



Laidlaw Scholars Undergraduate Leadership and Research Programme
Research Report

**Associations between Polymorphisms in the *NFKB1* Gene and
Premenstrual Symptoms**

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Introduction

Research Objectives

1. Primary Research Objective

The primary goal and key achievement of this research is to evaluate the association between 18 SNPs in the *NFKB1* gene and 15 premenstrual symptoms in a multi-ethnic cohort of young healthy women. Through this research, I hope to illuminate potential genetic underpinnings of premenstrual symptoms, which remain poorly understood.

2. Secondary Research Objectives

Through this experience, I aspire to become acquainted with the nuances of conducting research in academia. I also hope to sharpen my knowledge and skills with respect to the identification, exclusion, and analysis criteria of primary and secondary sources, as well as comparative methods of analysis.

In this journey, my ambition is to immerse myself in the intricate facets of academic research, sharpen my critical thinking abilities, and communicate complex ideas clearly to a diverse audience. This programme offers an opportunity to explore and solidify my research interests and contribute meaningfully to my chosen field.

Literature Review and Gap of Knowledge

1. Premenstrual Symptoms

Premenstrual symptoms (PMSx) occur during the luteal phase of the menstrual cycle, up to 14 days before menstruation; they can be classified into somatic, including bloating, cramps, headaches, fatigue and nausea, and psychological symptoms, such as anxiety, confusion, mood swings, and insomnia (Biggs & Demuth, 2011). It is estimated that up to 80-90% of women of reproductive age experience one or more PMSx before their menstruation, however, they are experienced differently and vary in severity among women (Lete et al., 2017). Furthermore, in what is known as premenstrual syndrome (PMS) diagnosed in approximately 20-32% of women, the severity of the symptoms can significantly impair day-to-day functioning and quality of life (Yonkers et al., 2009). Even though the prevalence of PMSx is very high and they negatively impact the majority of premenopausal women, their etiology is not yet well understood.

Whether PMSx appear or not is multifactorial and is mainly impacted by genetic and lifestyle factors including diet, stress, sleep, and physical activity (Jarosz et al., 2021). Anti-inflammatory agents have been shown to relieve various PMSx, suggesting a strong relationship between inflammation and PMSx (Gold et al., 2016). The role of several hormones and inflammatory markers have also been previously investigated and several mechanisms have been proposed for their involvement in PMSx (Lanza di Scalea & Pearlstein, 2017). In particular, inflammatory markers like interleukins, tumor necrosis factor alpha (TNF- α) and C-reactive protein (CRP) have been positively associated with PMSx and worsening severity of symptoms among individuals diagnosed with PMS (Bertone-Johnson et al., 2014; Gold et al., 2016). One source of these inflammatory mediators in the body is through their production by the NF- κ B pathway, where the

NFKB1 gene plays a crucial role. The role of the *NFKB1* gene in PMSx has not previously been characterized in the literature.

2. The NF- κ B Pathway and *NFKB1* gene

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway is a key transcriptional regulator integral to immune responses, inflammation, cell proliferation, and apoptosis (Goldhirsh et al., 2021). Activation of this complex pathway involves an intricate interplay of five subunits that can form both homo- and heterodimeric complexes, enabling them to bind DNA and regulate pro-inflammatory and anti-inflammatory gene expression in response to various stimuli (Cartwright et al., 2016).

Central to the NF- κ B pathway is the *NFKB1* gene found on chromosome 4 in humans (Franco-Jarava et al., 2022), which encodes the p105 protein. This precursor protein is proteolytically processed into the smaller p50 subunit which plays a dual role, functioning as both a repressor and an activator within the pathway. The role of p50 in inflammatory gene expression is dictated by its partnering subunit; when in a heterodimeric state, for instance paired with a p65 subunit, p50 increases pro-inflammatory gene expression, while p50 homodimers are typically regarded as transcriptional repressors (Cao et al., 2006).

The dysregulation, specifically chronic activation, of this pathway has been implicated in a variety of inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease (IBD), and asthma (Glas et al., 2006; Elkhawaga et al., 2021; Menzel et al., 2021). Furthermore, mutations or polymorphisms in the *NFKB1* gene have been associated with various human diseases – including cancers, underscoring its importance in maintaining cellular stability and response mechanisms (Fu et al., 2016).

A vast number of chronic inflammation symptoms, including migraines, depression, anxiety, fatigue, abdominal pain, and irritable bowel syndrome, overlap with common PMSx (Gold et al., 2016); this link suggests a potential involvement of the NF- κ B pathway in the occurrence and severity of PMSx. Variations or polymorphisms in the *NFKBI* gene may influence how this pathway is activated or suppressed, potentially affecting the severity and presence of inflammatory symptoms associated with PMS.

Methodology

1. Study Design and Population

For the purposes of this project, I conducted statistical analyses utilizing data from the Toronto Nutrigenomics and Health (TNH) study, which consisted of a multi-ethnic cross-sectional study conducted between 2004 and 2010 (Nielsen et al., 2023). The study population included 1,640 young and healthy males and females between 20 and 29 years old from various ethnic backgrounds living in Toronto. The TNH study was carried out with the aim of analyzing the impact of genetic variation on dietary patterns, biomarkers, and other health outcomes.

Given that this research project focused on premenstrual symptoms, only women were included as part of the study population. Smokers, hormonal contraceptive (HC) users, individuals with hormonal imbalances, and those under anti-depressants or anxiolytic medication were excluded due to the known influence of these factors on premenstrual symptoms (Biggs & Demuth, 2011; Jarosz et al., 2021).

2. Data Collection

Various biomarkers were collected from the TNH study population. Information on several health outcomes and other characteristics like age, sex, ethnicity, medical conditions, medications and dietary supplement use, diet, and physical activity was collected through the General Health and Lifestyle Questionnaire (GHLQ). Dietary intake was measured utilizing a Toronto-modified Harvard Food Frequency Questionnaire (FFQ). Data on 15 common premenstrual symptoms was also collected using a scale to measure presence and severity, ranging from none, mild, moderate, and severe (Jarosz et al., 2021).

3. Genotyping

DNA was obtained from blood samples collected after a 12-hour fast from participants. Sequenom MassARRAY was performed at the Princess Margaret Hospital to genotype various genes, including the 18 SNPs for the *NFKB1* gene: rs11722146, rs13117745, rs1599961, rs1609798, rs230511, rs230547, rs3774932, rs3774934, rs3774956, rs3774968, rs4648006, rs4648022, rs4648090, rs4648095, rs4648110, rs4648127, rs4698863, and rs7674640 (Merritt et al., 2018).

4. Statistical Analysis

Statistical analyses were conducted on RStudio using version 4.3.3 (2024-02-29 ucrt). I performed logistic regressions to determine the associations between the genotypes from the 18 SNPs in *NFKB1* and each of the 15 premenstrual symptoms included in the questionnaire. Although data on premenstrual symptoms were collected as an ordinal variable based on severity with four possible categories, it was transformed into a binary variable to facilitate logistic regressions. Symptoms were grouped into either present (1), including mild, moderate, and severe, or absent

(0). Given the multi-ethnic nature of the cohort, preliminary analyses for the two main ethnic groups, Caucasians and East Asians, were conducted to examine whether there were significant differences across ethnic groups. The significance level for p-values was set at 0.05, and 95% confidence intervals were computed for the odds ratios (OR) to determine the risk of experiencing each symptom for the three possible genotypes at each SNP. Adjustments were made for the following covariates: age, BMI, ethnicity, and physical activity, given their known associations with PMSx.

Results

Subject Characteristics

Participant characteristics stratified by ethnicity are detailed in Table 1. The study cohort comprised 652 female participants, with East Asians representing the largest ethnic group at 45.4%, followed by Caucasians at 35.6%, and South Asians constituting the smallest group at 11.5%. Age distribution varied significantly across ethnicities, with Caucasian participants being the oldest on average (23.27 ± 2.75 years), compared to East Asians (21.82 ± 2.08 years) and South Asians (21.91 ± 2.21 years) ($p < 0.001$). The analysis revealed significant differences in genetic variation across the 18 SNPs examined among the ethnic groups. Certain SNPs exhibited reduced genetic diversity within specific ethnic groups, where either a particular genotype was absent or represented by only a single individual. This lack of variation precluded the possibility of conducting logistic regression analyses for these genotypes within the affected subgroups, as seen by the dashes in Supplementary Tables 1, 3, 5 and 8-13. Notably, all East Asian participants were homozygous for the CC genotype at the rs4648022 SNP, with the T allele completely absent in this group. Furthermore, the rs4648095 SNP demonstrated a strikingly low level of genetic

diversity across the entire study population, as no individual in any ethnic group possessed the CC genotype.

Table 1: Participant characteristics among 652 subjects stratified by ethnicity

	Caucasians	East Asians	South Asians	Other	p-value
n (%)	232 (35.6)	296 (45.4)	75 (11.5)	49 (7.5)	
Age (years)	23.27 ±2.75	21.82 ±2.08	21.91 ±2.21	22.82 ±2.68	<0.001
BMI (kg/m²)	23.37 ±3.71	21.18 ±2.29	23.17 ±4.07	23.22 ±5.30	<0.001
PAL (mean (SD))	1.92 ±0.41	1.56 ±0.32	1.76 ±0.41	1.86 ±0.52	<0.001
rs11722146, n (%)					<0.001
GG	109 (47.0)	96 (32.4)	42 (56.0)	23 (46.9)	
GA	99 (42.7)	146 (49.3)	29 (38.7)	21 (42.9)	
AA	24 (10.3)	54 (18.2)	4 (5.3)	5 (10.2)	
rs13117745, n (%)					<0.001
CC	162 (69.8)	261 (88.2)	47 (62.7)	41 (83.7)	
CT	62 (26.7)	32 (10.8)	27 (36.0)	8 (16.3)	
TT	8 (3.4)	3 (1.0)	1 (1.3)	0	
rs1599961, n (%)					0.054
GG	94 (40.5)	99 (33.4)	38 (50.7)	12 (24.5)	
GA	104 (44.8)	147 (49.7)	29 (38.7)	27 (55.1)	
AA	34 (14.7)	50 (16.9)	8 (10.7)	10 (20.4)	
rs1609798, n (%)					0.004
CC	111 (47.8)	105 (35.5)	44 (58.7)	24 (49.0)	
CT	94 (40.5)	139 (47.0)	23 (30.7)	21 (42.9)	
TT	27 (11.6)	52 (17.6)	8 (10.7)	4 (8.2)	
rs230511, n (%)					<0.001
GG	105 (45.3)	91 (30.7)	43 (57.3)	24 (49.0)	
GA	100 (43.1)	149 (50.3)	29 (38.7)	20 (40.8)	
AA	27 (11.6)	56 (18.9)	3 (4.0)	5 (10.2)	
rs230547, n (%)					<0.001
CC	191 (82.3)	168 (56.8)	53 (70.7)	34 (69.4)	
CT	38 (16.4)	108 (36.5)	18 (24.0)	14 (28.6)	
TT	3 (1.3)	20 (6.8)	4 (5.3)	1 (2.0)	
rs3774932, n (%)					0.128
GG	66 (28.4)	65 (22.0)	19 (25.3)	19 (38.8)	
GA	120 (51.7)	155 (52.4)	36 (48.0)	23 (46.9)	
AA	46 (19.8)	76 (25.7)	20 (26.7)	7 (14.3)	
rs3774934, n (%)					<0.001
GG	185 (79.7)	118 (39.9)	40 (53.3)	37 (75.5)	
GA	46 (19.8)	139 (47.0)	27 (36.0)	9 (18.4)	
AA	1 (0.4)	39 (13.2)	8 (10.7)	3 (6.1)	
rs3774956, n (%)					<0.001
CC	89 (38.4)	78 (26.4)	38 (50.7)	10 (20.4)	

CT	101 (43.5)	145 (49.0)	28 (37.3)	28 (57.1)	
TT	42 (18.1)	73 (24.7)	9 (12.0)	11 (22.4)	
rs3774968, n (%)					0.22
GG	74 (31.9)	92 (31.1)	19 (25.3)	22 (44.9)	
AG	115 (49.6)	144 (48.6)	35 (46.7)	21 (42.9)	
AA	43 (18.5)	60 (20.3)	21 (28.0)	6 (12.2)	
rs4648006, n (%)					<0.001
CC	214 (92.2)	266 (89.9)	66 (88.0)	39 (79.6)	
CT	18 (7.8)	30 (10.1)	9 (12.0)	8 (16.3)	
TT	0	0	0	2 (4.1)	
rs4648022, n (%)					<0.001
CC	189 (81.5)	296 (100.0)	63 (84.0)	48 (98.0)	
CT	40 (17.2)	0	12 (16.0)	1 (2.0)	
TT	3 (1.3)	0	0	0	
rs4648090, n (%)					<0.001
GG	167 (72.0)	293 (99.0)	63 (84.0)	44 (89.8)	
GA	62 (26.7)	3 (1.0)	12 (16.0)	5 (10.2)	
AA	3 (1.3)	0	0	0	
rs4648095, n (%)					0.138
TT	217 (93.5)	259 (87.5)	67 (89.3)	43 (87.8)	
TC	15 (6.4)	37 (12.5)	8 (10.7)	6 (12.2)	
CC	0	0	0	0	
rs4648110, n (%)					<0.001
TT	145 (62.5)	261 (88.2)	49 (65.3)	40 (81.6)	
TA	80 (34.5)	32 (10.8)	25 (33.3)	9 (18.4)	
AA	7 (3.0)	3 (1.0)	1 (1.3)	0	
rs4648127, n (%)					0.504
CC	206 (88.8)	261 (88.2)	62 (82.7)	47	
CT	24 (10.3)	33 (11.1)	12 (16.0)	2 (4.1)	
TT	2 (0.9)	2 (0.7)	1 (1.3)	0	
rs4698863, n (%)					0.002
CC	109 (47.0)	102 (34.5)	45 (60.0)	19 (38.8)	
CT	97 (41.8)	140 (47.3)	23 (30.7)	23 (46.9)	
TT	26 (11.2)	54 (18.2)	7 (9.3)	7 (14.3)	
rs7674640, n (%)					0.486
TT	63 (27.2)	77 (26.0)	14 (18.7)	13 (26.5)	
TC	121 (52.2)	145 (49.0)	37 (49.3)	26 (53.1)	
CC	48 (20.7)	74 (25.0)	24 (32.0)	10 (20.4)	

Values are unadjusted means \pm standard deviation for continuous variables unless otherwise indicated.

Associations between AOC1 SNPs and premenstrual symptoms

The associations between the 18 SNPs in *NFKB1* and premenstrual symptoms, stratified by ethnicity, are shown in Tables 2-4 and Supplementary Tables 1-15. Preliminary analyses revealed differences across ethnicities, so the three main ethnic groups, Caucasians, East Asians, and South Asians, were analyzed separately.

Caucasians

In the Caucasian cohort, the homozygous AA genotype was significantly associated with a reduced risk of food cravings across three SNPs, namely rs11722146 (OR: 0.32; 95% CI: 0.13, 0.81; $p = 0.015$), rs1599961 (OR: 0.37; 95% CI: 0.16, 0.84; $p = 0.017$), and rs230511 (OR: 0.27; 95% CI: 0.11, 0.66; $p = 0.004$), as detailed in Tables 2-4. Specifically, Caucasian individuals with the AA genotype at rs11722146 exhibited a 68% reduction in the risk of food cravings, those with the AA genotype at rs1599961 showed a 63% reduction, and those with the AA genotype at rs230511 demonstrated a 73% reduction in risk when compared to Caucasian individuals with GG or GA genotypes. Notably, heterozygous individuals did not exhibit a significantly increased risk for any of these SNPs, and no gene-dosage effects of the minor A allele were detected. Additionally, these associations between the three SNPs and food-craving related phenotypes were not observed in the East Asian or South Asian populations.

East Asians

In the East Asian cohort, a significant association was identified between the homozygous AA genotype and an elevated risk of mood swings for the SNPs rs11722146 (OR: 2.57; 95% CI: 1.07, 6.17; $p = 0.035$) and rs230511 (OR: 2.76; 95% CI: 1.14, 6.67; $p = 0.023$), as outlined in Tables 3 and 4. These findings indicate that individuals of East Asian descent carrying the AA genotype at rs11722146 and rs230511 are nearly three times more likely to experience mood swings compared to those with GG or GA genotypes. Notably, the heterozygous GA genotype did not confer a significantly increased risk for mood swings, and no evidence of additive effects related to the minor A allele was observed. Furthermore, these genotype-phenotype associations were not replicated in the Caucasian or South Asian cohorts.

South Asians

In the South Asian cohort, the same AA genotype for the SNPs rs11722146 and rs230511 were found to be associated with a decreased risk of menstrual cramps. South Asian individuals with the AA genotype at rs11722146 showed a 92% reduced risk of menstrual cramps (OR: 0.08; 95% CI: 0.01, 0.93; $p = 0.040$), while individuals with the AA genotype at rs230511 showed a 95% reduced risk of menstrual cramps (OR: 0.05; 95% CI: 0.00, 0.80; $p = 0.031$), seen in Tables 3 and 4, as compared to their GG or GA South Asian counterparts. However, no evidence of additive effects related to the minor A allele was observed, and these associations between the AA genotype and the menstrual cramp phenotype were not seen in the Caucasian or East Asian cohorts

Table 2: Associations between rs1599961 and premenstrual symptoms stratified by ethnicity.

PMSx	rs1599961 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.41 (0.77, 2.57)	0.26	147 (49.7)	0.70 (0.41, 1.20)	0.19	29 (38.7)	1.84 (0.64, 5.25)	0.25
	AA	34 (14.7)	1.07 (0.46, 2.45)	0.88	50 (16.9)	0.59 (0.29, 1.18)	0.14	8 (10.7)	1.96 (0.37, 10.39)	0.42
Desire to be alone	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	0.70 (0.38, 1.27)	0.23	147 (49.7)	0.47 (0.27, 0.81)	0.007 **	29 (38.7)	1.39 (0.51, 3.79)	0.52
	AA	34 (14.7)	0.53 (0.22, 1.28)	0.16	50 (16.9)	0.80 (0.39, 1.61)	0.53	8 (10.7)	1.02 (0.20, 5.19)	0.98
Anxiety/ tension/ nervousness	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.03 (0.57, 1.85)	0.93	147 (49.7)	1.00 (0.59, 1.69)	0.99	29 (38.7)	2.64 (0.91, 7.68)	0.07
	AA	34 (14.7)	0.95 (0.41, 2.20)	0.91	50 (16.9)	1.09 (0.54, 2.20)	0.81	8 (10.7)	1.16 (0.19, 7.15)	0.87
Increased appetite/ food cravings	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	0.83 (0.45, 1.53)	0.55	147 (49.7)	0.96 (0.56, 1.64)	0.89	29 (38.7)	0.89 (0.31, 2.54)	0.82
	AA	34 (14.7)	0.37 (0.16, 0.84)	0.0168*	50 (16.9)	0.96 (0.47, 1.94)	0.91	8 (10.7)	0.56 (0.11, 2.86)	0.48
Bloating/ swelling/ breast tenderness	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.33 (0.65, 2.70)	0.43	147 (49.7)	1.42 (0.81, 2.49)	0.22	29 (38.7)	1.43 (0.46, 4.46)	0.53
	AA	34 (14.7)	0.66 (0.27, 1.63)	0.37	50 (16.9)	0.78 (0.38, 1.57)	0.48	8 (10.7)	0.20 (0.04, 1.13)	0.06
Clumsiness	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.07 (0.46, 2.47)	0.88	147 (49.7)	1.19 (0.60, 2.36)	0.61	29 (38.7)	0.62 (0.13, 2.95)	0.54
	AA	34 (14.7)	1.19 (0.37, 3.81)	0.76	50 (16.9)	0.71 (0.26, 1.95)	0.50	8 (10.7)	0.90 (0.08, 10.60)	0.93
Confusion/ difficulty concentrating/ forgetfulness	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.70 (0.79, 3.67)	0.18	147 (49.7)	1.12 (0.63, 1.98)	0.71	29 (38.7)	1.07 (0.29, 3.92)	0.92
	AA	34 (14.7)	1.38 (0.46, 4.11)	0.56	50 (16.9)	0.94 (0.43, 2.05)	0.88	8 (10.7)	3.33 (0.48, 23.31)	0.22
Cramps	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.19 (0.53, 2.67)	0.68	147 (49.7)	0.61 (0.34, 1.09)	0.10	29 (38.7)	0.57 (0.13, 2.43)	0.44
	AA	34 (14.7)	0.64 (0.24, 1.75)	0.38	50 (16.9)	0.77 (0.36, 1.65)	0.49	8 (10.7)	0.21 (0.03, 1.38)	0.10
Depression	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.35 (0.73, 2.50)	0.34	147 (49.7)	1.05 (0.59, 1.85)	0.88	29 (38.7)	1.76 (0.58, 5.37)	0.31
	AA	34 (14.7)	0.96 (0.39, 2.37)	0.92	50 (16.9)	0.63 (0.28, 1.44)	0.27	8 (10.7)	2.37 (0.43, 13.13)	0.32
Fatigue	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	0.90 (0.51, 1.60)	0.73	147 (49.7)	0.74 (0.44, 1.24)	0.25	29 (38.7)	1.43 (0.50, 4.06)	0.50
	AA	34 (14.7)	0.78 (0.35, 1.75)	0.55	50 (16.9)	0.63 (0.31, 1.25)	0.18	8 (10.7)	0.37 (0.07, 1.99)	0.24
Headaches	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.21 (0.62, 2.33)	0.58	147 (49.7)	1.01 (0.55, 1.86)	0.98	29 (38.7)	1.64 (0.56, 4.79)	0.35
	AA	34 (14.7)	1.36 (0.55, 3.37)	0.50	50 (16.9)	0.72 (0.30, 1.70)	0.45	8 (10.7)	0.27 (0.03, 2.57)	0.27
Insomnia	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	0.97 (0.40, 2.33)	0.94	147 (49.7)	0.66 (0.30, 1.45)	0.30	29 (38.7)	1.87 (0.43, 8.22)	0.40
	AA	34 (14.7)	1.01 (0.29, 3.47)	0.99	50 (16.9)	0.38 (0.10, 1.42)	0.15	8 (10.7)	-	-
Mood swings/ crying easily / irritability/ angry outbursts	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	0.84 (0.43, 1.64)	0.61	147 (49.7)	1.22 (0.69, 2.16)	0.49	29 (38.7)	1.10 (0.34, 3.55)	0.87
	AA	34 (14.7)	0.67 (0.27, 1.65)	0.39	50 (16.9)	1.65 (0.74, 3.67)	0.22	8 (10.7)	0.56 (0.10, 3.02)	0.49
Nausea	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.53 (0.75, 3.12)	0.24	147 (49.7)	0.81 (0.37, 1.77)	0.59	29 (38.7)	0.62 (0.13, 2.91)	0.54
	AA	34 (14.7)	0.65 (0.20, 2.16)	0.48	50 (16.9)	0.13 (0.02, 1.07)	0.06	8 (10.7)	0.64 (0.06, 6.86)	0.71
Sexual desire/ activity change	GG	94 (40.5)	1	1	99 (33.4)	1	1	38 (50.7)	1	1
	GA	104 (44.8)	1.29 (0.73, 2.29)	0.38	147 (49.7)	1.02 (0.60, 1.73)	0.95	29 (38.7)	1.60 (0.59, 4.36)	0.35
	AA	34 (14.7)	0.74 (0.33, 1.66)	0.47	50 (16.9)	1.05 (0.52, 2.12)	0.89	8 (10.7)	0.55 (0.09, 3.24)	0.50

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom

Table 3: Associations between rs230511 and premenstrual symptoms stratified by ethnicity.

PMSx	rs230511 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.26 (0.70, 2.27)	0.44	149 (50.3)	0.70 (0.41, 1.21)	0.20	29 (38.7)	1.44 (0.52, 4.00)	0.48
	AA	27 (11.6)	1.13 (0.46, 2.78)	0.80	56 (18.9)	1.01 (0.50, 2.03)	0.98	3 (4.0)	1.29 (0.09, 18.77)	0.85
Desire to be alone	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.61 (0.34, 1.11)	0.11	149 (50.3)	0.65 (0.38, 1.14)	0.13	29 (38.7)	1.34 (0.50, 3.62)	0.56
	AA	27 (11.6)	0.62 (0.24, 1.57)	0.31	56 (18.9)	0.94 (0.47, 1.88)	0.86	3 (4.0)	0.78 (0.06, 10.37)	0.85
Anxiety/ tension/ nervousness	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.00 (0.56, 1.77)	0.99	149 (50.3)	1.01 (0.59, 1.74)	0.96	29 (38.7)	2.18 (0.76, 6.24)	0.14
	AA	27 (11.6)	0.83 (0.33, 2.05)	0.68	56 (18.9)	0.87 (0.43, 1.74)	0.69	3 (4.0)	1.81 (0.13, 25.19)	0.65
Increased appetite/ food cravings	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.74 (0.41, 1.34)	0.32	149 (50.3)	0.94 (0.55, 1.61)	0.82	29 (38.7)	0.69 (0.25, 1.89)	0.46
	AA	27 (11.6)	0.27 (0.11, 0.66)	0.00383 **	56 (18.9)	1.36 (0.67, 2.75)	0.39	3 (4.0)	1.31 (0.10, 17.93)	0.84
Bloating/ swelling/ breast tenderness	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.42 (0.70, 2.85)	0.33	149 (50.3)	1.13 (0.64, 1.98)	0.68	29 (38.7)	0.76 (0.26, 2.18)	0.60
	AA	27 (11.6)	0.69 (0.27, 1.80)	0.45	56 (18.9)	0.95 (0.47, 1.94)	0.89	3 (4.0)	0.51 (0.04, 7.31)	0.62
Clumsiness	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.95 (0.42, 2.14)	0.91	149 (50.3)	1.04 (0.52, 2.06)	0.92	29 (38.7)	0.65 (0.14, 3.06)	0.58
	AA	27 (11.6)	0.75 (0.19, 2.88)	0.67	56 (18.9)	0.69 (0.26, 1.80)	0.44	3 (4.0)	-	-
Confusion/ difficulty concentrating/ forgetfulness	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.50 (0.71, 3.15)	0.28	149 (50.3)	1.11 (0.62, 1.99)	0.73	29 (38.7)	1.51 (0.42, 5.41)	0.52
	AA	27 (11.6)	1.29 (0.41, 4.07)	0.66	56 (18.9)	0.97 (0.46, 2.07)	0.94	3 (4.0)	2.85 (0.17, 48.46)	0.46
Cramps	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.10 (0.49, 2.46)	0.81	149 (50.3)	0.58 (0.32, 1.05)	0.07	29 (38.7)	0.40 (0.10, 1.68)	0.20
	AA	27 (11.6)	0.51 (0.18, 1.44)	0.20	56 (18.9)	0.93 (0.43, 1.99)	0.84	3 (4.0)	0.05 (0.00, 0.80)	0.0311 *
Depression	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.99 (0.54, 1.81)	0.98	149 (50.3)	1.32 (0.72, 2.40)	0.37	29 (38.7)	1.83 (0.61, 5.48)	0.27
	AA	27 (11.6)	0.75 (0.28, 1.99)	0.56	56 (18.9)	1.03 (0.47, 2.24)	0.94	3 (4.0)	2.25 (0.16, 32.50)	0.54
Fatigue	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.18 (0.67, 2.07)	0.56	149 (50.3)	0.84 (0.50, 1.42)	0.52	29 (38.7)	0.79 (0.29, 2.16)	0.63
	AA	27 (11.6)	0.54 (0.22, 1.32)	0.18	56 (18.9)	1.05 (0.53, 2.06)	0.89	3 (4.0)	0.24 (0.02, 3.42)	0.29
Headaches	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.22 (0.64, 2.30)	0.54	149 (50.3)	1.15 (0.61, 2.18)	0.66	29 (38.7)	1.21 (0.42, 3.46)	0.72
	AA	27 (11.6)	0.86 (0.31, 2.42)	0.78	56 (18.9)	1.15 (0.51, 2.58)	0.73	3 (4.0)	-	-
Insomnia	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.96 (0.40, 2.30)	0.92	149 (50.3)	0.87 (0.38, 1.98)	0.74	29 (38.7)	1.19 (0.27, 5.14)	0.82
	AA	27 (11.6)	1.36 (0.40, 4.65)	0.62	56 (18.9)	0.75 (0.24, 2.30)	0.61	3 (4.0)	-	-
Mood swings/ crying easily/ irritability/ angry outbursts	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	0.74 (0.39, 1.42)	0.37	149 (50.3)	1.00 (0.56, 1.77)	1	29 (38.7)	1.40 (0.43, 4.52)	0.57
	AA	27 (11.6)	0.80 (0.30, 2.13)	0.65	56 (18.9)	2.76 (1.14, 6.67)	0.0234 *	3 (4.0)	0.69 (0.05, 9.49)	0.78
Nausea	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.16 (0.58, 2.32)	0.67	149 (50.3)	0.52 (0.23, 1.17)	0.11	29 (38.7)	0.34 (0.06, 1.94)	0.22
	AA	27 (11.6)	0.72 (0.22, 2.37)	0.58	56 (18.9)	0.31 (0.08, 1.14)	0.08	3 (4.0)	1.43 (0.10, 21.51)	0.79
Sexual desire/ activity change	GG	105 (45.3)	1	1	91 (30.7)	1	1	43 (57.3)	1	1
	GA	100 (43.1)	1.16 (0.66, 2.03)	0.61	149 (50.3)	0.77 (0.45, 1.32)	0.34	29 (38.7)	1.72 (0.64, 4.67)	0.28
	AA	27 (11.6)	0.78 (0.33, 1.84)	0.56	56 (18.9)	0.87 (0.44, 1.72)	0.68	3 (4.0)	0.83 (0.06, 11.06)	0.89

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom

Table 4: Associations between rs11722146 and premenstrual symptoms stratified by ethnicity.

PMSx	rs11722146 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.44 (0.80, 2.58)	0.23	146 (49.3)	0.77 (0.45, 1.31)	0.33	29 (38.7)	1.09 (0.39, 3.02)	0.87
	AA	24 (10.3)	1.22 (0.47, 3.12)	0.68	54 (18.2)	1.00 (0.50, 1.99)	0.99	4 (5.3)	2.22 (0.24, 20.80)	0.48
Desire to be alone	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	0.83 (0.46, 1.49)	0.53	146 (49.3)	0.62 (0.36, 1.08)	0.09	29 (38.7)	1.46 (0.54, 3.96)	0.45
	AA	24 (10.3)	1.04 (0.41, 2.66)	0.93	54 (18.2)	0.99 (0.49, 1.98)	0.97	4 (5.3)	1.71 (0.20, 14.76)	0.62
Anxiety/ tension/ nervousness	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	0.95 (0.54, 1.69)	0.87	146 (49.3)	1.04 (0.61, 1.77)	0.89	29 (38.7)	1.80 (0.63, 5.16)	0.27
	AA	24 (10.3)	0.78 (0.30, 2.01)	0.60	54 (18.2)	0.78 (0.38, 1.57)	0.48	4 (5.3)	3.48 (0.39, 31.46)	0.26
Increased appetite/ food cravings	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	0.90 (0.50, 1.61)	0.71	146 (49.3)	0.86 (0.51, 1.47)	0.59	29 (38.7)	0.52 (0.19, 1.46)	0.21
	AA	24 (10.3)	0.32 (0.13, 0.81)	0.015*	54 (18.2)	1.32 (0.65, 2.70)	0.44	4 (5.3)	2.03 (0.17, 23.95)	0.57
Bloating/ swelling/ breast tenderness	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.24 (0.62, 2.48)	0.54	146 (49.3)	0.98 (0.56, 1.72)	0.95	29 (38.7)	0.83 (0.29, 2.37)	0.72
	AA	24 (10.3)	0.67 (0.25, 1.83)	0.43	54 (18.2)	0.90 (0.44, 1.85)	0.78	4 (5.3)	0.94 (0.08, 11.23)	0.96
Clumsiness	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.27 (0.57, 2.82)	0.56	146 (49.3)	1.00 (0.50, 1.96)	0.99	29 (38.7)	0.40 (0.07, 2.30)	0.30
	AA	24 (10.3)	0.57 (0.12, 2.80)	0.49	54 (18.2)	0.70 (0.27, 1.83)	0.47	4 (5.3)	3.10 (0.20, 48.14)	0.41
Confusion/ difficulty concentrating/ forgetfulness	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.63 (0.78, 3.40)	0.19	146 (49.3)	0.98 (0.55, 1.74)	0.95	29 (38.7)	1.22 (0.33, 4.53)	0.76
	AA	24 (10.3)	1.11 (0.32, 3.81)	0.87	54 (18.2)	0.85 (0.40, 1.82)	0.68	4 (5.3)	6.97 (0.63, 77.80)	0.11
Cramps	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.30 (0.59, 2.88)	0.52	146 (49.3)	0.58 (0.32, 1.03)	0.06	29 (38.7)	0.25 (0.06, 1.11)	0.06
	AA	24 (10.3)	0.57 (0.19, 1.68)	0.30	54 (18.2)	0.86 (0.40, 1.84)	0.69	4 (5.3)	0.08 (0.01, 0.93)	0.04*
Depression	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.23 (0.67, 2.23)	0.50	146 (49.3)	1.33 (0.73, 2.41)	0.35	29 (38.7)	1.46 (0.48, 4.40)	0.50
	AA	24 (10.3)	0.74 (0.26, 2.08)	0.56	54 (18.2)	1.11 (0.51, 2.40)	0.80	4 (5.3)	4.66 (0.49, 44.02)	0.17
Fatigue	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	0.98 (0.56, 1.71)	0.94	146 (49.3)	0.88 (0.52, 1.49)	0.64	29 (38.7)	0.62 (0.23, 1.70)	0.34
	AA	24 (10.3)	0.32 (0.12, 0.86)	0.02*	54 (18.2)	1.10 (0.56, 2.15)	0.79	4 (5.3)	0.57 (0.06, 5.10)	0.61
Headaches	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.21 (0.64, 2.26)	0.56	146 (49.3)	1.27 (0.67, 2.40)	0.45	29 (38.7)	0.88 (0.30, 2.57)	0.82
	AA	24 (10.3)	0.55 (0.17, 1.79)	0.32	54 (18.2)	1.28 (0.57, 2.88)	0.54	4 (5.3)	0.95 (0.08, 11.18)	0.97
Insomnia	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.09 (0.46, 2.58)	0.84	146 (49.3)	0.93 (0.41, 2.13)	0.87	29 (38.7)	1.13 (0.26, 4.83)	0.87
	AA	24 (10.3)	1.15 (0.29, 4.48)	0.84	54 (18.2)	0.81 (0.26, 2.50)	0.71	4 (5.3)	-	-
Mood swings/ crying easily / irritability/ angry outbursts	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	0.70 (0.37, 1.33)	0.27	146 (49.3)	0.96 (0.55, 1.70)	0.90	29 (38.7)	1.53 (0.47, 4.92)	0.47
	AA	24 (10.3)	0.64 (0.24, 1.75)	0.38	54 (18.2)	2.57 (1.07, 6.17)	0.0347 *	4 (5.3)	0.96 (0.08, 11.59)	0.98
Nausea	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.35 (0.67, 2.72)	0.40	146 (49.3)	0.57 (0.25, 1.27)	0.17	29 (38.7)	0.35 (0.06, 1.98)	0.23
	AA	24 (10.3)	1.17 (0.38, 3.62)	0.78	54 (18.2)	0.34 (0.09, 1.26)	0.11	4 (5.3)	1.02 (0.08, 13.38)	0.99
Sexual desire/ activity change	GG	109 (47.0)	1	1	96 (32.4)	1	1	42 (56.0)	1	1
	GA	99 (42.7)	1.30 (0.75, 2.28)	0.35	146 (49.3)	0.77 (0.45, 1.30)	0.32	29 (38.7)	1.47 (0.54, 3.98)	0.44
	AA	24 (10.3)	1.09 (0.44, 2.68)	0.85	54 (18.2)	0.94 (0.47, 1.86)	0.85	4 (5.3)	1.66 (0.19, 14.31)	0.64

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom

Discussions

Considering the high prevalence of premenstrual symptoms (PMSx) among premenopausal women and the current paucity of effective treatments, it is imperative to investigate the underlying genetic and neurological mechanisms to enhance our understanding and develop targeted interventions. The findings of this study underscore the existence of ethnic-specific susceptibilities to PMSx, linked to variations in specific polymorphisms. Moreover, the study highlights that these genetic variations are associated with both somatic and psychological manifestations of premenstrual symptoms, emphasizing the multifaceted nature of PMSx and the importance of a nuanced approach to its study and management.

Linkage disequilibrium analysis demonstrated that the SNPs rs11722146 and rs230511 exhibit strong linkage disequilibrium within the East Asian cohort ($D' = 0.972$; $R^2 = 0.921$). These values indicate a substantial non-random association between the alleles at these loci, suggesting that these SNPs are likely co-inherited, even though they are not in close physical proximity on the gene and are separated by other *NFKB1* SNPs. The strong linkage disequilibrium between these two SNPs may provide insight into their shared association with mood swings within this population, as the presence of one SNP is likely predictive of the other, thereby contributing to the manifestation of the same symptomatology in individuals carrying these genotypes.

We can conclude that variation in *NFKB1* genotypes impacts some premenstrual symptoms, suggesting that endogenous levels of inflammation may be important. The findings of this study indicate that genetic variation in the *NFKB1* gene is linked to both somatic and psychological premenstrual symptoms, including food cravings, mood swings, and menstrual cramps, among healthy premenopausal women.

Strikingly, the nature of these associations differed markedly between ethnic groups. Caucasians with the minor homozygous genotype at three SNPs (rs1599961, rs11722146, and rs230511) exhibited a significantly lower risk of food cravings. In contrast, East Asians with the minor homozygous genotype for rs11722146 and rs230511 showed an increased risk of mood swings. Meanwhile, South Asians carrying the same minor homozygous genotype for rs11722146 and

rs230511 demonstrated a reduced risk of menstrual cramps. It is noteworthy that the same two SNPs, rs11722146 and rs230511, emerged as critical genetic determinants across all ethnic cohorts studied. This consistent involvement of these SNPs across diverse populations suggests that they may play a central role in the genetic architecture of premenstrual symptoms. These findings imply that while the *NFKBI* gene may be a critical locus for PMSx susceptibility, the specific outcomes are likely modulated by ethnic-specific factors, such as differences in diet, hormonal regulation, or cultural practices that impact stress and inflammation.

This study was the first to investigate the associations between *NFKBI* genotypes and premenstrual symptoms and increases the knowledge on genetic variation and susceptibility to premenstrual symptoms in different ethnic groups. Despite the novel contributions of this study, several limitations must be acknowledged. The cross-sectional design inherently restricts causal inferences, and the retrospective data collection may have introduced recall bias, potentially overestimating symptom prevalence. Furthermore, the limited genetic variability in some polymorphisms, particularly within certain ethnic subgroups, constrained my ability to perform robust logistic regression analyses for all the SNPs .

Potential Impact and Further Directions for Research

By identifying specific genetic markers linked to the severity of PMS, this study could revolutionize the approach to diagnosing and treating PMS, paving the way for personalized, precision-based therapies. Targeted anti-inflammatory treatments, informed by an individual's genetic profile, could significantly enhance treatment efficacy while minimizing unnecessary side effects. This raises the possibility that personalized medical approaches, tailored to an individual's genetic and ethnic background, could be more effective in managing PMSx. The findings also suggest a need for further research into elucidating a genetic mechanism which might help explain why some women are more susceptible to PMSx and can aid them by providing better personalized recommendations for those who experience these symptoms, keeping in mind ethnic background and genetic differences. It also emphasizes the need for continual research in this field to help women manage these symptoms with personalized approaches.

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Supplementary Tables

Supplementary Table 1: Associations between rs13117745 and premenstrual symptoms stratified by ethnicity.

PMSx	rs13117745 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.87 (0.46, 1.63)	0.66	32 (10.8)	1.89 (0.84, 4.28)	0.12	27 (36.0)	1.97 (0.69, 5.58)	0.20
	TT	8 (3.4)	0.84 (0.19, 3.73)	0.81	3 (1.0)	1.70 (0.15, 19.62)	0.67	1 (1.3)	-	-
Desire to be alone	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.87 (0.45, 1.65)	0.66	32 (10.8)	0.84 (0.38, 1.86)	0.66	27 (36.0)	2.83 (1.01, 7.91)	0.04 *
	TT	8 (3.4)	0.94 (0.21, 4.23)	0.93	3 (1.0)	4.34 (0.37, 50.89)	0.24	1 (1.3)	-	-
Anxiety/ tension/ nervousness	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.75 (0.39, 1.42)	0.37	32 (10.8)	0.57 (0.25, 1.30)	0.18	27 (36.0)	1.06 (0.37, 3.02)	0.92
	TT	8 (3.4)	2.29 (0.52, 10.17)	0.27	3 (1.0)	0.76 (0.07, 8.79)	0.83	1 (1.3)	-	-
Increased appetite/ food cravings	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.72 (0.89, 3.30)	0.10	32 (10.8)	0.80 (0.38, 1.70)	0.56	27 (36.0)	1.97 (0.67, 5.77)	0.21
	TT	8 (3.4)	4.33 (0.51, 36.86)	0.18	3 (1.0)	1.43 (0.13, 16.30)	0.77	1 (1.3)	-	-
Bloating/ swelling/ breast tenderness	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.04 (0.50, 2.17)	0.91	32 (10.8)	0.86 (0.39, 1.88)	0.70	27 (36.0)	0.58 (0.20, 1.65)	0.30
	TT	8 (3.4)	0.75 (0.14, 3.99)	0.73	3 (1.0)	0.95 (0.08, 10.77)	0.97	1 (1.3)	-	-
Clumsiness	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.42 (0.14, 1.28)	0.12	32 (10.8)	1.45 (0.59, 3.61)	0.42	27 (36.0)	1.18 (0.26, 5.31)	0.82
	TT	8 (3.4)	1.43 (0.26, 7.81)	0.68	3 (1.0)	2.71 (0.23, 31.86)	0.43	1 (1.3)	-	-
Confusion/ difficulty concentrating/ forgetfulness	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.20 (0.06, 0.69)	0.01*	32 (10.8)	0.71 (0.29, 1.73)	0.46	27 (36.0)	2.14 (0.60, 7.66)	0.24
	TT	8 (3.4)	1.72 (0.37, 7.96)	0.48	3 (1.0)	4.65 (0.41, 52.75)	0.21	1 (1.3)	-	-
Cramps	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.21 (0.52, 2.83)	0.65	32 (10.8)	1.67 (0.69, 4.06)	0.26	27 (36.0)	0.75 (0.20, 2.81)	0.66
	TT	8 (3.4)	1.12 (0.13, 9.97)	0.92	3 (1.0)	0.92 (0.08, 10.47)	0.95	1 (1.3)	-	-
Depression	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.99 (0.51, 1.92)	0.97	32 (10.8)	1.41 (0.64, 3.09)	0.39	27 (36.0)	2.56 (0.85, 7.71)	0.09
	TT	8 (3.4)	1.00 (0.22, 4.49)	1	3 (1.0)	-	-	1 (1.3)	-	-
Fatigue	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.80 (0.44, 1.47)	0.48	32 (10.8)	0.85 (0.41, 1.78)	0.67	27 (36.0)	0.75 (0.27, 2.05)	0.57
	TT	8 (3.4)	0.70 (0.16, 2.96)	0.62	3 (1.0)	1.61 (0.14, 18.22)	0.70	1 (1.3)	-	-
Headaches	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.49 (0.23, 1.07)	0.07	32 (10.8)	0.46 (0.16, 1.39)	0.17	27 (36.0)	1.53 (0.52, 4.50)	0.43
	TT	8 (3.4)	2.34 (0.54, 10.26)	0.26	3 (1.0)	-	-	1 (1.3)	-	-
Insomnia	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	0.79 (0.30, 2.12)	0.64	32 (10.8)	0.24 (0.03, 1.81)	0.16	27 (36.0)	2.29 (0.52, 10.05)	0.27
	TT	8 (3.4)	0.94 (0.11, 8.27)	0.95	3 (1.0)	-	-	1 (1.3)	-	-
Mood swings/ crying easily/ irritability/ angry outbursts	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.82 (0.86, 3.85)	0.12	32 (10.8)	1.69 (0.66, 4.32)	0.27	27 (36.0)	0.87 (0.27, 2.77)	0.81
	TT	8 (3.4)	1.03 (0.19, 5.43)	0.98	3 (1.0)	0.90 (0.08, 10.55)	0.93	1 (1.3)	-	-
Nausea	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.05 (0.49, 2.22)	0.91	32 (10.8)	0.89 (0.25, 3.15)	0.86	27 (36.0)	0.39 (0.07, 2.18)	0.28
	TT	8 (3.4)	-	-	3 (1.0)	-	-	1 (1.3)	-	-
Sexual desire/ activity change	CC	162 (69.8)	1	1	261 (88.2)	1	1	47 (62.7)	1	1
	CT	62 (26.7)	1.45 (0.79, 2.68)	0.23	32 (10.8)	0.97 (0.45, 2.06)	0.93	27 (36.0)	1.04 (0.38, 2.84)	0.94
	TT	8 (3.4)	0.92 (0.22, 3.97)	0.92	3 (1.0)	0.79 (0.07, 9.03)	0.85	1 (1.3)	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom, or in the case of the South Asian cohort, there were not enough individuals with the minor TT genotype to run a logistic regression.

Supplementary Table 2: Associations between rs1609798 and premenstrual symptoms stratified by ethnicity.

PMSx	rs1609798 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.61 (0.89, 2.93)	0.12	139 (47.0)	0.82 (0.49, 1.38)	0.45	23 (30.7)	0.84 (0.28, 2.54)	0.76
	TT	27 (11.6)	1.26 (0.51, 3.07)	0.62	52 (17.6)	1.15 (0.57, 2.30)	0.70	8 (10.7)	2.90 (0.54, 15.46)	0.20
Desire to be alone	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	0.85 (0.47, 1.54)	0.59	139 (47.0)	0.67 (0.39, 1.15)	0.14	23 (30.7)	2.00 (0.68, 5.87)	0.2
	TT	27 (11.6)	0.86 (0.35, 2.14)	0.75	52 (17.6)	1.10 (0.55, 2.18)	0.79	8 (10.7)	3.49 (0.69, 17.80)	0.13
Anxiety/ tension/ nervousness	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.02 (0.58, 1.82)	0.93	139 (47.0)	0.83 (0.49, 1.39)	0.47	23 (30.7)	2.14 (0.71, 6.46)	0.17
	TT	27 (11.6)	0.82 (0.33, 2.02)	0.66	52 (17.6)	0.66 (0.32, 1.32)	0.24	8 (10.7)	0.94 (0.16, 5.71)	0.95
Increased appetite/ food cravings	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.05 (0.58, 1.91)	0.87	139 (47.0)	0.91 (0.54, 1.53)	0.71	23 (30.7)	0.92 (0.31, 2.75)	0.88
	TT	27 (11.6)	0.33 (0.14, 0.78)	0.01 *	52 (17.6)	1.24 (0.61, 2.50)	0.55	8 (10.7)	0.64 (0.13, 3.12)	0.57
Bloating/ swelling/ breast tenderness	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.29 (0.65, 2.60)	0.47	139 (47.0)	1.10 (0.63, 1.90)	0.74	23 (30.7)	1.33 (0.41, 4.34)	0.63
	TT	27 (11.6)	0.81 (0.31, 2.16)	0.68	52 (17.6)	0.89 (0.44, 1.81)	0.75	8 (10.7)	0.35 (0.07, 1.79)	0.2
Clumsiness	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.36 (0.61, 3.04)	0.44	139 (47.0)	0.93 (0.48, 1.82)	0.84	23 (30.7)	0.58 (0.10, 3.39)	0.53
	TT	27 (11.6)	0.53 (0.11, 2.54)	0.42	52 (17.6)	0.71 (0.27, 1.82)	0.47	8 (10.7)	0.82 (0.07, 9.18)	0.87
Confusion/ difficulty concentrating/ forgetfulness	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.74 (0.83, 3.63)	0.14	139 (47.0)	0.78 (0.45, 1.37)	0.39	23 (30.7)	1.88 (0.44, 7.97)	0.38
	TT	27 (11.6)	0.99 (0.29, 3.36)	0.99	52 (17.6)	0.64 (0.29, 1.37)	0.25	8 (10.7)	6.36 (0.99, 40.88)	0.047 *
Cramps	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.35 (0.60, 3.01)	0.46	139 (47.0)	0.71 (0.41, 1.25)	0.24	23 (30.7)	0.67 (0.15, 2.90)	0.58
	TT	27 (11.6)	0.71 (0.25, 2.04)	0.52	52 (17.6)	0.92 (0.44, 1.94)	0.82	8 (10.7)	0.21 (0.03, 1.31)	0.090 .
Depression	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.02 (0.56, 1.88)	0.94	139 (47.0)	1.13 (0.63, 2.01)	0.68	23 (30.7)	1.57 (0.47, 5.17)	0.45
	TT	27 (11.6)	0.91 (0.36, 2.34)	0.85	52 (17.6)	1.05 (0.49, 2.23)	0.91	8 (10.7)	4.12 (0.78, 21.84)	0.090 .
Fatigue	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	0.87 (0.50, 1.53)	0.63	139 (47.0)	0.93 (0.56, 1.56)	0.79	23 (30.7)	0.89 (0.30, 2.61)	0.83
	TT	27 (11.6)	0.39 (0.16, 0.95)	0.04 *	52 (17.6)	1.16 (0.59, 2.28)	0.67	8 (10.7)	0.70 (0.14, 3.45)	0.66
Headaches	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.31 (0.69, 2.47)	0.40	139 (47.0)	1.12 (0.60, 2.07)	0.73	23 (30.7)	0.87 (0.28, 2.72)	0.8
	TT	27 (11.6)	0.66 (0.22, 1.95)	0.45	52 (17.6)	1.27 (0.58, 2.81)	0.55	8 (10.7)	0.82 (0.13, 4.93)	0.82
Insomnia	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	0.96 (0.40, 2.29)	0.93	139 (47.0)	0.91 (0.41, 2.07)	0.83	23 (30.7)	1.08 (0.22, 5.24)	0.92
	TT	27 (11.6)	0.93 (0.24, 3.57)	0.92	52 (17.6)	0.83 (0.27, 2.51)	0.74	8 (10.7)	1.23 (0.11, 13.68)	0.86
Mood swings/ crying easily / irritability/ angry outbursts	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	0.63 (0.33, 1.21)	0.17	139 (47.0)	1.01 (0.58, 1.77)	0.96	23 (30.7)	1.46 (0.42, 5.05)	0.54
	TT	27 (11.6)	0.74 (0.28, 1.97)	0.54	52 (17.6)	2.42 (1.02, 5.78)	0.0448*	8 (10.7)	2.54 (0.26, 24.66)	0.41
Nausea	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.25 (0.62, 2.54)	0.53	139 (47.0)	0.47 (0.21, 1.07)	0.07	23 (30.7)	0.50 (0.09, 2.88)	0.43
	TT	27 (11.6)	1.29 (0.45, 3.69)	0.64	52 (17.6)	0.34 (0.09, 1.22)	0.10	8 (10.7)	0.57 (0.06, 5.93)	0.63
Sexual desire/ activity change	CC	111 (47.8)	1	1	105 (35.5)	1	1	44 (58.7)	1	1
	CT	94 (40.5)	1.35 (0.77, 2.37)	0.3	139 (47.0)	0.72 (0.43, 1.22)	0.22	23 (30.7)	1.62 (0.56, 4.70)	0.36
	TT	27 (11.6)	1.15 (0.49, 2.72)	0.75	52 (17.6)	0.81 (0.41, 1.60)	0.54	8 (10.7)	0.97 (0.19, 4.86)	0.97

Models were adjusted for age, BMI, and PAL.

Supplementary Table 3: Associations between rs230547 and premenstrual symptoms stratified by ethnicity.

PMSx	rs230547 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.25 (0.58, 2.72)	0.57	108 (36.5)	1.08 (0.66, 1.78)	0.76	18 (24.0)	0.71 (0.23, 2.25)	0.55
	TT	3 (1.3)	0.23 (0.02, 2.66)	0.24	20 (6.8)	1.99 (0.71, 5.60)	0.19	4 (5.3)	1.11 (0.11, 11.36)	0.93
Desire to be alone	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.10 (0.52, 2.35)	0.80	108 (36.5)	0.94 (0.56, 1.59)	0.83	18 (24.0)	0.47 (0.14, 1.55)	0.21
	TT	3 (1.3)	-	-	20 (6.8)	3.60 (1.34, 9.70)	0.01*	4 (5.3)	0.43 (0.04, 4.86)	0.49
Anxiety/ tension/ nervousness	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.37 (0.66, 2.83)	0.40	108 (36.5)	0.96 (0.58, 1.59)	0.88	18 (24.0)	0.32 (0.08, 1.28)	0.10
	TT	3 (1.3)	-	-	20 (6.8)	1.34 (0.52, 3.46)	0.55	4 (5.3)	0.59 (0.05, 6.72)	0.66
Increased appetite/ food cravings	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	2.27 (0.97, 5.29)	0.06	108 (36.5)	0.86 (0.52, 1.42)	0.55	18 (24.0)	0.69 (0.22, 2.17)	0.52
	TT	3 (1.3)	0.24 (0.02, 2.87)	0.26	20 (6.8)	1.37 (0.50, 3.72)	0.54	4 (5.3)	1.55 (0.13, 17.98)	0.72
Bloating/ swelling/ breast tenderness	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.63 (0.63, 4.23)	0.31	108 (36.5)	0.70 (0.42, 1.18)	0.18	18 (24.0)	1.26 (0.36, 4.38)	0.71
	TT	3 (1.3)	0.45 (0.04, 5.44)	0.53	20 (6.8)	1.79 (0.56, 5.70)	0.33	4 (5.3)	0.10 (0.01, 1.37)	0.08
Clumsiness	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.48 (0.54, 4.05)	0.44	108 (36.5)	1.21 (0.63, 2.30)	0.57	18 (24.0)	1.46 (0.30, 7.02)	0.63
	TT	3 (1.3)	-	-	20 (6.8)	1.48 (0.45, 4.88)	0.52	4 (5.3)	-	-
Confusion/ difficulty concentrating/ forgetfulness	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.52 (0.62, 3.76)	0.36	108 (36.5)	1.00 (0.58, 1.72)	0.99	18 (24.0)	0.62 (0.13, 2.93)	0.54
	TT	3 (1.3)	-	-	20 (6.8)	1.38 (0.51, 3.71)	0.53	4 (5.3)	2.42 (0.16, 36.16)	0.52
Cramps	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	0.75 (0.30, 1.91)	0.55	108 (36.5)	1.11 (0.65, 1.88)	0.71	18 (24.0)	4.55 (0.48, 42.75)	0.18
	TT	3 (1.3)	-	-	20 (6.8)	2.23 (0.69, 7.17)	0.18	4 (5.3)	0.81 (0.07, 9.84)	0.87
Depression	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.33 (0.62, 2.85)	0.46	108 (36.5)	1.11 (0.64, 1.94)	0.70	18 (24.0)	0.21 (0.04, 1.09)	0.06
	TT	3 (1.3)	0.82 (0.07, 9.94)	0.88	20 (6.8)	1.57 (0.58, 4.24)	0.38	4 (5.3)	0.64 (0.05, 7.51)	0.72
Fatigue	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.65 (0.80, 3.42)	0.17	108 (36.5)	0.77 (0.47, 1.26)	0.3	18 (24.0)	0.48 (0.15, 1.49)	0.2
	TT	3 (1.3)	-	-	20 (6.8)	0.93 (0.36, 2.39)	0.88	4 (5.3)	1.25 (0.11, 14.58)	0.86
Headaches	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	0.81 (0.34, 1.92)	0.63	108 (36.5)	1.16 (0.65, 2.07)	0.63	18 (24.0)	1.96 (0.60, 6.41)	0.26
	TT	3 (1.3)	1.25 (0.10, 14.98)	0.86	20 (6.8)	1.23 (0.41, 3.67)	0.71	4 (5.3)	-	-
Insomnia	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	1.23 (0.43, 3.55)	0.70	108 (36.5)	0.85 (0.37, 1.96)	0.7	18 (24.0)	0.28 (0.03, 2.97)	0.28
	TT	3 (1.3)	-	-	20 (6.8)	3.59 (1.11, 11.59)	0.03*	4 (5.3)	1.99 (0.15, 27.05)	0.6
Mood swings/ crying easily / irritability/ angry outbursts	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	2.06 (0.80, 5.29)	0.13	108 (36.5)	0.65 (0.38, 1.13)	0.12	18 (24.0)	0.62 (0.18, 2.14)	0.45
	TT	3 (1.3)	-	-	20 (6.8)	0.81 (0.28, 2.29)	0.68	4 (5.3)	1.36 (0.11, 16.46)	0.81
Nausea	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	0.60 (0.21, 1.67)	0.33	108 (36.5)	1.38 (0.62, 3.05)	0.42	18 (24.0)	3.05 (0.66, 14.06)	0.15
	TT	3 (1.3)	2.42 (0.20, 29.04)	0.48	20 (6.8)	1.16 (0.24, 5.58)	0.85	4 (5.3)	-	-
Sexual desire/ activity change	CC	191 (82.3)	1	1	168 (56.8)	1	1	53 (70.7)	1	1
	CT	38 (16.4)	0.96 (0.47, 1.96)	0.91	108 (36.5)	1.12 (0.68, 1.85)	0.66	18 (24.0)	0.62 (0.20, 1.98)	0.42
	TT	3 (1.3)	0.38 (0.03, 4.48)	0.44	20 (6.8)	1.63 (0.63, 4.21)	0.31	4 (5.3)	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom.

Supplementary Table 4: Associations between rs3774932 and premenstrual symptoms stratified by ethnicity.

PMSx	rs3774932 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.36 (0.71, 2.59)	0.35	155 (52.4)	1.25 (0.69, 2.25)	0.47	36 (48.0)	0.55 (0.16, 1.87)	0.33
	AA	46 (19.8)	0.91 (0.41, 2.00)	0.81	76 (25.7)	1.33 (0.67, 2.62)	0.41	20 (26.7)	0.30 (0.07, 1.18)	0.08
Desire to be alone	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.69 (0.85, 3.34)	0.13	155 (52.4)	0.57 (0.30, 1.06)	0.07	36 (48.0)	0.37 (0.11, 1.19)	0.09
	AA	46 (19.8)	2.13 (0.93, 4.88)	0.07	76 (25.7)	1.39 (0.70, 2.75)	0.35	20 (26.7)	0.39 (0.10, 1.49)	0.16
Anxiety/ tension/ nervousness	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.16 (0.61, 2.19)	0.65	155 (52.4)	0.92 (0.50, 1.69)	0.79	36 (48.0)	0.49 (0.15, 1.66)	0.25
	AA	46 (19.8)	1.06 (0.48, 2.36)	0.88	76 (25.7)	1.16 (0.58, 2.29)	0.68	20 (26.7)	0.56 (0.14, 2.18)	0.39
Increased appetite/ food cravings	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	2.16 (1.14, 4.11)	0.018 *	155 (52.4)	0.86 (0.47, 1.57)	0.61	36 (48.0)	0.92 (0.28, 3.08)	0.90
	AA	46 (19.8)	1.03 (0.48, 2.22)	0.95	76 (25.7)	1.10 (0.55, 2.20)	0.79	20 (26.7)	0.76 (0.20, 2.92)	0.68
Bloating/ swelling/ breast tenderness	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.67 (0.80, 3.48)	0.17	155 (52.4)	1.66 (0.90, 3.09)	0.11	36 (48.0)	2.94 (0.84, 10.29)	0.09
	AA	46 (19.8)	1.15 (0.47, 2.79)	0.76	76 (25.7)	1.21 (0.61, 2.43)	0.58	20 (26.7)	3.17 (0.77, 13.06)	0.10
Clumsiness	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	0.84 (0.33, 2.09)	0.70	155 (52.4)	0.82 (0.38, 1.76)	0.60	36 (48.0)	0.35 (0.05, 2.38)	0.27
	AA	46 (19.8)	1.33 (0.46, 3.87)	0.6	76 (25.7)	0.92 (0.38, 2.19)	0.84	20 (26.7)	1.19 (0.20, 7.18)	0.85
Confusion/ difficulty concentrating/ forgetfulness	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.39 (0.61, 3.19)	0.43	155 (52.4)	0.90 (0.47, 1.73)	0.76	36 (48.0)	0.26 (0.06, 1.13)	0.07
	AA	46 (19.8)	0.99 (0.34, 2.92)	0.99	76 (25.7)	0.98 (0.47, 2.04)	0.96	20 (26.7)	0.35 (0.07, 1.75)	0.19
Cramps	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.23 (0.54, 2.81)	0.62	155 (52.4)	0.70 (0.36, 1.33)	0.27	36 (48.0)	1.69 (0.42, 6.81)	0.45
	AA	46 (19.8)	1.09 (0.38, 3.10)	0.87	76 (25.7)	1.19 (0.56, 2.55)	0.65	20 (26.7)	6.37 (0.63, 64.23)	0.11
Depression	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.07 (0.55, 2.09)	0.83	155 (52.4)	0.98 (0.50, 1.91)	0.95	36 (48.0)	0.16 (0.04, 0.61)	0.01 **
	AA	46 (19.8)	0.85 (0.36, 1.98)	0.70	76 (25.7)	1.31 (0.62, 2.74)	0.48	20 (26.7)	0.24 (0.06, 1.00)	0.05 *
Fatigue	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.36 (0.74, 2.52)	0.32	155 (52.4)	1.25 (0.70, 2.25)	0.45	36 (48.0)	1.24 (0.38, 4.02)	0.71
	AA	46 (19.8)	1.51 (0.70, 3.28)	0.29	76 (25.7)	1.68 (0.86, 3.29)	0.13	20 (26.7)	1.63 (0.42, 6.27)	0.47
Headaches	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	0.81 (0.40, 1.62)	0.55	155 (52.4)	1.17 (0.56, 2.46)	0.68	36 (48.0)	0.68 (0.19, 2.40)	0.54
	AA	46 (19.8)	0.87 (0.36, 2.09)	0.76	76 (25.7)	1.82 (0.81, 4.08)	0.14	20 (26.7)	0.96 (0.25, 3.78)	0.96
Insomnia	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.09 (0.41, 2.89)	0.86	155 (52.4)	2.26 (0.63, 8.12)	0.21	36 (48.0)	0.63 (0.12, 3.44)	0.59
	AA	46 (19.8)	1.27 (0.39, 4.13)	0.69	76 (25.7)	4.38 (1.17, 16.30)	0.03 *	20 (26.7)	0.59 (0.08, 4.26)	0.6
Mood swings/ crying easily / irritability/ angry outbursts	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.14 (0.56, 2.31)	0.71	155 (52.4)	0.85 (0.43, 1.69)	0.64	36 (48.0)	0.43 (0.11, 1.71)	0.23
	AA	46 (19.8)	1.00 (0.42, 2.39)	1.00	76 (25.7)	0.54 (0.25, 1.14)	0.10	20 (26.7)	2.78 (0.41, 18.78)	0.29
Nausea	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.32 (0.59, 2.95)	0.49	155 (52.4)	3.89 (0.86, 17.51)	0.08	36 (48.0)	3.31 (0.33, 32.88)	0.30
	AA	46 (19.8)	1.32 (0.50, 3.53)	0.57	76 (25.7)	5.37 (1.14, 25.37)	0.03 *	20 (26.7)	5.62 (0.52, 61.18)	0.15
Sexual desire/ activity change	GG	66 (28.4)	1	1	65 (22.0)	1	1	19 (25.3)	1	1
	GA	120 (51.7)	1.23 (0.66, 2.29)	0.51	155 (52.4)	0.98 (0.54, 1.78)	0.94	36 (48.0)	1.28 (0.39, 4.16)	0.67
	AA	46 (19.8)	0.75 (0.35, 1.63)	0.47	76 (25.7)	0.98 (0.50, 1.94)	0.96	20 (26.7)	1.19 (0.32, 4.48)	0.79

Models were adjusted for age, BMI, and PAL.

Supplementary Table 5: Associations between rs3774934 and premenstrual symptoms stratified by ethnicity.

PMSx	rs3774934 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.19 (0.59, 2.41)	0.63	139 (47.0)	1.41 (0.85, 2.33)	0.18	27 (36.0)	2.42 (0.37, 15.88)	0.35
	AA	1 (0.4)	-	-	39 (13.2)	2.81 (1.24, 6.37)	0.01 *	8 (10.7)	3.97 (0.64, 24.80)	0.13
Desire to be alone	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.06 (0.53, 2.13)	0.87	139 (47.0)	0.97 (0.57, 1.66)	0.92	27 (36.0)	0.82 (0.15, 4.40)	0.82
	AA	1 (0.4)	-	-	39 (13.2)	2.30 (1.08, 4.87)	0.03 *	8 (10.7)	1.33 (0.27, 6.64)	0.72
Anxiety/ tension/ nervousness	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	0.86 (0.43, 1.71)	0.66	139 (47.0)	0.81 (0.49, 1.35)	0.42	27 (36.0)	2.39 (0.24, 24.07)	0.45
	AA	1 (0.4)	-	-	39 (13.2)	1.01 (0.48, 2.14)	0.97	8 (10.7)	4.59 (0.49, 43.10)	0.18
Increased appetite/ food cravings	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.66 (0.80, 3.44)	0.17	139 (47.0)	0.73 (0.44, 1.22)	0.23	27 (36.0)	0.77 (0.14, 4.13)	0.76
	AA	1 (0.4)	-	-	39 (13.2)	1.20 (0.55, 2.61)	0.65	8 (10.7)	1.24 (0.24, 6.37)	0.79
Bloating/ swelling/ breast tenderness	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.17 (0.52, 2.66)	0.70	139 (47.0)	1.02 (0.60, 1.73)	0.94	27 (36.0)	1.56 (0.28, 8.72)	0.61
	AA	1 (0.4)	-	-	39 (13.2)	1.22 (0.55, 2.73)	0.62	8 (10.7)	1.31 (0.25, 6.81)	0.75
Clumsiness	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.23 (0.48, 3.13)	0.67	139 (47.0)	0.86 (0.44, 1.66)	0.64	27 (36.0)	-	-
	AA	1 (0.4)	-	-	39 (13.2)	1.03 (0.40, 2.68)	0.95	8 (10.7)	-	-
Confusion/ difficulty concentrating/ forgetfulness	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.42 (0.62, 3.26)	0.40	139 (47.0)	0.94 (0.54, 1.63)	0.82	27 (36.0)	1.83 (0.16, 20.70)	0.62
	AA	1 (0.4)	-	-	39 (13.2)	1.30 (0.59, 2.85)	0.52	8 (10.7)	1.62 (0.15, 17.16)	0.69
Cramps	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	0.95 (0.38, 2.36)	0.91	139 (47.0)	1.20 (0.70, 2.04)	0.5	27 (36.0)	0.82 (0.07, 9.06)	0.87
	AA	1 (0.4)	-	-	39 (13.2)	3.17 (1.21, 8.33)	0.02 *	8 (10.7)	0.60 (0.06, 6.06)	0.66
Depression	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.21 (0.60, 2.43)	0.60	139 (47.0)	1.05 (0.60, 1.86)	0.86	27 (36.0)	1.93 (0.19, 20.04)	0.58
	AA	1 (0.4)	-	-	39 (13.2)	1.62 (0.74, 3.54)	0.22	8 (10.7)	3.91 (0.41, 37.17)	0.23
Fatigue	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.39 (0.72, 2.71)	0.33	139 (47.0)	1.22 (0.74, 2.01)	0.43	27 (36.0)	0.45 (0.07, 2.82)	0.39
	AA	1 (0.4)	-	-	39 (13.2)	1.25 (0.60, 2.61)	0.55	8 (10.7)	0.49 (0.08, 2.93)	0.43
Headaches	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	0.54 (0.23, 1.26)	0.15	139 (47.0)	1.33 (0.71, 2.49)	0.37	27 (36.0)	4.75 (0.45, 50.39)	0.19
	AA	1 (0.4)	-	-	39 (13.2)	3.00 (1.33, 6.74)	0.01 **	8 (10.7)	5.87 (0.58, 59.40)	0.13
Insomnia	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.19 (0.45, 3.18)	0.73	139 (47.0)	1.79 (0.73, 4.39)	0.2	27 (36.0)	0.51 (0.04, 7.15)	0.61
	AA	1 (0.4)	-	-	39 (13.2)	3.77 (1.28, 11.04)	0.02 *	8 (10.7)	1.41 (0.13, 14.84)	0.77
Mood swings/ crying easily / irritability/ angry outbursts	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.07 (0.50, 2.31)	0.85	139 (47.0)	0.89 (0.50, 1.56)	0.68	27 (36.0)	0.30 (0.03, 3.13)	0.31
	AA	1 (0.4)	-	-	39 (13.2)	0.60 (0.27, 1.32)	0.2	8 (10.7)	0.35 (0.03, 3.45)	0.36
Nausea	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	0.94 (0.41, 2.17)	0.88	139 (47.0)	1.82 (0.74, 4.45)	0.19	27 (36.0)	0.38 (0.04, 3.16)	0.36
	AA	1 (0.4)	-	-	39 (13.2)	2.53 (0.81, 7.88)	0.11	8 (10.7)	0.42 (0.06, 3.03)	0.38
Sexual desire/ activity change	GG	185 (79.7)	1	1	118 (39.9)	1	1	40 (53.3)	1	1
	GA	46 (19.8)	1.04 (0.54, 2.01)	0.91	139 (47.0)	1.12 (0.67, 1.87)	0.66	27 (36.0)	0.83 (0.16, 4.47)	0.83
	AA	1 (0.4)	-	-	39 (13.2)	1.35 (0.64, 2.84)	0.42	8 (10.7)	1.35 (0.27, 6.74)	0.71

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom, or in the case of the Caucasian cohort, there were not enough individuals with the minor AA genotype to run a logistic regression.

Supplementary Table 6: Associations between rs3774956 and premenstrual symptoms stratified by ethnicity

PMSx	rs3774956 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.55 (0.84, 2.87)	0.16	145 (49.0)	0.69 (0.39, 1.22)	0.20	28 (37.3)	1.54 (0.53, 4.45)	0.42
	TT	42 (18.1)	1.12 (0.52, 2.43)	0.77	73 (24.7)	0.93 (0.48, 1.82)	0.84	9 (12.0)	2.38 (0.49, 11.68)	0.28
Desire to be alone	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	0.73 (0.40, 1.35)	0.32	145 (49.0)	0.43 (0.24, 0.78)	0.005 **	28 (37.3)	1.71 (0.61, 4.77)	0.30
	TT	42 (18.1)	0.69 (0.31, 1.53)	0.35	73 (24.7)	0.74 (0.38, 1.44)	0.37	9 (12.0)	1.53 (0.33, 7.04)	0.58
Anxiety/ tension/ nervousness	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.05 (0.58, 1.90)	0.88	145 (49.0)	1.15 (0.65, 2.03)	0.64	28 (37.3)	2.43 (0.82, 7.19)	0.10
	TT	42 (18.1)	0.72 (0.33, 1.60)	0.42	73 (24.7)	0.99 (0.51, 1.92)	0.97	9 (12.0)	1.73 (0.34, 8.84)	0.50
Increased appetite/ food cravings	CC	89 (38.4)	rs	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	0.90 (0.48, 1.67)	0.73	145 (49.0)	0.94 (0.53, 1.66)	0.82	28 (37.3)	0.62 (0.22, 1.79)	0.37
	TT	42 (18.1)	0.44 (0.20, 0.94)	0.03 *	73 (24.7)	1.03 (0.53, 2.01)	0.92	9 (12.0)	0.67 (0.14, 3.20)	0.61
Bloating/ swelling/ breast tenderness	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.83 (0.87, 3.83)	0.11	145 (49.0)	1.39 (0.76, 2.53)	0.28	28 (37.3)	1.48 (0.47, 4.65)	0.49
	TT	42 (18.1)	0.80 (0.35, 1.84)	0.6	73 (24.7)	0.90 (0.46, 1.75)	0.75	9 (12.0)	0.29 (0.06, 1.42)	0.12
Clumsiness	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	0.96 (0.41, 2.26)	0.93	145 (49.0)	1.34 (0.64, 2.83)	0.43	28 (37.3)	0.40 (0.07, 2.40)	0.31
	TT	42 (18.1)	1.06 (0.36, 3.12)	0.92	73 (24.7)	0.76 (0.30, 1.93)	0.56	9 (12.0)	2.16 (0.29, 16.17)	0.44
Confusion/ difficulty concentrating/ forgetfulness	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.75 (0.79, 3.90)	0.17	145 (49.0)	1.18 (0.63, 2.19)	0.60	28 (37.3)	0.99 (0.25, 3.93)	0.98
	TT	42 (18.1)	1.56 (0.57, 4.28)	0.39	73 (24.7)	0.96 (0.46, 1.98)	0.91	9 (12.0)	5.50 (0.85, 35.64)	0.07
Cramps	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.27 (0.56, 2.88)	0.57	145 (49.0)	0.61 (0.33, 1.14)	0.12	28 (37.3)	0.32 (0.07, 1.46)	0.14
	TT	42 (18.1)	0.88 (0.33, 2.34)	0.79	73 (24.7)	0.88 (0.42, 1.84)	0.74	9 (12.0)	0.20 (0.03, 1.30)	0.09
Depression	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.05 (0.56, 1.97)	0.88	145 (49.0)	1.12 (0.60, 2.08)	0.73	28 (37.3)	1.57 (0.50, 4.93)	0.43
	TT	42 (18.1)	0.88 (0.38, 2.01)	0.76	73 (24.7)	0.82 (0.39, 1.74)	0.61	9 (12.0)	3.34 (0.66, 16.86)	0.14
Fatigue	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	0.95 (0.53, 1.70)	0.86	145 (49.0)	0.88 (0.50, 1.53)	0.64	28 (37.3)	1.02 (0.36, 2.88)	0.98
	TT	42 (18.1)	0.62 (0.29, 1.33)	0.22	73 (24.7)	0.89 (0.47, 1.69)	0.72	9 (12.0)	0.49 (0.10, 2.33)	0.36
Headaches	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.30 (0.67, 2.54)	0.43	145 (49.0)	1.38 (0.70, 2.74)	0.36	28 (37.3)	1.34 (0.45, 3.97)	0.59
	TT	42 (18.1)	0.96 (0.39, 2.32)	0.92	73 (24.7)	1.18 (0.53, 2.61)	0.69	9 (12.0)	0.59 (0.10, 3.63)	0.56
Insomnia	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.06 (0.43, 2.61)	0.91	145 (49.0)	0.76 (0.32, 1.79)	0.52	28 (37.3)	1.84 (0.42, 7.97)	0.41
	TT	42 (18.1)	1.08 (0.34, 3.42)	0.9	73 (24.7)	0.69 (0.25, 1.96)	0.49	9 (12.0)	-	-
Mood swings/ crying easily / irritability/ angry outbursts	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.02 (0.51, 2.03)	0.97	145 (49.0)	1.25 (0.69, 2.29)	0.46	28 (37.3)	1.53 (0.46, 5.13)	0.49
	TT	42 (18.1)	0.51 (0.23, 1.15)	0.1	73 (24.7)	1.92 (0.91, 4.05)	0.08	9 (12.0)	0.72 (0.14, 3.71)	0.69
Nausea	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.19 (0.57, 2.47)	0.65	145 (49.0)	0.84 (0.36, 1.96)	0.68	28 (37.3)	0.35 (0.06, 1.99)	0.23
	TT	42 (18.1)	1.00 (0.38, 2.61)	0.99	73 (24.7)	0.39 (0.12, 1.32)	0.13	9 (12.0)	0.46 (0.04, 4.81)	0.51
Sexual desire/ activity change	CC	89 (38.4)	1	1	78 (26.4)	1	1	38 (50.7)	1	1
	CT	101 (43.5)	1.40 (0.78, 2.52)	0.26	145 (49.0)	0.86 (0.49, 1.52)	0.60	28 (37.3)	1.53 (0.55, 4.24)	0.41
	TT	42 (18.1)	0.91 (0.43, 1.92)	0.8	73 (24.7)	1.00 (0.52, 1.93)	0.99	9 (12.0)	0.83 (0.17, 4.03)	0.81

Models were adjusted for age, BMI, and PAL.

Supplementary Table 7: Associations between rs3774968 and premenstrual symptoms stratified by ethnicity

PMSx	rs3774968 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.60 (0.85, 3.01)	0.14	144 (48.6)	0.89 (0.52, 1.53)	0.67	35 (46.7)	0.58 (0.17, 1.99)	0.38
	AA	43 (18.5)	0.84 (0.39, 1.83)	0.66	60 (20.3)	0.81 (0.41, 1.57)	0.53	21 (28.0)	0.28 (0.07, 1.10)	0.06
Desire to be alone	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.39 (0.73, 2.66)	0.32	144 (48.6)	0.66 (0.38, 1.17)	0.15	35 (46.7)	0.38 (0.12, 1.25)	0.10
	AA	43 (18.5)	1.92 (0.85, 4.30)	0.11	60 (20.3)	1.46 (0.74, 2.86)	0.27	21 (28.0)	0.36 (0.10, 1.37)	0.13
Anxiety/ tension/ nervousness	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.27 (0.68, 2.36)	0.45	144 (48.6)	1.27 (0.74, 2.21)	0.38	35 (46.7)	0.51 (0.15, 1.73)	0.27
	AA	43 (18.5)	1.16 (0.52, 2.57)	0.72	60 (20.3)	1.27 (0.64, 2.50)	0.49	21 (28.0)	0.52 (0.13, 2.02)	0.34
Increased appetite/ food cravings	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	2.16 (1.15, 4.05)	0.02 *	144 (48.6)	1.06 (0.61, 1.82)	0.84	35 (46.7)	0.90 (0.27, 3.00)	0.86
	AA	43 (18.5)	0.95 (0.44, 2.05)	0.90	60 (20.3)	0.98 (0.50, 1.91)	0.94	21 (28.0)	0.80 (0.21, 3.07)	0.74
Bloating/ swelling/ breast tenderness	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.76 (0.85, 3.64)	0.12	144 (48.6)	1.87 (1.06, 3.31)	0.03*	35 (46.7)	2.84 (0.81, 9.97)	0.10
	AA	43 (18.5)	1.03 (0.43, 2.47)	0.94	60 (20.3)	0.99 (0.50, 1.95)	0.98	21 (28.0)	3.34 (0.81, 13.68)	0.09
Clumsiness	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	0.81 (0.33, 1.99)	0.64	144 (48.6)	1.11 (0.55, 2.25)	0.77	35 (46.7)	0.36 (0.05, 2.49)	0.29
	AA	43 (18.5)	1.50 (0.53, 4.26)	0.45	60 (20.3)	0.93 (0.38, 2.30)	0.88	21 (28.0)	1.09 (0.18, 6.50)	0.92
Confusion/ difficulty concentrating/ forgetfulness	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.13 (0.51, 2.52)	0.76	144 (48.6)	0.96 (0.54, 1.74)	0.90	35 (46.7)	0.28 (0.06, 1.21)	0.08
	AA	43 (18.5)	1.18 (0.43, 3.25)	0.75	60 (20.3)	1.08 (0.53, 2.23)	0.83	21 (28.0)	0.31 (0.06, 1.54)	0.14
Cramps	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	0.97 (0.43, 2.20)	0.95	144 (48.6)	0.62 (0.34, 1.11)	0.10	35 (46.7)	1.65 (0.41, 6.66)	0.47
	AA	43 (18.5)	1.07 (0.36, 3.16)	0.90	60 (20.3)	1.11 (0.52, 2.37)	0.79	21 (28.0)	6.60 (0.66, 66.45)	0.10
Depression	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	0.95 (0.50, 1.82)	0.88	144 (48.6)	1.03 (0.56, 1.87)	0.93	35 (46.7)	0.16 (0.04, 0.64)	0.01 **
	AA	43 (18.5)	1.05 (0.46, 2.41)	0.90	60 (20.3)	1.22 (0.59, 2.53)	0.59	21 (28.0)	0.22 (0.05, 0.92)	0.03 *
Fatigue	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.54 (0.85, 2.81)	0.15	144 (48.6)	1.08 (0.64, 1.83)	0.78	35 (46.7)	1.19 (0.37, 3.88)	0.76
	AA	43 (18.5)	1.96 (0.90, 4.27)	0.09 .	60 (20.3)	1.19 (0.62, 2.30)	0.60	21 (28.0)	1.73 (0.46, 6.60)	0.41
Headaches	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.06 (0.54, 2.10)	0.86	144 (48.6)	1.19 (0.63, 2.25)	0.60	35 (46.7)	0.71 (0.20, 2.52)	0.59
	AA	43 (18.5)	1.05 (0.43, 2.54)	0.92	60 (20.3)	1.16 (0.53, 2.56)	0.71	21 (28.0)	0.89 (0.23, 3.47)	0.86
Insomnia	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.03 (0.40, 2.64)	0.95	144 (48.6)	1.49 (0.58, 3.82)	0.40	35 (46.7)	0.64 (0.12, 3.51)	0.60
	AA	43 (18.5)	1.33 (0.42, 4.18)	0.62	60 (20.3)	2.26 (0.78, 6.52)	0.13	21 (28.0)	0.58 (0.08, 4.14)	0.58
Mood swings/ crying easily / irritability/ angry outbursts	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.36 (0.69, 2.67)	0.37	144 (48.6)	0.73 (0.39, 1.37)	0.33	35 (46.7)	0.46 (0.12, 1.84)	0.26
	AA	43 (18.5)	1.33 (0.55, 3.20)	0.53	60 (20.3)	0.45 (0.22, 0.94)	0.03*	21 (28.0)	1.90 (0.34, 10.70)	0.46
Nausea	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	0.90 (0.42, 1.91)	0.77	144 (48.6)	2.18 (0.77, 6.20)	0.14	35 (46.7)	2.61 (0.25, 27.16)	0.41
	AA	43 (18.5)	1.23 (0.48, 3.13)	0.67	60 (20.3)	3.10 (0.98, 9.81)	0.05	21 (28.0)	7.21 (0.69, 75.80)	0.09 .
Sexual desire/ activity change	GG	74 (31.9)	1	1	92 (31.1)	1	1	19 (25.3)	1	1
	GA	115 (49.6)	1.28 (0.70, 2.33)	0.43	144 (48.6)	1.03 (0.60, 1.76)	0.93	35 (46.7)	1.35 (0.41, 4.40)	0.61
	AA	43 (18.5)	0.72 (0.33, 1.55)	0.40	60 (20.3)	1.06 (0.54, 2.08)	0.85	21 (28.0)	1.09 (0.29, 4.09)	0.89

Models were adjusted for age, BMI, and PAL.

Supplementary Table 8: Associations between rs4648006 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648006 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.06 (0.38, 3.00)	0.91	30 (10.1)	0.99 (0.45, 2.19)	0.98	9 (12.0)	3.64 (0.65, 20.38)	0.13
	TT	0	-	-	0	-	-	0	-	-
Desire to be alone	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.87 (0.31, 2.46)	0.79	30 (10.1)	0.58 (0.24, 1.39)	0.22	9 (12.0)	1.33 (0.30, 5.76)	0.70
	TT	0	-	-	0	-	-	0	-	-
Anxiety/ tension/ nervousness	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.77 (0.27, 2.18)	0.62	30 (10.1)	1.34 (0.61, 2.92)	0.46	9 (12.0)	1.01 (0.22, 4.74)	0.99
	TT	0	-	-	0	-	-	0	-	-
Increased appetite/ food cravings	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.48 (0.50, 4.38)	0.47	30 (10.1)	0.57 (0.26, 1.24)	0.15	9 (12.0)	0.96 (0.20, 4.67)	0.96
	TT	0	-	-	0	-	-	0	-	-
Bloating/ swelling/ breast tenderness	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.89 (0.28, 2.89)	0.85	30 (10.1)	0.77 (0.35, 1.73)	0.53	9 (12.0)	0.61 (0.14, 2.69)	0.51
	TT	0	-	-	0	-	-	0	-	-
Clumsiness	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.90 (0.57, 6.39)	0.30	30 (10.1)	1.13 (0.43, 2.99)	0.81	9 (12.0)	1.64 (0.22, 11.96)	0.62
	TT	0	-	-	0	-	-	0	-	-
Confusion/ difficulty concentrating/ forgetfulness	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.36 (0.41, 4.51)	0.61	30 (10.1)	0.89 (0.37, 2.13)	0.79	9 (12.0)	1.60 (0.26, 9.82)	0.60
	TT	0	-	-	0	-	-	0	-	-
Cramps	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	3.59 (0.45, 28.67)	0.23	30 (10.1)	1.17 (0.49, 2.80)	0.72	9 (12.0)	1.42 (0.15, 13.63)	0.76
	TT	0	-	-	0	-	-	0	-	-
Depression	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.77 (0.65, 4.79)	0.26	30 (10.1)	0.39 (0.13, 1.17)	0.09	9 (12.0)	1.76 (0.39, 8.00)	0.46
	TT	0	-	-	0	-	-	0	-	-
Fatigue	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.17 (0.44, 3.13)	0.75	30 (10.1)	0.71 (0.33, 1.54)	0.39	9 (12.0)	2.58 (0.46, 14.36)	0.27
	TT	0	-	-	0	-	-	0	-	-
Headaches	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.27 (0.44, 3.65)	0.66	30 (10.1)	1.04 (0.41, 2.61)	0.94	9 (12.0)	1.08 (0.23, 5.01)	0.92
	TT	0	-	-	0	-	-	0	-	-
Insomnia	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.43 (0.05, 3.44)	0.42	30 (10.1)	0.74 (0.20, 2.68)	0.65	9 (12.0)	0.91 (0.09, 8.97)	0.94
	TT	0	-	-	0	-	-	0	-	-
Mood swings/ crying easily / irritability/ angry outbursts	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.61 (0.21, 1.72)	0.35	30 (10.1)	0.80 (0.34, 1.88)	0.60	9 (12.0)	0.49 (0.10, 2.31)	0.36
	TT	0	-	-	0	-	-	0	-	-
Nausea	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	1.00 (0.30, 3.34)	0.99	30 (10.1)	1.95 (0.66, 5.74)	0.22	9 (12.0)	1.11 (0.11, 11.51)	0.93
	TT	0	-	-	0	-	-	0	-	-
Sexual desire/ activity change	CC	214 (92.2)	1	1	266 (89.9)	1	1	66 (88.0)	1	1
	CT	18 (7.8)	0.95 (0.35, 2.55)	0.91	30 (10.1)	1.67 (0.76, 3.64)	0.20	9 (12.0)	0.40 (0.07, 2.20)	0.28
	TT	0	-	-	0	-	-	0	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were not enough individuals with the minor TT genotype in any cohort to run a logistic regression

Supplementary Table 9: Associations between rs4648022 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648022 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.54 (0.26, 1.10)	0.09	0	-	-	12 (16.0)	1.45 (0.37, 5.69)	0.59
	TT	3 (1.3)	0.19 (0.02, 2.31)	0.19	0	-	-	0	-	-
Desire to be alone	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.74 (0.34, 1.59)	0.43	0	-	-	12 (16.0)	1.14 (0.30, 4.32)	0.85
	TT	3 (1.3)	0.76 (0.06, 9.16)	0.83	0	-	-	0	-	-
Anxiety/ tension/ nervousness	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	1.25 (0.61, 2.55)	0.55	0	-	-	12 (16.0)	0.64 (0.14, 2.85)	0.55
	TT	3 (1.3)	0.70 (0.06, 8.39)	0.78	0	-	-	0	-	-
Increased appetite/ food cravings	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	1.57 (0.73, 3.39)	0.24	0	-	-	12 (16.0)	1.48 (0.37, 6.00)	0.57
	TT	3 (1.3)	0.95 (0.08, 11.25)	0.97	0	-	-	0	-	-
Bloating/ swelling/ breast tenderness	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.92 (0.40, 2.11)	0.84	0	-	-	12 (16.0)	0.68 (0.17, 2.66)	0.57
	TT	3 (1.3)	0.10 (0.01, 1.25)	0.07	0	-	-	0	-	-
Clumsiness	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.34 (0.08, 1.54)	0.16	0	-	-	12 (16.0)	0.79 (0.08, 8.03)	0.84
	TT	3 (1.3)	1.98 (0.16, 24.76)	0.60	0	-	-	0	-	-
Confusion/ difficulty concentrating/ forgetfulness	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.24 (0.05, 1.06)	0.06	0	-	-	12 (16.0)	1.11 (0.19, 6.57)	0.91
	TT	3 (1.3)	1.18 (0.10, 14.67)	0.90	0	-	-	0	-	-
Cramps	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.88 (0.35, 2.24)	0.79	0	-	-	12 (16.0)	2.97 (0.31, 28.80)	0.34
	TT	3 (1.3)	0.24 (0.02, 2.92)	0.26	0	-	-	0	-	-
Depression	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.89 (0.41, 1.96)	0.78	0	-	-	12 (16.0)	1.49 (0.36, 6.23)	0.58
	TT	3 (1.3)	0.80 (0.06, 9.86)	0.86	0	-	-	0	-	-
Fatigue	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.68 (0.34, 1.37)	0.28	0	-	-	12 (16.0)	0.70 (0.18, 2.67)	0.59
	TT	3 (1.3)	0.28 (0.02, 3.30)	0.31	0	-	-	0	-	-
Headaches	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.56 (0.23, 1.37)	0.20	0	-	-	12 (16.0)	0.72 (0.16, 3.18)	0.65
	TT	3 (1.3)	1.47 (0.12, 18.46)	0.76	0	-	-	0	-	-
Insomnia	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.86 (0.28, 2.70)	0.80	0	-	-	12 (16.0)	0.40 (0.04, 4.38)	0.44
	TT	3 (1.3)	-	-	0	-	-	0	-	-
Mood swings/ crying easily / irritability/ angry outbursts	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	1.41 (0.60, 3.31)	0.43	0	-	-	12 (16.0)	0.54 (0.12, 2.39)	0.41
	TT	3 (1.3)	0.13 (0.01, 1.60)	0.11	0	-	-	0	-	-
Nausea	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	1.15 (0.49, 2.72)	0.74	0	-	-	12 (16.0)	0.67 (0.07, 6.57)	0.73
	TT	3 (1.3)	-	-	0	-	-	0	-	-
Sexual desire/ activity change	CC	189 (81.5)	1	1	296 (100.0)	1	1	63 (84.0)	1	1
	CT	40 (17.2)	0.99 (0.49, 2.01)	0.99	0	-	-	12 (16.0)	0.44 (0.10, 1.93)	0.27
	TT	3 (1.3)	0.47 (0.04, 5.55)	0.55	0	-	-	0	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were not enough individuals with the minor TT or the CT genotype to run a logistic regression.

Supplementary Table 10: Associations between rs4648090 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648090 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.60 (0.32, 1.11)	0.10	3 (1.0)	0.38 (0.03, 4.39)	0.44	12 (16.0)	0.90 (0.23, 3.61)	0.88
	AA	3 (1.3)	0.19 (0.02, 2.28)	0.19	0	-	-	0	-	-
Desire to be alone	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.61 (0.31, 1.19)	0.15	3 (1.0)	1.13 (0.10, 13.16)	0.92	12 (16.0)	1.09 (0.28, 4.22)	0.89
	AA	3 (1.3)	0.73 (0.06, 8.79)	0.81	0	-	-	0	-	-
Anxiety/ tension/ nervousness	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.29 (0.70, 2.40)	0.42	3 (1.0)	0.92 (0.08, 10.60)	0.95	12 (16.0)	0.62 (0.14, 2.78)	0.52
	AA	3 (1.3)	0.71 (0.06, 8.54)	0.79	0	-	-	0	-	-
Increased appetite/ food cravings	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.37 (0.72, 2.59)	0.34	3 (1.0)	0.34 (0.03, 3.93)	0.39	12 (16.0)	1.62 (0.39, 6.67)	0.50
	AA	3 (1.3)	0.95 (0.08, 11.30)	0.97	0	-	-	0	-	-
Bloating/ swelling/ breast tenderness	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.02 (0.49, 2.13)	0.95	3 (1.0)	0.90 (0.08, 10.28)	0.93	12 (16.0)	0.42 (0.11, 1.68)	0.21
	AA	3 (1.3)	0.10 (0.01, 1.27)	0.08	0	-	-	0	-	-
Clumsiness	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.56 (0.20, 1.57)	0.27	3 (1.0)	3.12 (0.26, 36.81)	0.37	12 (16.0)	0.67 (0.07, 6.88)	0.73
	AA	3 (1.3)	1.99 (0.16, 24.99)	0.59	0	-	-	0	-	-
Confusion/ difficulty concentrating/ forgetfulness	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.61 (0.25, 1.49)	0.27	3 (1.0)	5.69 (0.49, 65.41)	0.16	12 (16.0)	1.92 (0.37, 9.92)	0.43
	AA	3 (1.3)	1.22 (0.10, 15.25)	0.88	0	-	-	0	-	-
Cramps	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.01 (0.44, 2.30)	0.98	3 (1.0)	-	-	12 (16.0)	2.92 (0.30, 28.35)	0.35
	AA	3 (1.3)	0.24 (0.02, 2.97)	0.26	0	-	-	0	-	-
Depression	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.86 (0.44, 1.67)	0.65	3 (1.0)	-	-	12 (16.0)	1.51 (0.35, 6.41)	0.57
	AA	3 (1.3)	0.79 (0.06, 9.75)	0.85	0	-	-	0	-	-
Fatigue	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.19 (0.65, 2.18)	0.56	3 (1.0)	1.75 (0.15, 19.95)	0.65	12 (16.0)	0.81 (0.21, 3.11)	0.76
	AA	3 (1.3)	0.30 (0.03, 3.55)	0.34	0	-	-	0	-	-
Headaches	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.87 (0.43, 1.76)	0.70	3 (1.0)	-	-	12 (16.0)	0.86 (0.19, 3.88)	0.84
	AA	3 (1.3)	1.52 (0.12, 19.10)	0.75	0	-	-	0	-	-
Insomnia	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.28 (0.51, 3.18)	0.60	3 (1.0)	-	-	12 (16.0)	0.39 (0.04, 4.29)	0.44
	AA	3 (1.3)	-	-	0	-	-	0	-	-
Mood swings/ crying easily / irritability/ angry outbursts	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.79 (0.84, 3.79)	0.13	3 (1.0)	0.21 (0.02, 2.42)	0.21	12 (16.0)	0.44 (0.10, 2.01)	0.28
	AA	3 (1.3)	0.14 (0.01, 1.68)	0.12	0	-	-	0	-	-
Nausea	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	1.00 (0.47, 2.12)	0.99	3 (1.0)	-	-	12 (16.0)	0.65 (0.06, 6.55)	0.71
	AA	3 (1.3)	-	-	0	-	-	0	-	-
Sexual desire/ activity change	GG	167 (72.0)	1	1	293 (99.0)	1	1	63 (84.0)	1	1
	GA	62 (26.7)	0.88 (0.48, 1.61)	0.68	3 (1.0)	0.63 (0.06, 7.19)	0.71	12 (16.0)	0.42 (0.09, 1.87)	0.25
	AA	3 (1.3)	0.46 (0.04, 5.44)	0.54	0	-	-	0	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom, or in the case of the East Asian and South Asian cohorts, there were not enough individuals with the minor AA genotype to run a logistic regression.

Supplementary Table 11: Associations between rs4648095 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648095 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.02 (0.33, 3.15)	0.97	37 (12.5)	0.99 (0.49, 2.02)	0.98	8 (10.7)	7.07 (0.77, 65.10)	0.08
	CC	0	-	-	0	-	-	0	-	-
Desire to be alone	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	0.87 (0.28, 2.69)	0.80	37 (12.5)	0.62 (0.28, 1.35)	0.22	8 (10.7)	1.73 (0.37, 8.09)	0.48
	CC	0	-	-	0	-	-	0	-	-
Anxiety/ tension/ nervousness	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	0.80 (0.26, 2.46)	0.69	37 (12.5)	1.51 (0.75, 3.06)	0.25	8 (10.7)	1.25 (0.26, 6.07)	0.78
	CC	0	-	-	0	-	-	0	-	-
Increased appetite/ food cravings	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.53 (0.47, 5.04)	0.48	37 (12.5)	0.71 (0.35, 1.43)	0.33	8 (10.7)	0.80 (0.16, 4.16)	0.79
	CC	0	-	-	0	-	-	0	-	-
Bloating/ swelling/ breast tenderness	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.01 (0.27, 3.79)	0.99	37 (12.5)	0.96 (0.46, 2.03)	0.92	8 (10.7)	0.50 (0.11, 2.33)	0.37
	CC	0	-	-	0	-	-	0	-	-
Clumsiness	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.59 (0.41, 6.16)	0.50	37 (12.5)	1.09 (0.44, 2.68)	0.85	8 (10.7)	2.10 (0.28, 15.98)	0.47
	CC	0	-	-	0	-	-	0	-	-
Confusion/ difficulty concentrating/ forgetfulness	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.73 (0.50, 5.90)	0.38	37 (12.5)	1.25 (0.59, 2.64)	0.57	8 (10.7)	2.54 (0.38, 16.84)	0.33
	CC	0	-	-	0	-	-	0	-	-
Cramps	TT	217 (93.5)	1	1.0	259 (87.5)	1.0	1.0	67 (89.3)	1	1
	TC	15 (6.4)	3.02 (0.37, 24.38)	0.30	37 (12.5)	1.40 (0.62, 3.15)	0.41	8 (10.7)	1.28 (0.13, 12.63)	0.83
	CC	0	-	-	0	-	-	0	-	-
Depression	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	2.02 (0.69, 5.96)	0.20	37 (12.5)	0.38 (0.14, 1.03)	0.06	8 (10.7)	2.36 (0.49, 11.46)	0.28
	CC	0	-	-	0	-	-	0	-	-
Fatigue	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.06 (0.37, 3.07)	0.91	37 (12.5)	0.69 (0.34, 1.38)	0.29	8 (10.7)	2.23 (0.39, 12.85)	0.36
	CC	0	-	-	0	-	-	0	-	-
Headaches	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.32 (0.42, 4.13)	0.64	37 (12.5)	0.77 (0.32, 1.87)	0.56	8 (10.7)	1.36 (0.27, 6.75)	0.7
	CC	0	-	-	0	-	-	0	-	-
Insomnia	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	0.52 (0.06, 4.20)	0.54	37 (12.5)	0.61 (0.17, 2.17)	0.45	8 (10.7)	0.99 (0.10, 9.90)	0.99
	CC	0	-	-	0	-	-	0	-	-
Mood swings/ crying easily / irritability/ angry outbursts	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	0.60 (0.19, 1.87)	0.38	37 (12.5)	0.98 (0.44, 2.15)	0.95	8 (10.7)	0.70 (0.13, 3.75)	0.67
	CC	0	-	-	0	-	-	0	-	-
Nausea	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	0.97 (0.25, 3.74)	0.97	37 (12.5)	1.46 (0.51, 4.14)	0.48	8 (10.7)	-	-
	CC	0	-	-	0	-	-	0	-	-
Sexual desire/ activity change	TT	217 (93.5)	1	1	259 (87.5)	1	1	67 (89.3)	1	1
	TC	15 (6.4)	1.13 (0.38, 3.36)	0.82	37 (12.5)	1.34 (0.66, 2.72)	0.41	8 (10.7)	0.49 (0.09, 2.77)	0.41
	CC	0	-	-	0	-	-	0	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were not enough individuals with the minor CC genotype to run a logistic regression in any ethnic cohort.

Supplementary Table 12: Associations between rs4648110 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648110 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.81 (0.45, 1.46)	0.48	32 (10.8)	1.89 (0.84, 4.28)	0.12	25 (33.3)	2.11 (0.73, 6.09)	0.16
	AA	7 (3.0)	0.64 (0.13, 3.06)	0.57	3 (1.0)	1.70 (0.15, 19.62)	0.67	1 (1.3)	-	-
Desire to be alone	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.55 (0.30, 1.03)	0.06	32 (10.8)	0.84 (0.38, 1.86)	0.66	25 (33.3)	2.07 (0.75, 5.74)	0.15
	AA	7 (3.0)	1.02 (0.21, 4.91)	0.98	3 (1.0)	4.34 (0.37, 50.89)	0.24	1 (1.3)	-	-
Anxiety/ tension/ nervousness	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.97 (0.54, 1.74)	0.91	32 (10.8)	0.57 (0.25, 1.30)	0.18	25 (33.3)	0.96 (0.33, 2.79)	0.94
	AA	7 (3.0)	1.85 (0.39, 8.83)	0.44	3 (1.0)	0.76 (0.07, 8.79)	0.82	1 (1.3)	-	-
Increased appetite/ food cravings	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.38 (0.76, 2.50)	0.28	32 (10.8)	0.80 (0.38, 1.70)	0.56	25 (33.3)	2.16 (0.72, 6.48)	0.16
	AA	7 (3.0)	3.55 (0.41, 31.02)	0.25	3 (1.0)	1.43 (0.13, 16.30)	0.77	1 (1.3)	-	-
Bloating/ swelling/ breast tenderness	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.15 (0.57, 2.30)	0.69	32 (10.8)	0.86 (0.39, 1.88)	0.7	25 (33.3)	0.46 (0.16, 1.33)	0.14
	AA	7 (3.0)	0.61 (0.11, 3.46)	0.58	3 (1.0)	0.95 (0.08, 10.77)	0.97	1 (1.3)	-	-
Clumsiness	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.48 (0.18, 1.27)	0.14	32 (10.8)	1.45 (0.59, 3.61)	0.42	25 (33.3)	0.73 (0.15, 3.56)	0.69
	AA	7 (3.0)	1.61 (0.28, 9.21)	0.59	3 (1.0)	2.71 (0.23, 31.86)	0.43	1 (1.3)	-	-
Confusion/ difficulty concentrating/ forgetfulness	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.47 (0.20, 1.10)	0.08	32 (10.8)	0.71 (0.29, 1.73)	0.46	25 (33.3)	1.57 (0.44, 5.61)	0.48
	AA	7 (3.0)	1.08 (0.19, 6.16)	0.93	3 (1.0)	4.65 (0.41, 52.75)	0.21	1 (1.3)	-	-
Cramps	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.17 (0.53, 2.57)	0.69	32 (10.8)	1.67 (0.69, 4.06)	0.26	25 (33.3)	1.01 (0.26, 3.93)	0.99
	AA	7 (3.0)	0.94 (0.10, 8.71)	0.96	3 (1.0)	0.92 (0.08, 10.47)	0.95	1 (1.3)	-	-
Depression	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.80 (0.42, 1.49)	0.48	32 (10.8)	1.41 (0.64, 3.09)	0.39	25 (33.3)	2.27 (0.76, 6.78)	0.14
	AA	7 (3.0)	1.15 (0.24, 5.53)	0.86	3 (1.0)	-	-	1 (1.3)	-	-
Fatigue	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.24 (0.70, 2.19)	0.46	32 (10.8)	0.85 (0.41, 1.78)	0.67	25 (33.3)	0.77 (0.28, 2.13)	0.61
	AA	7 (3.0)	0.55 (0.11, 2.62)	0.45	3 (1.0)	1.61 (0.14, 18.22)	0.7	1 (1.3)	-	-
Headaches	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.80 (0.41, 1.56)	0.51	32 (10.8)	0.46 (0.16, 1.39)	0.17	25 (33.3)	1.50 (0.50, 4.47)	0.46
	AA	7 (3.0)	1.80 (0.36, 8.89)	0.47	3 (1.0)	-	-	1 (1.3)	-	-
Insomnia	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.18 (0.50, 2.80)	0.71	32 (10.8)	0.24 (0.03, 1.81)	0.16	25 (33.3)	2.71 (0.62, 11.85)	0.18
	AA	7 (3.0)	-	-	3 (1.0)	-	-	1 (1.3)	-	-
Mood swings/ crying easily / irritability/ angry outbursts	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	2.00 (0.99, 4.02)	0.05*	32 (10.8)	1.69 (0.66, 4.32)	0.27	25 (33.3)	0.72 (0.23, 2.31)	0.58
	AA	7 (3.0)	0.87 (0.16, 4.81)	0.87	3 (1.0)	0.90 (0.08, 10.55)	0.93	1 (1.3)	-	-
Nausea	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	0.95 (0.47, 1.93)	0.88	32 (10.8)	0.89 (0.25, 3.15)	0.86	25 (33.3)	0.43 (0.08, 2.40)	0.33
	AA	7 (3.0)	-	-	3 (1.0)	-	-	1 (1.3)	-	-
Sexual desire/ activity change	TT	145 (62.5)	1	1	261 (88.2)	1	1	49 (65.3)	1	1
	TA	80 (34.5)	1.17 (0.66, 2.06)	0.59	32 (10.8)	0.97 (0.45, 2.06)	0.93	25 (33.3)	0.97 (0.35, 2.69)	0.95
	AA	7 (3.0)	0.64 (0.13, 3.12)	0.58	3 (1.0)	0.79 (0.07, 9.03)	0.85	1 (1.3)	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom, or in the case of the South Asian cohort, there were not enough individuals with the minor AA genotype to run a logistic regression.

Supplementary Table 13: Associations between rs4648127 and premenstrual symptoms stratified by ethnicity

PMSx	rs4648127 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	1.61 (0.60, 4.27)	0.34	33 (11.1)	2.02 (0.90, 4.56)	0.09	12 (16.0)	3.05 (0.73, 12.81)	0.12
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Desire to be alone	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.50 (0.18, 1.41)	0.19	33 (11.1)	1.25 (0.59, 2.66)	0.56	12 (16.0)	2.28 (0.61, 8.52)	0.21
	TT	2 (0.9)	-	-	2 (0.7)	1.76 (0.11, 29.20)	0.69	1 (1.3)	-	-
Anxiety/ tension/ nervousness	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.41 (0.15, 1.17)	0.09	33 (11.1)	0.75 (0.35, 1.63)	0.47	12 (16.0)	1.00 (0.25, 3.97)	1.00
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Increased appetite/ food cravings	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	1.35 (0.53, 3.44)	0.52	33 (11.1)	0.75 (0.36, 1.58)	0.45	12 (16.0)	2.04 (0.47, 8.89)	0.33
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Bloating/ swelling/ breast tenderness	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	1.45 (0.47, 4.50)	0.52	33 (11.1)	0.78 (0.36, 1.66)	0.51	12 (16.0)	0.56 (0.14, 2.15)	0.39
	TT	2 (0.9)	-	-	2 (0.7)	0.47 (0.03, 7.83)	0.60	1 (1.3)	-	-
Clumsiness	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.26 (0.03, 2.08)	0.20	33 (11.1)	1.66 (0.70, 3.97)	0.25	12 (16.0)	0.87 (0.13, 5.76)	0.88
	TT	2 (0.9)	4.14 (0.23, 75.11)	0.33	2 (0.7)	-	-	1 (1.3)	-	-
Confusion/ difficulty concentrating/ forgetfulness	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.18 (0.02, 1.41)	0.1	33 (11.1)	0.67 (0.28, 1.62)	0.37	12 (16.0)	1.15 (0.25, 5.35)	0.86
	TT	2 (0.9)	3.08 (0.17, 54.76)	0.44	2 (0.7)	2.24 (0.14, 37.21)	0.57	1 (1.3)	-	-
Cramps	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	1.25 (0.35, 4.53)	0.73	33 (11.1)	1.73 (0.71, 4.18)	0.23	12 (16.0)	0.41 (0.08, 2.01)	0.26
	TT	2 (0.9)	-	-	2 (0.7)	0.44 (0.03, 7.31)	0.57	1 (1.3)	-	-
Depression	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.41 (0.13, 1.26)	0.12	33 (11.1)	1.59 (0.74, 3.42)	0.24	12 (16.0)	1.78 (0.46, 6.90)	0.4
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Fatigue	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.75 (0.32, 1.79)	0.52	33 (11.1)	1.03 (0.50, 2.15)	0.93	12 (16.0)	0.73 (0.20, 2.70)	0.63
	TT	2 (0.9)	-	-	2 (0.7)	0.82 (0.05, 13.57)	0.89	1 (1.3)	-	-
Headaches	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.77 (0.27, 2.21)	0.63	33 (11.1)	0.75 (0.29, 1.91)	0.54	12 (16.0)	1.75 (0.45, 6.84)	0.41
	TT	2 (0.9)	1.86 (0.10, 33.23)	0.67	2 (0.7)	-	-	1 (1.3)	-	-
Insomnia	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.67 (0.15, 3.04)	0.60	33 (11.1)	0.23 (0.03, 1.74)	0.15	12 (16.0)	4.34 (0.79, 23.81)	0.09
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Mood swings/ crying easily / irritability/ angry outbursts	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	2.55 (0.72, 8.99)	0.142	33 (11.1)	2.27 (0.84, 6.16)	0.11	12 (16.0)	0.93 (0.21, 4.23)	0.93
	TT	2 (0.9)	-	-	2 (0.7)	0.35 (0.02, 5.92)	0.47	1 (1.3)	-	-
Nausea	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	0.53 (0.15, 1.90)	0.33	33 (11.1)	0.86 (0.24, 3.04)	0.82	12 (16.0)	0.39 (0.04, 3.98)	0.42
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-
Sexual desire/ activity change	CC	206 (88.8)	1	1	261 (88.2)	1	1	62 (82.7)	1	1
	CT	24 (10.3)	1.28 (0.54, 3.05)	0.576	33 (11.1)	1.21 (0.58, 2.53)	0.61	12 (16.0)	2.29 (0.61, 8.55)	0.21
	TT	2 (0.9)	-	-	2 (0.7)	-	-	1 (1.3)	-	-

Models were adjusted for age, BMI, and PAL. Dashes (-) indicate there were no individuals with the given genotype presenting the given symptom, or in the case of the South Asian cohort, there were not enough individuals with the minor TT genotype to run a logistic regression.

Supplementary Table 14: Associations between rs4698863 and premenstrual symptoms stratified by ethnicity

PMSx	rs4698863 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.68 (0.92, 3.06)	0.09	140 (47.3)	0.71 (0.42, 1.21)	0.21	23 (30.7)	0.83 (0.28, 2.51)	0.74
	TT	26 (11.2)	0.99 (0.41, 2.41)	0.99	54 (18.2)	1.14 (0.57, 2.28)	0.72	7 (9.3)	2.21 (0.39, 12.55)	0.36
Desire to be alone	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	0.80 (0.44, 1.44)	0.45	140 (47.3)	0.83 (0.48, 1.43)	0.51	23 (30.7)	1.89 (0.65, 5.53)	0.24
	TT	26 (11.2)	0.76 (0.30, 1.93)	0.56	54 (18.2)	1.04 (0.52, 2.07)	0.92	7 (9.3)	2.63 (0.48, 14.29)	0.26
Anxiety/ tension/ nervousness	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	0.92 (0.52, 1.64)	0.77	140 (47.3)	0.95 (0.56, 1.61)	0.86	23 (30.7)	1.67 (0.55, 5.04)	0.36
	TT	26 (11.2)	0.85 (0.34, 2.10)	0.72	54 (18.2)	0.66 (0.33, 1.34)	0.25	7 (9.3)	1.07 (0.17, 6.77)	0.94
Increased appetite/ food cravings	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.07 (0.59, 1.94)	0.82	140 (47.3)	0.98 (0.58, 1.66)	0.93	23 (30.7)	0.91 (0.31, 2.71)	0.86
	TT	26 (11.2)	0.36 (0.15, 0.87)	0.02 *	54 (18.2)	1.13 (0.57, 2.26)	0.72	7 (9.3)	0.49 (0.09, 2.65)	0.40
Bloating/ swelling/ breast tenderness	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.12 (0.56, 2.21)	0.75	140 (47.3)	0.97 (0.56, 1.68)	0.9	23 (30.7)	1.41 (0.43, 4.57)	0.56
	TT	26 (11.2)	0.94 (0.34, 2.62)	0.9	54 (18.2)	0.99 (0.48, 2.02)	0.97	7 (9.3)	0.52 (0.09, 2.90)	0.45
Clumsiness	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.11 (0.49, 2.51)	0.80	140 (47.3)	0.90 (0.46, 1.76)	0.76	23 (30.7)	0.25 (0.03, 2.40)	0.22
	TT	26 (11.2)	0.85 (0.22, 3.32)	0.81	54 (18.2)	0.66 (0.25, 1.68)	0.38	7 (9.3)	0.91 (0.08, 10.41)	0.94
Confusion/ difficulty concentrating/ forgetfulness	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.53 (0.73, 3.19)	0.26	140 (47.3)	0.87 (0.49, 1.52)	0.61	23 (30.7)	1.85 (0.44, 7.71)	0.39
	TT	26 (11.2)	1.01 (0.30, 3.45)	0.98	54 (18.2)	0.63 (0.29, 1.37)	0.24	7 (9.3)	4.76 (0.66, 34.09)	0.11
Cramps	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.12 (0.51, 2.45)	0.78	140 (47.3)	0.65 (0.37, 1.16)	0.14	23 (30.7)	0.66 (0.15, 2.87)	0.57
	TT	26 (11.2)	0.79 (0.26, 2.45)	0.69	54 (18.2)	0.93 (0.44, 1.96)	0.84	7 (9.3)	0.17 (0.03, 1.14)	0.06
Depression	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.16 (0.63, 2.13)	0.62	140 (47.3)	1.03 (0.58, 1.83)	0.92	23 (30.7)	1.49 (0.46, 4.89)	0.50
	TT	26 (11.2)	0.85 (0.32, 2.26)	0.74	54 (18.2)	0.82 (0.38, 1.76)	0.61	7 (9.3)	2.97 (0.51, 17.37)	0.22
Fatigue	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	0.73 (0.42, 1.29)	0.28	140 (47.3)	0.93 (0.55, 1.55)	0.77	23 (30.7)	0.84 (0.29, 2.48)	0.76
	TT	26 (11.2)	0.31 (0.12, 0.80)	0.01 *	54 (18.2)	1.25 (0.64, 2.45)	0.51	7 (9.3)	0.50 (0.09, 2.77)	0.42
Headaches	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.38 (0.73, 2.60)	0.31	140 (47.3)	1.30 (0.69, 2.44)	0.41	23 (30.7)	0.65 (0.20, 2.10)	0.46
	TT	26 (11.2)	0.55 (0.17, 1.78)	0.31	54 (18.2)	1.32 (0.59, 2.93)	0.49	7 (9.3)	0.93 (0.15, 5.90)	0.94
Insomnia	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	0.89 (0.37, 2.12)	0.79	140 (47.3)	0.90 (0.40, 2.02)	0.79	23 (30.7)	1.10 (0.23, 5.33)	0.91
	TT	26 (11.2)	0.95 (0.25, 3.66)	0.94	54 (18.2)	0.77 (0.25, 2.35)	0.65	7 (9.3)	1.41 (0.12, 16.05)	0.78
Mood swings/ crying easily / irritability/ angry outbursts	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	0.54 (0.28, 1.03)	0.06	140 (47.3)	1.10 (0.62, 1.94)	0.74	23 (30.7)	1.40 (0.40, 4.89)	0.59
	TT	26 (11.2)	0.64 (0.24, 1.75)	0.39	54 (18.2)	1.71 (0.77, 3.79)	0.18	7 (9.3)	2.00 (0.20, 20.05)	0.55
Nausea	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.24 (0.62, 2.51)	0.54	140 (47.3)	0.49 (0.22, 1.13)	0.09	23 (30.7)	0.50 (0.09, 2.89)	0.43
	TT	26 (11.2)	1.05 (0.34, 3.18)	0.94	54 (18.2)	0.46 (0.14, 1.48)	0.19	7 (9.3)	0.67 (0.06, 7.23)	0.74
Sexual desire/ activity change	CC	109 (47.0)	1	1	102 (34.5)	1	1	45 (60.0)	1	1
	CT	97 (41.8)	1.52 (0.86, 2.67)	0.15	140 (47.3)	0.75 (0.44, 1.26)	0.28	23 (30.7)	1.70 (0.58, 4.93)	0.32
	TT	26 (11.2)	0.98 (0.41, 2.33)	0.96	54 (18.2)	0.92 (0.47, 1.80)	0.80	7 (9.3)	1.28 (0.24, 6.91)	0.77

Models were adjusted for age, BMI, and PAL.

Supplementary Table 15: Associations between rs7674640 and premenstrual symptoms stratified by ethnicity

PMSx	rs7674640 genotype	Caucasians			East Asians			South Asians		
		n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value	n (%)	Adjusted OR (CI 95%)	Adjusted p value
Acne/ skin blemish	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.45 (0.76, 2.78)	0.26	145 (49.0)	0.92 (0.52, 1.63)	0.76	37 (49.3)	0.54 (0.14, 2.07)	0.36
	CC	48 (20.7)	1.04 (0.48, 2.28)	0.91	74 (25.0)	0.75 (0.39, 1.44)	0.38	24 (32.0)	0.31 (0.07, 1.36)	0.11
Desire to be alone	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.10 (0.56, 2.16)	0.78	145 (49.0)	0.72 (0.40, 1.29)	0.27	37 (49.3)	0.34 (0.09, 1.26)	0.10
	CC	48 (20.7)	1.80 (0.81, 4.00)	0.15	74 (25.0)	1.00 (0.51, 1.95)	1.00	24 (32.0)	0.23 (0.05, 0.98)	0.04 *
Anxiety/ tension/ nervousness	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.00 (0.53, 1.90)	1.00	145 (49.0)	1.82 (1.00, 3.32)	0.0499 *	37 (49.3)	0.83 (0.22, 3.15)	0.78
	CC	48 (20.7)	1.11 (0.51, 2.43)	0.80	74 (25.0)	1.80 (0.91, 3.57)	0.09	24 (32.0)	0.67 (0.15, 2.94)	0.59
Increased appetite/ food cravings	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	2.26 (1.19, 4.30)	0.012*	145 (49.0)	1.01 (0.56, 1.80)	0.98	37 (49.3)	1.00 (0.26, 3.80)	1
	CC	48 (20.7)	1.31 (0.61, 2.83)	0.49	74 (25.0)	0.83 (0.43, 1.61)	0.59	24 (32.0)	0.59 (0.14, 2.51)	0.47
Bloating/ swelling/ breast tenderness	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.31 (0.62, 2.76)	0.47	145 (49.0)	1.53 (0.84, 2.78)	0.16	37 (49.3)	1.89 (0.50, 7.18)	0.34
	CC	48 (20.7)	1.05 (0.43, 2.58)	0.91	74 (25.0)	1.06 (0.54, 2.07)	0.87	24 (32.0)	3.09 (0.68, 14.04)	0.14
Clumsiness	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	0.81 (0.31, 2.11)	0.67	145 (49.0)	1.33 (0.61, 2.87)	0.47	37 (49.3)	0.67 (0.10, 4.69)	0.69
	CC	48 (20.7)	1.81 (0.64, 5.16)	0.26	74 (25.0)	1.15 (0.47, 2.82)	0.76	24 (32.0)	0.94 (0.12, 7.24)	0.95
Confusion/ difficulty concentrating/ forgetfulness	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.14 (0.49, 2.65)	0.75	145 (49.0)	1.26 (0.67, 2.39)	0.47	37 (49.3)	0.28 (0.06, 1.27)	0.09
	CC	48 (20.7)	1.22 (0.44, 3.37)	0.70	74 (25.0)	1.29 (0.62, 2.66)	0.49	24 (32.0)	0.17 (0.03, 1.01)	0.05 *
Cramps	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	0.99 (0.42, 2.31)	0.98	145 (49.0)	0.61 (0.33, 1.13)	0.12	37 (49.3)	1.20 (0.25, 5.77)	0.82
	CC	48 (20.7)	1.05 (0.36, 3.05)	0.93	74 (25.0)	1.02 (0.49, 2.14)	0.96	24 (32.0)	2.71 (0.36, 20.12)	0.32
Depression	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	0.83 (0.42, 1.64)	0.59	145 (49.0)	0.95 (0.51, 1.76)	0.86	37 (49.3)	0.17 (0.04, 0.71)	0.01 *
	CC	48 (20.7)	1.25 (0.56, 2.81)	0.59	74 (25.0)	0.87 (0.42, 1.80)	0.71	24 (32.0)	0.16 (0.03, 0.77)	0.02 *
Fatigue	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.72 (0.92, 3.22)	0.09	145 (49.0)	0.78 (0.44, 1.36)	0.38	37 (49.3)	0.80 (0.22, 2.92)	0.73
	CC	48 (20.7)	1.98 (0.91, 4.28)	0.08	74 (25.0)	0.79 (0.41, 1.51)	0.47	24 (32.0)	1.79 (0.41, 7.70)	0.43
Headaches	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.04 (0.51, 2.11)	0.92	145 (49.0)	0.96 (0.49, 1.86)	0.89	37 (49.3)	0.70 (0.18, 2.76)	0.60
	CC	48 (20.7)	1.06 (0.44, 2.54)	0.90	74 (25.0)	0.89 (0.41, 1.93)	0.77	24 (32.0)	0.89 (0.20, 3.88)	0.87
Insomnia	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	0.93 (0.35, 2.49)	0.89	145 (49.0)	1.83 (0.64, 5.22)	0.26	37 (49.3)	0.82 (0.13, 5.16)	0.83
	CC	48 (20.7)	1.37 (0.44, 4.25)	0.58	74 (25.0)	2.22 (0.71, 6.91)	0.17	24 (32.0)	0.51 (0.06, 4.50)	0.54
Mood swings/ crying easily / irritability/ angry outbursts	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.02 (0.50, 2.06)	0.97	145 (49.0)	0.75 (0.39, 1.45)	0.39	37 (49.3)	0.66 (0.14, 3.04)	0.59
	CC	48 (20.7)	1.14 (0.47, 2.78)	0.77	74 (25.0)	0.52 (0.25, 1.08)	0.08	24 (32.0)	1.07 (0.20, 5.90)	0.93
Nausea	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	0.85 (0.38, 1.86)	0.67	145 (49.0)	2.11 (0.67, 6.65)	0.20	37 (49.3)	1.83 (0.17, 19.66)	0.61
	CC	48 (20.7)	1.25 (0.50, 3.14)	0.63	74 (25.0)	3.18 (0.96, 10.56)	0.06	24 (32.0)	5.73 (0.51, 64.13)	0.15
Sexual desire/ activity change	TT	63 (27.2)	1	1	77 (26.0)	1	1	14 (18.7)	1	1
	TC	121 (52.2)	1.35 (0.72, 2.51)	0.35	145 (49.0)	1.12 (0.63, 1.99)	0.70	37 (49.3)	1.06 (0.29, 3.79)	0.93
	CC	48 (20.7)	0.77 (0.36, 1.66)	0.50	74 (25.0)	1.14 (0.59, 2.20)	0.69	24 (32.0)	0.70 (0.17, 2.90)	0.62

Models were adjusted for age, BMI, and PAL.