



## Catechol-O-Methyltransferase Val158Met Polymorphism Is Associated with Anxiety, Depression, and Widespread Pressure Pain Sensitivity in Women with Chronic, but Not Episodic, Migraine

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3 **TITLE PAGE**

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10 **TITLE**

11 Catechol-O-Methyltransferase (COMT) Val158Met Polymorphism is  
12 Associated with Anxiety, Depression and Widespread Pressure Pain  
13 Sensitivity in Women with Chronic, but not Episodic, Migraine  
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41 **Abstract**

42 **Objective:** To analyse the association between the rs4680 Catechol-O-Methyltransferase  
43 Val158Met polymorphism and to determine the association of this polymorphism with  
44 clinical, psychological and pain sensitivity variables in women with episodic or chronic  
45 migraine. **Methods:** Fifty women with episodic migraine, 50 with chronic migraine, and  
46 50 matched healthy women participated. After amplifying Val158Met polymorphism by  
47 polymerase chain reaction, we assessed genotype frequencies and allele distributions.  
48 Participants were classified according to the Val158Met polymorphism genotype into  
49 Val/Val, Val/Met, or Met/Met. A headache diary was used for collecting migraine pain  
50 features. Disability was assessed with Migraine Disability Assessment Scale, trait/state  
51 anxiety levels with the State-Trait Anxiety Inventory, and depression/anxiety with the  
52 Hospital Anxiety and Depression Scale. Pressure pain thresholds (PPT) were bilaterally  
53 assessed over the temporalis, the upper trapezius, the second metacarpal and the tibialis  
54 anterior. **Results:** The distribution of rs4680 Val158Met genotype was not significantly  
55 different between women with/without migraine ( $P=0.157$ ). No differences in migraine  
56 features were found depending on the Val158Met genotype. Women with the Met/Met  
57 genotype showed higher migraine-related disability than those with Val/Val or Val/Met  
58 genotype in both migraine groups ( $P<0.01$ ). Women with chronic, but not episodic,  
59 migraine with the Met/Met genotype exhibited higher depressive and anxiety levels and  
60 lower PPTs than those with Val/Val or Val/Met genotype. **Conclusion:** The Val158Met  
61 rs4680 polymorphism does not appear to be involved in predisposition to suffer from  
62 migraine; however, this genetic factor may be involved in the phenotypic expression of  
63 chronic migraine, since anxiety, depression and widespread pressure pain sensitivity  
64 was greater in those women with chronic, but not episodic, migraine with the Met/Met  
65 genotype.

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73 interest have been reported by the authors or by any individuals in control of the content  
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79 **Catechol-O-Methyltransferase (COMT) Val158Met Polymorphism is**  
80 **Associated with Anxiety, Depression and Widespread Pressure Pain**  
81 **Sensitivity in Women with Chronic, but not Episodic, Migraine**

82  
83 **Introduction**

84 Migraine is a primary headache disorder with a worldwide prevalence of 11.6%  
85 (13.8% females/6.9% males) (1). In the last Global Burden of Disease Study, migraine  
86 and tension-type headache were found to be the second most prevalent pain conditions  
87 in the world (2). In fact, general costs of headaches in Europe (€13.8 billion) mainly  
88 account for migraine and tension type headache (3).

89 It is accepted that the pathophysiology of migraine is associated with abnormal  
90 neuronal excitability leading to cortical spreading depression and to central sensitization  
91 of trigemino-vascular pathways (4). There are several factors that could affect the pain  
92 processing. One of these factors is genetics. Different genetic epidemiological studies  
93 have investigated the familial aggregation in migraine and it seems that an hereditary  
94 component can be present in some migraine types, i.e. hemiplegic migraine (5,6).

95 The catechol-O-methyltransferase (COMT) gene is one of the potential genetic  
96 determinants in chronic pain (7). The COMT is an enzyme involved in the metabolic  
97 degradation of several neurotransmitters, e.g., dopamine, norepinephrine, or epinephrine  
98 (8). The activity of the COMT gene can be affected by different polymorphisms such as  
99 rs4680, rs6269, rs4633, or rs4818. It seems that the rs4680 genetic polymorphism due to  
100 a G→A substitution at codon 158 of this gene, leading to a valine (Val) to methionine  
101 (Met) substitution, will result in differences within COMT gene activity related to pain  
102 sensitivity. In fact, a valine (Val) allele at codon 158 results in a high-activity variant  
103 (Val/Val) whereas a methionine (Met) at this codon position (Val/Met, Met/Met) results  
104 in low-activity variants (9). It has been found that subjects with the Met/Met genotype  
105 exhibit higher pain sensitivity, that is, lower pain thresholds to different stimuli (10,11),

106 and different brain responses to painful stimuli (12) than those subjects with the Val/Val  
107 genotype, supporting a role of this gene in nociceptive pain processing.

108         There are several studies investigating the role of Val158Met polymorphisms in  
109 migraine; although the results are inconsistent. The most recent meta-analysis did not  
110 observe a significant association between the Val158Met polymorphism and migraine  
111 (13). Similarly, a recent study, not included in the abovementioned meta-analysis, did  
112 not also reveal differences in Val158Met polymorphism distribution between subjects  
113 with migraine and healthy controls (14). Based on current evidence, it would seem that  
114 Val158Met polymorphism (rs4680) is not associated to a higher risk of suffering from  
115 migraine. However, it should be noted that most studies did not differentiate between  
116 episodic and chronic migraine. Similarly, another study including subjects with chronic  
117 migraine did not also find an association of the rs4680 Val158Met polymorphism with  
118 this subgroup (15).

119         Although no differences in Val158Met polymorphism distribution would exist  
120 between individuals with and without migraine, there is evidence suggesting a genetic  
121 influence of the COMT enzyme in several aspects of different chronic pain conditions,  
122 e.g., related-fatigue and pressure pain sensitivity in breast cancer survivors (16) or mood  
123 disorders (anxiety and depression) in women with fibromyalgia (17). Therefore, it is  
124 possible that the Val158Met polymorphism can also influence some phenotypic aspects  
125 in patients with migraine. In line with this hypothesis, Park et al found that individuals  
126 with migraine carrying the Met allele experienced worse migraine-associated nausea  
127 and vomiting and higher pain intensity of migraine attacks than those with the Val allele  
128 (18). No previous study has investigated the role of the Val158Met polymorphism in  
129 clinical, psychological and pain sensitivity outcomes in women with migraine.

130

131           Therefore, the aims of the current study were: 1) to investigate the association of  
132 the Val158Met polymorphism in women with episodic or chronic migraine; and 2) to  
133 determine the relevance of the Val158Met polymorphism with clinical, psychological,  
134 and pain sensitivity variables in women with migraine.

135

## 136 **Methods**

### 137 **Participants**

138           One hundred and twenty consecutive women with migraine were recruited from  
139 a Headache Unit located in a tertiary university-based hospital. They were diagnosed  
140 following the third edition of International Headache Society (ICHD-III) criteria down  
141 to third-digit level (code 1.1, 1.3) by an experienced neurologist (19). Migraine features  
142 including location, quality of pain, years with disease, frequency and intensity of pain  
143 attacks, family history, and medication intake were collected. To be included, subjects  
144 had to describe typical pain features of migraine pain (unilateral location, pulsating  
145 pain, high intensity, and aggravation during physical activity) and associated symptoms  
146 including photophobia, phonophobia, mild nausea or vomiting (19).

147           Participants were excluded if they presented any of the following: 1) other primary  
148 or secondary headache, including medication overuse headache; 2) history of cervical or  
149 head trauma; 3) pregnancy; 4) history of cervical herniated disk or cervical osteoarthritis  
150 on medical records; 5) any systemic medical disease, e.g., rheumatoid arthritis, lupus  
151 erythematosus; 6) comorbid fibromyalgia syndrome; 7) had received treatment including  
152 anesthetic blocks, botulinum toxin or physical therapy within the previous 6 months; or,  
153 8) male gender. All participants were carefully interviewed for assessing their medical  
154 history. Further a medical exam, including neuro-imaging examination (MRI or CT) of  
155 the head, was performed in all patients in order to identify any exclusion criteria.

156 Age-matched healthy women without history of headache diagnosis and without  
157 reporting a headache pain attack during the previous year were also included. Exclusion  
158 criteria for the control group were the same as for the headache groups. All participants  
159 signed the informed consent form before their inclusion in the study. The local Ethics  
160 Committee of Hospital Rey Juan Carlos, Spain (HRJ 07/14) approved the study design.

#### 161 **DNA Collection and COMT Genotyping**

162 Non-stimulated whole saliva samples were collected into collection tubes (passive  
163 drooling technique) according to standardized procedures. Saliva collections were made  
164 when participants were headache-free, or with a migraine intensity of less than 3 points  
165 (in those patients with high frequency of attacks). Immediately after collection, samples  
166 were centrifuged at 3000 rpm for 15min to obtain the cell sediment and they were stored  
167 at -20° C until the analysis. We prefer to use saliva instead of blood sampling because  
168 salivary collection is a non-invasive, stress-free and ethic suitable assessment method.

169 Laboratory technicians were blinded to the subject's condition. Genomic DNA  
170 was hence extracted from saliva cell sediments using the "Genomic DNA extraction and  
171 purification Kit" (Real Molecular Biology) following the manufacturer instructions. The  
172 single Val158Met (rs4680) nucleotide polymorphism was genotyped using a TaqMan®  
173 Drug Metabolism Genotyping Assays on a Real Time PCR ABI Prism 7000 Sequence  
174 Detection System (APPLIED BIOSYSTEM, USA) in the Genomic Unit at the Centro  
175 de Apoyo Tecnológico Universidad Rey Juan Carlos, Madrid (Spain). The 3 possible  
176 allelic variants were associated with different fluorescent dyes to proper identification  
177 of the different genotype forms: Val/Val (H/H), Val/Met (H/L), or Met/Met (L/L). The  
178 results are derived from a G→A substitution at the following sequence:

179 CCAGCGGATGGTGGATTTCGCTGGC [A/G] TGAAGGACAAGGTGTGCATGCCTGA

180

181

182 **Migraine Features**

183 A 4-weeks headache diary was used to register clinical features of migraine (20).  
184 The diary was used to calculate the following variables: 1, migraine intensity, calculated  
185 from the mean intensity of the days with s migraine attack as assessed with a 11-point  
186 numerical pain rate scale (21) (NPRS; 0: no pain, 10: maximum pain); 2, migraine  
187 frequency (days/month); and 3, migraine duration, calculated by dividing the total hours  
188 of the attack by the number of days with migraine (hours/attack).

189 **Psychological and Disability Variables**

190 The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the  
191 levels of anxiety and depression. This questionnaire includes 7-items scored at a 4-  
192 points scale for assessing anxiety (HADS-A) and other 7-items for assessing depressive  
193 (HADS-D) symptoms (22). Both scales are considered reliable and valid for assessing  
194 anxiety (Cronbach's  $\alpha$ : 0.83) and depression (Cronbach's  $\alpha$ : 0.82) (23). In subjects with  
195 headache, the HADS has shown good internal consistency (Cronbach's  $\alpha$ : 0.84) (24).

196 The State-Trait Anxiety Inventory (STAI) is a 40-items scale assessing separate  
197 dimensions of state anxiety (items 1-20, STAI-S) and trait anxiety (items 21-40, STAI-  
198 T) (25,26). The STAI-S assesses relatively enduring symptoms of anxiety at a moment,  
199 and the STAI-T scale measures a stable propensity to experience anxiety and tendencies  
200 to perceive stressful situations as threatening. Both scales have exhibited good internal  
201 consistency ( $\alpha$ : 0.89) and high reliability (ICC: 0.88) (27). Higher scores in both scales  
202 indicate greater levels of state or trait anxiety.

203 To assess the degree of related-disability in daily activities (work or school,  
204 family and social) caused by migraine, we used the Migraine Disability Assessment  
205 Scale (MIDAS) questionnaire. It consists of 5 questions related to days of partial or  
206 total loss within the last 3 months regarding 3 main activities: 1, paid work or school;

207 2, household chores; 3, family, social, or leisure activities (28). The final score comes  
208 from the sum of the missed days regarding the 3 activities.

### 209 **Widespread Pressure Pain Sensitivity**

210 The evaluation was held when patients were headache-free or, in those with high  
211 frequency of migraine, when the intensity of headache was less than 3 points on NPRS.  
212 Participants were asked to avoid any analgesic or muscle relaxant 24 hours prior to the  
213 examination. No change was made on the prophylactic treatment of the patients. All the  
214 participants attended a session for familiarization with the pressure test procedure over  
215 the wrist extensor muscles.

216 Pressure pain thresholds (PPTs), i.e. the minimal amount of pressure where a  
217 sensation of pressure changes to pain (29), were assessed with an electronic algometer  
218 (Somedic AB, Farsta, Sweden). The pressure was applied perpendicularly to the point at  
219 a rate of approximately 30 kPa/s. Participants were instructed to press the “stop button”  
220 when the sensation first changed from pressure to pain. The mean of 3 trials on each  
221 point was calculated and used for the main analysis. A 30sec resting period was allowed  
222 between trials for avoiding temporal summation (30). The reliability of pressure  
223 algometry has been found to be high (31,32).

224 To determine widespread pressure pain sensitivity, PPTs were bilaterally assessed  
225 over a trigeminal point (i.e. temporalis muscle), an extra-trigeminal point (i.e. C5/C6  
226 joint), and two distant pain-free points (i.e. the second metacarpal and tibialis anterior  
227 muscle) by an assessor blinded to the individual’s condition. The order of assessment  
228 was randomized between participants. Since no side-to-side differences were observed,  
229 mean of both sides were used in the analysis.

230

231

232 **Sample Size Calculation**

233 Sample size determination and calculations were based on detecting a moderate-large  
234 effect size of 0.7 on PPTs between migraine and healthy controls related to Val158Met  
235 genotype distribution, a 2-tailed test, with an alpha level ( $\alpha$ ) of 0.05, and a desired  
236 power ( $\beta$ ) of 90%. This generated a sample size of, at least, 42 participants per group.

237 **Statistical Analysis**

238 Data were analyzed with the SPSS statistical package (22.0 Version). Results are  
239 expressed as mean and 95% confidence interval (95% CI). The Kolmogorov-Smirnov  
240 test showed that all quantitative variables showed a normal distribution of the data ( $P >$   
241 0.05). Comparisons of genotype distribution and allele frequency among groups were  
242 performed on raw frequencies using an extended chi-squared test ( $\chi^2$ ). A  $\chi^2$  analysis of  
243 the Hardy-Weinberg equilibrium for the genotypes was conducted to determine whether  
244 the allele frequencies were stable within all groups. A 2x2 analysis of variance ANOVA  
245 was used to compare clinical and psychological variables according to the Val158Met  
246 polymorphism genotype (Val/Val, Val/Met, Met/Met) in women with migraine (episodic,  
247 chronic). A 3x3 mixed-model ANOVA was used to investigate differences in PPTs over  
248 each point (temporalis, C5-C6 joint, second metacarpal, tibialis anterior) according to  
249 the Val158Met genotype (Val/Val, Val/Met, Met/Met) and group (episodic migraine,  
250 chronic migraine, healthy control). Post-hoc analyses comparisons were conducted with  
251 the Bonferroni test. The statistical analysis was conducted at a 95% confidence level. A  
252 P value less than 0.05 was considered statistically significant.

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255

## 256 **Results**

257           One hundred and twenty (n=120) consecutive women presenting with headache  
258 were screened for eligibility criteria. Twenty (17%) were excluded for the following  
259 reasons: co-morbid headaches (n=7); previous head or neck trauma (n=6); receiving  
260 anaesthetic block in the past 3 months (n=5) or pregnancy (n=2). Finally, 50 women  
261 with chronic migraine (age: 43±12 years), 50 with episodic migraine (age: 42±13 years)  
262 satisfied all criteria, signed the informed consent, and agreed to participate. Further, 50  
263 age-matched women without headache (age: 43±11 years) were also included. **Table 1**  
264 summarizes clinical, psychological and pain sensitivity data of the sample. Women with  
265 chronic migraine exhibited significant higher headache frequency (P<0.001) and higher  
266 migraine-related disability (P=0.04) than those with episodic migraine. Further, women  
267 with episodic or chronic migraine exhibited higher widespread pressure pain sensitivity  
268 (P<0.001) than healthy women, without differences between them (P>0.9).

### 269 **Distribution of Val158Met Polymorphism in migraine**

270           The genotype distributions in women with and without migraine did not deviate  
271 from those expected based on the Hardy-Weinberg equilibrium. The distribution of the  
272 Val158Met genotypes ( $\chi^2=6.63$ ; P=0.157) was not significantly different among women  
273 with episodic or chronic migraine and healthy women (**table 2**).

### 274 **Clinical and psychological measures and Val158Met Polymorphism**

275           The mixed-model ANOVA did not reveal significant differences depending on  
276 the Val158Met polymorphism genotype (**table 3**) in both groups of migraine women for  
277 years with pain (F=0.874; P=0.420), migraine intensity (F=0.172; P=0.842), migraine  
278 frequency (F=1.986; P=0.143), and migraine duration (F=0.308; P=0.736).

279

280 Similarly, no significant differences depending on the Val158Met polymorphism  
281 genotype were either found (**table 4**) in both women with episodic or chronic migraine  
282 for STAI-T ( $F=0.340$ ;  $P=0.712$ ), and HADS-A ( $F=1.494$ ;  $P=0.188$ ). A significant group  
283 \* Val158Met genotype interaction was observed for HADS-D ( $F=4.369$ ;  $P=0.015$ ) and  
284 STAT-S ( $F=3.219$ ;  $P=0.045$ ): women with chronic migraine, but not those with episodic  
285 migraine, carrying the Met/Met genotype showed higher depressive and anxiety state  
286 levels than those carrying the Val/Val ( $P=0.01$ ) or Val/Met ( $P=0.04$ ) genotype. Finally,  
287 significant differences based on the Val158Met polymorphism genotype for the MIDAS  
288 ( $F=7.078$   $P<0.001$ ) were found in both migraine groups: women carrying the Met/Met  
289 genotype exhibited higher levels of related-disability than those with the Val/Val or the  
290 Val/Met genotype ( $P<0.01$ ) in both episodic and chronic migraine groups (**table 4**).

#### 291 **Pressure pain sensitivity and Val158Met polymorphism**

292 All patients with episodic migraine and 45 (90%) patients with chronic migraine  
293 were headache-free during PPT examination. The 3x3 mixed-model ANOVA revealed  
294 significant group\*Val158Met polymorphism genotype interactions for PPTs over the  
295 temporalis muscle ( $F=3.714$ ;  $P=0.025$ ), the second metacarpal ( $F=3.641$ ;  $P=0.024$ ), and  
296 tibialis anterior ( $F=3.431$ ;  $P=0.03$ ), but not for the C5-C6 zygapophyseal joint ( $F=1.479$ ;  
297  $P=0.212$ ). Women with chronic migraine with the Met/Met genotype showed lower PPT  
298 than women with chronic migraine with the Val/Met or Val/Val genotype ( $P<0.001$ ).  
299 No significant differences existed in PPTs between women with chronic migraine with  
300 the Val/Val or Val/Met genotypes ( $P>0.5$ ). **Table 5** shows PPT according to Val158Met  
301 polymorphism in women with episodic and chronic migraine and healthy women.

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303

304

## 305 **Discussion**

306           The current study found no differences in the genotype distribution and allele  
307 frequency of the Val158Met polymorphism between those women with migraine, either  
308 episodic or chronic, and healthy women. Further, the presence of the Met/Met genotype  
309 was associated to higher levels of anxiety, depression, disability and greater widespread  
310 pressure hyperalgesia, in women with the chronic, but not episodic, form of the disease.

### 311 **Val158Met polymorphism and migraine**

312           We did not observe significant differences in the distribution of the Val158Met  
313 polymorphism between women with episodic or chronic migraine and healthy women,  
314 supporting the assumption that this polymorphism is not involved in a predisposition to  
315 suffer from migraine. Our results agree with a recent systematic review concluding that  
316 the Val158Met polymorphism was not associated with migraine risk (13). Additionally,  
317 Takigawa et al did not also observe differences in the presence of other haplotypes of  
318 the COMT gene, e.g., rs4633, rs6267, rs6270 between individuals with migraine and  
319 healthy people (14). Nevertheless, since the rs4680 Val158Met polymorphism has been  
320 associated, in some studies, to different conditions, e.g., fibromyalgia syndrome (33) or  
321 temporomandibular pain (34), it is possible that it could be associated to some particular  
322 pain conditions rather than to chronic pain in general. Furthermore, since migraine is  
323 comorbid with other chronic pain syndromes, i.e. fibromyalgia (35), we do not know if  
324 different subgroups of patients with migraine and co-morbid conditions would lead to  
325 different associations. Obviously, the fact that the rs4680 Val158Met polymorphism is  
326 not associated with migraine does not exclude the role of genetics in this headache  
327 form. Therefore, future studies investigating the role of other genetic components in  
328 migraine are guaranteed.

329           It has been previously that the Val158Met can be associated with worse clinical  
330 presentation of migraine. For instance, individuals with migraine carrying the Met allele  
331 experienced higher pain intensity and worse migraine-associated symptoms than those  
332 with Val allele (18). We observed that women with migraine, either episodic or chronic,  
333 with the Met/Met genotype exhibited higher migraine-related disability as assessed with  
334 the MIDAS than those with Val/Met or Val/Val genotype. Further, a Met/Met genotype  
335 was also associated with higher depressive and anxiety state levels, but only within the  
336 chronic migraine group, suggesting that the Val158Met polymorphism can play a role in  
337 different psychological aspects. In fact, our results agree with previous studies showing  
338 that the Met allele is associated with anxiety-related behaviors in healthy women (36),  
339 with higher stress responses after a whiplash injury (37), or with higher psychological  
340 distress in fibromyalgia syndrome (38). A potential explanation for these findings could  
341 be related to the fact that individuals carrying the Met/Met genotype had greater brain  
342 activation of the limbic region as response to emotionally challenging situations (39,40).  
343 Additionally, Met/Met carriers exhibited lower activation of the dorso-lateral pre-frontal  
344 cortex and cingulate cortex than Val/Val carriers (41). Therefore, it is also possible that  
345 individuals with the Met/Met genotype exhibit different cortical activation patterns than  
346 those carrying the Val/Val genotype.

#### 347 **Val158Met polymorphism and pain hyperexcitability**

348           Another relevant finding of the current study is that women with chronic, but not  
349 episodic, migraine carrying the Met/Met genotype exhibited higher widespread pressure  
350 pain sensitivity than those with the Val/Val or Val/Met genotype. These findings would  
351 suggest that the Val158Met polymorphism could play a role within the nociceptive pain  
352 processing in the chronic form of the disease. A potential association of the Val158Met  
353 polymorphism with higher sensitivity to pressure pain has been previously observed in

354 children with chronic tension type headache (42) and women with fibromyalgia (43).  
355 Our study is the first reporting an association between the Val158Met polymorphism  
356 and widespread pressure pain sensitivity in chronic migraine. Several mechanisms could  
357 explain this association. For instance, a reduction within COMT gene activity associated  
358 with the Met allele at codon 158 of the Val158Met leads to a reduction in the content of  
359 enkephalins in some regions of the central nervous system associated with pain (9). This  
360 hypothesis would correlate with the presence of hyper-excitability of the central nervous  
361 system and of endogenous inhibitory pain pathways previously observed in adults with  
362 chronic migraine (44). In fact, migraine has been associated with a non-physiological  
363 production of some neuromodulators (45). Therefore, another potential mechanism may  
364 be an increase of catecholamine levels, which will promote stimulation of  $\beta$ 2-adrenergic  
365 receptors in the central nervous system, associated with a reduced COMT gene activity  
366 (46). Since individuals with migraine exhibit hyper-excitability of the central nervous  
367 system, it is possible that the presence of the Met/Met genotype, in some predisposed  
368 subjects, could contribute to this process. In fact, this hypothesis is also suggested in  
369 subjects with fibromyalgia (47).

### 370 **Limitations**

371 Although the results of this study are informative, potential limitations should be  
372 considered. First, we included women with migraine and derived from a specialized  
373 tertiary hospital center. Therefore, our results should be not extrapolated to men and to  
374 other primary headaches such as tension-type headache. Second, it is possible that the  
375 study was underpowered for other outcomes different than PPTs. Therefore, a greater  
376 sample size including patients from the general population would be needed to further  
377 confirm these results. Third, we only investigated the rs4680 nucleotide of Val158Met  
378 polymorphism. Future studies should include a greater number of polymorphisms and

379 other genes to further clarify their potential role in the phenotypic expression of chronic  
380 migraine.

381

## 382 **Conclusions**

383 No differences were found in the genotype distribution and allele frequency of  
384 the Val158Met polymorphism between women with migraine, either episodic or chronic  
385 and healthy women. The presence of the Met/Met genotype was associated with higher  
386 related-disability in both episodic and chronic migraine, and with higher depressive and  
387 anxiety levels, and higher pressure pain hyperalgesia but only in the chronic migraine  
388 group. Our results suggest that the rs4680 Val158Met polymorphism may contribute to  
389 the altered nociceptive pain processing in women with chronic migraine and may  
390 contribute to the chronification process.

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