Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy

A Two-year Multicenter Cohort Study

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CME

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT

Background: Chronic postsurgical pain (CPSP) has been linked to many surgical settings. The authors aimed to analyze functional genetic polymorphisms and clinical factors that might identify CPSP risk after inguinal hernia repair, hysterectomy, and thoracotomy.

Methods: This prospective multicenter cohort study enrolled 2,929 patients scheduled for inguinal hernia repair, hysterectomy (vaginal or abdominal), or thoracotomy. The main outcome was the incidence of CPSP confirmed by physical examination 4 months after surgery. The secondary outcome was CPSP incidences at 12 and 24 months. The authors also tested the associations between CPSP and 90 genetic markers plus a series of clinical factors and built a CPSP risk model.

Results: Within a median of 4.4 months, CPSP had developed in 527 patients (18.0%), in 13.6% after hernia repair, 11.8% after vaginal hysterectomy, 25.1% after abdominal hysterectomy, and 37.6% after thoracotomy. CPSP persisted after a median of 14.6 months and 26.3 months in 6.2% and 4.1%, respectively, after hernia repair, 4.1% and 2.2% after vaginal hysterectomy, 9.9% and 6.7% after abdominal hysterectomy, and 19.1% and 13.2% after thoracotomy. No significant genetic differences between cases and controls were identified. The risk model included six clinical predictors: (1) surgical procedure, (2) age, (3) physical health (Short Form Health Survey-12), (4) mental health (Short Form Health Survey-12), (5) preoperative pain in the surgical field, and (6) preoperative pain in another area. Discrimination was moderate (*c*-statistic, 0.731; 95% CI, 0.705 to 0.755).

Conclusions: Until unequivocal genetic predictors of CPSP are understood, the authors encourage systematic use of clinical factors for predicting and managing CPSP risk. **(Anesthesiology 2015; 122:1123-41)**

SINCE the discussion of chronic postsurgical pain (CPSP) commenced in 1998,[1] this late complication has proven to be a frequent cause of persistent pain in the general population[2] and has been linked to a wide range of surgical settings.[3,4] Risk factors, pathogenesis, and preventive strategies continue to be widely debated.[3–6] The main predictors described to date are female sex,[7] age,[8] psychosocial factors,[9,10] a history of pain in the region of surgery or other sites,[5,8,11] type of procedure,[3,4,12] nerve injury,[13] and postoperative pain intensity.[14] Additionally, genetic polymorphisms have been linked to varying sensitivity to pain,[15,16] susceptibility to certain painful conditions,[17] and

What We Already Know about This Topic

- Genetic contributions to persistent postoperative pain remain unknown

What This Article Tells Us That Is New

- Persistent postoperative pain was diagnosed in 18% of a population-based sample of 2,929 patients who had hernia repairs, hysterectomies, or thoracotomies
- The association of persistent pain with 90 genetic markers showed no evidence for genetic predisposition in a subset of 1,000 patients
- Six clinical factors predicted 73% of the persistent pain that developed

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The findings of this study were partially presented at the 2012 Euroanaesthesia Congress, Paris, France, June 9–12, 2012.

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response to analgesics,[18–20] leading some to suggest that such factors might explain why some patients develop chronic pain and others do not.[3,4,21] Studies with sufficient power to confirm the relevance of single-nucleotide polymorphisms (SNPs) have yet to be published, although they are potentially of considerable interest.

We hypothesized that within patient populations sharing the same surgical contexts and clinical–demographic risk for CPSP, genetic factors would identify individuals at risk for this complication. Our aims were to analyze functional genetic polymorphisms related to CPSP risk or protection and clinical predictors at 4 months after three types of surgery—inguinal hernia repair, hysterectomy, and thoracotomy. We also sought to determine pain interference with daily living at 4 months; the incidence of CPSP and pain intensity at 4, 12, and 24 months; and the rate of neuropathic pain in patients with CPSP at 4 months.

Materials and Methods

Study Design

This prospective multicenter cohort study enrolled patients scheduled for inguinal hernia repair, hysterectomy (vaginal or abdominal incision), or thoracotomy. Genetic associations in the subgroups of patients with and without CPSP (cases and controls) were compared.

Setting

Twenty-three Spanish hospitals (appendix) recruited patients from January 8, 2009, to December 31, 2010. Follow-up ended on December 31, 2012.

Participants

Candidates for inclusion were scheduled for inpatient or outpatient inguinal hernia repair (men), vaginal or abdominal hysterectomy (for nononcologic reasons or for cervical carcinoma *in situ*, but excluding other oncologic procedures), or thoracotomy (men) under general, regional, or local anesthesia with sedation (see table, Supplemental Digital Content 1, http://links.lww.com/ALN/B135, for patient distribution by diagnostic and surgical codes).

Candidates were excluded if they or their parents or grandparents had been born in the Canary Islands or outside Spain or if they were of Roma ethnicity. Candidates were also excluded if they were under 18 yr of age, needed reoperation, had a serious psychological disorder, were undergoing endoscopic or other procedures not requiring incision, or were relatives (parents, grandparents, children, grandchildren, or siblings) of patients already enrolled.

Cases were all patients with CPSP at 4 months; for the gene study, a control group was formed by selecting a block-randomized sample of CPSP-free patients from each surgical group.

Outcomes

The primary outcome was the incidence of CPSP confirmed by physical examination approximately 4 months after surgery based on the criteria of Macrae and Davies[22] published by the International Association for the Study of Pain. These criteria are as follows: (1) the pain should have developed after a surgical procedure; (2) the pain should be of at least two months' duration; (3) other causes for the pain, such as continuing malignancy or chronic infection, should be excluded; and (4) the possibility that the pain is continuing from a preexisting problem should be explored and exclusion attempted. Although these criteria specified waiting at least 2 months before diagnosing CPSP, others later proposed waiting at least 3 months[23,24] because of the possibility of persisting inflammatory changes and neuropathic pain.[25] We therefore chose to modify the criteria slightly, cautiously waiting approximately 4 months before diagnosing CPSP.

The secondary outcomes were (1) the incidence of CPSP reported in telephone interviews at 12 and 24 months and (2) the percentage of patients with CPSP at 4 months whose pain had neuropathic characteristics.

Data Collection

Designated anesthesiologists in each hospital's local research team attended training sessions on how to complete the clinical questionnaire and diagnose CPSP. Questionnaire variables and definitions are shown in Supplemental Digital Content 2, http://links.lww.com/ALN/B136. The following variables were collected before surgery and during hospitalization. Before surgery, the anesthesiologist administered the validated Spanish version[26] of the Hospital Anxiety and Depression Scale, which has proven useful for diagnosing anxiety or depression in patients without a prior history of psychiatric problems,[27] and version 2 of the Short Form Health Survey-12 (SF-12) questionnaire[28] to assess two components (physical and mental) of quality of life. Also recorded at this time were physical status according to the American Society of Anesthesiologists' classification; the presence of prior pain in the area of surgery and in other parts of the body expressed on a verbal numerical rating scale (VNRS) of 0 to 10 (0 = no pain; 10 = the worst imaginable pain) and history of treatment with analgesics; concomitant diseases; and any history of substance addiction to street drugs, alcohol, or smoking. Surgical variables were procedure, duration, techniques of regional and local anesthesia, doses of opioids and antihyperalgesic agents, and intraoperative complications. For 24 h after surgery, analgesia and postoperative pain (VNRS) were recorded.

Data were collected with a structured telephone questionnaire between 1 and 1.5 months after surgery (see Supplemental Digital Content 2, http://links.lww.com/ALN/B136); all the interviews were done by the same investigator (J. Cantillo). Patients who reported pain at that time were telephoned again between 2.5 and 3.5 months after surgery and, if pain was still present, were given an appointment for clinical examination between 3.5 and 4.5 months after surgery; this visit, during which CPSP was diagnosed, took place at the hospital. The examiner at this time was an anesthesiologist expert in pain management who used the following instruments: Brief

Pain Inventory (severity, analgesics, and interference with daily living), the Spanish SF-12 questionnaire, and the Douleur Neuropathique 4 questionnaire.[29] This third instrument assesses whether CPSP could be described as neuropathic, indicated by a positive response to 4 out of 10 items. The physical examination included determining the exact location of pain (noted in the Brief Pain Inventory) followed by testing for hypoesthesia (slight touch with a cotton swab, pinpricking with Von Frey filaments) as well as for dynamic allodynia (brushing) according to items specified in the Douleur Neuropathique 4 questionnaire. These tests were applied on both sides of the body. The patient also reported use of analgesics. Patients whose diagnosis of CPSP was confirmed at this time were interviewed by telephone again at 12 months and, if pain persisted, again at 24 months. If a patient was lost to follow-up, the National Health Service Death Register was checked.

Ethical Considerations

The study was approved by the clinical research ethics committees of the leading center, Parc de Salut Mar (file reference CEIC-IMAS: 2008/3080/I) and all other centers (appendix). Patients signed informed consent statements for data collection, DNA analysis, follow-up telephone contact, and a hospital appointment for physical examination. Otherwise, patients received routine care.

Sample Size

We targeted examining the presence of strong associations with CPSP, some of which had previously been reported in the literature. Using standard procedures,[30] we estimated that a minimum sample of approximately 500 cases and 500 controls was needed to have greater than 90% power to detect a risk allele with an odds ratio (OR) of 1.5 for CPSP in a simple allelic test, assuming an incidence of at least 10% for this late complication and risk allele frequencies of 0.1 or larger.

Based on findings that CPSP develops after 10% of inguinal hernia repair procedures, 10% to 30% of hysterectomies, and 30% to 40% of thoracotomies[3] and considering the numbers of these procedures recorded at the 23 participating hospitals in a previous epidemiological study in our area,[31] we planned to recruit a sample of 600 patients with CPSP in 2 yr. A 20% loss to follow-up was expected.

Extraction Details for Genotyping and SNP Selection

DNA extraction was only performed in volunteering patients with confirmed CPSP and in selected control patients without CPSP who were matched to cases by age, surgical specialty, sex, domicile, and hospital recruitment. For each patient, peripheral blood (5 ml) was drawn in the operating room immediately before surgery and placed in an ethylene diamine tetraacetic acid–treated tube. Each blood sample was identified using adhesive barcode labels. Barcode digits were registered twice in succession in the database to avoid misidentification. In addition to the blood samples, each collaborating center also retained the consent forms and questionnaires. Labeled samples were stored in a refrigerator at 4 to 5°C until they were shipped to a central laboratory within 1 week. The blood and questionnaires were then forwarded to the clinical laboratory (Echevarne Clinical Laboratory†), where they were stored in a freezer at −80°C.

DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's specifications. Genotyping was carried out with the Illumina Golden Gate protocol with VeraCode technology (Illumina‡) in the National Genotyping Centre (CEGEN, Barcelona, Spain). The selected SNPs were genotyped for each patient.

A total of 90 SNPs were included in the study (table 1). Eight-seven of the 90 SNPs were selected based on prioritizing functional genetic variants previously associated in the literature with pain sensitivity, chronic pain conditions, and related traits belonging to different genes whose protein products are linked to biological pathways that influence pain sensitivity.[15,18,20,32–35] Thus, SNPs with no proven influence on gene function at the time were not included. These 87 SNPs had minor allele frequencies in the general Caucasian population of up to 0.4 (National Center for Biotechnology Information§) and a homogeneous distribution along the gene and location inside the exons or near them, with a minor allele frequency of 0.1 using data from HapMap.‖ The process was carried out according to the suggestions published by Hoh *et al.*,[36] and TagSNPs with $R^2 > 0.8$ were selected according to Carlson *et al.*[37] These SNPs are related to two main functional categories:

Type 1: Genes encoding proteins that mediate the transmission of pain signals by sensory nerve fibers and by central nervous system pathways that mediate the perception of pain.

Type 2: Genes encoding proteins that mediate peripheral and central inflammatory responses related to tissue injury.

Finally, we included the three significant SNPs detected in the genome-wide association study of acute postsurgical pain in humans by Kim *et al.*,[20] bringing the total number of SNPs to 90.

Statistical Methods

Data are expressed as medians and 10th to 90th percentiles. Potential risk factors were evaluated for unadjusted bivariate association with CPSP occurrence based on the *t* test (continuous variables) or the Fisher exact test or chi-square test (categorical variables). Bivariate ORs and 95% CIs were also

† Available at: http://www.echevarne.com. Accessed November 10, 2014.

‡ Available at: http://www.illumina.com. Accessed November 10, 2014.

§ Available at: http://www.ncbi.nlm.nih.gov/snp. Accessed November 10, 2014.

‖ Available at: http://www.hapmap.ncbi.nlm.nih.gov. Accessed November 10, 2014.

Table 1. SNPs Genotyped, Their Associated Genes, Chromosomal Locations, and Functions

Gene Name	Chromosomal Location	Gene Function	Gene Symbol	SNP Number
Brain-derived neurotrophic factor	11p14.1	Major regulator of synaptic transmission. It is involved in the activity-dependent pathogenesis of nociceptive pathways that may lead to chronification of pain	*BDNF*	rs1048221 rs6265 rs8192466 rs2049046 rs908867
Catechol-*O*-methyltransferase	22q11.21–q11.23	Catechol-*O*-methyltransferase activity	*COMT*	rs4646312 rs6269
Dopamine receptor D2	11q23	Dopamine receptor activity	*DRD2*	rs6277 rs1076560 rs2734837 rs11608185 rs4936272 rs4648317 rs4322431 rs1799978 rs12364283
Fatty acid amide hydrolase	1p35-p34	Metabolism of the endogenous cannabinoid	*FAAH*	rs932816 rs4141964 rs2295633
γ-aminobutyric acid A receptor, α1	5q34	Neuronal inhibition	*GABRA1*	rs28364635 rs12658835
γ-aminobutyric acid A receptor, α2	4p12	Neuronal inhibition	*GABRA2*	rs519972 rs7678338 rs7689605 rs10028945
γ-aminobutyric acid receptor subunit β-2	5q34	Neuronal inhibition	*GABRB2*	rs3816596
Guanosine triphosphate cyclohydrolase 1	14q22.2	Involved in dopamine synthesis	*GCH1*	rs10483639 rs7142517 rs752688 rs4411417 rs9671371 rs12147422 rs8004445 rs998259 rs3783641 rs8007267
Glutamate receptor, ionotropic, kainite 3	1p34.3	Contribute to excitatory postsynaptic currents in many regions of the CNS	*GRIK3*	rs6691840
5-Hydroxytryptamine (serotonin) receptor 2C	Xq24	Serotonin receptor activity	*HTR2C*	rs179997
Interleukin-6 (interferon β2)	7p21	Cytokine activity; interleukin-6 receptor binding	*IL6*	rs13447446
Interleukin-10	1q31–q32	Cytokine activity; interleukin-10 receptor binding	*IL10*	rs1800896
Monoamine oxidase A	Xp11.3	Amine oxidase activity	*MAOA*	rs3788862 rs2283724 rs1800659 rs979606 rs979605
Melanocortin 4 receptor	18q22	Stimulator of adenylate cyclase	*MC4R*	rs9966412 rs2229616
Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor	14q13	Involved in immune and proinflammatory responses	*NFKBIA*	rs8904

(Continued)

Table 1. Continued

Gene Name	Chromosomal Location	Gene Function	Gene Symbol	SNP Number
Nitric oxide synthase 1 (neuronal)	12q24.2	Catalyze the generation of nitric oxide	*NOS1*	rs9658482 rs9658478 rs9658279
Opioid receptor, δ1	1p35.3	Inhibits neurotransmitter release by reducing calcium ion currents and increasing potassium ion conductance	*OPRD1*	rs1042114 rs533123
Opioid receptor, κ1	8q11.2	Receptor for dynorphins	*OPRK1*	rs702764 rs997917
Opioid receptor, μ1	6q24-q25	Receptor for endogenous and synthetic opioids	*OPRM1*	rs1799971 rs563649
Proenkephalin	8q12.1	Involved in pain perception and responses to stress	*PENK*	rs1975285
Proopiomelanocortin	2p23.3	Hormone activity	*POMC*	rs28932472 rs934778
Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	1q31.1	Mediator of inflammation	*PTGS2*	rs5275
Sodium channel, voltage-gated, type IX, α	2q24.3	Mediator of inflammation	*SCN9A*	rs6746030 rs12478318 rs6747673 rs9646771
Solute carrier family 6 (neurotransmitter transporter, noradrenaline member 2)	16q12.2	Norepinephrine transporter activity	*SCL6A2*	rs40434 rs36024 rs36017
Dopamine transporter or DAT1	5p15.3	Dopamine transporter activity	*SCL6A3*	rs40184 rs6350 rs12516948 rs403636
Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	17q11.1	Serotonin and monoamine transporter activity	*SCL6A4*	rs1979572 rs4325622 rs6352 rs140701 rs6355 rs2066713
Solute carrier organic anion transporter family, member 1A2	12p12.1	Mediates the Na(+)-independent transport of organic anions	*SLCO1A2*	rs11568563
Solute carrier organic anion transporter family, member 1B3	12p12.2	Mediates the Na(+)-independent uptake of organic anions	*SLCO1B3*	rs4149117 rs731358
Transcription factor 25	16q24.3	Transcriptional repressor	*TCF25*	rs3212366
Transforming growth factor, β1	19q13.1	Growth factor regulator	*TGFB1*	rs1800469
Tyrosine hydroxylase	11p15.5	Involved in synthesis of catecholamines	*TH*	rs3839874
Tumor necrosis factor	6p21.3	Cytokine activity	*TNFA*	rs1800629
Transient receptor potential cation channel, subfamily A, member 1	8q13	Receptor-activated nonselective cation channel involved in detection of pain	*TRPA1*	rs11988795
Transient receptor potential cation channel, subfamily V, member 1	17p13.3	Activator of sensory neurons that convey information about noxious stimuli to the CNS	*TRPV1*	rs8065080
Unknown gene	19p12	The potential function of this hypothetical gene is not known at present. GWAS revealed an association with analgesic onset.	*ZNF493-ZNF429*	rs2562456

(Continued)

Table 1. Continued

Gene Name	Chromosomal Location	Gene Function	Gene Symbol	SNP Number
Unknown gene	11q23.3	The potential function of this hypothetical gene is not known at present. GWAS found a significant association with analgesic onset.	*MPZL2-CD3E*	rs17122021
Unknown gene	1p21.3	The potential function of this hypothetical gene is not known at present. GWAS found a significant association with analgesic onset.	*RWDD3-EEF1A1P11*	rs6693882

CNS = central nervous system; GWAS = genome-wide association study; SNP = single-nucleotide polymorphism.

calculated. Collinearity between categorical variables was tested with the Cramer *V* test (between nominal variables) and Kendall tau-b coefficient (between ordinal variables).

A generalized linear mixed model (GLMM) with the variable recruitment center as a random factor was constructed using backward stepwise selection with CPSP as the dependent variable. Independent variables were selected for the model on the basis of the investigators' consensus on relevant measurable preoperative variables, the results of previous studies,[3–7,9,38] the bivariate analysis ($P < 0.05$), and correlation between variables (Kendall tau-b). At each step, the likelihood ratio was used to evaluate a potential risk factor. The cutoff for variable removal was set at a significance level of 0.05, and the adjusted ORs and corresponding 95% CIs were calculated.

A bootstrap method was used for internal validation of the subset of factors. A total of 1,000 computer-generated samples, each including 2,834 individuals, were derived from the sample by random selection with replacement. Within each bootstrap sample, the β coefficient was calculated using all selected factors. The reliability of predictor variables in the final GLMM was estimated by the 95% CI of the β coefficient in the bootstrap samples. Reliable predictors were retained if the 80% CI of bootstrap samples indicated statistical significance ($P < 0.05$). To assess the model's discrimination and predictive ability, we used the *c*-statistic expressed as a percentage (area under the receiver operating characteristic curve). GLMM calibration was assessed by the Hosmer–Lemeshow goodness-of-fit statistic as an estimate of agreement between observed and predicted outcomes.

Statistical Treatment of Genetic Analyses

For each SNP, allele and genotype frequency associations between the CPSP status and the presence of neuropathic pain were tested using SNPator.[39] In the genotype analysis, different inheritance models were tested in autosomic SNPs by comparing each genotype against the combination of the remaining two. Chi-square-based Pearson tests were applied to the resulting contingency tables to test for association. Allele frequency associations with pain intensity were also explored using the Wald test implemented in the PLINK suite.[40] Additional allele frequency testing was performed for CPSP status according to sex and type of surgery.

Haplotype blocks were defined by grouping genotyped SNPs by proximity, disallowing gaps greater than 50 kb. Haplotypes for each individual at each block were estimated using PHASE.[41] For each block, the frequency of each estimated haplotype was compared in cases and controls against the aggregation of all other estimated haplotypes for that block using SNPator.[39]

We report nominal *P* values for all statistical tests and performed multiple testing correction by means of a conservative Bonferroni strategy that considered all the tests in our analysis even if they are not independent of each other. Given that we performed allelic and genotypic tests for every marker and haplotypic tests for every gene, for a total of over 400 tests, we used a Bonferroni threshold of 10^{-4}.

Quality Assurance

To evaluate the quality of recruitment and data collection, independent observers audited the medical records of a random sample of 5% of the patients from 6 randomly chosen centers. Thus, 38 patient records (1.3% of the sample) were audited; the 102 items checked encompassed all variables directly involved in the predictive model plus others. This audit found 110 instances of error or missing data (2.8% of the data audited).

Results

For a total of 3,890 recruited patients, we detected protocol violation in 1% of the cases and 23.7% were lost to follow-up for the recording of outcome variables. Thus, data for 2,929 patients (75.3% of those recruited) were analyzed. Eighty-seven patients (3.0%) were lost between the first follow-up visit and the 2-yr telephone interview. Figure 1 shows patient flow from recruitment through 2 yr. Table 2 shows patient characteristics according to surgical procedure. DNA samples for genotyping were available for 2,854 patients (97.4%).

CPSP: Severity and Life Interference

Figure 2 shows the CPSP incidence after each procedure and each data collection time. Within a median (10th to 90th percentile) of 4.4 months (3.7 to 5.8), CPSP had developed in 527 patients (18.0%), in 13.6% of patients after hernia repair, 11.8% after vaginal hysterectomy, 25.1% after

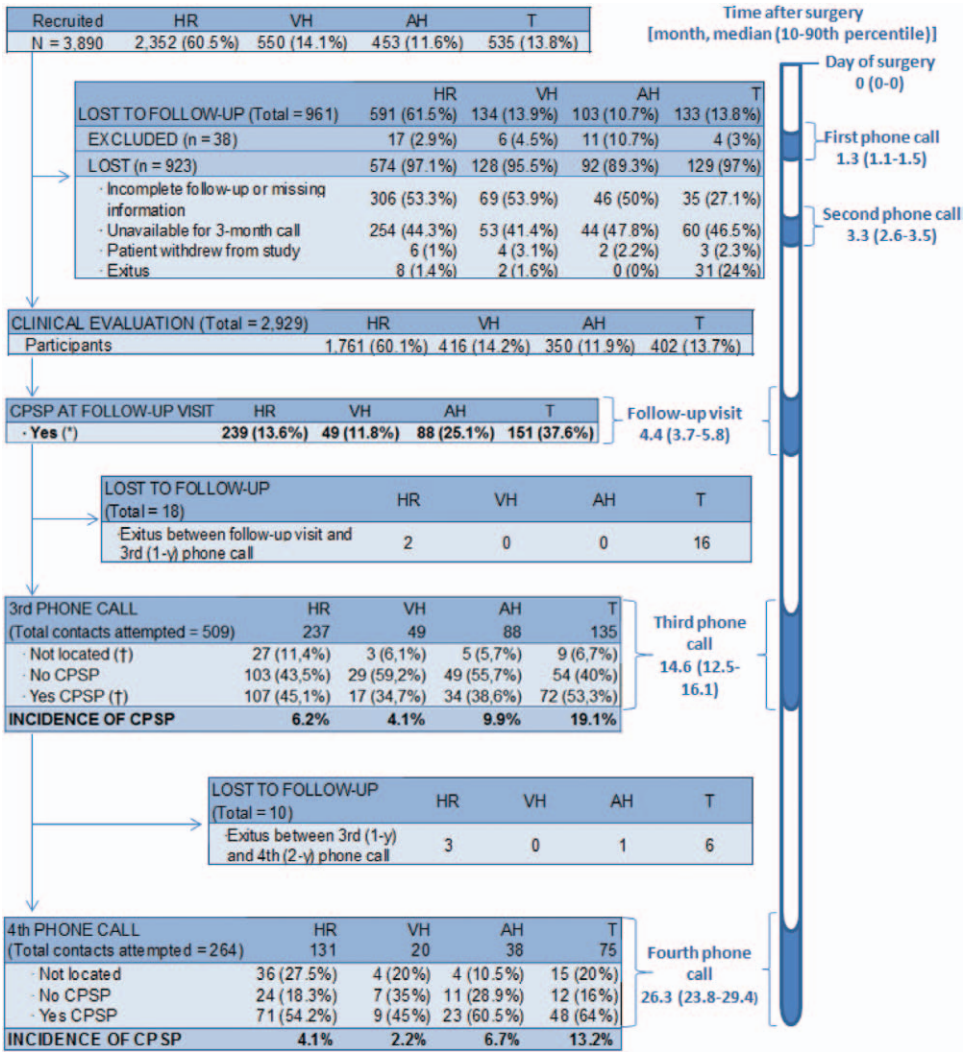

Fig. 1. Recruitment flowchart, showing numbers of patients recruited by type of surgery and those lost up until the times of the follow-up visit and phone interviews in the first and second years. Chronic postsurgical pain (CPSP) incidences at all data collection moments are included. *Candidates for the third telephone interview 1 yr after surgery. †Candidates for the fourth (final) telephone interview 2 yr after surgery. AH = abdominal hysterectomy; HR = hernia repair; T = thoracotomy; VH = vaginal hysterectomy.

abdominal hysterectomy, and 37.6% after thoracotomy. The follow-up interviews to report CPSP were completed at a median of 14.6 months (12.5 to 16.1) and 26.3 months (23.8 to 29.4).

Table 3 shows the incidence of CPSP, including neuropathic pain, and life-interference data obtained at the follow-up visit distributed by surgical procedure. The thoracotomy group had the highest incidence of neuropathic pain (55.0%) as assessed by the Douleur Neuropathique 4 questionnaire, and the vaginal hysterectomy group had the lowest (24.5%). The percentages of patients with a VNRS pain score higher than 3 ranged from 52.7% (thoracotomy) to 38.0% (hernia repair). CPSP interfered with daily activities (scores of > 3 out of 10, Brief Pain Inventory) after thoracotomy in 30.5% and after hernia repair in 18%. For patients who still had CPSP pain at 2 yr, the intensity did not decrease, remaining between 3 and 5 on the VNRS (table 4).

Genetic Study Exploring CPSP Associations

A total of 1,011 randomly selected samples (35.4% of the 2,854 available) were sent to be genotyped for 90 SNPs (505 cases, 506 controls); two samples were removed because of low genotyping success and four additional samples were removed because of incompatibilities between registered sex and sex imputed from genotypes. Thus, 1,005 samples (502 cases and 503 controls, table 5) were used in subsequent analyses. No significant deviations from Hardy–Weinberg equilibrium were found, and on comparing cases and controls (table 6), the subgroups were similar in all except two preoperative clinical variables (mental summary SF-12 score and preoperative pain in any nonsurgical area). The Bonferroni-corrected analysis showed no significant genetic differences in allele frequencies between patients with and without CPSP after any of the interventions studied (see table 7 and table 1, Supplemental Digital Content 3, http://links.lww.

Table 2. Patient Characteristics according to Surgical Procedure

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Total, n	1,761	416	350	402
Age, yr, median (10th–90th percentile)	60 (39–76)	63 (45.7–76)	48 (41–63.8)	64 (49–76)
BMI, kg/m^2, median (10th–90th percentile)	25.9 (22.3–30.1)	27.1 (22–33.3)	26.4 (21.5–35)	26.8 (21.7–32)
ASA physical status, n (%)				
1 (normal healthy patient)	543 (30.8)	76 (18.3)	100 (28.6)	54 (13.4)
2 (patient with mild systemic disease)	1,027 (58.3)	307 (73.8)	222 (63.4)	203 (50.4)
3 (patient with severe systemic disease)	187 (10.6)	33 (7.9)	28 (8.0)	143 (35.7)
4 (patient with severe systemic disease that is a constant threat to life)	4 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)
Anxiety, HADS, n (%)	318 (18.7)	138 (34)	165 (48.4)	118 (30.8)
Depression, HADS, n (%)	108 (6.3)	47 (11.5)	54 (15.8)	48 (12.6)
Preoperative score on the SF-12				
Physical summary, median (10th–90th percentile)	49.2 (34.6–56.7)	48.1 (33.1–57.2)	50.5 (31.8–58.6)	48.6 (30.2–57.8)
Mental summary, median (10th–90th percentile)	57.2 (42.6–64.2)	52.2 (36.6–62.7)	48.9 (30.6–61.6)	53.5 (35.4–64)
Duration of surgery, min, median (10th–90th percentile)	40 (25–74)	85 (50–145)	105 (65–180)	150 (77.4–240)
Hospital stay, d, median (10th–90th percentile)	0 (0–1)	3 (2–4)	4 (3–8)	5 (1–11)

ASA = American Society of Anesthesiologists; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; SF-12 = Short Form Health Survey-12 (version 2, in Spanish).

com/ALN/B137). Nonetheless, some allelic, genotypic, and haplotypic tests did show nominally significant *P* values for some SNPs or genes. In particular, two SNPs from *DRD2* in chromosome 11 (rs12364283 and rs4648317) presented low *P* values in some tests but in no case went beyond a conservative Bonferroni threshold of approximately 10^{-4}.

Clinical Risk Factors for CPSP

After bivariate analysis of 31 independent variables (table 8), collinearity analysis (rejection of correlation coefficients higher than 0.25), 18 independent variables entered the GLMM. These candidate predictors were surgical procedure, body mass index (< 24.44, 24.44 to 28.08, > 28.08), anxiety (Hospital Anxiety and Depression Scale score ≥ 8), depression (Hospital Anxiety and Depression Scale score ≥ 8), substance addiction, chronic obstructive pulmonary disease, hypertension, neurologic disease, cancer, preoperative pain in the surgical area (VNRS score > 3), preoperative pain in other areas (pain score > 3), previous experiences of surgery-related pain, family history of surgery-related pain, type of anesthesia, intraoperative intravenous opioid use, age (< 51, 51 to 64, > 64 yr), SF-12 physical summary (0 to 33.5, 33.6 to 55.1, > 55.1), and SF-12 mental summary (0 to 44.8, > 44.8). (These cutoffs were determined by distributing the CPSP data in deciles.)

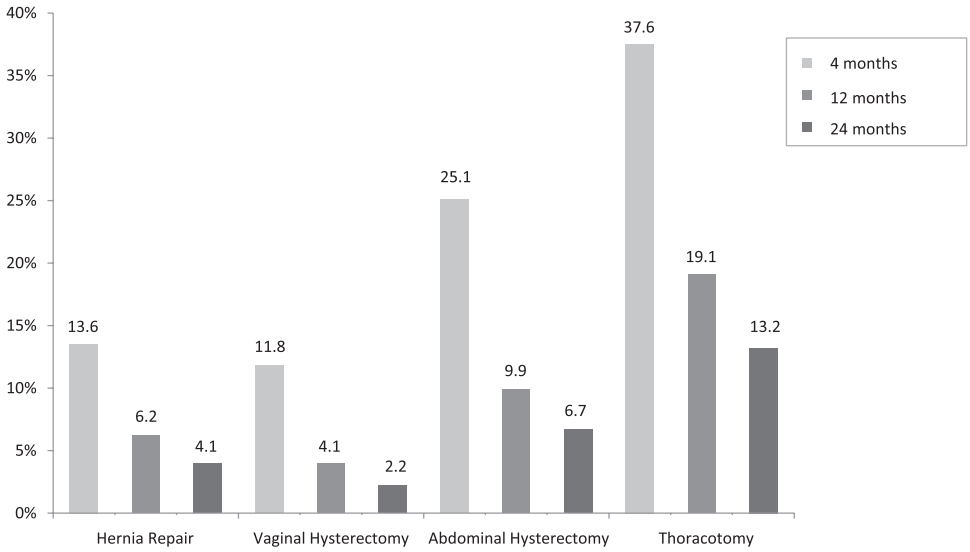

Fig. 2. Chronic postsurgical pain incidences 4, 12, and 24 months after surgery.

Table 3. Chronic Postsurgical Pain and Quality of Life at the 4-month Follow-up Visit

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Patients, n	239	49	88	151
DN4 questionnaire	238	49	88	151
Neuropathic pain, %	38.7	24.5	44.3	55.0
Brief Pain Inventory	237	49	86	150
Pain severity, %				
Worst pain in past 24 h—> 3, %	38.0	40.8	52.3	52.7
Average pain in past 24 h—> 3, %	20.6	26.2	23.6	25
Use of pain medication, %				
Any pain medication	24.9	38.1	52.8	60.5
Antiinflammatory and/or acetaminophen	28.3	54.7	68.1	70.5
Minor opioid with or without acetaminophen	1.2	11.9	0.0	9.3
Major opioid	0.0	0.0	0.0	8.4
Anticonvulsant and/or antidepressant	3.6	2.4	1.4	6.7
Other medications	2.4	0.0	1.4	0.8
Percentage of relief provided by drugs in past 24 h, median (10th–90th percentile)	40 (0–90)	50 (20–100)	50 (21–100)	50 (2–100)
Pain interference—> 3, %*				
General activity	18.0	26.8	18.1	30.5
Mood	10.2	26.8	34.7	26.3
Walking ability	15.0	29.3	19.4	17.8
Normal work	15.6	31.7	20.8	29.7
Relations with others	9.0	17.1	12.5	17.8
Sleep	4.2	14.6	12.5	25.4
Enjoyment of life	11.4	19.5	18.1	28.0
Four-month SF-12 scores				
Physical summary, median (10th–90th percentile)	47.1 (32.1–55.3)	42.3 (24.6–56.7)	42.3 (30.6–52.9)	35.9 (22.1–52.5)
Mental summary, median (10th–90th percentile)	53.9 (40.7–63.3)	44.8 (27.2–64.0)	44.3 (30.3–60.5)	51.4 (34.6–64.4)

* Percentages of patients with a verbal numerical rating scale score > 3 for pain.

DN4 = Douleur Neuropathique 4 questionnaire; SF-12 = Short Form Health Survey-12 (version 2, in Spanish).

The multivariable GLMM selected six CPSP predictors (table 9), which were retained in more than 95% of the bootstrap subsamples. Table 9 shows the adjusted ORs for these variables, along with the 95% CIs after bootstrapping. This six-variable mixed model identified more than 73% of the patients who developed CPSP, with a *c*-statistic of 0.731 (0.705 to 0.755). The calibration was good according to the Hosmer–Lemeshow chi-square test (χ^2 = 4.02; P = 0.855). According to GLMM-derived β coefficients, an individual's risk of CPSP might be calculated as follows: risk of CPSP = $1/(1 + e^{-\text{linear predictor}})$ where the linear predictor comprising the six independent risk factors was as follows: −3.37 + 0.50 × surgery (abdominal hysterectomy) + 0.28 × surgery (hernia repair) + 1.88 × surgery (thoracotomy) + 1.13 × age (< 51 yr) + 0.48 × age (51 to 64 yr) + 0.86 × physical SF-12 (< 33.5) + 0.52 × physical SF-12 (33.5 to 55.1) + 0.51 × mental SF-12 (< 44.8) + 0.41 × preoperative pain in surgical area (VNRS > 3) + 0.37 × preoperative pain in other area (VNRS > 3).

Table 2, Supplemental Digital Content 3, http://links.lww.com/ALN/B137, shows the GLMM for five of the six

Table 4. Course of CPSP Intensity Reported during Telephone Interviews

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Total, n	266	50	76	116
First phone call*	3 (1–6)	4 (1–6.9)	4 (1–7)	3.5 (1–6)
Total, n	225	49	84	146
Second phone call†	4 (2–6.4)	4 (2–7)	4 (2–6)	3.5 (2–7)
Total, n	105	13	32	70
Third phone call‡	4 (1.6–7)	5 (2–6)	5 (2–7.7)	4 (2–7)
Total, n	71	9	23	47
Fourth phone call§	4 (2–7)	4 (2–7.7)	5 (3–7.6)	4 (2–7)

Data are median (10th–90th percentile). Pain intensity was reported on a verbal numerical rating scale of 0 to 10 (0, no pain; 10, the worst imaginable pain).

* 1.3 months after surgery; † 3.3 months after surgery; ‡ 14.6 months after surgery; § 26.3 months after surgery.

CPSP = chronic postsurgical pain.

Table 5. Selection of Cases and Controls for Genotyping and Analysis of Associations with CPSP

	Hernia Repair (n = 1,761)	Vaginal Hysterectomy (n = 416)	Abdominal Hysterectomy (n = 350)	Thoracotomy (n = 402)
Cases, patients with CPSP (n = 527)	239	49	88	151
DNA sample unavailable (n = 22)	13	1	2	6
Selected for analysis (n = 505)	226	48	86	145
Material not valid for analysis (n = 3)	0	0	2	1
Total cases analyzed (n = 502)	226	48	84	144
Controls, patients without CPSP (n = 2,402)	1,522	367	262	251
Randomly selected for analysis (n = 523)	232	56	86	149
DNA sample unavailable (n = 17)	4	4	8	1
Selected for analysis (n = 506)	228	47	83	148
Material not valid for analysis (n = 3)	2	0	0	0
Total control patients (n = 503)	226	52	78	147

CPSP = chronic postsurgical pain.

predictors (excluding procedure type) applied to each of the four procedures (treating vaginal and abdominal hysterectomies separately). The *c*-statistics ranged from 0.731 (0.665 to 0.807) for vaginal hysterectomy to 0.645 (0.589 to 0.702) for thoracotomy. Table 3, Supplemental Digital Content 3, http://links.lww.com/ALN/B137, shows the GLMM for patients with neuropathic CPSP.

Discussion

The overall incidences of CPSP confirmed on physical examination at 4 months are consistent with previously reported rates for the same procedures,[3,4] with the exception of vaginal hysterectomy. Previous authors reported similar CPSP rates for vaginal and abdominal hysterectomy,[38] but we observed different CPSP behavior after these procedures and consider them to be separate settings. The rates had decreased by approximately half 1 yr after surgery and by two thirds after 2 yr, but we found no long-term studies with which to compare that finding.

Also interesting was our finding of a lower 4-month neuropathic pain rate than reported by others[3,4,42]; we attribute this difference to our reliance on exhaustive physical examination for diagnosis rather than postal questionnaires or patient charts. Finally, more than 20% of our CPSP patients reported moderate–intense pain at the diagnostic visit; that rate was similar to the 18.3% rate recorded in a population-based study of CPSP.[2] For patients who were still experiencing pain 2 yr later, the intensity had not diminished. We emphasize that pain was responsible for moderate–intense interference with daily activities for 18% to 30%, with walking for 15% to 29%, and with mood for 10% to 34%.

The comparison between 502 patients with confirmed CPSP and 503 selected controls without CPSP showed that a strong effect of genetic profile on this late complication is unlikely. Under the CPSP diagnostic criteria we applied at 4 months, and with case–control sample sizes that rendered a power of approximately 99% for detecting ORs higher than 1.9 in individual allelic tests, we conclude that any potential effects of the tested SNPs would be weaker than that threshold. We cannot, of course, formally exclude associations with SNPs that were not selected for tagging in this study.

Even though none of the studied SNPs survived multiple test correction, we note that the lowest allelic *P* values were for the association between CPSP and the dopamine D2 receptor (*DRD2*) gene SNPs rs12364283 and rs4648317. Both have been associated with enhanced *DRD2* expression[43] and several substance addictions—such as nicotine dependence (rs4648317[44])—as well as with inhibition and impulsivity related to D-amphetamine response effects on stop-task performance and mood (rs12364283[45]). These are but two of many SNPs linked to dopamine pathway dysregulation, which has also been observed in chronic pain unrelated to substance addiction.[46] Given the weak associations observed for these *DRD2* SNPs, we believe that they might still be candidates for more complex polygenic and multifactorial modeling. One recent study demonstrated an association between the HLA DQB1*03:02 allele and higher CPSP risk after one of the procedures we included (inguinal hernia repair) and after lumbar disk herniation.[21] We did not analyze HLA DQB1*03:02 because this pathway had not been directly linked to pain pathogenesis, but we think this new finding encourages further exploration of pathways not covered in the current study.

Thus, although we did not find any association between the 90 analyzed SNPs and CPSP, we cannot completely exclude the role of genetics in the development of CPSP. Our reasons are first, because our study was only powered to detect strong associations (OR > 1.9); second, because we selected SNPs to cover certain genes and did not exhaustively tag for all variations in every studied gene; and third, because reduced (or incomplete) penetrance, variable expressivity, and meiotic or mitotic epigenetic factors can contribute to the maintenance of CPSP. We think, however, that our findings do indicate that the positive results reported in other studies should probably be revisited critically until replicated.[21,47,48]

Table 6. Comparison of Variables of Interest between Cases and Controls in the Genetic Analysis

	Cases (n = 502)	Controls (n = 503)	
	No. (%)	No. (%)	*P* Value
Surgical specialty			
Hernia repair	226 (50.0)	226 (50.0)	0.938
Vaginal hysterectomy	48 (48.0)	52 (52.0)	
Abdominal hysterectomy	84 (51.9)	78 (48.1)	
Thoracotomy	144 (49.5)	147 (50.5)	
Place of origin*			
Andalusia	108 (47.8)	118 (52.2)	0.763
Aragon	9 (45.0)	11 (55.0)	
Castilla and Leon	24 (57.1)	18 (42.9)	
Castilla–La Mancha	23 (50.0)	23 (50.0)	
Catalonia	239 (51.0)	230 (49.0)	
Valencia	43 (43.4)	56 (56.6)	
Extremadura	18 (50.0)	18 (50.0)	
Galicia	9 (52.9)	8 (47.1)	
Murcia	10 (47.6)	11 (52.4)	
Others	18 (64.3)	10 (35.7)	
ASA			
ASA 1	139 (49.6)	141 (50.4)	0.614
ASA 2	276 (49.0)	287 (51.0)	
ASA 3 or ASA 4	86 (53.4)	75 (46.6)	
Age, yr			
18–51	216 (55.4)	174 (44.6)	0.018
> 51–64	154 (47.8)	168 (52.2)	
> 64	132 (45.1)	161 (54.9)	
Score on the SF-12 (physical summary)			
0–33.5	76 (59.8)	51 (40.2)	0.013
33.6–55.1	336 (49.8)	339 (50.2)	
> 55.1	77 (42.8)	103 (57.2)	
Score on the SF-12 (mental summary)			
0–44.8	146 (59.1)	101 (40.9)	0.001
> 44.8	343 (46.7)	392 (53.3)	
Anxiety (HADS), n (%)			
No	311 (47.8)	340 (52.2)	0.100
Yes	177 (53.3)	155 (46.7)	
Depression (HADS), n (%)			
No	427 (48.8)	448 (51.2)	0.132
Yes	61 (56.5)	47 (43.5)	
Preoperative pain, surgical area			
VNRS ≤ 3	374 (48.7)	394 (51.3)	0.169
VNRS > 3	127 (53.8)	109 (46.2)	
Preoperative pain, other areas			
VNRS ≤ 3	369 (47.0)	416 (53.0)	0.001
VNRS > 3	129 (60.0)	86 (40.0)	

* Locations are Spanish autonomous communities according to the Constitution of 1978; names are given in English when a form is commonly available.

ASA = American Society of Anesthesiologists; HADS = Hospital Anxiety and Depression Score; SF-12 = Short Form Health Survey-12 (version 2, in Spanish); VNRS = verbal numerical rating scale.

The CPSP risk model identified 73% of the patients with CPSP based on the following clinical predictors: (1) surgical procedure, (2) age, (3) physical health (SF-12 score), (4) mental health (SF-12 score), (5) preoperative pain in the surgical field, and (6) preoperative pain in another area. Although the discriminative power of the model is moderate, to our knowledge it is the first to offer some promise of assessing CPSP risk preoperatively, at least in the surgical settings studied. When we applied five of the six predictors (excluding procedure type) to each of the four procedures (treating vaginal and abdominal hysterectomies separately), we found that the model remained valid in each setting, although its predictive value is more robust in a mixed surgical population.

A clinical scoring system, based on the six easily recorded variables the model identifies, therefore merits external validation to test transportability to other settings. In contrast with a recent study by Althaus *et al.*,[49] who studied CPSP risk in a cohort of 150 patients undergoing a range of surgical procedures, we did not find that the presence of moderate or intense postsurgical pain substantially increased the predictive ability of the model. Thus, this factor was excluded for statistical reasons. However, we also emphasize our interest in identifying predictors available before surgery, such as psychological traits on which clinicians may be able to intervene. Such factors are probably related to patient hypervigilance[50] and are potentially related to certain gene polymorphisms in the dopamine pathway affecting pain perception.[51] Of the five CPSP predictors identified by Althaus *et al.*,[49] our findings are consistent with two: preoperative pain in the operating field and other preoperative pain. The relevance of preoperative pain in another area of the body is possibly attributable to poor functioning of endogenous pain inhibition mechanisms, as has been demonstrated in patients who develop CPSP after thoracotomy[14] and in several chronic pain settings.[52]

Factors related to surgery and anesthetic technique were not predictors of CPSP (table 4, Supplemental Digital Content 3, http://links.lww.com/ALN/B137). The lack of statistical relevance of anesthetic and analgesic variables may be attributable to the certain degree of variability in the execution of techniques in this study, reflecting a routine practice setting. In other words, an observational design, even when prospective, may make it difficult to identify factors as predictors if they are subject to small clinical variations. However, we did detect six other clinical risk factors for CPSP, and we think it is reasonable to suggest that anesthetic and analgesic factors may be less important to the development of CPSP in clinical circumstances than randomized trials might lead us to believe. Finally, although we detected a higher level of preoperative anxiety in patients with CPSP, anxiety was excluded from the model because it was strongly associated with results for the mental component of the SF-12, which was a stronger predictor.

One major strength of this study was its prospective, population-based, multicenter design with physician-diagnosed CPSP. We collected data for a representative random sample of surgical patients undergoing routine anesthetic procedures in a large genetically homogeneous population. This study was also the first to follow patients for 2 yr

Table 7. Results of Frequency Testing for Risk Alleles for CPSP in All Tested SNPs

Gene	SNP	Chromosome	Position	*P* Value	Risk Allele	OR (95% CI)
OPRD1	rs1042114	1	29.138.975	0.1636	G	1.20 (0.93–1.55)
OPRD1	rs533123	1	29.141.155	0.9907	C	1.00 (0.80–1.25)
GRIK3	rs6691840	1	37.325.477	0.7091	A	1.04 (0.85–1.27)
FAAH/NSUN4	rs932816	1	46.859.749	0.1251	A	1.16 (0.96–1.41)
FAAH	rs4141964	1	46.865.040	0.8462	G	1.02 (0.85–1.22)
FAAH	rs2295633	1	46.874.383	0.9675	C	1.00 (0.83–1.21)
Unknown gene*	rs6693882	1	96.145.968	0.2757	A	1.11 (0.92–1.33)
PTGS2	rs5275	1	186.643.058	0.8001	C	1.03 (0.85–1.24)
IL19/IL10	rs1800896	1	206.946.897	0.675	A	1.04 (0.87–1.24)
POMC	rs934778	2	25.389.224	0.7558	T	1.03 (0.86–1.24)
SCN9A	rs6746030	2	167.099.158	0.9196	A	1.01 (0.78–1.32)
SCN9A	rs6747673	2	167.144.974	0.4144	A	1.08 (0.90–1.28)
SCN9A	rs9646771	2	167.163.043	0.6842	C	1.04 (0.86–1.25)
GABRA4	rs7678338	4	46.922.107	0.6507	T	1.05 (0.86–1.27)
GABRA4	rs7689605	4	46.952.029	0.6494	A	1.08 (0.78–1.49)
GABRB1	rs10028945	4	47.428.305	0.8924	A	1.01 (0.84–1.23)
SLC6A3/CLPTM1L	rs12516948	5	1.391.369	0.6565	G	1.04 (0.87–1.24)
SLC6A3	rs40184	5	1.395.077	0.9359	A	1.01 (0.85–1.20)
SLC6A3	rs403636	5	1.438.354	0.1926	G	1.17 (0.92–1.47)
SLC6A3	rs6350	5	1.443.199	0.4853	C	1.13 (0.81–1.57)
GABRB2/GABRA6	rs3816596	5	160.975.332	0.6129	T	1.05 (0.87–1.26)
GABRA1/LOC100287123	rs12658835	5	161.275.302	0.6454	G	1.05 (0.86–1.28)
ATXN1	rs179997	6	16.318.633	0.0473	A	1.20 (1.00–1.44)
TNF/LTA	rs1800629	6	31.543.031	0.3355	G	1.14 (0.87–1.50)
OPRM1	rs1799971	6	154.360.797	0.337	A	1.12 (0.89–1.41)
OPRM1	rs563649	6	154.407.967	0.8261	A	1.04 (0.72–1.50)
OPRK1	rs702764	8	54.142.157	0.7637	T	1.04 (0.81–1.33)
OPRK1	rs997917	8	54.152.378	0.3819	C	1.09 (0.90–1.33)
PENK	rs3839874	8	57.353.827	0.2525	T	1.11 (0.93–1.32)
PENK	rs1975285	8	57.358.682	0.1082	C	1.19 (0.96–1.47)
TRPA1	rs11988795	8	72.949.601	0.8807	C	1.01 (0.84–1.22)
BDNFOS	rs6265	11	27.679.916	0.295	G	1.12 (0.91–1.37)
BDNF	rs2049046	11	27.723.775	0.1426	T	1.14 (0.96–1.36)
KIF18A/BDNF	rs908867	11	27.745.764	0.127	G	1.28 (0.93–1.77)
DRD2	rs6277	11	113.283.459	0.6926	T	1.04 (0.87–1.24)
DRD2	rs1076560	11	113.283.688	0.5758	C	1.08 (0.83–1.41)
DRD2	rs2734837	11	113.286.829	0.7506	G	1.03 (0.85–1.24)
DRD2	rs11608185	11	113.294.976	0.7529	T	1.03 (0.85–1.24)
DRD2	rs4936272	11	113.318.907	0.864	C	1.02 (0.85–1.21)
DRD2	rs4648317	11	113.331.532	0.0186	T	1.35 (1.05–1.74)
DRD2	rs4322431	11	113.332.956	0.3671	T	1.09 (0.90–1.33)
TMPRSS5/DRD2	rs1799978	11	113.346.351	0.8962	A	1.03 (0.69–1.53)
TMPRSS5/DRD2	rs12364283	11	113.346.955	0.0102	G	1.58 (1.11–2.23)
Unknown gene*	rs17122021	11	118.145.686	0.1005	T	1.17 (0.97–1.40)
SLCO1B3	rs4149117	12	21.011.480	0.5382	G	1.09 (0.84–1.41)
SLCO1A2	rs11568563	12	21.457.434	0.2388	A	1.23 (0.87–1.74)
NFKBIA	rs8904	14	35.871.217	0.0394	T	1.21 (1.01–1.44)
SAMD4A/GCH1	rs10483639	14	55.306.457	0.0713	C	1.24 (0.98–1.57)
SAMD4A/GCH1	rs7142517	14	55.306.804	0.3649	C	1.09 (0.90–1.31)
GCH1	rs752688	14	55.311.569	0.0514	T	1.27 (1.00–1.60)
GCH1	rs4411417	14	55.320.563	0.0458	C	1.27 (1.00–1.62)
GCH1	rs9671371	14	55.328.635	0.1016	T	1.18 (0.97–1.44)
LOC100289044/GCH1	rs12147422	14	55.344.015	0.3107	T	1.17 (0.87–1.57)
LOC100289044/GCH1	rs8004445	14	55.350.666	0.2536	G	1.19 (0.88–1.60)
LOC100289044/GCH1	rs998259	14	55.355.031	0.9864	C	1.00 (0.82–1.22)
GCH1/LOC100289044	rs3783641	14	55.360.139	0.0807	A	1.23 (0.97–1.56)
WDHD1/LOC100289044	rs8007267	14	55.378.991	0.2502	T	1.15 (0.90–1.47)

(Continued)

Table 7. Continued

Gene	SNP	Chromosome	Position	*P* Value	Risk Allele	OR (95% CI)
SLC6A2	rs40434	16	55.699.525	0.139	C	1.15 (0.96–1.38)
SLC6A2	rs36024	16	55.706.391	0.2056	C	1.12 (0.94–1.34)
SLC6A2	rs36017	16	55.718.818	0.141	G	1.14 (0.96–1.36)
TRPV1	rs8065080	17	3.480.447	0.9945	C	1.00 (0.84–1.20)
CCDC55	rs1979572	17	28.511.978	0.7896	C	1.02 (0.86–1.22)
SLC6A4	rs4325622	17	28.526.475	0.9607	T	1.00 (0.84–1.20)
SLC6A4	rs140701	17	28.538.532	0.557	G	1.05 (0.88–1.26)
SLC6A4	rs2066713	17	28.551.665	0.4839	C	1.07 (0.89–1.29)
MC4R/LOC728115	rs9966412	18	58.033.935	0.4191	C	1.11 (0.86–1.44)
Unknown gene*	rs2562456	19	21.666.210	0.3402	C	1.10 (0.90–1.35)
B9D2/TGFB1	rs1800469	19	41.860.296	0.5785	C	1.05 (0.88–1.27)
COMT	rs4646312	22	19.948.337	0.3568	C	1.09 (0.91–1.30)
COMT	rs6269	22	19.949.952	0.5077	G	1.06 (0.89–1.27)
COMT	rs4680	22	19.951.271	0.6067	G	1.05 (0.88–1.25)
MAOA	rs3788862	X	43.517.364	0.4551	A	1.10 (0.85–1.42)
MAOA	rs2283724	X	43.559.576	0.5271	G	1.08 (0.85–1.37)
MAOA	rs1800659	X	43.574.169	0.8307	C	1.03 (0.80–1.31)
MAOA	rs979606	X	43.601.142	0.8108	G	1.03 (0.80–1.33)
MAOA	rs979605	X	43.601.363	0.7978	T	1.03 (0.80–1.33)

* Unknown gene SNPs selected because they were significant in the genome-wide association study of Kim *et al.*[20]

CI = confidence interval; CPSP = chronic postsurgical pain; OR = odds ratio; SNP = single-nucleotide polymorphism.

Table 8. Distribution of Independent Variable Results in the Total Study Population of 2,929 Patients and in the 527 Patients with CPSP

	No. of Patients	No. (%) of Patients with CPSP	
	2,929	527 (18)	*P* Value
Variables entered into the multiple regression model			
Surgical specialty			
Hernia repair	1,761	239 (13.6)	< 0.0001
Vaginal hysterectomy	416	49 (11.8)	
Abdominal hysterectomy	350	88 (25.1)	
Thoracotomy	402	151 (37.6)	
Age, yr			
18–51	905	226 (25)	< 0.0001
> 51–64	919	161 (17.5)	
> 64	1,104	140 (12.7)	
BMI			
< 24.44	864	162 (18.8)	0.334
24.44–28.08	1,151	194 (16.9)	
> 28.08	863	166 (19.2)	
Score on the SF-12 (physical summary)			
0–33.5	284	81 (28.5)	< 0.0001
33.6–55.1	1,954	353 (18.1)	
> 55.1	609	80 (13.1)	
Score on the SF-12 (mental summary)			
0–44.8	569	154 (27.1)	< 0.0001
> 44.8	2,278	360 (15.8)	
Anxiety (HADS)			
No	2,096	326 (15.6)	< 0.0001
Yes	739	187 (25.3)	
Depression (HADS)			
No	2,577	447 (17.3)	0.001
Yes	257	66 (25.7)	

(Continued)

Table 8. Continued

	No. of Patients	No. (%) of Patients with CPSP	
	2,929	527 (18)	*P* Value
Substance addiction*			
No	1,441	209 (14.5)	< 0.0001
Yes	1,477	317 (21.5)	
Diagnosed chronic respiratory disease (COPD)			
No	2,473	415 (16.8)	< 0.0001
Yes	449	111 (24.7)	
Hypertension			
No	1,948	375 (19.3)	0.013
Yes	974	151 (15.5)	
Neurologic disease			
No	2,758	486 (17.6)	0.028
Yes	164	40 (24.4)	
Neoplastic disease			
No	2,389	365 (15.3)	< 0.0001
Yes	533	161 (30.2)	
Preoperative pain, surgical area			
VNRS ≤ 3	2,356	396 (16.8)	< 0.0001
VNRS > 3	559	130 (23.3)	
Preoperative pain, other areas			
VNRS ≤ 3	2,333	388 (16.6)	< 0.0001
VNRS > 3	576	134 (23.3)	
Previous experience of pain and surgery			
No	2,099	349 (16.6)	0.001
Yes	816	177 (21.7)	
Family history of pain and surgery			
No	2,578	460 (17.8)	0.019
Yes	214	52 (24.3)	
Type of anesthesia			
Regional or local infiltration	1,684	226 (13.4)	< 0.0001
General or combined	1,216	300 (24.7)	
Intraoperative intravenous opioid			
No	1,299	169 (13.0)	< 0.0001
Yes	1,598	357 (22.3)	
Other candidate variables not entered into the multiple regression model			
Education			
< 9 yr	1,143	174 (15.2)	0.002
≥ 9 yr	315	315 (19.9)	
Heart disease			
No	2,628	478 (18.2)	0.431
Yes	294	48 (16.3)	
Peripheral vascular disease			
No	2,706	495 (18.3)	0.147
Yes	216	31 (14.4)	
Chronic kidney disease			
No	2,854	512 (17.9)	0.574
Yes	68	14 (20.6)	
Hepatic disease			
No	2,829	505 (17.9)	0.243
Yes	93	21 (22.6)	
Diabetes mellitus			
No	2,573	463 (18.0)	0.196
Oral medication or diet	297	49 (16.5)	
On insulin	52	14 (26.9)	
Immunocompromised			
No	2,854	512 (17.9)	0.574
Yes	68	14 (20.6)	

(*Continued*)

Table 8. Continued

	No. of Patients	No. (%) of Patients with CPSP	
	2,929	527 (18)	*P* Value
Alcohol addiction* > 24 g/d			
No	2,580	451 (17.5)	0.044
Yes	342	75 (21.9)	
Smoking addiction*			
Never	1,536	225 (14.6)	< 0.0001
Former smoker	671	150 (22.4)	
Current smoker	715	151 (21.1)	
Street-drug addiction*			
No	2,886	518 (17.9)	0.302
Yes	32	8 (25.0)	
ASA physical status			
1 (normal healthy patient)	770	143 (18.6)	0.008
2 (patient with mild systemic disease)	1,755	291 (16.6)	
3 (patient with severe systemic disease)			
4 (patient with severe systemic disease that is a constant threat to life)	397	92 (23.2)	
Intraoperative intravenous remifentanil			
No	2,433	420 (17.3)	0.004
Yes	442	102 (23.1)	
Postsurgical pain at 24 h			
VNRS ≤ 3	2,547	426 (16.7)	< 0.0001
VNRS >3	306	89 (29.1)	

* When entered into the model, all types of addiction (smoking, alcohol, and street drugs) were grouped together. Considered separately, substance addiction included alcohol intake > 24 g/d, current smoking, former smoking, and use of street drugs (*e.g.*, cannabis, cocaine, and heroin).

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPSP = chronic postsurgical pain; HADS = Hospital Anxiety and Depression Scale; SF-12 = Short Form Health Survey-12 (version 2, in Spanish); VNRS = verbal numerical rating scale.

(range, 22.2 to 30.0 months) and to prospectively include all the variables considered relevant to chronic pain at the time of design.[53,54]

A potential limitation was the large number of data collectors (164 anesthesiologists) in 23 centers; however, we used a structured questionnaire and conducted three training sessions to prevent inconsistent collection that might have led to a center effect.[55] A second limitation was that we did not use a scale to analyze pain catastrophizing because the predictive value of this factor[10,56] had not yet been established when our study was designed. This attribute, defined as a tendency to misinterpret and exaggerate situations that may be threatening, has recently been shown to confer risk for CPSP.[56] A potential limitation with regard to hernia repair was that the type of mesh used for this procedure was not considered as a possible surgery-related risk factor. The final limitation relates to gender in the genetic analysis. We chose to include only men in the hernia repair and thoracotomy groups because of the difficulty in balancing gender in these samples: based on a previous descriptive study of surgical populations in our geographic setting, we estimated that women would only account for 28% and 22% of these groups, respectively.[31] In order to analyze the genetic factor in relation to clinical characteristics within surgical specialties, while enrolling large but not vast numbers of patients, we balanced the all-male thoracotomy and hernia repair groups against the two hysterectomy groups.

We conclude that the lack of unequivocal confirmation of genetic factors predisposing certain patients to CPSP necessitates our continued reliance on scoring clinical factors—particularly procedure, age, and preoperative quality of life and experience of pain—to guide interventions or vigilance against the development of this late complication. A surgical team's understanding of CPSP risk stratification has many applications in large healthcare systems or the management of individual cases. For benign conditions, high risk should lead to reassessment of surgery and deference to other treatment options,[57] especially in younger patients with concomitant pain or psychological comorbidity. Our model can facilitate trials of preventive strategies so that ineffective treatments that can have adverse effects or entail inconvenience can be avoided.[58,59] We encourage the further development of valid, transportable scoring systems to predict CPSP risk based on clinical factors in other surgical settings while the search for genetic and clinical interactions continues through more detailed multifactorial study.

Table 9. Independent Predictors of Risk for CPSP Identified in the Generalized Linear Mixed Model for Binomial Distribution with the Variable Recruitment Center as a Random Factor

	Bivariate Analysis	Multivariable Analysis*		Bootstrap Resampling†
	OR (95% CI)	OR (95% CI)		
	n = 2,834	β-coefficients	n = 2,834	OR (95% CI)
Surgical specialty				
Vaginal hysterectomy	1			
Abdominal hysterectomy	2.4 (1.6–3.6)	0.497	1.6 (1.1–2.5)	1.7 (1.1–2.6)
Hernia repair	1.2 (0.8–1.6)	0.278	1.3 (0.9–1.9)	1.3 (0.9–2.0)
Thoracotomy	4.5 (3.1–6.5)	1.875	6.5 (4.3–9.9)	6.7 (4.5–10.6)
Age, yr				
18–50	2.3 (1.8–2.9)	1.126	3.1 (2.4–4.0)	3.2 (2.4–4.1)
51–64	1.5 (1.2–1.9)	0.476	1.6 (1.2–2.1)	1.6 (1.2–2.1)
> 64	1			
SF-12 score (physical summary)				
0–33.5	2.6 (1.8–3.6)	0.862	2.4 (1.6–3.5)	2.4 (1.6–3.6)
33.6–55.1	1.4 (1.1–1.9)	0.517	1.7 (1.3–2.2)	1.7 (1.3–2.3)
> 55.1	1			
SF-12 score (mental summary)				
0–44.8	2 (1.6–2.5)	0.513	1.7 (1.3–2.1)	1.7 (1.3–2.1)
> 44.8	1			
Preoperative pain, surgical area				
VNRS ≤ 3	1			
VNRS > 3	1.5 (1.2–1.9)	0.413	1.5 (1.2–2.0)	1.5 (1.2–2.0)
Preoperative pain, other areas				
VNRS ≤ 3	1			
VNRS > 3	1.5 (1.2–1.9)	0.366	1.4 (1.1–1.9)	1.4 (1.1–1.9)

* *c*-statistic = 0.731; Hosmer–Lemeshow chi-square test (calibration), $\chi^2 = 4.02$; $P = 0.855$. † A total of 1,000 bootstrap subsamples were modeled.

CI = confidence interval; CPSP = chronic postsurgical pain; OR = odds ratio; SF-12 = Short Form Health Survey (version 2 in Spanish); VNRS = verbal numerical rating scale (0–10).

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Competing Interests

The authors declare no competing interests.

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Appendix

A. The GENDOLCAT Study Investigators by Center (n = 23). Centers are listed alphabetically; all cities are in Spain. PI refers to principal investigator; SC, steering committee.

Althaia, Xarxa Assistencial de Manresa, Manresa

Consuelo Ruiz (PI), M.D., Ph.D.; Carme Font, M.D.; Josep Delgado, M.D.; Lissette del M. Jiménez, M.D.; Mª Meritxell Sabrià, M.D.

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Paloma Ricós (PI), M.D.; Antoni Pérez, M.D.; Carme Subirà, M.D.; Daniel Neira, M.D.; Francisco José Añez, M.D.; Gladys Margarita Hernández, M.D.; Isabel Cabré, M.D.; Laura Silberman, M.D.; Manuel Eduardo López, M.D.; María Garolera, M.D.; María Teresa Guerrero, M.D.; Marina García, M.D.; Montserrat Yuste, M.D.; Noemí Pou, M.D.; Rosa Calatayud, M.D.

Consorci Sanitari de Terrassa, Terrassa

Carmen Martín (PI), M.D., Ph.D.; Ester Lombán, M.D.; Gisela Egido, M.D.; José Antonio Bernia, M.D., Ph.D.; Ricardo Leiro, M.D.; Xavier García, M.D.

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Jordi Troy (PI), M.D.; Antonia Bassols, M.D., Ph.D.; Carme Colilles, M.D.; Cristina Tremps, M.D.; Diana Fernández, M.D., Ph.D.; Joan Blázquez, M.D.; Josep Planell, M.D.; Magdalena Serra, M.D.; Martí Solà, M.D.; Mercedes Rosas, M.D.; Montserrat Cañellas, M.D., Ph.D.

Fundació Privada Hospital Asil de Granollers

Victor Espiga (PI), M.D.; Fernando Martínez, M.D.; María Teresa Vilalta, M.D.

Hospital Clínic de Barcelona, Barcelona

Ana Bogdanovich (PI), M.D.; Pinar de Santos, M.D., Ph.D.; Teresa Anglada, M.D., Ph.D.

Hospital Comarcal Sant Bernabé, Berga

Anna Vidal (PI), M.D.; Josep Mª Canudas, M.D.

Hospital General Universitario de Alicante, Alicante

Ana Mª Peiró (PI), M.D., Ph.D.; Luis Gómez, M.D.; Yolanda Sastre, M.D.

Hospital Lluís Alcanyís, Xàtiva

Vicente Domingo (PI), M.D., Ph.D.; Antonio Antolí, M.D.; Belén Bardisa, M.D.; Blanca Moro, M.D.; Gerardo Presencia, M.D.; Julián García, M.D.; Mª Teresa Crespo, M.D.; Ramón José Ferri, M.D., Ph.D.; Vicente Roselló, M.D.

Hospital Municipal de Badalona, Badalona

Dolors Sintes (PI), M.D.; Ana Sapé, M.D.; Candi Giralt, M.D.; Eduardo Esteva, M.D.; Elena Barceló, M.D.; Fernando Rey, M.D.; Joan Fornaguera, M.D.; Luis Martínez, M.D.; Montserrat Pijoan, M.D.; Raquel Mansilla, M.D.

Hospital Sant Rafael, Barcelona

Jose Luis Casbas (PI), M.D.; Antonio Monso, M.D., Ph.D.; Inma Garrido, M.D.; Joaquín Torres, M.D.; Laura Mahillo, M.D.

Hospital Santa María, Lleida

Gregorio Marco (PI), M.D., Ph.D.; Dolors Del Pozo, M.D., Ph.D.; Montserrat Torra, M.D.; Reis Drudis, M.D.

Hospital Universitari de Bellvitge, Hospitalet de Llobregat

Ancor Serrano (PI), M.D.; Antoni Sabaté, M.D., Ph.D.; Carmen Ribes, M.D.; Eugenia Martínez, M.D.; María Valcárcel, M.D.; Resurrección Sanzol, M.D.; Víctor Mayoral, M.D.

Hospital Universitari de Girona Dr. Josep Trueta, Girona

Josep Vilaplana (PI), M.D.; Antonio Villalonga, M.D., Ph.D.; Antoni Arxer, M.D.; Joaquim Pujol, M.D.

Hospital Universitari de la Santa Creu i Sant Pau, Barcelona

Elena Català (PI), M.D., Ph.D.; Ana Bueno, M.D.; Bartomeu Cantallops, M.D.; Immaculada India, M.D.; Mª Angeles Gil de Bernabé, M.D.; Mª Carmen Unzueta, M.D., Ph.D.; Mª Teresa Rivilla, M.D.; Marc Bausili, M.D.; Miren Revuelta, M.D.

Hospital Universitari Germans Trias i Pujol, Badalona

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