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Hormonally modulated migraine is associated with single-nucleotide polymorphisms within genes involved in dopamine metabolism

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ABSTRACT

Migraine is a complex trait in which multiple genetic loci, as well as environmental factors, likely contribute to its clinical manifestation. Many genetic associations reported in previous studies either have not been replicated to date or showed only marginal statistical significance, possibly due to the genetic heterogeneity of the common forms of migraine. One major phenotypic and possibly genetically identifiable migraine subgroup consists of women whose attacks are influenced by fluctuation in gonadal hormones. We hypothesized that for these women, the association between migraine attacks and the menstrual cycle might be attributable to an increased prevalence of genetic polymorphisms in the hypothalamic-pituitary-gonadal axis. We selected 21 such polymerphisms previously reported to be associated with the common forms of migraine and genotyped 1740 individuals (1132 migraineurs) to determine whether any of these selected polymorphisms occurred more frequently in females with hormonally modulated migraine. We were able to confirm the association of migraine with 3 genetic polymorphisms seen in previous studies (rs4680 [*COMT*], rs2283265 [*DRD*2], and rs7131056 [*DRD*2]). Interestingly, we found 2 additional genetic polymorphisms (rs2070762 [*TH*] and rs6356 [*TH*]) to be associated with migraine when defining the phenotype as hormonally modulated migraine.

Keywords: Genetic Polymorphism; Headache; Hypothalamic Hormone; Menstrual Cycle; Menstruation

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1. INTRODUCTION

Migraine is a debilitating, heterogeneous neurologic disorder affecting over 35 million Americans [1,2] and costing the American economy over 19 billion dollars annually [3,4]. Three-quarters of people with migraine are women [1,2]. Migraine is a complex trait in which multiple genetic loci, as well as environmental factors, likely contribute to its clinical manifestation [5]. Many genetic associations reported in previous studies either have not been replicated to date or showed only marginal statistical significance, possibly because of the genetic heterogeneity of common forms of migraine [6]. Given the clinical heterogeneity of migraine, it is important to clearly define the phenotype to better isolate the genetic component. One major phenotypic and possibly genetically identifiable migraine subgroup consists of women whose attacks are influenced by fluctuation in gonadal hormones. Given that almost 60% of women with migraine report that their attacks are more severe or frequent around the time of menstrual flow [7-10], variation in the genes coding for enzymes and receptors involved in the secretion and regulation of gonadal hormones may be a major source of migraine susceptibility.

Considerable circumstantial evidence implicates perturbation of the hypothalamic-pituitary-gonadal axis in migraine. Previous studies have shown that in some women, migraine attacks frequently are associated with dramatic decreases in estrogen during the menstrual cycle [11-13]. Furthermore, a rodent-based study showed enhanced sensitization of the trigeminal nucleus caudalis immediately after a decrease in ovarian hormone levels [14], consistent with differing trigeminal excitability among menstrual migraineurs [15].

Single-nucleotide polymorphisms (SNPs) rs1801132, rs2228480, and rs2234693 located within the estrogen

receptor 1 gene (*ESR*1 [MIM 133430]), rs4986938 located within the estrogen receptor 2 gene (*ESR*2 [MIM 601663]), and rs1042838 located within the progesterone receptor gene (*PGR* [MIM 607311]) have been associated with migraine previously [16-21]. The physiology of the hypothalamic-pituitary-gonadal axis is complex, and although the nature of its exact interaction with migraine is not yet understood, the crosstalk between dopamine, norepinephrine, and endorphins (neurotransmitters involved in the hypothalamic-pituitary-gonadal axis and in pain) is well known [22-26]. In fact, after the estrogen is converted to catechol estrogen, the metabolism of gonadotropin-releasing hormone (GnRH) and catecholamines are intimately influenced by one another. Catechol estrogens can inhibit tyrosine hydroxylase (*TH* [MIM 191290]) and compete for catechol-O-methyltransferase (*COMT* [MIM 116790]) (**Figure 1**) [26], indicating that estrogen levels may greatly influence catecholamine levels.

In previous studies, several genes involved in dopamine metabolism were implicated in migraine susceptibility. Genetic polymorphisms in *COMT* (rs4680), *TH* (rs 6356 and rs2070762), solute carrier family 6 member 3 (*SLC6A3* [MIM 126455]) dopamine transporter (rs40184), dopa decarboxylase (*DDC* [MIM 107930]) (rs2329340), dopamine beta-hydroxylase (*DBH* [MIM 609312]) (rs 1611115, rs2097629, and a 19-base pair insertion/deletion polymorphism [27] in the promoter region), and dopamine receptors D2 (*DRD*2 [MIM 126450]) (rs6275, rs1554929, rs2234689, rs2242592, rs2283265, rs7131056, and rs12363125) and D4 (*DRD*4 [MIM 126452]) (48-base pair tandem repeat in exon III [28]) have been found to be associated with migraine [29-38]. However, the vast majority of SNP associations listed above have not been replicated [31].

In this study, we hypothesized that the association between migraine and the menstrual cycle might be attributable to increased prevalence of polymorphisms within genes involved in the hypothalamic-pituitary-gonadal axis (observed previously in male and female migraineurs). We selected 21 such polymorphisms previously reported to be associated with the common forms of migraine and genotyped 1740 individuals (1132 migraineurs) to determine whether any of these selected polymorphisms occurred more frequently in females with hormonally modulated migraine (HMM).

2. METHODS

2.1. Study Population and Selection Criteria

All individuals who participated in this study gave informed consent. The informed consent forms and protocols of this study were approved by the Mayo Clinic Institutional Review Board.

Migraine cases were ascertained using questionnaires based on the International Headache Society's diagnostic criteria (The International Classification of Headache Disorders, second edition [ICHD-II]) [39]. All elements

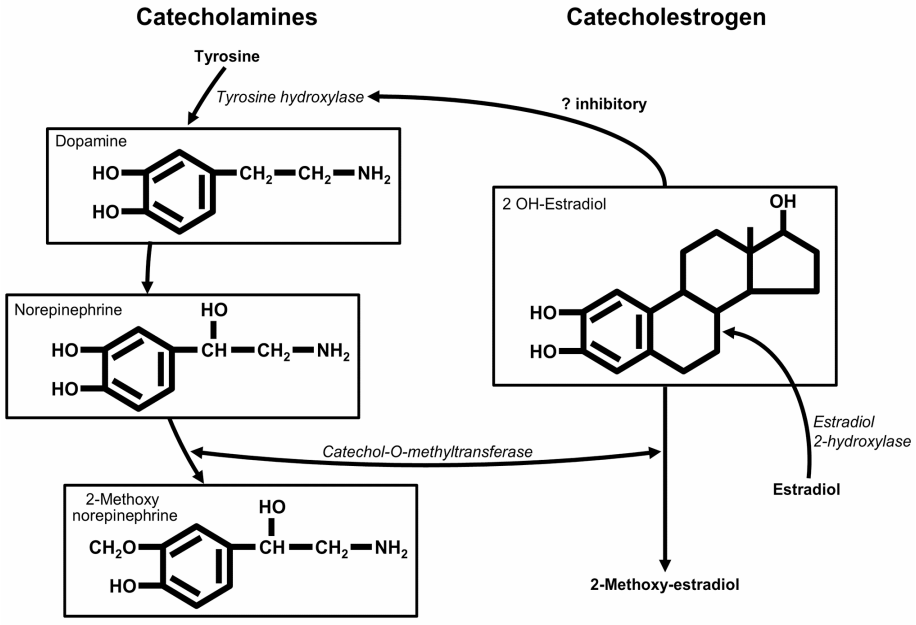

Figure 1. Catecholestrogens and their role in catecholamine metabolism. After estradiol is converted to catecholestrogen by estradiol 2-hydroxylase, the metabolism of gonadotropin-releasing hormone and catecholamines are intimately influenced by each other, as catecholestrogens can inhibit tyrosine hydroxylase and compete for catechol-O-methyltransferase (Adapted from Speroff and Fritz [26]. Used with permission).

of the clinical phenotype were stored in the Mayo Headache Registry, a computerized data entry system that allows complex analysis of any data element, either separately or in tandem. Patients included in the Mayo Headache Registry were seen specifically for headache concerns in the outpatient setting in the Headache Division of the Neurology Department at Mayo Clinic (Rochester, Minnesota) or were volunteers (*i.e*., Mayo employees and trainees or local residents). Study subjects were recruited from 2006 through 2011. All questionnaires were completed in the presence of the investigators or study staff to address any questions raised by the subject. Blood samples were collected from individuals with migraines diagnosed on the basis of the ICHD-II [39] and were included in the Mayo Migraine Genomic Library, a DNA repository of migraine cases and age- and sex-matched controls.

Control subjects were recruited from the same volunteer pools as the case subjects. Individuals who qualified as control subjects had to indicate that they never had a migraine or probable migraine headache, as determined by their responses to a questionnaire administered by the study staff. Family history also was considered; only those subjects whose parents and siblings also had no history of migraine were included in the Mayo Migraine Genomic Library as controls.

Among the phenotypic data elements obtained from all female subjects was whether the migraine attacks occurred with greater frequency and intensity around the time of menstrual flow. The possible responses to this question were: 1) yes, the migraine attacks occur with greater frequency and intensity around the time of menstruation; 2) no, the migraine attacks do not occur with greater frequency and intensity around the time of menstruation; 3) I do not know; or 4) this question does not apply to me. Although human recall is imperfect, these 4 choices provide 2 answers for women who are unsure of the relationship of their attacks with menstruation; this increases the likelihood that the subjects are accurate in their response and minimizes recall bias.

The purpose of this study was to investigate the relationship between genotype and the phenotypic trait of menstrual modulation of migraine attacks, rather than to examine the characteristics of individual attacks. Thus, we opted not to use the ICHD-II appendix provisional diagnoses of pure menstrual migraine or menstrual-related migraine for this study because they required headaches to occur within 2 days (before or after) the first day of menstrual flow. Although such narrow definitions are important in therapeutic trials, they are not optimal in a large genetic-association study.

2.2. Genetic Polymorphism Selection and Analysis

We conducted a literature search and identified 21 polymorphisms in genes involved in the hypothalamic-pituitary-gonadal axis, which drives menstrual flow [16-21,27,29-36]; these polymorphisms previously were reported to be associated with the common forms of migraine (**Table 1**). We aimed to determine whether any of these associations held true in our study population.

Our initial analysis comparing cases and controls was performed using the entire dataset (males and females) to determine whether we could replicate findings found in previous studies. Our second analysis specifically considered only female cases and controls. Our third analysis compared women with nonhormonally modulated migraine (NHMM) vs female controls. Lastly, we compared women with HMM vs female controls.

2.3. Genotyping

DNA isolation was performed at the Biospecimens Accessing and Processing Core Facility at Mayo Clinic. Briefly, DNA from whole blood was purified using the Flex Star genomic DNA isolation instrument (Autogen, Inc) and the Flexigene DNA kit (Qiagen, Inc). Once purified, the DNA was quantified with a Nanodrop ND-8000 spectrophotometer (Thermo Fisher Scientific, Inc).

The DNA samples were activated through a chemical reaction with biotin. Biotinylated DNA was purified to remove excess biotin. Assay oligonucleotides were hybridized to the DNA, and the mixture was bound to streptavidin-conjugated paramagnetic particles. Hybridized oligonucleotides underwent allele specific primer extension and ligation, and the products formed a synthetic template that was amplified via a polymerase chain reaction (PCR). The strand containing the fluorescent signal in the PCR products was isolated and hybridized to VeraCode universal capture bead sets (Illumina, Inc.) via an address sequence. The BeadXpress reader system and BeadStudio data analysis software (Illumina, Inc.) were used to automatically identify alleles. The genotype of the SNP was determined by the ratio of the relative fluorescent levels of the 2 bead types.

The variable number of tandem repeats (VNTR) polymorphisms in both the *DBH* and *DRD*4 genes was analyzed using a 3730XL DNA sequencer (Applied Biosystems, Inc.). Briefly, PCR amplification was performed using TaqGold, with specific primers to amplify the regions of interest (Applied Biosystems, Inc). For *DBH* VNTR, the forward primer sequence was 5’-NEDAATCAGGCACATGCACCTCC-3’, and the reverse primer sequence was 5’-GGCCCTGAGGAATCTTACAGG-3’. For *DRD*4 VNTR, PCR was performed with the primer set 5’-6FAM-AGGACCCTCATGGCCTTG-3’ and 5’-GCGACTACGTGGTCTACTCG-3’. Genotypes were identified using GeneMapper software (Applied Biosystems, Inc). Allele identification was based on known ge-

Table 1. Genetic polymorphisms in the hypothalamic-pituitary-gonadal axis previously reported to be associated with migraine.

Reference SNP Number	Gene Name	Encoded Protein	Chromosome	Study
rs40184	*SLC6A3*	Solute carrier family 6 (neuro-transmitter transporter, dopamine), member 3	5	32
rs1801132 rs2228480 rs2234693	*ESR1*	Estrogen receptor 1	6	19 17.21 16
rs2329340	*DDC*	Dopa decarboxylase (aromatic L-amino acid decarboxylase)	7	33
rs1611115 rs2097629 Promoter region, 19 base pair insertion/deletion	*DBH*	Dopamine beta-hydroxylase (dopamine beta-mono-oxygenase)	9	34 32 35.36
rs6275 rs1554929 rs2234689 rs2242592 rs2283265 rs7131056 rs12363125	*DRD2*	Dopamine receptor D2	11	38 31 31 31 31 32 31
rs6356 rs2070762	*TH*	Tyrosine hydroxylase	11	31 31
rs1042838	*PGR*	Progesterone receptor	11	16
Exon III, 48-base pair tandem repeat	*DRD4*	Dopamine receptor	11	37
rs4986938	*ESR2*	Estrogen receptor 2 (ER beta)	14	17
rs4680	*COMT*	Catechol-O-methyltransferase	22	29.30

notype and size standards described in previous studies [28,36].

2.4. Statistical Analyses

Before conducting statistical analyses, general quality control checks were performed on the genotype data. Polymorphisms with call rates less than 95%, SNPs with minor allele frequencies less than 5%, and polymerphisms that deviated from Hardy-Weinberg equilibrium ($P < 10^{-5}$) were closely examined because these are indicators of potential clustering problems. Samples with call rates less than 95% were excluded from the analysis. The association of each polymorphism with migraine was evaluated by logistic regression using age and sex as covariates to account for confounding variables. Di-allelic markers were tested using the additive genetic model, in which genotypes are coded as 0, 1, or 2, according to the number of rare variants. The VNTR was tested using indicators for carrier status of the common variants and by using a single count for the number of repeats. The *t* test and χ^2 test were used to test for group differences of continuous and categorical variables, respectively.

3. RESULTS

3.1. Study Population

Our study population included 1740 subjects (1132 cases, 608 controls). **Figure 2** shows how cases and controls were further divided into subgroups on the basis of sex and presence or absence of HMM. Age and race (percentage white) were similar between cases and controls (**Table 2**). Results remained statistically significant when conducting statistical analyses among whites only.

3.2. Identification of SNPs Associated with Migraine

Table 3 summarizes the SNPs with confirmed association with migraine. With logistic regression analyses applied to the full study cohort, we identified SNPs rs4680 (*COMT*), rs2283265 (*DRD2*), and rs7131056 (*DRD2*) as being associated with migraine. Considering the female-only subgroup, rs4680 (*COMT*) was still significantly associated with migraine. No SNPs were associated with migraine when comparing females with NHMM (n = 364) vs controls (n = 350); specifically, the *COMT* SNP rs 4680 was not significantly associated with migraine in this subgroup (odds ratio, 1.18; 95% CI, 0.95 - 1.42; $P = 0.13$).

When comparing women with HMM vs female controls, we again identified SNPs from *COMT* and *DRD2*. However, we also identified 2 additional SNPs, rs2070762 and rs6356 (both within *TH*), as having significant association with migraine. Of note, SNP rs7131056 (*DRD2*) was not significantly associated with migraine in this subgroup (OR, 1.10; 95% CI, 0.90 - 1.35; $P = 0.35$).

Table 2. Study population characteristics.

	All (N = 1740)	Controls		Cases			
		All (n = 608)	Females (n = 350)	All (n = 1132)	Females (n = 892)	HMM (n = 464)	NHMM (n = 364)
Age, mean (SD), y	33.89 (8.22)	34.49 (8.09)	34.71 (7.95)	33.57 (8.27)	33.30 (7.90)	34.72 (7.81)	32.07 (7.87)
Range	18 - 50	19 - 50	21 - 50	18 - 50	18 - 50	18 - 50	18 - 49
White race, No. (%)	1651 (94.89)	555 (91.29)	333 (95.14)	1096 (96.82)	867 (97.20)	452 (97.41)	351 (96.43)

Abbreviations: HMM, hormonally modulated migraine; NHMM, nonhormonally modulated migraine.

Table 3. SNPs associated with migraine.

Group	Cases, No.	Controls, No.	SNP (Gene)	Odds Ratio (95% CI)	*P* Value
All cases (N = 1740)	1132	608	rs4680 (*COMT*)	1.25 (1.09 - 1.45)	0.001
			rs2283265 (*DRD2*)	1.22 (1.01 - 1.47)	0.04
			rs7131056 (*DRD2*)	1.18 (1.03 - 1.35)	0.02
Females only (n = 1242)	892	350	rs4680 (*COMT*)	1.2 (1.02 - 1.43)	0.03
HMM vs female controls (n = 814)	464	350	rs4680 (*COMT*)	1.23 (1.02 - 1.52)	0.03
			rs2283265 (*DRD2*)	1.37 (1.05 - 1.82)	0.02
			rs2070762 (*TH*)	1.23 (1.01 - 1.49)	0.04
			rs6356 (*TH*)	1.24 (1.01 - 1.53)	0.04

Abbreviations: HMM, hormonally modulated migraine; SNP, single-nucleotide polymorphism.

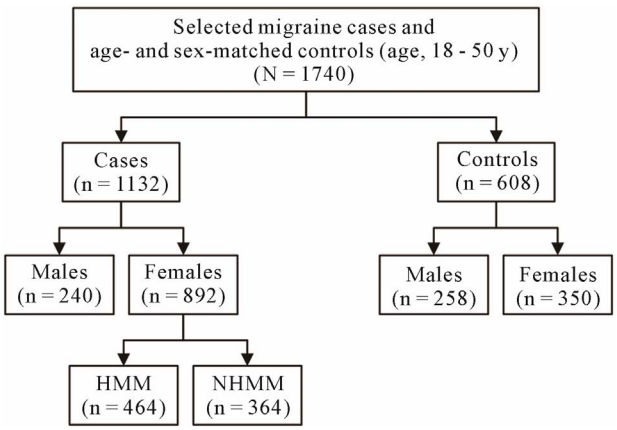

Figure 2. Study population. Blood samples were collected from individuals with a migraine diagnosis and from age- and sex-matched controls. Details of classification criteria are described in the Methods. HMM denotes hormonally modulated migraine; NHMM, nonhormonally modulated migraine.

4. DISCUSSION

In our large cohort of 1740 individuals, we surveyed 21 genetic polymorphisms previously shown to be associated with migraine, with gene products that were involved in the hypothalamic-pituitary-gonadal axis. We were able to confirm the association of migraine with 3 SNPs: rs4680 (*COMT*), rs2283265 (*DRD2*), and rs7131056 (*DRD2*) [29,30,32,40]. To our knowledge, this is the first study to confirm these associations to date.

We then tested our hypothesis that the genetic polymorphisms previously reported to be associated with migraine were more common in females whose migraine attacks were influenced by their menstrual cycle. When we defined the clinical phenotype as women with HMM, 4 SNPs (rs4680, rs2283265, rs2070762, and rs6356) located within genes *COMT*, *DRD2*, and *TH* showed significant associations, even though the number of cases in the subgroup was smaller than the initial study group. However, the rs7131056 (*DRD2)* association was no longer significant in this subanalysis, possibly because of the smaller number of cases. No SNPs were found to be associated with migraine when cases were limited to women with NHMM.

By narrowing the study group to a more homogenous clinical migraine phenotype, we were able to better detect the association of several genetic polymorphisms with migraine. Our findings suggest that women with HMM may have an underlying pathophysiologic mechanism that is distinct from that of women whose migraines are not modulated by the hypothalamic-pituitary-gonadal axis. Conversely, these findings also suggest that women with NHMM may be a more genetically heterogeneous group, or at least their association with migraine is not based on variation in the hypothalamic-pituitary-gonadal axis-related genes that we studied.

Notably, all genetic polymorphisms found to be associated with migraine in the current study were involved in dopamine metabolism. Why might this be the case? One possibility is that dopamine metabolism is an important interface between the hypothalamic-pituitary-gonadal axis and pain modulation. Dopamine in the central nervous system is known to have a role in pain modulation [40,41] and in fact has been implicated in migraine pathophysiology [42]. In rodent models, dopamine can block nociceptive signal transmission at the level of the trigeminocervical complex by binding D2-like receptors

[43]. Also, trigeminal nociceptive transmission is influenced by the dopaminergic A11 nucleus [44]. Other key players in dopamine metabolism have also been shown to affect pain modulation. Inhibition of *COMT* increased pain sensitization in mice [45], and stress-induced analgesia was altered in *COMT*-deficient mice [46].

Dopamine is important not only in pain modulation but also in the catechol estrogen metabolism pathway. Specifically, in the brain, estrone and estradiol can be converted into catechol estrogens by 2-hydroxylase. At the level of the anterior pituitary, catechol estrogens may compete with dopamine for dopamine-binding sites and may even inhibit the synthesis and metabolism of dopamine [47]. In rats, catechol estrogens decrease the turnover rate of dopamine in the corpus striatum [48]. Also, animal studies have shown that dopamine influences GnRH production at the level of the hypothalamus [49-52]. In fact, in vitro data suggest that dopamine can stimulate GnRH secretion from the human hypothalamus [53]. Some evidence suggests that D1 receptor stimulation increases pituitary responsiveness to GnRH in women [54]. Clearly, dopamine and estrogen pathways are intimately associated on several levels, which may explain the association of dopamine-related genetic polymorphisms with migraine in women whose headaches are influenced by their menstrual cycles.

As with other complex traits, clinical heterogeneity confounds identification of the genetic underpinnings of migraine. Thus, careful detailed ascertainment of clinical phenotype in the sample population is likely to be of great importance. The ability to segregate case subjects into more clinically homogenous groups on the basis of biologic characteristics may prove invaluable for unraveling the genetic components of complex traits such as migraine.

A possible weakness of our study was the relative lack of ethnic diversity in our cohort. Migraine affects individuals across all racial groups. However, given our geographic location (Rochester, Minnesota), greater than 90% of subjects were white in both the case and control groups, and the remaining subjects comprised more than 20 different ethnicities. Nevertheless, when conducting statistical analyses among whites only, our results remained statistically significant.

In this study, by defining the clinical phenotype as women with HMM, we were better able to identify additional associated genetic polymorphisms. Intriguingly, all the genetic polymorphisms that we identified or confirmed as significantly associated with migraine were in genes involved in dopamine metabolism. Dopamine is important not only in pain modulation but also in catechol estrogen metabolism. The importance of dopamine in migraine may be due to its function at the interface of the hypothalamic-pituitary-gonadal axis and pain modulation. More studies investigating this association are needed.

5. ACKNOWLEDGEMENTS

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