Association Between Polymorphisms of DRD2, COMT, DBH, and MAO-A Genes and Migraine Susceptibility

A Meta-Analysis

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Abstract: Some epidemiological studies have investigated the relationship between genetic polymorphisms of DRD2, COMT, DBH, and MAO-A and migraine susceptibility, but the results are still inconsistent. Thus, our aim was to further assess the association through a meta-analysis.

We examined 5 single nucleotide polymorphisms (SNPs) in 4 genes, including DRD2 rs1799732 and rs6275, DBH rs7239728, MAI-A-VNTR, and COMT rs4680, and performed a meta-analysis of 11 published case–control studies including 3138 cases and 4126 controls. Odd ratios (ORs) with 95% confidence intervals (95% CIs) were used to evaluate the association between the 5 genetic polymorphisms and migraine susceptibility.

There was no significant relationship between migraine susceptibility and 4 genetic polymorphisms of DRD2 rs1799732 and rs6275, DBH rs7239728, and MAO-A-VNTR. Nevertheless, decreased risk of migraine was observed to be in association with COMT rs4680 polymorphism in overall analysis (AA vs. GG: OR = 0.76, 95% CI = 0.60–0.97, \(P_{\text{Het}} > 0.642, I^2 = 0\)), and in Caucasian group after subgroup analysis (AA vs. GG + GA: OR = 0.75, 95% CI = 0.58–0.96, \(P_{\text{Het}} > 0.433, I^2 = 0\)).

Studied polymorphisms of DRD2, DBH, and MAO-A genes may not be associated with migraine susceptibility. However, COMT rs4680 polymorphism may decrease the risk of migraine, especially in Caucasians. The failure to evaluate environmental influence and provide adjusted effect size estimates highlights the need for additional studies in a large number to take these factors into consideration, thus better elucidating the role of the genes tested in migraine.

(Medicine 94(47):e2012)

Abbreviations: 95% CIs = 95% confidence intervals, COMT = catechol-O-methyltransferase, DRD2 = dopamine receptor D2, HWE = Hardy–Weinberg equilibrium, MAO = monoamine oxidases A, Met = methionine, ORs = odd ratios, SNPs = single nucleotide polymorphisms, Val = valine.

INTRODUCTION

Migraine, the most common neurological disease, seriously threatens the health of people all over the world, and has some symptoms including headache, nausea, vomiting, fatigue, irritability, and nervousness. Patients with migraine are generally aged from 25 to 50, and the risk of migraine in females is 3 times higher than that in males.1–3 Genetic factors have been found to be involved in the etiology of the disease.4–7

Dopamine, a hormone and neurotransmitter of catecholamine and phenethylamine, plays an important role in the repair of nervous system in human brain and associates with decreased dopamine activities. Several diseases in nervous system are associated with dysfunctions of dopamine system, including migraine and Parkinson disease. Dopamine receptor D2 (DRD2) gene locates on chromosome 11q22.2–22.3, and its most studied single nucleotide polymorphisms (SNPs) include rs1799732 and rs6275. The former, a deletion polymorphism (−141C Ins/Del), correlates with reduced DRD2 expression, and the latter is a synonymous polymorphism locating in exon 7 of DRD2 gene.

Isoenzymes monoamine oxidases A (MAO), involved in catabolism of monoamine neurotransmitters, catalyzes oxidative deamination and participates in functional regulation of cell structures.5,9 MAO gene can be divided into 2 subtypes of MAO-A and MAO-B according to different distributions and autoimmune features of cells.10,11 MAO-A gene locates on chromosome Xp11.23, and has a high affinity to endogenous neurotransmitters, and one of its most studied SNP, VNTR, contains a 30 bp long repeated sequence. Catechol-O-methyltransferase (COMT) is an enzyme inactivating catecholamines. The COMT gene functional polymorphism rs4680 can affect the enzyme activities.12 DBH gene, with 12 exons and a length of 23 kb, locates on chromosome 9q34.13 The SNP rs7239728 in the promoter region of DBH gene is associated with phenotypic variations in plasma.

Genetic factors have been implicated in enzyme activities, and they, to some extent, can result in DNA damage, and finally cause the occurrence of diseases. Several studies have investigated the relationship between genetic polymorphisms of DRD2, COMT, DBH, and MAO-A genes and migraine susceptibility.14–24 But the results are conflicting rather than conclusive. Our meta-analysis combining 3138 cases and 4126 controls aims to provide a more precise estimation of the association. Pooled odd ratios (OR) was the main outcome of this meta-analysis.
MATERIALS AND METHODS

Search Strategy and Inclusion Criteria
We searched Pubmed, CNKI, and Embase for relevant studies using the combination of the items “DRD2” or “COMT” or “DBH” or “MAO-A,” “polymorphism,” and “migraine.” All eligible studies evaluating the association between polymorphisms of the 4 genes and migraine susceptibility were selected according to the following criteria: with a case–control design; stating sufficient data for calculating pooled ORs with 95% confidence intervals (95% CIs). Studies were precluded if they were case-only studies, duplicates or with unrated titles and abstracts. As all analyses were performed based on previous published researches, the ethical approval and patient consent are not required.

Data Extraction
Two investigators independently extracted requisite data from all eligible studies according to the identical criteria. The extracted data included: the name of first author, publication year, ethnicity, country of origin, numbers of cases and controls, genotyping methods, genotype frequencies, and P-value for Hardy–Weinberg equilibrium (HWE) in control group. Inconsistent data were discussed between the 2 investigators until reaching a consensus.

Quality Assessment
Assessment of the methodological quality of observational studies was done independently by 2 investigators. A risk-of-bias score modified from a previous meta-analysis was used (Table S1; http://links.lww.com/MD/A513). The score has 4 domains: information bias: ascertainment of cases and controls, assessment of genotyping assay, confounding bias: population domains: information bias: ascertainment of cases and controls, and migraine bias score modified from a previous meta-analysis was used (Table S1; http://links.lww.com/MD/A513). The score has 4 domains: information bias: ascertainment of cases and controls, assessment of genotyping assay, confounding bias: population domains: information bias: ascertainment of cases and controls, and migraine bias.

Statistical Analysis
Pooled ORs with 95% CIs were utilized to evaluate the relationship between polymorphisms of the 4 genes and migraine susceptibility. Heterogeneity among included studies was detected by Q test and I2 metric. Pooled ORs were calculated with a fixed-effects model when \( P \text{-value} > 0.05 \) and \( I^2 < 50\% \), which indicated low possibility of heterogeneity; otherwise, a random-effects model was used. Publication bias was examined by Begg funnel plot and Egger test. HWE was assessed in control group. Inconsistent data were discussed between the 2 investigators until reaching a consensus.

RESULTS

Study Characteristics
As displayed in Figure 1, a total of 133 articles were identified from databases, and 122 of them were precluded for duplicates, unrelated titles and abstracts, case-only studies, and obvious irrelevance. Finally, 11 papers were included into our meta-analysis. All these studies had a low risk of bias, with the total score ranging from 14 to 17. The main characteristics of included studies are displayed in Table 1.
### TABLE 1. Principal Characteristics of the Studies Included in the Meta-Analysis

| Author/Year | SNP    | Country/Race | Source of Control | Means for Genotyping                                                                 | Cases | Controls | P-Value for HWE |
|-------------|--------|--------------|------------------|-------------------------------------------------------------------------------------|-------|----------|-----------------|
| Maude/2001  | DRD2   | UK/Caucasian | Population-hospital | Polymerase chain reaction                                                             | 200   | 464      | NA              |
| Ghosh/2013  | rs1799732 | India/Asian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 335   | 200      | 0.080           |
| Lea/2000    | DRD2   | India/Asian  | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 177   | 182      | 0.400           |
| Ghosh/2013  | rs6275 | India/Asian  | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 335   | 200      | 0.129           |
| Ishii/2012  | COMT   | Japan/Asian  | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 91    | 119      | 0.783           |
| Erdal/2011  | rs4680 | Turkey/Asian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 62    | 64       | 0.755           |
| Hagen/2006  | DBH    | Norway/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 365   | 1468     | 0.633           |
| Park/2007   |         | Korea/Asian  | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 97    | 94       | 0.745           |
| Lea/2000    | DBH    | Australia/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 142   | 136      | 0.074           |
| Fernandez/2006 |       | Australia/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 269   | 265      | 0.238           |
| Todt/2009   |         | Germany/Caucasian | Population | ABI sequencer                                                                       | 636   | 639      | 0.368           |
| Ghosh/2013  |         | Australia/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 335   | 200      | 0.077           |
| Marzinak/2004 | MAO-A-VNTR | Germany/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 94    | 95       | 0.003           |
| Ishii/2012  |         | Japan/Asian  | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 71    | 88       | 0.355           |
| Filit/2005  |         | Croatia/Caucasian | Population | Polymerase chain reaction-restriction fragment length polymorphism                    | 77    | 96       | 0.068           |

HWE = Hardy–Weinberg equilibrium; NA = not available; SNP = single nucleotide polymorphism.

### TABLE 2. Polymorphisms of DRD2, COMT, DBH, and MAO-A Genes and Migraine Risk

| Polymorphism | Study Number | Group | Odds Ratio/95% Confidence Interval |
|--------------|--------------|-------|----------------------------------|
| DRD2 rs1799732 | 2            | Total | 11.55 (0.67–0.78) |
|              |              | Caucasian | 1.44 (0.65–3.21) |
| DRD2 rs6275   | 3            | Total | 0.94 (0.67–1.32) |
|              |              | Caucasian | 0.95 (0.71–1.26) |
| COMT rs4680   | 3            | Total | 1.09 (0.54–2.20) |
| DBH rs72393728 | 3            | Total | 1.02 (0.86–1.22) |
| MAO-A-VNTR    | 3            | Total | 0.69 (0.27–1.80) |

11 = wild homozygote; 12 = heterozygote; 22 = rare homozygote; 1 = wild allele; 2 = rare allele.
migraine-related symptoms and headache.33 Evidence from a murine model suggests that dopamine receptors usually appear in the trigeminovascular pathway and that dopamine is able to inhibit nociceptive trigeminovascular transmission.34 These reports highlight the central role of dopamine in migraine and make the dopamine-related genes such as DRD2, COMT, DBH, and MAO-A candidates.

Accumulating evidence supports a relationship between these genes and migraine development. A 7-transmembrane receptor protein of the dopamine pathway predominantly expressed in pars compacta of the substantia and neostriatum is encoded by the DRD2.35 Genetic polymorphisms in this locus are known to have important functional consequences. Expression-based research in vitro revealed 2 times higher expression levels of DRD2 in individuals with Ins/Ins of rs1799732 than those with Del/Del.36 Multiple studies in human models have also connected rs6275 to DRD2 transcript instability and reduced translational efficiency.37 Several other polymorphisms in the gene, such as rs7131056 can directly affect the function of DRD2 product.28 For rs7239728, a promoter polymorphism in DBH, has been linked to phenotypic variability in DBH activity in plasma.38 Migraineurs versus controls have been reported to have significantly lower plasma norepinephrine levels.39 The DBH catalyzes the dopamine-to-norepinephrine conversion, and reduced DBH activity in individuals with rs7239728 might be a cause of lower norepinephrine in migraineurs.15 The VNTR polymorphism in the MAO-A gene is associated with higher enzyme expression of MAO-A.40 The functional impact leads to increased MAO-A activity, a cause of hypermetabolism of amine neurotransmitters and decreased levels of serotonin, conditions previously implicated in migraine pathophysiology.41 All these results point to the high possibility of a relationship between DRD2, DBH, MAO-A and risk of migraine.

Multiple epidemiological studies have investigated the association between migraine susceptibility and polymorphisms of the four genes DRD2, COMT, DBH, and MAO-A. The study by Ghosh et al15 demonstrated no significant association between DRD2 rs6275 polymorphism and susceptibility to migraine. In another large-scale study, the researchers provided opposite results by showing an increased risk of migraine associated with DRD2 rs6275 and 1799732 polymorphisms.14 Fernandez et al27 found no significant relationship between DBH rs72393728 polymorphism and migraine susceptibility in their research. For the MAO-A-VNTR polymorphism, Ishii et al.40 identified an increased risk of migraine. In addition, the study in Finns by Tamminimaki and Mannisto45 demonstrated some evidence for an increase in the migraine risk associated with COMT rs4680 polymorphism.

In our meta-analysis, there was no significant association between migraine susceptibility and 4 SNPs in 3 genes, including DRD2 rs1799732 and rs6275, DBH rs7239728, and MAO-A-VNTR. However, COMT rs4680 polymorphism was associated with a decreased risk of migraine, especially in Caucasians. There are abundant data supporting these findings. The rs4680 polymorphism results in a transition of valine (Val) to methionine (Met) at codon 158, and it is the amino acid substitution causes decreased thermostability and enzymatic activity and increased dopamine-degrading activity.33–45 While the findings for DRD2 rs1799732 and rs6275, DBH rs7239728, and MAO-A-VNTR are inconsistent with the results from previous functional studies previously introduced in this section, the results identified for COMT rs4680 are in accordance with the published reports.

FIGURE 2. Forest plot of migraine susceptibility associated with COMT rs4680 polymorphism under AA versus GG + GA genetic model.

OR = 0.75, 95% CI = 0.58–0.96, $P_{\text{het}} > 0.433$, $I^2 = 0$, as displayed in Figure 2. No signals of relationship were seen in other genetic models tested (Table 2).

Sensitivity Analysis
Sensitivity analysis was conducted by excluding one single study at a time to observe alterations in whole results which had no substantial difference before and after the deletions, suggesting our meta-analysis results were stable and credible.

Publication Bias
The shape of the funnel plot seemed symmetrical (Fig. 3), implying negligible publication bias. Additionally, Egger test provided further statistical evidence for the absence of significant bias ($P = 0.748$).

DISCUSSION
Although the pathophysiology of migraine remains incompletely understood, an effect conferred by dopamine was implicated almost 40 years ago.32 Such influence is further illustrated by an observation that dopamine shows signs of hypersensitivity in patients with migraine and that dopamine receptors can mediate nociception, autonomic responses, and vascular tone.33 Dopamine antagonists have reportedly been used to eliminate
Due to some limitations, the present findings should be explained prudently. First, we demonstrated evidence for the absence of association for DRD2 rs1799732, DRD2 rs6275, DBH rs7239728, MAO-A-VNTR and the presence of association for COMT rs4680. These results may be caused by the limited data available for each polymorphism. Hence, we cannot exclude the probability that the association for the former 4 polymorphisms will be significant and that the association for the latter would be lost after the enlargement of the sample size. Second, we put equal emphasis on English and non-English publications during literature search. However, only those papers written in English were identified. In addition, no unpublished data were included. Thus, selection bias may have occurred, though there was no indication of significant bias in Begg funnel plot and Egger test. Third, we merely assessed the genetic effects on migraine risk, not considering environmental influence. Fourth, the results were based on unadjusted data, which might affect the accuracy of the results. Finally, subgroup analyses based on age, gender, and other potential confounding variables were not performed because of insufficient data.

In conclusion, our meta-analysis demonstrates a significant association between decreased risk of migraine and COMT rs4680 polymorphism, but no association for DRD2 rs1799732, DRD2 rs6275, DBH rs7239728, and MAO-A-VNTR. Large-scale studies where gene-environment interactions are considered and adjusted effect is estimated are needed to determine the role of these dopamine-related genes in migraine, thus providing new insights into the mechanisms that underlie the disease pathogenesis.

REFERENCES

1. Morotti M, Remorgida V, Venturini PL, et al. Progestin-only contraception compared with extended combined oral contraceptive in women with migraine without aura: a retrospective pilot study. *Eur J Obstet Gynecol Reprod Biol.* 2014;183:178–182.
2. Tali D, Menahem I, Vered E, et al. Upper cervical mobility, posture and myofascial trigger points in subjects with episodic migraine: case-control study. *J Bodyw Mov Ther.* 2014;18:569–575.
3. Jes Olesen, Marie-Germaine Bousser, Hans-Christoph Diener, et al. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24(Suppl. 1):9–160.
4. Inchauspe CG, Pilati N, Di Guilimi MN, et al. Familial hemiplegic migraine type-I mutated cav2.1 calcium channels alter inhibitory and excitatory synaptic transmission in the lateral superior olive of mice. *Hear Res.* 2015;319:56–68.
5. Kinder S, Ossig C, Wienecke M, et al. Novel frameshift mutation in the CACNA1A gene causing a mixed phenotype of episodic ataxia and familiar hemiplegic migraine. *Eur J Paediatr Neurol.* 2015;19:72–74.
6. Guler S, Gurkan H, Tozikr H, et al. An opposite-direction modulation of the COMT Val158Met polymorphism on the clinical response to intrathecal morphine and triptans. *J Pain.* 2013;14:1097–1106.
7. Corominas R, Ribases M, Camina M, et al. Two-stage case-control association study of dopamine-related genes and migraine. *BMC Med Genet.* 2009;10:95.
8. Park JW, Lee KS, Kim JS, et al. Genetic contribution of catechol-O-methyltransferase polymorphism in patients with migraine without aura. *J Clin Neurol.* 2007;3:24–30.
9. Messori R, Freitag CM, Marziniak M, et al. The functional Val158Met variant of the COMT gene is not associated with migraine with or without aura. *J Headache Pain.* 2006;7:165–166.
10. Hagen K, Pettersen E, Stovner LJ, et al. The association between migraine headache and Val158Met polymorphism in the catechol-O-methyltransferase gene with susceptibility to typical migraine. *Neurogenetics.* 2000;3:35–40.
11. Peroutka SJ, Price SC, Wilhoit TL, et al. Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. *Mol Med.* 1998;4:14–21.
12. Cargnin S, Magnani F, Viana M, et al. An opposite-direction modulation of the COMT Val158Met polymorphism on the clinical response to intrathecal morphine and triptans. *J Pain.* 2013;14:1097–1106.
30. Ishii M, Shimizu S, Sakairi Y, et al. MAOA, MTHFR, and TNF-beta genes polymorphisms and personality traits in the pathogenesis of migraine. Mol Cell Biochem. 2012;363:357–366.

31. Filic V, Vladic A, Stefulj J, et al. Monoamine oxidases A and B gene polymorphisms in migraine patients. J Neurol Sci. 2005;228:149–153.

32. Sicuteri F. Dopamine, the second putative protagonist in headache. Headache. 1977;17:129–131.

33. Chen SC. Epilepsy and migraine: the dopamine hypotheses. Med Hypotheses. 2006;66:466–472.

34. Bergerot A, Storer RJ, Goodysby PJ. Dopamine inhibits trigeminovascular transmission in the rat. Ann Neurol. 2007;61:251–262.

35. Plante-Bordeneuve V, Taussig D, Thomas F, et al. Evaluation of four candidate genes encoding proteins of the dopamine pathway in familial and sporadic Parkinson’s disease: evidence for association of a DRD2 allele. Neurology. 1997;48:1589–1593.

36. Arinami T, Gao M, Hamaguchi H, et al. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. Hum Mol Genet. 1997;6:577–582.

37. Duan J, Wainwright MS, Comeron JM, et al. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. Hum Mol Genet. 2003;12:205–216.

38. Cubells JF, Krnulzer HR, McCance-Katz E, et al. A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. Mol Psychiatry. 2000;5:56–63.

39. Martinez F, Castillo J, Pardo J, et al. Catecholamine levels in plasma and CSF in migraine. J Neurol Neurosurg Psychiatry. 1993;56:1119–1121.

40. Gentile G, Missori S, Borro M, et al. Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine. J Headache Pain. 2010;11:151–156.

41. Panconesi A. Serotonin and migraine: a reconsideration of the central theory. J Headache Pain. 2008;9:267–276.

42. Tammimaki A, Mannisto PT. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. Pharmacogenet Genomics. 2012;22:673–691.

43. Chen J, Song J, Yuan P, et al. Orientation and cellular distribution of membrane-bound catechol-O-methyltransferase in cortical neurons: implications for drug development. J Biol Chem. 2011;286:34752–34760.

44. Witte AV, Floel A. Effects of COMT polymorphisms on brain function and behavior in health and disease. Brain Res Bull. 2012;88:418–428.

45. Hernaus D, Collip D, Lataster J, et al. COMT Val158Met genotype selectively alters prefrontal [18 F] fallypride displacement and subjective feelings of stress in response to a psychosocial stress challenge. PLoS ONE. 2013;8:e65662.