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Gene-Environment Contributions to Young Adult Sexual Partnering

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Abstract To date, there has been relatively little work on gene-environment contributions to human sexuality, especially molecular analyses examining the potential contributions of specific polymorphisms in conjunction with life experiences. Using Wave III data from 717 heterozygous young adult sibling pairs included in the National Longitudinal Study of Adolescent Health, this article examined the combined contributions of attendance at religious services and three genetic polymorphisms (in the dopamine D4 receptor [*DRD4*]), dopamine D2 receptor [*DRD2*]), and the serotonin transporter promoter [*5HTT*]) to sensation seeking, a personality construct related to sexual behavior, and the number of vaginal sex partners participants had in the year before interview. Data analyses used an Allison mixed model approach to account for population stratification and correlated observations. *DRD4* was unrelated to sensation seeking and to the number of sex partners in tests of both main effects and in interaction with religious attendance. Contrary to hypothesis, presence of the A1 *DRD2* allele was associated with having had fewer sex partners in the past year. Associations between the *5HTT* allele and sex partners varied by religious attendance, but again the patterns of associations were contrary to hypothesized relationships and were small in magnitude. These findings underscore the necessity of using more comprehensive multiple gene-multiple life experience approaches to investigations of complex behaviors such as sexual patterns.

Keywords Dopamine · Serotonin · Number of sexual partners · Gene-environment interaction · Sensation seeking

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Introduction

To date, investigations of biological contributors to sexuality have included pubertal timing and status, hormone levels and hormonal change, physiological reactivity, and genes. In general, where significant associations have been documented, this body of work indicates that early pubertal timing or more advanced pubertal status (Flannery, Rowe, & Gulley, 1993; Halpern, Udry, Campbell, & Suchindran, 1993), higher levels of testosterone or increases in testosterone (Finkelstein et al., 1998; Halpern, Udry, & Suchindran, 1997, 1998; Udry, Billy, Morris, Groff, & Raj, 1985; Udry, Talbert, & Morris, 1986), and lesser physiological reactivity, as measured by cortisol change (Brody, 2002; Halpern, Campbell, Agnew, Thompson, & Udry, 2002), are associated with heightened sexual interest and ideation, earlier sexual transition (i.e., first vaginal intercourse), or higher levels of various types of partnered and non-partnered activity for both males and females. Although there are exceptions (e.g., Udry et al., 1985), the strength of "main effect"

associations between biological variables and sexual behavior measures is typically small. However, the examination of interactions among biological factors, or between biological and social/contextual factors, has sometimes yielded greater predictive power (e.g., Halpern, Udry, Campbell, Suchindran, & Mason, 1994; Miller et al., 1999).

There is relatively little work on genetic contributions to human sexuality and fertility, but results of biometrical (behavioral genetic) analyses support the proposition that there are genetic contributions to the timing of first sexual transition (Dunne et al., 1997; Guo & Tong, 2006; Martin, Eaves, & Eysenck, 1977; Rodgers, Rowe, & Buster, 1999), and to fertility expectations and outcomes (e.g., completed family size) (Kohler & Christensen, 2000; Rodgers & Doughty, 2000; Rodgers, Kohler, Kyvik, & Christensen, 2001). More recently, molecular analyses that allow for an examination of associations between variations in genes (alleles that occur in more than one form or polymorphisms) and various aspects of human personality and behavior have begun to appear in the literature. In human studies focused on complex characteristics and behavior, work has focused largely on personality dimensions such as novelty seeking (Benjamin, Ebstein, & Belmaker, 2002), substance use and abuse (Noble et al., 1993; Wong, Buckle, & Van Tol, 2000), aspects of mental health such as depression and schizophrenia (Caspi et al., 2003; Joyce & Meador-Woodruff, 1997), and aggression (Caspi et al., 2002).

Dopamine and novelty seeking

Dopamine is one of the most important catecholamine neurotransmitters in the brain, and plays a role in a variety of appetitive behaviors. There are two classes of dopamine receptors, D1-like (D1 and D5) and D2-like (D2, D3, and D4). The D4 dopamine receptor gene (*DRD4*) has a 48 base pair VNTR (variable number of tandem repeats) in the third exon, which can consist of 2 to 11 repeats (Van Tol et al., 1992). Alleles with two repeats (*DRD4* ∗ 2R–8 to 10% of humans), four repeats (*DRD4* ∗ 4R–60 to 64% of humans), and seven repeats (*DRD4* ∗ 7R–14 to 21% of humans) are the most common (Chang, Kidd, Livak, Pakstis, & Kidd, 1996; Missale, Nash, Robinson, Jamer, & Caron, 1998). The seven repeat variant of D4 (*DRD4* ∗ *7R*) has been of special interest because it (versus lower repeat numbers of the 48 base-pair) appears to confer functional differences (Van Tol et al., 1992).

Many studies have examined the relationship between the 7-repeat *DRD4* polymorphism and novelty seeking in humans (Benjamin et al., 2002; Paterson, Sunohara, & Kennedy, 1999; Wong et al., 2000). Novelty seeking is conceptualized as a tendency toward excitement in response to novel stimuli or cues for possible reward; it is hypothesized to be associated with dopaminergic activity because of the behavior activating effects of dopamine. Novelty seeking reflects impulsive, exploratory, or sensation seeking behavior, and thus is conceptually similar to Zuckerman's (1979) construct of sensation seeking, a relatively stable personality dimension with a biological foundation (Zuckerman & Cloninger, 1996). Novelty or sensation-seeking is of interest in studies of risk behavior because higher levels have been associated with substance abuse (e.g., Bardo, Donohew, & Harrington, 1996; Hillman & Haskin, 2000; Wong et al., 2000), earlier sexual initiation, and greater levels of sexual activity among adolescents and young adults (Halpern et al., 2002; Horvath & Zuckerman, 1993; Stanton, Li, Cottrell, & Kaljee, 2001).

Findings to date are mixed in demonstrating an association between *DRD4* and novelty seeking in humans (For reviews, see Benjamin et al., 2002; Paterson et al., 1999; Wong et al., 2000). When an association is found, individuals with one or two long (7 repeat) *DRD4* alleles have significantly higher novelty seeking scores than individuals with short alleles (Benjamin et al., 2000; Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein, Nemanov, Klotz, Gritsendo, & Belmaker, 1997; Ebstein et al., 1996; Noble et al., 1998, Ono et al., 1997; Tomitaka et al., 1999). Multiple studies, however, have failed to find bivariate relationships between *DRD4* and novelty seeking (e.g., Gelernter et al., 1997; Hill, Zezza, Wipprecht, Locke, & Neiswanger, 1999; Jonsson et al., 1997; Malhotra et al., 1996; Poston et al., 1998; Sullivan et al., 1998; Vandenbergh, Zonderman, Wang, Uhl, & Costa, 1997) or have found associations in the opposite direction (Ekelund, Lichtermann, Jarvelin, & Peltonen, 1999). Some investigators have suggested that an association between *DRD4* ∗ 7R and novelty seeking might only be evident in the context of other specific genetic and environmental factors (Comings, 1998; Gelernter et al., 1997). Animal models have consistently indicated that dopamine is facilitative of sexual activity (Hull et al., 1999; Melis & Argiolas, 1995; van Furth, Wolterink, & van Rhee, 1995). For humans, novelty seeking could function as a mediator between *DRD4* and sexual patterns.

The TaqIA D2 dopamine receptor (*DRD2*) minor A1 allele has also been of interest because of its empirical association with alcoholism, especially severity and timing of onset (Kono et al., 1997; Pato, Macciardi, Pato, Verga, & Kennedy, 1993; Wong et al., 2000), and other types of substance abuse (Comings, Muhleman, Ahn, Gysin, & Flanagan, 1994; Goldman, Urbanek, Guenther, Robin, & Long, 1997; Noble, 2003; Noble et al., 1993, 1998; O'Hara et al., 1993). However, as with studies of the D4 receptor, other work has failed to replicate these associations for D2 (e.g., Berrettini & Persico, 1996; Gelernter, Kranzler, & Satel, 1999; O'Hara et al., 1993). There is also evidence of an *DRD2* by environmental stress interaction. For example, stress is associated with lower cognitive functioning in children (Berman &

Noble, 1997) and with severity of physiological alcohol dependence or severity of alcohol problems (Bau, Almeida, & Hutz, 2000; Madrid, MacMurray, Lee, Anderson, & Comings, 2001) in individuals who have the A1 allele but not in those without the allele. In addition, the A1 polymorphism in D2, in combination with the 7-repeat *DRD4* polymorphism, has been linked to higher novelty seeking scores compared to scores for individuals who have only one of the polymorphisms (Noble et al., 1998). These gene-gene and gene-environment interactions suggest the utility of simultaneously considering multiple alleles in conjunction with relevant environmental contexts.

Dopamine and sexual behavior

We identified three studies that have examined associations between dopamine polymorphisms and some aspect of human sexual behavior. Miller et al. (1999) examined associations between polymorphisms in dopamine receptor genes (D1, D2, D4) and the age at first sexual intercourse in an area probability sample of 430 white couples. In these analyses, D4 polymorphisms were unrelated to age at first sex, but a variation in the D2 gene was associated with a later age at first sex and increased the variance accounted for in the model from .19 (based on 10 psychosocial variables) to .24. An interaction term between D1 and D2 was also significant and increased the variance accounted for in the full model to .31. Given dopamine's role in activation, arousal, and reinforcement (virtually all substances of abuse act on the dopaminergic system), these findings suggest a facilitative role for dopamine in sexual motivation.

More recently, Guo and Tong (2006) examined the association between variations in *DRD4* and transition to first sex using 2552 siblings (monozygotic and dizygotic twins, and full biological siblings) included in the National Longitudinal Study of Adolescent Health (Add Health). In the Guo and Tong analysis sample, the 2-repeat (9%), 3-repeat (3%), 4-repeat (65%), and 7-repeat (20%) VNTR of the *DRD4* gene accounted for almost 98% of the observed variants. Their analyses indicated no associations between the 2-repeat or the 7-repeat alleles and the timing of sexual transition. However, Guo and Tong did find an association between the relatively rare *DRD4* 3-repeat allele and sexual transition. Higher proportions of the Wave III young adult Add Health participants who had the any-3R genotype in *DRD4* had their first intercourse experience in adolescence compared with participants who had other *DRD4* genotypes (hazard ratio of 1.23 for the full analysis sample).

Finally, Hamer (2002) reported an association between the *DRD4* 7-repeat polymorphism and number of sexual partners in a sample of 315 middle-aged men, most of whom were from sibling pairs. Among heterosexual men (apparently defined by self-identification), those who had the long *DRD4* polymorphism were more likely to have ever had sex with a man (but not with more women) than heterosexual men without the long allele. Among homosexual men, those with the long allele had sex with about five times as many women as men without the long allele. The long allele was also associated with having more male partners among homosexual men, but differences were smaller.

Serotonin

In contrast to the appetitive effects of dopamine, serotonin (*5HTT*), another neurotransmitter, has inhibitory effects, and reduced serotonergic transmission may contribute to decreased impulse control. For example, deficits in serotonin metabolism are associated with poor performance on delay-of-gratification tasks in young rhesus monkeys (Bennett et al., 1999) and with the process of hedonic dysregulation, which is thought to be involved in the development of drug dependence (Koob et al., 2004). Deficits in serotonin metabolism have also been associated with avoidance traits (Munafo et al., 2003), depression (Owen & Nemeroff, 1994), impulsive personality disorders and alcohol abuse (Coccaro, 1992; LeMarquand, Pihl, & Benkelfat, 1994), and decreased reward dependence and persistence (Ebstein et al., 1997). Reward dependence is a tendency to behave in ways that elicit social approval and succor. The 5HTT gene contains a 44 base pair VNTR in its promoter, with the long variant showing greater basal activity than the short variant (Heils et al., 1996; Lesch et al., 1996). Presence of the short allele at either serotonin transporter SLC6A4 locus (i.e., reduced gene expression and activity) is associated with negative emotionality, and in the context of particular life experiences, may be associated with elevated impulsivity and stress reactivity. However, as with dopamine, empirical support for serotonin associations with personality and emotionality are mixed (Lesch et al., 2002).

Serotonin and sexuality

We have found only one report investigating a possible association between the serotonin promoter polymorphism described above and human sexual behavior. Hamer (2002) reported a statistically significant association with frequency of sexual activity among men (same sample as described above). Men with at least one copy of the short variant had sex more frequently than men without it (2/3 of men with a short allele had sex once a week or more often versus 1/3 of men without a short allele). Anxiety did not appear to mediate the association.

Present analyses

Of the identified studies examining associations with sexual behavior, either only a single polymorphism was examined (both as a main effect and in interaction with several socioeconomic factors) (Guo & Tong, 2006) or multiple genes were investigated without assessment of their potential interactions with social and contextual information (Miller et al., 1999). Work on other types of behavior (e.g., aggression, depression) has suggested the importance of examining gene-environment interactions in investigations of complex behavior (Caspi et al., 2002, 2003). Given the small proportions of variance accounted for when only biological factors are considered and the theoretical necessity of including multiple levels of the developmental system in analyses (Gottlieb, 2003), it is imperative that genetic studies of behavior incorporate biological, behavioral, and social factors, and examine their interactions with each other and with genetic characteristics. In the present analyses, we apply this more comprehensive approach to sexual behavior by examining whether gene-gene and gene-environment interactions predicted sensation seeking and reports of number of sex partners in the past year. We examine number of sex partners as our outcome because of the behavioral relevance to sexually transmitted diseases (STDs), which are most prevalent during adolescence and young adulthood (Weinstock, Berman, & Cates, 2004), and the linkages between rate of partnering and sensation seeking (Halpern et al., 2002). As noted earlier, sensation seeking is one of the more widely studied personality dimensions in the human molecular genetic literature. We investigated multiple polymorphisms (the D2, D4, and *5HTT* polymorphisms described above), in combination with the experience of attendance at religious services during adolescence. We first tested models of sexual partnering that included gene-gene and gene-environment interactions. We then examined gene associations with sensation seeking as a potential personality mediator of an association between genotype and sexual partnering. We selected religious attendance during adolescence as the environmental variable because indicators of religiosity have been associated with the timing of adolescent sexual transition (Whitehead, Wilcox, Rostosky, Randall, & Wright, 2001) and with number of sex partners (Miller & Gur, 2002; Whitehead et al., 2001). Although patterns vary based on gender and race/ethnicity, findings generally indicate that higher religiosity (measured by religious attendance, importance of religion or other indicators) is associated with an older age at first sex and with having fewer sex partners in the past year. We examined interactions between attendance and three polymorphisms: the exon 3 *DRD4* VNTR (7-repeat), *DRD2* TaqIA (presence of A1), and a VNTR in the promoter region of the serotonin transporter.

Based on earlier findings linking the 7-repeat polymorphism of *DRD4* with novelty seeking and the A1 *DRD2* allele with substance use (a behavior that tends to covary with riskier patterns of sexual behavior), we formulated three hypotheses:

1. Presence of the long (7-repeat) allele of *DRD4*, the A1 allele of *DRD2*, higher sensation seeking, and less frequent attendance at religious services would each be associated with more sex partners in the past year;
2. Gene-gene and gene-environment interactions would yield stronger associations with number of sex partners, such that (a) presence of the "risky allele" of either dopamine genotype and the short *5HTT* allele, in combination with infrequent religious attendance, would be associated with the greatest number of sex partners; (b) absence of the *DRD4* long allele and the A1 *DRD2* alleles, presence of the long *5HTT* serotonin allele, and frequent religious attendance would yield the fewest sex partners, (c) other gene-environment combinations (e.g., long dopamine alleles present but high religious attendance) would yield intermediate numbers of sex partners.
3. Assuming demonstration of a *DRD4*/sensation seeking association, the addition of sensation seeking to the number of sex partners model would attenuate the association between *DRD4* and partnering.

Our models also included other sociodemographic characteristics that are associated with sexual behavior patterns: biological sex, age, race/ethnicity, parental education (serving as a socioeconomic proxy), and participant's marital status.

Method

Participants

We analyzed Wave III data from 1434 participants who were part of the genetic subsample (monozygotic and dizygotic twins, full siblings, half siblings, unrelated adolescents living in the same household) of the National Longitudinal Study of Adolescent Health (Add Health). Add Health began as a probability-based, nationally representative survey of U.S. adolescents who were enrolled in grades 7 through 12 during the 1994–1995 school year (Wave I) (Harris et al., 2003). Two subsequent waves of interviews have been completed, between April and August, 1996 (Wave II), and between August 2001 and April 2002 (Wave III). At Wave III, participants were 18–26 years old. The Add Health data sets are well-suited for our purposes because they are based on a large, nationally representative sample, and measures of multiple polymorphisms, personality characteristics, and life experiences are available, thereby allowing for examination

of several gene-gene and gene-environment interactions. In addition, the Wave III interview taps a developmental period characterized by high levels of sexual activity and high STD prevalence (Miller et al., 2004; Weinstock et al., 2004).

Our study sample was restricted to full heterozygous sibling pairs across different families (one pair per family). The genetic subsample included 2574 participants, but only 1978 were in sibling pairs. Of those, 1606 were in heterozygous pairs from different families and qualified for our sample. Of these, complete information on the alleles and other variables of interest was available for about 90%, or 1434 individuals (717 pairs). As shown in Table 1, the mean age of participants in the analysis sample at Wave III was 21.9 years ($SD = 1.7$). Slightly more than half of the participants were female and the majority were non-Hispanic white. About 13% of the sample was Hispanic, 16% black, and 7% Asian. The majority of participants were not married or cohabitating, had parents who were educated beyond high school, and attended religious services less than weekly.

All Add Health protocols were reviewed and approved by the Institutional Review Board for the Protection of Human Subjects in the School of Public Health at the University of North Carolina at Chapel Hill.

Measures

Outcome: Number of sexual partners in past year

In Wave III, participants were asked how many different partners they had vaginal intercourse with in the past 12 months. Participants in our analysis sample who had not yet had sex ($n = 217$) were coded as having had 0 sex partners.

Table 1 Descriptive characteristics of participants

Variable	*N* (%)
Female	736 (51.32)
Male (ref)	698 (48.68)
Hispanic	185 (12.90)
Black	228 (15.90)
Asian	106 (7.39)
Other race	33 (2.3)
White (ref)	882 (59.21)
Parent was college graduate	549 (38.28)
Parent had some education beyond high school	297 (20.71)
Parent was high school graduate	432 (30.13)
Parent had less than high school education (ref)	156 (10.88)
Steady dating partner	618 (43.10)
No current steady partner	347 (24.20)
Married/cohabiting (ref)	469 (32.71)
Religious attendance low or none	814 (56.76)
Religious attendance high (ref)	620 (43.24)

Sensation seeking

At Wave III, seven slightly modified items from the Disinhibition subscale of Zuckerman's (1979) sensation seeking measure were included in the interview. The Cronbach alpha coefficient for this subscale in the analysis sample was 0.68. The Disinhibition subscale taps a "more traditional type of sensation seeking, which seeks release and social disinhibition through drinking, partying, gambling, and sex" (Zuckerman, 1979, p. 103). Participants were asked to pick between pairs of statements, with one statement of the pair reflecting disinhibited behavior or preferences (e.g., "I like wild, uninhibited parties" versus "I like quiet parties with good conversation"). For each "disinhibited" statement selected, a participant received one point, up to a maximum of seven.

Biological sex

Participant's sex was coded male (referent) or female.

Age

Age at Wave III was coded as a continuous variable and centered on the median for analyses.

Race and ethnicity

Participants were asked in Wave I if they were of Hispanic or Latino origin. They were also asked "what is your race?" and were allowed to mark one or more of the following options: white, black or African American, American Indian or Native American, Asian or Pacific Islander, or "other" race. From this information, we constructed a single race/ethnicity variable: Hispanic, Non-Hispanic black, Asian, Other, or Non-Hispanic white (referent).

Parental education

The highest level of education was determined for each parent. Parental education, as used in analyses, reflects the higher level of education attained by either parent, if there are two in the household, as of the Wave I interview. Higher education was categorized as less than high school (referent), high school graduate, some education beyond high school, and college graduate.

Marital status

Marital status was categorized as no current steady partner, steady dating partner (relationship of 3 months or longer) and married/cohabiting (referent), at Wave III.

Religious attendance

Participants were asked how often they attended religious services in the past 12 months at the Wave I interview. Response options ranged from never to more than once a week. Participants were coded as attending less than weekly (low or none) versus attending weekly or more often (referent).

Genetic polymorphisms

At the Wave III interview, DNA was extracted from buccal cells collected from monozygotic and dizygotic twins, and full siblings, all of whom were part of the original Add Health "genetic sample" intended for biometric analyses. DNA extraction and genotyping was conducted at the Institute for Behavioral Genetics at the University of Colorado at Boulder. Among the polymorphisms examined were the dopamine D4 receptor (*DRD4*), the dopamine D2 receptor (*DRD2*), and the serotonin transporter (*5HTT*). Details on isolation and assay methods (all modifications of published methods) are available at http://www.cpc.unc.edu/projects/addhealth/files/biomark.pdf (Smolen & Hewitt, 2000).

Dopamine D4 receptor (DRD4)

The *DRD4* gene, which maps to 11p15.5, contains a 48 bp VNTR in the third exon (8). This VNTR can consist of 2 to 11 repeats. The presence of the allele with 7 repeats (R7) at either loci for each individual was coded 1; all others were coded 0.

TaqIA dopamine D2 receptor (DRD2)

The gene encoding the dopamine D2 receptor maps to 11q23, and has a polymorphic TaqI restriction endonuclease site about 2500 bp downstream (3′ untranslated region) from the coding region of the gene. This site is designated the TaqIA site. Presence of the A1 allele at either loci for each individual was coded as 1; all others were coded 0.

Serotonin transporter (5HTT)

The *5HTT* gene contains a VNTR in its promoter (locus symbol SLC6A4), with the long variant showing greater basal activity than the short variant (Lesch et al., 1996). Therefore, presence of the short allele at either loci for each individual was of interest as a risk indicator and is coded 1; all others were coded 0.

Procedure

For our analyses, we applied the Allison mixed model approach to account for population stratification and test for linkage and association between the alleles of interest and the outcomes: sensation seeking and sexual partnerships (Allison, Heo, Kaplan, & Martin, 1999). Population stratification occurs when breeding groups are separated by geography or culture and these groups develop different frequencies of alleles at the locus of interest. The groups may also display different phenotype distributions for reasons unrelated to the locus of interest, producing an apparent association between the locus of interest and the phenotype even when the locus does not affect the phenotype and is not linked to genes that do (Allison & Neale, 2001; Ewens & Speilman, 1995) (see Appendix for a fuller discussion of the issue of population stratification and analytical approaches). Interaction terms were used to test whether the relationship between the alleles and the outcomes varied by the presence of other alleles or life experience. For the sexual partner outcome, we incorporated a Poisson error distribution and log link into the mixed model to accommodate the count variable outcome (versus a normally distributed continuous outcome). When a Poisson distribution is used, the exponent of the coefficient of interest can be interpreted as an Incident Rate Ratio (IRR). The IRR is the factor by which the count will increase for every unit increase of X. The IRR-1 is the percent change one can expect in the count.

First, we created simple models of sensation seeking and the number of sexual partners using only the genetic variables. Then, we created a full model by simultaneously including all variables of interest and the proposed interaction effects between alleles and religious attendance. Non-significant terms and those not supported by likelihood tests were then dropped from the final models.

Table 2 Descriptive statistics for analysis variables

Variable	*N* (%)
Any D4 long (7 repeat) alleles	504 (35.15)
No D4 long alleles (ref)	930 (64.85)
Any D2 A1 alleles	644 (44.91)
No D2 A1 alleles (ref)	790 (55.09)
Any 5HTT transporter short alleles	939 (65.48)
No 5HTT transporter short alleles (ref)	495 (34.52)
0 partners last year	334 (23.29)
1 partner last year	707 (49.30)
2 partners last year	190 (13.25)
3 partners last year	81 (5.65)
4 partners last year	39 (2.72)
5 partners last year	36 (2.51)
6 or more partners last year	47 (3.28)
Sensation seeking *M* (*SD*)	2.70 (1.90)

Table 3 Parameter estimates for main effect and gene-environment interaction models

	Alleles only model			Main effects model			Final model		
	Estimate	*p*	IRR	Estimate	*p*	IRR	Estimate	*p*	IRR
Intercept	0.4008	<.0001		0.4147	.0010		0.5063	<.0001	
Any D2 long alleles	−0.1318	.0222	0.88	−0.1274	.0280	0.75	−0.1148	.0473	0.89
Any serotonin transporter short alleles	−0.1271	.0296	0.88	−0.0541	*ns*	0.95	−0.3481	<.0001	—
Less than weekly religious attendance				0.1496	.0088	1.16	−0.1223	*ns*	—
Short serotonin allele and less than weekly religious interaction							0.4723	<.0001	—
Allele and religion combinations based on above interaction term (reference of no short serotonin allele and weekly or more religious)									
Short serotonin allele and less than weekly religious attendance									1.00
No short serotonin allele and less than weekly religious attendance									0.88
Short serotonin allele and weekly or more religious attendance									0.71
Female				−0.2555	<.0001	0.77	−0.2200	<.0001	0.80
Current Age				−0.0328	.0361	0.97	−0.0321	.0381	0.97
Race/ethnicity (reference of white)									
Hispanic				0.0115	*ns*	1.01	0.01170	*ns*	1.01
Black				0.3594	<.0001	1.43	0.3311	<.0001	1.39
Asian				−0.5250	.0004	0.59	−0.5239	.0003	0.59
Other Race				0.1971	*ns*	1.22	0.1871	*ns*	1.29
Parental education (reference of less than high school education)									
High school graduate				−0.0771	*ns*	0.93			
Some education beyond high school				0.1428	*ns*	1.15			
College graduate				−0.0939	*ns*	0.91			
Marital status (reference married/cohabiting)									
No steady partner				−0.0940	*ns*	0.91			
Steady partner				0.1511	.0294	1.16			

Results

Genetic and behavioral characteristics

As shown in Table 2, about a third of the sample carried a long *DRD4* (7 repeat) allele, and almost 45% had an A1 *DRD2* allele. The majority of the sample carried at least one short serotonin allele (*5HTTT* short). Almost a quarter of participants had no sex partners in the past year, and almost half only had one. The mean number of sexual partners in the past year was 1.5, and ranged from 0 to 45. The mean sensation seeking score was 2.7 ($SD = 1.9$), and ranged from 0 to 7. Sensation seeking scores were positively and significantly associated with number of sex partners in the past year ($r = 0.19$, $p < .0001$).

Multivariate models

For models of number of sexual partners in the past year, the main effect term for the *DRD4* polymorphism was not significant, and all interaction terms that included it were not supported by likelihood tests. Therefore, the *DRD4* variable was dropped from further analysis. In a simple model that included only the indicators for the two remaining alleles, both had significant associations with the number of partners in the past year. The *DRD2* A1 polymorphism yielded an estimated IRR of 0.88, indicating a 12% reduction in the number of sexual partners in the past year compared to participants without the long allele. The *5HTT* short polymorphism also produced an estimated IRR of 0.88 (see Table 3). Note that the direction of each relationship was the opposite of that hypothesized.

Next, we created a main effects model that included the participant's sex, race/ethnicity, current age, marital status, parental education, and religious attendance (see Table 3). The *DRD2* A1 allele remained significant, associated with fewer partners. Being female, older, or Asian were also associated with fewer partners. Attending religious services less than weekly, having a steady dating partner, or being black was each associated with having more partners in the past year.

To explore gene-gene and gene-environment interactions, we tested interaction terms between the *DRD2* and *5HTT* polymorphisms, and between each polymorphism and each of the sociodemographic and experience variables. The full model was then reduced based on likelihood comparisons

to produce our final model (Table 3). The *DRD2* A1 polymorphism remained inversely associated with number of sex partners, with an IRR that was virtually identical to that found in the main effects model. There was a significant interaction between the *5HTT* short allele and religious attendance (a likelihood ratio test comparing the final model with and without the interaction term support inclusion, $\chi^2 = 8.1$, $df = 1$, $p < .01$). Compared with the referent category of no short *5HTT* allele and weekly religious attendance (the referent category was expected to be associated with the fewest sex partners), the combined presence of the short *5HTT* allele and lower religious attendance (expected to yield the greatest number) was not significantly associated with the number of partners. Furthermore, the combination of the short *5HTT* allele and high religious attendance was associated with about a 30% reduction in the number of sexual partnerships compared to high religious attendance and no short allele (Table 3). The combination of no short *5HTT* allele and lower levels of religious attendance was also associated with fewer sexual partnerships (about 12% lower) compared to weekly religious attendance and no short allele. Sex, age, and race/ethnicity were significantly related to the number of partners. Females reported fewer partners than males, Asians reported fewer partners than whites, blacks reported more partners than whites, and older participants reported slightly fewer partners than younger participants.

To examine the potential role of sensation seeking as a mediator between the *DRD2* and *5HTT* polymorphisms and number of partners, we tested the relationship of these alleles with sensation seeking using mixed models. However, neither allele was significantly associated with the sensation seeking score, so sensation seeking was not considered a viable mediator and was dropped from further analyses.

Discussion

Much of the past work examining gene-behavior associations in humans has used a simple bivariate approach. This literature is replete with non-replications and with associations in the opposite direction from that originally reported. Attempts to incorporate a life experience in analyses of genetic contributions to behavior (e.g., Caspi et al., 2002) have yielded promising and theoretically sound findings, but have also suffered from non-replication (e.g., Haberstick et al., 2005). Following Gottlieb (2003), we implemented a more complex model in which we examined the associations of multiple genetic polymorphisms, multiple psychological and social characteristics, gene-gene interactions, and gene-environment interactions with sexual partnering in the past year. We proposed that the personality dimension of sensation seeking, long the focus of gene-personality studies and a predictor of sexual behavior, would serve as a mediator between the interactions of genetic polymorphisms and life experiences examined and numbers of sexual partners. However, we found that the polymorphisms associated with sexual partnering were unrelated to sensation seeking. Thus, there was no empirical support for the personality dimension of sensation seeking as a mediator. We did find, however, a significant "main effect" of the *DRD2* polymorphism and a significant interaction between the *5HTT* polymorphism and attendance at religious services in modeling the outcome number of sex partners in the past year. However, patterns of associations for each of these terms were inconsistent with our hypotheses. We expected the A1 *DRD2* allele to be associated with more sex partners, but it was associated with fewer. We had also expected the short serotonin/lower religious attendance combination to be associated with the greatest number of sex partners and the absence of a short serotonin allele combined with high religious attendance to be associated with the fewest partners. There was, however, no significant difference in number of sex partners between these two combinations. The other combinations, reflecting the presence of only one "risk" factor, fell at intermediate numbers of partners, but not in the anticipated direction. In contrast, the directions of association between sexual partnering and the main effect terms for sociodemographic characteristics, sensation seeking, and religious attendance were as expected and consistent with past literature.

As noted by Gottlieb (2003), "developmental theory holds that there can be no genetic effects on behavior independent of the environment and there are probably no environmental effects on behavior independent of genetic activity" (p. 351). We agree with this tenet, but were unable to provide an illustration of it for this behavioral outcome, even though we examined multiple genes in the context of a personality dimension and life experience (i.e., sensation seeking and attendance at religious services during adolescence) that have often been linked with sexual patterns. Although our hypotheses regarding gene-gene and gene-environment interactions were not supported, our model represents one of the first attempts to test a model that specifies a psychosocial mechanism through which genetic factors may contribute to sexual behavior. More broadly, the model also represents an effort to incorporate multiple levels of a developmental system (e.g., genetic, psychological, social/contextual) in our examination of sexuality. In these ways, the work contributes to this literature despite null findings.

There are some limitations in our measures that may have contributed to these patterns of results. As we elaborate below, information about structural polymorphisms is static, and does not capture dynamic biological processes that contribute to behavior. This is a major limitation of the present work, as well as all other investigations of associations between genetic polymorphisms and behavior. Further, our measure of sensation seeking is limited to only one of its

component dimensions, disinhibition, and the full scale of disinhibition items was not included in the Add Health interview. Finally, we have examined only one indicator of sexual patterns. Future work using more comprehensive measures that capture partnering patterns, and their context, over time could yield different insights. However, other investigations of complex human behavior, subject to similar limitations of measurement, have detected significant gene-environment interactions. As we elaborate below, we attribute the continuing problem of null findings and non-replication to the early stages of these lines of inquiry and to the challenges of effectively implementing statistical models that adequately capture dynamic developmental systems.

Sexual patterns represent complex behaviors that are simultaneously influenced by multiple biological, multiple psychological, and multiple socio-contextual factors over time. Thus, the multiple-gene/life experience model implemented here, although more comprehensive than what has typically been attempted in past work, likely remains too simple, given the vast distance between genotype and phenotype (see Johnston and Edwards (2002) for an illustration of the large number of steps that exist between genetic activity and behavior), and the typically small magnitude of single biological factors.

DNA contributes to behavior through proteins, which serve as neurotransmitters, enzymes, etc. To date, work in behavioral genetics has been limited to measures of structural or sequence differences, which may or may not have functional significance, rather than measures of gene expression and/or of the particular proteins being produced. To produce a protein, DNA must first be transcribed to make messenger RNA, which is then spliced before carrying its codon pattern from the nucleus to the cytoplasm of the cell. Translation is the process of using the messenger RNA to code for a polypeptide chain. These chains fold into proteins individually or may combine with other chains to form proteins. Because each of these steps involves an array of control mechanisms that responds to the cellular environment and various feedback mechanisms, protein production is also influenced by multiple other biological (e.g., hormonal) and experiential factors. The phenomenon of RNA-editing alone further complicates the goal of linking particular genes to particular proteins (Gottlieb, 2003). In short, genes do not shape behavior directly; it is the coaction of multiple factors at the molecular and higher levels of the developmental system that lead to behavior and development (Gottlieb & Halpern, 2002).

Further technical advances, such as microarray analysis, which allow for the simultaneous measurement of many genes, may help to strengthen behavior genetic research. This would allow for the incorporation of many genetic indicators, rather than just the three we were able to include here. However, other biological factors also play important roles and should be considered in conjunction with genetic factors. Inclusion of genetic and other biological measures in large scale, population-based studies that provide large sample sizes may also improve the ability to examine the co-action of larger combinations of biological and experiential factors as they contribute to the development of sexual patterns over the life course, and perhaps to improve the replicability of findings about gene-environment contributions to complex behavior. However, the need to tap gene expression and its timing will remain.

In addition to the expansion of numbers of genes and their interactions with multiple biological and psychological factors and social experiences, it will be important in future work to develop further biosocial theory to guide empirical investigations and to address the bidirectional processes that link coacting elements within the developmental system (see Gottlieb and Halpern (2002) and Gottlieb (2003)). In the present analyses, we could not examine genetic information in conjunction with other biological systems such as hormones and neurotransmitters, a task that is critical (see Johnston and Edwards (2002) for an illustrative conceptual model) but more possible with animal models. Clearly future work must find innovative ways to begin this biological integration in human research. Finally, even though our analysis sample was relatively large, sample size and the complexity of statistical models that would be required, limited the breadth of psychosocial factors and life experiences examined. This limitation may be addressed to some extent by the increasing inclusion of genetic data in large scale surveys. However, as Gottlieb (2003) and others have argued, attempts to more deeply integrate multiple levels of the developmental system through individual life course analysis are needed to truly further our understanding of sexual development.

Appendix: Population stratification

Association and linkage studies are common methods to explore how genotypes and phenotypes are connected. Association studies can use samples of unrelated individuals and test for an association between phenotypes and the genotypes at a specific locus. These studies can be relatively easy to conduct compared to more complex sample configurations and can have substantial power to detect associations (Allison & Neale, 2001; Cardon & Palmer, 2003). However, spurious associations from confounding due to population stratification are a major limitation of this approach (Allison & Neale, 2001). Population stratification occurs when breeding groups are separated by geography or culture and these groups develop different frequencies of alleles at the locus of interest through various mechanisms such as selection or genetic drift. The groups may also display different phenotype distributions because of different environments, different allele

frequencies at some other loci, or for other reasons unrelated to the locus of interest. In this way, an association between the locus of interest and the phenotype may be observed even when the locus does not affect the phenotype and is not linked to genes that do (Ewens & Speilman, 1995). Because population stratification occurs between breeding groups it can cause differences between families but it cannot cause differences within families. However, true allelic effects will be present within or between families when there is a difference in alleles. To address the problem of population stratification, samples of families can be used to create models that account for parental genotypes. Significant association in this type of study implies that the allele is both linked to and associated with a phenotypic characteristic. Linkage means that the locus of interest is either physically linked (on the chromosome) or is itself the locus where the genotype causes variation in the phenotype.

If parental genotype is unknown, conditioning on full heterozygous sibships can also eliminate confounding by population stratification. Allison et al. (1999) presented a joint test of linkage and association with quantitative traits that uses a mixed-model approach. A mixed model can test for linkage and control for stratification by evaluating variation due to genotype within a sibship. This model is fundamentally different from approaches such as Generalized Estimating Equations (GEE), which account for clustered data but do not condition on family and therefore do not control for stratification. In addition, unlike some other proposed tests that condition on sibships, standard software packages such as SAS can be used and multiple allele combinations and environmental interactions can be incorporated (Allison & Neale, 2001).

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