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Association of Diamine oxidase (*DAO*) variants with the risk for migraine from North Indian population

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ABSTRACT

Background: Migraine is a common neurovascular disorder affected by various levels of neurotransmitters. Low histamine metabolism is also related with pathophysiology of migraine. As diamine oxidase (*DAO*) gene variants are linked with higher levels of histamine in migraine patients, we investigated the possible relationship of two variants rs2052129 and rs10156191of this gene with migraine risk in North Indian population.

Methods: A case-control study for 250 migraine patients and 250 matched healthy controls was conducted by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: We found statistically significant differences in allelic frequencies of rs2052129 (p = .009, OR = 1.462; 95% CI: 1.098–1.947) and rs10156191 (p = .019, OR = 1.430; 95% CI: 1.060–1.928) variants in *DAO* gene. For rs1015691, we were able to show statistically significant association at all genotypic, dominant and allelic levels in both MA (for T allele, p = .020; OR = 1.662, 95% CI: 1.083–2.551) as well as in female subgroup (for T allele, p = .025, OR = 1.460; 95% CI: 1.049–2.033). But no such significant association was found in clinical sub grouping of migraine in rs2052129 as p > .05. However in gender analysis, protective effect of T allele in male migraine patients for rs2052129 (OR < 1) was found.

Conclusions: Our findings clearly indicated that female patient with rs10156191T allele and in MA subgroup showed an increased risk for migraine. Our data also indicated that rs2052129T variant showed a significant role in migraine susceptibility of this population.

1. Introduction

Migraine is a multi-factorial disorder having a prevalence of approximately 12% with a female: male ratio of 2–3:1 (Lipton et al., 2007; De Vries et al., 2006). Finding genes for different forms of common migraine (with and without aura) and their pathogenic roles in defining this disorder have not gained much success yet. Candidate gene association and genome-wide association studies have been used to reveal the possible relation among various SNPs and migraine risk (Anttila et al., 2013; Chasman et al., 2011). These studies are mostly related with neurotransmitters including serotonergic and dopaminergic systems and have inconsistent and inconclusive outcomes (Freilinger et al., 2012). Even interethnic variability occurs in these association studies as some genes which were associated with Indian population (Ghosh et al., 2013) showed negative results with that of Chinese (An et al., 2013; Fan et al., 2014), Swedish (Ran et al., 2014) or Spanish (Sintas et al., 2015).

Apart from neuro-tansmitters like serotonin and dopamine, histamine might have a significant role in pathogenesis of migraine (Alstadhaug, 2014).It has been reported that histamine-rich foods may trigger migraine attacks. In migraine patients, histamine concentrations in plasma are reported to be increased during headache attacks and for symptom-free periods as compared with controls as (p < .001) (Maintz and Novak, 2007). Histamine *N*-methyltransferase (*HNMT*) and Diamine oxidase (*DAO*) or amiloride binding protein 1(*ABP1*) are the two

Abbreviations: DAO, Diamine oxidase; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; SNP, Single nucleotide polymorphism; HNMT, Histamine *N*-methyltransferase; ABP1, Amiloridebinding protein 1; MO, Migraine without aura; MA, Migraine with aura; OPD, Outpatient department; HWE, Hardy-Weinberg equilibrium; OR, Odds ratios; CI, Confidence intervals; SD, Standard deviation

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enzymes, responsible for degradation of histamine whereas hystidine decorboxylase enzyme can synthesize it by decorboxylation from its precursor histidine. *HNMT* is related with degradation of intracellular histamine where as *DAO* is mainly for scavenging extracellular one after its release (Preuss et al., 1998; Wang et al., 2002). *DAO* enzyme has three common non-synonymous single nucleotide polymorphisms (SNPs) that are: rs10156191 (Thr16Met), rs1049742 (Ser332Phe) and rs1049793 (His645Asp) which can reduce protein's activity by altering its form (Ayuso et al., 2007; Garcia-Martin et al., 2007). Another SNP rs2052129 (G4586 T), present in promoter region of gene, has been related with decreased transcriptional activity of *DAO* (Maintz et al., 2011). Various studies have reported that the patients with minor alleles of rs1049793, rs10156191 and rs2052129 SNPs have lower serum *DAO* activity on comparison with controls (Garcia-Martin et al., 2015).

The purpose of this study is to find a link between two functional SNPs i.e. rs2052129 and rs10156191 (related with reduced *DAO* activity) with migraine risk in North Indian population. This is the first case-control association study to investigate the role of these variants in common migraine patients from this population.

2. Methods

2.1. Subjects

We studied 250 migraine patients [55 males (22%) and 195 females (78%)], and excluded other headache types, according to the guidelines recommended by International Classification of Headache disorders, 3rd edition (International Headache Society, 2013) and 250 controls [65 males (26%) and 185 females (74%)]. Migraineurs were recruited from those who visited OPD of ESIC medical College & Hospital, Faridabad, India. Migraine patients were diagnosed as having either migraine with aura (MA) or migraine without aura (MO). Controls were healthy volunteers matched for sex and age with patients who did not suffer from migraine and any other types of headaches. A written informed consent from all the subjects was taken prior to this study and it was further cleared by different Ethics Committees of JMI, New Delhi and that of ESIC Medical College & Hospital, Faridabad. These subjects were also taken in other case-control studies conducted by our group (Kaur et al., 2018, 2019).

2.2. `Genotyping

Genotyping was performed in genomic DNA isolated by both salting out method (Miller et al., 1988) as well as from whole genomic DNA extraction kit (from Banglore Genei) after collecting 5 ml venous blood in EDTA vials from subjects. Polymorphisms were checked via polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to detect SNPs. Self designed primers used for rs10156191 were:

Sense primer- 5′ATTCCATGGCCCTAACCTGAG 3′.

Antisense primer-5′GTGCACTGCCTTCAGCTCTT 3′.

Whereas for rs2052129 were as follows:

Sense primer-5′GCCAGGGTAGCTAAGGCTATG 3′.

Antisense primer-5′ ACTCCTGAGCCACGAACTTTT 3′.

Cycling conditions for this study were: An initial denaturation was done for 5 min at 95 °C, then there were 35 cycles of denaturation at 94 °C for 30 s, annealing at 62 °C for rs2052129 and 56 °C for rs10156191 for 30 s respectively, and extension at 72 °C for 90 s followed by a final extension at 72 °C for 7 min. Restriction enzymes used in RFLP for rs2052129 and rs10156191 were *DrdI* and *MscI* (from New England, Biolabs) respectively. PCR products of 188 bp for rs2052129 were digested into 98 bp and 90 bp for minor allele A by *Drd I* enzyme and 228 bp PCR products of rs10156191 were divided into 142 bp and 86 bp fragments for minor allele T by *MscI* at 37 °C. The outcomes of PCR followed by restriction analysis of these SNPs are shown in Figs. 1-4.

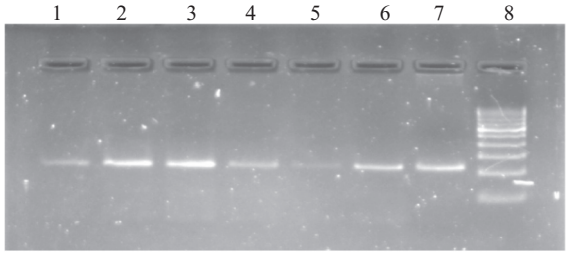

Fig. 1. Lane: 1–7 showing PCR products of 228 bp for rs10156191SNP.
Lane: 8-100 bp DNA ladder.

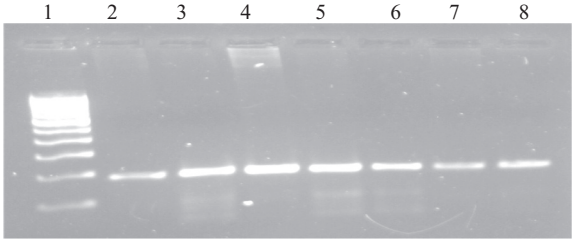

Fig. 2. Lane: 2–8 showing PCR products of 188 bp for rs2052129 SNP.
Lane: 1-100 bp DNA ladder.

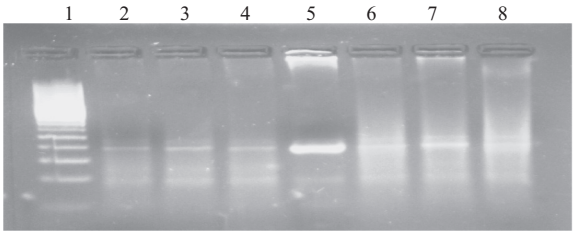

Fig. 3. Lane-2-8 showing GT (3 fragments: 188 bp, 98 bp and 90 bp) of rs2052129 SNP.
Lane-5-showing GG (1fragment of 188 bp).
Lane-1 50 bp DNA ladder.

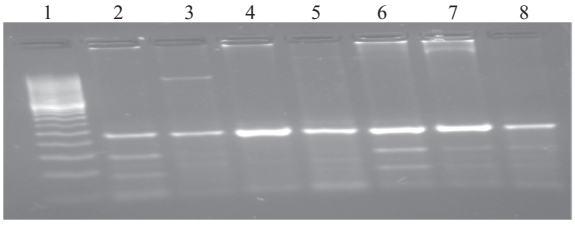

Fig. 4. Lane-2, 6, 7 and 8 showing CT (3 fragments: 228 bp, 142 bp and 86 bp) of rs10156191 SNP.
Lane-3, 4 and 5 showing CC (1 fragment: 228 bp).
Lane-1 50 bp DNA ladder.

2.3. Statistical analysis

Hardy-Weinberg equilibrium (HWE) was confirmed for subjects using Chi-square goodness of fit test. Statistical analysis was performed using SPSS 24.0 and $p < .05$ was taken statistically significant for this data. The risk of migraine was taken as odds ratios (OR) for mutant allele carriers with 95% confidence intervals (CI) between groups. Comparison of allelic and genotypic frequencies was done by Chi-squared test. The categorical variables were represented by numbers and percentages however continuous variables were shown as means ± standard deviation (SD) for this test. Power analysis was done using Quanto 1.2.4. The SNPs were to show a twofold increase in risk of

Table 1
Genotypic and allelic distribution of rs2052129 polymorphism in this study.

	Genotypic distribution N (%)			Allelic distribution N (%)	
	GG	GT	TT	G	T
Migraine(250)	132(52.8)	90(36)	28(11.2)	354(70.8)	146(29.2)
HC(250)	148(59.2)	94(37.6)	8(3.2)	390(78)	110(22)
MO(180)	96(53.3)	70(38.9)	14(7.8)	262(72.8)	98(27.2)
MA(70)	38(54.3)	24(34.3)	8(11.4)	100(71.4)	40(28.6)
Male migraine (55)	42(76.4)	9(16.4)	4(7.2)	93(84.5)	17(15.5)
Female migraine (195)	104(53.3)	86(44.1)	5(2.6)	294(75.4)	96(24.6)
Male control (65)	33(50.8)	26(40)	6(9.2)	92(70.8)	38(29.2)
Female control (185)	98(53)	72(38.9)	15(8.1)	268(72.4)	102(27.6)

migraine with 250 case-controls used here with significance level set at 0.05. The prevalence of migraine was taken as 0.12. By assuming the minor allele frequencies as 22% for rs2052129 and 19.4% for rs10156191 in control groups we achieved 45.3 and 37.4% power for rs2052129 and rs10156191 respectively.

3. Results

This study included a cohort of 250 migraine patients (70 MA and 180 MO) and 250 healthy controls. The mean age of patients was 34.55 ± 6.699 years and that of controls was 35.40 ± 6.123 years. All subjects were matched both in age (p = .139) and gender (p = .295). In migraine group 28% MA and 72% MO were included. Two SNPs (rs2052129 and rs10156191) present in *DAO* gene were selected in our study to find any association of theirs with risk for migraine. All the genotypic frequencies both in patients (p = .646) and controls (p = .295) were in HWE for rs10156191. But for rs2052129 the genotypic frequencies of controls (p = .131) were in HWE but for patients (p = .041) these were out of HWE. The genotypic and allelic frequency distributions for selected SNPs in this study were given in Tables 1-2.

3.1. Association study of rs2052129 polymorphism

The frequencies of genotypes of SNP rs2052129 were significantly different between patients and controls (p = .019).The frequency of TT genotype was 11.2% in migraine patients as compared with 3.2% in controls shown in Table 1. Similarly the frequency of risk allele T was 29.2% in patients which was significant on comparing with that of controls (p = .009, OR = 1.462; 95% CI: 1.098–1.947). On sub group analysis there was variation in frequencies of T allele in MA (28.6%) and MO (27.2%) on comparison with controls (22%) but this difference did not confer any statistical significance as clear in Table 1. In gender analysis frequencies of GT and GG genotypes in male migraine were 16.4 and 76.4% on comparison with that of 40 and 50.8% in control migraine (p = .004). In addition, allelic distribution showed significant difference in male migraine samples (p = .013, OR = 0.443; 95% CI: 0.233–0.840) on comparison with that of male controls. But as the OR < 1, T allele showed a protective effect in male migraine samples. However no such results were reported at allelic level in female migraine patients as shown in Table 3.

Table 2
Genotypic and allelic distribution of rs10156191 polymorphism in this study.

	Genotypic distribution N (%)			Allelic distribution N (%)	
	CC	CT	TT	C	T
Migraine(250)	137(54.8)	98(39.2)	15(6)	372(74.4)	128(25.6)
HC(250)	165(66)	73(29.2)	12(4.8)	403(80.6)	97(19.4)
MO(180)	108(60)	63(35)	9(5)	279(77.5)	81(22.5)
MA(70)	35(50)	30(42.9)	5(7.1%)	100(71.4)	40(28.6)
Male migraine (55)	37 (67.3)	12(21.8)	6(10.9)	86(78.2)	24(21.8)
Female migraine (195)	95(48.7)	88(45.1)	12(6.2)	278(71.3)	112(28.7)
Male control (65)	41(63.1)	19(29.2)	5(7.7)	101(77.7)	29(22.3)
Female control (185)	117(63.2)	56(30.3)	12(6.5)	290(78.4)	80(21.6)

3.2. Association study of rs10156191 polymorphism

The distributions of genotypes of SNP rs10516191 differed statistically between controls and migraine (p = .002) groups.The frequency of C allele was74.4% (372C alleles) and for T allele was 25.6% (128 T alleles) in migraineurs as in Table 2. Hence we found significant associations in migraine samples for this SNP at allelic (p = .019, OR = 1.430; 95% CI: 1.060–1.928) and dominant levels ((p = .010, OR = 1.601; 95% CI: 1.116–1.928) on comparison with controls. On clinical sub grouping of patients, similar trend was observed for MA at genotypic (p = .015, OR = 1.941; 95% CI: 1.135–3.320) and allelic levels (p = .020, OR = 1.662; 95% CI: 1.083–2.551). But no such association was reported in MO subgroup. The frequencies of C and T alleles for female migraine were 71.3 and 28.7% which were significant on comparison with 80.6 and 19.4% of female controls. We found similar association in female migraine patients on comparison with female controls both at dominant (p = .005, OR = 1.811; 95% CI: 1.201–2.729) as well as at allelic levels (p = .025, OR = 1.460; 95% CI: 1.049–2.033) in gender analysis as shown in Table 4.

4. Discussion

We have done a case- control association study in North Indian population for Diamine oxidase polymorphism. This is the first reported case-control study for two SNPs (rs2052129 and rs10156191) in this gene from this population. As women are more prone to develop migraine than men, our study comprised of > 70% females. It has been reported that histamine plays a crucial role in migraine pathophysiology (Ku et al., 2006; Gazerani et al., 2003) and levels of histamine are higher in migraine patients (Haimart et al., 1987). There have been several reports of spontaneous release of histamine from leukocytes in migraine patients which are further proved by experimental models that dural mast cells could play a significant role in migraine pathophsiology (Selmaj, 1984). Much work has not been done in *DAO* SNPs polymorphisms in migraine but studies having other disorders related with histamine such as hyper sensitivity (Agúndez et al., 2012), rhinitis (García-Martín et al., 2007) or ulcerative colitis (García-Martin et al., 2006) have been reported.

In this study, we enrolled 250 migraine patients and 250 healthy controls and reported a significant association of risk of migraine development with both SNPs and with gender. As rs2052129T allele is mainly for decrease activity of *DAO* enzyme expression and could be a cause for high levels of histamine in migraine patients. In concordance with this hypothesis, we reported in the present study that for SNP rs2052129, the frequency of TT genotype was more in patients than that of controls, and rs2052129T allele reported a increased risk for migraine patients as OR = 1.462 with 95%CI = 1.098–1.947.Whereas in subgroup analysis, males migraine with rs2052129T allele showed a protective effect of migraine. Reason behind this may be the selection bias for this allele in male subgroup as patients were not in Hardy-Weinberg equilibrium for this SNP. For rs10156191 a statistically significant difference was reported for T allele at genotypic and allelic levels in migraine patients with that of healthy controls and showed the odds ratio for T allele as 1.430 (95% CI = 1.060–1.928). Similar trend

Table 3
Association study of rs2052129 polymorphism in the studied subjects.

	Genotypic model				Dominant model		Allelic model	
	GT vs GG		TT vs GG		GT + TT vs GG		T vs G	
	p value	OR (95% CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)
Migraine vs HC	0.709	1.074(0.740–1.558)	0.001**	3.924(1.728–8.910)	0.150	1.297(0.910–1.848)	0.009**	1.462(1.098–1.947)
MO vs HC	0.501	1.148(0.768–1.716)	0.032*	2.698(1.091–6.675)	0.226	1.270(0.863–1.869)	0.078	1.326(0.969–1.816)
MA vs HC	0.985	(0.994(0.561–1.763)	0.011*	3.895(1.373–11.050)	0.462	1.222(0.717–2.083)	0.156	1.418(0.929–2.166)
MM vs MHC	0.004**	0.272(0.112–0.659)	0.346	0.524(0.137–2.010)	0.495	0.825(0.475–1.434)	0.013*	0.443(0.233–0.840)
FM vs FHC	0.579	1.126(0.742–1.708)	0.030*	0.314(0.110–0.897)	0.003**	0.349(0.176–0.692)	0.354	0.858(0.620–1.186)

*p < .05; **p < .01, statistically significant; CI = confidence Interval; OR = odds ratio; MA = migraine with aura; MO = migraine without aura; HC = healthy controls; MM = male migraine; MHC = male healthy controls; FM = female migraine; FHC = female healthy controls.

was reported for T allele for MA (OR = 1.206) and female migraine patients (OR = 1.460). It has been reported in previous studies that women show higher *DAO* enzyme activity and have higher inter-individual variability than men (Garcia-Martin et al., 2007). Similarly our results revealed association of these SNPs with migraine in gender analysis. These results were also similar to Maintz et al. (2011)who reported the risk for a lower *DAO* activity with increased frequencies of minor alleles in rs2052129, rs10156191, rs2268999 and rs1049742 SNPs. They found that reporter gene assays at rs2052129 showed a lower promoter activity ($p = .016$) of the minor allele. The expression of mRNA in *DAO* was lower ($p = .002$) in peripheral blood mononuclear cells of homozygous carriers of the minor allele at rs2052129, rs2268999, rs10156191 than that of homozygous carriers of the major allele. Our findings were also similar to that of Garcia-Martin et al. (2015) which reported that defect allele positivity for *DAO* SNP rs10156191 is 1.61(95% CI = 1.31–2.37) for overall migraine patients and 2.08 for migraine women. Although they showed an increase in frequency of rs2052129G allele which was contradictory with our results as we found higher frequency of rs2052129T allele in migraineurs which is responsible for decrease in enzyme expression in them. Another study by Meza-Velázquez et al. (2017) showed significant association of mutant C2029G *DAO* SNP polymorphism with migraine women (OR = 1.6; 95% CI = 1.1–2.1). But this nonsynonymous SNP was different from our study. Both the SNPs taken in present study are reported to alter *DAO* enzyme activity in vivo (Ayuso et al., 2007). Rs10156191T allele encodes a protein with amino acid substitution in the position 16 as Met instead of Thr in wild type protein and reduces intrinsic activity of enzyme and its ability to metabolize circulating histamine (Maintz et al., 2011). As frequency of T allele is more in female migraineurs, it can be expected that decreased clearance of circulating histamine could be the reason for developing migraine. Major drawback of our study was the small sample number. To validate these findings more replication studies on this gene polymorphisms from various ethnical backgrounds with larger sample size is a must.

5. Conclusion

This study is the first to report any genetic association of rs2052129 and rs10156191 SNPs in DAO gene in North Indian population. For rs10156191 we reported a significant association at all levels for migraine patients, MA and female subgroup. Hence female patient with rs10156191T allele and in MA subgroup showed an increased risk for migraine. The increase of variants rs2052129T and rs10156191T in patients may be related with reduced *DAO* gene activity which further is implicated in pathophysiology of migraine. Further studies from various populations and other SNPs in this gene along with a check on *DAO* serum activity in migraine patients and controls are required to strengthen our results.

Ethics approval and consent to participate

This study was approved by Ethics Committees from JMI, New Delhi and from that of ESIC Medical College & Hospital, Faridabad. A written informed consent from all the subjects was taken prior to this study.

Consent for publication

A written consent form from all the subjects was taken that this work is for publication in future.

Availability of data and materials

Not applicable.

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Table 4
Association study of rs10156191 polymorphism in the studied subjects.

	Genotypic model				Dominant model		Allelic model	
	CT vs CC		TT vs CC		CT + TT vs CC		T vs C	
	p value	OR (95% CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)
Migraine vs HC	0.013*	1.617(1.108–2.360)	0.311	1.505(0.682–3.324)	0.010*	1.601(1.116–2.298)	0.019*	1.430(1.060–1.928)
MO vs HC	0.192	1.318(0.870–1.997)	0.766	1.146(0.467–2.812)	0.203	1.294(0.870–1.924)	0.269	1.206(0.865–1.681)
MA vs HC	0.021*	1.937(1.107–3.392)	0.231	1.964(0.650–5.932)	0.015*	1.941(1.135–3.320)	0.020*	1.662(1.083–2.551)
MM vs MHC	0.410	0.700(0.300–1.635)	0.659	1.330(0.374–4.722)	0.631	0.831(0.390–1.769)	0.927	0.972(0.527–1.793)
FM vs FHC	0.003**	1.935(1.258–2.977)	0.629	1.232(0.529–2.866)	0.005**	1.811(1.201–2.729)	0.025*	1.460(1.049–2.033)

*p < .05; **p < .01, statistically significant; CI = confidence Interval; OR = odds ratio; MA = migraine with aura; MO = migraine without aura; HC = healthy controls; MM = male migraine; MHC = male healthy controls; FM = female migraine; FHC = female healthy controls.

Authors' contributions

All authors contributed equally in the preparation of the manuscript and read and approved the final version.

Additional file 1 Figures showing PCR products and restriction digestion products of selected SNPs

Declaration of Competing Interest

The authors declare that they have no competing interests.

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