Menopause: The Journal of The North American Menopause Society
Vol. 27, No. 4, pp. 459-462
DOI: 10.1097/GME.0000000000001481
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OPEN

ORIGINAL STUDY

Relationship between *BRSK1* rs12611091 variant and age at natural menopause based on physical activity

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Abstract

Objectives: The rs12611091 variant in the BR serine/threonine kinase 1 gene is one of the variants previously associated with age at natural menopause. So far, this variant has not been replicated in Taiwanese women. The purpose of this study was to determine the association between rs12611091 and age at natural menopause based on physical activity.

Methods: A total of 1,758 women were eligible for analysis whose information about menopause was collected from the Taiwan Biobank. Multiple linear regression analysis was used for analysis.

Results: The mean age (standard deviation) at natural menopause was 50.82 (3.59) years. Of the eligible participants, 56.94% were rs12611091 CC carriers, 36.69% were TC carriers, and 6.37% were TT carriers. Compared to CC carriers, TC and TT carriers were associated with early menopause ($\beta = -0.42$, $P = 0.02$ and -0.87, $P = 0.01$, respectively). There was a significant interaction between rs12611091 and physical activity (P for interaction $= 0.02$). Compared to rs12611091 CC carriers, TC and TT carriers who were physically inactive were significantly associated with earlier menopause ($\beta = -0.88$, $P < 0.01$ and -1.25, $P = 0.02$, respectively).

Conclusion: We demonstrated that rs12611091 variant was associated with age at natural menopause especially among inactive women in Taiwan. That is, women with TC and TT genotypes who were physically inactive were significantly associated with earlier natural menopause compared to those with CC genotype.

Key Words: Biobank – Genetics – Menopause – Physical Activity.

Menopause is one of the important physiological events in a woman's life. It is a unique phenomenon for women that represents the end of reproductive life and has both clinical and health implications. The mean age at natural menopause (ANM) is 51 years in industrialized nations compared to 48 years in nonindustrialized nations.[1-3] Early menopause occurs before the age of 45 years and is associated with osteoporosis and cardiovascular disease risk, whereas late menopause, which occurs at the age of 54 years or older, is a well-established risk factor for breast and endometrial cancers.[4-6] Premature ovarian insufficiency occurs before the age of 40 years and the estimated prevalence is 1% of the general population.[7] In addition, women with premature ovarian insufficiency do not always stop menstruating. They, however, retain some degree of ovarian function unlike those with early or late menopause, which marks an irreversible state of ovarian senescence.[7]

Menopause has been associated with both modifiable and nonmodifiable risk factors,[3] some of which include socio-demographic, dietary, reproductive, demographic, and genetic factors. Compared with other Asian women, Taiwanese women have been associated with a higher percentage of menopause awareness.[8]

Previous studies have highlighted how behavioral and life-style factors are associated with ANM.[9,10] These factors have, however, not fully explained the age variance at which menopause commences.[11] Heritability serves as a major factor in determining menopause. According to the European Society for Human Reproduction and Embryology, ANM is 85% genetically determined.[12] Polymorphisms in several genes have previously been associated with the onset of menopause.[4,13] Despite the successful identification of those variants, not much has been done to replicate some of those variants in Asia. The rs12611091

Received August 20, 2019; revised and accepted September 19, 2019.
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Funding/support: This work was supported by the Ministry of Science and Technology (MOST 105-2627-M-040-002, 106-2627-M-040-002, 107-2627-M-040-002, 108-2621-M-040-001).

Financial disclosure/conflicts of interest: None reported.
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variant in the BR serine/threonine kinase 1 (*BRSK1*) gene is one of the variants previously associated with ANM. So far, this variant has not been replicated in Taiwanese women, for most genetic studies on menopause have focused on women of European ancestry.[14]

One of the modifiable lifestyle factors associated with ANM includes physical exercise. Findings on the links between menopause and physical activity have been conflicting, one of which showed that more physical activity was associated with late menopause, even though the association was not so strong.[15] Others have found no association with early menopause.[16] Women who did regular exercise for at least 3.2 hours/week were significantly associated with later menopause.[17] Despite variations in previous findings, exercise has predominantly positive outcomes for it has improved menopause-related health problems including cardiovascular disease, osteoporosis risk, and changes in body composition.[18] In the current study, we examined the association between rs12611091 variant, ANM, and physical activity among women in Taiwan.

METHODS

Study participants and data source

Data from Taiwan Biobank participants recruited at assessment centers across Taiwan from 2008 to 2016 were used in the current study. All participants aged 30 to 70 years had been provided signed consent to participate in Taiwan Biobank. Information about lifestyle factors representing physical activity, dietary habits, smoking and alcohol consumption, and menopausal status had been collected via self-report in questionnaires. Initially, we enrolled menopausal women ($n = 3{,}415$) and excluded those with missing information ($n = 1{,}657$). Eligible for analysis were 1,758 menopausal women. ANM was defined as a complete absence of a menstrual period for 12 consecutive months without a hysterectomy and was based on self-report. The selected characteristics were age, body mass index (BMI), physical activity, smoking, alcohol consumption, menarcheal age (age of first menstrual period), breastfeeding, labor, marital status, and vegetarian diet. Stratification was based on physical activity, which was defined as exercise three times per week for more than 30 minutes every time. The Institutional Review Board of Chung Shan Medical University approved this study.

Variant selection/genotyping

We selected ANM-associated variant (rs12611091), which has been replicated among Chinese but not Taiwanese women. Genotyping was performed using the Axiom-Genome Wide Array Plate (Affymetrix, Santa Clara, CA). We included only participants with call rates greater than 90% and excluded single nucleotide polymorphisms (SNPs) whose minor allele frequency were less than 0.05. Also excluded were SNPs whose genotypes deviated from the Hardy-Weinberg equilibrium.

Statistical analysis

We used the PLINK 1.09 beta and SAS 9.3 software (SAS Institute, Cary, NC) for data management and statistical analyses. A *t* test was used to compare differences between continuous variables, whereas the Chi-square test was used for the categorical variables. Multiple linear regression analysis was used to estimate the association between rs12611091 and ANM based on physical activity. Age, BMI, smoking, alcohol drinking, age at menarche, breastfeeding, parity, marital status, and vegetarian diet controlled for in our analyses. Data were presented as mean ± standard deviation (SD) for continuous variables.

RESULTS

Table 1 shows the basic characteristics of participants and their association with ANM. The mean age (SD) at natural menopause was 50.82 (3.59) years. Of the 1,758 eligible participants, 56.94% were CC carriers, 36.69% were TC carriers, and 6.37% were TT carriers. Compared to rs12611091 CC carriers, TC and TT carriers were associated with early menopause ($\beta = -0.42$, $P = 0.02$ and -0.87, $P = 0.01$, respectively). Also significantly associated with ANM was current vegetarian diet ($\beta = -0.99$, $P = 0.01$), BMI ($\beta = 0.09$, $P = 0.01$), nulliparity ($\beta = 1.73$, $P = 0.03$), and age and menarche ($\beta = 0.11$, $P = 0.04$). Table 2 shows the basic characteristics of participants according to physical activity. The mean age (SD) at natural menopause did not differ significantly between active and inactive menopausal women ($P = 0.08$). Active compared to inactive menopausal

TABLE 1. *Basic characteristics of participants and their associations with age at natural menopause*

	n (%)	β	*P*
rs12611091			
CC	1,001 (56.94)	Ref.	–
TC	645 (36.69)	−0.42	0.02
TT	112 (6.37)	−0.87	0.01
Age at menopause	50.82 ± 3.59	–	–
Age, y	58.93 ± 5.59	0.18	<0.01
BMI, kg/m^2	23.89 ± 3.17	0.09	0.01
Smoking			
Current	23 (1.31)	Ref.	–
Non	1,735 (98.69)	−0.45	0.54
Drinking			
Current	18 (1.02)	Ref.	–
Non	1,740 (98.98)	0.60	0.46
Physical activity			
Yes	1,051 (59.78)	Ref.	–
No	707 (40.22)	−0.01	0.97
Age at menarche, y	14.04 ± 1.58	0.11	0.04
Breastfeeding			
Yes	1,196 (68.03)	Ref.	–
No	562 (31.97)	−0.26	0.15
Parity			
Children	1,734 (98.63)	Ref.	–
No children	24 (1.37)	1.73	0.03
Marital status			
Married	1,332 (75.77)	Ref.	–
Never married	9 (0.51)	0.54	0.68
Divorced/widowed	417 (23.72)	−0.02	0.93
Vegetarian			
Non	1,583 (90.05)	Ref.	–
Former	79 (4.49)	−0.38	0.33
Current	96 (5.46)	−0.99	0.01

Results are presented as n (%) or as mean ± standard deviation (SD).
β = beta coefficient.

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TABLE 2. *Basic characteristics of study participants stratified by physical activity*

	Inactive	Active	*P*
rs12611091			0.17
CC	421 (59.55)	580 (55.19)	
TC	241 (34.09)	404 (38.44)	
TT	45 (6.36)	67 (6.37)	
Age at menopause, y	50.63 ± 3.66	50.94 ± 3.54	0.08
Age, y	57.82 ± 5.48	59.68 ± 5.54	<0.01
BMI, kg/m^2	24.17 ± 3.34	23.69 ± 3.04	0.01
Smoking			0.01
Current	16 (2.26)	7 (0.67)	
Non	691 (97.74)	1,044 (99.33)	
Drinking			0.02
Current	12 (1.7)	6 (0.57)	
Non	695 (98.3)	1,045 (99.43)	
Age at menarche	14.04 ± 1.58	14.03 ± 1.57	0.97
Breastfeeding			0.06
Yes	463 (65.49)	733 (69.74)	
No	244 (34.51)	318 (30.26)	
Parity			0.16
Children	694 (98.16)	1,040 (98.95)	
No children	13 (1.84)	11 (1.05)	
Marital status			0.09
Married	521 (73.69)	811 (77.16)	
Never married	6 (0.85)	3 (0.29)	
Divorced/widowed	180 (25.46)	237 (22.55)	
Vegetarian			0.08
Non	619 (87.55)	964 (91.72)	
Former	40 (5.66)	39 (3.71)	
Current	48 (6.79)	48 (4.57)	

Results are presented as n (%) or as mean ± standard deviation (SD).
BMI, body mass index.

women were older (59.68 ± 5.54 vs 57.82 ± 5.48 y, $P < 0.01$). Inactive menopausal women had a higher BMI (24.17 ± 3.34 vs 23.69 ± 3.04 kg/m^2, $P = 0.01$). Table 3 is a multiple linear regression analysis showing the association of rs12611091 genotypes and other covariates with ANM among active and inactive women. There was a significant interaction between rs12611091 and physical activity (P for interaction = 0.02). Compared to rs12611091 CC carriers, TC and TT carriers who were physically inactive were significantly associated with early menopause ($\beta = -0.88$, $P < 0.01$ and -1.25, $P = 0.02$, respectively). The association of the genotypes with ANN in physically active women were, however, not significant. Nulliparous women who were physically active were associated with later ANM ($\beta = 4.17$, $P = 0.01$). Menarcheal age had a significant association with ANM only in physically active women ($\beta = 0.17$, $P = 0.02$ vs $\beta = 0.02$, $P = 0.78$).

DISCUSSION

In the current study, we investigated whether habitual physical activity is associated with rs12611091 genotypes and ANM among women in Taiwan. We found that Taiwanese women with rs12611091 TC and TT genotypes were significantly associated with earlier menopause ($\beta = -0.42$, $P = 0.02$ and -0.87, $P = 0.01$, respectively) compared to those with CC genotype. We also found a significant interaction between the rs12611091 variant and physical activity. Interactions were also tested for this variant and other characteristics including age, BMI, smoking, alcohol drinking, age at menarche, breastfeeding, parity, marital status, and vegetarian diet but the results were not significant (data not shown). Further analysis of our data demonstrated that the association of rs12611091 with ANM was significant only in women who were physically inactive. Prior genetic studies on menopausal age have involved only women of European ancestry.[19] Therefore, modifiable lifestyle factors that may be associated with genetic variants and ANM have not been widely investigated. Although linked to decreased concentrations of reproductive hormones, habitual physical activity during adolescence and adulthood has been associated with later menopause.[10] Other findings have, however, revealed no associations.[20] Despite these results, we replicated the *BRSK1* rs12611091 variant and found a significant association with ANM particularly among women who were physically inactive. We cannot rule out chance as an explanation of the observed interaction considering that the underlying mechanism remains to be clarified.

Age at menarche, smoking, BMI, and race are some of the factors that have been independently and significantly linked to ANM.[21-24] As stated earlier, associations with physical activity have, however, been controversial.[24] In the present study, where exercise was adequately considered in our analyses, we found significant associations between age at menarche and ANM particularly among women who were physically active. We also found that current smokers in both physically active and inactive groups were associated with a slightly earlier ANM compared to those who never smoked, even though the results were not significant. Other studies have demonstrated that ANM is related to the timing and amount of smoking in a dose-response manner.[22,25,26]

In the current study, we used a large-scale sample size and results indicated that rs12611091 variant in the *BRSK1* gene which has shown significant association with menopause in other populations was also associated with ANM among women in Taiwan. The modifying role of physical activity on this menopause-associated variant, however, requires replication in additional studies. Despite our large sample size, complete information of more than half the population (mainly vegetarians) was not available in the biobank. In addition, both ANM and age at menarche were self-reported; hence, information bias cannot be ruled out.

TABLE 3. *Association of rs12611091 genotypes and physical activity with age at natural menopause*

	Inactive		Active	
	β	*P*	β	*P*
rs12611091				
CC	Ref.	–	Ref.	–
TC	−0.88	0.01	−0.10	0.66
TT	−1.25	0.02	−0.48	0.28

SNP∗exercise, 0.02. Adjusted for age, body mass index, smoking, alcohol drinking, age at menarche, breastfeeding, parity, marital status, and vegetarian diet.
β, beta coefficient.

CONCLUSIONS

In summary, we have provided more knowledge about the association between *BRSK1* rs12611091 variant and ANM based on physical activity. Our findings indicated that rs12611091 variant was associated with ANM among women in Taiwan. Stratification by physical activity showed that this association was significant only among inactive women. That is, women with TC and TT genotypes who were physically inactive were significantly associated with earlier natural menopause compared to those with CC genotype. These preliminary findings support the necessity for more replication studies involving menopausal women in Taiwan.

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