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# AGE AT FIRST SEXUAL INTERCOURSE, GENES, AND SOCIAL CONTEXT: EVIDENCE FROM TWINS AND THE DOPAMINE D4 RECEPTOR GENE\*

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*We carried out two distinct types of genetic analysis with data from the National Longitudinal Study of Adolescent Health. The first was a non-DNA twin analysis using monozygotic (identical) and same-sex dizygotic (fraternal) twins. The second analysis investigates the association between age at first sexual intercourse and the 48-bp repeat polymorphism in the dopamine receptor D4 gene (DRD4). The twin analysis shows that MZ twins correlate their timing of first sex to a much greater extent than do the same-sex DZ twins. Our analysis of the polymorphisms in DRD4 indicates that those with an any-3R genotype experienced a risk of first sexual intercourse 23% ( $p = .016$ ), 233% ( $p = .0001$ ), 28% ( $p = .012$ ), and 69% ( $p = .006$ ) higher than those with an other/other (or any-4R) genotype in the all-ethnicities ( $n = 2,552$ ), Asian, white, and Hispanic samples, respectively. The risk of first sex does not differ between the two genotypes in the African American sample. These results were obtained after adjusting the standard socioeconomic covariates, including gender, parental education, family structure, and community poverty in the regression model. Evidence from both twin and genetic-variant analyses points to a role of genes in the timing of first sexual intercourse.*

**E**arly initiation of sexual intercourse has been shown to be a risk factor for teenage pregnancy (Division of STD Prevention 2000) and sexually transmitted diseases (STDs; Abma and Sorenstein 2002; Burk et al. 1996; Burkett et al. 1992; Kahn et al. 2002; Latka et al. 2001; Ley et al. 1991). Adolescents, both male and female, who are younger at first sexual intercourse are less likely to have used a contraceptive method (Abma et al. 1997; Mosher and McNally 1991; Sonenstein et al. 1998).

In spite of recent declines, the teenage pregnancy rate is still 3 to 10 times as high in the United States as in other industrialized countries (Alan Guttmacher Institute 1994; Singh and Darroch 2000). The long-standing public concerns of the social and personal consequences of teenage pregnancy and childbearing is manifested in the large number of programs created to prevent these pregnancies (Kirby 1997) and in recent legislation (e.g., the Welfare Reform Act of 1996).

Each year, about 3 million adolescents are infected by an STD (Institute of Medicine 1997). About 25% of all STD patients in the United States are adolescents. Chlamydia, gonorrhea, vaginitis, and pelvic inflammatory disease all have the highest prevalence rates among adolescents, and these diseases become dramatically less prevalent with increasing age (Hatcher, Trussell, and Stewart 1998). Adolescents are more susceptible to STDs than

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adults because they have a higher probability of having multiple sexual partners and because female adolescents are biologically more susceptible to the infections (Institute of Medicine 1997). Young ages of first sexual intercourse have been identified as a major predictor for human papilloma virus (HPV) infection (Burk et al. 1996; Burkett et al. 1992; Kahn et al. 2002; Ley et al. 1991), cervical dysplasia, and cervical cancer (Crane 1990; Cyrus-David et al. 2002; LaVecchia et al. 1986).

## OBJECTIVE

The purpose of the present study was to investigate genetic influences on age at first sexual intercourse among 2,552 adolescents who were interviewed three times—in 1994–1995 (Wave I), 1995–1996 (Wave II), and 2002 (Wave III)—for the National Longitudinal Study of Adolescent Health (Add Health; see Harris et al. 2003). We carried out the investigation using both the classic twin design and the candidate gene approach. In the latter, we examined the association between age at first sex and the 48-bp repeat polymorphism in the dopamine receptor D4 gene (*DRD4*). In the final analysis, we incorporated genetic influences into the standard demographic and socioeconomic model of age at first sex.

## PREVIOUS STUDIES

Numerous previous studies demonstrated the association between the timing of first sexual intercourse and socioeconomic factors, including gender, ethnicity, parental education, family structure, and community-level factors (Billy, Brewster, and Grady 1994; Brewster, Billy, and Grady 1993; Hogan and Kitagawa 1985; Moore et al. 1995; Mott et al. 1996; Sonnenstein et al. 1998; Upchurch et al. 1998). Other studies explored the connection between the initialization of sexual intercourse and biological influences, such as male sex hormones and pubertal development (Morris 1986; Newcomer and Udry 1984; Udry and Billy 1987; Udry et al. 1985; Udry, Talbert, and Morris 1986).

A small number of studies have investigated genetic influences on age at first sex. Martin, Eaves, and Eysenck (1977) explored the cultural and other environmental influences on age at first sex using a sample of identical and fraternal twins. Dunne et al. (1997) examined age at first sexual intercourse for two age cohorts of monozygotic (MZ) twins and dizygotic (DZ) twins from the Australian Twin Registry. The younger cohort was born after the period 1952–1953, and the older cohort was born before it. Dunne et al. reported much higher genetic contribution to the variance in age at first intercourse in the younger cohort (72% for males and 49% for females) than in the older cohort (0% for males and 32% for females). The cohort differences were interpreted as a result of a gene-by-environment interaction: In the more tolerant social environment since the 1950s, individuals' biological characteristics played a more pronounced role in a person's initiation of sexual activity.

Using mainly pairs of full siblings, half siblings, and cousins—and a small number (32) of same-sex twin pairs of unknown zygosity—from the National Longitudinal Study of Youth (NLSY), Rodgers et al. (1999) identified a genetic contribution to age at first sex in the all-ethnicities sample (heritability: 0.37), the white sample (0.51), and the male sample (0.54). No genetic contribution to age at first sex was found in the African American sample. In terms of specific gene effects, Miller et al. (1999) investigated the relationship between the polymorphisms in the dopamine receptor D1 (*DRD1*), D2 (*DRD2*), and D4 (*DRD4*) genes and age at first sexual intercourse in a sample of 414 middle-class, non-Hispanic, European American men and women. Their analysis demonstrated a positive association between the presence of the 2 allele of *DRD2* and age at first sex.

## TWIN ANALYSIS

We carried out two distinct types of genetic analysis. The first was a non-DNA analysis using MZ and same-sex DZ twins, which tells us whether there is an aggregate genetic

contribution to age at first sex. Our second analysis investigated the association between age at first sex and a polymorphism in the dopamine receptor D4 gene (*DRD4*).

The genetic information in twin data lies in the distinction between identical (MZ) and fraternal (DZ) twins. Identical twins developed from a single zygote (one egg fertilized by one sperm) that divides into two separate cell masses within the first two weeks of development; they are, in essence, genetic clones. Fraternal twins develop from two separate zygotes (two eggs separately fertilized by two sperm). Fraternal twins have, on average, half of their genes in common, just like any two full siblings. Comparing identical and fraternal twins enables researchers to separate genetic from environmental influences without measuring genes at the molecular level. If there is a greater similarity in the timing of first sexual intercourse within identical twin pairs than with fraternal twin pairs, then genes must have contributed to the timing of first sex. This argument holds regardless of the number of genes involved or whether the forms of the genes involved are dominant or recessive.

The design of the twin study makes two assumptions. First, the “equal environments” assumption requires that the environments of identical twins are no more similar to each other than are the environments of fraternal twins. If the experiences of identical twins are more similar and thus make them more alike, genetic influences would be overestimated. More similar treatment of identical twins in certain aspects of life (e.g., being dressed alike when young and/or given similar or rhyming names), however, does not automatically discredit twin studies. In our case, what is crucial is whether the special way identical twins might be treated affects the age at first sex.

The second assumption presumes that there is little or no assortative mating; this refers to the tendency of people to marry people who are like them in height, intelligence, personality, and so forth. Assortative mating could distort estimates of genetic influences in family studies. Children of similar parents would be more likely to receive the same genes for some traits than children of more dissimilar parents. For this reason, assortative mating would exaggerate genetic similarity for fraternal twins, but it would not affect genetic similarity for identical twins because they are 100% similar genetically, with or without parental assortative mating. Violating this assumption would underestimate genetic influences. Violations of the assumption of equal environments and the assumption of assortative mating thus have opposite effects and tend to cancel each other to a certain extent.

The assumption of equal environments has been tested in a number of ways and seems to hold for most outcome variables (Bouchard and Propping 1993). An ingenious approach used twins who were miscategorized by their parents (Kendler et al. 1993; Scarr and Carter-Saltzman 1979). When parents treated identical twins as fraternal twins because of miscategorization, the mislabeled twins were as similar in behaviors and traits as identical twins who were correctly categorized, suggesting that labeling a twin pair may have only moderate consequences for the twin design.

## ANALYSIS OF GENETIC VARIANTS

With the tremendous advances in molecular genetics over the past two decades (Risch 2000), twin and other biometrical studies are no longer the only strategy for studying genetic contributions to human traits and behaviors. It is increasingly possible to investigate complex human traits at the level of molecular genetics. In this part of the analysis, we investigated the association of the 48-bp repeat polymorphism of the *DRD4* gene with age at first sexual intercourse among 2,552 adolescents and young adults in Add Health whose DNA data are available (Harris et al. 2003).

Although genes in multiple pathways are likely to influence risky sexual behaviors among adolescents and youth, we focused on the *DRD4* gene in one regulatory pathway in the central nervous system. *DRD4*, which maps 11p15.5 spanning 3.4 kb, is one of the five

types of dopamine receptors. A functional VNTR<sup>1</sup> (or variable number of tandem repeats) polymorphism has been identified in the third exon<sup>2</sup> in the *DRD4* gene, the region coding for the third intracellular loop of the receptor (Van Tol et al. 1992). The genetic variant is a 16 amino acid<sup>3</sup> (48-bp) repeat polymorphism, which is repeated 2 to 11 times, with the two-repeat (2R), three-repeat (3R), four-repeat (4R), and seven-repeat (7R) accounting for about 98% of the alleles<sup>4</sup> (Lichter et al. 1993; Van Tol et al. 1992).

The *DRD4* gene may play a significant role in sexual behavior because of the importance of the mesolimbic dopaminergic system in the brain reward circuits. In the dopaminergic system, the availability of the dopamine levels depends on the release, reuptake, and receptor binding of the synaptic neurotransmitters,<sup>5</sup> such as *DRD4*. Biochemical work suggests that by modulating reward for behavior via the meso-limbic circuitry of the brain, these neurotransmitters may be involved in regulation of "pleasure" behaviors such as eating, sexual behavior, and drugs of abuse (Salamone 1994). Extensive *in vitro*<sup>6</sup> biochemical studies of *DRD4* protein variants in the 16 amino acid (48-bp) repeat polymorphism suggest that the exon III 2R and 7R alleles have decreased affinity for dopamine and transmit weaker intracellular signals in comparison with the much more common 4R protein (Asghari et al. 1995; Jovanovic, Guan, and Van Tol 1999; Oak, Oldenhof, and Van Tol 2000). Swanson et al. (2000) suggested that the inhibitory neurons utilizing these "suboptimal" *DRD4* receptors would need increased dopamine for "normal" function. Such increased dopamine levels could result from a variety of compulsive, impulsive, and addictive behaviors, including novelty seeking, ADHD, risky sexual behavior, substance abuse, alcoholism, smoking, binge eating, and compulsive gambling. This is the hypothesized reward deficiency syndrome suggested by Blum et al. (1996), who reported an association between alcoholism and a polymorphism in the dopamine D2 receptor gene.

We examined the relative risks of first sex by age among individuals with 2R, 3R, 4R, and 7R of *DRD4*. Ding, Wang, and colleagues (Ding et al. 2002; Grady et al. 2003; Wang et al. 2004) proposed a general model of the origin of the various alleles in *DRD4*. They sequenced the entire *DRD4* locus in 103 individuals who were homozygous<sup>7</sup> for 2R, 4R, or 7R variants of the 48-bp VNTR in *DRD4* using individuals of African, European, Asian, North and South American, and Pacific Island ancestry. While the 4R/4R homozygotes displayed little linkage disequilibrium (LD)<sup>8</sup> over the region examined, the 7R/7R individuals exhibited dramatically stronger LD surrounding the 7R allele. The researchers showed that the less common alleles in *DRD4* could have arisen by a one-step recombination<sup>9</sup>/mutation

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1. VNTR is a chromosomal locus at which a particular repetitive sequence is present in different numbers in different individuals of a population. Most of a person's DNA sequence is identical to the DNA sequences of others. However, there are inherited regions of DNA that can vary from one individual to another. Variations in DNA sequence among individuals are termed *polymorphisms*. Sequences with a high degree of polymorphism are very useful for DNA analysis, which often attempts to link human outcomes to variations in DNA sequence. VNTRs, short tandem repeats (STRs; discussed later), and single nucleotide polymorphisms (SNPs; discussed later) are classes of DNA polymorphisms.

2. An exon is a section of a gene that is part of the final processed mRNA molecule, in contrast to intron sections, which are excluded in the mRNA processing.

3. The 16 amino acids are compounds that link together to make proteins.

4. Different forms (different DNA sequences) of a gene are called *alleles*, which may be found at a given location on members of a homologous set of chromosomes. Structural variations between alleles may lead to different phenotypes for a given trait.

5. Neurotransmitters are chemicals that allow the movement of information from one neuron across the gap between it and the adjacent neuron.

6. *In vitro*, "within glass" in Latin, is an experimental method in which the experiment is performed in a test tube or outside a living organism or cell.

7. *Homozygous* refers to having identical alleles at the corresponding gene location on homologous chromosomes.

8. LD is the association of specific alleles at different loci.

9. Recombination usually denotes a genetic event that occurs during the formation of sperm and egg cells.

event from the common and ancient (> 300,000 years old) 4R alleles. They proposed that the 4R allele has been the most common allele throughout most of early human history. In contrast, the much less common alleles arose as a rare mutation much more recently—about 40,000–50,000 years ago—after undergoing positive selection in certain environments. The behavioral traits associated with the 2R, 3R, and 7R alleles could have once given a selective advantage, resulting in a permanent presence of these alleles in human populations. Therefore, the ancestry 4R genotype should be considered a baseline against which the non-4R genotypes (including 3R) should be compared in tests of gene-behavior associations (Grady et al. 2003).

## GENETIC VERSUS SOCIOECONOMIC INFLUENCES

The advances in molecular genetics over the past two decades have identified more than 1,200 specific genes for disorders such as Huntington's disease, cystic fibrosis, Duchenne's muscular dystrophy, hereditary nonpolyposis colon cancer, and heritable breast cancers (Botstein and Risch 2003). Almost all of these human disorders are genetically "simple" or Mendelian traits, which are basically determined by the genetic sequence at a single chromosomal locus. These simple Mendelian traits are rare. Almost all common diseases, such as heart disease, hypertension, diabetes, and cancer, and almost all human traits/behaviors that are interesting to social scientists, such as age at first sexual intercourse, are "complex" or non-Mendelian. Multiple genes, multiple environmental factors, and interactions among genetic and environmental factors are thought to influence complex traits.

The *DRD4* gene is unlikely to be a "sex" gene itself. The gene is more likely associated with a predisposition for a number of related behaviors, including early initialization of sex. The gene may have a moderate effect on certain behaviors and may interact with environment to exert such an effect, that is, whether the genetic predisposition leads to the behavior may often depend on environmental conditions.

The idea of genotype-environment interactions is well-illustrated in the recent work of Caspi et al. (2002, 2003) and Guo and Stearns (2002). In a 2002 article in *Science* magazine, Caspi et al. investigated the role of genotype in violent behavior among maltreated children. Boys who were maltreated early in life are at risk of becoming violent offenders. But not all children respond to maltreatment in the same way. The study found that a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) modifies the effect of maltreatment. Only maltreated children with a genotype generating low levels of MAOA expression tended to develop the violent behavior problem. Maltreated children with a genotype that produces high levels of MAOA activity were less affected.

In the present study, the influence of a genetic variant on age at first sex may depend on the social and cultural meanings of the behavior for the adolescent in a particular social and cultural environment. The socioeconomic factors, such as family structure, parental education, and neighborhood-level poverty (Billy et al. 1993; Hogan and Kitagawa 1985; Upchurch et al. 1998), are environmental candidates for investigating such gene-environment interactions.

## SAMPLES

### Add Health

We used data from Add Health, which started as a nationally representative sample of more than 20,000 adolescents in grades 7–12 in 1994–1995 in the United States (Harris et al. 2003). The respondents were then followed up by two additional in-home interviews in 1995–1996 (Wave II) and 2002 (Wave III). Add Health is school-based, and the adolescents were from 134 schools. The school sample was stratified by region, ethnic mix, size, urbanicity (urban/suburban/rural), and school type (public/private/parochial).

## The Twin Sample and the Sibling Sample

The data for our non-DNA biometrical analysis came from the twin sample within the Add Health study, which deliberately incorporated the behavior-genetic design as a component in an otherwise traditional survey. Our biometrical analysis uses 305 pairs of MZ twins and 269 pairs of same-sex DZ twins. We excluded biological full siblings; the age difference within a pair of siblings is likely to exaggerate genetic contribution because the age difference tends to make full siblings more different than DZ twins regarding age at first sex, and this difference will be attributed to genetic sources if siblings are combined with DZ twins in the analysis. Different-sex DZ twins were essentially excluded for similar reasons.

In Waves I and II, the classification of the twins into MZ and DZ pairs was based primarily on self-reports of confusability of appearance (Rowe, Jacobson, and Oord 1999). Recently, in Wave III, the zygosity of twins was redetermined at the DNA level through a comparison of their match on 12 unlinked STRs (see footnote 1).

In Wave III in 2002, DNA samples were collected from a subset (the sibling sample) of the Add Health sample. The subset consisted of 2,597 MZ twins, DZ twins, and full biological siblings. The DNA/sibling sample is considerably larger than the twin sample used for the biometrical analysis. The genomic DNA was isolated from buccal cells<sup>10</sup> by using a modification of published methods (Freeman et al. 1997; Lench, Stanier, and Williamson 1988; Meulenbelt et al. 1995; Spitz et al. 1996).

## MEASURES

### Age at First Sexual Intercourse

At each of the three waves, the Add Health respondents were asked about their sexual histories. They were first screened by the question, "Have you ever had sexual intercourse? When we say sexual intercourse, we mean when a male inserts his penis into a female's vagina." If the respondent's answer was yes, he or she was then asked, "In what month and year did you have sexual intercourse for the very first time?" To protect confidentiality and reduce nonresponse, this section of the interview was self-administered by audio Computer-Assisted Self-Interview (CASI). The sensitive questions were read to respondents by means of audio headphones. Respondents were given instructions on how to complete their answers on the computer.

A number of previous studies examined the accuracy of the reported dates for age at first sex (Alexander et al. 1993; Lauritsen and Swicegood 1997; Rodgers, Billy, and Udry 1982; Siegel, Aten, and Roghmann 1998; Upchurch et al. 2002). These studies showed that boys are more likely than girls to provide inconsistent reports regarding their age at first sex. The youngest boys were the least likely to provide accurate reports about their sexual experiences. Upchurch et al. (2002) showed that, at Wave II of the Add Health study, white and African American boys were more likely than white girls to revise their ages at first intercourse reported at Wave I to older ages.

The reporting errors, however, appear to be largely random and, more importantly, have little impact on the estimated ages at first intercourse or the effects of socioeconomic and demographic predictors of age at first sex (Lauritsen and Swicegood 1997; Upchurch et al. 2002; Wu, Martin, and Long 1999). Using Wave I and II Add Health data, Upchurch et al. (2002) conducted seven analyses of age at first sex, with each set based on a different assumption about which the reported date of first intercourse was considered true. The seven analyses arrived at very similar conclusions.

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10. Buccal cells are the cells from the inner lining of the mouth. These cells are routinely shed and replaced by new cells. As the old cells die, they accumulate in the saliva in the mouth and can easily be collected by a simple procedure using mouthwash.

In our analyses, when a reporting inconsistency arose, we gave priority to the report obtained at a later wave because older adolescents tend to give more accurate reports (Siegel et al. 1998). Reporting errors probably have a larger impact on our twin analysis than our analysis of genetic variants, which can be viewed for this purpose as similar to Upchurch et al.'s analysis (2002).

### DNA Preparation and Genotyping

The Wave III Add Health study collected buccal cell DNA from a subset of the Add Health sample. Genomic DNA was isolated at the Institute for Behavioral Genetics at the University of Colorado (<http://www.cpc.unc.edu/projects/addhealth/>) using a modification of published methods (Freeman et al. 1997; Lench et al. 1988; Meulenbelt et al. 1995; Spitz et al. 1996). The average yield of DNA was  $58 \pm 1 \mu\text{g}$ . The buccal DNA samples have been used for the assessment of nearly 48,000 genotypes, which include STRs, VNTRs, and SNPs.

The assay used was a modification of the method of Sander et al. (Sander et al. 1997). This method results in polymerase chain reaction (PCR) products of (in bp) 379 (2R), 427 (3R), 475 (4R), 523 (5R), 571 (6R), 619 (7R), 667 (8R), 715 (9R), and 763 (10R). A series of chi-square tests, each within a self-reported ethnic group (European, African American, and Hispanic), reveals no deviation from the Hardy-Weinberg equilibrium. Of the nine alleles in the polymorphism, the 2R (9%), the 3R (3%), the 4R (65.3%), and the 7R (20.4%) account for a total of 97.7% of the variants observed in our sample. Our analysis focuses on these alleles and the genotypes associated with these alleles.

### Descriptive Statistics and Socioeconomic Predictors

Table 1 provides the descriptive statistics for the variables we use in this analysis. The 3R allele frequency (the total number of 3R alleles divided by twice the total number of individuals) in the all-ethnicities sample is about 3%, with the frequency for Asians being the lowest (1.6%) and for whites the highest (3.9%). Because only two individuals are homozygous (having two copies of the same allele) for 3R, the genotype frequency (proportion of individuals having one or two 3R alleles) is about twice as high as the allele frequency. The genotype frequency is 5.9% for the all-ethnicities sample, 3.2% for the Asian sample, 7.8% for the white sample, 3.0% for the Hispanic sample, and 3.6% for the African American sample. The genotype frequency is a more relevant statistic for our analysis than the allele frequency. The descriptive statistics related to 2R and 7R are not presented.

Consistent with the population in the United States, whites are by far the largest group represented in the Add Health study (57%); but Add Health oversampled Asians (7.3%), African Americans (18.4%), and Hispanics (14.6%). A slightly higher proportion of females than males are included in the Add Health sibling sample. Family structure is a variable of four categories: two-biological-parent families (61% in the combined sample); single-parent families (22%); stepparent families (13.2%); and other types of families (3.4%), including families with adopted and foster children. Parental education also has four categories: less than a high school diploma (11.2%), high school diploma (27.7%), some college (20.1%), and at least a college degree (36.1%). Add Health measured the level of education of both the mother and the father of each respondent. We used the higher of the two when both were available. For the 5% of the respondents missing information on parental education, we created a separate category. Poverty at the neighborhood level was measured by the proportion of families living below the official poverty line in a census block group, which is the smallest geographic area for which the Census Bureau publishes sample data. In 1990, block groups averaged 452 housing units, or 1,100 individuals. The block groups are divided into low-poverty (55.6%), median-poverty (19.1%), and high-poverty (18.3%) categories. The two cutoff points for the three categories are 11.6% (the median proportion of families in a block group living below the poverty line)

**Table 1. Means and Standard Deviations (in parentheses) of Variables for the Add Health Sibling Sample, by Race/Ethnicity**

	All Ethnicities	Asian	White	Hispanic	African American
3R (allele)	0.030	0.016	0.039	0.015	0.019
Any 3R (genotype)	0.059 (0.235)	0.032 (0.177)	0.078 (0.269)	0.030 (0.170)	0.036 (0.187)
Ethnicity					
White	0.571 (0.495)				
Asian	0.073 (0.260)				
African American	0.184 (0.388)				
Hispanic	0.146 (0.353)				
Other	0.026 (0.160)				
Female	0.522 (0.500)	0.478 (0.501)	0.526 (0.500)	0.505 (0.501)	0.549 (0.498)
Family Structure					
Two biological parents	0.613 (0.487)	0.747 (0.436)	0.673 (0.469)	0.629 (0.484)	0.370 (0.483)
Single parent	0.220 (0.414)	0.108 (0.311)	0.159 (0.365)	0.202 (0.402)	0.468 (0.500)
Stepparent	0.132 (0.339)	0.091 (0.289)	0.149 (0.356)	0.126 (0.333)	0.094 (0.292)
Other families	0.034 (0.183)	0.054 (0.226)	0.019 (0.137)	0.043 (0.203)	0.068 (0.252)
Parental Education					
High school diploma	0.277 (0.447)	0.124 (0.330)	0.291 (0.454)	0.223 (0.417)	0.336 (0.473)
Less than high school diploma	0.112 (0.316)	0.075 (0.265)	0.053 (0.224)	0.355 (0.479)	0.115 (0.319)
Some college	0.201 (0.401)	0.156 (0.364)	0.222 (0.416)	0.145 (0.353)	0.189 (0.392)
College degree or more	0.361 (0.480)	0.575 (0.496)	0.404 (0.491)	0.204 (0.404)	0.283 (0.451)
Missing	0.049 (0.216)	0.070 (0.256)	0.030 (0.171)	0.073 (0.260)	0.077 (0.266)
Neighborhood Poverty					
< 11.6 %	0.556 (0.497)	0.785 (0.412)	0.653 (0.476)	0.470 (0.500)	0.243 (0.429)
11.6%–23.9%	0.191 (0.393)	0.129 (0.336)	0.194 (0.396)	0.210 (0.408)	0.198 (0.399)
≥ 23.9 %	0.183 (0.386)	0.043 (0.203)	0.091 (0.287)	0.237 (0.426)	0.479 (0.500)
Missing	0.070 (0.255)	0.043 (0.203)	0.062 (0.242)	0.083 (0.277)	0.081 (0.273)
Number of Individuals	2,552	186	1,457	372	470

*Note:* Numbers in parentheses are standard deviations.

and 23.9% (the 75th percentile of the proportion of families in a block group living below the poverty line). We again created a separate category for those missing information on neighborhood poverty (7%).

Our preliminary check shows that the proportion of MZ twins having had first sex is not significantly different from that among the DZ twins, indicating that the two types of twins are probably sampled from the same population (data not shown).

## STATISTICAL PROCEDURES

We used survival analysis in both the twin analysis and the analysis of genetic variants because of the right censoring in our data—a large number of individuals had not had sexual intercourse by the end of the Add Health study. Previous genetic studies on age at first sex (Dunne et al. 1997; Miller et al. 1999; and Rodgers et al. 1999) used linear regression, assuming that the age at first sex is known for all individuals in the sample. Our Add Health respondents were aged 19–26 at Wave III, and the proportion who had not had first sex ranged from about 10%–15% at age 26 to about 20%–30% at age 19. These censored times must be dealt with in the framework of survival analysis (Cox and Oakes 1984).

### Twin Analysis

For linear outcome variables, the technique of variance decomposition is routinely used to estimate the proportions of the variance in the outcome variable (e.g., body mass index) due to genetic, shared environmental, and nonshared environmental (including measurement errors) factors. The proportion of the variance due to genetic contribution is defined as *heritability*, which conveys the magnitude of genetic contribution to the outcome in a particular population. The analysis can be accomplished by Pearson's correlation, structural equation models (Neale and Cardon 1992), or multilevel models (Guo and Wang 2002).

In this analysis, we estimated the genetic contribution to age at first sex by using the shared frailty survival models or multilevel survival models (Clayton 1978; Guo and Rodríguez 1992):

$$h(t_{ij} | w_j) = w_j h_0(t) \exp(\beta' x_{ij}), \quad (1)$$

where the hazard function  $h(t_{ij} | w_j)$  for person  $i$  in twin pair  $j$  at time  $t$  satisfies the multiplicative frailty model (1),  $w_j$  is the realized value of the random effect shared by the two members of pair  $j$ ,  $h_0(t)$  represents a baseline hazard, and  $\beta' x_{ij}$  is the usual linear predictor. The random effect  $W_j$  is assumed to have a gamma distribution with the index  $\alpha$ , the scale  $\alpha^{-1} = \phi$ , and the density  $f(w_j) = w_j^{\alpha-1} e^{-\alpha w_j} \alpha^\alpha / \Gamma(\alpha)$ , with mean  $E(W_j) = 1$  and variance  $(W_j) = \phi$ . The baseline hazards are assumed to follow a piecewise exponential distribution with cutoff points at ages 15, 16, 17, 18, and 20.

In the case of linear outcome variables, genetic contribution in terms of heritability can be calculated from the random parameters (within- and between-pair variances) from multilevel models. In the case of survival data, genetic contribution can be calculated using the between-pair variance  $\phi$  from a gamma shared frailty model. This calculation is based on an interpretation of  $\phi$  first suggested by Clayton (1978) and then generalized by Guo and Rodríguez (1992) to the multivariate case. Clayton showed that the ratio of the two hazards is constant over time and equal to  $1 + \phi$  (2). In the ratio, the numerator is the conditional hazard of Twin 1 at age  $t_1$  given that Twin 2 experienced the event at age  $t_2$ ; the denominator is the conditional hazard of Twin 1 at age  $t_1$  given that Twin 2 has survived at least to age  $t_2$ .

$$\frac{h(t_1 | T_2 = t_2)}{h(t_1 | T_2 > t_2)} = 1 + \phi, \quad (2)$$

where  $T_1$  and  $T_2$  are survival times of Twin 1 and Twin 2, respectively. An estimated  $\phi$  of 0.5, for example, would suggest that the hazard of Twin 1 is raised by 50% if Twin 2 in the pair experienced the event at  $t_2$ , relative to what it would be if the other member had not experienced the event by  $t_2$ . Thus,  $\phi$  may be considered a measure of the within-pair "correlation" of the age at first sex. If  $\phi$  calculated from the MZ sample is significantly larger than that from the DZ sample, we consider it evidence for genetic contribution to the timing of first sexual intercourse.

### Analysis of Genetic Variants

This analysis consists of two steps. First, we compare, in graphs, the life-table-based probability of having had first sexual intercourse at given ages across genotypes and ethnicities. Second, we use the following piecewise exponential survival regression model to estimate the association between the *DRD4* genotypes and age at first sex:

$$h(t_{ijk}) = h_0(t_k)\exp(\beta'x_{ij}), \quad (3)$$

where  $k$  indexes the intervals within which the hazard is assumed to be constant. Model (3) could be estimated by any computer procedure that estimates the Poisson regression (Holford 1980; Laird and Olivier 1981) if the individuals in our DNA sample were independent. To control for the dependence among the siblings in our Add Health data, we estimated Eq. (3) using the generalized estimating equations (GEE; Liang and Zeger 1986), which have long been established in the statistical literature as a standard approach for addressing correlated data.

## RESULTS

### Biometrical Twin Analysis

Table 2 presents models of genetic contribution to age at first sexual intercourse with the estimated coefficients, hazard ratios, and  $p$  values from the shared frailty survival models. These results are based on the samples of MZ and same-sex DZ twins. The key estimate for our purpose is  $\hat{\phi}$ , the variance of the shared random effect or frailty, which was estimated to be 0.173 ( $p = .004$ ) for the combined twin sample, 0.314 ( $p < .001$ ) for the MZ twin sample, and 0.024 ( $p = .395$ ) for the same-sex DZ twin sample. The estimate of 0.314 suggests that the risk of first sex is heightened by 31.4% for the index twin if the other twin in an identical twin pair has had sex already as compared with what it would be if the other twin had not had sex. In contrast, among the same-sex fraternal twins, the risks of first sex do not appear to be related.

The three shared frailty survival models shown in Table 2 all include the standard parameters for the baseline hazards, gender, and ethnicity. Compared with whites, Asians experienced a much lower rate of first sex (about 42% lower in the all-twins model), and African Americans had a substantially higher rate of first sex (about 28% in the all-twins model). The rate of first sex peaked at ages 17–18 and then declined thereafter.

The models shown in Table 3 include the same set of parameters when appropriate, but only the random parameters are presented. Within both the male and female samples, the MZ twins, but not the same-sex DZ twins, correlate in the timing of first sex. The random parameter estimate from the white male sample is 0.694 and is highly statistically significant. The same parameter estimate in the white female sample is in the same direction and is statistically significant at the 10% level.

We attempted to incorporate the opposite-sex DZ twins into the analysis in two ways. We estimated the random parameter using only the opposite-sex DZ twins, and we estimated the random parameter using the combined sample of the same-sex DZ twins

**Table 2. Biometrical Estimate of Genetic Contribution to Age at First Sexual Intercourse: Coefficients, Hazard Ratios, and  $p$  Values From Shared Frailty Survival Models (Add Health twin samples)**

	MZ + Same-Sex DZ Twins			MZ Twins			Same-Sex DZ Twins		
	$\beta$	exp( $\beta$ )	$p$ Value	$\beta$	exp( $\beta$ )	$p$ Value	$\beta$	exp( $\beta$ )	$p$ Value
Intercept	-4.526	0.011	0.000	-4.709	0.009	0.000	-4.359	0.013	0.000
Male	—	—	—	—	—	—	—	—	—
Female	0.115	1.122	0.151	0.191	1.210	0.115	0.052	1.053	0.623
White	—	—	—	—	—	—	—	—	—
Asian	-0.540	0.583	0.021	-0.479	0.619	0.083	-0.768	0.464	0.192
African American	0.248	1.282	0.012	0.303	1.353	0.052	0.175	1.191	0.161
Hispanic	0.069	1.071	0.550	0.205	1.227	0.221	-0.083	0.920	0.600
Other race/ethnicity	0.122	1.130	0.589	-0.005	0.995	0.989	0.250	1.284	0.376
Baseline Hazards									
< 15	—	—	—	—	—	—	—	—	—
16	2.497	12.140	0.000	2.488	12.041	0.000	2.503	12.218	0.000
17	2.910	18.349	0.000	2.907	18.295	0.000	2.908	18.316	0.000
18	3.253	25.871	0.000	3.423	30.653	0.000	3.038	20.863	0.000
20	2.865	17.553	0.000	3.054	21.192	0.000	2.660	14.292	0.000
> 20	2.617	13.698	0.000	3.059	21.299	0.000	2.042	7.703	0.000
Number of Pairs	574			305			269		
-2 Log-Likelihood	802.34			403.6			386.08		
$\phi$	0.173		0.004	0.314		0.000	0.024		0.395

**Table 3. Biometrical Estimate of Genetic Contribution to Age at First Sexual Intercourse: Coefficients, Hazard Ratios, and  $p$  Values From Shared Frailty Survival Models, by Gender and Ethnicity (Add Health twin samples)<sup>a</sup>**

	Male		Female		White Male		White Female	
	MZ Twins	DZ Twins	MZ Twins	DZ Twins	MZ Twins	DZ Twins	MZ Twins	DZ Twins
Number of Pairs	154	136	151	133	90	81	80	71
$\phi$	0.262	0.088	0.352	0.000	0.694	0.000	0.199	0.000
$p$ Value	0.032	0.250	0.003	0.49	0.001	1.000	0.099	0.50

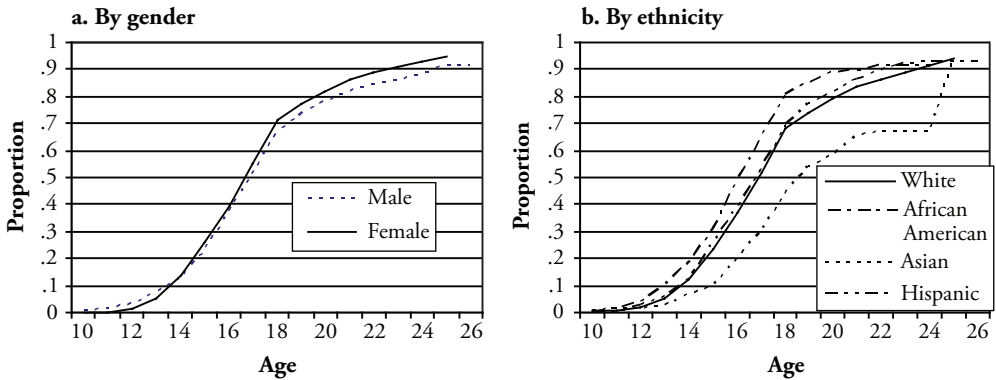
<sup>a</sup>The results are presented only for whites because the sample sizes of African Americans and Asians are very small.

and the opposite-sex DZ twins. In both cases, the random parameter was not significantly different from zero (data not shown).

### Analysis of Genetic Variants

Figure 1 shows the proportion having had first sexual intercourse at given ages by gender (Panel a) and by ethnicity (Panel b) for the Add Health sibling sample ( $N = 2,552$ ). About

**Figure 1.** Proportion of Those Who Had First Sexual Intercourse at Given Ages: Add Health Sibling Sample ( $N = 2,552$ )

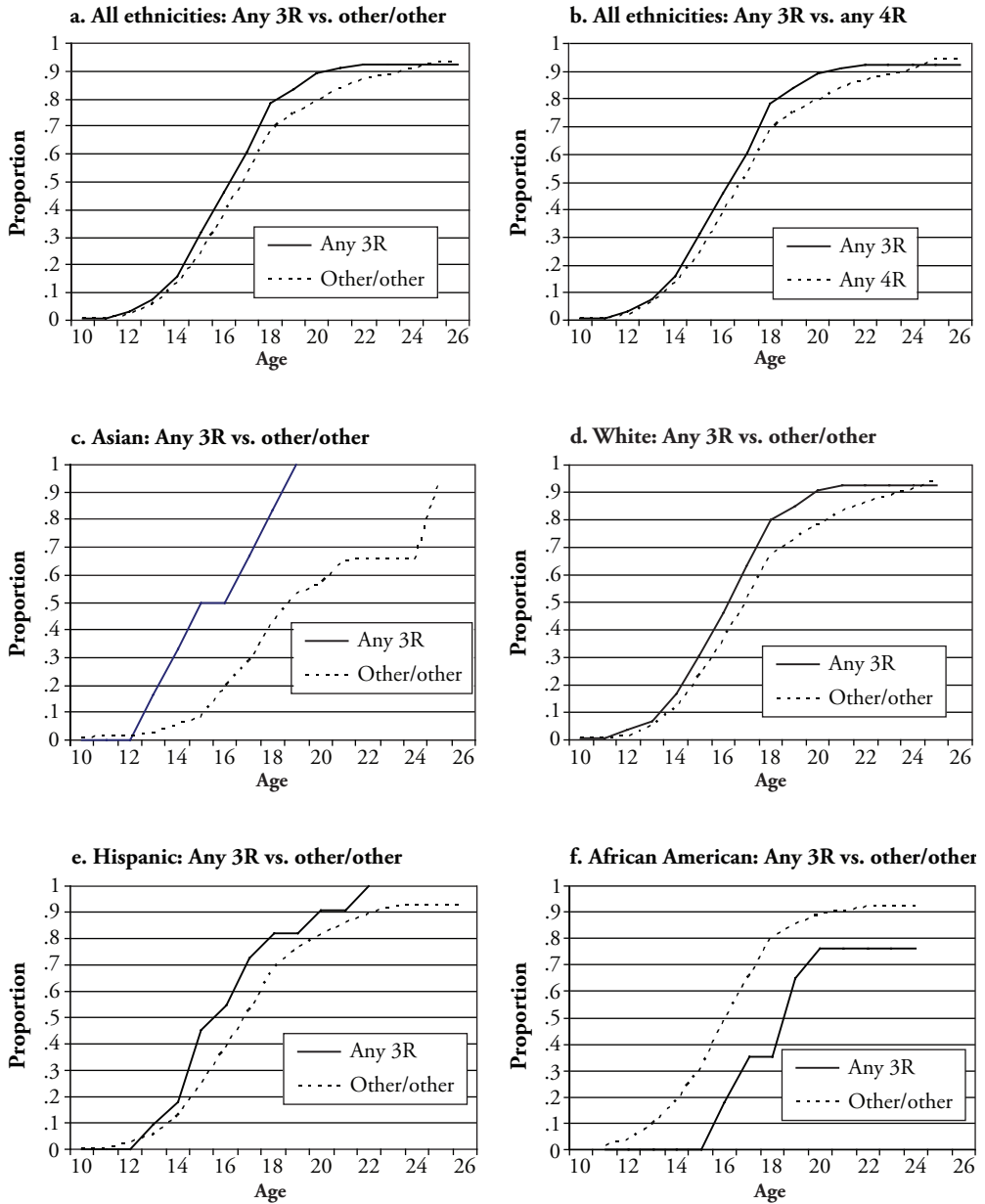


70% of the adolescents had had first sex by age 18, and slightly higher proportions of the girls had had first sex than boys starting from the ages of 17–18. Substantially higher proportions of African American adolescents had had first sex than adolescents in the other ethnic groups. Similar proportions of white and Hispanic adolescents had had first sex, and the proportions for Asians are much lower. We repeated the analysis presented in Figure 1 using the entire Add Health sample of 20,198 individuals. The results (data not shown) are very similar to those in Figure 1, indicating that our results from the sibling sample may be generalized to the entire Add Health sample.

Figure 2 provides the exploratory results for the association between the any-3R genotype and the risk of first sex. Panel a of Figure 2 gives the proportion having had first sex for all ethnicities by the two genotypes: those with any 3R and those with none. Higher proportions with the any-3R genotype had initialized sexual intercourse in adolescence than those with other genotypes, suggesting an association between the any-3R genotype and a higher risk of initializing sexual intercourse in adolescence. Panel b of Figure 2 is the same as Panel a except that the reference category (the other genotypes) contains only the any-4R genotype, which is the dominant genotype and accounts for more than 65% of all alleles in the sample. The findings in Panels a and b are almost identical.

In Panels c–f of Figure 2, we present the proportion of respondents having had first sex at given ages by genotype for Asians, whites, Hispanics, and African Americans. For Asians, the difference between the two genotypes is striking. The 3R is a rare allele, and only six individuals in the Asian sample belong to the any-3R genotype. Yet, by age 18–19, all with at least one 3R allele had initialized sexual intercourse. These six Asians had first sex at ages 13, 14, 15, 17, 18, and 19, respectively. In contrast, about 50% of the Asians with the none-3R genotype were still virgins at age 19. In both the white and Hispanic samples, the proportions having had first sex for the any-3R genotype are higher than those for the none-3R genotype. This pattern of a higher risk for the any-3R genotype appears to be reversed in the African American sample. However, this apparent difference in the African American sample was not statistically significant, even at the 10% level, in any of regression analyses we conducted. We reestimated the exploratory results suggested by Figure 2 in piecewise exponential GEE survival models. We estimated two sets of models. The first set estimated the effects of genetic variants, gender, and ethnicities for the all-ethnicities sample as well

Figure 2. Proportion Who Had First Sexual Intercourse at Given Ages by Genotype



as for the ethnicity-specific samples. The second set estimated the effects of genetic variants side by side with the effects of not only gender and ethnicity but also family structure, parental education, and poverty at the neighborhood level. In both sets of the models, the association of the any-3R genotype with age at first sexual intercourse is evident. Because

the two sets of results concerning the genetic effects (both parameter estimates and  $p$  values) are almost identical, only the results from the second set are presented (see Table 4).

The all-ethnicities model suggests that the risk of initializing sexual intercourse is 23% ( $p = .016$ ) higher for those with an any-3R genotype than for those with other genotypes. This increase in the risk of first sex associated with the any-3R genotype is 233% ( $p = .0001$ ) for Asians, 28% ( $p = .012$ ) for whites, and 69% ( $p = .006$ ) for Hispanics. The estimated genotype effect in the African American sample is not statistically significant ( $p = .216$ ).

In the all-ethnicities sample, growing up in a single-parent family or a stepparent family raises the risk of first sex by 23% ( $p = .001$ ) or 36% ( $p < .0001$ ), respectively, as compared with growing up in a two-biological-parent family. The effects of family structure in the African American sample are very similar to those in the all-ethnicities sample, whereas the effects in the Asian sample are not statistically significant. For Hispanics, growing up in a single-parent family appears to make one particularly vulnerable, being associated with an increase of 70% ( $p < .0001$ ) in the risk of first sex. For whites, only stepfamilies are associated with a 30% higher risk of first sex ( $p = .002$ ). In the all-ethnicities sample, parents' college degree was associated with a 26% decrease in the risk of first sex for their children, relative to those whose parents had only a high school diploma. We found a similar effect of parental education among Asians and whites, but not among Hispanics or African Americans. Poverty at the neighborhood level does not seem to have an impact on the risk of first sex in addition to the included individual and familial predictors.

We estimated two additional models (data now shown) of age at first sex on demographic and socioeconomic predictors, with one model based on the sibling sample of 2,552 individuals and the other based on the entire Add Health sample of 20,198 individuals. The two sets of results are quite similar, suggesting again that our findings based on the sibling sample may be generalizable to the U.S. adolescent population.

### Multiple Testing and Population Stratification

We carried out three comparisons (2R, 3R, and 7R) against the baseline 4R. In genetics research, an adjustment is often required to control for the increased error rate when multiple tests are conducted. We applied the Bonferroni procedure (Hochberg and Tamhane 1987) by using an adjusted level of significance  $\alpha / m$ , where  $m$  is the number of tests. Thus, for three tests, our new level of significance shrinks to  $\alpha / m = 0.05 / 3 = 0.016$ . All our previously statistically significant results still hold under the Bonferroni correction concerning any-3R in the all-ethnicity, Asian, white, and Hispanic samples. Note that the Bonferroni procedure tends to overcorrect the problem of multiple comparison because the procedure assumes independence among the multiple tests.

We used three strategies to address the potential impact of population stratification (Cardon and Palmer 2003). First, we included self-reported race/ethnicity as controls in the all-ethnicity model (Table 4) so that comparisons across genotypes are made within each race/ethnicity. The four self-reported ethnicity categories (European Americans, African Americans, East Asians, and Hispanics) have been shown to have a near-perfect correspondence with the categories determined by 326 microsatellite markers (Tang et al. 2005). Second, we reestimated the effects of the *DRD4* variants within the Asian, white, African American, and Hispanic samples, respectively, to eliminate the possibility of population stratification related to race/ethnicity (Table 4). Our third strategy takes advantage of the detailed categories of self-reported race/ethnicity in Add Health; we repeated our analyses after eliminating those individuals who designated themselves as multiracial/multiethnic (data not shown). In keeping with the census policy, Add Health respondents were allowed to mark as many ethnicity categories as they felt applied to them (Harris et al. 2003). About 7.5% of African American participants and 3.5% of Hispanic participants marked more than one category. Less than 1% of whites marked more than one racial/ethnic category.

Of those who marked more than one ethnic category, the large majority (86%) marked two ethnic categories, and 12% marked three ethnic categories. None of the tests of population stratification have changed our substantive conclusions.

## SUMMARY, DISCUSSION, AND CONCLUSION

### Twin Analysis

The biometrical analyses of twins (Tables 2 and 3) show that the identical twins correlate in the timing of first sexual intercourse to a substantially greater extent than do fraternal twins, suggesting a significant genetic contribution to the timing of first sex. This finding was demonstrated repeatedly in four samples: the entire sample consisting of identical and same-sex fraternal twins of both genders and all ethnicities, the male sample, the female sample, and the white male sample. The finding in the white female sample was similar in magnitude but was statistically significant only at the 10% level. This analysis was not performed for the African American, Hispanic, or Asian samples because of the sharply reduced sample sizes. More specifically, our analyses suggest that the risk of having first sex for an identical twin increases by 20%–60% (depending on the sample of the analysis) if the other twin in the pair has already had first sex, relative to the case in which the other twin is still a virgin. This correlation was not found among fraternal twins.

The absence of the correlation among the DZ twins (when the correlation among MZ twins is substantial) has been observed for a number of conditions, including autism and trisomy 21. Two explanations are typically provided. First, the observed phenomenon could be due to genetic dominance at multiple loci that influence the condition (Fisher 1930; Kirk et al 2001). Second, the condition could be produced by two-way gene-gene interactions at a number of loci (Eaves 1988). Recent developments in epigenetics have offered another explanation (Beaudet 2002; Jiang, Bressler, and Beaudet 2004). *Epigenetics* refers to changes in gene function that are stable and potentially heritable and that do not entail a change in DNA sequence. The epigenetic theory suggests the possibility of the rise of a de novo epigenetic condition in sperm or eggs, thus potentially leading to a concordance of nearly 100% for MZ twins and nearly 0% for DZ twins. Still another explanation could be errors in reporting age at first sex.<sup>11</sup> This explanation assumes that (1) the random reporting errors reduce the within-pair correlation in age at first sex in twin analysis and (2) the reduction in the correlation for MZ and DZ twins is approximately the same. Then, a reduction similar in strength across the two types of twins would underestimate the correlation (the parameter  $\phi$ ) in both MZ and DZ twins, but the difference in the correlation of the timing of first sexual intercourse between MZ and DZ twins would remain approximately the same, which is fundamental evidence for a genetic contribution to age at first sex. Thus, our twin analysis could have correctly estimated the genetic contribution even if the within-pair correlation among both MZ and DZ twins is underestimated.

### Analysis of Genetic Variants

Our analysis at the molecular level shows consistently that the any-3R genotype in the *DRD4* gene is associated with a much higher risk of initializing sexual intercourse than that associated with other genotypes, which include the genotypes associated with the 4R allele, the 7R allele, and the 2R allele. We combined the one-3R and the two-3R genotypes because of the extremely small sample of the two-3R genotype. In separate analyses, we included in the reference category only the dominant 4R allele; our basic findings remained

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11. In the linear case without censoring, random reporting errors would increase the variance of the age at first sex for Twin 1 and Twin 2 but would not affect the covariance between the two twins and thus would reduce the within-pair correlation.

**Table 4. Association of the Any-3R Genotype in the DRD4 With Age at First Sexual Intercourse: Coefficients and Hazard Ratios of Piecewise Exponential GEE Survival Model by Ethnicity With Demographic and Socioeconomic Predictors (Add Health sibling samples)**

	All Ethnicities			Asian			White			Hispanic			African American			
	$\beta$	$e^{\beta}$	p Value	$\beta$	$e^{\beta}$	p Value	$\beta$	$e^{\beta}$	p Value	$\beta$	$e^{\beta}$	p Value	$\beta$	$e^{\beta}$	p Value	
Intercept	-4.29	0.01	< .0001	-4.75	0.01	< .0001	-4.33	0.01	< .0001	-4.28	0.01	< .0001	-3.95	0.02	< .0001	
Other/other	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Any 3R	0.21	1.23	0.016	1.20	3.33	0.0001	0.25	1.28	0.012	0.52	1.69	0.006	-0.33	0.72	0.216	
White	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Asian	-0.51	0.60	< .0001	—	—	—	—	—	—	—	—	—	—	—	—	
African American	0.19	1.21	0.003	—	—	—	—	—	—	—	—	—	—	—	—	
Hispanic	0.06	1.06	0.323	—	—	—	—	—	—	—	—	—	—	—	—	
Other Race/Ethnicity	0.32	1.38	0.005	—	—	—	—	—	—	—	—	—	—	—	—	
Female	0.11	1.11	0.009	0.029	1.03	0.870	0.15	1.16	0.006	0.07	1.08	0.497	0.02	1.03	0.788	
Estimates for the Baseline Hazard Omitted <sup>a</sup>																
Family structure																
Two biological parents	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Single parent	0.21	1.23	0.001	0.01	1.01	0.973	0.04	1.04	0.628	0.53	1.70	< .0001	0.26	1.30	0.010	
Stepparent	0.31	1.36	< .0001	0.25	1.28	0.489	0.26	1.30	0.002	0.16	1.18	0.251	0.38	1.47	0.017	
Other families	0.47	1.60	0.005	0.83	2.28	0.000	0.45	1.57	0.369	0.82	2.27	0.049	0.33	1.39	0.168	



unaltered. We also compared the genotypes based on the 2R allele and the 7R allele with those based on the most frequent 4R allele; no differences were found in the timing of first sexual intercourse among these genotypes.

The initial set of evidence was provided by Figure 2, which shows the proportion or probability of having had first sex by given ages, by genotype, and by ethnicity. Among Asians, whites, and Hispanics, the differences by genotype took place mainly during adolescence before ages 18–20. Between ages 20 and 26, the differences actually decreased.

The heightened risk was estimated to be 28% for whites, 233% for Asians, and 69% for Hispanics (Table 4). The genetic variant is not related to age at first sex among African Americans. Rather than viewing these dissimilar estimates across ethnicities as disparate, we find them to be interesting and revealing. The influence of the 3R genotype on age at first sex is likely to vary by the particular social environment in which the individual lives. In our case, each ethnicity may represent a different set of environmental conditions.

The social pressure for being sexually active among adolescents has long been thought to vary by ethnicity (DeLamater 1981; Udry and Campbell 1994). Previous findings indicated that environmental factors such as religiosity (Regnerus and Uecker 2006) and sexual media (sexual content in music, movies, television, and magazines; Brown et al. 2006) are much less predictive of adolescent sexual behavior among African Americans than among whites. Furstenberg et al. (1987) attributed the much higher probability of being sexually active among African American adolescents than among white adolescents primarily to the contextual normative differences in the acceptability of early intercourse. Our own analysis (Table 4) shows that African Americans have a higher risk (30%) of first sex than whites, Asians have a much lower risk (43%) than whites, and Hispanics have a risk that is similar to that for whites. Our analysis also shows that the levels of these ethnicity-specific risks of first sex are inversely related to the increased risk of first sex associated with the any-3R genotype. Asians have by far the lowest risk of first sex, but for Asians, the percentage increase in the risk of first sex associated with the risky genotype is by far the highest. African Americans have the highest risk of first sex, but the risky genotype does not increase the risk significantly.

These preliminary findings concerning gene-environment interactions suggest the hypothesis that the genetic predisposition for initialization of sex might play a smaller role in an environment in which cultural pressure for early sex is strong than it does in an environment in which such cultural pressure is milder. In the former environment, the cultural pressure may be so overwhelming that the influence from the genetic predisposition might be suppressed.

Adding the usual socioeconomic predictors of age at first sex (Table 4) does not alter the findings regarding the 3R genotype, indicating that there might be little correlation between the 3R genotype and the family structure, parental education, and neighborhood poverty. We estimated models with interaction terms between the 3R genotype and the socioeconomic predictors; the resulting models do not add significant explanatory power to the models in Table 4 (data not shown). Our interaction models are likely to be underpowered because of the small proportions of the 3R genotype in our samples.

### Limitations and Final Remarks

We have recognized the limitation of investigating one polymorphism in the *DRD4* gene. Although it is biologically plausible that the functional variants are causally related to the timing of first sexual intercourse, an alternative explanation is that other functional variants within the *DRD4* gene or in an adjacent region are in linkage disequilibrium with the 3R variants. These other variants could be the real early-sex-predisposing polymorphisms. Additional work that uses additional genetic variants within and near the *DRD4* gene is needed to replicate our findings. Our study is also limited because the 3R allele

is rare in our samples, and it is possible that some of our findings could be attributable to chance. For this reason, it is important that these findings be replicated in a much larger population-based study. Although our analysis addressed confounding at the level of main ethnic groups (which is usually the primary concern of population stratification), there may exist “cryptic” or unobserved population structure within each self-reported ethnicity (Pritchard, Stephens, and Donnelly 2000). A general solution to unobserved population structure at any level requires genotyping data for mother-father-child trios, a large number of unlinked genetic markers, or a large number of informative sibling pairs. None of these is available in Add Health at this point.

Implicitly or explicitly, an analysis of demographic behavior typically assumes that individuals are the same at birth. Under such an assumption, all differences across individuals would be automatically attributed to environmental influences. Parallel to this typical practice, attempts have been made to incorporate potential individual differences prior to birth. In a seminal paper on human mortality, Vaupel, Manton, and Stallard (1979) used “frailty” to describe all unmeasured individual-specific natural endowment for survival and let it be represented by a random variable. The work that followed (e.g., Guo and Rodríguez 1992; Heckman and Singer 1984; Trussell and Richards 1985) addressed various related methodological and substantive issues. The limitation in this line of work is obvious. How much of the unmeasured frailty, heterogeneity, or endowment is due to environmental sources and how much is due to genetic or other biological sources is unknown. Indeed, all unmeasured frailty or heterogeneity is treated as a black box. More important, further understanding of the mechanisms of the black box looks unpromising.

This situation has changed markedly because of the dazzling developments in molecular genetics over the past two decades. Each particular demographic behavior is potentially influenced by numerous genes, many environmental factors, and the interactions between the two, not to mention biological influences at other levels (e.g., epigenetics and gene expression). Granted, the progress toward a good understanding of these mechanisms is likely to be slow. Nevertheless, taking advantage of recent advances in molecular genetics and a combination of twin and DNA data, we have demonstrated that deciphering some of the mechanisms in the black box may be possible.

In conclusion, our twin and DNA analyses produced evidence pointing to a role of genes in the timing of first sexual intercourse. Our analyses also suggest a case of gene-environment interaction. Our future work will attempt to identify the specific environmental factors that were proxied by ethnicity and that might have moderated the expression of the risky genotype in the timing of first sexual intercourse.

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