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Interplay of Genetic Risk Factors and Parent Monitoring in Risk for Nicotine Dependence

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Abstract

Background—Several studies have found replicable associations between nicotine dependence and specific variants in the nicotinic receptor genes *CHRNA5(rs16969968)* and *CHRNA3(rs3743078)*. How these newly identified genetic risks combine with known environmental risks is unknown. This study examined whether the level of parent monitoring during early adolescence modified the risk of nicotine dependence associated with these genetic variants.

Methods—In a cross-sectional case control study of US-based community sample of 2027 subjects, we use a systematic series of regression models to examine the effect of parent monitoring on risk associated with two distinct variants in the nicotinic receptor genes *CHRNA5(rs16969968)* and *CHRNA3(rs3743078)*.

Results—Low parent monitoring as well as the previously identified genetic variants were associated with an increased risk of nicotine dependence. An interaction was found between the SNP(*rs16969968*) and parent monitoring ($p=0.034$). The risk for nicotine dependence increased significantly with the risk genotype of SNP(*rs16969968*) when combined with lowest quartile parent monitoring. In contrast, there was no evidence of an interaction between SNP(*rs3743078*) and parent monitoring ($p=0.80$).

Conclusions—The genetic risk of nicotine dependent associated with *rs16969968* was modified by level of parent monitoring, while the genetic risk associated with *rs3743078* was not, suggesting that the increased risk due to some genes may be mitigated by environmental factors such as parent monitoring.

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Declaration of Interest:

Drs. LJ Bierut, AM Goate, AJ Hinrichs, JP Rice, and JC Wang are listed as inventors on a patent (US 20070258898) held by Perlegen Sciences, Inc., covering the use of certain SNPs in determining the diagnosis, prognosis, and treatment of addiction. Dr. N Saccone is the spouse of Dr. S Saccone who is listed on the above patent. Dr. Bierut has acted as a consultant for Pfizer, Inc. in 2008.

Keywords

nicotine dependence; parent monitoring; phenotype; gene-environmental interaction; nicotinic receptor genes; case control study

INTRODUCTION

Tobacco smoking is a serious public health problem associated with significant morbidity and mortality (1). The prevalence of current smoking in US adults remains high: 20.8% in 2006 (2). Adolescents continue to initiate smoking (3–5), and many who smoke become dependent (6). Increasing our understanding of the etiology of nicotine dependence is critical for identifying new opportunities for interventions to prevent development of nicotine dependence and treatments to improve cessation rates. It has been understood for some time that both genes and environmental factors influence the development of nicotine dependence (7–10). However, the synthesis of specific genetic and environmental risks for nicotine dependence is just beginning (11,12). In this study, we examine whether level of parent monitoring modifies the risk of nicotine dependence associated with two genetic variants in the nicotinic receptor genes *CHRNA5(rs16969968)* and *CHRNA3(rs3743078)*.

Genetic variants in the nicotinic receptor gene cluster on chromosome 15 show important associations with nicotine dependence (13–15). There is evidence of at least two distinct signals in this gene cluster. The most compelling finding is with rs16969968, a non-synonymous coding SNP in exon 5 of *CHRNA5*, the $\alpha 5$ nicotinic receptor subunit gene which appears to be a functional variant (13). Another SNP, rs3743078, is a proxy for rs578776 in the 3' UTR of *CHRNA3* which has a low correlation with rs16969968 ($r^2 = 0.15$), is also strongly associated with nicotine dependence. These two genetic associations have been replicated in several independent studies (16–20). The same gene cluster on chromosome 15 was also reported to be associated with lung cancer (18,21–23).

Opportunities to initiate smoking and to smoke regularly are important steps in the development of nicotine dependence and are necessary for the expression of genetic vulnerability. Level of parent monitoring of children's whereabouts and activities may significantly impact smoking opportunities and thereby influence risk of nicotine dependence. Indeed, higher parent monitoring is associated with reduced risk of smoking during adolescence (24–26), and appears to have continuing effects up to young adulthood (27). The least monitored children may be more easily exposed to environments where cigarettes are readily available and to peers who smoke cigarettes. This environmental exposure to cigarettes and to opportunities to smoke may not only increase the risk for smoking initiation, but also increase the risk for becoming dependent on nicotine for individuals with or without genetic susceptibility for nicotine dependence.

Relating genetic vulnerability and parent monitoring, Dick and colleagues have recently published two longitudinal studies of Finnish adolescent twins examining parent monitoring and number of cigarettes smoked in which they observed substantial moderation effects associated with prior parent monitoring: under high parent monitoring 15% of the variance in smoking was attributable to additive genetic risk whereas under low parent monitoring 60% of the variance in smoking was attributable to additive genetic risk (28,29). This suggests that high levels of parent monitoring may restrict expression of genetic predisposition for adolescent smoking. Such environmental moderation of genetic risk may extend to nicotine dependence in adulthood.

Such twins-based studies are highly informative for identifying the interplay between specific environmental risk factors and the general heritability of a phenotype. However, by their nature, these studies do not identify which specific genetic risks are modified by environmental exposures. Using data from the Collaborative Genetic Study of Nicotine Dependence (COGEND), we extend this research on the modifying effects of parent monitoring to examine nicotine dependence among adults and specific high priority genetic variants. With previous findings showing risk genotype (AA) for SNP rs16969968 and protective genotype (CC) for SNP rs3743078, a proxy for rs578776, associated with nicotine dependence as two distinct genetic risk factors (14), we test whether the genetic risks associated with these genotypes vary with level of parental monitoring during middle childhood. We test specifically if genetic and environmental risks are additive, and if there is a multiplicative interaction between them. Our key hypothesis on this relationship is that the known genetic risks will be highest among those with deviant parent monitoring, defined as lowest quartile in parent monitoring score. To the extent this hypothesis is supported, risk of nicotine dependence associated with these genes may be mitigated by interventions targeting parent monitoring.

METHODS

Subjects

All subjects (1032 cases and 995 controls) were selected from the Collaborative Genetic Study of Nicotine Dependence (COGEND), a US-based community sample aged 25–44 years of age from Detroit and St. Louis, recruited through telephone screening. The Institutional Review Board approved the study and all subjects provided informed consent to participate. Blood samples were collected from each subject for DNA analysis and submitted together with electronic phenotypic data to the NIDA Center for Genetic Studies (<http://www.nidagenetics.org/>). All subjects self-identified as being of European descent (30). See Table 1 for the sample characteristics.

Nicotine Dependent Case Definition—Nicotine dependent cases were identified as current smokers with a Fagerström Test for Nicotine Dependence (FTND) score of 4 or more (maximum score of 10) (31). The FTND is a quantitative scale commonly used for the definition of nicotine dependence and allows selection of extreme-scoring cases and controls (32).

Non-Dependent Smoking Control Definition—Controls were defined as smokers (individuals who smoked at least 100 cigarettes lifetime), but who never had any symptoms of dependence (lifetime FTND=0). The threshold of 100 cigarettes smoked over the lifetime is commonly used and has been employed by several major surveys such as National Survey on Drug Use and Health. By selecting controls who smoked, we focused on those genetic effects that are specific to the development of nicotine dependence rather than smoking initiation. Subjects with an FTND score of 1, 2, or 3 were excluded from this study. This design was to create a comparison between active nicotine dependent cases and a clean control group without ANY symptoms of dependence (FTND=0). This contrast was created to maximize the power to detect differences in any genetic or environmental risks between cases and controls.

Measurements

Genetic Data—Blood samples were collected for genetic analyses. Initial genotyping was performed by Perlegen Sciences using custom arrays as previously detailed and follow up genotyping was done by the Center for Inherited Disease Research (CIDR) using Illumina

Golden Gate technology (14,15,30). For this study, we focused on two SNPs, rs16969968 and rs3743078 (a proxy for rs578776), located in *CHRNA5* and *CHRNA3* respectively.

Parent Monitoring—All subjects were personally interviewed using the Semi-Structured Assessment for Nicotine Dependence (SSAND) which was developed specifically for COGEND and was modeled after the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (33,34) and Composite International Diagnostic Interview (CIDI) (35). As part of the assessment interview, level of parent monitoring in middle childhood (grades 7–8) was assessed in relation to an 9-item scale, adapted and modified from Capaldi and Patterson (1989) (36) and shown to be reliable (Cronbach's $\alpha=0.83$). The construct validity of the parent monitoring scale used in this study was supported by the robust associations between parent monitoring and the child problem outcomes (24). The reliability and validity of the same instrument has been reported in previous studies (38,47–49). The focus of these items is on the supervision and monitoring provided by parent or other responsible caretakers, including babysitters and other after-school or evening caretakers. The subjects were prompted in the interview to report the parent monitoring they experienced in childhood. The questions asked the subjects to report on the degree to which their parent expected a specific time for them to come home, noticed them coming home later than expected, and arriving home soon after they arrived home from school. In addition, the questions asked the subjects to report the degree to which they told parent when they would be back, left a note about where they were going, checked in with parent before going out again, knew how to get in touch with parent, and talked with parent about their plans for the coming day. Responses were made on a 5 point scale from “all of the time” to “never”. The subject's responses to these standardized items were summed to form an ordinal scale. For analyses, we used pre-specified categories (i.e., quartiles) and the distribution of parent monitoring and SNPs were presented in Table 1. Low parent monitoring was defined by the lowest quartile in the parent monitoring sum of scales. These are subjects who reported their parents sometimes, hardly ever or never monitored them during middle childhood whereas the subjects in higher quartiles reported their parents monitored them all of the time or most of the time.

Analyses

Our primary association analyses of case-control status use logistic regression models which include age and gender as covariates. A standard series of regression equations to test main effects and gene – environment interaction were used. After the initial set of univariate logistic regression models for each covariate, we examined the main effects of each SNP and environmental risk factors jointly.

$$\text{Gene\&Environment Effect on Phenotype } \ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 G + \beta_2 h \quad \text{Equation 1}$$

$$\text{Gene} \times \text{Environment Interaction} \ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 G + \beta_2 h + \beta_3 hG \quad \text{Equation 2}$$

where p is the probability of being a case, α is the intercept, h is parent monitoring coded in quartiles, and G represents genotype. Equation 1 provides adjusted estimates of risk due to genotype and environmental exposure; Equation 2 provides a test of genotype by environmental exposure interaction. Age and gender was also included as covariates in the models. For each SNP, we examined whether there is a statistically significant multiplicative

interaction between parent monitoring risk levels and the risk gene represented by the SNP, as described in Regression Equation 2 in the above diagram. The interactions between specific risk and protective genotypes and lowest quartile parenting monitoring were tested. In addition, dummy variables were created to combine the genetic risk and environmental risk levels in multivariate models using the group with least genetic risk and highest quartile parent monitoring as the reference group.

As reported previously, after accounting for the linkage disequilibrium (LD) structure in the region, rs16969968 and rs3743078 (a proxy for rs578776) were identified to be two distinct, significant associations with nicotine dependence. The LD between rs3743078 and rs16969968 was r^2 (squared correlation)=0.15 overall with $D'=-1.0$, due to the LD being in repulsion phase. The prior joint genotype analysis showed the zero cells for certain combination genotypes between the two SNPs (14). For example, the high risk genotype AA at rs16969968 occurs only in combination with the homozygous risk genotype CC at rs3743078. Joint analysis of the uncorrelated SNPs rs3743078 and rs16969968 indicates that these two variants each exert independent influence on nicotine dependence vulnerability. These two variants demonstrate an interesting evolutionary history, with the risk allele for rs16969968 occurring on the background of the higher risk variant for rs3743078. Although not all genotype combinations occur because of this history, the three genotypes at one locus on a fixed background for the other demonstrate a clear pattern of altered risk. Therefore, in order to verify the above analyses, we conducted our test of interaction logistic regression models for rs16969968 while holding constant the genotype of rs3743078, and vice versa.

RESULTS

Testing Main Effects of Parent Monitoring and Genes on Nicotine Dependence

In bivariate logistic regression models, nicotine dependence was found to be associated with the lowest quartile parent monitoring, genotype (AA) of rs16969968, and genotypes (CG, GG) of rs3743078, adjusting for age and gender (Table 2 bivariate models).

Testing Genes by Parent Monitoring Interactions for Risk of Nicotine Dependence

Rs16969968 and Parent Monitoring—The hypothesis of a possible multiplicative interaction between risk genotype (AA) and environmental risk (lowest quartile parent monitoring) was tested in Multivariate model 2 (Table 2 left panel). This model showed an interaction between the risk genotype (AA) of rs16969968 and lowest quartile of parent monitoring ($p=0.034$), controlling for age and gender. Due to the evolutionary relationship between rs16969968 and rs3743078 as detailed in the methods section, we tested this result and the interaction between lowest quartile parent monitoring and risk genotype of rs16969968 (AA) while holding the rs3743078 genotype constant (GG) by conducting the same analyses in subjects with the same genotype for rs3743078 (CC) (14). We found a similar interaction between the risk genotype (AA) of rs16969968 and lowest quartile parent monitoring ($p=.009$).

Rs3743078 and Parent Monitoring—In contrast to the findings with rs16969968, there was no evidence of an interaction between rs3743078 and parent monitoring ($p=.80$, see multivariate model 2 in Table 2 right panel). Because rs16969968 and rs3743078 are two evolutionarily related SNPs with distinct genetic effects (14), we tested this result and the interaction between lowest quartile parent monitoring and risk genotype of rs3743078 (CG/GG) while holding the rs16969968 genotype constant (GG) by conducting the same analyses in subjects with the same genotype for rs16969968 (GG). The interaction between rs578776 and parent monitoring was still not significant in the multivariate logistic

regression model, even when another genetic risk factor rs16969968 was held constant ($p=.60$).

Illustrating the Combined Genetic Risk (rs16969968, rs3743078) and Parent Monitoring Risk

In order to illustrate more clearly the risk for nicotine dependence based on the combined genetic and environmental risk factors, we present in Figure 1 estimates from a multivariate logistic regression model for rs16969968. Using the group with higher quartiles of parent monitoring and lowest risk genotype (GG) as the reference group, Figure 1 displays the odds ratios for varying levels (higher quartiles vs. lowest quartile) of parent monitoring combined with genetic risk levels of rs16969968 (GG, GA, AA). Proceeding from the left panel with lowest risk genotype (GG) to the right panel with highest risk genotype (AA), we observe the pattern of increased genetic risk indicated by the dotted broken lines. Further, the right panel shows that the effects of the risk genotype (AA) were not homogeneous across levels of parent monitoring. The genetic risk was markedly increased in the lowest quartile of parent monitoring, compared with higher levels of parent monitoring.

Figure 2 shows the corresponding results for rs3743078, using the group with highest quartile parent monitoring and risk genotype (CC) as the reference group. Figure 2 shows an increasing trend in odds ratios with intensified environmental risk levels. We observed effects of protective genotypes, but the environmental risk patterns across genetic risk levels were similar.

DISCUSSION

Our study represents one of the first examples in which specific genes and environmental risks are jointly studied to understand how environmental risk might modify the genetic risks for nicotine dependence. Testing the hypothesis that level of parent monitoring modifies the known risk of nicotine dependence associated with two distinct variants in nicotinic receptors (*CHRNA5* and *CHRNA3*), we found a statistically significant interaction between level of parent monitoring and SNP rs16969968 (*CHRNA5*) but not SNP rs3743078 (*CHRNA3*).

A family environment which is characterized by parents who sometimes, hardly ever or never monitored their middle school aged children's whereabouts fell into the lowest quartile of parent monitoring whereas higher quartiles are characterized by parents who monitored their children most or all of the time. For example, 72.6% of subjects in lowest quartile parent monitoring reported sometimes, hardly ever or never left a note for their parents about where they were going, in contrast with only 5.1% of subjects in higher quartiles. About 42.3% of subjects in lowest quartile parent monitoring reported parents sometimes, hardly ever or never knew if they came home an hour late on weekends, in contrast with only 2.8% of subjects in higher quartiles. In addition, we found in our data that the association between levels of parent monitoring and nicotine dependence is not linear. Individuals with the lowest quartile of parent monitoring was associated with a significantly increased risk and there was no gradient in the remaining three quartiles. This is consistent with a prior study showing only the lowest quartile level of parent monitoring was associated with a sustained higher risk of drug initiation (24). Furthermore, when we tested the interactions between the risk genotype and each of the quartiles of parent monitoring, we found a similar non-linear effect showing the interaction only between the risk genotype and the lowest quartile, without gradient in the remaining three quartiles.

The finding that the genetic risk associated with rs16969968 was reduced in subjects with high parent monitoring, and increased in subjects with low parent monitoring suggests that

exposure to low parent monitoring during the middle school period creates an environment that allows for greater opportunity to express this genetic predisposition. These results are in line with findings from the Finnish twin studies, which suggest that parent monitoring modifies the importance of genetic influences on adolescent smoking; genetic influences assuming a far greater importance at low levels of parent monitoring (28,29).

In contrast, however, the genetic risk associated with another SNP rs3743078 did not vary with level of parent monitoring. Protective genotypes of rs3743078 and parent monitoring showed independent and additive associations with nicotine dependence. Thus these results indicate the likely complexity of the interplay between specific genetic and environmental risks for nicotine dependence.

The results of this study should be interpreted in the context of several limitations. First, our assessment of parent monitoring was based on self report, as elicited with multi-item questions, which is less comprehensive than multi-informant assessments from both parents and children (37). Second, the retrospective nature of this study's ascertainment of childhood environmental risk exposures is subject to recall bias, which may have affected the validity and reliability of reported parent monitoring. However, this concern is reduced somewhat given that our main effects association of parent monitoring with nicotine dependence is consistent with longitudinal work among adolescents (24). Third, our measure of parent monitoring is one of various instruments assessing parent monitoring, and does not differentiate different aspects of parenting practices such as parent involvement and parent discipline (24,38). Fourth, we also have to be cautious in labeling parent monitoring solely as an environmental risk, as parent monitoring itself may be influenced by both genetic and environmental factors, reflecting both genetically-influenced characteristics of the parents (39–42), though neither genetic variant examined here was correlated with parent monitoring ($r=0.03$, $p=0.18$ for rs16969968; $r=-0.03$, $p=0.18$ for rs3743078). Fifth, we found no significant difference in the associations between parent monitoring and nicotine dependence between the genders in this data by testing the interaction between gender and parent monitoring ($p=0.071$). The genetic risks associated with the risk genotype rs16969968 were not statistically different across gender (OR=2.15 for men; 1.82 for women). Because of the possible difference in parent monitoring across gender, we redefined our lowest quartile parent monitoring within each gender group to ensure that the comparisons are made within the same gender group. In gender-stratified analyses, we found the similar pattern of stronger gene-modifying effects of parent monitoring in females than in males. In women, OR for risk genotype = 1.49 with higher monitoring increased to 4.08 with low parent monitoring. In men, OR for risk genotype = 2.03 with higher monitoring increased to 2.76 with low parent monitoring. However, there is a potential gender difference in the interaction between lowest quartile parent monitoring and risk genotype of rs16969968, which may be beyond the statistical power of the current study sample. However, there are many more environmental and personal risk factors (e.g., childhood adversity, peer use, parental smoking, and personality characteristics) as well as specific genes that influence the development of nicotine dependence than were examined here (43–46). The variance (r^2) explained by these two SNPs and parent monitoring is 4.2%. We anticipate the discovery of many more genetic and environmental risks associated with the development of nicotine dependence. More complex and complete models will need to be developed in the future. Another limitation is the ascertainment bias. The estimation of gender-specific prevalence of nicotine dependence needs to take into account the ascertainment bias. However, we were able to control for the potential confounding effects of gender in our study when examining the association between genetic/environmental risks and nicotine dependence in multivariate regression models. Caution is needed in interpreting our findings on the interplay between genetic risk and parent monitoring because replications in independent samples are necessary.

The statistical power in testing gene-environment interaction is a function of sample size, prevalence and relative risk of risk genotype, prevalence and relative risk of environmental factors, type I error, and hypothesized G*E interaction relative risk. The power of our study sample (N=2027) to detect a gene-environment interaction relative risk of 2.50 or higher between SNP rs16969968 (risk genotype frequency 12.5%) and low parent monitoring (prevalence 22.9%) is estimated to be 0.70 at $\alpha=0.05$. We found a significant interaction between rs16969968 and parent monitoring. Our study sample has the sufficient power greater than 0.80 to detect a gene-environment interaction relative risk of 1.85 or higher between SNP rs3743078 (protective genotype frequency 40.2%) and low parent monitoring (prevalence 22.9%) at $\alpha=0.05$. However, we found no significant interactions between rs3743078 and parent monitoring.

While acknowledging the limitations of our work, we note that this work complements prior research on parent monitoring (24,29,38), and provides novel and significant findings. In addition to estimating how parent monitoring may alter the overall genetic risk, we extended the results to adults, and more importantly to the study of specific risk genotypes. It is also important to note that the difference in results between our two SNPs suggest that environmental modification of genetic risk is not uniform. Therefore, it is critical to look at specific genetic risks as some may be modified by an environmental factor while other genetic risks may not be.

Although replication of this study's results are needed, our findings strengthen the case for development and rigorous testing of prevention strategies that target parent monitoring as a potentially malleable risk factor for nicotine dependence, in particular among individuals with the high risk genotype of rs16969968. It is possible that those with moderate to high parent monitoring during middle school ages have significantly more limited opportunities for experimenting with tobacco or smoking regularly, and the likelihood of developing nicotine dependence for those individuals is reduced despite the increased genetic risk. This possibility is consistent with previous studies that suggested that higher levels of parental involvement/reinforcement might help shield youths from substance exposure opportunity from mid-childhood to early adulthood, indicating a possible mechanism of protection against early-onset substance involvement (38), and which creates an environment that minimizes the opportunity to express genetic predispositions. However, when adolescents receive low parent monitoring, it creates a different environment that allows for greater opportunity to express genetic predispositions to develop nicotine dependence. Though parent monitoring is good for all, in the context of the genetic risk for nicotine dependence, it is more salient for those with the rs16969968 risk genotype.

These results are beginning to fill gaps in our understanding of the joint association of specific genes and environmental risk factors with nicotine dependence. The presence of an interaction between identified risk genes and environmental factors suggests that environmental risk factors may accentuate the effect of specific risk genes for nicotine dependence. Identification of environmental factors that might modify the expression of specific risk genes will allow for the development of more effective interventions. These analyses lay the ground work for future prospective studies.

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Figure 1.
Odds Ratios for Nicotine Dependence: Synthesizing Risk SNP rs16969968 and Environmental Risk (Low Parent Monitoring)

Figure 2.
Odds Ratios for Nicotine Dependence: Synthesizing Risk SNP rs3743078 and Environmental Risk (Low Parent Monitoring)

Table 1

Study Sample Characteristics

	Total		Nicotine Dependent		Controls	
			Current FTND ≥ 4		Lifetime FTND=0	
Total	2027	100%	1032	100%	995	100%
Gender, N (%)						
Male	781	38.5%	475	46.0%	306	30.8%
Female	1246	61.5%	557	54.0%	689	69.2%
Age, years, Mean (SE)	36.4	0.12	36.9	0.17	35.9	0.18
SNP Rs1696968, N(%)^a						
GG	869	42.9%	403	39.1%	466	46.9%
GA	903	44.6%	462	44.8%	441	44.4%
AA	253	12.5%	166	16.1%	87	8.7%
SNP Rs3743078, N(%)^b						
CC	1208	59.8%	656	63.5%	552	55.9%
CG	707	35.0%	335	32.5%	372	37.6%
GG	105	5.2%	41	4.0%	64	6.5%
Parent Monitoring, N(%)^c						
Higher quartiles	1529	77.1%	711	71.0%	818	83.3%
lowest quartile	455	22.9%	291	29.0%	164	16.7%

^a N=2025,

^b N=2020,

^c N=1984, due to missing data on specific variables.

Table 2

Logistic Regression Models of Nicotine Dependence: Risk SNP (rs16969968, Rs3743078) and Environmental Risk (Parent Monitoring)

Bivariate Models	Models with SNP rs16969968				Models with SNP rs3743078			
	OR	95% CI	P		OR	95% CI	P	
AGE								
	1.04	1.02	1.05	<.001	1.04	1.02	1.05	<.001
Gender								
Female	1.0(ref)				1.0(ref)			
Male	1.92	1.60	2.30	<.001	1.92	1.60	2.30	<.001
Risk SNP								
GG	1.0(ref)				1.0(ref)			
GA	1.21	1.00	1.46	0.044	.76	.63	.91	.003
AA	2.21	1.65	2.95	<.001	.54	.36	.81	.003
Parent Monitoring								
Higher quartiles	1.0(ref)				1.0(ref)			
Lowest quartile	2.04	1.65	2.53	<.001	2.04	1.65	2.53	<.001
Multivariate Model 1								
AGE	1.04	1.02	1.06	<.001	1.04	1.02	1.06	<.001
Gender								
Female	1.0(ref)				1.0(ref)			
Male	1.85	1.53	2.24	<.001	1.86	1.54	2.25	<.001
Risk SNP								
GG/GA	1.0(ref)				1.0(ref)			
AA	1.94	1.46	2.58	<.001	.75	.63	.91	.003
Parent Monitoring								
Higher quartiles	1.0(ref)				1.0(ref)			
Lowest quartile	1.88	1.50	2.35	<.001	1.85	1.48	2.31	<.001
Multivariate Model 2 (test of interaction)								
AGE	1.04	1.02	1.06	<.001	1.04	1.02	1.06	<.001
Gender								
Female	1.0(ref)				1.0(ref)			
Male	1.85	1.53	2.24	<.001	1.86	1.54	2.25	<.001
Risk SNP								
GG/GA	1.0(ref)				1.0(ref)			
AA	1.67	1.22	2.28	.001	.74	.60	.92	.006
Parent Monitoring								
Higher quartiles	1.0(ref)				1.0(ref)			

1.0(ref): reference category; OR: odds ratio; LB: lower bound; UB: upper bound; 95% CI: confidence interval