Published in final edited form as:
Headache. 2009 February 1; 49(2): 235–244. doi:10.1111/j.1526-4610.2008.01207.x.

Association between polymorphisms in the β2-adrenoceptor gene and migraine in women

Markus Schürks, MD, MSc[1], **Tobias Kurth, MD, ScD**[1,2,3], **Paul M Ridker, MD, MPH**[1,3], **Julie E. Buring, ScD**[1,2,3,4], and **Robert Y. L. Zee, MD, PhD**[1]

1 *Division of Preventive Medicine, Department of Medicine; Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

2 *Division of Aging, Department of Medicine; Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

3 *Department of Epidemiology, Harvard School of Public Health, Boston, MA*

4 *Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, MA*

Abstract

Objective—To investigate the role of three common polymorphisms in the β2 adrenoceptor gene in migraine.

Background—Migraine has been associated with increased risk of cardiovascular disease and asthma in which β2 adrenoceptors play an important role; β adrenoceptor antagonists are used in migraine prevention. However, the role of variants in the β2 adrenoceptor gene in migraine is unclear.

Methods—Association study among 23,753 white women, participating in the Women's Health Study, for whom we had information on migraine at baseline and genotype status of the polymorphisms rs1042713 (Gly16Arg), rs1042714 (Gln27Glu), rs1800888 (Thr164Ile). Migraine was self-reported and we distinguished between any history of migraine, active migraine with and without aura, and prior migraine (history of migraine but not active migraine) in our analyses.

Corresponding author: Tobias Kurth, MD, ScD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, 3rd fl, Boston, MA 02215-1204, USA, Phone: 617-732-8355; Fax: 617-731-3843, E-mail: tkurth@rics.bwh.harvard.edu.

Full disclosures

Dr. Schürks has received within the last 5 years investigator-initiated research funds from the Deutsche Forschungsgemeinschaft and an unrestricted research grant from Merck, Sharp and Dohme.

Dr. Kurth has received within the last 5 years investigator-initiated research funding as Principal or Co-Investigator from the National Institutes of Health, Bayer AG, McNeil Consumer & Specialty Pharmaceuticals, and Wyeth Consumer Healthcare; he is a consultant to i3 Drug Safety, and received an honorarium from Organon for contributing to an expert panel.

Dr. Ridker has received within the last 5 years investigator-initiated research funding and research support from the National Heart, Lung, and Blood Institute, the Doris Duke Charitable Foundation, the Leducq Foundation, the Donald W. Reynolds Foundation, the American Heart Association, the James and Polly Annenberg La Vea Charitable Trusts, AstraZeneca, Bayer, Bristol-Myers Squibb, Dade-Behring, Novartis, Pharmacia, Roche, Sanofi/Aventis, and Variagenics. Dr Ridker reports being listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and has served as a consultant to Schering-Plough, Sanofi/Aventis, AstraZeneca, Isis Pharmaceuticals, Dade-Behring, and Interleukin Genetics.

Dr. Buring has received within the last 5 years investigator-initiated research funding and support as Principal Investigator from the National Institutes of Health (the National Heart, Lung, and Blood Institute, the National Cancer Institute, and the National Institute of Aging) and Dow Corning Corporation; research support for pills and/or packaging from Bayer Heath Care and the Natural Source Vitamin E Association; honoraria from Bayer for speaking engagements; and serves on an external scientific advisory committee for a study by Procter & Gamble.

Dr. Zee has received within the last 5 years research support from the National Heart, Lung, and Blood Institute, the Doris Duke Charitable Foundation, the Leducq Foundation, the Donald W. Reynolds Foundation, and Roche.

Results—At baseline 4,339 women reported any history of migraine. Of these 3,041 had active migraine (1,221 migraine with aura, 1,820 migraine without aura) and 1,298 prior migraine. No migraine was reported by 19,414 women. Genotype- and haplotype-based analyses did not show an association of any of the gene variants tested with any history of migraine. The multivariable-adjusted odds ratios (ORs) (95% confidence intervals) for any history of migraine in the additive model were 1.0 (0.96–1.05) for rs1042713, 1.0 (0.95–1.05) for rs1042714, and 0.84 (0.68–1.05) for rs1800888. In the haplotype analysis the ORs ranged from 0.83 (0.67–1.03) to 1.01 (0.94–1.07) with Gly16-Glu27-Thr164 as the reference. We also did not find associations in the genotype- and haplotype-based analyses within migraine-specific subgroups.

Conclusions—Our results do not support a role of three investigated polymorphisms in the β2 adrenoceptor gene in migraine pathophysiology.

Keywords

migraine; β2 adrenoceptor; ADRB2; women

Introduction

Migraine is a common primary headache disorder characterized by recurrent headache attacks associated with autonomous symptoms.[1] The pathophysiology of migraine involves both neuronal and vascular dysfunctions.[2] It has been hypothesized that an underlying cerebral hyperexcitability triggers cortical spreading depression (CSD). CSD probably activates the trigeminal system, resulting in perivascular neurogenic inflammation and sensitisation of the trigeminovascular system. Vessel pulsation then leads to excess activation of trigeminal nerve fibres and brain stem activation. Trigeminal neurons relay nociception to the thalamus and thalamocortical projections provoke pain perception.[3] Many neurotransmitters with vasoactive properties are involved in this complex pain circuit. Potent vasoconstrictors including serotonin (5-HT) and epinephrine terminate migraine attacks, while vasodilators may provoke them.[4]

Several aspects suggest an important role of peripheral β2-adrenoceptors in the pathophysiology of migraine. First, epidemiological studies have linked migraine to both cardiovascular disease (CVD)[5–10] and asthma[11, 12] in which β2-adrenoceptors play an important physiologic role.[13–15] Second, antagonists at β adrenoceptors are effective preventive treatments for migraine.[16] Since penetration of the blood-brain barrier does not appear to be essential for the preventive action of βadrenoceptors antagonist,[17] β2-adrenoceptors located on vascular smooth muscle cells, the endothelium, and on prejunctional nerve terminals on cerebral and peripheral vasculature, represent important candidates involved in the pathophysiology of migraine. β2-adrenoceptors are highly polymorphic.[18] Three exonic polymorphisms in the β2-adrenoceptor gene (*ADRB2*) are functionally relevant;[19] Arg16Gly and Gln27Glu have been shown to affect receptor down-regulation, while Thr164Ile affects G-protein coupling.[20–22]

We thus sought to investigate whether these *ADRB2* exonic gene variants associate with migraine in a large prospective cohort of over 23,000 apparently healthy Caucasian women from the Women's Health Study (WHS).

Subjects and Methods

Study Population

The WHS was a randomized, placebo-controlled trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among apparently healthy women. The design, methods, and results have been described in detail previously.

[23, 24] Briefly, a total of 39,876 U.S. female health professionals aged ≥45 years at baseline in 1993 without a history of CVD, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent and the Institutional Review Board of Brigham and Women's Hospital approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables.

Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) from 28,345 participating women prior to randomization. After excluding participants with missing migraine and genotype information on the ADRB2 at baseline, we were left with information on 25,156 women in the data set. We further excluded non-white women (n=1,403) to avoid race-specific genetic interaction, leaving 23,753 white women for analyses.

Assessment of migraine

Participants were asked on the baseline questionnaire: "Have you ever had a migraine headache?" and "In the past year, have you had a migraine headache?" From this information, we categorized women into "no migraine history" and "any history of migraine." Furthermore, we distinguished between "active migraine," which includes women with self-reported migraine during the year prior to completing the baseline questionnaire, and "prior migraine," which includes women who reported ever having had a migraine but none in the year prior to completing the questionnaire. Those participants who reported active migraine were asked details about their migraine attacks, including attack duration of 4 to 72 hours; unilateral location of pain; pulsating quality; inhibition of daily activities; aggravation by routine physical activity; nausea or vomiting; sensitivity to light; and sensitivity to sound. In previous studies of the WHS,[8, 25] we have shown good agreement with modified 1988 International Headache Society (IHS) criteria for migraine.[26] Specifically, we showed that among WHS participants who provided a blood sample and reported active migraine, 83.5% fulfilled all but one modified IHS criteria (code 1.7, migrainous disorder) and 46.6% fulfilled all modified IHS criteria for migraine (code 1.1).[8] Participants who reported active migraine were further asked whether they had an "aura or any indication a migraine is coming." Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura.

DNA genotyping

Genotype determination for the *ADRB2* polymorphisms (Gly16Arg – rs1042713, Gln27Glu – rs1042714, Thr164Ile – rs1800888) was accomplished using multiplex polymerase chain reaction (PCR) and immobilized probe-based assays developed for multi-locus variant detection (Roche Molecular Systems, Alameda, CA) essentially as described elsewhere.[27] Genotype scoring was carried out by two independent observers. Discordant rates (<2%) were resolved by a further joint reading and, where necessary, by a repeat genotyping. All results were scored blinded to migraine status.

Statistics

We compared baseline characteristics of participants with respect to their migraine status using chi-square test for categorical variables and t-test for continuous variables.

Genotype and allele frequencies between women with any history of migraine and without migraine were compared using chi-square analysis. Linkage disequilibrium (LD) was examined as described by Devlin and Risch, using Lewontin's D' as the LD measure.[28] We used logistic regression analysis to evaluate the association between each of the polymorphisms (rs1041713, rs1042714, rs1800888) and migraine. Previous studies in the WHS[8] and our study

have shown imbalances in a number of baseline physical and lifestyle characteristics between women with and without migraine, thus these characteristics may also affect the association between gene variants and migraine. Hence, in multivariable analyses, we adjusted for the following covariates: age (continuous), body mass index (continuous), exercise (never, <1/week, 1–3/week, ≥4/week), postmenopausal hormone use (never, past, current), history of oral contraceptive use (yes, no), postmenopausal status (premenopausal, postmenopausal, biologically uncertain, unclear), history of hypertension (yes, no), alcohol consumption (never, 1–3 drinks/month, 1–6 drinks/week, >1 drink/day), and smoking (never, past, current <15 cigarettes/day, current ≥15 cigarettes/day).

We incorporated a missing value indicator if the number of women with missing information on covariates was ≥100 or imputed a value otherwise. We calculated odds ratios (OR) and 95% confidence intervals (CI) for 1) any history of migraine, 2) active migraine with aura, 3) active migraine without aura, and 4) prior migraine.

Haplotype inference and estimation were determined from genotype data using the Expectation-Maximization algorithm.[29, 30] In addition, the possible associations between haplotypes and the pre-defined clinical outcomes were examined by a maximum likelihood-based approach as described previously.[29, 30] Analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC) and HAPSTAT;[29, 30] a computer program posted on the website: http://www.bios.unc.edu/~lin. All p-values were two-tailed. For the genotype and haplotype analyses we considered $p<0.01$ significant, while for all other analyses we chose a significance level of $p<0.05$.

Results

At baseline 4,339 (18.3%) women reported any history of migraine. Of these, 3,041 (70.1%) reported active migraine and 1,298 (29.9%) prior migraine (history of migraine but not active migraine in the year prior to the baseline questionnaire). Among active migraineurs 1,221 (40.2%) had migraine with aura and 1,820 (59.8%) migraine without aura. No history of migraine was reported by 19,414 women.

The baseline characteristics of women according to migraine status are presented in Table 1. Women with any history of migraine were slightly younger and had a higher body mass index compared with women without migraine. Furthermore, women with any history of migraine were less physically active, more likely to be premenopausal, to use postmenopausal hormones, and to have used oral contraceptives. They also drank less alcohol and smoked less. History of hypertension was equally distributed in both groups.

The observed genotype distribution for marker rs1042714 was in Hardy-Weinberg-Equilibrium in the group of women with no history of migraine (chi-square with 1 degree of freedom: p-value: 0.77). However, the genotype distributions for markers rs1042713 and rs1800888 (chi-square with 1 degree of freedom: p-value: 0.0018 and 0.016) were in Hardy-Weinberg-Disequilibrium, which is most likely due to the large sample size, rendering the test statistic susceptible to minor allele frequency variations. There was no difference in the genotype and allele distribution for any of the 3 polymorphisms between women with and without migraine (Table 2). The polymorphisms tested were in strong linkage disequilibrium among each other (rs1042713-rs1042714: D'=0.99; rs1042713-rs1800888: D'=1.0; rs1042714-rs1800888: D'=1.0).

Results from the single-marker analyses, controlling for age and the aggregate of covariates, did not show an association between rs1042713 and rs1042714 and any history of migraine (Table 3). These results were very similar for active migraine with and active migraine without aura, and women with prior migraine. The multivariable-adjusted odds ratio in the additive

model for rs1800888 was suggestive of a protective role for the variant allele (OR=0.84; 95% CI: 0.68–1.05). This effect was slightly more pronounced in women with active migraine without aura (OR=0.74; 95% CI: 0.53–1.05). However, none of the results were significant.

Table 4 lists haplotype frequencies >1%. They were similarly distributed between women without and women with any history of migraine. Gly16-Glu27-Thr164 was the most frequent haplotype. Haplotype Gly16-Gln27-Ile164 was present in < 1% of women with active migraine without aura and was not further considered for the haplotype-based analysis in this subgroup. In haplotype-based analysis we did not find any evidence for an association between the haplotypes tested and any history of migraine (Table 5). The results remained unchanged regardless of analyzing women with active migraine with aura, women with active migraine without aura, and women with a prior history of migraine separately.

Discussion

In this large study of over 23,000 Caucasian women, we did not find a single-marker association between three functionally relevant polymorphisms in the *ADRB2* gene and migraine or migraine aura status. Although the ORs for rs1800888 were suggestive of a protective effect, particularly in active migraine without aura, the results were not statistically significant. Further, analysis using haplotype information also did not reveal any association with any of the migraine groups.

The importance of β-adrenoceptors in the pathophysiology of migraine has long been hypothesized, since β-adrenoceptor antagonists are well-established in migraine prevention.[16] However, mainly β1-adrenoceptors have been favored.[31] Moreover, migraine research has been largely focused on the cortical hyperexcitability and thus cerebral β-adrenoceptors. β-adrenoceptors are widely distributed throughout the brain, including the brain stem and the thalamus.[32, 33] In addition, animal studies in migraine have shown that chronic treatment with propranolol suppresses CSD[34] and have suggested that β-adrenoceptors, most likely β1-adrenoceptors, in the thalamus are involved in nociception.[35] However, this concept disregards the vascular aspect in migraine pathophysiology and several findings advocate an important role of peripheral β2-adrenoceptors.

Firstly, epidemiological studies have linked migraine, especially migraine with aura, with an increased risk of ischemic stroke,[5–7] major ischemic CVD, including coronary heart disease[8, 10] and an elevated Framingham risk score for coronary heart disease.[9] Moreover β2 adrenergic receptors (ADRB2) play an important role in the pathogenesis of cardiovascular disorders[13] and common polymorphisms have been shown to modulate the risk for myocardial infarction.[36] Secondly, recent studies have suggested an association between migraine and asthma.[11, 12] β2-adrenoceptors are important in the pathophysiology of asthma and polymorphisms in the *ADRB2* gene have been reported to influence treatment response in asthma.[14, 15] Thirdly, a dysfunction of the sympathetic nervous system is a striking feature among migraine patients,[37] which is also mirrored by a higher lifetime prevalence and frequency of syncope and orthostatic intolerance in migraine patients.[38] This results from altered peripheral vascular reactivity, which is primarily determined by alpha- and β2-adrenoceptors.[39] Fourthly, antagonists at β-adrenoceptors are recommended as first line preventive treatment[16] and are also used in some forms of autonomic dysfunction.[40] Finally, β-adrenoceptor antagonists that poorly penetrate the blood-brain barrier, for example atenolol, are also effective in migraine prevention, suggesting a peripheral side of action.[17]

Experimental studies have provided evidence for the functional relevance of the three non-synonymous polymorphisms in *ADRB2* investigated. While Arg16Gly and Gln27Glu aggravate β2-adrenoceptor downregulation, Thr164Ile impairs G-protein coupling.[20–22] This

polymorphism has been suggested to modulate the risk for progression of congestive heart failure,[41] and haplotype analyses of the Arg16Gly and Gln27Glu polymorphisms have found a higher frequency of the Gly16-Gln27 haplotype for bronchial hyperresponsivness.[42] Furthermore, a recent report has associated the Gly16-Gln27-Ile164 haplotype with the risk for myocardial infarction.[36]

Our study has several strengths, including the large number of participants and women with migraine, use of standardized questionnaires, and the homogenous nature of the cohort, which may reduce confounding.

Several limitations of our study should be considered when interpreting our results. First, migraine and aura status were self-reported and were not classified according to strict IHS criteria.[26] For example, women were not asked if they had moderate or severe headache intensity, which is among the diagnostic criteria for migraine. Thus, non-differential misclassification is possible, which may have obscured a true *ADRB2*-migraine association. However, our migraine ascertainment allowed us to classify migraine according to modified IHS criteria,[8, 25] which showed consistent agreement with modified 1988 IHS criteria of migraine. Second, our aura definition was broad and we had no further details to classify participants according to the IHS criteria for migraine aura. Although our aura prevalence is close to other large population-based studies,[43, 44] misclassification is possible. Third, participants were all white female health professionals age ≥45, thus generalizability to other female populations or men may be limited. However, *a priori* we have no reason to believe that the pathophysiology of migraine differs between women and men. Finally, association studies like the present one only examine the possible association between a phenotype and the actually tested polymorphism(s) and respective haplotypes. Such studies cannot exclude the possibility that examination of a different polymorphism(s) –not in linkage disequilibrium with the variants tested– might lead to different results.

Several reasons may account for our negative result. First, migraine is a complex disease with a polygenic origin, a wide phenotypic distribution, and various potential co-morbidities.[45] β2-adrenoceptors may only play a role in a subgroup of patients suffering from certain co-morbid conditions. Thus, in future investigations of migraineurs with certain co-morbid phenotypes might be warranted. Second, β-adrenoceptors may be of pharmacogenetic rather than disease-specific relevance. This may be part of the reason why only about 50% of migraine patients respond to treatment with β-adrenoceptor antagonists.[16, 31] Third, a gene-environment interaction needs to be considered. Given the established increased risk for cardiovascular disease and stroke in migraine patients,[6, 8, 10] the presence of *ADRB2* polymorphisms may modify this risk. Finally, the dysfunction of the sympathetic nervous system seen in migraine may also be related to other sympathetic co-transmitters or their receptors.[37]

Acknowledgements

We are indebted to the participants in the Women's Health Study for their outstanding commitment and cooperation; to the entire Women's Health Study staff for their expert and unfailing assistance.

Funding and Support

The Women's Health Study is supported by grants from the National Heart, Lung, and Blood Institute (HL-43851), and the National Cancer Institute (CA-47988). The research for this work was supported by grants from the Donald W. Reynolds Foundation, the Leducq Foundation, and the Doris Duke Charitable Foundation. The authors also thank F. Hoffmann La-Roche and Roche Molecular Systems, Inc. for supporting the genotype-determination financially and with in-kind contribution of reagents and consumables. Dr. Schürks was supported by a grant from the Deutsche Forschungsgemeinschaft. The funding agencies played no role in the design, conduct, data management, analysis, or manuscript preparation related to this manuscript.

Abbreviations

CSD
cortical spreading depression

5-HT
serotonin

ADRB2
β2-adrenocptor gene

WHS
Women's Health Study

IHS
International Headache Society

References

1. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24(Suppl 1): 9–160. [PubMed: 14979299]
2. Moskowitz MA. Pathophysiology of headache-past and present. Headache 2007;47(Suppl 1):S58–63. [PubMed: 17425711]
3. Iadecola C. From CSD to headache: a long and winding road. Nat Med 2002;8:110–112. [PubMed: 11821889]
4. Humphrey PP. The discovery of a new drug class for the acute treatment of migraine. Headache 2007;47 (Suppl 1):S10–19. [PubMed: 17425704]
5. Buring JE, Hebert P, Romero J, et al. Migraine and subsequent risk of stroke in the Physicians' Health Study. Arch Neurol 1995;52:129–134. [PubMed: 7848119]
6. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 2005;64:1020–1026. [PubMed: 15781820]
7. Stang PE, Carson AP, Rose KM, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology 2005;64:1573–1577. [PubMed: 15883318]
8. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. JAMA 2006;296:283–291. [PubMed: 16849661]
9. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. Neurology 2005;64:614–620. [PubMed: 15728281]
10. Kurth T, Gaziano JM, Cook NR, et al. Migraine and risk of cardiovascular disease in men. Arch Intern Med 2007;167:795–801. [PubMed: 17452542]
11. Aamodt AH, Stovner LJ, Langhammer A, Hagen K, Zwart JA. Is headache related to asthma, hay fever, and chronic bronchitis? The Head-HUNT Study. Headache 2007;47:204–212. [PubMed: 17300360]
12. Davey G, Sedgwick P, Maier W, Visick G, Strachan DP, Anderson HR. Association between migraine and asthma: matched case-control study. Br J Gen Pract 2002;52:723–727. [PubMed: 12236275]
13. Johnson JA, Terra SG. Beta-adrenergic receptor polymorphisms: cardiovascular disease associations and pharmacogenetics. Pharm Res 2002;19:1779–1787. [PubMed: 12523655]
14. Matheson MC, Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ. Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults. J Hum Genet 2006;51:943–951. [PubMed: 16946993]
15. Thakkinstian A, McEvoy M, Minelli C, et al. Systematic review and meta-analysis of the association between {beta}2-adrenoceptor polymorphisms and asthma: a HuGE review. Am J Epidemiol 2005;162:201–211. [PubMed: 15987731]
16. Silberstein SD. Preventive treatment of migraine. Trends Pharmacol Sci 2006;27:410–415. [PubMed: 16820222]

17. Johannsson V, Nilsson LR, Widelius T, et al. Atenolol in migraine prophylaxis a double-blind cross-over multicentre study. Headache 1987;27:372–374. [PubMed: 3308768]
18. Liggett SB. beta(2)-adrenergic receptor pharmacogenetics. Am J Respir Crit Care Med 2000;161:S197–201. [PubMed: 10712374]
19. Reihsaus E, Innis M, MacIntyre N, Liggett SB. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. Am J Respir Cell Mol Biol 1993;8:334–339. [PubMed: 8383511]
20. Chong LK, Chowdry J, Ghahramani P, Peachell PT. Influence of genetic polymorphisms in the beta2-adrenoceptor on desensitization in human lung mast cells. Pharmacogenetics 2000;10:153–162. [PubMed: 10762003]
21. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol 1995;13:25–33. [PubMed: 7598936]
22. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry 1994;33:9414–9419. [PubMed: 7915137]
23. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. J Womens Health Gend Based Med 2000;9:19–27. [PubMed: 10718501]
24. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304. [PubMed: 15753114]
25. Bensenor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE. Low-dose aspirin for migraine prophylaxis in women. Cephalalgia 2001;21:175–183. [PubMed: 11442551]
26. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8 (Suppl 7):1–96.
27. Zee RY, Hoh J, Cheng S, et al. Multi-locus interactions predict risk for post-PTCA restenosis: an approach to the genetic analysis of common complex disease. Pharmacogenomics J 2002;2:197–201. [PubMed: 12082592]
28. Devlin B, Risch N. A comparison of linkage disequilibrium measures for fine-scale mapping. Genomics 1995;29:311–322. [PubMed: 8666377]
29. Lin DY, Zeng D. Likelihood-based inference on haplotype effects in genetic association studies. Journal of the American Statistical Association 2006;101:89–104.
30. Lin DY, Zeng D, Millikan R. Maximum likelihood estimation of haplotype effects and haplotype-environment interactions in association studies. Genet Epidemiol 2005;29:299–312. [PubMed: 16240443]
31. Limmroth V, Michel MC. The prevention of migraine: a critical review with special emphasis on beta-adrenoceptor blockers. Br J Clin Pharmacol 2001;52:237–243. [PubMed: 11560555]
32. Reznikoff GA, Manaker S, Rhodes CH, Winokur A, Rainbow TC. Localization and quantification of beta-adrenergic receptors in human brain. Neurology 1986;36:1067–1073. [PubMed: 3016604]
33. van Waarde A, Visser TJ, Elsinga PH, et al. Imaging beta-adrenoceptors in the human brain with (S)-1'-[18F]fluorocarazolol. J Nucl Med 1997;38:934–939. [PubMed: 9189145]
34. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 2006;59:652–661. [PubMed: 16450381]
35. Shields KG, Goadsby PJ. Propranolol modulates trigeminovascular responses in thalamic ventroposteromedial nucleus: a role in migraine? Brain 2005;128:86–97. [PubMed: 15574468]
36. Zee RY, Cook NR, Reynolds R, Cheng S, Ridker PM. Haplotype analysis of the beta2 adrenergic receptor gene and risk of myocardial infarction in humans. Genetics 2005;169:1583–1587. [PubMed: 15520258]
37. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache 2004;44:53–64. [PubMed: 14979884]
38. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine: the population-based CAMERA study. Neurology 2006;66:1034–1037. [PubMed: 16606915]

39. Guimaraes S, Moura D. Vascular adrenoceptors: an update. Pharmacol Rev 2001;53:319–356. [PubMed: 11356987]
40. Lamarre-Cliche M. Drug treatment of orthostatic hypotension because of autonomic failure or neurocardiogenic syncope. Am J Cardiovasc Drugs 2002;2:23–35. [PubMed: 14727996]
41. Liggett SB, Wagoner LE, Craft LL, et al. The Ile164 beta2-adrenergic receptor polymorphism adversely affects the outcome of congestive heart failure. J Clin Invest 1998;102:1534–1539. [PubMed: 9788966]
42. D'Amato M, Vitiani LR, Petrelli G, et al. Association of persistent bronchial hyperresponsiveness with beta2-adrenoceptor (ADRB2) haplotypes. A population study. Am J Respir Crit Care Med 1998;158:1968–1973. [PubMed: 9847294]
43. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537–542. [PubMed: 10449117]
44. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 2001;41:646–657. [PubMed: 11554952]
45. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. Curr Opin Neurol 2005;18:305–310. [PubMed: 15891417]

Table 1

Baseline characteristics of participants in the Women's Health Study according to migraine status (n=23,753) *

Characteristics	No migraine N=19,414	Any history of migraine N=4,339	p-value†
Age, mean (SD), y	55.0 (7.3)	53.7 (6.5)	<0.0001
Body mass index, mean (SD), kg/m^2	25.9 (4.9)	26.1 (5.0)	0.015
History of hypertension	24.3	25.6	0.09
Physical activity			
Never	37.1	38.1	<0.0001
<1/week	19.2	21.6	
1–3/week	31.9	29.7	
≥4/wk	11.8	10.6	
Menopausal status			
Premenopausal	27.6	27.6	<0.0001
Postmenopausal	55.4	50.0	
Biologically uncertain	13.1	17.9	
Unclear	3.9	4.5	
Postmenopausal hormone therapy			
Never	49.3	44.2	<0.0001
Past	8.8	9.3	
Current	41.9	46.5	
History of oral contraceptive use			
No	31.5	25.1	<0.0001
Yes	68.2	74.4	
Not sure	0.3	0.5	
Alcohol consumption			
Never	42.7	46.3	<0.0001
1–3 drinks/month	13.0	14.2	
1–6 drinks/week	33.1	31.0	
≥1 drink/day	11.2	8.5	
Smoking status			
Never	50.7	53.3	0.01
Past	37.8	35.8	
Current <15 cigarettes/day	4.2	3.7	
Current ≥15 cigarettes/day	7.3	7.2	

* data are expressed as percentages unless otherwise stated.

† p-values for chi-square test for categorical variables, and t-test for continuous variables.

Proportions may not add up to 100 due to rounding or missing values.

Table 2

Genotype and allele frequencies in women according to migraine status

Frequencies	No migraine N=19,414	Any history of migraine N=4,339	p-value*
Genotype, % rs1042713 (Gly16Arg)			
Gly16Gly16	39.4	39.4	
Gly16Arg16	47.6	47.5	
Arg16Arg16	13.0	13.1	0.99
Allele			
Gly16	0.63	0.63	
Arg16	0.37	0.37	0.94
Genotype, % rs1042714 (Gln27Glu)			
Gln27Gln27	31.9	31.8	
Gln27Glu27	49.2	49.4	
Glu27Glu27	18.9	18.8	0.99
Allele			
Gln27	0.57	0.56	
Glu27	0.43	0.44	0.95
Genotype, % rs1800888 (Thr164Ile)			
Thr164Thr164	97.35	97.8	
Thr164Ile164	2.61	2.2	
Ile164Ile164	0.04	0	0.15
Allele			
Thr164	0.99	0.99	
Ile164	0.01	0.01	0.09

* p-values for chi-square test.

Table 3

Age- and multivariable adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for migraine according to single nucleotide polymorphisms in the *ADRB2* gene

Polymorphism	Age-adjusted			Multivariable-adjusted*		
	OR	95% CI	p-value	OR	95% CI	p-value
Any history of migraine (n=4,339)						
rs1042713 (Arg16Gly)						
additive mode	1.00	0.96–1.05	0.88	1.00	0.96–1.05	0.88
dominant mode	1.00	0.94–1.08	0.89	1.00	0.94–1.08	0.90
recessive mode	1.00	0.91–1.11	0.93	1.01	0.91–1.11	0.90
rs1042714 (Gln27Glu)						
additive mode	1.00	0.95–1.05	0.97	1.00	0.95–1.05	0.98
dominant mode	1.00	0.94–1.08	0.94	1.01	0.94–1.08	0.88
recessive mode	0.99	0.91–1.08	0.88	0.99	0.91–1.08	0.89
rs1800888 (Thr164Ile)						
additive mode	0.84	0.67–1.04	0.11	0.84	0.68–1.05	0.13
dominant mode	0.85	0.68–1.05	0.13	0.85	0.68–1.06	0.16
recessive mode	…	…	…	…	…	…
Active migraine with aura (n=1,221)						
rs1042713 (Arg16Gly)						
Additive mode	1.01	0.93–1.10	0.76	1.02	0.93–1.10	0.69
dominant mode	1.07	0.95–1.21	0.24	1.08	0.96–1.22	0.22
recessive mode	0.91	0.76–1.08	0.28	0.91	0.76–1.09	0.32
rs1042714 (Gln27Glu)						
additive mode	1.00	0.92–1.09	0.95	1.00	0.92–1.09	0.99
dominant mode	1.02	0.90–1.15	0.81	1.01	0.90–1.15	0.84

Polymorphism	Age-adjusted			Multivariable-adjusted*		
	OR	95% CI	p-value	OR	95% CI	p-value
recessive mode	0.99	0.85–1.15	0.86	0.98	0.85–1.14	0.83
rs1800888 (Thr164Ile)						
additive mode	0.89	0.61–1.29	0.53	0.90	0.62–1.31	0.59
dominant mode	0.90	0.61–1.31	0.58	0.91	0.62–1.33	0.63
recessive mode	….	….	….	….	….	….
Active migraine without aura(n=1,820)						
rs1042713 (Arg16Gly)						
additive mode	0.99	0.92–1.06	0.68	0.99	0.92–1.06	0.70
dominant mode	0.97	0.88–1.07	0.52	0.97	0.88–1.07	0.53
recessive mode	1.01	0.87–1.16	0.92	1.01	0.88–1.17	0.89
rs1042714 (Gln27Glu)						
additive mode	1.01	0.94–1.08	0.78	1.01	0.94–1.08	0.80
dominant mode	1.03	0.93–1.14	0.61	1.03	0.92–1.14	0.63
recessive mode	0.99	0.88–1.13	0.93	0.99	0.88–1.12	0.90
rs1800888 (Thr164Ile)						
additive mode	0.74	0.53–1.04	0.08	0.74	0.53–1.05	0.09
dominant mode	0.75	0.53–1.05	0.09	0.75	0.53–1.06	0.10
recessive mode	….	….	….	….	….	….
Prior migraine(n=1,298)						
rs1042713 (Arg16Gly)						
additive mode	1.02	0.94–1.11	0.68	1.01	0.93–1.10	0.75
dominant mode	0.99	0.88–1.11	0.89	0.99	0.88–1.11	0.82
recessive mode	1.09	0.93–1.28	0.30	1.08	0.92–1.28	0.33

Polymorphism	Age-adjusted			Multivariable-adjusted*		
	OR	95% CI	p-value	OR	95% CI	p-value
rs1042714 (Gln27Glu)						
additive mode	0.99	0.91–1.07	0.71	0.99	0.91–1.07	0.81
dominant mode	0.96	0.86–1.09	0.54	0.97	0.86–1.09	0.61
recessive mode	1.01	0.87–1.16	0.94	1.01	0.88–1.17	0.86
rs1800888 (Thr164Ile)						
additive mode	0.91	0.64–1.30	0.62	0.92	0.65–1.32	0.66
dominant mode	0.93	0.64–1.33	0.67	0.94	0.65–1.34	0.72
recessive mode	….	….	…..	….	….	….

*controlling for: age, body mass index, physical activity, hormone replacement therapy, oral contraceptive use, postmenopausal status, history of hypertension, alcohol consumption, and smoking categories.

Table 4

Haplotype frequencies of the 3 single nucleotide polymorphisms in the *ADRB2* gene (rs1042713, rs1042714, rs1800888) by migraine status

Haplotype	No history of migraine N=19,414	Any history of migraine N=4,339	Active migraine with aura N=1,221	Active migraine without aura N=1,820	Prior migraine N=1,298
Gly16-Gln27-Thr164	0.185	0.187	0.184	0.189	0.186
Gly16-Gln27-Ile164	0.013	0.011	0.012	--	0.012
Gly16-Glu27-Thr164	0.434	0.434	0.434	0.434	0.429
Arg16-Gln27-Thr164	0.367	0.367	0.368	0.364	0.371

Only haplotype frequencies >1% are shown.

Table 5

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for haplotypes >1% by migraine status: Gly16-Glu27-Thr164 as the reference haplotype

Haplotypes	OR	95% CI	p-value
Any history of migraine			
Gly16-Glu27-Thr164	1.00	Reference	----
Gly16-Gln27-Thr164	1.01	0.94; 1.07	0.81
Gly16-Gln27-Ile164	0.83	0.67; 1.03	0.09
Arg16-Gln27-Thr164	1.00	0.95; 1.05	1.00
Active migraine with aura			
Gly16-Glu27-Thr164	1.00	Reference	----
Gly16-Gln27-Thr164	0.99	0.88; 1.11	0.86
Gly16-Gln27-Ile164	0.88	0.60; 1.28	0.50
Arg16-Gln27-Thr164	1.00	0.91; 1.10	0.99
Active migraine without aura			
Gly16-Glu27-Thr164	1.00	Reference	----
Gly16-Gln27-Thr164	1.02	0.93; 1.12	0.65
Arg16-Gln27-Thr164	0.99	0.92; 1.07	0.86
Prior migraine			
Gly16-Glu27-Thr164	1.00	Reference	----
Gly16-Gln27-Thr164	1.02	0.91; 1.14	0.77
Gly16-Gln27-Ile164	0.92	0.64; 1.33	0.67
Arg16-Gln27-Thr164	1.02	0.93; 1.12	0.66