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Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation

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Abstract. – BACKGROUND: Risk factors for suicide are at least partially heritable and functional polymorphisms of targeted genes have been suggested to be implicated in the pathogenesis of this phenomenon. However, other studies examining the association between specific gene variants and suicide revealed inconsistent findings. We aims to evaluate the possible association between MAO-A3, CYP1A2*1F and GNB3 gene variants, hopelessness and suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation.

METHODS: 56 women were genotyped for MAO-A3, CYP1A2*1F and GNB3 gene variants. Participants were also assessed using Beck Hopelessness Scale (BHS), the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A), and the Suicidal History Self-Rating Screening Scale (SHSS).

RESULTS: Patients with higher total scores on affective dysregulated temperaments are more likely to have higher BHS (11.27±5.54 vs. 5.73±3.81; t19.20 = -3.57; $p < 0.01$) and higher SHSS total scores (4.79±3.31 vs. 1.05±2.31; t17.74 = –3.90; $p < 0.001$) than those with lower total scores. 67% of patients in the dysregulated group has BHS total scores >= 9 indicating high levels of hopelessness. No association was found between MAO-A3, CYP1A2*1F and GNB3 gene variants and suicidal risk as assessed by BHS and SHSS.

CONCLUSIONS: This study did not sustain the association between MAO-A3, CYP1A2*1F and GNB3 gene variants and increased suicidal risk in patients with chronic migraine and affective temperamental dysregulation. Further studies investigating the gene-environment interaction or focusing on other genetic risk factors involved in suicidal behaviour are needed.

Key Words:
Gene variants, Chronic migraine, Suicidal behaviour, Affective temperaments, Hopelessness.

Introduction

Suicidal behaviour is a major cause of death and morbidity worldwide. Approximately 1 million people died by suicide in the year 2000 and for every completed suicide, there are at least between 10 and 40 attempted suicides[1,2]. A strong bidirectional association has been suggested between psychiatric disorders, migraine and suicide, presumably including common neuropathic mechanisms. However, this relationship has often been clinically discussed rather than systematically studied[3,4]. Risk factors for suicidal behaviour are suggested to be at least partially heritable (about 40-50%)[5], including genetic variants that have been implicated in the pathogenesis of this complex phenomenon. A recent systemic review of suicide[6] has suggested that additive genetic factors contribute significantly to suicidal behaviour and are largely independent of the inheritance of psychiatric disorder. Genetic factors presumably affect suicide risk but the mechanism and magnitude of the genetic contribution is still poor understood[7].

Dysfunctions in monoamine neurotransmission have been demonstrated to be associated with suicidal behaviour. Although some studies investigated the possible association between MAO-A gene variant and suicide, the exact rela-

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tionship between MAO-A activity and suicide has far to be known. The MAO-A gene is located on the short arm of the X chromosome (Xp11). This gene has a functional polymorphism associated with transcriptional activity in which there is a variable number tandem repeat (VNTR) in the upstream region (MAO-A-uVNTR). However, whether MAO-A functional polymorphism is implicated in determining suicidal behaviour is still a matter of debate. Also, another large group of genes with the relative gene variants have been investigated: P450 (CYP450) family of genes. CYPs are involved in the metabolism and elimination of approximately 5-10% of many commonly prescribed drugs including psychotropic medications. CYP2D6 metabolizes at least 30% of the commonly prescribed drugs whereas the rest is accounted by other subunits such as CYP1A2, CYP2C9, CYP2C19 and CYP2E1[8]. In humans, CYP1A2 enzyme is encoded by the CYP1A2 gene. Overall, 12 single-nucleotide polymorphisms in CYP1A2 have been identified of which only CYP1A2*1C (G >A) and CYP1A2*1F (C >A) have been demonstrated to be of functional significance[9,10]. CYP1A2*1C functional polymorphism results in a significantly reduced induction of CYP1A2 gene whereas CYP1A2*1F (C >A), an intronic polymorphism identified approximately in one out of eight healthy volunteers[10]. Subjects who were homozygous for A allele resulted more likely (1.6-fold) to have an higher metabolic activity compared with the other genotypes in this category. Detecting genetic variations in drug-metabolizing enzymes may be useful in recognizing individuals who may more frequently experience adverse drug reactions with conventional doses of certain medications. Although a considerable number of association studies on other candidate genes have been reported in different populations, no study in literature has actually, to our knowledge, extensively investigated the possible association between CYP1A2 polymorphisms and suicidal behaviour.

Also, heterotrimeric guanine nucleotide-binding proteins genes (commonly known as G proteins) and integrating signals between receptors and effector proteins have been investigated. Subunit beta-3 is a protein that in humans is encoded by the GNB3 gene. A single-nucleotide polymorphism (C825T) in this gene has been associated with essential hypertension and obesity[11-14]. This polymorphism has been also associated with the occurrence of the splice variant GNB3-s which appears to have increased activity. To our knowledge, no studies exist in literature about the possible association between MAO-A, CYP1A2, GNB3 gene variants, hopelessness, affective temperaments and suicidal risk. Therefore, we aimed to evaluate the relationship between MAO-A3, CYP1A2*1F and GNB3 gene variants, hopelessness and suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation.

Methods

Participants

Participants are 56 women with chronic migraine[15] followed as outpatients at Sant'Andrea Hospital of Rome, between October 2010 and November 2011. The mean age is 50.75 (years), SD = 10.96 (range: 30-74 years). None of these patients had previous diagnoses of psychiatric disorders. Exclusion criteria were the presence of any condition affecting the ability to complete the assessment. To assess eligibility, patients were evaluated by a clinician who judged their ability to complete psychometric measures (see below), educational level (at least five years of primary education) and whether they had any severe medical condition (information kept in the medical record) that would impair their ability to complete the psychometric measures. Clinical and socio-demographic data are summarized in Table II. Each participant provided a written informed consent. The study protocol received ethics approval from the local Research Ethics Review Board. Women were approached during medical visits by a medical doctor and informed that the present study was part of a research activity designed to gather information that would be helpful in ameliorating the care. Patients receiving information about the purpose of the study were subsequently approached by two other medical doctors who explained and administered psychometric instruments. Psychometric instruments were filled out anonymously. One-hundred and ninety-three patients were initially screened for eligibility of which 76 were considered eligible. All patients were Italian native speakers. Of the initial 193 patients, 117 were excluded for the following reasons: 17 did not gave their informed consent to take part in the study, for 80 patients it was not possible to perform. Those patients who refused to take part to the study did not differ in terms of age or socio-demographic characteristics from

those who participated. Of the 76 patients who accepted to participate in the study, twenty subjects were excluded because it was not possible to administer psychometric instruments (those patients were not able to complete psychometric instruments and although stating the intent to participate in the study, they dropped out from both treatment and medical visits) (an eligibility rate of 86.8%). Finally, 56 patients were considered and included in the present study.

Genetic Analysis

We studied the following DNA polymorphisms: an untranslated variable number of tandem repeats (uVNTR) of 30 basepairs located about 1.1 kb upstream of the ATG initiation codon of MAO-A gene; a A C substitution and at position –163 and a G A transition at position –3860 in the 50 noncoding region of the CYP1A2 gene, indicated as *1F allele (rs762551) and *1C allele (rs2069514), respectively; an A G transition at position –392 in the promoter region of CYP3A4 gene, indicated as *1B allele (rs2740574) and a C T transition at nucleotide 825 (rs5443) in the coding sequence of G protein b3 subunit (GNB3) gene which produces a truncated form of the protein. Genomic DNA was isolated from peripheral blood using the X-tractor Gene system (Corbett Life Science, Sidney, Australia). The MAO-A promoter region polymorphism was genotyped on the basis of previously described method[16]. Identification of the amplified fragments size was performed by microchannel electrophoresis on chip, using the Agilent 2100 Bioanalyzer system (Agilent Technologies, Santa Clara, CA, USA). All the single nucleotide polymorphisms were genotyped by pyrosequencing technology (Pyrosequencer PyroMark ID system, Biotage AB and Biosystems, Uppsala, Sweden). Forward, reverse and sequencing primers were obtained by PSQ Assay Design software (Biotage AB and Biosystems, Uppsala, Sweden). PCR primer pairs and sequencing primer for each SNP are reported in Table I.

Briefly, regions covering the SNP of interest were amplified as follows: after initial denaturation (95°C, 10 min), a thermal cycler protocol (35 cycles) was employed cycling 20 s at 95°C, 20 s at 48°C, followed by 30 s extension at 72°C; a final extension of 5 min at 72°C was added. All polymerase chain reactions (PCR) reactions were performed in a final volume of 50 μl containing 40 ng of genomic DNA, 10 pmol of each primer, 0.2 mL dNTPs (deoxynucleotide triphosphatase), the appropriate concentration of $MgCl_2$ (Table I), PCR buffer and 1 U of *Taq* DNA polymerase (Takara Bio Inc., Otsu, Japan). Single-stranded DNA was isolated from the PCR reaction using the Pyrosequencing Vacuum Prep Workstation (Biotage, Uppsala, Sweden) and Streptavidin Sepharose TM High Performance beads (Amersham Biosciences, Uppsala, Sweden) that bind to the biotinylated primer. After washing in 70% ethanol, incubation in denaturing buffer and flushing with wash buffer, the beads were then released into a 96-well plate containing annealing buffer and the specific sequencing primer. Annealing was performed at 80°C for 2 min followed by cooling at room temperature. Then realtime sequencing was performed.

Measures

Participants completed a sociodemographic interview at intake, the Beck Hopelessness Scale (BHS)[17]; the Temperament Evaluation of the Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A)[18]; and the Suicidal History Self-Rating Screening Scale (SHSS)[19].

SHSS

Respondents were administered the SHSS, a 12-item (Yes/No) questionnaire developed by the

Table I. Primers and Mg^{2+} concentrations for PCR amplification and pyrosequencing.

SNPs	Forward primer (5'–3')	Reverse primer (5'–3')	Sequencing primer (5'–3')	Mg^{2+} concentration (mM)
CYP1A2*1C	CTTCTTGGATGCTTATGA	[a]TGTAATTCCAGCTACTCG	ACCGCAACCTCCGCC	1
CYP1A2*1F	[a]AGTGGAAACTGAGATGAT	ATACCAGAAAGACTAAGC	CTACCATGCGTCCTG	1
CYP3A4*1B	GGGATGAATTTCAAGTAT	[a]GGGTTCTTATCAGAAACT	CAGCCATAGAGACAAGG	1
GNB3 C825T	ACGAGAGCATCATCTG	[a]ATGGAGTCCCAGACAT	ATCTGCGGCATCACG	1.5

[a]Biotin molecule attached.

Authors to obtain information about previous suicidal ideation, planning, or attempts, both in the previous year and lifetime. It consists of two parts: the first part explores suicidal risk in the past twelve months, while part two explores lifetime suicidal risk. The SHSS scores range between 0-12. The SHSS had a Cronbach's alpha (α) reliability of 0.75 for Part I and 0.80 for Part II, for 851 undergraduate students and an inter-item mean correlation of 0.35 (Part 1: 0.31; Part 2: 0.41).

BHS

The BHS is a 20-item scale for measuring negative attitudes about the future. Beck originally developed this scale in order to predict who would commit suicide. Responding to the 20 true or false items on the BHS, individuals can either endorse a pessimistic statement or deny an optimistic statement. Scores range between 0-20, with higher scores indicating greater hopelessness. Research consistently supports a positive relationship between BHS scores and measures of depression, suicidal intent, and current suicidal risk[20]. The BHS may, therefore, be used as a proxy indicator of suicide potential. Studies on the Italian population have been carried out and successfully validated the scale[21,22].

TEMPS-A

The TEMPS-A is a self-reportmeasure of affective temperaments that define the bipolar spectrum, with depressive (D), cyclothymic (C), hyperthymic (H), irritable (I), and anxious (A) subscales[18]. The TEMPS-A has been validated in Italian populations[22].

Analysis

To reveal temperamental groupings (or clusters) within the data set, the Authors used a Two Step Cluster Analysis procedure. This procedure can handle categorical and continuous variables, using a likelihood distance measure that assumes that the variables in the model are independent. Empirical internal testing indicates that the procedure is fairly robust to violations of both the assumption of independence and distribution type. The two steps of the Two Step Cluster Analysis procedure's algorithm can be summarized as follows (1). The procedure begins with the construction of a Cluster Features (CF) tree. The tree begins by placing the first case at the root of the tree in a leaf node that contains data on the variables of the case. Each successive case is then added to an existing node or forms a new node, based upon its similarity to existing nodes and using the distance measure as the similarity criterion. A node that contains multiple cases contains a summary of information about those cases. Thus, the CF tree provides a capsule summary of the data file. (2) The leaf nodes of the CF tree are then grouped using an agglomerative clustering algorithm. The agglomerative clustering can be used to produce a range of solutions. To determine which number of clusters is ''best'', each of these cluster solutions is compared using Schwarz's Bayesian Criterion

Table II. Clinical and socio-demographic data about the sample.

Participants	Mean/SD	Frequency/percentage
Age (years)	50.75 (10.96)	
Psychiatric diagnosis		0 (0)
Comorbidity with chronic migraine		
– Migraine with sensory aura		23 (41.1)
– Migraine without sensory aura		1 (1.8)
– Migraine with sensory aura tension-type headache)		11 (19.6)
– Migraine without sensory aura (tension-type headache)		9 (16.1)
Duration of migraine attacks	24.9 (7.5)	
Illness duration (years)	26.8 (7.9)	
Alcohol abuse		26 (46.4)
Smoking		15 (26.8)
Cigarettes (number)	10.7	
Medications		
– Triptans		47 (83.9)
– FANS		17 (30.3)
– Phenothiazines		6 (10.7)
– Alcaloids		8 (14.3)
Medications abuse		5 (8.9)

Table III. Genotypic frequencies and percentages of MAOA u-VNTR polymorphism, A163C CYP1A2*1F, C825T GNB3.

Enzyme	Genotypic variants	Frequency	Percentage
MAO-A	3R/3R	5	8.9
	3R/4R	13	23.2
	4R/4R	15	26.8
	4R/5R	9	16.1
	5R/5R	11	19.6
	Minor alleles	4	5.4
CYP 1A2*F	1F/1A	14	25
	1A/1A	4	7.1
	1F/1F	38	67.9
GNB3	TC	28	50
	CC	23	41.1
	TT	5	8.9

(BIC) or the Akaike Information Criterion (AIC) as the clustering criterion. For the analysis, the procedure was allowed to automatically determine the number of clusters, and the Authors selected log-likelihood distance measure and the BIC as the clustering criteria.

Comparisons between clusters were performer using t-tests and e One-way Fisher exact tests for tables of contingency 2 × 2. If not otherwise indicated, statistical tests are two tailed with $p < 0.05$. All analyses were performed with SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Table III reported the genotypic frequencies and percentages of MAO-A u-VNTR polymorphism, A163C CYP1A2*1F, C825T GNB3.

The two cluster analysis indicates that participants may be clustered into two groups based on their scores at the TEMPS-A. The first group includes 41 patients (73% of the total sample) whereas the second group includes 15 patients (27% of the total sample). The first group is characterized by lower total scores in the depressive, ciclothymic, irritable and anxious subscales compared to the second group (for more datails, see Table IV). Therefore, the second group may be considered as a group of patients with a high dysregulated affective temperament component. Patients with higher total scores on affective dysregulated temperaments (compared to patients with lower total scores) are more likely to have higher BHS total scores (11.27±5.54 vs 5.73±3.81; $t_{19,20} = -3.57$; $p < 0.01$) and higher SHSS total scores (4.79±3.31 vs 1.05±2.31; $t_{17,74} = -3.90$; $p < 0.001$). Approximately 67% of patients included in the

Table IV. Differences between patients with high levels of dysregulated temperaments and patients with low levels of dysregulated temperaments.

	Patients with low levels of dysregulated temperaments	Patients with high levels of dysregulated temperaments	Test	$p <$
Age (years)	51.58 ± 11.40	47.73 ± 9.01	$t_{49} = 1.03$	0.31
CYP 1A2 *F 1F/1A variant	12.2%	33.3%		0.08
GNB3 TC, TT variants	39.0%	60.0%		0.14
MAO-A 3R variant	43.5%	80.0%		0.06
BHS ≥ 9	15.0%	66.7%	–	–
BHS	5.73 ± 3.81	11.27 ± 5.54	$t_{19,20} = -3.57$	0.01
SHSS	1.05 ± 2.31	4.79 ± 3.31	$t_{17,74} = -3.90$	0.001
TEMP-A DEP	0.36 ± 0.14	0.72 ± 0.14	$t_{54} = -8.53$	0.001
TEMP-A CYC	0.31 ± 0.18	0.66 ± 0.12	$t_{38,35} = -8.50$	0.001
TEMP-A HYP	0.51 ± 0.18	0.37 ± 0.26	$t_{19,02} = 1.90$	0.07
TEMP-A IRR	0.16 ± 0.09	0.39 ± 0.14	$t_{54} = -7.45$	0.001
TEMP-A ANX	0.41 ± 0.16	0.74 ± 0.12	$t_{54} = -7.08$	0.001

dysregulated group has BHS total scores ≥ 9 indicating high levels of hopelessness. The coexisting elevated total scores at the BHS and SHSS indicate an high suicidal risk.

The two groups are not different for any other variable. Approximately 80% of patients with high dysregulated temperament has a MAO-A3 variant vs. 44% of patients included in the group with low dysregulated temperaments (this difference is not statistically significant, $p = 0.06$). Similarly, approximately 60% of patients included in the group with high dysregulated temperament has a GNB3 common variant vs. 39% of patients with low scores in the dysregulated temperament (difference not statistically significant, $p = 0.06$). The two groups are not different for the percentage of therapeutic success (44.00±33.62 vs. 58.21±30.07; $t_{31} = 0.96$; $p = 0.35$), although patients with high dysregulated temperament have a lower percentage of therapeutic success compared to those with a lower dysregulated temperament.

Discussion

This is, to our knowledge, the first study investigating the role of MAO-A, CYP1A2, GNB3 functional polymorphisms, hopelessness and suicidal risk in a sample of patients with chronic migraine and affective temperamental dysregulation.

The most relevant finding which was found was that patients with higher total scores on affective dysregulated temperamental component are more likely to have higher BHS total scores and higher SHSS total scores when compared to patients with lower total scores. Specifically, approximately 67% of patients included in the dysregulated group has BHS total scores ≥ 9. Our previous studies replicated this finding[23-26]. Our reports showed that affective temperaments could be a useful tool in screening and identifying those who are at higher risk of suicidal behaviour. Also, temperaments appear as important predictors of both suicide risk and psychopathology and may be used in clinical practice for better delivery of appropriate care.

However, no association was found between MAO-A, CYP1A2, GNB3 functional polymorphisms, hopelessness and suicidal risk as assessed by both BHS and SHSS.

This last finding is consistent with some studies suggesting that there is no association between MAO-A functional polymorphisms and suicide attempts in subjects with bipolar disorder[27,28], major affective disorder[29], schizophrenia[30], heroin dependence[31] or psychiatric disorders[32]. Similarly, a lack of association between some functional polymorphisms of targeted genes and completed suicide had also been reported[33].

However, a number of contributions had indeed suggested the existence of a significant association between specific gene variants of targeted genes and suicide. It has been suggested that MAO-A functional polymorphism of the promoter region resulting in a modification of the activity of monoamine transmission in the central nervous system may be associated with behavioural disorders. Sabol et al[34] showed that the MAO-A gene with functional polymorphism that contains 3.5 or 4 repeats was transcribed 2-10 times more efficiently than polymorphism with 2, 3, or 5 repeats. Subjects having MAO-A 3.5R and 4R alleles (high enzymatic activity) showed higher impulsivity/aggressiveness as well as higher suicidal risk and depression than those with MAO-3R and 5R alleles (low enzymatic activity).

Also, several single nucleotide polymorphisms in specific genes involved in metabolism and target mechanisms of triptans determining different responses to triptans administration have been described[35,36]. In a first study aimed at detecting connections between genotypes and response to triptans administration, a significant association was found in 104 chronic migraine between MAOA-4R allele, CYP1A2*1F variant (reduced metabolic activity) and lower response to triptans[35]. Also, in another sample including 150 patients with chronic migraine a significant association was found between MAOA-uVNTR polymorphism and the grade of response to triptan administration[36].

Sabol et al[34] suggested that 3R and 4R alleles are the most common alleles among different ethnic populations. In our sample, 15 subjects (26.8%) has been identified as having MAO-A 4R/4R genotypic variant, 13 (23,2%) MAO-A 3R/4R genotypic variant, 11 (19,6%) MAO-A 5R/5R genotypic variant, 9 (16,1%) MAO-A 4R/5R genotypic variant, and 5 (8,9%) as having MAO-A 3R/3R genotypic variant. Only four subject (5.4%) were found to have MAO-A minor (2R/3R, 4R/6R and 5R/6R) genotypic variants.

Manuck et al[37] reported that MAO-A 4R allele was linked to high levels of aggressiveness and impulsivity and low responsiveness to serotonin confirming that MAO-A uVNTR polymorphism

was one of the most important serotonin-related single nucleotide polymorphism able to modulate vulnerability to suicide[38].

The association between MAO-A allele having high enzymatic activity and depression-related suicide in male subjects had been reported[39]. The Authors suggested that the risk of suicide attempts was 3.1 times greater among carriers with high enzymatic activity compared to carriers with low enzymatic activity.

Some other studies[40,41] reported the existence of an association between MAO-A functional polymorphism and suicide attempts. Courtet et al[32] suggested that MAO-A functional polymorphism was related to only violent suicide attempts.

Our results are also contrary to earlier studies suggesting an association between the MAO-A polymorphism and suicide attempt in female patients with bipolar disorder[42] and in female psychiatric patients with childhood trauma history[41]. Other contributions have reported an association between MAO-A 4R and suicide in depressed males, but not in community subjects. The Authors suggested that MAO-A 4R allele might affect vulnerability to suicide through the mediating factor of depressive symptoms[43]. Also, Lung et al[43] reported that males with 4R/4R genotypic variant were more likely (OR = 1.586) to develop depressive symptoms when compared to males with 3R/3R genotypic variant. It's important to note that they considered a sample of male patients with major depressive disorders and no comorbidity whereas our sample was exclusively composed of female outpatients with major affective disorders and comorbid chronic migraine. This might be a substantial difference.

In addition, we failed to demonstrate an association between the CYP1A2 and GNB3 genotypic variants and suicidal risk as assessed by BHS and SHSS. No previous researches exist, to our knowledge, in literature regarding the possible association between these genotypic variants and suicidal risk. Some studies in literature support the association between CYP1A2 genotypic variant, treatment outcome and response to medications in major depression.

Lin et al[44] suggested that that genetypic variants of the CYP1A2 region may be indicators of treatment response to antidepressant drugs in patients with affective disorders. Similarly, Laika et al[45] reported that the presence of genetic variants in the CYP1A2 region was associated with therapeutic outcome and treatment response in psychiatric inpatients. Other studies did not replicate these findings. Serretti et al[46] found that the investigated allelic variations of the cytochrome P450 do not play a major role in antidepressant response in a sample of two hundred and seventy-eight patients affected by major depression.

Also, few investigations in literature sustained the association between GNB3 gene variant and major depression but not suicide. A C825T polymorphism located in exon 10 of GNB3 was first described in 1998 and the T allele was reported to be associated with alternative splicing and with increased signal transduction in human cells[47]. The 825T allele has been described to be associated with hypertension, obesity, and depression in several disease-association studies. Also, it had been showed that patients with major depressive disorder bearing the T allele had a more severe symptomatology and a better response to antidepressant treatment compared to patients without the T allele[48].

The present findings must be considered in the light of the following limitations. First, these are preliminary data that did not allow us to generalize the present findings and replication in independent larger samples is needed. Most of genetic studies are limited by the small sample size that did not allow to detect the modest genetic effect in suicide liability.

Also, additional factors may be associated with suicide in major affective patients including socio-demographic factors such as level of education, age, marital status, personality characteristics, and anxiety symptoms. Lung et al[43] suggested that MAO-A uVNTR variants are commonly associated with different psychiatric symptoms and the genetic effect varies with gender. The fact that our sample was composed of only female outpatients may represent a selection bias. Also, 8.9% of these patients had medication overuse headache (MOH) that may complicate every type of headache and should be managed with the withdrawal of the overused drugs together with a detoxification treatment[49].

Importantly, suicide is a complex phenomenon determined by a series of psychophysiological processes. It has been suggested that an heritable and state-independent characteristic that co-segregates with the condition might be a candidate trait to improve the chances of finding a relationship between this complex behaviour and genotype[50]. For example, impulsivity is an important component of suicidal behaviour and it could be a suitable endophenotype of suicide attempts in genetic studies[51]. In our report, impulsivity was

not assessed impeding further examination of the relationship between MAO-A gene variant and impulsivity.

Another important issue comes from gene-environment interaction. Considering that genotype does not influence suicidal behaviour by itself but can interact with other environmental factors to cause this complex behaviour[41,52], using an objective measurement of environmental factors might help to elucidate the possible gene-environment interaction. The lack of psychosocial assessments has also prevented the exploration of the possible interaction between gene and environment. Overall, inaccurate diagnostic grouping, lack of investigation of interaction effects, and uncontrolled potential confounding factors might have determined inconsistent results.

Finally, the present results do not allow definite conclusions to be drawn and future studies are needed in order to elucidate a more comprehensive analysis of the effective functional link between MAO-A, CYP1A2, GNB3 gene variants and suicide.

Conclusions

Affective temperaments may be considered as a reliable predictor of suicidal risk. They could be useful tools for clinicians in identifying those patients who are at higher risk of suicidal behaviour. The non-significant association which was found between those gene variants and suicidal risk may suggest that they contribute only partially in determining suicidal behaviour; however, these results may be presumably related to the small sample size.

The possible effect of gene-gene interaction or gene-environment interaction on suicidal behaviour or violent suicide could not be adequately considered. Further additional studies are needed to evaluate the psychopathology of the relationship between MAO-A, CYP1A2, and GNB3 functional polymorphisms and different subtypes of mental diseases.

Statement of Interest

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