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The Association of an Alpha2C Adrenoreceptor Gene Polymorphism with Vasomotor Symptoms in African American Women

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Abstract

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Supplemental Digital Content:

SDC 1: The number of women and visits observed at each menopause stage by genotype

Objective: The alpha 2C adrenoreceptor deletion 322–325 (ADRA2C del 322–325) polymorphism has been associated with autonomic activity and thermoregulation, which are implicated in the vasomotor symptom (VMS) mechanism. The ADRA2C del (322–325) has higher prevalence in African American women, a group known to experience more frequent and bothersome VMS. We assessed whether the ADRA2C del (322–325) genotype is associated with increased frequency of VMS in African American women.

Methods: DNA samples from African American (N=400) women participating in the Study of Women's Health Across the Nation (SWAN) were genotyped for the ADRA2C del (322–325) polymorphism. Longitudinal data on VMS was obtained from the SWAN Repository. The relation of ADRA2C del (322–325) genotypes, [deletion/deletion (D/D); insertion/deletion (I/D); insertion/insertion (I/I)] with VMS over the menopause transition for up to 12 years of follow up was examined using generalized estimating equations. Primary models considered the outcome of frequent VMS (6 or more days in the prior two weeks versus VMS <6 days in the prior two weeks) by stage of menopause.

Results: Four-hundred DNA samples from African American women were included. Seventy-five women (18.8%) were found to carry the homozygous variant allele (D/D). There was no significant difference in the trajectory of frequent VMS over the menopause transition between women with D/D and I/I + I/D genotypes (P=0.39).

Conclusions: In this preliminary study among African American women in SWAN, ADRA2C del (322–325) was not significantly related to self-reported VMS. Further studies are warranted to help us understand the role of the adrenergic system in the physiology of VMS to tailor medical therapy to patient needs.

Keywords

Vasomotor symptoms; hot flashes; night sweats; Alpha2C adrenoreceptor; African American women

Introduction

Vasomotor symptoms (VMS) are one of the most common symptoms reported during the menopausal transition, and are experienced by 60–80% of women.^{1,2} However, the physiology of VMS (hot flashes and night sweats) is still not completely understood. A number of central and peripheral systems interact to cause VMS. VMS appear to be due, in part, to a narrowed thermoneutral zone allowing small elevations in body temperature to trigger symptoms of sweating and flushing.³ The autonomic nervous system also appears to play a key role, with findings of significant decreases in vagal control of the heart (as indexed by heart rate variability) during VMS.^{4–6} Additional evidence indicates increased central norepinephrine (via urinary metabolites) release with VMS.⁷ Thus, the autonomic system appears to be important to the pathophysiology of VMS, but its precise role has not been clearly elucidated. Defining these mechanisms can enable us not only to better understand their underlying physiology, but to develop a wider array of therapies to target these pathways.

There has been limited demonstration of genetic polymorphisms associated with VMS. Notably, the ADRA2C del (322–325) adrenoreceptor is a deletion polymorphism that has been associated with an increased norepinephrine response to stress,⁸ and appears to be an important regulator of autonomic activity. This deletion has also been associated with thermoregulation.⁹

The alpha2C deletion has been found to be particularly frequent in African American women; specifically, African Americans are ten times more likely to have the deletion than whites.^{10,11} Notably, African American women are more likely to report VMS than white, Hispanic or Asian women. Additionally, African American women have more frequent, severe, persistent and bothersome VMS.^{1,12–14}

The Study of Women's Health Across the Nation (SWAN) is one of the largest, most comprehensive cohort studies of the menopause transition in the United States. We investigated whether the ADRA2C del (322–325) genotype was associated with VMS among African American women over a period of up to 12 years of follow up.

Methods

Sample

The Study of Women's Health Across the Nation is a longitudinal multisite study of women through the menopause transition that began in February 1996. SWAN recruitment protocols have been described elsewhere.¹⁵ Of the 3302 women enrolled in SWAN, 935 were African American. Baseline enrollment criteria included women age 42 to 52 who had a uterus and at least one ovary, had at least one menstrual period in the 3 months before study entry, and who were not pregnant, lactating, or using exogenous hormones. The study recruited from seven locations; African American women were recruited from Boston, Pittsburgh, Detroit, and Chicago. Institutional Review Board approval was obtained at each clinical site, and written informed consent was obtained.

During years 6 and 7 of the SWAN study, DNA samples were collected from women who agreed to participate in the SWAN Genetics Study. Samples were collected from 412 of the 935 African American SWAN participants and stored in the SWAN repository.¹⁶ This analysis included only African American women with data in the SWAN Genetics repository. DNA material was obtained from all 412 samples and analyzed for the ADRA2C del (322–325) polymorphism. Six women were not included because their genotype could not be determined. Visits up to year 12 of the SWAN study were included. Out of 4872 potential observations, 402 were excluded because neither the frequency of hot flashes nor night sweats was collected. An additional 1157 observations were excluded from analysis for the following reasons: current use of medications that impact VMS (hormone therapy (N=452), aromatase inhibitors (N=12), clonidine (N=115), selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) (N=388)) and inability to determine menopause stage (hysterectomy or bilateral oophorectomy prior to the visit (N=415) or unknown uterine/ovarian surgical status (N=212)). Reasons for excluding an observation are not mutually exclusive. Of the 406 women with known genotype, six

were not included because they met exclusion criteria at every visit. The final sample included 400 women and 3313 observations.

Materials and measures

Questionnaires and physical exam parameters were collected at the baseline visit and approximately annually at follow-up visits. Baseline demographic data included education level, and annual physical and medical history data included age, menopause stage (premenopausal: had a menstrual period in the last 3 months with no change in menstrual regularity in the previous 12 months; early perimenopausal: had a menstrual period in the past 3 months with decreased regularity in menses in the previous 12 months; late perimenopausal: no menses in the last 3–11 months; postmenopausal: lack of menses in the prior 12 or more months),¹⁷ body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac history (history of angina or heart attack), physical activity, and smoking.

Vasomotor symptoms

Vasomotor symptoms (hot flash and night sweats) were evaluated based on questionnaire data collected at study visits from baseline to year 12. Hot flash and night sweat frequency were each evaluated by asking how often the participant experienced the symptom in the past two weeks (Not at all, 1–5 days, 6–8 days, 9–13 days and every day). Responses greater than or equal to 6 days were considered frequent.¹³ Hot flashes and night sweats were considered together for analysis (reporting either symptom as frequent VMS). Hot flash/night sweat bother was also evaluated beginning in year 7 through year 12 by asking participants how much they were usually bothered by hot flashes or flushes. Responses were: Not at all, very little, moderately, and “a lot”. VMS data was collected for each participant as they transitioned through the menopause stages, for up to 12 years of follow-up.

Genotyping

DNA samples were collected during years 6 and 7 of the SWAN study from buccal cells and whole blood, via previously described methods.¹⁶ Samples were analyzed for the ADRA2C del (322–325) polymorphism. Samples were typed in the Center for Pharmacogenomics Genotyping Core Lab at the University of Florida. The isolated DNA samples were first normalized to 20 ng/ul and then used for PCR followed by Sanger Sequencing for genotyping ADRA2C (322–325 Ins/Del) polymorphism. The following PCR primers; Forward 5'-GTGGAGCCGGACGAGAGC-3', Reverse 5'-GGCGCGACAGGAAGAACTC-3', were used for PCR amplification. The PCR reaction was prepared for 25 ul reaction using PlatinumTaq DNA polymerase and buffer reagents (Invitrogen, ThermoFisher, Carlsbed, CA). The PCR was performed for 45 cycles under the following conditions: 94°C for 4 minutes, 94°C for 30seconds, 62°C for 30 seconds, 72°C for 30 seconds and final extension for 10 minutes at 72°C. The PCR product was then sequenced bidirectionally by Sanger sequencing using the Forward 5'-GCGGTGCGGACGGGACAG-3' and Reverse 5'-GGCGCGACAGGAAGAACTC-3' sequencing primers. The sequencing results were analyzed using Sequencer 5.1 software to

call the Ins/Del genotypes. Six samples could not be genotyped because of PCR and Sanger sequencing reaction failure due to the poor DNA quality, possibly caused by DNA degradation.

Statistical analysis

Demographic information and medical history at each woman's first contributed visit was compared by genotype via T-tests, Chi-square tests, and Fisher's exact tests. Hardy-Weinberg equilibrium (HWE) was tested using a chi-square test of our observed genotype distribution against the expected distribution under HWE. The primary aim of this study was to determine whether VMS differed between women homozygous for the deletion (D/D) and women heterozygous (I/D) or homozygous for the wild type (I/I). To assess whether VMS were associated with genotype, the probability of VMS across the five stages of menopause (pre, early peri, late peri, early post, and late post) was modeled using a generalized estimating equations (GEE) model with a logit link and an exchangeable working correlation matrix. The model included terms for menopause stage, genotype, and an interaction between menopause stage and genotype. It was pre-specified that any demographic and medical history variables differing between the genotypes at the 0.05 significance level would be included as covariates in the final analysis. No potential covariates met this threshold. Using a cross-sectional analysis and assuming, based on previously published SWAN data¹⁸ that the rate of frequent VMS is 35% in African American women in the I/I +I/D group, a sample size of 300 in the I/I+I/D group and 75 in the D/D group provides approximately 80% power to detect an odds ratio of 2 using a two-sided, 0.05 level test. Using a longitudinal analysis, leveraging the repeated measures per-woman across the SWAN visits, the detectable difference between the genotype groups in this study would be smaller. Secondary outcomes included incidence of any vasomotor symptoms, hot flashes and night sweats considered separately, and hot flash/night sweat bother.

Results

400 African American women and 3313 observations were included in this analysis, and the median number of observations contributed per woman was 9 (IQR: 6, 11). Seventy-five women (18.8%) were found to be homozygous for the ADRA2C del (322–325) deletion allele (D/D) and 325 (81.3%) heterozygous (I/D) or homozygous for the wild type allele (I/I). There was no evidence that the genotype distribution violated Hardy-Weinberg assumptions ($p=0.32$). Demographic or medical history characteristics did not significantly differ by genotype status (Table 1). The number of women and visits observed at each menopause stage by genotype is included in the supplemental content (Table S1).

Analysis of the primary outcome, frequent VMS, demonstrated that the trajectory of frequent VMS symptoms over the menopause transition was similar between the genotypes ($p=0.39$). At each stage, the report of frequent VMS symptoms was similar between the groups (pre: OR=0.29, 95% CI (0.07, 1.23); early peri: OR= 0.83, 95% CI (0.50, 1.41), late peri: OR=1.15, 95% CI (0.61, 2.19); early post: OR=1.00, 95% CI (0.52, 1.89); late post: OR=0.93, 95% CI (0.57, 1.52)) (Figure 1).

Analysis of secondary outcomes similarly found that the trajectory of any VMS over the menopause transition did not differ by ADRA2C genotype ($p=0.51$). The report of any VMS was similar at each menopause stage (pre: OR=0.60, 95% CI (0.29, 1.24); early peri: OR=1.02, 95% CI (0.67, 1.56), late peri: OR=1.14, 95% CI (0.51, 2.54); early post: OR=1.19, 95% CI (0.53, 2.69); late post: OR=0.77, 95% CI (0.46, 1.29)). Hot flashes and night sweats considered separately yielded comparable nonsignificant results ($p=0.61$ for hot flashes and $p=0.22$ for night sweats). Finally, we considered VMS bother, with no significant differences between the genotypes in VMS bother ($p=0.54$), or in hot flash or night sweat bother considered separately ($p=0.72$, $p=0.45$).

Discussion

In this preliminary investigation, we evaluated a potential genetic susceptibility towards vasomotor symptoms, homozygosity for the ADRA2C del (322–325). We found that this polymorphism was not associated with self-reported VMS frequency or bother.

Increased adrenergic activity has been implicated in the pathophysiology of VMS.⁷ There are three functionally distinct ADRA2C that are located in different parts of the human body. The alpha-2C adrenoreceptor (alpha2C-AR) has been found in the basal ganglia, olfactory tubercle, hippocampus, and cerebral cortex of the brain.^{19–21} Outside of the brain, the mRNA of the alpha2C-AR has been found in all tissues examined except for the liver, gallbladder, thymus, and bone marrow.²² The alpha2C-AR has been found to be related to increased sympathetic tone and release of norepinephrine, and has also been found to be related to temperature control.^{23–24} It is implicated in the stress response, inducing stress-induced increases in plasma corticosterone. Additionally, it has been found to play a role in establishing brain dopamine and serotonin balance,²⁵ as well as in the processing of sensory information and emotional activities.²⁶ The ADRA2C deletion 322–325 is associated with increased pain perception and cold-induced vasoconstriction.^{23,27} Because of the role of the alpha2C-AR in these functions, which are related to the physiology of VMS, we hypothesized that variations in this receptor may contribute to increased VMS.

There is a high degree of inter-individual variability in the alpha 2-ARs. This is largely due to genetic variations, with substantial haplotype variations which impacts receptor transcript and protein expression.²⁸ However, there may be other mechanisms involved such as environmental influences that could alter receptor expression or function.²⁸ Alternatively, there may be genetic variations in other regions of the gene that could be related to vasomotor symptoms. It is possible that the alpha2C-AR does play a role in VMS, but the specific deletion 322–325 polymorphism does cause a significant change in the degree of reported symptoms.

The inclusion of only African American participants may have limited the ability of this study to detect a difference in VMS symptoms based on the presence of the alpha2C-AR del (322–325). We restricted the study population to African American women because the mutation is ten times more prevalent in the African American population¹¹ and African American patients report an increased frequency and severity of VMS.^{1,12–14} For example, the ADRA2C del (322–325) conveys a 5-fold risk for heart failure in African American

patients; the deletion was also found to be associated with increased risk of heart failure in white patients, but to a lesser degree.¹¹ It is possible, however, that there is an association of the alpha2C-AR with vasomotor symptoms in other racial/ethnic groups. This study was also limited by the use of questionnaires to quantify vasomotor symptoms, generating outcomes based on subjective data rather than objective physical measures. The study's sample size was limited to data pre-existing in the SWAN study. Power calculations indicated that cross-sectionally, an odds ratio of at least 2 would be detectable at 80% power. However, given the relatively limited sample size and few premenopausal observations, results should be interpreted as preliminary. Larger studies are needed to further confirm that no meaningful association exists.

A strength of this study is that it is the first to investigate the association between vasomotor symptoms and the ADRA2C del (322–325) polymorphism, which is relevant to a number of parameters related to VMS. This is one of the few studies to attempt to identify genetic factors implicated in the frequency of VMS.²⁹

Conclusions

Our study did not find a difference in vasomotor symptoms among African American women with and without the ADRA2C del (322–325) polymorphism. Given our small sample size, these data are preliminary to motivate future research. Based on prior evidence that dysregulation in the autonomic nervous system may lead to an increased occurrence of hot flashes, further investigation is warranted to determine the pathways responsible for generating VMS. With a deeper understanding of this complex symptom affecting the majority of postmenopausal women, new therapies may be generated that can serve as non-hormonal alternatives for women with VMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1: Vasomotor Symptoms over the menopause transition

This was a longitudinal analysis of 400 women transitioning through the menopause stages. Panel A The observed percentage of patients with frequent vasomotor symptoms by genotype at each SWAN visit over the menopause transition. The numbers below the graph give the total number of participants observed at each visit by genotype. Panel B The model estimated population average probability of frequent vasomotor symptoms at each menopause stage by genotype. The lines above and below each point denote 95% confidence limits. The trajectory of frequent vasomotor symptoms over time did not differ by genotype. Panels C and D give the same for any vasomotor symptoms.

Table 1:

Sample characteristics at the first contributed visit by genotype

	I/I or I/D (N=325)	D/D (N=75)	P-value
	Mean $\pm$ SD	Mean $\pm$ SD	
BMI (kg/m ²)	31.5 $\pm$ 7.5	31.4 $\pm$ 7	0.91
Waist Circumference (cm)	93.4 $\pm$ 16.3	93.1 $\pm$ 14.5	0.89
SBP (mmHg)	124.8 $\pm$ 20.3	125 $\pm$ 21	0.94
DBP (mmHg)	76.4 $\pm$ 11.3	77.7 $\pm$ 13.9	0.45
Age (years)	45.9 $\pm$ 2.9	46.1 $\pm$ 2.7	0.73
	No./No. Obs (%)	No./No. Obs (%)	
Depressed (CESD 16+)	87/325 (26.8)	16/75 (21.3)	0.33
Current Smoker	78/317 (24.6)	18/74 (24.3)	0.96
Diabetes	23/321 (7.2)	6/73 (8.2)	0.76
Use of Cholesterol Medication	6/325 (1.8)	2/75 (2.7)	0.65
Anticoagulant Use	13/323 (4.0)	3/75 (4)	>0.99
History of Angina or Heart Attack	10/320 (3.1)	2/73 (2.7)	>0.99
Physical Activity			
Much /Somewhat less than other women	87/314 (27.7)	13/72 (18.1)	0.22
About the same as other women your age	113/314 (36)	31/72 (43.1)	
Somewhat/Much more than other women	114/314 (36.3)	28/72 (38.9)	
Menopause Stage			0.09 ^a
Pre	170/325 (52.3)	31/75 (41.3)	
Early Peri	150/325 (46.2)	44/75 (58.7)	
Late Peri	1/325 (0.3)	-	
Early Post	2/325 (0.6)	-	
Late Post	2/325 (0.6)	-	
Education			
High school diploma or less	94/316 (29.7)	18/70 (25.7)	0.23
Vocational/training school after High School grad	141/316 (44.6)	27/70 (38.6)	
College or higher	81/316 (25.6)	25/70 (35.7)	
Any Hot Flashes or Night Sweats ^b	165/325 (50.8)	37/75 (49.3)	0.82
Any Hot Flashes	123/325 (37.8)	28/74 (37.8)	>0.99
Any Night Sweats	130/323 (40.2)	27/75 (36.0)	0.50
Frequent Hot Flashes or Night Sweats ^b	55/325 (16.9)	9/75 (12.0)	0.29
Frequent Hot Flashes (6+Days)	43/325 (13.2)	7/74 (9.5)	0.38
Frequent Night Sweats (6+Days)	38/323 (11.8)	5/75 (6.7)	0.20

^aP-value from comparing proportion of women pre-menopause vs other^bReported frequency (days with the symptom) in the previous 2 weeks

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; CESD=Center for Epidemiological Studies Depression Scale Score

Note: The first contributed observation was the baseline SWAN visit for 378 (94.5%) of women.

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