 3) school. To assess home-exposure we include a variable that asks respondents if cigarettes are available in their homes. Friend smoking exposure is assessed by response to a question that asks respondents to report the number of their three closest friends that smoke. If respondents reported any number of smoking friends they were coded "1" and if they reported that none of their three closest friends smoked then they received a score of "0". Finally, using the full in-school survey (roughly 80,000 students), school-level usage prevalence was estimated for all schools by dividing the number of smokers by the total number of respondents per school. In total, school level information was obtained from 131 schools. The variable included in the models is a continuous variable measuring the percent of students who reported smoking within the past year.

Preliminary Results

As a preliminary step, ACE heritability estimates based on the comparison between intra-twin correlation between identical and fraternal same-sex twins were calculated using the following formulae:

$$A = 2(r_{mz} - r_{dz})$$
$$C = 2r_{dz} - r_{mz}$$
$$E = 1 - r_{mz}$$

According to these results (estimates not presented), roughly one-third of the variation in regular smoking among adolescents may be attributed to genetic characteristics (A) unique to individuals although the bulk of the variation in this

behavior (nearly one-half) can be explained by the shared environment among siblings. The estimates for heritability are consistent with estimates obtained from adult populations for smoking initiation but are significantly lower than comparable estimates for consistent tobacco use (Li et al. 2003).

[TABLE 2 ABOUT HERE]

To more fully examine the association between genotype and smoking outcomes, Table 2 presents parameter estimates from a series of Cox proportional hazards models that describe the effect of the DAT1 genotype on the risk of regular smoking. As discussed earlier, these models estimate the timing of the onset of regular smoking in months among those who reported no regular smoking in Wave I. The estimates in Table 3 control for age (years), gender, race (non-Hispanic white vs. all others), mother's education (years), and grade point average. According to the results, DAT1 genotype is positively and significantly associated with an increase in the risk of regular smoking in adolescence. The likelihood ratio $(\chi^2 = 26.70, df = 1, p < .001)$ suggests that the inclusion of this one covariate significantly improves the overall model fit.[2]

Models 2-4 are intended to assess the relative contribution of smoking environment characteristics to overall model fit. As expected having friends that smoke, the presence of cigarettes in the household, and attending a school with a high number of smokers positively increases the risk of smoking regularly among adolescents. Interestingly however, none of these well established risk factors for smoking (Alexander et al. 2001; Vink et al. 2003) are as strong of a predictor as the single variable assessing the number of long alleles on DAT1. Even taken together, the improvement in the overall model fit (Model 5) is only slightly better than the change from the baseline model to

Model 1. There is a great deal of concern regarding the selection of adolescents with DAT1 into high smoking environments but this does not appear to be the case as the estimated net effect of DAT1 increases after considering the smoking environment characteristics (Model 6). The survival estimates as a function of genotype are plotted in Figure 1.

[Figure 1 About Here]

The goal of the preceding analysis was to consider the relative impact of the social environment vis-à-vis genetic characteristics in determining smoking behaviors among adolescents. However, one of the primary aims of this paper is to examine the role of the social environment as a moderating mechanism. In other words, as stated earlier, the effects of genotype (DAT1) should depend on the environment in which adolescents are socialized. Thus, Cox proportional hazards models similar to the one presented in Model 1 of Table 2 were estimated separately for adolescents based on the number of social contexts in which they are exposed to smokers (friends, family, or school). We originally estimated a model for adolescents with summary scores for their smoking environments of 0, 1, 2, and 3. However, only 9 adolescents from smoking environments with scores of 0 began smoking regularly by Wave II and all nine of these adolescents had a DAT1 genotype of 10-10. Thus, the model failed to converge. Accordingly, we estimated an interaction with genotype and the standardized smoking environment measure as a continuous variable. This measure includes the percent of smokers in the schools, the number of friends (0-3) that smoke, the presence of cigarettes in the home, and maternal/paternal reports of smoking.

This single variable was then included as a predictor of smoking (see Table 3) and a subsequent model was estimated with this variable interacted with genotype. The direction and magnitude of the results are consistent with the genetic distinction/novelty seeking hypotheses, although the parameter estimates do not reach traditional levels of statistical significance.

[Table 3 About Here]

Conclusion

This paper makes an important contribution to the emergent role of Sociologists in the fields of Biodemography and Behavioral Genetics. To better understand the mediating and moderating nature of the social environment, Sociologists stand to make important comments regarding the operationalization and measurement of the 'environment' as well as providing insights into the interpretation of results. Here, the social environment is seen as important in at lesat two ways: 1) variables associated with social-demographic and socio-economic characteristics remain powerful predictors of regular smoking; 2) the relationship between genotype and phenotype –with respect to this genotype and this phenotype– is conditional upon the social environment. Thus, we argue that the social environment should be considered a fundamental cause of the genotype-phenotype relationship with respect to smoking behaviors among adolescents.

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Table 1. Social environment by genotype interactions: The direction of the anticipated association between DAT1 and regular smoking among adolescents as a function of the level of smoking in adolescent's environments.

	Prevalence of Smoking in Social Environments	
	Low	High
Direct Genetic Effect	+	+
Social Expression	0	+
Novelty Expression/Genetic Distinction	+	0

Table 2. Cox proportional hazards estimates: regular smoking onset among adolescents

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
DAT1 Genotype	3.67 ***					3.77 **
Friends smoke		3.16 **			2.88 *	3.07 **
Cigarettes in the Household			2.37 *		2.17 *	2.05 *
School smoking				1.17 *	1.15 +	1.15 +
School smoking^2				0.99 +	0.99 +	1.00
Smoking context						
Likelihood ratio	26.70 ***	23.96 ***	14.30 **	6.92 *	39.46 ***	66.10 ***

Note: *** p < .001, ** p <.01 * p<.05, + p <.10
Source: National Longitudinal Study of Adolescent Health (Waves I-II; genetically informative sample only).
All estimates weighted. Robust standard error estimates calculated for family level clustering.

Figure 1. Survival estimates: Based on Cox proportional hazards model

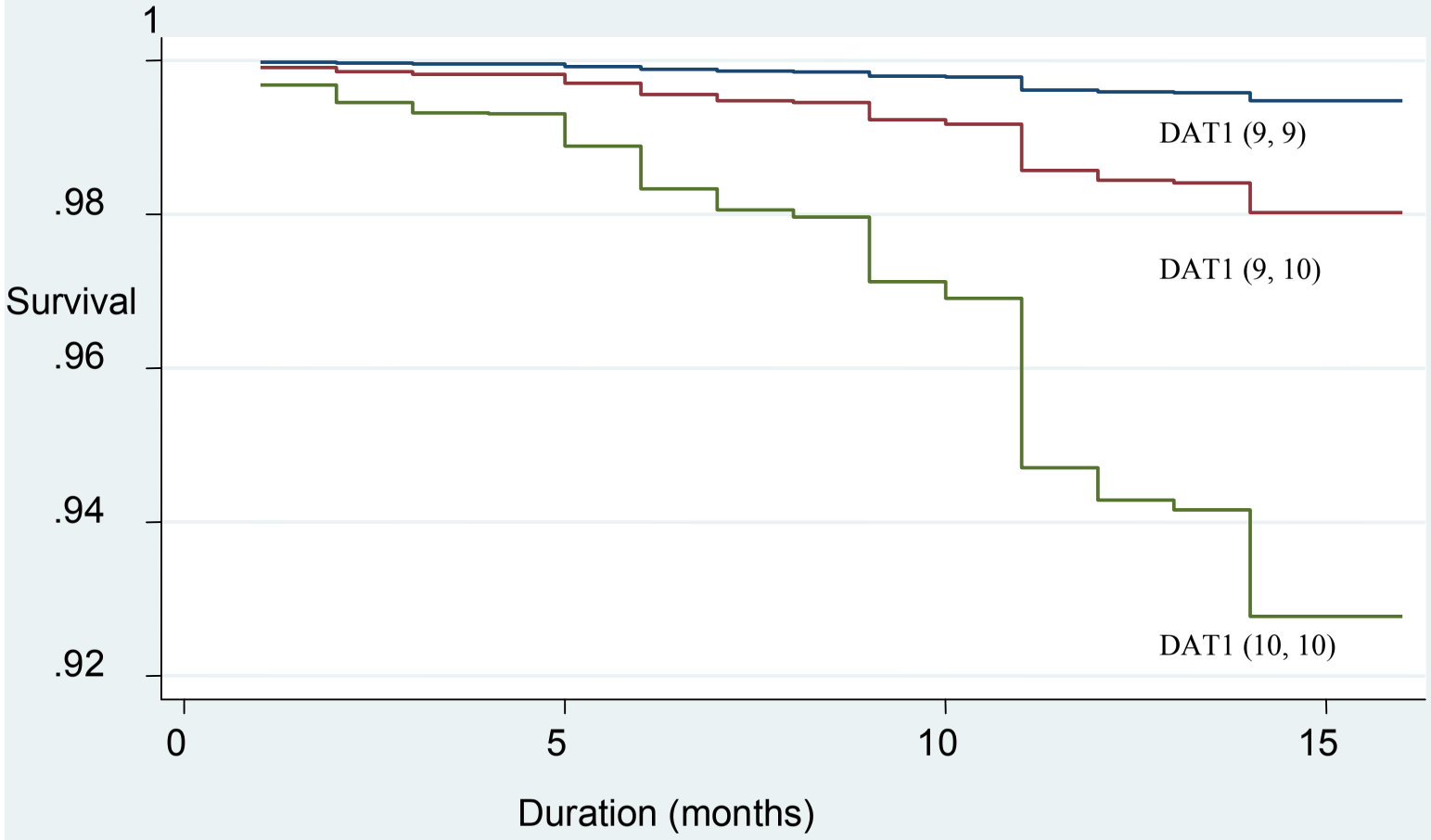

Table 3. Cox proportional hazards estimates: genotype by social environment interactions

	Hazard Ratio	Robust standard error	z	p>|z|
		Main Effects		
Smoking Environment (SE)	2.06	0.49	3.03	0.002
DAT1	3.53	1.36	3.27	0.001
		Main Effects with Interaction Term		
Smoking Environment (SE)	5.69	8.12	1.22	0.223
DAT1	4.14	2.16	2.71	0.007
SE*DAT1	0.70	0.36	-0.69	0.492