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BRIEF COMMUNICATION

Dopamine-beta-hydroxylase 19-bp insertion/deletion polymorphism affects medication overuse in patients with chronic migraine

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Abstract

Dopamine-beta-hydroxylase (DBH) enzyme activity is modulated at the genetic level by the presence of several polymorphisms. Among these, the 19-bp insertion/deletion (I/D) polymorphism (rs72393728/rs141116007) was investigated in several genetic association studies for its correlation with the susceptibility to develop episodic migraine, but conflicting results were achieved. In the present study we analyzed this genetic variant in a carefully characterized population of migraineurs encompassing both episodic and chronic migraine (with and without medication overuse) with the aim to perform a replication study and verify any possible correlation with migraine endophenotypes. Genotyping of the DBH 19-bp I/D polymorphism was performed on 400 migraine patients and 204 healthy individuals. The associations between genotypic frequencies and the clinical and sociodemographic features of migraineurs were then investigated. The DBH 19-bp I/D polymorphism did not correlate with migraine susceptibility or most clinical variables, with the exception of a statistically significant correlation within the subgroup of patients affected by chronic migraine were the individuals carrying the deleted (D) allele were significantly more prone to abuse in analgesics. As a result of this finding, the DBH 19-bp I/D polymorphism does not influence migraine susceptibility, but it might contribute to the development of medication overuse in patient with chronic migraine.

Keywords Migraine · Dopamine-beta-hydroxylase · 19-bp insertion/deletion polymorphism · Medication overuse · Genetic

Piero Barbanti and Fiorella Guadagni contributed equally to this work.

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Abbreviations

DBH	Dopamine-beta-hydroxylase
DA	Dopamine
MO	Medication overuse
BioBIM	Interinstitutional Multidisciplinary BioBank
MwoA	Without aura
MwA	With aura
CM	Chronic migraine
OR	Odds ratio

Introduction

A large series of evidence suggest that dopamine (DA) is involved in the pathophysiology of episodic migraine and might play an even greater role in the development of chronic migraine (CM) and medication overuse (MO) [1].

Specific genes related to DA metabolism and function have been explored to explain migraine susceptibility, clinical phenotype, and comorbidity [2–11]. Among these, the dopamine-

beta-hydroxylase (DBH) gene, encoding for an enzyme catalyzing the conversion of DA to norepinephrine (NE) [12], could play a pivotal role in migraine pathophysiology [1, 13].

DBH enzyme levels are a heritable genetic trait [14] and several functional polymorphisms, mainly located in the 5′ region of the DBH locus, contribute to 80% of its inter-individual variability [15, 16]. The gene encoding for DBH (OMIM: *609312), mapped on chromosome 9q34 [17], is composed of 12 exons and spans approximately 23 kb. Several association studies focused on a possible involvement of polymorphisms at this locus in the genetic predisposition to episodic migraine (but not to chronic migraine), considering the single or combined effect of different genetic variants [4–6, 9, 10, 18, 19]. Among these, the 19-bp I/D polymorphism has showed a positive association with migraine, even though conflicting results were achieved [4, 6, 8–10, 18] (Table 1). Furthermore, meta-analysis studies that analyze some of the reports we cited reported no significant association between migraine susceptibility and the DBH I/D polymorphism [21, 22]. This diallelic variant, previously indicated as rs72393728 and today identified with the access code rs141116007 in dbSNP, is located in the promoter region of DBH gene, approximately 4.7 kb upstream to the transcriptional start site [23]. From a functional point of view, this variant is statistically associated to plasma DBH enzyme levels, the deletion and the insertion alleles being correlated to low and high DBH activity, respectively [20].

Assuming that the most common limitation of genetic studies on migraine is a poor clinical characterization of patients, we investigated the DBH 190-bp I/D polymorphism not only in episodic but also in chronic migraine (with and without MO) in biological samples stored in the Interinstitutional Multidisciplinary BioBank (BioBIM) [24] from a population of extremely phenotypically detailed Caucasian patients, with the aim to provide a replication study on association with migraine susceptibility [25], and to detect any possible correlation with specific migraine subtypes or endophenotypes [26, 27].

Materials and methods

Population study

We recruited 400 consecutive unrelated Caucasian patients affected by migraine that had been evaluated at our Headache and Pain Unit (IRCCS San Raffaele Pisana, Rome) from January 2012 to June 2015. The cohorts of patients included migraine without aura (MwoA, $n = 199$; M/F = 40/159; mean age 40.28 ± 9.39 years), migraine with aura (MwA, $n = 71$; M/F = 23/48; mean age 39.40 ± 10.49 years), and chronic migraine (CM, $n = 130$; M/F = 17/113; mean age 40.62 ± 10.58 years) with and without MO (CM/MO+, $n = 115$; CM/MO−, $n = 15$) [28]. As control population we enrolled, 204 unrelated healthy individuals matched to the patients for age, gender, and ethnicity (M/F = 65/139; mean age 40.05 ± 10.60 years). An informative and consent form, approved by the institutional Ethics Committee of San Raffaele Scientific Institute IRCCS, was viewed and signed by patients and healthy controls who approved their blood sampling for research purposes. The protocol was approved by the institutional review board at the San Raffaele Scientific Institute and has therefore been performed in accordance with the ethical standards defined in the 1964 Declaration of Helsinki. All subjects gave an informed consent prior to their inclusion in the study.

Assessment of migraineurs' clinical characteristics

All patients underwent a complete physical, funduscopic, and neurological examination. Detailed information on the full set of lifestyle, behavioral and sociodemographic factors, migraine features, concomitant diseases, and medications were gathered by specifically trained neurologists with face-to-face interviews using a semistructured questionnaire [24, 27].

Migraine clinical features included family history, disease duration, frequency and duration of attacks, quality, intensity and location of pain, presentation with aura, accompanying symptoms, prodromes and postdromes, presence of dopaminergic symptoms (yawning, somnolence, vomiting), presence of unilateral cranial parasympathetic symptoms (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, eyelid swelling, or forehead/facial sweating) [27], triggers, alleviating factors, allodynia, duration of chronic migraine, putative chronifying factor, previous and current preventive and acute treatments, presence and duration of MO, drug overused and their amount, and responsiveness to triptans [24, 29].

DNA extraction and genotyping

Anticoagulated EDTA whole blood samples were collected and processed according to our biobanking Standard Operative Procedures [30]. Genomic DNA was isolated using the Isolate II Blood DNA Kit (Bioline) according to the manufacturer's instructions. The 19-bp I/D polymorphism was determined by a standard PCR amplification in a GeneAmp PCR System 9700 (Applied Biosystems) using the HotStarTaq Master Mix Kit (QIAGEN) as follows: an initial denaturing step at 95 °C for 15 min, 32 cycles at 94 °C for 30 s, 58 °C for 30 s and 72 °C for 1 min, and a final extension step at 72 °C for 10 min. Primers (F5′-TGCAAAAATCAGGCACATGC-3′ and R 5′-TCCA ATAATTTGGCCTCAATC-3′) were selected from the DBH Ensemble sequence database (Ensembl: ENSG00000123454). Amplified PCR products were separated on a 2.5% agarose gel, generating two fragments of different size according to the presence of the 19-bp insertion (165 bp) or deletion (146 bp). All determinations were repeated on PCR products obtained from

Table 1 Reported association studies between 19-bp I/D DBH polymorphism and migraine

Patients (M/F)	Headache subtype (number)	Healthy controls (M/F)	Country	Race-ethnicity	DBH polymorphisms	Comment on the 19-bp I/D polymorphism	Reference
142	-Migraine with aura (78) -Migraine without aura (64)	136	Australia	Caucasian	− 19-bp I/D -(AC)n Dinucleotide repeat	No association	[4]
269 (72/197)	-Migraine with aura (166) -Migraine without aura (103)	265 (72/193)	Australia	Caucasian	− 19-bp I/D -A444G	Significant association with migraine ($P = 0.011$), in particular between the D/D genotype, migraine with aura, and male gender ($P = 0.003$)	[6]
270	Migraine with aura (270)	272	Germany	Caucasian	− 19-bp I/D -rs1076153 -rs2797849 -rs3025388 -rs2007153 -rs1108581 -rs2873804 -rs1541332 -rs2797853 -rs2097629 -rs1611131	No association	[8]
301	-Migraine with aura (99) -Migraine without aura (202)	202	India	Asian	− 19-bp I/D -rs6275	Significant association of the D allele with migraine ($P = 0.027$), in particular with female gender ($P = 0.016$)	[9]
1° cohort: 208 (64/144) 2° cohort:127 (34/93)	-Migraine with aura (77) -Migraine without aura (131) -Migraine with aura (28) -Migraine without aura (99)	200 (75/125)	India	Asian	− 19-bp I/D -rs1611115	Significant association of the I/D genotype with migraine with aura ($P = 0.022$) and of the D variant with migraine ($P = 0.032$) and female gender ($P = 0.014$)	[10]
1° cohort: 170 (43/127) 2° cohort: 245 (35/210)	-Migraine with aura (90) -Migraine without aura (80) -Migraine with aura (204) -Migraine without aura (41)	455 (89/366)	Australia	Caucasian	rs6271 rs1611115	Significant association of the rs161111 C allele with migraine in the first and the second populations ($P = 0.004$ and $P = 0.013$)	[18]

The (AC)n dinucleotide repeat [4], the SNPs 444 G/A (rs1108580) [20], and − 1021 C/T (rs16111115) [16, 18] are in linkage disequilibrium with the 19-bp I/D

new nucleic acid extractions in order to exclude preanalytical and analytical bias.

Statistics

The Hardy-Weinberg equilibrium for the DBH insertion/deletion polymorphism was assessed via the chi-square goodness-of-fit test for each migraine patient group (MwA, MwoA, CM) as well as for control group. In small-sized sample it was used the exact method based on Haldane procedure [31].

Association of DBH I/D genotype was assessed for each migraine patient group with respect to the variables (a) gender, (b) familiarity, (c) pain location, (d) unilateral autonomic symptoms, (e) dopaminergic symptoms, (f) menstrual migraine, (g) migraine prophylaxis, (h) MO, (i) comorbid neuropsychiatric, (j) cardiovascular, (k) endocrino-metabolic, or (l) other systemic disorders. The Akaike information criterion (AIC) was used to choose the best model of inheritance in each genotype-variable association (namely, codominant (I/I vs D/D vs I/D), dominant (I/I vs I/D + D/D), recessive (D/D vs I/I + I/D), and

overdominant (I/D vs I/I + D/D)), and the chi-square test was used for finding statistical significance (alternatively the Fisher exact test (FE) or Fisher-Freeman-Halton test (FFH) were used according to the structure of the contingency table if the cell count < 5). The Sidak correction was applied to account for type-I error inflation due to multiple comparisons through "a" to "l" variables yielding $P < 0.0043$. The odds ratio (OR) with 95% confidence interval (95% CI) was used to show strength of genotype-variable association [32].

The Kaplan-Meier analysis was used to compare via the log-rank test the onset age between MwoA, MwA, and CM groups, setting statistical significance $P < 0.05$.

All calculations were performed with StatsDirect 2.7.2 (StatsDirect Ltd., UK) And SPSS 20 (IBM, USA), except where otherwise stated. The post hoc statistical power of both the genotype-variable association study and median onset age via log-rank test exceeded 80% for an effect size as large as OR 3.5 (equivalent to medium-sized effect like Cramer's V 0.35 and Cohen's d 0.75) and was computed using G*Power 3.1.3 (Universiat Kiel, Germany).

Results

Our migraine population included 199 patients affected by MwoA (49.7%), 71 by MwA (17.8%), 130 by CM (32.5%), and 204 healthy control individuals. The number of controls was sufficient for the power of the study and the allele frequencies we identified are congruent with those reported in the dbSNP dataset (https://www.ncbi.nlm.nih.gov/projects/SNP/ snp_ref.cgi?, $R_s = 141{,}116{,}007$) and 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/). Table 2 reports genotypes and allele frequencies of the 19-bp I/D DBH polymorphism.

We found no association between the DBH 19-bp I/D polymorphism and migraine susceptibility, gender, age of onset, and other clinical variables. No significant difference emerged between genotypic frequencies of MwA and MwoA and those predicted by the Hardy-Weinberg equilibrium (chi-square $P = 0.72$ and $P = 0.39$, respectively); by contrast, the CM group showed a significant disequilibrium (chi-square, $P = 0.04$) (Table 2).

Notably, DBH 19-bp I/D polymorphism was significantly associated with MO in CM patients carrying the D allele according to a dominant inheritance model (corresponding to I/D + D/D genotypes, chi-square test, $P = 0.001$), and to this concern the OR of abusing analgesics was 7.15 (95% CI 2.12–24.04). In order to investigate further this feature, CM group was partitioned according to MO occurrence, thereby finding a large subpopulation of abusers (CM/MO+, $N = 115$) against very few non-abusers (CM/MO−, $N = 15$) (Fig. 1). Both CM/MO+ (chi-square $P = 0.22$) and CM/MO− (exact P value, $P = 0.06$) were found in agreement with HW Besides, the DBH 19-bp Ins/Ins genotype resulted significantly associated with absence of drug overuse in chronic migraine according to a dominant inheritance model (FE test, $P = 0.006$) showing OR as large as 6.79 (95% CI 1.95–29.70) (Fig. 1). We also did not find association between DBH 19-bp I/D polymorphism and the amount of per month acute medications ($P = 0.928$).

Finally, the median age of onset did not differ between the migraine groups regardless of MO stratification (log-rank test, $P = 0.884$) (see Fig. 2 for the comparative cumulative frequency distribution of the onset age in each group).

Discussion

The present study suggests a correlation between DBH 19-bp I/D polymorphism and MO in patients affected by CM and

Table 2 Distributions of genotype and allele frequencies of the DBH polymorphism 19-bp I/D observed in patients and controls

	N	19-bp I/D genotypes (%)			19-bp I/D alleles (%)		HW (*P* value)
		DD	ID	II	D	I	
Controls	204	50 (24.5)	97 (47.6)	57 (27.9)	197 (48.3)	211 (51.7)	0.49
All patients with migraine	400	98 (24.5)	180 (45.0)	122 (30.5)	376 (47.0)	424 (53.0)	0.05
Migraine with aura	71	18 (25.3)	34 (47.9)	19 (26.8)	70 (49.3)	72 (50.7)	0.72
Migraine without aura	199	46 (23.1)	93 (46.7)	60 (30.2)	185 (46.5)	213 (53.5)	0.39
Chronic migraine							
Any	130	34 (26.1)	53 (40.8)	43 (33.1)	121 (46.5)	139 (53.5)	0.04
With medication oversuse	115	32(27.8)	51 (44.4)	32 (27.8)	115 (50.0)	115 (50.0)	0.22
Without medication overuse	15	2 (13.3)	2 (13.3)	11 (73.4)	6 (20.0)	24 (80.0)	0.06*

Values are given as no. (%)

HW Hardy-Weinberg equilibrium

*Rounded exact P value (actual $P = 0.0559$) was calculated by the method described in ref. [32]

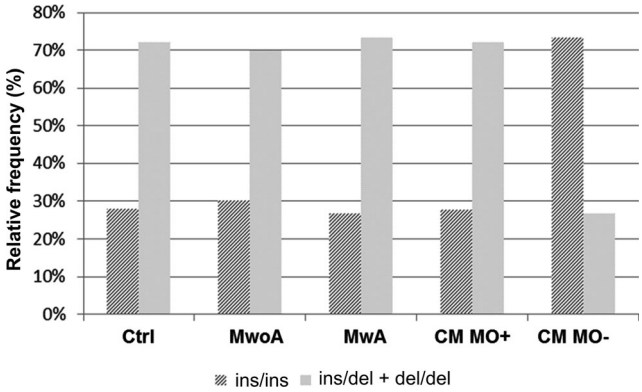

Fig. 1 Distributions of genotype and allele frequencies of the DBH polymorphism 19 bp I/D observed in healthy controls (CRTL), migraine without aura (MwoA), migraine with aura (MwA), chronic migraine with medication overuse headache (CM MO+), and chronic migraine without medication overuse headache (CM MO−)

does not support the previous hypothesis of an association between the polymorphism and MwoA or MwA.

We did not find any correlation between the DBH 19-bp I/D polymorphism (implicated in plasma DBH activity) and the predisposition to episodic migraine even when carefully considering an unusually wide set of clinical parameters or when considering putative endophenotypes such as "dopaminergic migraine" [1]. This discrepancy with previous DBH 19-bp I/D polymorphism investigations is likely to arise from the fact that we enrolled a larger number of patients with detailed sociodemographic and clinical characterization of migraine patients recruited in our migraine biobank, considered a broader spectrum of migraine forms—including for the first time also CM with and without

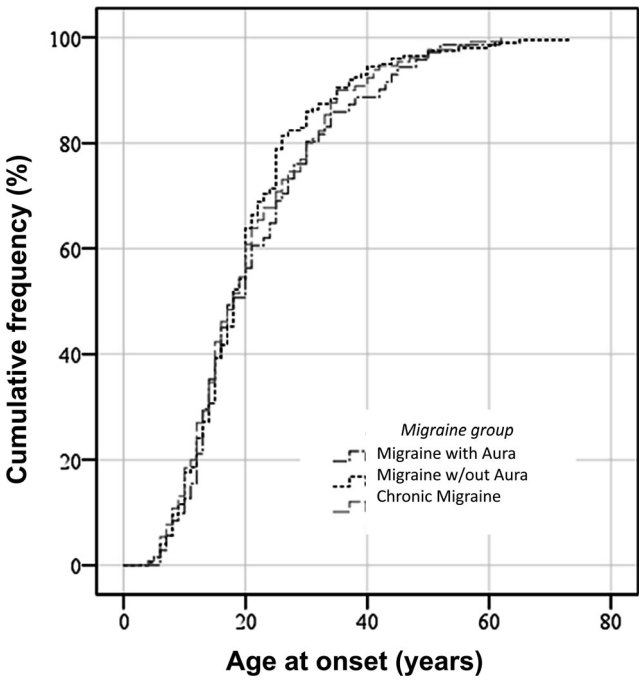

Fig. 2 Cumulative frequency distribution (Kaplan-Meier) of onset age in migraine groups

MO—and tried to correlate the DBH 19-bp I/D polymorphism with putative migraine endophenotypes [26, 27].

In fact, recent studies show the need for stratigraphy not only according to aura status and IHS criteria but also with "additional diagnostic features used for clinical characterization of migraine, e.g., photophobia, phonophobia, and nausea" [33].

In addition, previous meta-analysis performed on some of the studies we cited report no significant association between migraine susceptibility and the DBH 19-bp I/D polymorphism [21, 22].

The new meaningful finding of our study is that Caucasian patients with CM harboring the D allele are heavily prone to develop MO (OR = 7.15) in sharp contrast with those carrying the I allele who, conversely, have an OR of 6.79 not to overuse analgesics. We acknowledge that patients affected by CM/MO+ were exceedingly more numerous (88.5%) than those suffering from CM/MO− (11.5%), a frequently encountered situation in tertiary-referral centers dedicated to the management of more complex and disabling headaches, and that the number of patients with CM/MO− is very low for sub-analysis. However, this group represents the result of a detailed process of stratification that has highlighted a very rare clinical feature in a large population of migraineurs [34] and the statistical power of the study (> 80%) was elevated enough to suggest that this is a remarkable finding.

In particular, our data suggests that while an increased dopaminergic tone (consequent to lower DBH activity) predispose in D allele carriers to MO, a lower dopaminergic activity in CM patients carrying the I allele (inducing increased DBH activity) could somehow protect them from MO. Current knowledge indicates that MO may be genetically determined and does involve dopaminergic neurotransmission. Individuals with positive MO family history have a three-fold increase in MO risk [35]. MO liability has been related to the genetic variability of the DA transporter gene, namely, an allele 10 under-representation [7]. The TT genotype of the DA2 receptor gene (DRD2) NcoI polymorphism has been seen as an independent predictor for unsuccessful detoxification in individuals affected by CM/MO+ [36]. Patients affected by CM/MO+ show a 15-fold higher DA plasma levels than controls [37], manifest persistent dysfunctions in the mesocorticolimbic dopamine circuit (substantia nigra/ventral tegmental area complex) which could represent a preexisting MO-leading biological trait [38] and reveal a persistent hypofunction of the orbitofrontal cortex (OFC) which could reflect "an underlying, genetically determined, liability to medication overuse" [39]. The OFC receives a dopaminergic input from the ventral tegmental area [40] and plays an important role in controlling impulsive decision-making. Several evidences suggest that an impairment of OFC, as well as the inhibition of dopaminergic signaling, may render individuals vulnerable to psychiatric disorders associated to abnormal levels of impulsivity or substance abuse [41]. An indirect evidence of the involvement of DA circuitry in MO is also provided by a recent study which

documented a paradoxical decreased short-term potentiation (a DA-correlated phenomenon) in patients with MO—but not in those with CM or healthy controls when delivering 5-Hz trains of repetitive transcranial magnetic stimulation [42].

From the mentioned evidence, we could speculate that a lower dopaminergic activity in patients affected by CM carrying the I allele (which leads to an increased DBH activity, hence to reduced DA levels) could counteract prefrontal cortex hypofunction, somehow protecting them from MO risk.

The strength of our study is the detailed sociodemographic and clinical characterization of migraine patients which allowed correlations with a number of as yet neglected migraine features/endophenotypes. Limitations include the low number of patients with CM/MO− and the exclusive genotyping of the 19-bp I/D only, without considering other DBH polymorphisms that may well affect DBH activity. It has to be considered, however, that previous migraine studies, mostly focused on this polymorphism (Table 1) and that the 19-bp I/D, have shown to be in linkage disequilibrium with other polymorphisms strongly affecting DBH levels, such as the (AC)n dinucleotide repeat [4], the SNPs 444 G/A (rs1108580) [20] and − 1021 C/T (rs16111115) [16, 18].

Conclusions

In conclusion, the DBH 19-bp I/D polymorphism seems to influence MO in CM patients but does not influence migraine susceptibility or phenotype. Further studies on larger and of different ethnicity populations are imperative to understand the exact DBH involvement in MOH pathophysiology.

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Authors' contributions MLDM and DL carried out the molecular genetic studies, participated in the molecular analysis, and drafted the manuscript. PB and RP conceived of the study, participated in its design and coordination, and helped to draft the manuscript. GE, LF, CA, and PB participated in patient's recruitment. CI collected and interpreted the data and performed statistical analysis. DDM, PF, and FG conceptualized and designed the study, revised the manuscript, and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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Compliance with ethical standards

Competing interests P. Barbanti has received consultancy fees from Allergan, Bayer, electroCore, and Visupharma, and advisory fees from Abbott and Merck. M.L. De Marchis, C. Ialongo, G. Egeo, L. Fofi, C. Aurilia, D. Lovero, D. Della-Morte, P. Ferroni, F. Guadagni, and R. Palmirotta report no disclosures relevant to the manuscript.

Ethics approval and consent to participate The study was approved by the institutional Ethics Committee of San Raffaele Scientific Institute IRCCS and the patients gave written consent to participate.

Availability of data and materials Part of the dataset supporting the conclusions of this article is available on request to the corresponding author.

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