A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain

Joint symptoms are very common in elderly persons and are a major cause of disability and a reduced quality of life. Patients with radiographic evidence of joint damage are predisposed to joint pain, but the severity of the joint damage is only weakly related to the severity of the pain experienced (1). Whether or not chronic pain develops in a damaged joint is partly determined by genetic variations, with heritability estimates for joint pain ranging from 35% to 65% (2,3). Thus, patients in whom chronic pain develops might possess a combination of genetic variations that increase their sensitivity to pain. The catechol-O-methyltransferase enzyme (encoded by the COMT gene; 22q11) degrades catecholamine neurotransmitters such as norepinephrine and dopamine. Inhibition of COMT in animal models was shown to increase pain sensitivity (4,5). Therefore, genetic variants associated with low COMT activity have the potential to increase pain.

The aim of this study was to examine whether a well-known functional polymorphism in COMT (Val158Met) influences osteoarthritis (OA)-related pain. The methionine variant results in lower thermolability of the enzyme and 3–4-fold lower enzyme activity compared with the valine variant. The Met allele (low activity) has been shown to be associated with higher pain sensitivity (6,7). However, all previous studies examined relatively small study populations, while pain related to OA was never examined (8).

The present study population comprised participants in the Rotterdam Study, a large prospective population-based cohort study of Caucasian subjects ages 55 years and older, living in the Ommoord district of Rotterdam, The Netherlands. The study was designed to investigate the incidence and determinants of chronic disabling diseases in the elderly. The rationale for and design of the Rotterdam Study have been described previously (9). The study was approved by the Medical Ethics Committee of Erasmus Medical Center, and written informed consent was obtained from each subject. The current study is based on 3,033 subjects (1,736 women and 1,297 men) for whom genotype data were available for the COMT Val158Met polymorphism and for whom data were available for both radiographic hip OA and hip symptoms at the time when baseline measurements were obtained.

All subjects were scored for radiographic hip OA, defined as a Kellgren/Lawrence score of ≥2 in either the left hip or right hip, as described previously (10). Hip symptoms in the previous month were assessed by interview. Hip pain was defined as pain in the right and/or left hip in the month preceding the interview. Genotypes of the Val158Met polymorphism were determined with the TaqMan allelic discrimination assay, using the Assay-by-Design service (www.appliedbio-systems.com) (for details, see ref. 11). The frequency of the low-activity allele of COMT (158Met) was 55%, and genotypes followed Hardy-Weinberg distribution.

In the total population, carriers of the 158Met allele had a 30% increased risk of hip pain, which reached borderline significance (Table 1). From this population-based sample, we next selected patients in whom radiographic hip OA was diagnosed; only a portion of these patients had joint symptoms. Within this group, carriers of the 158Met variant had an almost 3-fold higher risk ($P = 0.02$) of hip pain as compared with carriers of the Val/Val genotype (Table 1). This effect was fully driven by the female carriers. Female carriers of the 158Val allele were 4.9-fold more likely to have pain (95% confidence interval 1.6–14.8, $P = 0.005$), while radiographic damage to the hip was present in both genotype groups. These associations were not affected by adjustments for age and body mass index, 2 well-known risk factors for OA.

In conclusion, the low-activity allele of COMT (158Met) that was present in 55% of the Caucasian population in this study is associated with increased hip pain in patients with radiographic damage of the hip. The association was present only in women. This sex difference could be attributable to the lower power of this study in men, because more women were in the study, and more women also had hip pain (15% of men versus 30% of women). In addition, it is known that COMT expression is regulated by estrogens (12), and postmenopausal women have very low levels of estrogens compared with elderly men.

Our results illustrate the possibility of (genetically) identifying a high-risk group of patients in whom pain is likely to develop. Although our findings need to be replicated in other large study populations, they might have important clinical implications, given the high prevalence of the COMT

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**Table 1.** Demographic characteristics and hip pain in patients from the Rotterdam Study, according to COMT genotype*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population (n = 3,033)</th>
<th>Patients with radiographic hip OA (n = 288)</th>
<th>Female patients with radiographic hip OA (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Val/Val +</td>
<td>Met/Val +</td>
<td>Val/Val +</td>
</tr>
<tr>
<td>Age, mean ± SD years</td>
<td>65.6 ± 6.8</td>
<td>66.1 ± 6.7</td>
<td>69.6 ± 7.1</td>
</tr>
<tr>
<td>Body mass index, mean ± SD kg/m²</td>
<td>26.3 ± 3.5</td>
<td>26.3 ± 3.5</td>
<td>26.5 ± 3.4</td>
</tr>
<tr>
<td>No. with hip pain/total no. (%)</td>
<td>60/631 (9.5)</td>
<td>289/2,113 (12)</td>
<td>8/56 (14.3)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Reference</td>
<td>2.9 (1.2–6.1)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Odds ratios (ORs) are adjusted for age and sex, if applicable. OA = osteoarthritis; 95% CI = 95% confidence interval.
low-activity allele. It is possible that in some patients with OA, pain is treated more effectively with drugs affecting neurotransmitter uptake. Our results also highlight the importance of studying joint-related pain as a separate trait in genetic epidemiologic studies.

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**AUTHOR CONTRIBUTIONS**

Dr. van Meurs had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study design.** Van Meurs, Uitterlinden, Hofman, Pols, Bierma-Zeinstra.

**Acquisition of data.** Van Meurs, Uitterlinden, Stolk.

**Analysis and interpretation of data.** Van Meurs, Uitterlinden, Stolk, Kerkhof, Hofman, Pols, Bierma-Zeinstra.

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