

## Case Control Study

## e Catechol-O-Methyltransferase Val158Met Polymorphism is Associated with Pain and Disability, but not Widespread Pressure Pain Sensitivity, in Women with Carpal Tunnel Syndrome

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**Background:** The genetic influence of Val158Met polymorphisms, one of the potential genetic determinants for nociceptive processing, has not been previously investigated in women with carpal tunnel syndrome (CTS).

**Objectives:** To investigate the association between the Val158Met polymorphism with CTS and to assess the relationship between the Val158Met polymorphism and the clinical outcomes and widespread pressure pain hypersensitivity in women with CTS.

**Study Design:** Case control study.

**Setting:** Neurology department at an urban hospital.

**Method:** One hundred nine ( $n = 109$ ) women (mean age:  $47 \pm 9$  years) with a clinical and electrodiagnostic diagnosis of CTS and 109 matched healthy women participated. After amplifying the Val158Met polymorphism by polymerase chain reactions, rs4680 genotype frequencies and allele distributions were calculated. We classified individuals according to their Val158Met polymorphism: Val/Val, Val/Met, Met/Met. The intensity of the pain was assessed with a numeric rating scale (0-10) and disability was determined with the Boston Carpal Tunnel Questionnaire. Pressure pain thresholds were bilaterally assessed over median, radial, and ulnar nerve trunks; C5-C6 facet joints; and carpal tunnel and tibialis anterior muscles.

**Institutional Review Board:** The study project was approved by the local human research committee (HUFA-12/14). All participants signed an informed consent prior to their inclusion in the study.

**Results:** The distribution of the 3 Val158Met genotypes (Val/Val, Val/Met, Met/Met) and alleles was not significantly different between women with CTS and healthy women ( $\chi^2 = 0.498$ ;  $P = 0.780$ ). Women with CTS carrying the Met/Met genotype showed higher levels of pain and disability than those with the Val/Met genotype ( $P < 0.01$ ) and with the Val/Val genotype ( $P < 0.001$ ). No differences in the years with pain ( $P = 0.954$ ), age ( $P = 0.740$ ), depression ( $P = 0.530$ ), severity of CTS ( $P = 0.744$ ) or presence of unilateral-bilateral symptoms ( $P = 0.279$ ) existed depending on the rs4680 Val158Met genotype. No significant differences in widespread pressure pain sensitivity were observed in any of the points depending on the rs4680 Val158Met genotype ( $P > 0.315$ ).

**Limitations:** We only recruited women from a specialized department.

**Conclusion:** Current results indicated that the Val158Met polymorphism seems not to be a risk factor for the development of CTS; however, it was associated with increased perception of pain and higher disability scores.

**Key words:** Catechol-O-methyltransferase gene, carpal tunnel syndrome, polymorphism pressure pain thresholds, sensitivity.

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**C**arpal tunnel syndrome (CTS) is one of the most common neuropathies of the upper extremity associated with a compression of the median nerve at the wrist (1). In the general population, it has been found to have a prevalence rate of 3.8% (2) and an incidence rate of 1.8/1,000 (3). A recent study of active workers (4) reported an annual prevalence of 3.1% for CTS, representing approximately 4.8 million people in the US (4). This study also found an overall lifetime prevalence of CTS of 6.7% among workers (4). CTS aggregates health costs of approximately \$2 billion annually in the US (5).

This condition has previously been considered a localized compression of the median nerve at the carpal tunnel; however, recent theories and evidence support the concept that CTS pain involves both central and peripheral sensitization mechanisms (6). In fact, the presence of bilateral heightened pain hypersensitivity, not related to electro-diagnostic findings (7), in individuals with CTS has been demonstrated (8-10). Therefore, it is well accepted that central nervous system changes in nociceptive processing accompany the peripheral nerve dysfunction typically associated with CTS.

The existence of individuals' differences in the response to painful stimuli suggests that potential genetic factors can be involved in nociceptive pain modulation. The catechol-O-methyltransferase (COMT) gene is one of the several potential genetic determinants for nociceptive processing; however, its role in chronic pain remains controversial. The Val158Met single-nucleotide polymorphism leads to a substitution of valine (Val) with methionine (Met) at codon 158 on chromosome 22q11. This enzyme is involved in the metabolic degradation of several neurotransmitters such as dopamine, norepinephrine, and epinephrine (11). It has been reported that genetic polymorphism due to a G→A substitution at codon 158 of the COMT gene and leading to a Val to Met substitution results in gene activity differences. The presence of a Val allele results in high enzymatic activity, whereas the presence of a Met allele results in low enzymatic activity (12,13). It is accepted that those with the Val/Val genotype (higher enzymatic activity) exhibit reduced pain sensitivity than those with the Met/Met genotype (lower enzymatic activity), suggesting that this genotype predisposes for chronic pain and that genetic variability in the gene encoding Val158Met can be important for development of hyperalgesia (14-16).

Several studies have tried to identify if any specific genotype of the Val158Met gene is related to the presence of chronic musculoskeletal pain; however, the re-

sults are conflicting. For instance, 2 systematic reviews analyzing the evidence in relation to the presence of the Val158Met polymorphism in fibromyalgia syndrome have reported contradictory results (17,18). To date, scientific data on the effect of this polymorphism in the development of neuropathic pain are scarce. In fact, the only published study to date examining the relationship of the Val158Met polymorphism and neuropathic pain found no association (19). However, this study included individuals with complex regional pain syndrome I and II, failed low back surgery syndrome, peripheral and cranial nerve neuralgia, phantom limb pain, and postherpetic neuralgia, but did not include patients with CTS (19). The genetic role of Val158Met polymorphism in the development of CTS has not yet been investigated.

Additionally, there is increasing evidence demonstrating the genetic influence of the Val158Met polymorphism in the phenotypic expression and progression in different chronic pain conditions. The presence of the Met/Met genotype has been associated with higher disability, depression, and anxiety in women with fibromyalgia (20,21). Other studies found that patients with chronic tension-type headache (22), breast cancer (23), and long-lasting low back pain, sciatica, or lumbar disc herniation (24) with the Met/Met genotype exhibit worse clinical features (higher pain intensity or fatigue, longer length of the disease) and higher pressure pain sensitivity than those patients with the Val/Val or Val/Met genotype of the Val158Met polymorphism.

To the best of the authors' knowledge, no previous study has investigated the role of the 3 genotypes of the Val158Met polymorphism in the genetic susceptibility and the phenotypic expression and progression in women with CTS. We therefore compared the frequency of the single-nucleotide polymorphism rs4680 genotypes among patients with CTS and healthy individuals to examine whether this polymorphism could be a factor contributing to development of CTS. We also investigated whether any genotype of the Val158Met polymorphism can modulate nociceptive processing and clinical outcomes regarding the progression of pain and disability in CTS.

Therefore, the aims of our study were to assess the association between the Val158Met polymorphism in women with CTS; to analyze the relationship between the Val158Met polymorphism and clinical outcomes regarding the progression of pain and disability in women with CTS; and to investigate if the Val158Met polymorphism is related to widespread pressure hypersensitivity

in CTS. We hypothesized that the Met/Met genotype of the Val158Met polymorphism will be more prevalent in patients with CTS than in healthy people and also that it is associated with greater widespread pressure pain hypersensitivity and worse clinical outcomes than Val/Val and Val/Met genotypes.

## **METHODS**

**Institutional Review Board:** The study project was approved by the local human research committee (HUFA-12/14). All participants signed an informed consent prior to their inclusion in the study.

### **Participants**

Consecutive women diagnosed with CTS by an experienced neurophysiologist from the Neurology and Traumatology Department of Hospital Universitario Fundación Alcorcón, Spain, were screened for eligibility criteria. They were required to present both clinical and electrophysiological findings of CTS (25). To be eligible to participate, patients had to exhibit at least 4 of 5 of the following clinical findings: pain and paresthesia in the median nerve distribution without extramedian nerve territory symptoms; increasing symptoms at night; Tinel sign; Phalen sign; self-reported hand strength deficits. Symptoms had to be present for at least 6 months. No restriction for unilateral/bilateral symptoms or severity of the diagnosis was considered.

Additionally, the electro-diagnosis examination had to reveal deficits of sensory and motor nerve conduction of the median nerve according to standardized guidelines of the American Association of Electrodiagnosis, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation (26,27). A median nerve sensory conduction velocity less than 40 mm/s and a median nerve distal motor latency greater than 4.20 ms were considered as abnormal. Individuals with minimal (abnormal segmental-comparative tests only), moderate (abnormal median nerve sensory velocity conduction and distal motor latency), mild (abnormal median nerve sensory velocity conduction and normal distal motor latency) or severe (absence of median nerve sensory response and abnormal distal motor latency) CTS were included (28). Women with moderate/mild CTS were grouped as in a previous study (7). Sensory and motor conduction studies of the radial and ulnar nerves were conducted to rule out radial or ulnar nerve involvement.

Patients were excluded if they exhibited any of the following criteria: if any sensory/motor deficit in ulnar

or radial nerve was present; previous interventions with surgery or steroid injections; multiple diagnoses of the upper extremity (i.e., cervical radiculopathy, lateral epicondylalgia); history of neck, shoulder or arm trauma; history of a systemic disease causing CTS (e.g., diabetes mellitus, or thyroid disease); history of systemic musculoskeletal conditions (e.g., rheumatoid arthritis, fibromyalgia); if the patient was actively involved with or seeking litigation at the time of the study; pregnancy.

Finally, healthy women were also recruited from volunteers who responded to a local announcement. They were excluded if they exhibited a history of upper extremity or neck pain, surgery, fractures, or any other neurological disorder. The study project was approved by the local human research committee (HUFA-12/14). All patients and participants signed an informed consent prior to their inclusion in the study.

### **Self-reported measures**

A 10 cm Numeric Rating Scale (29) (0: no pain, 10: maximum pain) was used to assess mean current level of hand pain, and worst and lowest levels of hand pain experienced in the preceding week. The Spanish version (30) of the Boston Carpal Tunnel Questionnaire (31) (BCTQ) was used to determine disability. This questionnaire evaluates 2 domains: the functional status scale assesses ability to perform 8 common hand-related tasks; the symptom severity scale includes 11 items assessing pain severity, numbness, and weakness at night and during the day. Each question is answered on a 5 point scale (1: no complaint; 5: severe complaint), with higher scores indicating greater severity (0-5). The BCTQ has been shown to be valid, reliable, and responsive for use in individuals with CTS (32).

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

Nonstimulated whole saliva samples were collected from each patient and participant into collection tubes (passive drooling technique) according to standardized procedures. Saliva collections were made with the patients and participants seated and leaning forward with their heads tilted down. The collections were made between 9:00 a.m. and 11:00 a.m. All of them had abstained from any kind of exercise from the previous day. Those who smoked were asked not to do so for 2 days before the collection sampling. They were all asked not to eat or drink or chew gum for one hour before the sampling. Immediately after collection, samples were

centrifuged at 3,000 rpm for 15 minutes to obtain cell sediment and they were stored at -20°C until the main analysis. We prefer to use saliva instead of blood sampling because saliva collection is a noninvasive, stress-free, and ethically suitable assessment method.

Laboratory technicians were blinded to the patients' condition. Genomic DNA was extracted from saliva sediments using "Genomic DNA Extraction and Purification Kit" (Real Molecular Biology, Valencia, Spain) following the manufacturer's instructions. The single Val158Met (rs4680) nucleotide polymorphism was genotyped using an Applied Biosystems® TaqMan® Drug Metabolism Genotyping Assays on a Real Time PCR ABI Prism 7000 Sequence Detection System (Life Technologies, Grand Island, NY) in a Genomic Unit, Centro de Apoyo Tecnológico, Universidad Rey Juan Carlos, Madrid, Spain. The 3 possible haplotypes were associated with different fluorescent dyes to allow the identification of the different genotypes: Val/Val, Val/Met, or Met/Met. The results are derived from a G→A substitution at the following sequence:

CCAGCGGATGGTGGATTTCGCTGGC [A/G] -  
TGAAGGACAAGGTGTGCATGCCTGA

### Pressure Pain Thresholds

Pressure pain thresholds (PPT), the minimum amount of pressure when a sense of pressure changes to pain (33), were assessed with an electronic algometer (Somedic AB®, Farsta, Sweden). The pressure was applied at an approximate rate of 30 kPa/s, with the algometer placed perpendicular to the application point. Patients were instructed to press a switch when the sensation changed from pressure to pain. The mean of 3 trials was calculated and used for the main analysis. A 30-second resting period was allowed between each measure. The reliability of pressure algometry has been found to be high (Intraclass Correlation: 0.91, 95% Confidence Interval [CI] 0.82 - 0.97) (34).

Pressure pain sensitivity was only assessed within the group of women with CTS. They were asked to avoid any analgesic or muscle relaxant 24 hours prior to the testing. They attended a preliminary session for familiarization with the test procedure. PPTs were measured bilaterally over the median (over the cubital fossa medial to and adjacent to the biceps tendon), radial (where it passes through the lateral intermuscular septum between the medial and lateral heads of the triceps brachii to enter the mid- to lower-third of the humerus), and ulnar (over the groove between the medial epicondyle and the olecranon) nerves, the articular

pillar of the C5-C6 facet joint, the carpal tunnel, and the muscle belly of the tibialis anterior according to previous studies (7,8). The order of assessment was randomized between patients and the assessor was blinded to the Val158Met condition.

### Statistical Analysis

Data were analyzed with the SPSS statistical package Version 19.0 (IBM Corporation, Armonk, NY). Results are expressed as mean and 95% CI. The Kolmogorov-Smirnov test showed that all quantitative variables showed a normal distribution of the data ( $P > 0.05$ ). Comparisons of genotype distribution and allele frequency between groups were performed on raw frequencies using a Chi-squared test ( $\chi^2$ ). A  $\chi^2$  analysis of the Hardy-Weinberg equilibrium for the genotypes was conducted to determine whether the allele frequencies were stable within patients and controls. A one-way mixed analysis of variance (ANOVA) was used to compare pain intensity and disability according to the Val158Met polymorphism genotype (Val/Val, Val/Met, Met/Met) within women with CTS. A 2-way ANOVA test was used to investigate differences in PPT over each point (median, radial, ulnar nerve, carpal tunnel, C5-C6 facet, tibialis anterior muscle) with side (affected/unaffected) as the within-patients factor and Val158Met polymorphism genotype (Val/Val, Val/Met, Met/Met) as the between-patients factor. For women with unilateral CTS, sides were classified as affected or unaffected, whereas in those with bilateral symptoms, the most painful side was considered the affected side and the less painful side as the unaffected side. Post-hoc analyses comparisons were done with a Holm-Bonferroni correction (35). The statistical analysis was conducted at a 95% confidence level. A  $P$  value  $< 0.05$  was considered statistically significant.

## RESULTS

### Clinical data of the sample

Two hundred ( $n = 200$ ) consecutive patients with CTS from January 2012 through February 2013 were screened for eligibility criteria. Finally, 109 (55%) women with CTS, aged 30 to 63 years old (mean:  $47 \pm 9$  years) satisfied all the eligibility criteria and agreed to participate. The reasons for exclusion were the following: previous surgery ( $n = 35$ ), previous steroid injections ( $n = 26$ ), fibromyalgia ( $n = 11$ ), whiplash syndrome ( $n = 7$ ), pregnancy ( $n = 5$ ), diabetes ( $n = 5$ ), and age above 65 ( $n = 2$ ).

All patients were right-hand dominant. Twenty-seven patients (25%) showed minimal CTS, 48 (44%) had moderate/mild CTS, and the remaining 34 (31%) presented severe CTS. Twenty-eight (26%) had unilateral symptoms (22 right side, 6 left side) whereas 81 (74%) showed bilateral symptoms (50 had the right hand more affected, and 31 the left hand). No significant differences ( $\chi^2 = 2.261$ ;  $P = 0.462$ ) in the distribution of women with unilateral or bilateral symptoms existed depending on severity.

The mean duration of hand pain in the total sample was  $3.3 \pm 2.0$  years (95% CI 2.7 - 3.9), the mean current level of pain was  $4.9 \pm 1.3$  (95% CI 4.4 - 5.3), the worst level of pain experienced in the preceding week was  $6.7 \pm 1.4$  (95% CI 6.3 - 7.1), and the lowest level of hand pain in the preceding week was  $1.8 \pm 1.0$  (95% CI 1.3 - 2.2). The BCTQ functional status scale score of the total sample was  $2.3 \pm 0.6$  (95% CI 2.2 - 2.6) and the BCTQ symptom severity scale score was  $2.6 \pm 0.5$  (95% CI 2.5 - 3.8). Finally, the Beck Depression Inventory-II score of the total sample was  $4.1 \pm 1.7$  (95% CI 3.5 - 4.6).

In addition, 109 matched healthy women without any upper extremity symptom, aged 30 to 62 (mean:  $46 \pm 10$  years) were also included ( $P = 0.763$ ).

### Distribution of Val158Met polymorphism genotypes

The Val158Met genotype distributions in women with CTS and healthy women did not deviate from those expected based on the Hardy-Weinberg equilibrium. The distribution of Val158Met COMT genotypes was not significantly different ( $\chi^2 = 0.498$ ;  $P = 0.780$ ), between women with CTS and healthy women (Table 1).

### Clinical data and Val158Met polymorphism in CTS

A one-way ANOVA test revealed significant dif-

ferences depending on Val158Met polymorphism genotype for mean level of current pain ( $F = 13.254$ ;  $P < 0.001$ ), the worst level ( $F = 8.026$ ;  $P < 0.001$ ) and the lowest level ( $F = 4.475$ ;  $P = 0.014$ ) of pain experienced the previous week; and the BCTQ functional status ( $F = 10.487$ ;  $P < 0.001$ ), and the BCTQ symptom severity ( $F = 13.924$ ;  $P < 0.001$ ) scales, but not in years with pain ( $F = 0.047$ ;  $P = 0.954$ ), age ( $F = 0.302$ ;  $P = 0.740$ ) and depression ( $F = 0.638$ ;  $P = 0.530$ ). In such a way, women with CTS carrying the Met/Met genotype experienced higher levels of pain and disability than those women with the Val/Met ( $P < 0.01$ ) and with the Val/Val ( $P < 0.001$ ) genotype, without differences between Val/Val and Val/Met genotypes (all,  $P > 0.209$ ).

Further, no significant differences in the distribution of women with minimal, mild/moderate, or severe CTS ( $\chi^2 = 1.954$ ;  $P = 0.744$ ) or with unilateral/bilateral symptoms ( $\chi^2 = 5.081$ ;  $P = 0.279$ ) existed depending on the COMT genotype (Table 2). details clinical data depending on Val158Met polymorphism genotype in women with CTS {this is not a complete sentence}

### Widespread pressure pain sensitivity and Val158Met polymorphism in CTS

The 2-way ANOVA did not reveal significant differences between Val158Met COMT polymorphism genotype for PPT over the median nerve (Val158Met polymorphism:  $F = 0.896$ ,  $P = 0.410$ ; side:  $F = 0.002$ ,  $P = 0.955$ ), ulnar nerve (Val158Met polymorphism:  $F = 1.191$ ,  $P = 0.315$ ; side:  $F = 0.026$ ,  $P = 0.871$ ), radial nerve (Val158Met polymorphism:  $F = 0.796$ ,  $P = 0.452$ ; side:  $F = 0.011$ ,  $P = 0.918$ ), C5-C6 facet (Val158Met polymorphism:  $F = 0.948$ ,  $P = 0.389$ ; side:  $F = 0.001$ ,  $P = 0.971$ ), carpal tunnel (Val158Met polymorphism:  $F = 0.509$ ,  $P = 0.602$ ; side:  $F = 0.100$ ,  $P = 0.753$ ), and tibialis anterior muscle (Val158Met polymorphism:  $F = 0.393$ ,  $P = 0.676$ ; side:  $F = 0.510$ ,  $P = 0.476$ ). No significant Val158Met

Table 1. Distribution of Val158Met genotypes and alleles of the Catechol-o-methyltransferase (COMT) gene in women with carpal tunnel syndrome (CTS) and healthy women.

	Women with CTS (n = 109)	Healthy Women (n = 109)
<b>Val158Met Polymorphism Genotype</b>		
Val/Val	40 (37%)	45 (41%)
Met/Val	46 (42%)	42 (39%)
Met/Met	23 (21%)	22 (20%)
<b>Alleles</b>		
Val	126 (58%)	132 (60%)
Met	92 (42%)	87 (40%)

Table 2. Differences in clinical and demographic variables in women with carpal tunnel syndrome according to Val158Met polymorphism genotype.

Variable	Val/Val (n = 40)	Val/Met (n = 46)	Met/Met (n=23)
Age (Years)	45 ± 10 (42 - 48)	45 ± 9 (42 - 48)	46 ± 8 (43 - 50)
Years with Pain (Years)	3.3 ± 3.4 (2.3 - 4.4)	3.2 ± 2.7 (2.3 - 4.0)	3.4 ± 3.2 (2.0 - 4.7)
Severity (Minimal / Moderate / Severe)	10 / 19 / 11	12 / 17 / 17	5 / 12 / 6
Side (Left / Right / Bilateral)	4 / 5 / 31	2 / 12 / 32	0 / 5 / 18
Depression (BDI-II, 0-21)	4.4 ± 3.4 (3.3 - 5.5)	3.8 ± 2.2 (3.1 - 4.4)	4.1 ± 2.2 (3.6 - 4.5)
<b>Pain Intensity (NRS, 0-10)</b>			
Mean Current Level of Pain*	4.2 ± 2.6 (3.3 - 5.0)	4.5 ± 2.1 (3.9 - 5.1)	6.9 ± 1.0 (6.5 - 7.4)
Worst Pain Experienced Preceding Week*	5.8 ± 2.4 (5.1 - 6.2)	6.7 ± 2.1 (6.1 - 7.3)	8.1 ± 1.4 (7.5 - 8.7)
Lowest Pain Experienced Preceding Week*	1.4 ± 2.0 (0.7 - 2.2)	1.3 ± 1.7 (0.8 - 1.8)	2.7 ± 2.2 (1.7 - 3.6)
<b>Boston Carpal Tunnel Questionnaire (BCTQ, 0-5)</b>			
Functional Status Scale*	2.1 ± 0.6 (1.9 - 2.3)	2.3 ± 0.6 (2.1 - 2.5)	2.8 ± 0.7 (2.5 - 3.2)
Symptom Severity Scale*	2.3 ± 0.5 (2.2 - 2.5)	2.6 ± 0.5 (2.4 - 2.7)	3.1 ± 0.6 (2.8 - 3.3)

Values are expressed as means ± standard deviation (95% confidence interval) except for severity and side of the symptoms

\* Statistically significant differences between Met/Met genotype compared to Val/Val ( $P < 0.001$ ) and Val/Met ( $P < 0.01$ ) genotypes

Table 3. Differences in pressure pain thresholds over nerve tissues in women with carpal tunnel syndrome according to Val158Met polymorphism genotype.

	Median Nerve	Ulnar Nerve	Radial Nerve
<b>Women with Carpal Tunnel Syndrome Val/Val Genotype (n = 40)</b>			
Affected	194.7 ± 46.7 (178.6 - 210.8)	299.6 ± 63.4 (274.6 - 323.4)	218.5 ± 49.3 (199.8 - 237.1)
Non-affected	193.5 ± 48.7 (177.5 - 209.6)	313.4 ± 63.8 (289.1 - 337.8)	217.4 ± 53.8 (198.8 - 235.9)
<b>Women with Carpal Tunnel Syndrome Val/Met Genotype (n = 46)</b>			
Affected	182.9 ± 48.8 (167.9 - 197.9)	284.3 ± 66.7 (261.6 - 307.1)	215.1 ± 59.2 (197.8 - 232.4)
Non-affected	185.8 ± 42.4 (170.8 - 200.8)	276.2 ± 65.3 (253.5 - 298.9)	207.0 ± 57.9 (189.7 - 224.3)
<b>Women with Carpal Tunnel Syndrome Met/Met Genotype (n = 23)</b>			
Affected	194.1 ± 42.4 (172.9 - 215.3)	285.5 ± 64.0 (253.3 - 317.7)	218.3 ± 58.4 (193.8 - 242.7)
Non-affected	192.4 ± 44.2 (171.2 - 213.6)	284.6 ± 63.5 (252.4 - 316.8)	215.7 ± 60.1 (205.7 - 254.6)

polymorphism x side interaction was found (all,  $P > 0.636$ ). Tables 3 and 4 detail widespread PPT by Val158Met polymorphism in women with CTS.

## Discussion

The current study found no differences in the genotype distribution and allele frequency of the Val158Met polymorphism between women with CTS and healthy women. The presence of the Met/Met genotype in women with CTS was associated with higher intensity pain and disability, but not with higher widespread pressure pain hypersensitivity. Current results indicate that the Val158Met polymorphism seems not to be a risk factor for the development of CTS; however it

was associated with increased perception of pain and higher disability scores.

Our findings suggest that Val158Met polymorphism does not seem to be involved in a predisposition for women to develop CTS. Twenty-three (21%) women with CTS and 22 (20%) healthy women exhibited the Met/Met genotype. The distribution of Val158Met polymorphism genotypes and the percentage of the Met/Met genotype in our healthy women were similar to that reported in previous studies (17-24,36-40) supporting that our sample of healthy people could be considered as representative of the general population.

In accordance with our results, Val158Met polymorphism also has not been associated with chronic

Table 4. Differences in widespread pressure pain thresholds in women with carpal tunnel syndrome according to Val158Met polymorphism genotype.

	C5-C6 Facet Joint	Carpal Tunnel	Tibialis Anterior Muscle
<b>Women with Carpal Tunnel Syndrome Val/Val Genotype (n = 40)</b>			
Affected	182.5 ± 44.5 (167.5 - 197.6)	346.3 ± 87.1 (315.3 - 377.4)	326.1 ± 74.8 (301.7 - 350.5)
Non-affected	185.1 ± 45.9 (170.1 - 200.1)	345.2 ± 87.4 (314.2 - 376.3)	318.9 ± 75.9 (294.5 - 343.3)
<b>Women with Carpal Tunnel Syndrome Val/Met Genotype (n = 46)</b>			
Affected	177.1 ± 45.7 (163.0 - 191.1)	334.9 ± 86.4 (306.1 - 363.9)	318.0 ± 80.3 (295.2 - 340.7)
Non-affected	174.5 ± 43.1 (160.5 - 188.6)	339.1 ± 87.9 (310.1 - 368.1)	306.0 ± 84.0 (283.2 - 328.7)
<b>Women with Carpal Tunnel Syndrome Met/Met Genotype (n = 23)</b>			
Affected	173.3 ± 45.4 (153.4 - 193.1)	335.6 ± 82.2 (294.6 - 376.6)	317.8 ± 73.0 (285.7 - 350.0)
Non-affected	172.4 ± 42.7 (152.6 - 192.2)	319.2 ± 83.1 (278.2 - 360.1)	313.4 ± 76.8 (281.2 - 345.5)

musculoskeletal pain (36) or widespread pain (37). On the contrary, the Val158Met polymorphism has been associated with other conditions, e.g., fibromyalgia (38,39) and temporomandibular pain (40). It is possible that Val158Met polymorphisms are more related to specific pain syndromes rather than to chronic pain in general. In fact, the role of the Val158Met polymorphism is controversial (41). In agreement with this hypothesis, Segall et al (42) discussed that the role of this enzyme is different in nociceptive and neuropathic pain.

Nevertheless, the fact that the Val158Met polymorphism is not involved in CTS does not negate the role of genetics in this pain condition. We found that women with CTS carrying the Met/Met genotype exhibited higher intensities of pain symptoms and disability than those with the Val/Val or Val/Met genotypes. Although CTS is generally considered an entrapment neuropathy at the carpal tunnel, current results would suggest a potential genetic influence in the phenotypic expression of the disease. The regulating role of the Val158Met polymorphism in the phenotypic expression of some chronic musculoskeletal pain conditions is not new since previous studies have reported that the presence of the Met/Met genotype was associated with higher disability in fibromyalgia (20,21), a longer duration of symptoms in chronic tension type headache (22), long lasting pain in those with low back pain and sciatica (24), higher severity of headaches and more associated symptoms in migraine (43). However, the current study is the first one demonstrating the influence of Val158Met polymorphism in the phenotypic expression in a neuropathic pain condition such as CTS.

Determining the mechanisms involved in the regulating role of the Val158Met polymorphism in pain and disability in women with CTS are beyond the scope of

this study; however, a few hypotheses can be discussed. The first possible mechanism can be related to the fact that reduction in COMT gene activity associated with the Met allele at codon 158 leads to a reduction in the content of enkephalin (e.g., endogenous opioid-like peptides) in areas of the central nervous system associated with the pain experience (14). A second mechanism may be that reduced COMT activity would result in elevated levels of catecholamines, e.g., epinephrine, promoting the production of persistent pain states via stimulation of  $\beta$ 2-adrenergic receptors in the peripheral and central nervous system (44). Nackley et al (45) found that systemic suppression of COMT activity increased sensitivity by activating  $\beta$ 2 and  $\beta$ 3-adrenergic receptors, supporting this hypothesis. However, it has been recently suggested that differences between the contribution of COMT activity in neuropathic and nociceptive pain is driven by a  $\beta$ 2 and possibly  $\alpha$ -1 receptors mediated "switch" (42).

More recent theories include a Val158Met polymorphism influence in the response of cortical and sub-cortical areas. Mobascher et al (46) reported stronger activation within cortical and subcortical areas including the core regions of cerebral pain processing, i.e. the "pain matrix," particularly in the secondary somatosensory cortex, the insula, the amygdale, and mostly the posterior portion of the anterior cingulate cortex in Met/Met patients than in Val/Val and Val/Met carriers. Loggia et al (47) also found higher activation of the periaqueductal gray matter, lingual gyrus, cerebellum, hippocampal formation, precuneus, cuneus, superior and middle occipital gyri, and cerebellum in those carrying the Met/Met genotype. These studies hypothesized that the more sustained recruitment of the pain matrix in Met/Met carriers represents a com-

pensatory mechanism counteracting the lower neuronal levels of enkephalin. A recent study has shown that patients with CTS exhibit neuroplastic changes in the brain caused by the nociceptive barrage (48). It is possible that regulation of the phenotypic expression by Val158Met polymorphisms in CTS is related to cortical plastic changes.

In line with this hypothesis, Vossen et al (49) found that the Met allele was associated with augmented cortical processing of experimental pain in patients with chronic pain, but not in healthy people, supporting the notion that COMT influence is more important in individuals with already heightened sensitization. Similarly, Jensen et al (50) reported that Val158Met differences may be more expressed in individuals where the inhibitory nociceptive system is more sensitive. It is interesting to note that current evidence supports the presence of heightened pain sensitization in the central nervous system in CTS (6-10). Surprisingly, we found that widespread pressure pain hypersensitivity was not significantly different depending on the Val158Met polymorphism in our sample of women with CTS.

Our results are contrary to those previously reported in breast cancer survivors where the Met/Met genotype was associated with higher pressure sensitivity at the neck (23) but similar to those found in women with fibromyalgia syndrome where no differences were observed among any of the 3 genotypes (21). These discrepancies can be related to the fact that Val158Met variations are more related to thermal pain than to mechanical pain (51), suggesting that this polymorphism might have different effects on different pain modalities. Further, it is also possible that widespread pressure hypersensitivity, a common phenomenon found in CTS (6,7), is not related to genetic influences.

The results of this study can be placed in the context of personalized medicine, whereby treatments for various diseases are tailored to the genetic characteristics of individuals (52). Likewise, genetic research can identify subgroups of patients who might benefit from symptoms intervention and contribute to developing personalized therapies for individuals with more severe symptoms. The association of the Met/Met genotype with increased pain symptoms and disability may be of importance for the identification of subgroups of

patients with CTS. This association in patients with CTS may contribute to open perspectives into the understanding of the pathophysiology of CTS. However, we should recognize that an individual polymorphism in a potential risk gene does not act in isolation, but in combination with a host of environmental and genetic factors to increase risk for particular manifestations.

Although the results of our study are informative, some limitations should be recognized. First, the sample was composed of white women with CTS recruited from an urban hospital. Therefore, extrapolating these results to more diverse populations should be conducted with caution. Second, it is possible that our sample size was not enough to detect small differences in the presence of the Met/Met genotype between groups; but this is unlikely since the distribution of the Met/Met genotype was almost the same in both groups (21% patients vs. 20% healthy women). An estimated sample size of 554 individuals in each group would be able to detect the small differences in the distribution of Val158Met polymorphism reported in our study. Third, since we only included women, our results should not be extrapolated to men with CTS. Fourth, we only investigated the rs4680 single nucleotide polymorphism of the Val158Met gene. Future studies should investigate the influence of a greater number of polymorphisms and other potential genetic factors in patients with CTS.

## **CONCLUSION**

We found no differences in the genotype distribution and allele frequency of the Val158Met polymorphism between women with CTS and healthy women. The presence of the Met/Met genotype, but not the Val/Val and Val/Met genotypes was associated with higher intensity pain and disability, but not with higher widespread pressure pain hypersensitivity in women with CTS. Current results would suggest that the Val158Met polymorphism does not appear to be involved in a predisposition to suffer from CTS; but it was associated with increased perception of pain and higher disability scores. It is likely that genetic factors can play a complex role in the manifestation of CTS-related symptoms. Future studies including larger sample sizes and both men and women with CTS are needed to further confirm our results.

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