Multiple Loci Modulate Opioid Therapy Response for Cancer Pain

Antonella Galvan, Frank Skorpen, Pal Klepstad, Anne Kari Knudsen, Torill Fladvad, Felicia S. Falvella, Alessandra Pigni, Cinzia Brunelli, Augusto Caraceni, Stein Kaasa, and Tommaso A. Dragani

Abstract

**Purpose:** Patients treated with opioid drugs for cancer pain experience different relief responses, raising the possibility that genetic factors play a role in opioid therapy outcome. In this study, we tested the hypothesis that genetic variations may control individual response to opioid drugs in cancer patients.

**Experimental Design:** We tested 1 million single-nucleotide polymorphisms (SNP) in European cancer patients, selected in a first series, for extremely poor (pain relief ≤40%; n = 145) or good (pain relief ≥90%; n = 293) responses to opioid therapy using a DNA-pooling approach. Candidate SNPs identified by SNP-array were genotyped in individual samples constituting DNA pools as well as in a second series of 570 patients.

**Results:** Association analysis in 1,008 cancer patients identified eight SNPs significantly associated with pain relief at a statistical threshold of P < 1.0 × 10⁻³, with rs12948783, upstream of the RHBDL2 gene, showing the best statistical association (P = 8.1 × 10⁻³). Functional annotation analysis of SNP-tagged genes suggested the involvement of genes acting on processes of the neurologic system.

**Conclusion:** Our results indicate that the identified SNP panel can modulate the response of cancer patients to opioid therapy and may provide a new tool for personalized therapy of cancer pain. *Clin Cancer Res;* 17(13); 4581–7. ©2011 AACR.

Introduction

Pain is the most dreaded symptom in patients with malignant disease. Indeed, each year several millions of men and women of all ages suffer from some form of invasive cancer associated with pain requiring chronic opioid treatment. At present, opioids are virtually the only analgesics able to control moderate and severe cancer pain.

Although opioids are widely used to treat cancer pain, clinical studies indicate great variability among individuals with regard to the efficacy of these drugs and their side effects (1, 2). Many studies have investigated the potential genetic basis of individual variability in opioid drug response, but almost all have focused on a few candidate genes involved in opioid pharmacokinetics or pharmacodynamics, and results are not consistent among these, often small, studies (3, 4). For example, the catecholamines dopamine, epinephrine, and norepinephrine and their hydroxylated metabolites are substrates for the enzyme catechol-O-methyltransferase (COMT) encoded by the *COMT* gene, in which genetic variations have been associated with variations in pain perception and in doses of opioids required for pain treatment; however, discrepancies in the results from different association studies on COMT polymorphisms and pain perception have been reported, possibly due to the small size of the studies (reviewed in ref. 5).

The human mu 1 opioid receptor (*OPRM1*) gene, which is the main pharmacologic target of opioids, contains more than 100 polymorphisms, and these polymorphisms might affect opioid binding affinity to the receptor and, consequently, opioid-induced analgesia, tolerance, and dependence. However, a recent meta-analysis casts doubt on the clinical relevance of the *OPRM1* 118A>G polymorphism suggested by both preclinical and clinical studies as a candidate in personalized cancer pain therapy (6).

A complex genetics underlying interindividual differences in opioid response is expected in light of the biochemical and biological complexity of the drug response and of pain control. Indeed, opioid effects are governed by drug-related absorption, distribution, metabolism, intrinsic efficacy of the receptors involved, and by signal pathways downstream of the receptors. Because each of these steps in pain control is modulated by several genes, each of which can exist in allelic forms in the general population, a
A genome-wide comprehensive analysis would be required to identify all genetic factors involved.

In this study, we conducted the first genome-wide association study (GWAS) in cancer patients treated with opioids using a 1-million single-nucleotide polymorphism (SNP)-array to identify new genetic variations that modulate individual pain relief.

Patients and Methods

Study design

The European Pharmacogenetic Opioid Study (EPOS) represents a multicentric effort to examine symptoms, pharmacology, and pharmacogenomics related to the use of opioids. Recruitment criteria of patients included a regularly scheduled opioid treatment that was stable for at least 3 days. Opioids administered to more than 5% of patients included morphine, oxycodone, and fentanyl. The study includes 2,294 cancer patients treated with opioids for moderate or severe pain and recruited from 17 centers of 11 European countries. The participation of the Research Steering Committee from the European Association for Palliative Care (EAPC) facilitated international cooperation in the study.

The study collected demographic and personal data, as well as malignant diagnosis and opioid treatment details from cancer patients. Opioid doses were converted to equivalent total daily oral morphine doses (7). Pain was assessed by completing the Brief Pain Inventory (BPI; ref. 8). Functional status was measured by the Karnofsky performance status score. Further details about the EPOS series, including opioid doses and recruitments, have been reported (7). The study collected whole blood for genetic analysis and has established a biobank.

Pain relief phenotype and DNA pool construction

The pain relief phenotype under study is semi-quantitative and determined based on the BPI, a robust and psychometric validated method to assess the subjective severity of pain. Pain relief is measured using an 11-point numerical rating scale, from 0%, representing "no pain relief" to 100% or "complete pain relief," that is, 0%, 10%, 20%, etc. (9).

For DNA pool preparation, we first defined the cancer patients as "good" or "poor" responders to opioid therapy, based on their pain relief phenotype score of 90% or more or 40% or less, respectively (Fig. 1). Selection was stratified by gender and country of origin, with a 1:2 matching of "poor" and "good" responders, to obtain a balanced representation of patients in the 2 groups. DNA pools of "good" (n = 293; mean pain relief = 94.1%) and "poor" (n = 145; mean pain relief = 27.0%) responders were created using equal amounts of fluorimetrically measured DNA from each sample.

SNP genotyping

SNP-array analysis of each of the 2 DNA pools was carried out using the HumanOmni1-Quad BeadChip (Illumina), which allows analysis of 1,140,419 genetic markers, including more than 20,000 markers in more than 300 important gene regions related to drug absorption, distribution, metabolism, and excretion; several of the SNPs map to opioid receptor or metabolism genes (http://www.illumina.com/products/humanomni1_quad_bead-chip_kits.ilmn). We carried out 12 replicas to verify genotype reproducibility and to estimate technical variability. Data were obtained as intensity signals, which were used to determine the allelic frequencies of each genetic marker.

Translational Relevance

Pain is a common complication of almost all types of advanced cancer, and treatment with opioids produces variable responses of pain relief among individuals. Indeed, a variable percentage of cancer patients experiences reduced or poor benefit from opioid therapy, with impairment of their quality of life. Our association study in 1,008 European cancer patients identified 8 single-nucleotide polymorphisms (SNP) that are statistically associated with pain relief, which together might modulate the response of cancer patients to opioid therapy and might serve as targetable tools to design new drugs. Our functional annotation analysis of SNP-tagged genes revealed, for the first time, the involvement of genes acting on processes of the neurologic system rather than on opioid metabolism or pharmacodynamics. Thus, the identified SNP panel may provide a new tool for personalized therapy of cancer pain.

Figure 1. Distribution of the pain relief phenotype (0%–100%) in cancer patients of the EPOS series. Bar indicates the number of cancer patients genotyped in the first (red) and second (green) series or those who were not analyzed (yellow).
and to reconstruct the number of chromosomes carrying each of the 2 possible alleles. Individual samples were genotyped using MassARRAY (Sequenom, Inc.), as described previously (10).

Gene analysis
To explore the role of the associated variants in the biological context, we mapped the best statistically associated SNPs in the DNA pools (n = 486; \( P < 1.0 \times 10^{-3} \)), using the Ensembl database to identify genes that are possibly involved in pain relief response, and analyzed the gene list for enrichment in ontologic annotation terms using the DAVID Functional Annotation Tool and Clustering (ref. 11; http://david.abcc.ncifcrf.gov/home.jsp).

Statistical analyses
Chromosome counts of the "poor" and "good" pain relief groups, from which DNA pools were prepared, were reconstructed based on allelic frequencies assessed in SNP-array hybridization, and the resulting 2 \( \times \) 2 contingency tables were tested by \( \chi^2 \) analysis. Association analyses between SNPs and the pain relief phenotype (categorical variable, "poor" or "good" responders, or quantitative variable) were carried out using PLINK software (12), which included analysis of the Hardy–Weinberg equilibrium (HWE), linkage disequilibrium between SNPs, and population-based associations between phenotypes and genotype/allelotype (Supplementary Fig. S1).

Results
The study population for which pain relief values were available included 1,907 patients from 4 ethnic groups: (i) Caucasian, including Hispanic (n = 1,859), (ii) African (n = 13), (iii) Oriental (n = 4), and (iv) other (n = 29), and from 11 European countries of origin. Patients included in the DNA pools constituted the first series (n = 438), whereas the second series of 570 EPOS patients was selected based on pain relief phenotype score \( \geq 90\% \) or \( \leq 50\% \) to extend the results of the GWAS (Fig. 1). Table 1 lists the phenotypic characteristics of patients analyzed in the present study. The pain relief mean value was slightly higher in the second series (76.5 \( \pm \) 1.1 vs. 71.9 \( \pm \) 1.6; \( P = 0.014 \), on ANOVA), whereas no statistically significant differences were observed in the mean total oral morphine equivalent opioid dose (Table 1).

Preliminary analysis for factors that might confound the assessment of the pain relief phenotype revealed a weak effect of gender (\( P = 0.019 \)) and a strong effect of country of origin (\( P < 2.2 \times 10^{-16} \), on ANOVA; Supplementary Table S1). No statistically significant association between the pain relief phenotype and age of patients, ethnicity, or tumor type was found. Thus, we normalized the pain relief phenotype by the country mean value and adjusted analyses for gender as covariate.

### Table 1. Phenotypic characteristics of EPOS cancer patients examined for response to opioid therapy

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>First series</th>
<th>Second series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good responders</td>
<td>Poor responders</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>293</td>
<td>145</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>73</td>
</tr>
<tr>
<td>Median age (range)( ^a )</td>
<td>61 (32–88)</td>
<td>63 (18–66)</td>
</tr>
<tr>
<td>Country of origin</td>
<td>CH</td>
<td>DE</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain relief (percentage score; mean ( \pm ) SE)</td>
<td>94.1 ( \pm ) 0.3</td>
<td>27.0 ( \pm ) 1.1</td>
</tr>
<tr>
<td>Total oral morphine equivalent opioid dose (mg; mean ( \pm ) SE)</td>
<td>287 ( \pm ) 28</td>
<td>402 ( \pm ) 56</td>
</tr>
</tbody>
</table>

\( ^a \)Age in years.

Abbreviations: CH, Switzerland; DE, Germany; DK, Denmark; FI, Finland; GB, Great Britain; IS, Iceland; IT, Italy; LT, Lithuania; NO, Norway; SE, Sweden.
Genes involved in neurologic system processes may modulate pain relief

In our search for genetic variations associated with individual pain relief, we analyzed the EPOS subjects showing the extreme phenotypic values of pain relief in order to reduce the bias in the subjective pain relief assessment of the borderline categories and to allow testing for genetic effects on response to pain therapy in the best candidate subjects (Fig. 1).

GWAS, using a DNA-pooling strategy and 1-million SNP-array, detected 173,851 informative SNPs, with overall minor allelic frequency more than 0.1 and coefficient of variation of allelic frequency of (SD/mean) more than 0.08. Statistical associations of these SNPs are visualized by Manhattan plot (Fig. 2). Analysis of chromosome counts obtained from allelic frequencies in DNA pools of "good" and "poor" responders identified 486 SNPs at the statistical threshold of \( P < 1.0 \times 10^{-3} \) (chi-squared test; Fig. 2; Supplementary Fig. S1).

To explore the role of the associated variants in the biological context, we identified the genes tagged by these 486 SNPs. A list of 226 known genes, either near or containing a SNP, was obtained and analyzed using the Functional Annotation Tool (http://david.abcc.ncifcrf.gov/home.jsp), which identified as the best statistically significant gene ontologic annotation terms those linked to the nervous system, such as the "neurological system process," "transmission of nerve impulse," and "synaptic transmission." Notably, the best term was the "neurological system process," which included 31 genes (\( P = 3.5 \times 10^{-5}; \) Table 2). Interestingly, 10 of these 31 genes were members of the olfactory receptor family. Use of Functional Annotation Clustering gave similar results, with the most highly significant cluster including the annotation terms "transmission of nerve impulse," "synaptic transmission," and "cell–cell signaling" (not shown).

A genetic profile controls pain relief

Among the 486 candidate SNPs identified by statistically significant differences (\( P < 1.0 \times 10^{-3}; \) on chi-squared test) between "poor" and "good" responders in chromosome counts, we selected 72 SNPs associated with the pain relief phenotype (at \( P < 1.0 \times 10^{-5} \) threshold value) for genotyping in individual samples constituting the DNA pools, and in the second series of 570 EPOS patients by MassARRAY (Table 1; Fig. 1). Six SNPs failed PCR or MassEXTEND primer design, and another 7 failed genotyping. Of the 59 genotyped SNPs, 2 showed significant deviation from the HWE (\( P < 1.0 \times 10^{-5} \)), reducing the number of markers to 57 SNPs.
Association analysis in the first series indicated that 54 of the 57 SNPs were significantly associated with the poor and good responder categories at \(P < 0.05\) (logistic analysis), confirming the robustness of our DNA-pooling approach, which produces reliable results and is time- and cost-effective, in agreement with other reports (13, 14). SNP rs12948783, which maps to chromosome 17 upstream of the RHBDF2 gene, showed the strongest association \((P = 1.1 \times 10^{-7})\).

Analysis of the total sample size of 1,088 cancer patients for the quantitative pain relief phenotype, allowing an increased statistical power of the study, pointed to 8 SNPs associated at the statistical threshold of \(P < 1.0 \times 10^{-5}\), with the strongest allelic association, again, for SNP rs12948783 \((RHBDF2; P = 1.1 \times 10^{-5};\) linear model; Table 3; Supplementary Fig. S1).

Genotype-phenotype analysis for rs12948783 SNP in 936 patients (72 genotypes were missing) showed that patients homozygous for the rare allele, that is, the AA genotype, experienced a low normalized pain relief value \((\text{mean} \pm \text{SE}, 80\% \pm 9\%; n = 23)\) that did not differ statistically from that of patients with the GA genotype \((\text{mean} \pm \text{SE}, 88.5\% \pm 3\%; n = 243)\). Comparison of the subjects carrying the rare allele \((\text{AA or GA genotypes}, n = 266)\) with patients carrying the common GG genotype \((\text{mean} \pm \text{SE}, 104\% \pm 1\%; n = 670)\) showed a highly statistically significant association \((P = 8.1 \times 10^{-9})\) with patients carrying the GG genotype and with almost complete pain relief (Fig. 3).

### Discussion

Opioid efficacy for the treatment of pain in cancer patients varies greatly among individuals, suggesting a role for genetic factors in pain relief outcome. Unlike previous pharmacogenetic studies that have tested genetic variations of a few candidate genes in a small number of subjects, our present study represents the first use of genome-wide scanning in a large number of opioid-treated cancer patients to identify genetic variations that may explain differences in pain relief.

Pain relief, an inherently subjective parameter, was indeed the phenotype quantified through the BPI method in cancer patients included in the EPOS study; surprisingly, we found a significant correlation between pain relief and country of origin, but not with ethnicity. The association with country of origin might rest in subtle variations in phenotype definitions related to each country or in organizational differences between health care services in various European countries that introduce variability in selection of patients at EPOS recruitment, although the BPI questionnaire is officially recognized and recommended by EAPC and has been validated across cultures and languages. The lack of association between pain relief and ethnicity may be genuine, although the non-homogeneous distribution of patients into 4 ethnic groups \((97.6\% \) of patients were ethnically Caucasian) may undermine the statistical power to detect effects linked to ethnicity.

<table>
<thead>
<tr>
<th>Term</th>
<th>Gene count</th>
<th>(P^{a})</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GO:0050877 ~ neurological system process</td>
<td>31</td>
<td>(3.5 \times 10^{-5})</td>
<td>ABLIM1, OR8U9, AGTPBP1, SYT5, KCNA1, COL2A1, OR4C6, RAX2, OR4S2, ELOVL4, OR8K3, DMD, OR4C11, OR5AS1, KCNE1, OR5AP2, COL4A4, COL18A1, OR5R1, OR11L1, PCDH15, AFF2, NRXN1, OR5T3, ACCN1, SLC17A6, SBF2, ABAT, TBL1X, NCAN, PTENP1</td>
</tr>
<tr>
<td>GO:0007155 ~ cell adhesion</td>
<td>17</td>
<td>(6.1 \times 10^{-3})</td>
<td>COL18A1, PLXNC1, NRP1, C21ORF29, NELL1, ACTN1, COL2A1, PCDH15, NRXN1, BTBD9, ITGB1, CDH12, CD96, SORBS1, NCAN, JAM2, SPON1</td>
</tr>
<tr>
<td>GO:0022610 ~ biological adhesion</td>
<td>17</td>
<td>(6.2 \times 10^{-3})</td>
<td>COL18A1, PLXNC1, NRP1, C21ORF29, NELL1, ACTN1, COL2A1, PCDH15, NRXN1, BTBD9, ITGB1, CDH12, CD96, SORBS1, NCAN, JAM2, SPON1</td>
</tr>
<tr>
<td>GO:0019226 ~ transmission of nerve impulse</td>
<td>11</td>
<td>(6.8 \times 10^{-3})</td>
<td>COL4A4, ACCN1, SLC17A6, SYT5, AGTPBP1, SBF2, DMD, KCNA1, ABAT, NRXN1, NCAN</td>
</tr>
<tr>
<td>GO:0007268 ~ synaptic transmission</td>
<td>10</td>
<td>(7.1 \times 10^{-3})</td>
<td>COL4A4, ACCN1, SLC17A6, SYT5, AGTPBP1, SBF2, DMD, KCNA1, ABAT, NRXN1, NCAN</td>
</tr>
<tr>
<td>GO:0050890 ~ cognition</td>
<td>20</td>
<td>(7.4 \times 10^{-3})</td>
<td>COL18A1, ABLIM1, OR5R1, OR8U9, OR11L1, PCDH15, AFF2, COL2A1, OR4C6, OR5T3, RAX2, OR4S2, ELOVL4, OR8K3, OR4C11, OR5AS1, OR5AP2, KCNE1, TBL1X, PTENP1</td>
</tr>
</tbody>
</table>

\(^{a}\) Calculated by the DAVID functional annotation tool, using a modified Fisher's exact test.

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**Table 2.** Gene ontologic analysis by DAVID of the 226 genes defined by the 486 SNPs most significantly \((P < 0.001)\) associated with allelic imbalance in the SNP-array analysis of DNA pools from "poor" or "good" responders to opioid therapy for cancer pain.
Table 3. List of 8 SNPs associated with the quantitative pain relief phenotype in 1,008 European cancer patients treated with opioids

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chromosome</th>
<th>Position (Mb)</th>
<th>Gene</th>
<th>Minor allele</th>
<th>Common allele</th>
<th>First and second combined series</th>
<th>First series</th>
<th>Second series</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs13421094</td>
<td>2</td>
<td>157.8</td>
<td>G</td>
<td>A</td>
<td></td>
<td>Frequency of the minor allele</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>rs12211463</td>
<td>6</td>
<td>93.5</td>
<td>G</td>
<td>T</td>
<td></td>
<td>P &lt; 10^-6</td>
<td>8.0 × 10^-5</td>
<td>3.9 × 10^-7</td>
</tr>
<tr>
<td>rs7757130</td>
<td>6</td>
<td>113.4</td>
<td>A</td>
<td>C</td>
<td></td>
<td>P &lt; 10^-6</td>
<td>5.8 × 10^-4</td>
<td>1.5 × 10^-6</td>
</tr>
<tr>
<td>rs2473967</td>
<td>6</td>
<td>113.6</td>
<td>C</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2884129</td>
<td>10</td>
<td>17.6</td>
<td>G</td>
<td>T</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs7104613</td>
<td>11</td>
<td>14</td>
<td>T</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs12948783</td>
<td>17</td>
<td>72</td>
<td>RHBDF2</td>
<td>A</td>
<td>G</td>
<td>P &lt; 10^-6</td>
<td>3.8 × 10^-7</td>
<td>2.2 × 10^-8</td>
</tr>
<tr>
<td>rs10413396</td>
<td>19</td>
<td>49.5</td>
<td>ZNF235</td>
<td>T</td>
<td>G</td>
<td>P &lt; 10^-6</td>
<td>2.1 × 10^-8</td>
<td>8.1 × 10^-4</td>
</tr>
</tbody>
</table>

aSNPs genotyped in individual cancer patients by MassARRAY and showing statistically significant association (P < 10^-3) with pain relief; SNPs with statistically significant deviation from the HWE (P < 10^-3) were excluded.

bP and β regression coefficient values were obtained by allelic association of SNPs with country-normalized pain relief phenotype (linear model adjusted by gender).

cP values obtained by χ² analysis on reconstructed chromosome numbers in DNA pools.

Analysis of candidate SNPs defined a set of 8 genetic markers associated with individual response to opioid therapy. Focusing on SNPs with a statistically significant lower pain relief phenotype, the rs12948783 gene was associated with the best statistical association (P = 8.1 × 10^-10). This SNP maps to a site of unknown function on chromosome 17. The rs12948783 gene encodes RHBDF2, a protein that promotes the attachment of spinal cord and sensory neuron cells and the outgrowth of neurites.

In vitro, the RHBDF2 protein has been shown to be involved in the modulatory effect of genetic polymorphisms on the perception of pain. Nonetheless, it remains possible that opioid therapy modifies the involvement of genes related to pain perception. In summary, the results provide evidence that genetic variability can influence the perception and response to opioid therapy, suggesting a potential role for genetic testing in individualizing opioid therapy.
poor response would receive higher starting doses of opioids. Moreover, genes tagged by these polymorphisms may provide a target for new therapeutic strategies to control cancer pain perception.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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