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Variants in *CYP17* and *CYP19* Cytochrome P450 genes are associated with onset of Alzheimer's disease in women with Down syndrome

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Abstract

*CYP17*and *CYP19* are involved in the peripheral synthesis of estrogens, and polymorphisms in *CYP17* and *CYP19* have been associated with increased risk of estrogen-related disorders. Women with Down syndrome (DS) have early onset and high risk for Alzheimer's disease (AD). We conducted a prospective community-based cohort study to examine the relationship between SNPs in *CYP17* and *CYP19* and cumulative incidence of AD, hormone levels and sex hormone binding globulin in women with DS. Two hundred and thirty-five women with DS, 31 to 67 years of age and nondemented at initial examination, were assessed for cognitive and functional abilities, behavioral/psychiatric conditions and health status at 14–20 month intervals over five assessment cycles. We genotyped these individuals for single-nucleotide polymorphisms (SNPs) in *CYP17* and *CYP19*. Four SNPs in *CYP17* were associated with a two and one half-fold increased risk of AD, independent of *APOE* genotype. Four SNPs in *CYP19* were associated with a two-fold increased risk of AD, although three were significant only in those without an *APOE* ε4 allele. Further, carrying high risk alleles in both *CYP17* and *CYP19* was associated with an almost four-fold increased risk of AD (OR=3.8, 95% CI, 1.6–9.5) and elevated sex hormone binding globulin in postmenopausal women. The main effect of the *CYP17* and *CYP19* variants was to decrease the age at onset. These findings suggest that genes contributing to estrogen bioavailability influence risk of AD in women with DS.

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Keywords

Estrogen; Down syndrome; Alzheimer's disease; *CYP17*; *CYP19*; aromatase; genetics

INTRODUCTION

Estrogen has several neuroprotective effects, and loss of estrogen after menopause may play a role in the cognitive declines associated with AD [1] Both cross-sectional and prospective studies have found an association between early age at menopause, low estrogen levels and increased risk of cognitive impairment and AD [2–14], although results vary with assay sensitivity[15] and some studies have found high levels of total estradiol in women with AD [15, 16]. Estrogen levels are reduced in postmortem brains from women with AD, compared with age- and gender-matched non-demented adults [17]. In addition, functional evidence for a role of low estrogen in AD has been provided by experiments in which estrogen deficiency accelerated amyloid plaque formation in an amyloid precursor protein-mutant (APP23) transgenic mouse model of AD [18].

Variation in age at onset and risk of AD may, therefore, be influenced by genetic factors that affect estrogen levels in the brain. Two key genes, *CYP17* and *CYP19*, encode cytochrome P450 enzymes necessary for the peripheral synthesis of estrogens and are expressed in neurons as well as gonads [19, 20]. *CYP17*, located on chromosome band 10q24.3, encodes the cytochrome P450c 17α enzyme and mediates both 17α-hydroxylase and the 17,20-lyase activities in steroidogeneisis to produce dehydroepiandrosterone(DHEA) and androstenedione. *CYP19*, located on chromosome band 15q21.1, codes for the enzyme aromatase, which catalyzes the conversion of androstenedione to estrone and testosterone to estradiol. Genetic polymorphisms in *CYP17* and *CYP19* have been associated with variation in hormone levels [21–23], age at onset of menopause [24–26], and increased risk of breast cancer, osteoporosis and other estrogen related disorders [27–34]. If polymorphisms in these genes are associated with decreased or altered synthesis of estrogen, they may in turn indicate a lower lifetime exposure to estrogen and increased risk of disease related to low estrogen levels.

Several studies have examined the possible roles of these genes in AD. One study failed to find an association between the A2 restriction fragment length polymorphism (RFLP) in *CYP17* and AD [35], while several, but not all, studies of *CYP19* have found associations with risk for AD, both for single nucleotide polymorphisms (SNPs) and haplotype blocks [36–42].

Adults with Down syndrome (DS) are strongly predisposed to AD [43], so analysis of susceptibility factors in this population can potentially be more sensitive than comparable analyses in the general population. In this study, we investigated the relationship between SNPs in coding and promoter regions of *CYP17* and *CYP19* and cumulative incidence of AD in women with DS and examined the relationship of these SNPs with hormone levels and sex hormone binding globulin.

MATERIALS AND METHODS

Subjects

The initial cohort included a community-based sample of 279 women with DS. Of these 279 women, 242 (86.7%) agreed to provide a blood sample and were genotyped. All individuals were 31 years of age or older at study onset and resided in New York, New Jersey, Pennsylvania or Connecticut. In all cases, a family member or correspondent provided

informed consent, including for blood sampling and genotyping, and participants provided assent. The participation rate was 74.6%. The distribution of level of intellectual disability and residential placement did not differ between participants and those who refused. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of Columbia University Medical Center and the New York State Institute for Basic Research in Developmental Disabilities.

Clinical Assessment

Assessments were repeated at 14–20 month intervals over five cycles of data collection and included evaluations of cognition and functional abilities, behavioral/psychiatric conditions and health status. Cognitive function was evaluated with a test battery designed for use with individuals with Down syndrome varying widely in their levels of intellectual functioning, as described previously [9]. Structured interviews were conducted with caregivers to collect information on changes in cognition, function, adaptive behavior and medical status. Past and current medical records were reviewed for all participants. Participants showing declines in cognition and in adaptive behavior were evaluated by a study neurologist to confirm the presence of dementia and to determine the presence or absence of medical/psychiatric conditions other than AD that might result in or mimic dementia.

Classification of Dementia

The classification of dementia status, dementia subtype and age at onset was determined during a clinical consensus conference where information from all available sources was reviewed. Classifications were made blind to *CYP17* and *CYP19* genotype or information on hormone levels. We classified participants into two groups, following the recommendations of the AAMR-IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability[44]. Participants were classified as nondemented if they were without cognitive or functional decline, or if they showed some cognitive and/or functional decline that was not of sufficient magnitude to meet dementia criteria (n=164). Participants were classified as demented if they showed substantial and consistent decline over the course of follow-up of at least one year duration and had no other medical or psychiatric conditions that might mimic dementia (n=78). Age at meeting criteria for dementia was used to estimate age at onset of dementia. Only participants with probable or possible AD were included in the analysis. Of the 78 participants with dementia, three had a history of stroke or TIA and were excluded from the analyses. Four additional participants with dementia were also excluded because their findings suggested the presence of another non-AD medical or psychiatric condition, leaving 164 nondemented and 71 demented women in the analysis. In all cases, these exclusions were also made without knowledge of *CYP17/CYP19* genotype.

Ascertainment of Serum Hormone Levels

Non-fasting blood samples were collected between 10:00 am and 3:00 pm. Blood was separated in a refrigerated centrifuge and, after separation, sera were frozen at − 20° C until assay. Total estradiol and estrone (free + bound) were measured using no-extraction solid-phase ^{125}I-radioimmunoassay kits (Diagnostic Systems Laboratories, Inc. Webster, TX). Sensitivity or minimum detection level for estradiol was 4 pg/ml, and intra-assay and inter-assay coefficients of variation (CV) were 4.3% and 10.5%, respectively. Sensitivity or minimum detection level for estrone was 11 pg/ml and intra-assay and inter-assay CV's were 7.9% and 15.6%, respectively. Human Follicle Stimulating Hormone (FSH), Progesterone (P), and Sex-Hormone Binding Globulin (SHBG) were measured by immunometric assays using Immulite systems (Diagnostic Products Corporation, Los Angeles, CA). We used two commercial controls for the SHBG assays, the first with a mean level of 4.8 nmol/l and the second with a mean level of 82nmol/l. Sensitivity was 0.1 mIU/ml for FSH, 0.2 ng/ml for P,

and 0.2 nmol/l for SHBG. Intra- and inter assay CV's were respectively 1.9% and 5.0% for FSH, 6.0% and 7.9 % for P, and 6.4% and 8.7% for SHBG. Bioavailable estradiol was measured by ammonium sulfate precipitation of SHBG-bound estradiol and calculated as the product of percentage non-SHBG bound and total estradiol. The inter-assay coefficient of variation was 13% [45].

DNA isolation and genotyping

Genomic DNA was extracted from peripheral blood leukocytes, using the FlexiGene DNA kit (Qiagen). Isolation of DNA and genotyping were performed blind to the dementia status of the participant. SNPs reported to be associated with estrogen related disorders (breast cancer, osteoporosis) and prior studies of AD were selected. Additional SNPS were selected to provide coverage of the gene. We analyzed 7 SNPs in the *CYP17* region. One at the 3′ end of the gene, 5 in the transcribed region and one in the promoter region. We analyzed 24 SNPs in the *CYP19* region, 23 in the transcribed region and one in the promoter. SNPs were genotyped using TaqMan^R PCR assays (Applied Biosystems) with PCR cycling conditions recommended by the manufacturer, and by PreventionGenetics using proprietary array tape technology. Accuracy of the genotyping (≥97%) was verified by including duplicate DNA samples, by comparing the TaqMan^R and array tape data with results of restriction digestion polymorphisms (RFLPs) for several of the SNPs, and by testing for Hardy-Weinberg equilibrium.

Apolipoprotein E genotypes

APOE genotyping was carried out by PCR/RFLP analysis using *Hha*I (*Cfo*I) digestion of an *APOE* genomic PCR product spanning the polymorphic (cys/arg) sites at codons 112 and 158, followed by acrylamide gel electrophoresis to document the restriction fragment sizes [46]. Participants were classified according to the presence or absence of at least one *APOE* ε4 allele.

Menopausal Status

Menopausal status was ascertained through menstrual charts in medical records, medical record review, interviews with caregivers and family members, and survey of primary care physicians and gynecologists. We were able to ascertain menopausal status for 204 of the 235 participants with both *CYP17* and *CYP19* genotypes (86.8%). Three women (1.3%) had never menstruated. Hormone results were available for 114 of 146 postmenopausal women (78%).

Potential Confounders

Potential confounders included the presence of an *APOE* e4 allele, level of intellectual disability, body mass index (BMI), and ethnicity. Level of intellectual disability was classified as mild to moderate (IQ from 35–70) or profound to severe (IQ < 34), based on IQscores obtained before onset of AD. BMI was calculated as weight in kilograms divided by the squared height in square meters, (kg/m^2), and was measured at each evaluation. The baseline measure of BMI was used in the analysis and was included as a continuous variable. Ethnicity was categorized as white or non-white.

Statistical Analyses

Prior to association analysis, we tested all SNPs for Hardy-Weinberg Equilibrium (HWE) using the HAPLOVIEW program [47] and all were found to be in Hardy-Weinberg equilibrium; because of low minor allele frequencies for some *CYP19* SNPs, some cells had no observations. Participants were classified as carrying none, one, or two copies of the minor allele and analyses were conducted with participants who were homozygous for the

common allele as the reference group. For SNPs with low minor allele frequencies, participants were classified as carrying no copies of the minor allele or carrying at least one copy of the minor allele. In preliminary analyses, the χ^2 test (or the Fisher's exact test when any cell had <5 subjects) was employed to assess the association between AD and SNP genotypes as well as other possible risk factors for AD including ethnicity, level of intellectual disability and *APOE* genotype. Analysis of variance (ANOVA) was used to examine BMI and age by AD status. We used Cox proportional hazards modeling to assess the relationship between *CYP17* and *CYP19* genotypes and age at onset of AD, adjusting for ethnicity, BMI, level of intellectual disability and the presence of an *APOE* ε4 allele. The time to event variable was age at onset for participants who developed AD and age at last assessment for participants who remained nondemented throughout the follow-up period. We repeated these analyses among participants who did not carry the *APOE* ε4 allele. Samples sizes were too small to examine the relation of SNP genotypes to AD among participants carrying the ε4 allele. To address potential false positives arising from multiple testing, we computed empirical p-values for hazard ratios. Specifically, using the same multivariate Cox model that adjusts for ethnicity, level of intellectual disability, baseline body mass index, and the presence of the apolipoprotein E e4 allele, we simulated the data 100 times while "shuffling" (i.e., randomly assigning) dementia status to each subject, but kept the real genotype data and other covariates unchanged. This step generates the null distribution of no association. By counting the number of replicates that exceed the observed hazards ratio, we estimated the empirical p-value for each SNP.

We also examined the relation of carrying risk alleles in both *CYP17* and *CYP19* to cumulative incidence and age at onset of AD, using one SNP from each gene with the strongest relation to AD to minimize multiple testing (rs6163 from *CYP17* and rs1870049 from *CYP19*). We then used multivariate General Linear Modeling to compare hormone levels by combined genotype among post-menopausal women. In these analyses, participants were classified as carrying no copies or at least one copy of the risk alleles in both genes.

RESULTS

Demographic characteristics

The mean age of participants at baseline was 48.9 years (range 31.5 to 67.6) and 88 percent of the cohort was white. The mean length of follow-up was 4.5 years. Table 1 presents the demographic characteristics of the participants according to AD status. Participants with AD were significantly older than nondemented participants at baseline (53.3 vs. 47.0 years) and were more likely to carry at least one copy of the *APOE* ε4 allele (28.2% vs. 20.5%), but did not differ in the distribution of intellectual disability, ethnicity or BMI. The mean age at onset of AD was 54.9 ± 5.1 years.

Analysis of SNPS in CYP17 and CYP19

Table 2 presents the locations, distributions and minor allele frequencies (MAF) of *CYP17* SNPs and the association between *CYP17* genotypes and the hazard ratio for AD, for the total group and for those without an ε4 allele. After adjusting for age, ethnicity, level of intellectual disability, BMI and the presence of an *APOE* ε4 allele, women who were homozygous for the G allele at rs3740397, the T allele at rs10786712, the A allele at rs6163, or the G allele at rs743572 had a 2.5-fold increase in the hazard rate compared with women carrying no copies of these alleles (HR for rs37403977 (GG) = 2.6, 95% CI, 1.3–5.6; HR for rs10786712 (TT) =2.6, 95% CI, 1.2–5.2; HR for rs6163 (AA) = 2.6, 95% CI, 1.2–5.4; HR for rs743572 (GG) = 2.5, 95% CI, 1.2–5.2) (Table 2). Women who were heterozygous for the minor alleles at rs37403977, rs10786712, rs6163 and rs743572 had an approximately 2-

fold increase in the hazard rate as indicated in Table 2. Empirical p-values for these SNPs were <0.05 (data not shown). These associations were essentially unchanged when the analysis was restricted to women not carrying an *APOE* ε4 allele (Table 2).

Tables 3a and 3b list the locations of SNPs, distributions and MAF of *CYP19* SNPs and the association between *CYP19* genotypes and the hazard ratio for AD. Among the total group of women, those who were homozygous or heterozygous for the C allele at rs3751592 had a 1.6 fold increase in the hazard rate (HR (CC,CT) = 1.6, 95% CI, 1.01–2.7)(Table 3a). However, this associations was only of borderline significance after adjustment for multiple testing.($p_{empirical}$= 06). Among women without an *APOE* ε4 allele, women who were homozygous or heterozygous for the minor allele at rs3751592 (CC, CT), heterozygous for the minor allele at rs7168331 (CG), homozygous or heterozygous for the minor allele at rs1870049 (CC, CT) and rs6493497 (AA, AG) had an approximately 2-fold increase in the hazard rate compared with women homozygous for the common allele (Table 3b). These SNPs remained significant after adjustment for multiple tests ($p_{empirical}$ <0.05) (data not shown).

We used Cox proportional hazards modeling to examine the cumulative incidence of AD by combined *CYP17* rs6163/*CYP19* rs1870049 genotypes, which had the most robust support for association in the current dataset among *APOE* ε4 non-carriers (Table 4). For this analysis, genotype groups were classified as: (a) participants who did not carry a risk genotype for either of the two SNPs (*CYP17* rs6163 (CC) + *CYP19* rs18770049 (TT)); (b) those with a risk genotype for only one of the two SNPs (*CYP17* rs6163 (AA or AC) and *CYP19* rs1870049 (TT)) or (*CYP17* (CC) and *CYP19* (CC or CT)); and (c) those with risk genotypes for both SNPs (*CYP17*(AA or AC) and *CYP19* (CC or CT)). To simplify the genetic model, we restricted the analysis of combined genotypes to women without the *APOE* ε4 allele. Compared with women without either higher risk genotype, the hazard ratio for those with a high risk genotype in both *CYP17* rs6163 and *CYP19* rs1870049 was 3.8 (95% CI, 1.6–9.5) and the hazard ratio for those who were homozygous or heterozygous for only one of the high risk genotypes was 2.2 (95% CI: 0.98–5.1) (Table 4). The main effect of the *CYP17* and *CYP19* variants was to decrease age at onset rather than to increase total cumulative incidence (Figure 1). Mean survival time was 63.3 years in those with no risk alleles, 59.5 years in women with risk alleles in either *CYP17* or *CYP19* and 57.5 years in women carrying a high risk alleles in both CYP17 and CYP19. Among post-menopausal women, SHBG was elevated in women carrying risk alleles in both *CYP17* and *CYP19* (Table 5).

DISCUSSION

Four SNPs in *CYP17* were associated with a two and one-half-fold increased risk of AD, independent of *APOE* genotype. Women with DS with the GG genotype at *CYP 17* rs3740397, the TT genotype at *CYP17* rs10786712, the AA genotype at *CYP17* rs6163 or the GG genotype at *CYP17* rs743572 had a two and one half-fold increased risk of AD, compared with women without these risk genotypes. These four intronic SNPs cover a 9.3kb region with high linkage disequilibrium (minimum pairwise D′>0.9), and the three SNPs at the 5′ end are located within 756bp (Figure 2). Among the SNPs that were significant, we observed a dose/response relationship with the risk alleles, suggesting an additive model. Two other SNPs in *CYP7*, rs10883783 and rs4919687 are also in high linkage disequilibrium with these SNPs but were not associated with increased risk for AD. This lack of association is likely explained by the very low frequency of the homozygous genotype for these two SNPs (7.5% and 2.6% in controls), which makes them statistically non-informative.

Four SNPs in *CYP19* were associated with an approximately two-fold increased risk of AD. Among these SNPs, the 3 SNPs clustering in the 5′ end of the gene were associated with AD only among non-carriers of the *APOE* ε4 allele (Figure 3). The one SNP that was significantly associated with risk for AD in the total group (rs3751592) was of only borderline significance after adjustment for multiple testing, suggesting that the influence of polymorphisms in *CYP19* may be stronger in those without an *APOE* ε4 allele. The relatively small sample size of this cohort of women with DS limits our ability to detect small effects, but our findings point to regions of the gene where additional modifiers of risk may be located.

Neuroprotective mechanisms of estrogen may involve increases in cholinergic activity [48–50], antioxidant properties [51], and protection against the neurotoxic effects of beta amyloid [52–54]. Among post-menopausal women, we found elevated baseline levels of SHBG in those with risk alleles in both *CYP17* and *CYP19*, but no relationship with levels of estradiol or other hormones. However, the dramatic loss of estrogen after menopause makes estradiol levels after menopause less informative than in premenopausal women and the results of observational studies examining associations of endogenous sex hormones with dementia in postmenopausal women have been inconsistent. The median age at baseline of women who developed dementia during the follow up period was 52.7 years, approximately 7 years beyond the median age at menopause of 46 years in this population. Thus, we believe that the low levels of postmenopausal estrogen makes estrogen a less sensitive marker of how these SNPs may be related to AD. In contrast, SHBG increases with age [55, 56]. SHBG binds strongly and specifically to estradiol, reducing its availability to bind to receptors and initiate responses. Among postmenopausal women, elevated SHBG has been independently associated with increased risk for dementia or cognitive decline in a number of studies [3, 5, 14, 57, 58], even after adjustment for bioavailable estradiol [14]. Muller and colleagues [14] have suggested that increased SHBG levels could be a preclinical marker for dementia. The presence of SHBG in the human brain has suggested its involvement in neurophysiology and neuropathology, possibly through clearance of beta amyloid [59]. Determination of the relation of SNPS to estrogen metabolism and SHBG will require longitudinal study of premenopausal women through onset of menopause.

Previous studies of the relationships of polymorphisms in *CYP17* and *CYP19* to risk of AD have been inconsistent. A small case control study examined the restriction fragment length polymorphism A2 variant in *CYP17* and found no association with AD [35]. Studies of the relation of SNPS in *CYP19* to AD have also had varied results, with some SNPs associated with increased overall risk of AD (37) and others associated with AD primarily in women [41], in those with an ε4 allele [36] or in interaction with other AD- related genes [38, 39]. Our study is limited by our relatively small sample size, but power analyses showed that we had sufficient power, given the allele frequencies of the selected SNPS, for a minimum detectable relative risk between 2.0 and 2.3, consistent with the effects sizes we have observed. We suggest that the positive genetic associations of AD onset with estrogen biosynthesis polymorphisms that we report here may reflect the greater sensitivity to AD-related genetic factors among the high risk population of women with DS.

Women with DS are at high risk for early onset of AD, related, at least in part, to triplication and overexpression of the gene for the beta amyloid precursor protein, *APP*, located on chromosome 21 [60]. The present study points to the role of genetic variants that influence estrogen biosynthesis in modifying this risk through several different pathways. Our results support and extend findings from several prior studies suggesting that variants in *CYP17* and *CYP19* modify the risk for estrogen related disorders and AD, and it is of particular interest that these variants can influence the development of AD in the high-risk group of women with DS. Analysis of additional genetic variants influencing estrogen biosynthetic pathways

and estrogen receptor activity in brain cells will be useful for further testing this hypothesis and may, in turn, suggest relevant protective therapies.

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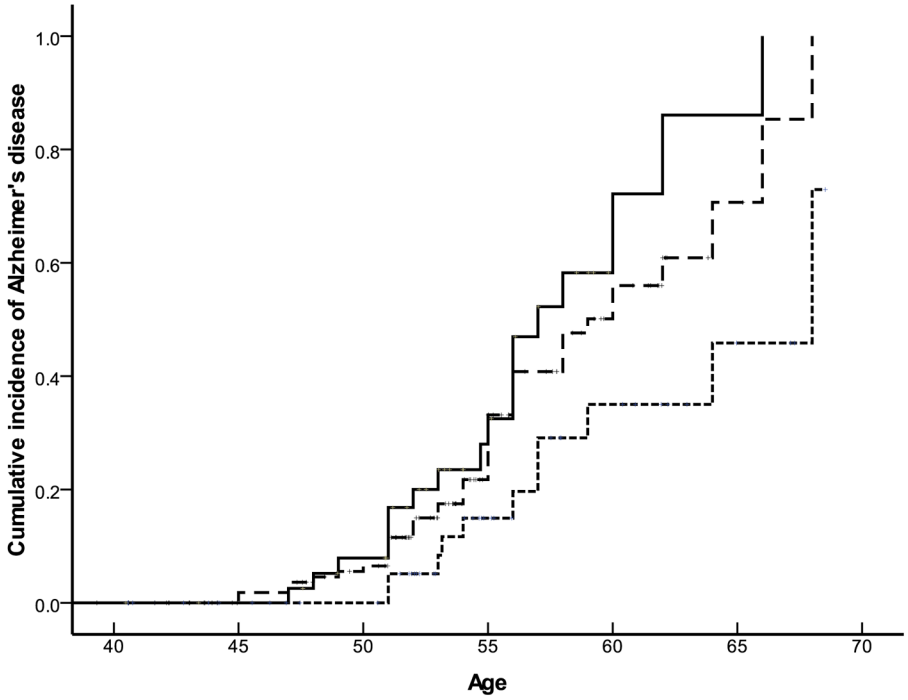

Figure 1.

Cumulative incidence of AD by combined *CYP17/CYP19* genotypes.

Risk alleles in both genes

Risk allele in one gene

No risk allele

P (risk allele in one gene = 0.06) vs No risk allele

P (risk allele in both genes) = .004 vs no risk allele

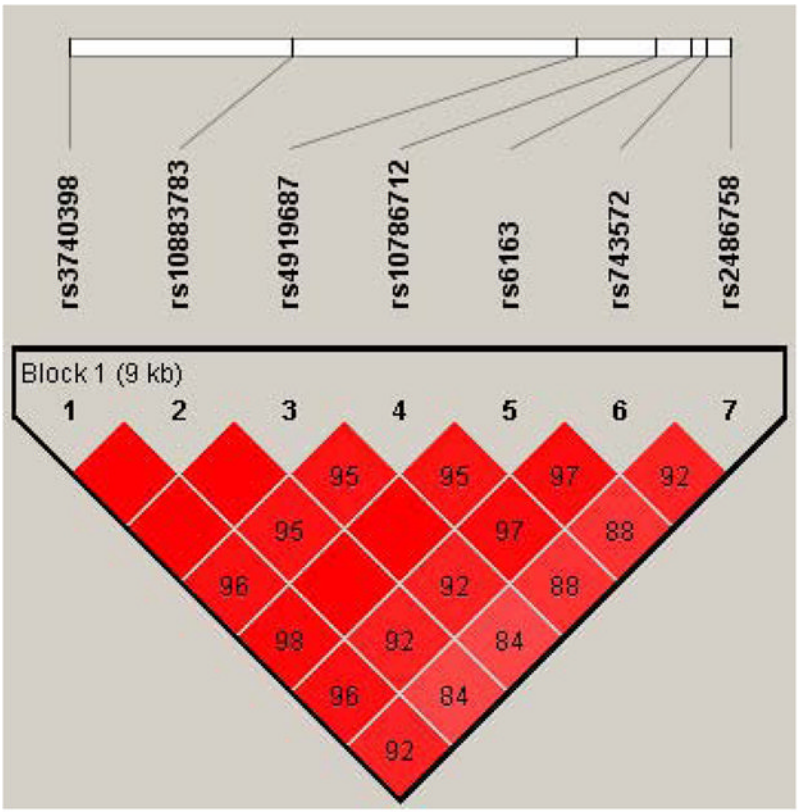

Figure 2.
LD patterns for SNPs in *CYP17*.

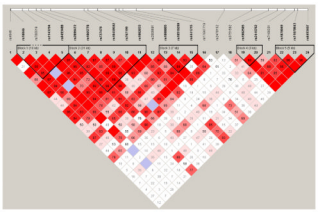

Figure 3.
LD patterns for SNPs in *CYP19*

Table 1

Demographic Characteristics by AD Status for women with Down syndrome

Characteristic	Nondemented	Demented
Sample size	164	71
Age at Baseline (mean ± S.D.)**	47.0 ± 6.3	53.3 ± 5.0
Level of intellectual disability (n,%)		
Mild/Moderate	97 (59.1)	34 (47.9)
Severe/Profound	67 (40.9)	37 (52.1)
Ethnicity (n, %)		
White	142 (86.6)	65 (91.5)
Non-White	22 (13.4)	6 (8.5)
Body Mass Index (mean ± S.D.)*	29.8 ± 6.7	28.2 ± 6.1
APOE ε4 allele (n,%)*	33 (20.5)	20 (28.2)

* $p < .10$

** $p < .05$

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Table 2

Relation of *CYP17* genotypes to risk of AD for women with Down syndrome.

	Total Group				APOE ε4 allele non carriers			
CYP17 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
rs10883783 (104581142) MAF (T) 0.281					rs10883783 (104581142) MAF (T) 0.288			
TT	14	2 (14.3)	0.8	0.2–3.6	11	1 (9.1)	0.4	0.04–2.7
AT	99	33 (33.3)	1.4	0.8–2.4	77	23 (29.9)	1.2	0.7–2.2
AA	113	31 (27.4)	1.0	reference	84	23 (27.4	1.0	reference
rs3740397** (104582665)[a] MAF (G) 0.400					rs3740397** (104582665)[a] MAF (G) 0.406			
GG	35	14 (40.0)	**2.6**	**1.3–5.6**	25	8 (32.0)	2.0	0.8–5.1
CG	111	35 (31.5)	**1.8**	**1.01–3.3**	89	27 (30.3)	**2.1**	**1.02–4.2**
CC	79	17 (21.5)	1.0	reference	57	12 (21.1)	1.0	reference
rs4919687 (104585238) MAF (T) 0.28					rs4919687 (104585238) MAF (T) 0.288			
TT	14	2 (14.3)	0.8	0.2–3.5	11	1 (9.1)	0.4	0.05–2.7
CT	98	32 (32.7)	1.4	0.8–2.3	77	23 (29.9)	1.2	0.7–2.2
CC	113	33 (29.2)	1.0	reference	84	25 (29.8)	1.0	reference
rs10786712** (104586386) MAF (T) 0.405					rs10786712** (104586386) MAF (T) 0.415			
TT	38	15 (39.5)	**2.6**	**1.2 – 5.2**	29	9 (31.0)	1.9	0.8–4.7
CT	113	38 (33.6)	**1.9**	**1.1 – 3.4**	89	29 (32.6)	**2.2**	**1.1–4.3**
CC	82	18 (22.0)	1.0	reference	59	13 (22.0)	1.0	reference
rs6163** (104586914) MAF (A) 0.408					rs6163** (104586914) MAF (A) 0.416			
AA	37	14 (37.8)	**2.6**	**1.2 – 5.1**	27	9 (33.3)	2.2	0.9–5.4
AC	117	40 (34.2)	**2.0**	**1.1 – 3.4**	94	30 (31.9)	**2.2**	**1.1–4.5**
CC	81	17 (21.0)	1.0	reference	58	12 (20.7)	1.0	reference
rs743572** (104587142) MAF (G) 0.398					rs743572** (104587142a) MAF (G) 0.402			
GG	34	14 (41.2)	**2.5**	**1.2 – 5.2**	**24**	8 (33.3)	1.9	0.8–4.8
AG	117	39 (33.3)	**1.9**	**1.05 – 3.3**	**95**	30 (31.6)	**2.1**	**1.04–4.1**
AA	82	18 (22.0)	1.0	reference	59	13 (22.0)	1.0	reference
rs2486758 (104587470) MAF (C) 0.225					rs2486758 (104587470) MAF (C) 0.229			

	Total Group				APOE ε4 allele non carriers			
CYP17 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
CC	14	4 (28.6)	0.7	0.25 – 2.1	9	3 (33.3)	0.7	0.2–2.4
CT	77	17 (22.1)	0.7	0.38 – 1.2	63	16 (25.4)	1.0	0.5–2.0
TT	140	50 (35.7)	1.0	reference	105	32 (25.4)	1.0	reference

Physical position (bp) on chromosome: Hg18, March 2006 assembly, dbSNP build 130, ┼ Not all markers available for every participant. Cox Proportional Hazards Model, adjusted for age, ethnicity, level of intellectual disability, baseline body mass index, and the presence of the apolipoprotein E (*APOE*) ε4 allele.

** $p < .05$

Table 3a

Relation of *CYP19* genotypes to risk of AD in women with Down syndrome.

Total Group									
CYP19 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**CYP19 Genotype**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
rs4646 (49290136)[a] MAF (A) 0.247					rs1008805 (49336891)[a] MAF (C) 0.406				
AA/AC	106	39 (33.1)	0.7	0.4–1.2	CC	40	17 (42.5)	0.7	0.3–1.4
CC	118	29 (27.4)	1.0	ref	CT	97	24 (24.7)	0.7	0.4–1,2
					TT	86	25 (29.1)	1.0	ref
rs10046 (4290278) MAF (G) 0.461					rs10519299 (49338638) MAF (G) 0.462				
GG	48	14 (29.2)	0.9	0.4–2.0	GG	56	17 (30.4)	1.2	0.6–2.4
AG	113	33 (29.2)	0.6	0.4–1.1	CG	97	24 (24.7)	1.0	0.5–1.8
AA	64	20 (31.3)	1.0	ref	CC	70	25 (35.7)	1.0	ref
rs700519 (49295260) MAF (T) 0.047					rs4441215 (49344251) MAF (C) 0.403				
CT	16	6 (37.5)	1.6	0.7–3.8	CC	43	17 (39.5)	0.6	0.3–1.2
CC	215	64 (29.8)	1.0	ref	CG	98	25 (25.5)	0.7	0.4–1.2
					GG	85	26 (30.6)	1.0	ref
rs1143704 (49297994) MAF (A) 0.463					rs17647719 (49355496) MAF (C) 0.057				
AA	46	13 (28.3)	0.8	0.4–1.6	CC/CT	24	9 (37.5)	1.6	0.8–3.4
AT	112	32 (28.6)	0.6	0.4–1.1	TT	204	59 (28.9)	1.0	ref
TT	61	20 (32.8)	1.0	ref					
rs6493488 (49301214) MAF (G) 0.429					rs2470152 (49382264) MAF (A) 0.489				
GG	48	(13 (27.1)	0.8	0.4–1.6	AA	64	21 (32.8)	0.7	0.4–1.5
CG	96	28 (29.2)	0.8	0.5–1.4	AG	96	29 (30.2)	1.0	0.6
CC	83	27 (32.5)	1.0	ref	GG	63	17 (27.0)	1.0	ref
rs2899472 (49303347) MAF (A) 0.291					rs3751592[**] (49393870) MAF (C) 0.329				
AA	19	10 (52.6)	2.02	0.97–4.2	CC/CT	121	42 (34.7)	**1.6**	**1.01–2.7**
AC	85	19 (22.4)	0.85	0.48–1.5	TT	104	26(25.0)	1.0	ref
CC	121	39 (32.2)	1.0	Ref					
rs1065778 (49307498) MAF (T) 0.485					rs1902585 (49401198) MAF (G) 0.498				

Total Group									
CYP19 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**CYP19 Genotype**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
TT	57	17 (29.8)	0.7	0.4–1.2	GG	57	11 (19.3)	0.7	0.3–1.4
CT	106	31 (29.2)	0.7	0.4–1.4	CG	108	39 (36.1)	1.2	0.7–2.2
CC	60	19 (31.7)	1.0	ref	CC	61	18 (29.5)	1.0	ref
rs727479 (49321839) MAF (G) 0.338					rs2445762 (49405000) MAF (G) 0.299				
GG/GT	132	38 (28.8)	0.8	0.5–1.3	GG/AG	112	38 (33.9)	1.1	0.7–1.9
TT	95	31 (32.6)	1.0	Ref	AA	112	29 (25.9)	1.0	ref
rs10459592 (49323433) MAF (T) 0.432					rs7168331 (49408275) MAF (C) 0.423				
TT	47	15 (31.9)	0.8	0.4–1.6	CC	41	15 (36.6)	1.1	0.5–2.4
GT	108	31 (28.7)	0.9	0.5–1.6	CG	111	38 (34.2	1.3	0.7–2.5
GG	74	23 (31.1)	1.0	ref	GG	72	16 (22.2)	1.0	ref
rs767199 (49327679) MAF (G) 0.491					rs1870049 (49412515) MAF (C) 0.163				
AA	55	18 (32.7)	1.4	0.7–2.9	CC/CT	68	24 (35.3)	1.3	0.8–2.2
AG	110	31 (28.2)	1.0	0.6–2.0	TT	157	44 (28.0)	1.0	ref
GG	60	19 (31.7)	1.0	ref					
rs1062033 (49335230) MAF (C) 0.450					rs11070843 (49473843) MAF (G) 0.147				
CC	49	16 (32.7)	1.3	0.6–2.5	GG/AG	60	22 (36.7)	1.4	0.8–2.4
CG	103	27 (26.2)	1.0	0.6–1.8	AA	162	46 (28.4)	1.0	ref
GG	74	25 (33.8)	1.0	ref					
rs2008691 (49335602) MAF (G) 0.149					rs6493497 (49418127) MAF (A) 0.154				
AG/GG	64	17 (26.6)	1.1	0.8–2.0	AA/AG	63	23 (26.5)	1.3	0.8–2.2
AA	163	52 (31.9)	1.0	ref	GG	162	45 (27.8)	1.0	ref

[a]Physical position (bp) on chromosome, Hg18, March 2006 assembly, dbSNP build 130, ┼ Not all markers available for every participant. Cox Proportional Hazards Model, adjusted for age, ethnicity, level of intellectual disability, baseline body mass index, and the presence of the apolipoprotein E (*APOE*) ε4 allele.

** $p < .05$

Table 3b

Relation of *CYP19* genotypes to risk of AD in women with Down syndrome.

Non APOE ε4 allele carriers									
CYP19 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**CYP19 Genotype**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
rs4646 (49290136) MAF (A) 0.254					rs1008805 (49336891) MAF (C) 0.379				
AA/AC	77	20 (20.0)	0.9	0.5–1.6	CC	26	12 (46.2)	1.3	0.6–2.9
CC	94	18 (26.9)	1.0	ref	CT	77	18 (23.4)	0.7	0.3–1.4
					TT	67	18 (26.9)	1.0	ref
rs10046 (4290278) MAF (G) 0.462					rs10519299 (49338638) MAF (G) 0.476				
GG	37	9 (24.3)	1.5	0.7–3.5	GG	43	12 (27.9)	0.7	0.3–1.5
AG	84	25 (29.8)	0.7	0.4–1.4	CG	76	19 (25.0)	0.7	0.3–1.2
AA	50	14 (28.0)	1.0	ref	CC	51	17 (33.3)	1.0	ref
rs700519 (49295260) MAF (0.038)					rs4441215 (49344251) MAF (C) 0.387				
CT	12	4 (33,3)	1.3	0.4–3.7	CC	28	12 (42.9)	1.2	0.6–2.6
CC	163	46 (28.)	1.0	ref	CG	77	18 (23.4)	0.7	0.4–1.4
					GG	67	19 (28.4)	1.0	ref
rs1143704 (49297994) MAF(A) 0.458					rs17647719 (49355496) MAF (C) 0.057				
AA	34	8 (23.5)	1.4	0.6–3.5	CC/CT	19	7 (36.8)	1.6	0.7–3.8
AT	85	24 (28.2)	0.7	0.4–1.4	TT	155	42 (27.1)	1.0	ref
TT	48	14 29.2)	1.0	ref					
rs6493488 (49301214) MAF (G) 0.419					rs2470152 (49382264) MAF (A) 0.494				
GG	35	8 (22.9)	1.5	0.6–3.4	AA	48	14 (29.2)	1.4	0.6–3.2
CG	75	22 (29.3)	0.8	0.4–1.5	AG	72	22 (30.6)	1.2	0.6–2.4
CC	63	19 (30.2)	1.0	ref	GG	50	12 (24.0)	1.0	ref
rs2899472 (49303347) MAF (A) 0.28					rs3751592** (49393870) MAF (C) 0.325				
AA	17	8 (47.1)	1.8	0.8–4.0	CC/CT	92	30 (32.6)	**2.1**	**1.1–3.8**
AC	63	12 (19.0)	0.6	0.3–1.1	TT	79	19 (24.1)	**1.0**	**ref**
CC	93	29 (31.2)	1.0	ref					
rs1065778 (49307498) MAF (T) 0.485					rs1902585 (49401198) MAF (G) 0.485				
TT	41	11 (26.8)	1.4	0.6–3.2	GG	43	7 (16.3)	0.5	0.2–1.4

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Non APOE ε4 allele carriers									
CYP19 Genotype	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**	**CYP19 Genotype**	**N**	**AD (n,%)**	**Rate Ratio**	**95% CI**
CT	84	24 (28.6)	0.8	0.4–1.5	CG	81	29 (35.8)	1.5	0.7–3.1
CC	46	13 (28.3)	1.0	ref	CC	48	13 (27.1)	1.0	ref
rs727479 (49321839) MAF (G) 0.341					rs2445762 (49405000) MAF (G) 0.312				
GG/GT	101	28 (27.7)	1.0	0.5–1.7	GG/AG	90	27 (30.0)	1,0	0.6–1.9
TT	72	22 (30.6)	1.0	Ref	AA	80	21 (26.3)	1.0	ref
rs10459592 (49323433) MAF (T) 0.434					rs7168331** (49408275) MAF (C) 0.421				
TT	34	11 (32.4)	1.2	0.5–2.5	CC	29	10 (34.5)	1.4	0.6–3.6
GT	84	22 (26.2)	0.9	0.5–1.8	CG	85	30 (35.2)	**2.2**	**1.0–4.7**
GG	57	17 (29.8)	1.0	ref	GG	56	10 (17.9)	1.0	ref
rs767199 (49327679) MAF (A) 0.497					rs1870049** (49412515) MAF (C) 0.152				
AA	42	12 (28.6)	0.7	0.3–1.7	CC/CT	48	19 (39.6)	**2.0**	**1.1–3.6**
AG	87	24 (27.6)	0.6	0.3–1.2	TT	124	30 (24.2)	**1.0**	**ref**
GG	43	13 (30.2)	1.0	ref					
rs1062033 (49335230) MAF (C) 0.451					rs11070843 (49413843) MAF (G) 0.134				
CC	38	11 (28.9)	0.7	0.3–1.6	GG/AG	42	17 (40.5)	1.7	0.9–3.1
CG	79	20 (25.3)	0.6	0.3–1.2	AA	127	32 (25.2)	1.0	ref
GG	55	18 (32.7)	1.0	ref					
rs2008691 (49335602) MAF (G) 0.171					rs6493497** (49418127) MAF (A) 0.142				
GG/AG	52	12 (23.1)	1.0	0.5–2.1	AA/AG	44	18 (40.9)	**1.8**	**1.01–3.0**
AA	121	28 (31.4)	1.0	ref	GG	128	31 (24.2)	**1.0**	**ref**

[a]Physical position on chromosome: Hg 18, March 2006 assembly, dbSNP build 130, ┼ Not all markers available for every participant. Cox Proportional Hazards Model, adjusted for age, ethnicity, level of intellectual disability, baseline body mass index, and the presence of the apolipoprotein E (*APOE*) ε4 allele.

**$p < .05$

Table 4

Relation of combined CYP17/19 SNP genotype to AD among women who do not carry the APOE ε4 allele.

CYP17/19 SNP combined genotype	N	AD (n,%)	Hazard Ratio*	95% CI
rs6163 (AA or AC) + **rs1870049** (CC or CT)**	34	15 (44.1)	**3.8**	**1.6–9.5**
rs6163 (AA or AC) + **rs1870049** (TT) OR **rs6163** (CC) + **rs1870049** (CC or CT)	99	27 (27.3)	2.2	0.98–5.1
rs6163 (CC) + **rs1870049** (TT)	42	8 (19.1)	1.0	reference

** $p < .05$

Table 5

Hormone levels at baseline in post-menopausal women

Hormone	No Risk Alleles (n= 24)	One Risk Allele (n= 69)	Two Risk Alleles (n= 21)	P value
Estradiol (E_2) level in pg/ml (mean ± S.E.)[I]	43.6 (7.7)	36.5 (4.5)	39.3 (8.2)	0.86
Bioavailable ($BioE_2$) Estradiol in pg/ml (mean ± S.E.)[I]	15.3 (3.0)	15.7 (1.8)	13.7 (3.2)	0.72
Estrone (E_1) level in pg/ml (mean ± S.E.)[I]	29.3 (6.7)	36.0 (3.9)	35.2 (6.8)	0.96
SHBG level in pg/ml (mean ± S.E)[1I]	58.2 (9.6)	48.1 (5.7)	73.4 (10.3)	0.05
FSH level in pg/ml (mean ± S.E.)[2 I]	45.8 (6.2)	45.1 (3.6)	50.2 (6.6)	0.79
Progesterone level in pg/ml (mean ± S.E.)[2]	0.14 (0.2)	0.34 (0.1)	0.10 (0.2)	0.41

[1] SHBG = Sex Hormone Binding Globulin:

[2] FSH= Follicle StimulatingHormone:

[3] DHEAS= Dehydroepiandrosterone:

[I] Multivariable analysis of variance, adjusted for age at baseline