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GENETIC POLYMORPHISMS ASSOCIATED WITH THE DEVELOPMENTAL TIMING OF PUBERTAL MATURATION AND SUBSEQUENT ONSET OF SEXUAL BEHAVIOR IN FEMALE ADOLESCENTS

by

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As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Cathleen B. Hunt entitled

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and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Aurelio J. Figueredo — Date: 11/06/02

James E. King — Date: 11/6/02

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Aurelio J. Figueredo — Date: 11/06/02

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DEDICATION

For my Mom

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

ABSTRACT

Previous genetic research has identified many human genes with allelic variation that are associated with differences in hormone synthesis. Still other non-genetic biological research has shown that increased levels of hormones are predictive of onset of puberty and that pubertal maturation is one of the strongest predictors of sexual activity onset. Studies informed by evolutionary theory have also shown that family context, such as the presence or absence of the biological father in early childhood, can predict pubertal maturation and, indirectly, subsequent sexual activity. This study was unique in that no research to date had attempted to use genetic markers as direct predictors of pubertal maturation and subsequent onset of sexual behavior in adolescents. Two genes of particular interest included the androgen receptor (AR) gene and the cytochrome P450c17-α gene (CYP17).

Saliva samples (for genetic marker identification), pubertal status, and sexual behavior measures were gathered bi-annually from 248 post-menarcheal females over 2-3 years. Hierarchical linear modeling and growth curve analyses revealed that the A1/A1 allele of the CYP17 gene was predictive of the presence of a biological father, which predicted age at menarche. Later ages at menarche predicted lower onset level of sexual development and earlier ages at menarche predicted higher onset levels of sexual development; however, lower onset levels of sexual development predicted faster rates of sexual development. These findings show that genetic markers can be used to help identify variation in timing of pubertal development. Also, these results provide

additional insight into understanding the differences in rates of sexual development among girls and suggest that there are mediating factors that may be buffering girls with higher onset levels of sexual development from progressing through sexual stages faster.

INTRODUCTION

The objective of this study is to determine whether specific genetic polymorphisms are predictive of pubertal maturation timing in female adolescents and, if so, whether those same polymorphisms are predictive of the onset of sexual behavior. Previous genetic research has identified many human genes with allelic variation that are associated with differences in hormone synthesis and one study has shown that genes in the dopaminergic family are predictive of onset of sexual activity. Still other non-genetic biological research has shown that increased levels of hormones are predictive of onset of puberty and that pubertal maturation is one of the strongest predictors of sexual activity onset, such as first intercourse. Studies informed by evolutionary theory have also shown that bio-social factors, such as the absence of the biological father in early childhood, are predictive of precocious pubertal maturation and, indirectly, subsequent sexual activity. This study is unique in that no research to date has attempted to use genetic markers as direct predictors of pubertal maturation and onset of sexual behavior in adolescents. For this study, two genes of particular interest include: the androgen receptor (AR) gene and the cytochrome P450c17-α gene (CYP17).

Specific Aims

The specific aims of this study are to: 1) genotype a female adolescent population and identify individuals by their allelic variants of the above mentioned two genes 2) determine whether possession of specific allelic variants of the two genes predicts developmental timing of pubertal maturation 3) determine whether possession of the

same allelic variants predicts the onset level (i.e., intercept) of sexual behavior, including first intercourse 4) determine whether the onset level of sexual behavior influences the development rate (i.e., slope) of sexual behavior, and 5) determine whether father absence acts as a mediating predictor in this genetic model of pubertal maturation and subsequent sexual behavior.

Genetic Polymorphisms

Two genetic markers have been chosen for this study because of their association with hormonal and metabolic processes that affect the rate and timing of pubertal maturation. The androgen receptor (AR) gene is located on the X chromosome and is a member of the thyroid and steroid hormone receptor gene family. The AR gene is involved in mediating the effects of androgens, such as testosterone on normal male sex differentiation and pubertal development in normal males and females. The AR gene contains a sequence of repeated occurrences of the nucleotide triplet cytosine-adenine-guanine (CAG) that varies in length in normal individuals in the range of 11-31 repeats (Edwards, Hammond, Jin, Caskey, & Chakraborty, 1992). A genotype survey of more than 45 nuclear families within four human ethnic groups revealed that 17-19 repeats were most common in African-Americans, accounting for approximately 42% of allelic variation; 19-21 repeats were most common in Caucasians (approximately 47% of allelic variation), 21-24 repeats were most common in Mexican-Americans (approximately 54% of allelic variation), and 21-23 repeats (approximately 46% of allelic variation) were most common in Asians (Edwards, Hammond, Jin, Caskey, & Chakraborty, 1992).

The biological significance of the CAG repeat expansion within the AR gene has been demonstrated by in-vitro studies, in which larger CAG repeat lengths exhibited decreased transcription capability of the AR gene, and thus, reduced production of androgen (Chamberlain, Driver, & Miesfeld, 1994). These repeat lengths, or allelic variations, occur more often in this gene than in other steroid receptor genes (Tilley, Marcelli, & McPhaul, 1990), and can result in a wide range of phenotypic expression, from complete androgen insensitivity associated with an increased feminization of traits to increased androgen sensitivity associated with masculinization of traits.

The P450c17-α gene (CYP17) located on chromosome 10 codes for the production of cytochrome, a key enzyme that mediates both steroid 17α-hydroxylase and 17,20 lyase activities that are responsible for the production of androgens and estrogens (Feigelson, Coetzee, Kolonel, Ross & Henderson, 1997; Picado-Leonard & Miller, 1987). An untranslated portion of the 5' region of this gene contains a single base pair polymorphism that creates a Sp1-type (CCACC box) promoter site upstream from the initiation of translation, but downstream from the transcription start site (Carey, et al., 1994). This base pair change creates a recognition site for the *Msp*AI restriction enzyme that creates two alleles (A1 and A2). This base pair change also creates a CCACC box and it is believed that the number of 5' promoter elements correlates with promoter activity; A2 possesses more promoter elements and is believed to correlate with more promoter activity and, therefore, an increased rate of transcription (Kadonaga, Jones, & Tijan, 1986). A recent study has shown that the A1/A1genotype is associated with later

age at menarche than A1/A2 or A2/A2 genotypes (Feigelson, Coetzee, Kolonel, Ross & Henderson, 1997), suggesting that the CYP17 genotype may be a marker for the onset of menarche in young adolescent females.

CYP17 genotype frequencies for approximately 285 women within three ethnic groups revealed that 26.1%, 38.7%, and 30.4% of Asian, African-American, and Mexican-American women, respectively, possess the A1/A1 genotype, whereas approximately 50% of women from all three of these ethnic groups possess the A1/A2 genotype (Feigelson, Coetzee, Kolonel, Ross & Henderson, 1997). Genotype frequencies from another study showed that 69% of Caucasian women possessed at least one copy of the A2 allele (Carey, et al., 1994). Sociobiological studies on adolescents, including studies using data from girls to be used in the current study, have shown that African-American girls reach age at menarche approximately 0.4 years earlier than Caucasian girls and girls of other ethnicities (Halpern, Udry, & Suchindran, 1997; Halpern, Udry, Campbell, & Suchindran, 1999; Herman-Giddens et al., 1997). This information indicates that although a greater number of African-American women than women of other ethnicities possess one marker (i.e., A1/A1 for CYP17) that should predispose them to later ages at menarche, there are other genetic factors, and most likely environmental factors, that are contributing to an earlier onset of menarche in African-American girls.

Pubertal Maturation and Sexual Behavior

The previous genetic markers are indicators of variation in pubertal maturation, but few if any genetic markers have been linked to sexual behavior. The DRD1 and

DRD2 genes that are associated with the dopaminergic system have been found to be linked to age at first intercourse; however, these findings show that this association was stronger among males than females (Miller et al., 1999). Still, there is other evidence demonstrating that pubertal timing and sexual development are inherited characteristics. For example, menarcheal timing is similar for mothers and daughters (e.g., Campbell & Udry, 1995) for monozygotic twins (Meyer, Eaves, Heath & Martin, 1991; Treloar & Martin, 1990), and between sisters (Chern, Gatewood, & Anderson, 1980). With the timing and rate of puberty appearing to be genetically orchestrated (Olsen, 1992), it would be expected that this genetic effect may contribute to the resemblance of timing of first sexual intercourse as well. Indeed, twin research has shown that age at first intercourse is more similar for monozygotic sister twins than dizygotic sister twins (Martin, Eaves, & Eysenck, 1977).

Other biologically-based research has also discovered a relationship between pubertal development and sexual behavior. For example, results from a sociobiological study found that physical maturation, independently from chronological age, predicted heightened sexual activity in females (Flannery, Rowe, & Gulley, 1993). Another study showed that testosterone and changes in testosterone in adolescent females were significantly related to the timing of subsequent transition to first intercourse (Halpern, Udry, & Suchindran, 1997). A few studies of adolescent sexual behavior have considered the simultaneous effects of both pubertal timing and friends' sexual activity (Smith, Udry, & Morris, 1985; Udry, 1988). One of the same studies, found that girls in the earlier

stages of puberty were less likely to be sexually active, irrespective of their friends' level of sexual activity (Smith, Udry, & Morris, 1985). Physically mature girls, however, were more likely to resemble their friends on levels of sexual activity (e.g., kissing, various stages of petting, or intercourse). Similarity in heritable personality and intellectual traits may also contribute to girls' resemblance for pubertal timing. Overall, these results indicate that genetic precursors may influence pubertal timing and, directly or indirectly, subsequent sexual behaviors. The primary importance of this study is to determine whether genetic predictors of puberty can act as genetic predictors of sexual behavior as well.

The previously mentioned studies indicate that pubertal onset is associated with onset of sexual activity. It is important to note, however, that these studies do not report that onset of puberty *causes* onset of sexual activity. Accurate interpretations of these data indicate that the biological and physical changes associated with puberty are most likely the same biological and physical changes that ultimately lead to the behavioral onset of sexual activity. For example, hormonal changes and increases in testosterone associated with puberty may also be related to increased feelings of sexual desire. As girls' interests in sexual activity increase they may seek out sexual experiences. It may also be the case that the physical changes (i.e., widening of hips, enlargement of breasts) that correspond to the onset of puberty in girls are attractive to young males and may even act as evolutionary-based cues that indicate to males that girls are physically mature and have reached an age of reproductive capability. These physical changes may entice males to

seek out sexual relationships with these girls and could, in part, account for girls' onset of sexual activity. In addition to the genetic predictors of puberty, this study will also investigate the changes in sexual feelings and sexual behavior that are associated with the physical changes of reaching puberty and determine whether allelic variation in the previously mentioned markers accounts for differences in level of sexual activity.

Life-History Theory: Father Absence, Timing of Menarche, and Sexual Activity

Developmental biologists were of the first to note that the ultimate description of an organism is not just a description of its adult phase, but that of its life cycle or life history. The life-history consists of age-specific schedules of mortality and fecundity, as well as traits that are either directly the result of these schedules, such as life span and age at first reproduction, or that are directly connected to them, such as growth, body size, and developmental trajectory (e.g., Bonner, 1965). A basic tenet of this life-history theory is the principle of allocation; that energy used for one purpose cannot be used for another. For living organisms this means that natural selection has created an optimal allocation pattern that results in investing more energy into one life function over others. Evolutionary ecologists have further specified that in order for any organism to reproduce, effort must be apportioned among three fundamental tasks: growth and development, mating, and parenting (e.g., Hill, 1993). Relative to other species, humans emphasize growth and development, as seen in the prolonged period of juvenile dependence and delayed sexual maturation. And in contrast to most other mammals, we are unusual for the importance we attach to pair bonds and for the high levels of

biparental care required to raise children to maturity. Still, despite these generalizations about our species, there remains a substantial amount of variance in the way that humans manage these three tasks (i.e, growth and development, mating, and parenting).

Through the process of natural selection, humans have evolved the adaptation to be flexible in the adoption of a life-history trajectory that will be optimal based on environmental conditions, both physical and social. If the environment is hostile, then extended growth and development as well as parenting becomes a luxury and the optimal choice for energy expenditure becomes reproducing. A quantity-based strategy is adopted and a disproportionate amount of energy is then placed into reproducing earlier in the lifespan and reproducing many offspring. In contrast, if the environment affords safety and security, then reproducing can be delayed and efforts can be spent in growth and development. A quality-based strategy is adopted and energy can be invested into a few, quality offspring later in the lifespan.

According to bio-social models, the family environment in early childhood is the most salient environment affecting this life-history trajectory. More specifically, these models define how childhood family relations can affect the developmental trajectories of girls' pubertal maturation and subsequent sexual behavior (Steinberg, 1988). According to these models, early experiences induce either the 'quality' or 'quantity' pattern of mating and reproduction (Belsky, 1997; Belsky, Steinberg, & Draper, 1991; Chisholm, 1996; Hill,1993). Girls whose early family experiences lead them to perceive others as untrustworthy and relationships as unstable or unpredictable, such as the absence of a

father, will develop behavior patters that function to reduce the age of biological maturation within their range of plasticity, lead them to engage in precocious sexual activity, and orient them toward short-term as opposed to long-term pair bonds (see Kim, Smith, & Palermiti, 1997 for review). In life-history terms, stressful childhood conditions will lead to a disproportionate amount of effort and energy being invested in mating, not parenting. Evolutionary psychologists term this precocious development 'unrestricted, short-term, or liberal sociosexuality' by which girls, because of their unstable earlier environments, require less time with and weaker attachments to their sexual partners before engaging in sexual activity with them (Gangestad & Simpson, 1990). In contrast, girls whose experiences allow them to perceive others as trustworthy, stable, and predictable will have delayed maturation and sexual activity onset. This trajectory of restricted, long-term, or conservative sociosexuality motivates girls to establish and maintain pair-bonds that facilitate the ability to invest in child rearing later in life. Sociosexually restricted girls require relatively more time, stronger attachments, and more closeness to their romantic partners before engaging in sexual activities.

This life-history theory of socialization recognizes the adaptiveness of precocious pubertal maturation and subsequent precocious sexuality under conditions where the physical or social childhood environment is stressful. Early maturation and sexuality helps increase the chances of successful reproduction for an individual who may not have chances later on because stressful conditions would prevent it (Belsky, Steinberg & Draper, 1991). Bio-social researchers have found support for this developmental model.

For example, Surbey (1998, 1990) found that girls who experienced father absence in childhood reached menarche 4 to 5 months earlier than girls who experienced mother absence; furthermore, longer periods of father absence predicted earlier onset of menstruation in adolescence. Additional research by Moffitt, Caspi, Belsky, and Silva (1992) showed that girls raised in families characterized by conflict reached menarche approximately 2 months earlier than girls raised under relatively harmonious conditions. Interestingly, results from this same study found that father absence had a direct and even stronger effect on age at menarche than family conflict; girls raised without their biological father reached menarche approximately 3 months earlier than girls who were raised with their biological father. Still other studies that have linked precocious pubertal development to earlier sexual activity have shown that girls who reached menarche early also began dating at an earlier age; precocious dating was directly linked to frequency of boyfriends and intercourse partners (Kim, Smith, & Palermiti, 1997). Similarly, Udry and colleagues (Udry, Kovenock, Morris, & van den Berg, 1995) found that earlier maturation in childhood was associated with a younger age at first intercourse.

Summary

A review of genetic research has shown that variants of the AR and CYP17 genes are associated with differing levels of hormones that affect the onset timing of pubertal maturation, which for females is usually measured as age at menarche. Bio-social research has shown that the family context in early childhood, such as the presence or absence of the biological father, can also influence or mediate pubertal timing onset.

Other biological-based studies reveal that age at menarche predicts the timing of onset of sexual activities and behavior, such as first intercourse. Finally, life-history theory suggests that the onset level of sexual activity and behavior should affect the rate of sexual development.

Hypotheses

1) AR gene: Fewer repeats will be associated with higher levels of androgen. This should predict androgenic characteristics in females with precocious pubertal timing and earlier onset of sexual activity. 2) CYP17 gene: The A1/A1 genotype will predict later ages at menarche and more delayed onset of sexual activity than females with the A1/A2 or A2/A2 genotype. 3) The onset level (i.e., intercept) of sexual behavior will predict the rate (i.e., slope) of sexual behavior development, and 4) As part of a replication of previous research, girls who report the absence of their biological father will have earlier ages at menarche that will influence their sexual development trajectory.

Significance

The proposed study is significant for the following reasons: 1) The study directly identifies adolescent females on two genotypes associated with variation in pubertal timing. 2) The study predicts pubertal maturation based on known genotypes on the two markers. 3) The study tests whether possession of specific pubertal alleles predicts timing of sexual activity, such as first timing of intercourse. 4) This study will allow confirmation of past biological-based research that demonstrates that father absence can influence age at menarche, and that age at menarche predicts timing of sexual activity

(i.e., precocious puberty predicts precocious sexual activity; delayed puberty predicts delayed sexual activity). 5) Finally, genetic and biological information about adolescent sexual development and behavior has important implications for public health. Findings from this study may provide insight on identifying youths at risk for potentially problematic behavior, such as precocious sexual activity.

METHOD

Participants

The sample includes 248 post-menarcheal females (125 African-American; 123 Caucasian) who participated in the Biosocial Factors in Adolescent Development (BFAD) study at the University of North Carolina, which began in 1989 and followed subjects over 2-3 years (i.e., 5 data waves, collected semi-annually). Subjects were randomly selected from student lists supplied by a county school district in North Carolina. The mean age at study entry was 13.35 (SD = .60) years with a minimum age of 12 years and a maximum age of 14 years. Fifty-two percent of participants were 13 years at study entry and 42% were 14 years in age. The average age at menarche for African-American girls was 11.35 years in age (SD = 1.14, min=8, max= 14; for Caucasian girls the average age at menarche was 11.80 years in age (SD = .97, min=9, max=14).

Saliva Samples for DNA Analysis

As part of a semi-annual physical examination, a 5-ml saliva sample was collected during the exam. DNA was extracted from these saliva samples in Dr. David C. Rowe's laboratory at the University of Arizona.

AR gene assay. A Polymerase Chain Reaction (PCR) isolating the AR gene CAG repeat section was created using the following primers: AR-1, 5'-GCCTGTTGAACTCTTCTCAGC-3', and AR-2, 5'-GCTGTGAAGGTTGCTGTTCCTC-3'. A mixture of 25 µl containing 5ng/µl genomic DNA, 25 pmol of each primer, 1x reaction buffer 950mM KCL, 1/5mM $MgCl_2$, and 10mM Tris (pH 9.0 at room

temperature), 200μM deoxynucleic triphosphates (dNTPs), and 4 units of Taq polymerase (Promega or Qiagen) was used as the base source for creating PCR products. An initial denaturation step of 5 minutes at 95°C was followed by 35 cycles of amplification at 95°C for 1 minute, 65°C for 2 minutes, and extension at 72°C for 1.5 minutes. The final extension was at 72°C for 8.5 minutes. PCR products were separated by agarose gel electrophoresis, and stained with ethidium bromide to identify the total bp length.

CYP17 gene assay. A PCR fragment isolating the 1-bp change in the 5' untranslated region was created using the following primers: CYP-1, 5'-CATT- CGCAC TCTGGAGTC-3', and CYP-2, 5'-AGGCTCTTGGGGTACTTG-3'. The PCRs were carried out in 25μl aliquots containing about 5ng/μl of genomic DNA, 50pmol of each primer, 1x reaction buffer 950mM KCL, 1/5mM $MgCl_2$, and 10mM Tris (pH 9.0 at room temperature), 100μM dNTPs, and 1 unit of Taq polymerase. An initial denaturation step of 5 minutes at 94°C was followed by 30 cycles of amplification at 94°C for 1 minute, annealing at 57°C for 1 minute, and extension at 72°C for 1 minute. The final extension was at 72°C for 5 minutes. The PCR products from the amplification process were digested for 3 hours at 37°C using *Msp*AI, separated by agarose gel electrophoresis, and stained with ethidium bromide to identify the bp change.

Presence/Absence of Biological Father

At time of study entry, girls were asked whether their biological father was absent from their home. Participating girls were subsequently coded as having their biological

father absent (0) or present (1). Fifty-four percent of girls were living with their biological father at study entry.

Pubertal Measures

pubertal development. The semi-annual physical exam also included measures of height, weight, blood pressure, skinfold measures (i.e., body fat) at four body sites, circumference measurements at five body sites, and Tanner Stages of pubertal development (Tanner, 1962). Yearly self-report questionnaire items included the Tanner stage rating of breast development and amount of pubic hair, leg hair, axillary hair, changes in hip width, and rating of body "curviness." A validity study by Halpern, Udry, and Suchindran (1997) found that these items based on females' self-reports are correlated with pediatricians' assessment scores on these same items ($r = .82$). In the final data analysis, the self-reported Tanner stage rating of breast development and amount pubic hair, age at menarche, and the item comparing development to other girls were used as indicators of pubertal timing for females.

age at menarche. Only post-menarcheal girls were eligible for participation in the study. At the time of study entry, participants were asked their age in years at which they started their first menstrual cycle.

Sexual Behavior and Activity

Subjects completed a confidential behavior checklist that was self-administered during the five semi-annual data collections and designed to document incidents of social and sexual activity. Sexual activity questions were based on the Heterosexual Behavior

Inventory developed by Bentler (Bentler, 1968a, 1968b) that had been modified for adolescent appropriateness and used in earlier cross-sectional and panel studies in this research line (Halpern, Udry, & Suchindran, 1997; Smith, Udry, & Morris, 1985; Udry, 1988).

coital status. Girls were asked at the time of study entry whether or not they had engaged in sexual intercourse. If girls answered 'yes,' they were asked to report the age at which they first had sex with a boy. This question was also asked in each of the five semi-annual questionnaires.

coital activity and number of partners. Girls reported how many times they had intercourse with a boy, if ever. The semi-annual questionnaires also asked girls to report how many boys, counting the first one, had they ever had sex with.

light and heavy petting activity. Girls reported their amount of petting activity. Light petting was measured as the mean response to six items about how often the girl:

- Held hands with a boy (0-never, 1-one time, 2-two to three times, 4-more than ten times)
- Put her arms around a boy or boy put his arms around the girl
- Kissed a boy
- Necked with a boy (hugged or kissed a boy for a long time)
- Had a boy feel her breasts over her clothes
- Felt a boy's penis over his clothes

Heavy petting was measured as the mean response to four items about how often the girl:

- Had a boy feel her breasts under her clothes
- Felt a boy's penis under his clothes
- Had a boy feel her private parts over her clothes
- Had a boy feel her private parts under her clothes or with no clothes on

anticipation of sexual encounters in future. This score was the mean score of the following z-scored items:

- How *likely* is it that you will have sex with a boy in the next year? (1-sure it won't happen, 2-probably won't happen, 3-even chance '50-50' it will happen, 4-probably won't happen, 5-sure it will happen)
- How much do you think you would *like* to have sex in the next year? (scored on a 5-point answer scale with responses ranging from 1-would dislike very much to 5-would like very much)
- Do you *plan* to have sex in the next year? (scored yes/no).

frequency of sexual thoughts. A mean score was calculated using the following z-scored items:

- How often do you think about sex? (a single item with 6-point answer scale ranging from 0-never to 5-several times a day)
- Do you ever have dreams or fantasies that turn you on sexually? (scored yes/no),

- Do you ever have daydreams or fantasies about having sex (sexual intercourse)? (scored yes/no)

masturbation. The mean score of two items was used to measure the amount of masturbation girls engaged in:

- Since this time *last month*, about how many times have you played with your private parts until you came?
- Since this time *last month*, about how many times have you played with your private parts without coming?

sociosexual strategy behaviors. Several z-scored items were averaged to develop a composite score indicating whether girls engaged in short- or long-term sociosexual strategy behaviors. Items included:

- The number of boys gone steady with in the last 6 months
- The number of times gone out alone with a boy in the last 6 months (5-point answer scale ranging from 0-never to 4-more than 10 times)
- In the last 6 months the number of times got a new boyfriend
- Light petting activity scores (see above)
- Heavy petting activity score (see above)
- How often had sex with a boy (5-point answer scale ranging from 0-never to 4-more than 10x)
- Had sex with more than one boy (yes/no)
- The number of boys counting the first boy have ever had sex with

- The number of times had sex in last 6 months (5-point answer scale ranging from 0-never to 4-more than 10 times).

Lower scores on this scale indicated more conservative (i.e., 'quality' reproductive strategy) sociosexual behaviors whereas higher scores were indicative of more liberal (i.e., 'quantity' reproductive strategy) sociosexual behaviors.

sociosexual strategy attitudes. A composite sociosexual strategy attitude score included the following items:

- What would be the most important thing you would look for in a steady boyfriend or a boy you want to go out with? (1-personality/smarts, 1.5 other, don't know, missing, 2-looks, money, popularity; lower scores indicated more conservative sociosexual attitudes)
- If you could pick would you rather 1-go out with only one boy for a long time, or 2-go out with lots of different boys
- The 'anticipation of sexual encounters in future' score (see above)
- It's okay for people my age to neck or make-out (5-point answer scale ranging from 1-strongly disagree to 5-strongly agree)
- It's okay for people my age to have sex (5-point answer scale ranging from 1-strongly disagree to 5-strongly agree)
- For each pair of sentences below, indicate which one best tells what you like or how you feel: (1- if you like having sex with a certain boy you will never get bored with him; indicating more conservative sociosexual

attitudes, 2- even though you like having sex with a certain boy, you may get bored of him; indicating more liberal sociosexual attitudes)

- For each pair of sentences below, indicate which one best tells what you like or how you feel: (1- I like boys who like to do the same things I do; indicating more conservative sociosexual attitudes, 2- I like boys who are good-looking; indicating more liberal sociosexual attitudes)
- For each pair of sentences below, indicate which one best tells what you like or how you feel: (1- a girl usually changes boyfriends because she gets unhappy with her present boyfriend; indicating more conservative sociosexual attitudes, 2-a girl usually changes boyfriends because she gets bored with her present boyfriend; indicating more liberal sociosexual attitudes)

Lower scores on this scale indicated more conservative (i.e., 'quantity' reproductive strategy) sociosexual attitudes whereas higher scores were indicative of more liberal (i.e., 'quality' reproductive strategy) sociosexual attitudes.

Data Analyses

As mentioned earlier, girls completed questionnaires on a semi-annual basis, resulting in 5 waves of data collection over approximately 2- 3 years of study participation. The objectives of this study required that specific alleles predict pubertal maturation and subsequent sexual behaviors. The Hardy-Weinberg distribution assumes that allelic forms of genes have an equal chance of combing with each other and that

these alleles are picked randomly from the gene pool. Chi-square analyses were used to test the AR and CYP17 gene frequencies for departures from Hardy-Weinberg equilibrium, which would indicate that the allelic combinations were not random and that selection processes may be operating on maximizing an adaptive genotype (i.e., displays a higher frequency).

Individual growth curve parameters for all sexual development scores on which repeated measures were obtained were calculated by least-squares estimation, plotting scores over time and calculating a regression line (Figueredo, Brookes, Leff, & Sechrest, 2000). One advantage of the growth curve analysis is that parameters of both intercepts and slopes that are based on all the observations for each individual are generally much more reliable that single scores measured in a cross-sectional sample. A second advantage is that growth curve analysis is a random effects model so homogeneity of rates of change across time is not assumed (Laird & Ware, 1982; Bryk & Raudenbush, 1992). It would be unreasonable to expect that the biological and psychological sexual development of girls occurs at identical rates across individual girls and growth curve parameters explicitly model potentially unequal rates of change (Rogosa, Bradnt, & Zimowski, 1982). Each participant was initially treated as a separate case for analysis and the following regression parameters were estimated: the intercept, representing the best estimate of the starting value on sexual development, and the slope, or unstandardized regression weight, representing the direction and magnitude of average change in status on sexual development over time. The times of measurement used in these individual regressions

were the 5 semi-annual data collection waves over the 2-3 year study period. Because the girls in this study were considered to still be at the relative beginning of their sexual development, the slopes were theoretically expected to be linear; however, a natural logarithmic transformation of time that would indicate the maintaining of a constant level of sexual activity was also tested and compared to the individual linear slopes.

Hierarchical linear models were used to determine the significance of predictor variables for the causal model. These models were used to distinguish direct effects from mediating effects. For example, the hierarchical models helped determine whether gene variation was directly predictive of age at menarche or if the gene effect must be moderated through the presence or absence of a biological father. Overall, these models were used to show the order, the significance, and size of the causal effects.

RESULTS

Genetic Analyses

Table 1 presents the expected and observed allele frequencies of the two genetic markers chosen for this study. Expected and observed frequencies for the CAG gene, χ^2 (5, N = 100) = .37, p = 1.0, and the CYP17 gene, χ^2 (2, N = 100) = .423 p = .81, were indistinguishable indicated that there were no departures from Hardy-Weinberg equilibrium. The Hardy-Weinberg equilibrium was also stable across ethnicities; allele frequencies for both the CAG and CYP17 for Black and Caucasian girls were almost identical (i.e., African-Americans CYP17 A1/A1: .05 A1/A2: .33 A2/A2: .62; Caucasian CYP17 A1/A1: .04 A1/A2: .32 A2/A2: .64).

Correlations and Factor Analysis

Table 2 shows the correlations between pubertal development, the sexual-related behaviors variables and the sexual activity variables. With the exception of three, all variables were significantly correlated with each other indicating that the pubertal, sexual behavior, and sexual activity variables would be candidates to be included in one sexual development factor. The high correlations among pubertal, sexual ideation, and sexual behavior measures is also indication that these variables are best understood as components of the same measure of life-history, or reproductive, strategy. For example, pubertal development is correlated with coital activity (r = .21) and sociosexual behaviors (r = .18), which is concordant with a quantity-based reproductive strategy; girls who develop physically earlier are also more likely to engage in sexual behaviors earlier.

As seen in Table 3, these nine dependent variables were tightly linked with the girls' overall sexual development. A principal factor analysis using a squared multiple correlation as a prior communality estimate followed by a promax (i.e., oblique) rotation confirmed that these nine variables could be collapsed into one sexual development factor that was stable across all 5 time periods and that accounted for an average total of 78 percent of the variance from the original dependent variables. The averaged eigenvalue (i.e., final communality estimates) from all 5 time periods was 4.09 (range: 3.85 to 4.28) and the averaged standardized Cronbach alpha reliability score was 0.84 (range 0.82 to 0.85). Table 3 shows the Sexual Development factor pattern and factor correlations averaged across the five study time-periods.

A final set of correlations between the genetic markers, biological father status, age at menarche and the Sexual Development factor are shown in Table 4. The strongest correlation was between biological father status and age at menarche ($\underline{r} = .22$) in that girls who lived with their biological fathers were having later ages at menarche.

Descriptive Statistics

Figure 1 shows average z scores and standard errors of pubertal development and sexual development over the 5 time periods. Sexual development, which was measured as the scores from the sexual development factor, steadily increased over the five time periods. Puberty scores increase steadily, but plateaus at Time 4 and 5. The stabilizing of puberty scores at the last two time periods is due to the decrease in pubertal variance

among the girls at these later stages when most girls have reached full pubertal maturation.

Growth Curve Analysis

Both a linear and a natural logarithmic transformation of time were compared prior to the individual regression analyses to determine the most accurate direction and average change of sexual development over time. A relative Goodness-of-Fit (ΔR^2 = R^2 linear - R^2 logarithmic transformation) comparison showed there was no significant difference between the linear and logarithmic transformation regression models (.88 - .86 = .02; $p < .01$) in the amount of variance accounted for in sexual development (Cohen & Cohen, 1983). If there had been ceiling effects in sexual development over the study time-period in that girls' scores leveled-off over time, a logarithmic transformation would have demonstrated a better fit and accounted for more variance in sexual development. However, since there was no statistical difference between the two, the linear model of sexual development that assumes a steady increase of sexual activity over time was applied across the sexual development factor for all subsequent growth curve models. The statistical products of the growth curve analysis, intercepts and slopes of sexual development, were used as the dependent variable in subsequent hierarchical models.

Hierarchical Linear Models

A series of four hierarchical linear models was used to test for significant predictors in the overall causal model of sexual development. The first hierarchical linear model tested whether allelic combination for the two genes, CAG and CYP17, was

predictive of whether girls were living with their biological father (i.e., family context or environment). As seen in Table 5, the CYP17 gene predicted the biological father status of the girls, but the CAG gene did not. Sixty-four percent of A1/A1 girls lived with their biological fathers, whereas 47% of A1/A2 and only 36% of A2/A2 girls lived with their biological father.

The next model was used to determine whether the presence of a biological father, CAG allelic combination, and CYP17 allelic combination was predictive of age at menarche. This model showed that biological father status predicted age at menarche, but that the CAG and CYP17 genes did not. The average age at menarche for girls who did not live with their biological father was 11.32 (SD = 1.10), whereas the average for girls who did live with their biological father was 11.80 (SD = 1.03).

The third model used the previous three predictors (i.e., CAG, CYP17, and biological father status) with the addition of age at menarche to determine the influence on starting level of girls' sexual development at study onset (i.e., the intercept of the sexual development factor); as seen in Table 5, age at onset of menarche was directly predictive of onset level of sexual development. Table 6 shows average onset level of sexual development by age at menarche; as expected, as the age at menarche increases the onset level of sexual activity decreases. Finally, the final model used the previous model's independent variables with the inclusion of the intercept of sexual development as predictors of the slope of sexual development (i.e., rate of sexual development over time; see Table 5). This final model showed that the intercept of sexual development

predicted the slope of sexual development such that higher levels of sexual development onset predicted slower rates of sexual development over time. In other words, girls who's level of sexual development onset was more conservative had steeper, faster rates of sexual development.

Based on the results of the four hierarchical models, a series of separate final regression models were used to create final standardized parameter estimates (i.e., standardized beta weights) for the overall model. Specifically, the final parameter estimates were derived from: the CYP17 gene's effect on biological father status, biological father status on age at onset of menarche, age at menarche on the intercept of sexual development, and the intercept of sexual development on the slope of sexual development.

Figure 2 presents the relationship and causal process among these observed and latent variables associated with sexual development. Possession of CYP17 variants predicted biological father status (i.e., family context or environment) in that girls who possessed A1 alleles (i.e., A1/A1 or A1/A2; higher scores on the CYP17 gene) lived with their biological father ($\beta = .173$, $R^2 = .03$). Living with a biological father predicted later ages of menarche ($\beta = .142$, $R^2 = .02$). Later ages at menarche were associated with lower onset scores (i.e., intercepts) on sexual development ($\beta = -.270$, $R^2 = .07$). Finally, lower or more conservative onset scores of sexual development predicted faster rates of sexual development over time ($\beta = -.188$, $R^2 = .04$).

DISCUSSION

The major objectives of this study were to genotype a sample of adolescent females and test whether the allelic variation for two genes was part of a causal model of pubertal development and subsequent sexual activity. The CYP17 gene was found to be predictive of girls' biological father status in that girls with the A1/A1 genotype (hypothesized to predict later ages at menarche) lived with their biological father more than heterozygote or A2/A2 girls. Although the CYP17 gene was not predictive of age at menarche as expected, it appears that this gene is acting as a proxy for larger genetic effects or biological predispositions that work to create a family environment that would include the presence or absence of a biological father. If girls living with their biological father are also more likely to be living with their biological mother, then it is possible that girls who inherited a genetic predisposition from their parents that allows them to engage in stable, long-lasting relationships are also girls who eventually adopt a 'quality' over 'quantity' reproductive strategy, which is partly reflected in their age at menarche. These genetic results that place the presence of the biological father as a mediating force between the CYP17 gene and age at menarche indicate that this gene is indicative of the life trajectory that eventually will lead to precocious or delayed pubertal maturation.

These genetic results also provide further evidence that pubertal and sexual developmental trajectories are set early in childhood and are, at least in part, inherited qualities. However, this study used only two genes as markers for pubertal development and sexual behavior. As research in this area continues, a greater number of genetic

markers may be found that indicate, or do not indicate, the timing of pubertal onset and sexual development. Continued research will also help to further explain the roles that environmental and genetic factors play in determining onset of puberty and sexual behavior.

This study used genetic and behavioral information from individuals and only looked at biological father status as an environmental context variable. Other genetic information valuable to understanding pubertal timing and sexual development will come from family studies and behavioral genetic methods that use genetic marker information and measured trait-similarity among parents and offspring and among siblings. This type of information will allow researchers to look at possible inherited gene effects from parents, gene and environment correlations, as well as shared environmental effects besides biological father status, as explanations for pubertal onset and sexual behavior.

Still, these results do confirm other research showing that living with the biological father delays age at menarche, which in turn is predictive of level of onset of sexual activity. Like previous studies, girls with earlier ages at menarche had higher onset levels of sexual development and activity, such as more reported light and heavy petting, higher frequency of sexual thoughts, and for non-virgins more sexual experience and a greater number of sexual partners.

Scores on the sexual development factor, which included the nine dependent variables of sexual attitudes and behavior scores, increased steadily over the 5 study time periods. Pubertal development also increased steadily along with sexual development

until the last time period, at which time pubertal development stabilized. Overall, these results suggest that pubertal development is concordant with increasing levels of sexual behavior and activity. Since girls cannot decrease in level of pubertal maturation, the measured plateau of pubertal development at Times 4 and 5 is most likely due to the lack of variance and a ceiling effect in pubertal development by the end of the study period. Girls entered the study post-menarcheal and most of them had reached full maturation by the later stages of the study.

The growth curve analyses showed that the level of sexual development onset was predictive of the rate of sexual development in that girls with lower levels of sexual onset (i.e., restricted socio-sexuality) had faster rates of sexual development. Conversely, girls with higher onset levels of sexual development at the beginning of the study time period had lower, or 'flatter,' rates of sexual development over the study time period. This finding is important in that it shows that girls who reach menarche later initiate their sexual activity conservatively, but once they do initiate sexual activity their rate of development is more accelerated than girls who reached menarche earlier and had higher, more advanced, levels of sexual development onset. These findings also indicate that girls who do initiate sexual behaviors earlier are not necessarily maximizing their sexual development and activity at earlier ages; their rate of sexual development is slower suggesting that these girls are spending more time at the increasing levels of sexuality. For example, a girl who has an early onset of menarche might begin her sexual activity with heavy petting whereas a later maturer might begin her sexual activity at light petting.

However, according to the results from this study a girl who began her sexual onset with heavy petting would remain at this stage longer than a later developing girl who would quickly move on to heavy petting and other more advanced sexual activities and behaviors.

The findings from this study show that genetic markers can be used to help identify variation in timing of pubertal onset. This information alone is valuable for two reasons. One, it shows that more research is needed in order to understand the genetic underpinnings of puberty. It is not enough to understand the proximate biological processes that develop during a lifetime; the inherited properties that are mediated by the environment and lead to differences in pubertal timing must be understood as well. Second, this research shows that genetic information that is predictive of pubertal timing, or mediated by other factors that lead to determination of pubertal timing, can be used as a tool to identify girls at risk for precocious sexual behavior, which is associated with risks such as teen pregnancy.

Finally, these findings provide additional insight into understanding the differences in rates of sexual development among girls. Higher onset levels but slower rates of sexual development in some girls implies that there might be mediating factors that hold these girls for longer times at the levels of sexual development. A slower progression through the stages of sexual development may be buffering these girls from advanced sexual behaviors (e.g., unprotected sex) at earlier ages that would normally put them at greater risk for teen pregnancy and sexually transmitted diseases. In contrast, girls

with later ages at menarche had lower sexual development onset scores, but they were also older and progressed more quickly through the development stages. These older girls may have a mental maturity that allows them to progress through the stages faster; one possibility being a 'peer effect' in which older girls are catching-up to the behavior of friends who have already progressed through more stages of sexual development. Identifying the mediating factors of slower and faster development is the next step in this line of research and would be especially helpful in understanding the risks associated with precocious sexual development.

APPENDIX A: FIGURES

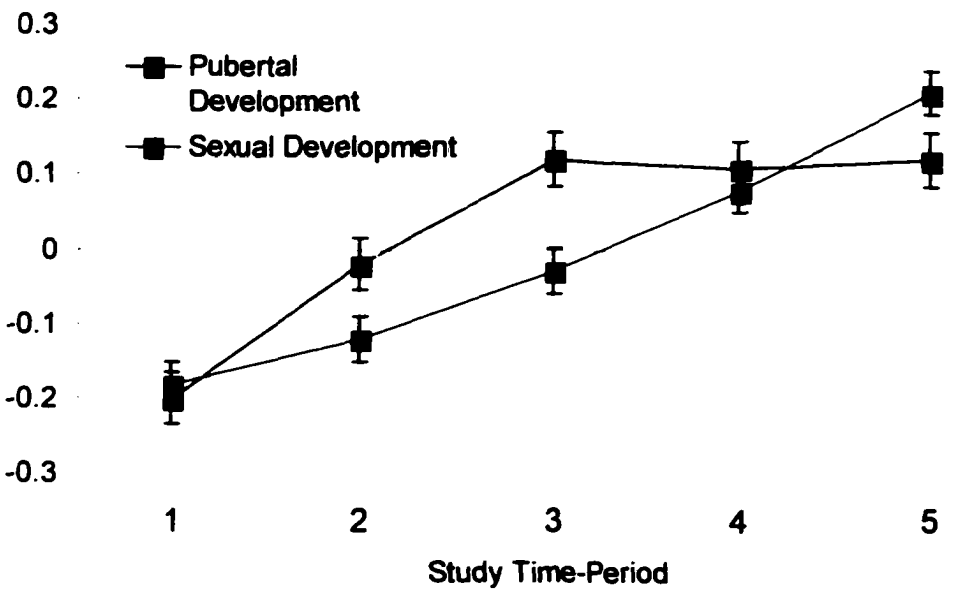

Figure 1. Average z-scores and standard errors of pubertal development and sexual development by the 5 study time-periods.

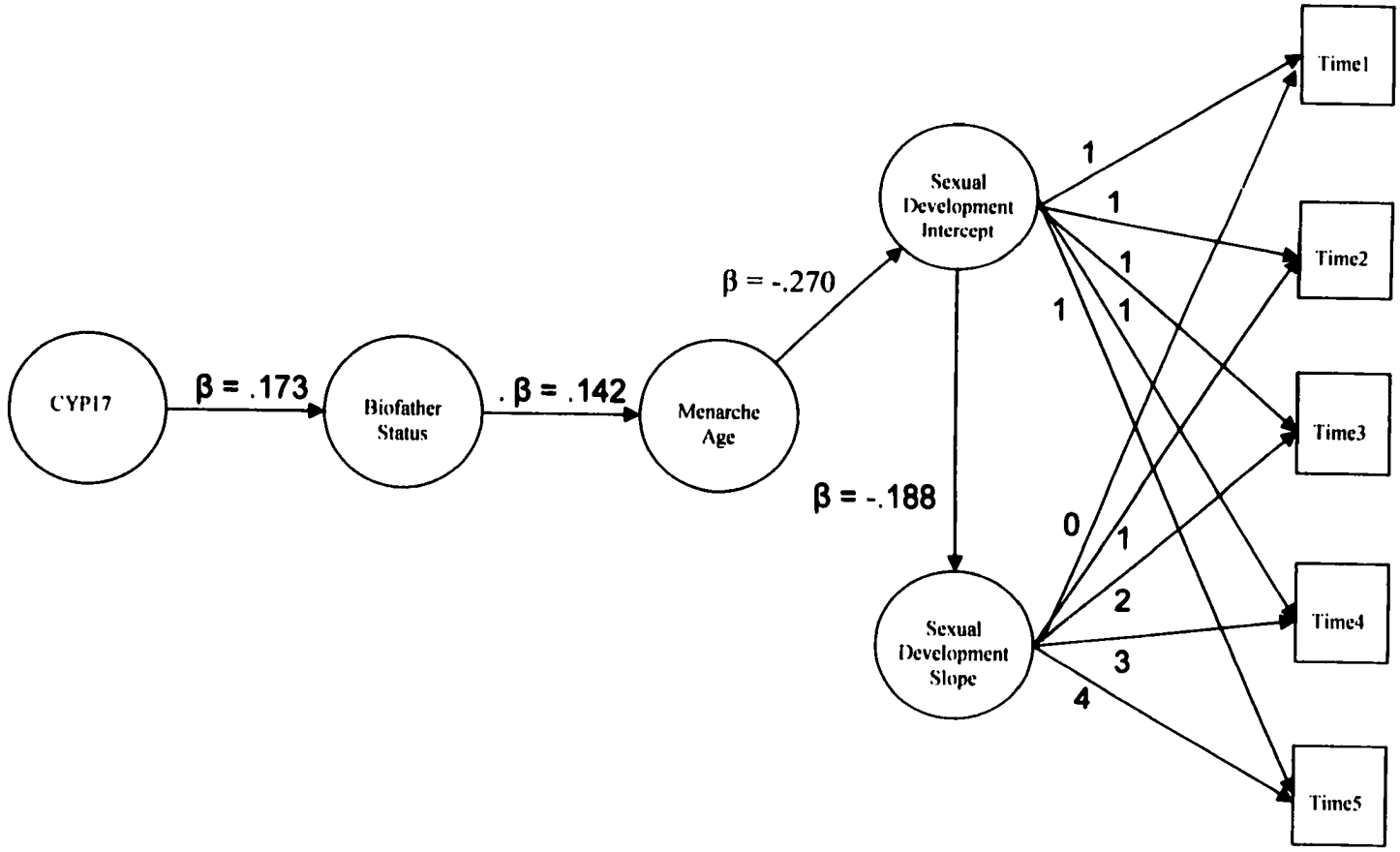

Figure 2. Causal model and associated standardized beta weights of sexual development.

APPENDIX B: TABLES

Table 1

Expected and Observed Frequencies of Allelic Combinations for Genetic Markers

	Allelic Frequencies	
Allelic Combinations	Expected	Observed
Androgen Receptor (CAG)*		
Short/Short	.01	.01
Med/Med	.53	.52
Long/Long	.03	.03
Short/Med	.13	.13
Short/Long	.03	.02
Med/Long	.27	.28
CYP17**		
A1/A1	.64	.63
A1/A2	.31	.33
A2/A2	.04	.05

*$p = 1.0$.

**$p = .81$.

Table 2

Correlations Between Pubertal Development, Sexual Behavior, and Sexual Activity Variables

Variable	1	2	3	4	5	6	7	8	9
1. Pubertal Development	--	.21*	.10*	.16*	.18*	.18*	.00	.18*	.04
2. Coital Activity		--	.33*	.52*	.67*	.62*	.18	.80*	.24*
3. Number of Partners			--	.17*	.24*	.20*	.11*	.68*	.07*
4. Light Petting				--	.79*	.61*	.27*	.74*	.37*
5. Heavy Petting					--	.66*	.27*	.74*	.37*
6. Future Sex Anticipation						--	.36*	.61*	.57*
7. Sexual Thoughts Frequency							--	.23*	.31*
8. Sociosexual Behaviors								--	.27*
9. Sociosexual Attitudes									–

*$p < .05$.

Table 3

Sexual Development Factor: Factor pattern Scores and Factor Correlations Averaged Across 5 Study Time-Periods

	Sexual Development Factor	
Dependent Variables	Factor Loadings	Factor Correlations
Puberty Development	.20	.33
Coital Activity	.80	.76
Number of Partners	.56	.56
Light Petting	.77	.77
Heavy Petting	.83	.82
Future Sex Anticipation	.77	.80
Sexual Thoughts Frequency	.35	.49
Sociosexual Behaviors	.92	.80
Sociosexual Attitudes	.47	.54

Note. All correlations are significant at $p < .01$.

Table 4

Correlations Between Genetic Markers, Biological Father Status, Age at Menarche, and Sexual Development Factor

Variable	1	2	3	4	5
1. Androgen Receptor (CAG)	--	.10*	.13*	-.03	-.02
2. CYP17		--	.17*	-.05	.01
3. Biological Father Status			--	.22*	-.09*
4. Menarche Age				--	-.10*
5. Sexual Development Factor					–

*$p < .05$.

Table 5

Results from Hierarchical Linear Models Testing the Causal Model of Sexual Development

		Model Estimate			
Dependent Variable	Parameter	Estimate	SE	p	Model R^2
Biological Father Status					
	CAG	.00	.00	.16	.05
	CYP17	.15	.07	.02*	
Age at Onset of Menarche					
	Biofather	.43	.19	.02*	.05
	CAG	-.01	.01	.17	
	CYP17	-.16	.15	.28	
Intercept Sex. Development (ISD)					
	Menarche	-.20	.04	.00*	.08
	Biofather	-.11	.09	.25	
	CAG	.00	.00	.94	
	CYP17	.06	.07	.39	
Slope Sexual Development					
	ISD	-.05	.02	.03*	.05
	Menarche	.01	.01	.60	
	Biofather	-.03	.03	.33	
	CAG	.00	.00	.81	
	CYP17	-.01	.02	.57	

* Significant predictor.

Note. Parameters are listed in order of model entry.

Table 6

Average Level of Onset of Sexual Development by Age at Menarche

	Sexual Development Intercept		
Age at Menarche in Years	M	SD	n
9	.155	.631	13
10	.176	.704	21
11	-.221	.554	70
12	-.232	.511	100
13	-.411	.442	43

APPENDIX C: HUMAN SUBJECTS APPROVAL

Human Subjects Committee

THE UNIVERSITY OF
ARIZONA.
HEALTH SCIENCES CENTER

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7 May 2001

Cathleen Hunt, M.A.
Advisor: David C. Rowe, Ph.D.
Department of Psychology
Psychology Building, Room 135
PO BOX 210067

RE: GENETIC POLYMORPHISMS ASSOCIATED WITH THE DEVELOPMENTAL TIMING OF PUBERTAL MATURATION AND SUBSEQUENT ONSET OF SEXUAL BEHAVIOR IN FEMALE ADOLESCENTS

Dear Ms. Hunt:

We received documents concerning your above cited project. This project involves the secondary analysis of existing questionnaire data and saliva samples [existing datasets and specimens with randomly assigned ID numbers to be provided by Carolyn Halpern, Ph.D., PI of the "Genetic Contributions to Biopsychosocial Models of Adolescent Sexuality and Risk-Taking" conducted at the University of North Carolina at Chapel Hill (letter from Dr. Halpern, IRB approval letter, consent form, and data collection instruments submitted for review)]. Regulations published by the U.S. Department of Health and Human Services [45 CFR Part 46.101(b) (4)] exempt this type of research from review by our Institutional Review Board.

Thank you for informing us of your work. If you have any questions concerning the above, please contact this office.

Sincerely,

Rebecca Dahl

Rebecca Dahl, R.N., Ph.D.
Director
Human Subjects Protection Program

RD/js
cc: Departmental/College Review Committee

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