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HUMAN GENOME EPIDEMIOLOGY (HuGE) REVIEW

CYP17 Gene Polymorphisms: Prevalence and Associations with Hormone Levels and Related Factors. A HuGE Review

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The cytochrome P-450c17α (*CYP17*) gene, located on chromosome 10q24.3, encodes the enzyme cytochrome P-450c17α, which functions at key branch points in steroid hormone biosynthesis. Three polymorphisms have been described, but only the single base-pair change in the 5′-untranslated region (5′-UTR) has been investigated to any great extent. In single studies, the variant was associated with reduced messenger RNA level in ovarian cells but not with messenger RNA level in breast tissue. Homozygosity for the 5′-UTR variant is most common in East Asian (32%) and Japanese (22%) populations and is less common among White (mainly European and North American (14%)) and Black (mainly African-American (13%)) populations, but selection biases are likely to have affected these frequency estimates. Genotype appears to influence circulating estrogen levels in premenopausal women, while studies of relations with hormone levels in men have produced inconclusive results. However, relatively few studies have been conducted. Seven of 11 retrospective studies suggested a modest association between genotype and age at menarche. Random error in recall of age at menarche is likely to have attenuated this relation. Associations between genotype and postmenopausal estrogen use and bone mass have been observed in single studies. Further investigation of relations between genotype and hormone levels, exogenous hormone use, and markers of hormonal status may advance understanding of hormonally mediated diseases.

CYP17; epidemiology; genetics; gonadal steroid hormones; hormones; menarche; polymorphism (genetics); steroid 17-alpha-hydroxylase

Abbreviations: CI, confidence interval; CYP17, cytochrome P-450c17α; HRT, hormone replacement therapy; mRNA, messenger RNA; 5′-UTR, 5′-untranslated region.

Editor's Note: *This article is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).*

GENE

The cytochrome P-450c17α (*CYP17*) gene, located on chromosome 10q24.3, encodes the enzyme cytochrome P-450c17α, which functions at key branch points in steroid hormone biosynthesis in the adrenal gland, ovary, and gonads (1, 2). Specifically, cytochrome P-450c17α mediates both steroid 17α-hydroxylase activity, which coverts pregnenolone to dehydroepiandrosterone, and 17,20-lyase activity, which generates androstenedione from progesterone. These androgens may then be converted to estrone, testosterone, and estradiol (3) (figure 1). The discovery that the *CYP17* gene is polymorphic prompted investigation of the role of gene variants in the etiology of diseases and conditions in which estrogens or androgens play an important role, notably breast cancer, polycystic ovary syndrome, endometrial cancer, and prostate cancer. Unraveling whether genotype influences steroid hormone metabolism and/or is related to markers of endogenous hormonal state would aid

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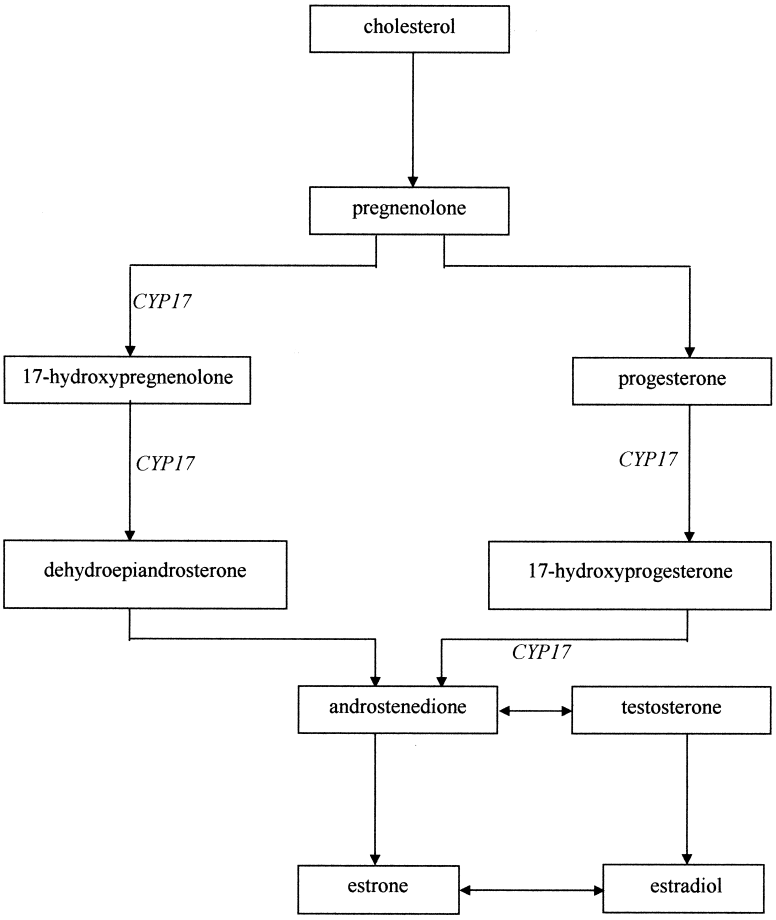

FIGURE 1. Pathway of steroid hormone synthesis and metabolism, including the role of the cytochrome P-450c17α (*CYP17*) gene.

in the understanding of hormonally mediated conditions. In this paper, we review and synthesize the findings of studies on the prevalence and effects of polymorphisms in the *CYP17* gene.

GENE VARIANTS

There are numerous mutations in the *CYP17* gene, the majority of which are extremely rare (4, 5). Three common polymorphisms have been described (6–8), but only one, in the 5′-untranslated region (5′-UTR), has been extensively investigated. This polymorphism involves a single base-pair change (T→C) in the promoter region, 34 base pairs upstream from the initiation of translation and downstream from the transcription start site (6). The variant creates a recognition site for the *Msp*AI restriction enzyme. In line with the literature, we will refer to the common allele as *A1* and the variant allele, –34T→C, as *A2*. Thus, we will refer to homozygosity for the common allele as "*A1A1*" rather than use the base-pair designate CC, heterozygosity as "*A1A2*" (rather than CT), and homozygosity for the variant allele as "*A2A2*" (rather than TT); this nomenclature was used in all of the literature reviewed.

The *A2* variant is thought to create an additional Sp-1-type (CCACC box) promoter site. Because the number of promoter elements may correlate with promoter activity (9), it has been postulated that the variant might result in increased transcription (6, 10). However, in the only molecular transcription study carried out to date, an additional binding site created by the polymorphism did not seem to be utilized (11).

Miyoshi et al. (12) studied messenger RNA (mRNA) expression in tumor tissue from 67 women with breast cancer and in normal breast tissue from another 51 women who also had breast cancer. While the mean *CYP17* mRNA level was significantly higher in the tumor samples than in the normal breast tissue, there were no significant differences in mRNA levels between carriers and noncarriers of the variant allele in either the normal breast tissue group or the tumor tissue group. However, intratumoral estradiol levels were significantly higher in carriers than in noncarriers. Daneshmand et al. (13) measured *CYP17* mRNA expression in ovarian thecal cells (connective tissue cells from the Graafian follicle) obtained from 51 premenopausal women undergoing hysterectomy and bilateral oophorectomy for reasons unrelated to ovarian disorders. Mean

mRNA levels decreased with the number of variant alleles; compared with levels in cells from persons homozygous for the common *A1* allele, levels in heterozygotes were approximately halved, and levels in *A2* homozygotes were approximately half those observed in heterozygotes (13). These functional effects require confirmation.

Two further polymorphisms in *CYP17* have been reported. Miyoshi et al. (8) identified a G→A polymorphism at nucleotide 1951 in the promoter region. Crocitto et al. (7) reported that intron 6 contains a C→A transition at nucleotide 5471. Information is lacking on the functional effects of these polymorphisms, if any, and on relations with the 5′-UTR polymorphism.

POPULATION FREQUENCIES

We searched MEDLINE and EMBASE for papers published from 1990 to June 2003, using the Medical Subject Headings "cytochrome P-450" and "steroid 17 alpha-monooxygenase" and the text words "CYP17" and "P-450c17." We identified further relevant studies by hand-searching reference lists in published articles. Once studies were identified, they were reviewed, and those including at least 50 subjects without cancer or other diseases were included in our analyses. Several studies were studies of men diagnosed as having benign prostatic hyperplasia or prostate enlargement or men who had lower urinary tract symptoms consistent with this diagnosis; these studies were excluded, since the results might not be generalizable. Studies of prostatic tissue obtained from men undergoing radical prostatectomy were excluded for the same reason. From the remaining studies, we extracted data on numbers and sources of subjects and numbers of subjects with each genotype. We calculated frequencies and associated 95 percent confidence intervals among heterozygotes and homozygotes for all of the studies identified. We assessed Hardy-Weinberg equilibrium of genotype frequencies for individual studies using the Pearson χ^2 test. A significance level of $p < 0.05$ was used to reject the null hypothesis that the genotype frequencies were in equilibrium.

For ethnic groups for which there were several studies, we pooled the data to compute a more precise estimate of the homozygous variant frequency. Articles in which the ethnicity of the study subjects was described as "mixed" were excluded from this analysis. Data from African-American series were combined with data on African Blacks; data from Japanese-American series were combined with data from Japan; and data from Asian-American series were combined with data from studies conducted elsewhere in Asia (i.e., Singapore and Taiwan). Series were considered White if the sample was described as "predominantly White" or included at least 85 percent White subjects.

5′-UTR polymorphism

Web table 1 shows findings from 50 reports containing data on the frequency of heterozygous and homozygous variants (8, 10, 11, 13–59). (This information is described in the first of two supplementary tables; each is referred to as "Web table" in the text and is posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm), as well as on the *Journal*'s website (http://aje.oupjournals.org).) Some of the series in the table overlap, but the extent of this is not clear. Several of the studies suffered from one or more of the following limitations: 1) the study had a small sample size; 2) there was a lack of information on the source of the subjects and/or the criteria used to select subjects; and 3) the study was not population based, comprising instead hospital patients, persons who had undergone medical investigations, or volunteers, without a clearly defined sampling frame. This makes it difficult to determine whether apparent geographic or ethnic variation reflects true differences or simply selection or participation bias. In addition, these issues may hinder generalizability.

Figure 2 shows the pooled frequency of *A2* homozygosity across ethnic groups. *A2* homozygosity is most common among persons of East Asian origin. When we pooled data from three studies from Taiwan (21–23), one study from Singapore (20), and one study of persons of Asian or Indian-Pakistani origin living in Canada (36), the frequency of *A2* homozygosity was 32 percent (95 percent confidence interval (CI): 29.8, 35.1). In the Japanese series, which included six studies from Japan (8, 15–19) and a study of Japanese Americans (44), *A2* homozygotes comprised 22 percent of the subjects (95 percent CI: 20.4, 24.1).

The pooled frequency of *A2* homozygosity for White populations from North America, Europe, and Australia was considerably lower than the frequency for Asians: 14 percent (95 percent CI: 13.5, 15.0). Within North America, the prevalence in White populations was 11–19 percent. In the studies from Australia, the frequencies were 11 percent and 15 percent (55–57). Within Europe, there was no evidence of a strong geographic distribution, but most of the data were from Nordic countries, Iceland, and the United Kingdom, where the frequency ranged from 7 percent to 17 percent. Few data from other parts of Europe were available. In St. Petersburg, Russia, the frequency was 23–25 percent (28). In a small series from Greece, no *A2* homozygotes were observed (25), but the genotype frequencies were not in Hardy-Weinberg equilibrium.

Data for other ethnic groups and geographic areas were limited. In two studies of Hispanic-American women, 18 percent (95 percent CI: 13.6, 14.8) were *A2* homozygotes (44, 48). In African Americans, the frequency of *A2A2* homozygosity was 6–16 percent. In the single study from Africa (14), 9 percent of Nigerian men were *A2A2* homozygous. The pooled estimate for all Black populations was 13 percent (95 percent CI: 10.8, 16.1).

Other polymorphisms

From one study (7), the frequency of the variant allele of the intron 6 polymorphism was estimated to be 21 percent among Asians and 5 percent among African Americans. With regard to the polymorphism in the promoter region, the variant *A* allele was present in 5 percent (10 of 184) of volunteers in Osaka, Japan (8).

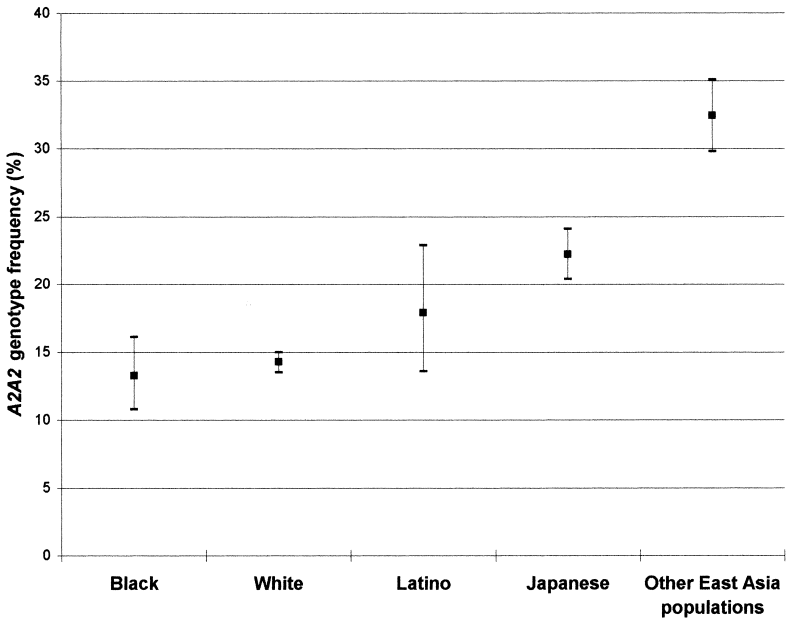

FIGURE 2. Pooled frequency of the cytochrome P-450c17α (*CYP17*) *A2A2* genotype, by ethnic group. Bars, 95% confidence interval. Studies included in the pooled estimate for each ethnic group are as follows—*Black*: Kittles et al. (14), Lunn et al. (22), Lai et al. (36), Feigelson et al. (44), and Weston et al. (48); *White*: Kristensen et al. (11), Kittles et al. (14), Lunn et al. (22), Mitrunen et al. (23), Diamanti-Kandarakis et al. (25), Gudmundsdottir et al. (26), Marszalek et al. (27), Kuligina et al. (28), Bergman-Jungeström et al. (29), Wadelius et al. (30), Allen et al. (31), Techatraisak et al. (32), Dunning et al. (33), Young et al. (34), Lai et al. (36), Haiman et al. (38), Haiman et al. (39), Chang et al. (40), Feigelson et al. (41), Feigelson et al. (44), Garner et al. (47), Weston et al. (48), McCann et al. (50), Ambrosone et al. (51), García-Closas et al. (52), Zmuda et al. (53), Stanford et al. (54), Spurdle et al. (56), and Cui et al. (57); *Latino*: Feigelson et al. (44) and Weston et al. (48); *Japanese*: Miyoshi et al. (8), Huang et al. (15), Habuchi et al. (16), Kado et al. (17), Hamajima et al. (18), Gorai et al. (19), and Feigelson et al. (44); *Other East Asia*: Wu et al. (20), Huang et al. (21), Lunn et al. (22), Yu et al. (23), and Lai et al. (36).

ASSOCIATIONS BETWEEN THE 5′-UTR POLYMORPHISM AND HORMONE LEVELS OR MARKERS OF ENDOGENOUS HORMONAL STATE

Genetic variation in *CYP17* has been postulated to cause differences in circulating hormone levels. This is a possible mechanism by which the gene might influence risk of disease. We reviewed studies of the association between *CYP17* genotype and circulating hormone levels, markers of hormonal status (e.g., age at menarche), or phenotypes associated with an abnormal hormonal milieu (e.g., male pattern baldness). We identified these studies using the search strategy described above, but because there were relatively few such studies, no restriction by number of subjects was applied.

Studies in females

Hormone concentrations. The relation between the 5′-UTR polymorphism and endogenous hormone concentrations has been investigated in six studies of disease-free women (13, 25, 35, 39, 41, 52), all but one of them studies of premenopausal women (table 1). The hormones measured differed between studies. Interpretation of the findings of these studies is complicated by methodological difficulties in adequately characterizing hormones that vary in level over the menstrual cycle. A single measurement taken at any time during the cycle appears to be reasonably reliable for the determination of levels of dehydroepiandrosterone sulfate, sex hormone-binding globulin, and androstenedione (60, 61). For estradiol and progesterone, and possibly for free androgens, a single measurement is less informative but appears to be most consistent if taken on specific days of the cycle (estradiol: days 9–11; progesterone: days 17–21; free androgen: days 12–15) (61).

A priori, it might be expected that the *A2* allele would be associated with higher estrogen levels via its postulated effect on promoter activity and transcription. The first study in this area was consistent with this hypothesis (41). Feigelson et al. (41) recruited 83 Latina, African-American, and Asian volunteers aged 18–33 years who had never had a pregnancy lasting 12 weeks or more, were not obese, had not taken oral contraceptives or hormonal medications in the previous 3 months, and whose current menstrual cycle was ovulatory and expected to be 25–32 days in length. Mean serum estradiol levels on day 11 were 11 percent higher in heterozygotes and 57 percent higher in *A2* homozygotes than in *A1* homozygotes (p for trend = 0.04). Day 22 estradiol concentrations were also elevated in *A2* carriers, but to a lesser extent (heterozygotes: +7 percent; homozygotes: +28 percent; p for trend = 0.06). Day 22 progesterone levels were

TABLE 1. Findings from studies of the relation between polymorphisms in the 5′-untranslated region of the cytochrome P-450c17α (*CYP17*) gene and hormone levels in women

Area of study	Subjects		Hormones measured	Results by genotype	Published reference
	Type	No.			
Europe					
Greece	Women visiting an outpatient endocrine clinic; mean age = 33 years (SD*, 7.9)	50	Serum total testosterone	In comparison with *A1* HMZs*, mean total testosterone levels were 15% higher in HTZs* ($p > 0.05$)	Diamanti-Kandarakis et al. (25)
North America					
Canada	Nulliparous women aged 17–35 years (338 White, 76 Asian, 26 Indian-Pakistani, 13 Black, and 41 of other/mixed ethnicity); 215 used combined OCs*	494	Urinary levels of 2-OHE* and 16α-OHE	In comparison with *A1* HMZs, the median 2-OHE:16α-OHE ratio was 6% lower in HTZs ($p = 0.36$) and 18% lower in *A2* HMZs ($p = 0.01$); after adjustment for use of OCs, age, body mass index, current smoking, and ethnic group, the 2-OHE:16α-OHE ratio was significantly lower in *A2* HMZs than in other women ($p = 0.02$)	Jernström et al. (35)
United States	Latina, African-American, and Asian volunteers aged 18–33 years, recruited through advertisements, who had never had a pregnancy of ≥12 weeks, were not obese, and had not taken OCs or hormonal medications in the past 3 months, with a currently ovulatory menstrual cycle estimated to be of 25–32 days	83	Serum estradiol—days 11 and 22 of cycle; serum progesterone—day 22 of cycle	Adjusted† geometric mean concentration compared with that of *A1* HMZs—day 11 estradiol: 11% higher in HTZs and 55% higher in *A2* HMZs ($p_{trend} = 0.04$); day 22 estradiol: 7% higher in HTZs and 28% higher in *A2* HMZs ($p_{trend} = 0.06$); day 22 progesterone: 24% higher in HTZs and 30% higher in *A2* HMZs ($p_{trend} = 0.04$)	Feigelson et al. (41)
United States	Postmenopausal women recruited into the Nurses' Health Study in 1976 with a blood sample collected in 1989–1990 who were cancer free in 1996 and had not used hormone replacement therapy within 3 months of blood drawing	462‡	Plasma estradiol, estrone, estrone sulfate, testosterone, androstenedione, DHEA*, and DHEAS*	Adjusted§ geometric mean level in *A2* HMZs compared with that in *A1* HMZs—estradiol: 12% lower ($p = 0.13$); estrone: 11% higher ($p = 0.05$); estrone sulfate: 8% higher ($p = 0.17$); testosterone: 6% higher ($p = 0.40$); androstenedione: 5% higher ($p = 0.50$); DHEA: 7% higher ($p = 0.47$); DHEAS: 2% higher ($p = 0.82$)	Haiman et al. (39)
United States	Disease-free premenopausal women with established menstrual periods, of whom 51 were undergoing total abdominal hysterectomy and bilateral oophorectomy for nonovarian reasons unrelated to polycystic ovary syndrome; mean age of all subjects = 35.6 years (SD, 4.5); 63% White, 5% Asian, 18% African American, and 12% Hispanic	256¶	Serum testosterone, follicular fluid androstenedione, follicular fluid estradiol	Mean levels in HTZs compared with those in *A1* HMZs—testosterone: 2% higher; androstenedione: 40% higher; estradiol: 72% higher	Daneshmand et al. (13)
United States	Premenopausal women (aged ≤45 years) with established menstrual cycles (≥5 years since menarche) who were not taking OCs, pregnant, or breastfeeding; >6 months since last pregnancy; time since last menstrual period ≤ 33 days; selected from cytologically normal women with no history of cervical neoplasia from the Kaiser Permanente health maintenance organization cohort; classified as being in the early follicular (0–9 days since onset of last menses, $n = 52$), late follicular (10–14 days since onset, $n = 54$), or luteal (≥15 days since onset, $n = 112$) phase of the menstrual cycle; 30% nulliparous; 92.6% White, 3.7% Black, and 3.7% other	218‡	Serum estradiol, progesterone, testosterone, androstenedione, and DHEA	Adjusted# geometric mean concentrations compared with those in *A1* HMZs—1) estradiol, early follicular phase: 18% higher in HTZs and 8% higher in *A2* HMZs (p_{het}* = 0.78); 2) estradiol, late follicular phase: 23% lower in HTZs and 45% lower in *A2* HMZs ($p_{het} = 0.78$); 3) estradiol, luteal phase: 5% lower in HTZs and 15% higher in *A2* HMZs ($p_{het} = 0.72$); 4) progesterone, early follicular phase: 30% higher in HTZs and 114% higher in *A2* HMZs ($p_{het} = 0.14$); 5) progesterone, late follicular phase: 14% higher in HTZs and 40% lower in *A2* HMZs ($p_{het} = 0.14$); 6) progesterone, luteal phase: 32% higher in HTZs and 16% lower in *A2* HMZs ($p_{het} = 0.21$); 7) DHEA, all women: 1% lower in HTZs and 2% lower in *A2* HMZs ($p_{het} = 0.97$); 8) androstenedione, all women: 0.3% higher in HTZs and 7% higher in *A2* HMZs ($p_{het} = 0.38$); 9) testosterone, all women: 4% higher in HTZs and 12% higher in *A2* HMZs ($p_{het} = 0.27$)	García-Closas et al. (52)

* SD, standard deviation; HMZs, homozygotes; HTZs, heterozygotes; OCs, oral contraceptives; OHE, hydroxyestrone; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; p_{het}, p value for heterogeneity.

† Adjusted for ethnicity.

‡ The number of subjects included in each analysis varied slightly.

§ Adjusted for body mass index, age, laboratory batch, date of blood drawing, time of blood drawing, and fasting status.

¶ Number successfully genotyped for *CYP17*; number of subjects included in hormone analysis was not reported.

Adjusted for age, number of days since last menstrual period, time of blood collection, assay batch number, ethnic group, age at menarche, number of full-term pregnancies, and alcohol intake.

24 percent and 30 percent higher in heterozygotes and *A2* homozygotes, respectively, than in *A1A1* homozygous women (p for trend = 0.04). Similarly, among 256 premenopausal women of mixed ethnicity, Daneshmand et al. (13) observed 72 percent higher mean estradiol levels in heterozygotes than in *A1* homozygotes. Furthermore, in a study of urine levels of (biologically inactive) 2-hydroxyestrone and (biologically active) 16α-hydroxyestrone among 494 nulliparous Canadian women aged 17–35 years, the 2-hydroxyestrone:16α-hydroxyestrone ratio was significantly lower in *A2* homozygotes than in women with other genotypes; this finding was adjusted for oral contraceptive use, body mass index, smoking status, and ethnic group (35).

In contrast, García-Closas et al. (52), who measured estradiol and progesterone in premenopausal women according to phase of the menstrual cycle (early follicular: 0–9 days from the onset of last menses (n = 52); late follicular: 10–14 days from onset (n = 54); luteal: ≥15 days from onset (n = 112)), found that differences in estradiol and progesterone levels by genotype varied according to cycle phase. However, none of the differences were statistically significant.

Theoretically, *CYP17* genotype could affect androgen levels either directly, because of the enzyme's role in the generation of dehydroepiandrosterone and androstenedione, or indirectly, through the enzyme's effects on estrogen levels and the link between androstenedione, testosterone, estrone, and estradiol (figure 1). With regard to premenopausal women, Daneshmand et al. (13) found that androstenedione concentrations were 40 percent higher in heterozygotes than in *A1* homozygotes but testosterone levels did not differ. In a small study carried out in Greece, the mean level of serum total testosterone was 15 percent higher in heterozygotes than in *A1A1* homozygotes (25). García-Closas et al. (52) found testosterone to be 4 percent higher in heterozygotes and 12 percent higher in *A2* homozygotes than in *A1* homozygotes, but this finding was not statistically significant. In that study, androstenedione and dehydroepiandrosterone levels were not associated with genotype.

Haiman et al. (39) measured serum hormone fractions in 462 postmenopausal women from the Nurses' Health Study who were without cancer and were not taking postmenopausal hormones. Compared with women with the *A1A1* genotype, *A2A2* subjects had slightly higher levels of estrone (+11 percent; p = 0.05) and estrone sulfate (+8 percent; p = 0.17). Estradiol levels were slightly lower (–12 percent; p = 0.13). Concentrations of testosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate varied little between *A2* and *A1* homozygotes. These results differed from those previously published for a subgroup of the subjects (38).

Age at menarche, onset of puberty, age at menopause, and years of menstruation. Age at menarche is at least partly hormonally mediated (62). Eleven studies have investigated associations between the 5′-UTR polymorphism and age at menarche in women without cancer or other diseases (10, 18–20, 33, 36, 38, 43, 46, 48, 51). All of these studies involved asking adult women to recall their age at menarche, an approach that is likely to result in random error; bias seems unlikely. In a small longitudinal study of women in their twenties in whom menarche and age had been prospectively recorded, the misclassification rate was 25 percent when the women were grouped into three categories based on recalled age at menarche (<12.0, 12.0–12.9, or ≥13.0 years) (63). These results may provide some indication of the possible extent of misclassification in the studies of *CYP17* and age at menarche; the effect of such misclassification would be to reduce observed differences between genotypes.

Overall, seven of the 11 studies were compatible with a modest association between *A2A2* genotype and earlier menarche. Five of the 11 studies summarized mean age at menarche according to genotype (18, 19, 33, 36, 48). Four of these observed a slightly lower age at menarche in *A2A2* women than in *A1A1* women, but the differences were small and not statistically significant (18, 19, 36, 48). The remaining six studies presented data on proportions of women who had experienced menarche above or below a particular age; three were consistent with a lower age at menarche among *A2* carriers (10, 20, 51) and three were not (38, 43, 46).

Kadlubar et al. (49) assessed associations between breast development, a marker of puberty onset, and genotype in 137 US girls with a mean age of 9.5 years. Consistent with the observations related to age at menarche, a greater proportion of girls with the *A2A2* genotype had experienced the onset of puberty (66 percent) in comparison with girls with other genotypes (51–52 percent), although this finding was based on small numbers (18 girls with the *A2A2* genotype) and the association was not statistically significant.

Gorai et al. (19) observed that mean age at natural menopause did not differ significantly by genotype among 333 postmenopausal Japanese women. Heterozygous women had a slightly greater average number of years of menstruation than either group of homozygotes (p = 0.090) because they had a younger mean age at menarche. Ambrosone et al. (51) observed that 62 percent of *A1A1* women had experienced menopause at age 48 years or younger, as compared with 53 percent of women with the *A2* allele. Feigelson et al. (10) reported that age at menopause was not associated with *CYP17* genotype but did not show their results.

Use of postmenopausal hormones. Feigelson et al. (44) investigated 749 postmenopausal women with no current or prior history of breast, ovarian, endometrial, or cervical cancer from a large multiethnic cohort established using driver's license files in Hawaii and Los Angeles, California, and found that *A2A2* women were half as likely as *A1A1* women to be current users of hormone replacement therapy (HRT) (odds ratio = 0.52, 95 percent CI: 0.31, 0.86). This intriguing association was present in all four ethnic groups studied. In four smaller studies carried out in the United States, where postmenopausal hormone use has been relatively high (64, 65), data were available on frequencies of HRT use by genotype among women who served as control subjects for cancer cases (39, 46, 51, 66). Three of these control series were nested within cohort studies (39, 46, 66) and the other was population based (51). In a study conducted by Helzlsouer et al. (46) among 115 women aged 60.2 years (standard deviation, 11.5) who were primarily of European origin, only 14 percent of *A2A2* homozygous women had ever used HRT, as reported retrospectively by self-completed questionnaire, as compared with 31 percent

of heterozygotes and 34 percent of women with the *A1A1* genotype. This is consistent with the observation of Feigelson et al. (44). In contrast, in an analysis of 554 predominantly White women from the Nurses' Health Study, there were no differences by genotype in the frequencies of never, past, and current use of HRT, as reported on questionnaires returned by subjects at 2-year intervals during the period 1976–1996 (39). Ambrosone et al. (51) also found no difference in frequencies of HRT use (assessed through retrospective interview) by genotype among 188 women of European origin, but they did not distinguish between *A1A2* and *A2A2* subjects. Using data nested in the same cohort as that of Feigelson et al. (44) but from a different random sample, comprising 391 postmenopausal women with no history of endometrial, breast, or ovarian cancer, McKean-Cowdin et al. (66) found that a slightly higher proportion of *A2* carriers (25 percent) had used estrogen replacement therapy without progestins at baseline (at ages 45–75 years) than *A1A1* women (19 percent).

A possible concern is publication bias in the reporting of data on the relation between the *CYP17* polymorphism and HRT use. The study that had findings consistent with the report of Feigelson et al. (44) was substantially smaller than the Nurses' Health Study, in which no relation was found. Investigation of this association was not the purpose of any of these studies and was not commented on by the authors.

The ways in which *CYP17* might influence HRT use are not clear, but it is possible that they could be related to differences in levels of circulating hormones between women with different genotypes. For example, one possibility is that *A2A2* women may have higher estrogen levels prior to menopause and thus may suffer less from menopausal symptoms than women with other genotypes, who initially have lower estrogen levels.

Breast density. Because breast density has been shown to be a strong independent predictor of breast cancer risk, Haiman et al. (67) investigated whether the extent of breast density measured by mammogram was related to genotype. A total of 152 African-American women and 244 White women who had been diagnosed with breast cancer, and for whom information on mammographic density in the contralateral (cancer-free) breast was available, were evaluated. Mean percentage breast density (percentage of the breast comprising mammographically dense tissue) was associated with age, menopausal status/HRT use, body mass index, parity, age at first birth, and age at menarche. Among African-American women, there was no difference in breast density (adjusted for the other predictors of density) according to *CYP17* genotype. In White women, those who were *A2A2* homozygous had higher density than women with other genotypes, but this finding was not statistically significant. It is not clear whether these results would be generalizable to the population of women at risk of breast cancer (as opposed to those with the disease).

Studies in males

Hormone concentrations. Four studies (31, 37, 42, 53) have evaluated the relation between genotype and hormone concentrations in nondiseased men (table 2). Regarding the accuracy of the hormone levels assessed in these studies, a single measurement of testosterone and the metabolite dihydrotestosterone is thought to reliably reflect mean levels over a period of 1 year (68), whereas little is known about the reliability of a single measurement of the other hormones investigated.

No association between genotype and mean total testosterone level has been observed (31, 37, 53). In one study of White males in the United States (53), median levels of bioavailable testosterone were significantly higher in *A2* homozygotes than in *A1* homozygotes, but this pattern was not observed among vegetarians in the United Kingdom (31). The single study of dihydrotestosterone found no association with genotype (37).

In a study described in abstract form only (42), a statistically significant trend of decreasing levels of androstanediol glucuronide, a marker of 5α-reductase activity, with increasing number of *A2* alleles was observed, but this was not confirmed in two other studies (31, 37). No clear associations with estradiol (37, 53), sex hormone-binding globulin (31, 53), or luteinizing hormone (31) were observed in the few studies in which these factors were investigated (table 2).

Markers of hormonal status. With regard to markers of hormonal status in men, male pattern baldness, waist:hip ratio, stature, and bone mass have been investigated in single studies (37, 53, 69, 70). The findings are summarized in Web table 2 (posted on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm), as well as on the *Journal*'s website (http://aje.oupjournals.org)). The only statistically significant associations observed were between the *A2A2* genotype and stature and the cross-sectional area of the femoral neck (53).

LABORATORY TESTS

The 5′-UTR polymorphism is detected most easily using polymerase chain reaction amplification followed by restriction fragment length polymorphism analysis involving digestion with *Msp*AI. Several different primer sets have been developed (6, 10, 32). The promoter region polymorphism was identified by single-strand conformation polymorphism (8). Since it destroys a recognition site for *Nae*I, it could be detected routinely using restriction fragment length polymorphism methods. The single study that has reported on the intron 6 polymorphism detected it using single-strand conformation polymorphism methods (7).

Few studies have explicitly reported data on the proportion of specimens that were successfully analyzed and assigned a *CYP17* genotype. In two articles in which these data were shown, Dunning et al. (33) successfully genotyped 97 percent of blood samples provided by breast cancer cases for the 5′-UTR polymorphism and Helzlsouer et al. (46) assigned genotypes to 97 percent of blood samples obtained from breast cancer cases and controls combined. Few data are available on the success rate for DNA extraction or the repeatability of genotyping, which, together with the percentage of specimens successfully genotyped, are important indicators of the analytical validity of the methods used (71). Information is lacking on the sensitivity and specificity

TABLE 2. Findings from studies of the relation between polymorphisms in the 5′-untranslated region of the cytochrome P450c17α (*CYP17*) gene and hormone levels in men

Area of study	Subjects		Hormones measured	Results by genotype	Published reference
	Type	No.			
Europe					
United Kingdom	White male vegetarians recruited into the EPIC* Study in 1994–1997; recruited from magazines, societies, and relatives of participants; no diagnosis of cancer or other serious condition influencing hormone levels; mean age = 47 years	622	Serum testosterone, bioavailable testosterone, SHBG*, luteinizing hormone, and AAG*	Adjusted† mean level in *A2* homozygotes compared with *A1* homozygotes—testosterone: 2% higher (p = 0.446)‡; bioavailable testosterone: 2% lower (p = 0.477)‡; SHBG: 11% higher (p = 0.128)‡; luteinizing hormone: 3% higher (p = 0.266)‡; AAG: 9% lower (p = 0.256)‡	Allen et al. (31)
North America					
United States	Men of African-American, Asian, White, and Latino origin§	458	Serum AAG	Significant trend of decreasing AAG levels with increasing number of *A2* alleles (p = 0.008)	Makridakis et al. (42)
United States	Male physicians aged 40–84 years in 1982 (when blood samples were collected) who were free of prostate cancer and had no history of myocardial infarction, stroke, transient ischemic attack, or unstable angina; predominantly White	374	Serum estradiol, testosterone, dihydrotestosterone, and AAG	Adjusted¶ geometric mean level in *A2* homozygotes compared with *A1* homozygotes—estradiol: 0.3% lower (p = 0.94); testosterone: 7% higher (p = 0.24); dihydrotestosterone: 3% higher (p = 0.82); AAG: 3% higher (p = 0.58)	Haiman et al. (37)
United States	White men recruited from voter's lists who were taking part in a study of osteoporosis risk and were not being treated for osteoporosis, had not had hip replacement surgery, and were not taking hormones or hormone inhibitors; mean age = 66 years	333	Serum testosterone (total and bioavailable), estradiol (total and bioavailable), and SHBG	Median level in *A2* homozygotes compared with *A1* homozygotes—total testosterone: 6% higher (p = 0.835)#; bioavailable testosterone: 20% higher (p = 0.019)#; total estradiol: no difference (p = 0.906)#; bioavailable estradiol: 12% higher (p = 0.382)#; SHBG: 8% lower (p = 0.441)#	Zmuda et al. (53)

* EPIC, European Prospective Investigation into Cancer and Nutrition; SHBG, sex hormone-binding globulin; AAG, androstanediol glucuronide.

† Adjusted for age, time of sampling, time since last food consumption, and time between collection and processing.

‡ p for heterogeneity in hormone concentrations between genotypes (*A1A1*, *A1A2*, *A2A2*).

§ Results were reported only in abstract form.

¶ Adjusted for age and smoking status.

Kruskal-Wallis test for heterogeneity in median levels across genotypes (*A1A1*, *A1A2*, *A2A2*).

of the restriction fragment length polymorphism methods used for detecting the true underlying genotype.

CONCLUSIONS AND PRIORITIES FOR RESEARCH

Geographic and ethnic variation in prevalence

We have observed distinct geographic and ethnic variation in the prevalence of the *A2* variant of the 5′-UTR polymorphism. Homozygosity for the variant appears to be more common in Japanese and other East Asian populations than in White populations in Europe and North America. The prevalence in Blacks was similar to that in Whites, but the available data on Blacks pertain almost exclusively to African Americans. In the single study of African Blacks (14), the frequency was lower than that in African Americans. Data on Hispanic populations are limited to two small US series (44, 48) in which the frequency was intermediate between that for Whites and that for East Asian populations.

Although 50 published reports located contained data on the *A2A2* genotype frequency, many studies were of series that were unlikely to be representative of the general population. Thus, it not clear to what extent the observed variation might be due to the selected nature of many of the study series. Moreover, several ethnic groups (e.g., African Blacks; Asian populations other than those in Japan, Singapore, and Taiwan) have been relatively little studied. Therefore, further large population-based studies are needed in order to clarify the extent to which the prevalence of the 5′-UTR polymorphism varies by geographic area, ethnic group, and age. The functional consequences of the polymorphism are still unclear, and further investigation is needed to clarify them.

As regards the intron 6 and promoter region G→A polymorphisms, almost nothing has been published on genotype frequency, gene function, or gene-disease associations. Already compiled population-based series or case-control or cohort studies might provide a relatively rapid route for the

documentation of genotype frequencies and investigation of genotype-disease associations. If either polymorphism proved to be relatively common and/or to be related to disease, functional studies would be warranted.

Hormone levels

Interest in *CYP17* in the etiology of particular diseases arose because of the key role of the gene in estrogen biosynthesis, and genetic variation, once discovered, was postulated to cause interindividual differences in circulating hormone levels. Some (but not all) of the relevant studies are consistent with the hypothesis that the *A2* variant, by altering gene function in some way, alters hormone concentrations—at least, estrogen levels in premenopausal women. For postmenopausal women, the evidence is limited to one study (39) that included women not using HRT and that had null findings. The dominant sites for steroid hormone production in pre- and postmenopausal women are the ovaries and adrenal glands, respectively, and it has been suggested that *CYP17* expression may differ between these sites (39). For men, the findings are inconsistent and inconclusive.

Methodological issues. Interpretation of studies of hormones in women is complicated by the methodological difficulties involved in adequately characterizing hormone levels, which vary over the menstrual cycle. For men, for hormones other than testosterone and dihydrotestosterone, little is known about the reliability of a single measurement. Hormone concentrations can vary by ethnic group, and this means that findings for one ethnic group may not be generalizable to another (72, 73). Additional difficulties are caused by several other factors: 1) hormone levels change with age (52, 74); 2) levels of some hormones are associated with anthropometric factors such as body mass index and waist: hip ratio (75–77); and 3) hormone levels may be influenced by behaviors such as tobacco smoking, alcohol consumption, and physical activity (52, 76–79). This suggests that genotype-hormone analyses should be adjusted for a range of possible confounders. Some hormones are interrelated: For example, the level of sex hormone-binding globulin determines levels of free estradiol and testosterone. This presents another issue of confounding. In addition, it is not clear whether what is biologically relevant with regard to disease risk is the total amount of a particular hormone or the free amount.

Therefore, further investigation is required to resolve the question of whether *CYP17* genotype influences hormone concentrations in both sexes. Studies of different ethnic groups are needed. Both total and free hormone levels should be determined where relevant. Possible confounding of the association between genotype and one particular hormone by other hormones should be investigated. For women, repeated measurements should be taken at different points in the menstrual cycle, and pre- and postmenopausal women should be investigated separately. The effects (where relevant) of gravidity, use of exogenous hormones (e.g., oral contraceptives), and exposure to other lifestyle factors that can modulate hormone levels also require consideration.

Interactions. Other genes are in operation in the androgen and estrogen pathways (including *SRD5A2*, *HSD17B*, *COMT*, *CYP1A1*, and *CYP19*), and it seems likely that hormone levels, to the extent that they are under genetic control, are determined by the relative balance in the activities of the range of enzymes controlled by these genes. Thus, investigation of only a single polymorphism in a single gene (i.e., *CYP17*) is likely to be overly simplistic. There is currently a paucity of data on the effects of combinations of polymorphisms on hormone levels; therefore, the joint effects of *CYP17* and other polymorphic genes involved in steroid biosynthesis require elucidation.

Age at menarche and other hormonally mediated factors

The evidence on whether *CYP17* genotype affects hormonally mediated factors such at age at menarche is inconsistent and/or limited. The findings of most studies are compatible with the existence of a modest association between *A2A2* genotype and earlier menarche. While this might be interpreted as consistent with the postulated effect of the *A2* allele on estrogen levels, the associations have generally not been statistically significant. Synthesis of the findings of these studies is complicated by the fact that different authors have presented their results differently. Pooled analysis of findings from the current studies, with adjustment for years of recall, might help to clarify this matter in the short term. Stratification by ethnic group might also be helpful. The single study of breast development in young girls (49) supported an association between puberty and genotype. Further studies in girls and young women should be undertaken, where ethically possible, to complement the retrospective studies carried out in adult women.

Potential associations between *CYP17* and age at menopause, breast density, and (in both sexes) bone mass/stature require further study. The current evidence is very limited.

HRT and use of other exogenous hormones

The association between HRT and *CYP17* reported by Feigelson et al. (44)—*A2* homozygotes were half as likely to use HRT as *A1* homozygotes—is intriguing. Findings from the other four studies with available data on this issue (39, 46, 51, 66), all of which were smaller, are inconsistent. If it is confirmed, the association suggests that HRT may be a confounder of some gene-disease associations (e.g., the association with breast cancer), and hence genotype relative risks for these diseases should be adjusted for HRT use.

The possible *CYP17*-HRT association is consistent with the postulated effects of *CYP17* on circulating estrogen levels. Associations between genotype and lifestyle factors have been observed for other polymorphic genes. For example, the *CYP2A6* genotype has been associated with the likelihood of taking up tobacco smoking (80), and the *ALDH2* genotype has been associated with whether people consume alcohol (81). Further investigations of the relation of *CYP17* genotype to HRT and use of other exogenous hormones (e.g., oral contraceptives) might be illuminating. Use of exogenous hormones in a population is clearly influenced by culture, attitudes, medical prescribing practices, and press coverage of the results of research studies and medical opinion. Thus, studies carried out in populations

where patterns of use differ from those in the United States would be very informative. Particularly valuable would be exploration of reasons for use or nonuse (poor tolerance, side effects, etc.). In the longer term, this might lead to the formulation of exogenous hormones tailored to specific genetic makeups. In the context of the current controversy surrounding the relative benefits and adverse effects of HRT (82, 83), such research would be most valuable.

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APPENDIX TABLE. Internet sites providing genetic information

Site	Sponsor	World Wide Web URL
Human Genome Epidemiology Network	Centers for Disease Control and Prevention, Atlanta, Georgia	http://www.cdc.gov/genomics/hugenet/default.htm
Public Health Genetics Unit	Institute of Public Health, University of Cambridge, Cambridge, United Kingdom	http://www.phgu.org.uk/index.php
Online Mendelian Inheritance in Man	National Library of Medicine, Bethesda, Maryland	http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM&cmd=Limits
GenAtlas	Université René Descartes, Paris, France	http://www.dsi.univ-paris5.fr/genatlas
GeneCards	Weizmann Institute of Science, Rehovot, Israel	http://www.cgal.icnet.uk/genecards
National Center for Biotechnology Information	National Library of Medicine, Bethesda, Maryland	http://www.ncbi.nlm.nih.gov/
Human Genome Mapping Project*	Medical Research Council, London, United Kingdom	http://www.hgmp.mrc.ac.uk/
The Genome Web	Medical Research Council, London, United Kingdom	http://www.hgmp.mrc.ac.uk/GenomeWeb/

* Includes links to other sites via The Genome Web.