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Genetic and phenotypic markers of pain in patients with hemophilia

© O.K. LEVCHENKO, O.S. PSHENICHNIKOVA, V.L. SURIN, T.Yu. POLYANSKAYA, V.Yu. ZORENKO, G.M. GALSTYAN, V.G. SAVCHENKO

National Research Center for Hematology, Moscow, Russian Federation

ABSTRACT

Objective. To study the effect of functional polymorphisms on the profile of psychophysical parameters in patients with hemophilia.

Material and methods. A prospective study was conducted on 21 patients with hemophilia A and B. All patients underwent total knee replacement for severe hemophilic arthropathy. Various psychophysical parameters were analyzed prior to surgery, on the day of surgery, within 3 days after surgery, after 10 days and 6 months. We assessed questionnaire scores, pain intensity, need for perioperative analgesia, long-term outcomes and analyzed functional SNPs in the genes *COMT* (rs4818, rs4680), *OPRM1* (rs1799971) and *SCN9A* (rs6746030).

Results. Patients with different SNP alleles in the *COMT* gene had similar phenotypic characteristics ($p>0.05$). According to literature data, carriers of the rare A allele in the *SCN9A* gene usually feel the most severe pain. According to our results, these patients (AG genotype, allele A was not detected in homozygous form) had less NRS scores of pain syndrome within 3 days after surgery compared to carriers of GG genotype with the same perioperative analgesic consumption (1—5 versus 3—7 points, $p<0.05$). These data require further analysis. A rare G allele in the *OPRM1* gene influenced postoperative pain intensity (total rank pain index 37 vs. 16, total ICPI score 13 vs. 2.5 in 10 days after surgery), physical (25 vs. 52.5 points) and mental (44 vs. 74 points) health, vitality (50 vs. 70 points), overstrain level (18 vs. 13 points) and fatigue (21 vs. 32 points), ability to cope with stress (19 vs. 28 points), resistance to stress (10 vs. 6 points) and quality of sleep (14 vs. 19 points) ($p<0.05$ for all the mentioned indicators).

Conclusion. Thus, an initial hypothesis about genetic component in formation of pain in patients with hemophilia is confirmed. This study has several limitations. However, it is the first trial devoted to relationship between phenotypic and genotypic characteristics of pain in patients with hemophilia. Application of this methodology in large-scale studies can reveal new factors associated with the risk of severe acute and chronic pain, and ensure creation of differentiated pain treatment regimens.

Keywords: *pain, genetics, hemophilia, genes, COMT, OPRM1, SCN9A.*

INFORMATION ABOUT THE AUTHORS:
Levchenko O.K. — https://orcid.org/0000-0003-1425-4370
Pshenichnikova O.S. — https://orcid.org/0000-0001-5752-8146
Surin V.L. — https://orcid.org/0000-0002-1890-4492
Polyanskaya T.Yu. — https://orcid.org/0000-0002-4143-3094
Zorenko V.Yu. — https://orcid.org/0000-0002-2049-850X
Galstyan G.M. — https://orcid.org/0000-0001-8818-8949; e-mail: gengalst@gmail.com
Savchenko V.G. — https://orcid.org/0000-0001-8188-5557
Corresponding author: Galstyan G.M. — e-mail: gengalst@gmail.com

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Most patients with severe hemophilia suffer from joint pain throughout their lives [1, 2]. Forced intake of various analgesic drugs in these patients results complications. Non-steroidal anti-inflammatory drugs are accompanied by gastric mucosa lesion, platelet disaggregation and recurrent bleeding. These processes contribute to destruction of normal tissues and development of arthrosis. Various patients with hemophilia and concomitant severe pain take narcotic analgesics [3, 4]. Long-term use of opioids leads to increased pain sensitivity and opioid-induced hyperalgesia.

Individual differences in pain response are used for analysis of nociceptive mechanisms and personalized approach to pain. Multiple factors modulating pain suggest a comparative assessment of their effect on pain perception. Genetic factors make a significant contribution to individual differences in pain sensitivity [5]. Associations between functional polymorphisms and different types of pain have been identified for many genes. These data were used to create a database with a summary table of relationships (https://humanpaingenetics.org/hpgdb/).

Some genetic variants alter the occurrence, transmission and processing of nociceptive information or local availability of active analgesics and their effect. Each individual genetic variant has a moderate effect on pain perception. However, multiple types form a variety of pain sensitivity in the world population [6]. Associations with chronic postoperative pain and differences in opioid requirements are most often observed for the *COMT*, *OPRM1* and *SCN9A* genes [7–12].

SCN9A gene localized at the locus 2q24.3 of the second chromosome encodes alpha subunit of closed sodium channel NaV1.7. The last one is mainly found in pain-signaling neurons of spinal ganglia (nociceptors). This channel is essential in these cells since it increases depolarization for signal enhancement [9, 10]. Single nucleotide polymorphism (SNP) rs6746030 (c.3448 G>A, R1150W) in exon 18 of the *SCN9A*

gene is followed by replacement of positively charged amino acid arginine (R) with a non-polar tryptophan (W). This replacement increases potential-dependence from 7.9 to 11 mV towards depolarization. As a result, significant effect on the neuronal activity of spinal ganglia, depolarization of resting potential and doubling action potential are observed [9]. It was shown that rs6746030 polymorphism is significantly associated with pain perception in various diseases (osteoarthritis, sciatica, phantom pain after amputation, pain in small pelvis after gynecological surgeries). Clinical and experimental studies confirmed the additive model of effect. Thus, AA genotype carriers feel the most severe pain while GG genotype carriers — the weakest pain [10, 13].

OPRM1 gene localized at the 6q25.3 locus of chromosome 6 is well studied within the framework of antinociceptive system. This gene encodes μ-opioid receptor belonging to rhodopsin receptors associated with G-protein [11, 12, 14—16]. This receptor is the main target for non-selective narcotic analgesics (morphine, fentanyl, promedol), and can also bind to endogenous opioids (for example, β-endorphins). Its activation results inhibition of adenylate cyclase, decrease in current through voltage-gated calcium channels, and opening of some potassium channels. Hyperpolarization associated with advanced potassium flow and calcium entry suppression reduces release of mediator. As a result, delayed conduction of excitation through the nociceptive tract is observed [16]. To date, over 100 SNPs have been identified in the *OPRM1* gene [15]. Most often, correlation of opioid analgesic consumption with rs1799971 polymorphism (c. 118A>G, N40D) was noted. This polymorphism is associated with reduced number of N-glycosylation sites from five to four on extracellular part of receptor [11, 12, 15]. It was also shown that rs1799971 minor allele reduces signaling efficiency of μ-opioid receptor in the SII brain region. The last one is essential factor influencing intensity of pain sensations [14].

Catechol-O-methyltransferase (*COMT*) is the main degrading enzyme in metabolic pathways of catecholaminergic neurotransmitters including dopamine, epinephrine and norepinephrine [17, 18]. *COMT* gene localized at the locus 22q11.2 of the 22nd chromosome encodes this enzyme. Associations with pain intensity and need for opioids were most often noted for this gene [7, 8, 19-22]. The rs4680 (c.472G>A, p. Val158Met) polymorphism is the most studied in this gene. This polymorphism affects thermal stability, and minor allele A is followed by 3-4-fold decrease in *COMT* activity [18, 22]. Perhaps, reduced activity leads to accumulation of epinephrine and norepinephrine in peripheral and central nervous system with subsequent overstimulation of nociceptive β 2/3-adrenergic pathways and high pain sensitivity in 158A allele carriers [20]. The rs4680 polymorphism is characterized by codominant inheritance pattern with the lowest enzyme activity in AA genotype carriers, the highest activity in GG genotype carriers and intermediate activity in AG genotype carriers [17]. Another polymorphism in the *COMT* gene, rs4818 (c.408C>G, p.Leu136 =), is a synonymous substitution. This polymorphism probably affects enzyme translation through modification of mRNA secondary structure [8]. Some authors revealed correlation between the need for opioids in acute pain and GG genotype. In other reports, a joint contribution of rs4818 and rs4680 polymorphisms has been noted [7, 12, 19, 23].

Development of VIII and IX coagulation factor concentrates was valuable for arthroplasty of large joints including total knee arthroplasty. These procedures significantly improve quality of life in patients with hemophilia [24]. The number of surgeries is growing steadily all over the world. Surgical treatment is often the only option in patients with arthrosis and concomitant hemophilia or other comorbidities [25]. However, according to the literature, many patients without hemophilia who underwent total knee arthroplasty experience only slight relief. Persistent postoperative pain for several years after surgery is observed in 44% of patients, while 15% of patients suffer from severe pain [26, 27]. This study is devoted to analysis of the incidence of postoperative acute and chronic pain in patients with hemophilia who underwent total knee arthroplasty, psychophysical and genetic risk factors associated with this phenomenon and assessing their real prognostic significance.

The aim of the study was to analyze the effect of functional genetic polymorphisms on psychophysical parameters in patients with hemophilia.

Material and methods

A prospective pilot study was performed at the National Medical Research Center of Hematology for the period from January 2018 to February 2019. There were 21 patients with hemophilia A and B. All patients underwent total knee arthroplasty for severe hemophilic arthropathy. Various parameters were assessed at several time points: preoperative day; day of surgery, 1st, 2nd and 3rd postoperative days, 10 days and 6 months after surgery. Examination included the following mandatory stages: questionnaire, algometry (testing for pain threshold and pain tolerance), assessment of intraoperative and postoperative need for analgesics, blood sampling with subsequent genetic examination, analysis of long-term outcomes. A questionnaire (over 40 questions) was conducted on the day before surgery to determine various characteristics of pain and psychosocial sphere. Pain intensity was assessed within 3 days after surgery using 10-point numeric rating scale (NRS). Some parameters were also evaluated in 10 days after surgery. Telephone interviewing after 6 months was carried out to determine long-term results and identify patients with chronic pain syndrome.

Inclusion criteria:

1. Severe hemophilia type A or B.
2. Age 25-45 years.
3. Male gender.
4. Total knee arthroplasty is performed for the first time.
5. Unilateral total knee arthroplasty.
6. Total knee arthroplasty under endotracheal anesthesia.
7. Caucasian race (in order to avoid inaccuracies in genetic analysis).
8. The same scheme of intraoperative and postoperative anesthesia and analgesia in all patients.
9. Signed informed consent.

Exclusion criteria:

1. Failure to meet the inclusion criteria.
2. Concomitant disease accompanied by pain syndrome: any other diagnosis, except for hemophilic arthropathy (diabetes mellitus, connective tissue diseases, inflammatory diseases).
3. Chronic opioid addiction.
4. Any mental disorders, dementia, delirium, or any other cognitive disorders impairing cooperation with patients.
5. Exploration or any knee surgery that is not primary unilateral total knee arthroplasty.
6. More than one previous large joint arthroplasty.

7. Over three previous surgical interventions.
8. Severe infectious complications, uncontrolled by adequate antibacterial, antifungal and antiviral therapy.
9. Severe multiple organ failure.
10. Patients who did not sign informed consent.

Surgical technique

All procedures were carried out by surgical team of the department of reconstructive orthopedics for patients with hemophilia at the National Medical Research Center of Hematology. They applied the same technology. Indications for total knee arthroplasty were carefully established for each patient. These indications included severe chronic pain and functional impairment in knee joint.

Analgesia and anesthesia

Surgery was performed under endotracheal anesthesia. All patients received opioid and non-opioid analgesics in intraoperative and postoperative period. An amount of administered opioid analgesic (fentanyl) in intraoperative period was taken into account. On the first day after surgery, opioid analgesic (morphine) was administered using patient-controlled analgesia (PCA).

Surgical intervention was performed in compliance with the following stages: midline incision on anterior surface of the knee joint; dissection of skin and subcutaneous fatty tissue in layer-by-layer fashion, medial arthrotomy; total arthroplasty using bone cement for fixation of the components. A mandatory stage was wound drainage due to possible hemorrhagic complications.

Pain intensity assessment

Pain syndrome and its psychosocial effect were analyzed using international questionnaires. We used 10-point numeric rating scale: 0 — no pain, 10 — the most severe pain imaginable. Patients filled the McGill pain questionnaire characterizing sensory and affective components of pain syndrome; Von Korff questionnaire (pain syndrome intensity, as well as social maladjustment grade); WOMAC — knee pain, stiffness and functionality questionnaire; LANSS — questionnaire for neuropathic pain [28–31]. We also used the questionnaires for assessing the influence of pain on sleep, anxiety, depression, fatigue, stress — (PSS, Perceived Stress Scale; FSS, Fatigue Severity Scale; PCS, The Pain Catastrophizing Scale). We also assessed pain threshold and pain tolerance by pressure (tensalgometry). Mechanical force (pressure) was delivered using algometer. Bilateral compression points were localized on the trapezius muscle in the upper back approximately 5 cm lateral to CVIII spinous processes. We considered pressure associated with feeling of pain rather pressure (pain threshold), pressure associated with unbearable pain or maximum pressure range (20 kg) (pain tolerance). This test was performed before surgery [32, 33].

Genetic survey

A single blood sampling in a test tube with EDTA (ethylenediaminetetraacetate) was carried out in order to analyze functional genetic polymorphisms in three genes: rs4818 and rs4680 in *COMT* (catechol-O-methyltransferase), rs1799971 in *OPRM1* (mu-opioid receptor460) and rs6746030 in *SCN9A* (α-subunit of the voltage-gated sodium channel Nav1.7).

DNA was harvested from nuclear cells of peripheral blood after selective lysis of erythrocytes in 0.8% ammonium chloride solution in accordance with the standard procedure. The last one included exposure to sodium dodecyl sulfate (0.5%) and proteinase K (200 μg/ml) for 16-18 hours at 37°C or 2 hours at 65° C followed by phenolic extraction.

For genotyping of patients by functional SNPs, we used amplification in the PCR Master Mix system (Thermo Scientific, USA) with 0.01-0.02 μg of genomic DNA and 10 pmol of each primer **(Table 1)** under the following conditions: 94°C — 1 min, 62°C — 1 min, 72°C — 3 min (30 cycles). Oligonucleotide primers were synthesized at the Syntol CJSC (Russia).

Genotyping of rs1799971 polymorphism in the *OPRM1* gene was carried out considering the results of amplification product hydrolysis with restriction endonuclease *Taq I*. A recognition site for this enzyme was created using a primer. The PCR fragment (165 nucleotide pairs) formed in this system either remained intact (if the polymorphic locus had nucleotide A) or disintegrated into the fragments of 144 and 21 nucleotide pairs (if the polymorphic locus had nucleotide G) after exposure to endonuclease *Taq I*. Genotyping of polymorphisms rs6746030 in the *SCN9A* gene, rs4818 and rs4680 in the *COMT* gene was carried out using Sanger sequencing data. PCR fragments for sequencing were purified in Wizard columns (Promega, USA).

PCR and restriction hydrolysis products were visualized in ultraviolet light after separation by electrophoresis in 6% polyacrylamide gel (PAGE) and staining with ethidium bromide.

Sequencing was carried out at the Center for Shared Use "Genome" of the Engelhardt Institute of Molecular Biology (Moscow) using the BigDye Terminator v.3.1 reagent kit (Applied Biosystems, USA). Subsequent analysis of reaction products was performed using ABI PRISM 3100Avant automatic sequencer (Applied Biosystems, USA).

Genotyping data were compared with questionnaire data, psychophysical parameters.

Table 1. **Oligonucleotide primers used in the study**

Gene	SNP	Primer	5'-3'-sequence
COMT	rs4818*	COMTdd	CACCTCTCCTCCGTCCCCAA
	rs4680	COMTR	CAGGCATGCACACCTTGTCCTTCG
OPRM1	rs1799971	OPRMd	CAACTTGTCCCACTTAGATGt**
		OPRMr	CCGAAGAGCCCCACCACGCA
SCN9A	rs6746030	SCNd	GGTTGAGGGAGTATCACAGA
		SCNr	GAGCAGGATCATGAGGACAA

Note. * — Accession number in the dbSNP database; ** — lowercase letter indicates the nucleotide changed to form a restriction endonuclease recognition site.

Statistical analysis

Psychophysical parameters were analyzed using STATISTICA 8.0 software package (StatSoft, Inc., USA). All tests were two-sided at a significance level of α=0.05. Distribution of all parameters significantly deviated from the normal one (Kolmogorov-Smirnov test and Shapiro-Wilk's *W* test, p>0.05). In this regard, median, minimum and maximum values were used in descriptive statistics. Mann — Whitney *U*-test or Kruskal — Wallis ANOVA test was used to compare groups of patients with different genotypes. This study had a pilot design. Therefore, we did not correct significance level for multiple pairwise comparisons.

Exact test for deviation from Hardy-Weinberg equilibrium was performed for all polymorphisms in software environment R (34 R Core Team (2019) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) [34] using "genetics" package. Linkage disequilibrium (LD) D 'test was additionally performed for SNPs in the *COMT* gene since they are close together. For all the studied polymorphisms, codominant inheritance and additive model of genotype-to-phenotype influence have been shown [10-13, 15, 17]. Therefore, we did not consider dominant and recessive models.

Results

Descriptive statistics of polymorphisms in the *COMT*, *OPRM1* and *SCN9A* genes is shown in **Table 2**. Analysis of genotype incidences in hemophilia patients showed that homozygous CC genotype in the polymorphic locus rs4818 of the *COMT* gene was found in 57.1% of cases, heterozygous CG genotype — 28.6% of cases, homozygous GG genotype — in 14,3% of cases. In another polymorphic locus rs4680 of the *COMT* gene, heterozygous AG genotype was the most common (42.8%), while homozygous genotypes AA and GG were found with the same incidence (28.6%) **(Table 2)**. In the polymorphic locus rs6746030 of the *SCN9A* gene, homozygous GG genotype was found in 83.3% of cases, heterozygous AG genotype — 16.7% of cases, homozygous AA genotype was absent. In the polymorphic locus rs1799971 of the *OPRM1* gene, homozygous AA genotype was the most common (76.2%), heterozygous AG genotype — 23.8% of cases, homozygous GG genotype was not detected **(Table 2)**. None of the polymorphisms significantly deviated from the Hardy — Weinberg equilibrium state. Linkage disequilibrium test showed a significant linkage between rs4818 and rs4680 (99.9%). However, this may also be associated with a significant predominance of major homozygous genotypes in our sample.

There were no significant differences between the phenotypic characteristics in hemophilia patients with different alleles of polymorphic loci in the *COMT* gene (p>0.05).

Patients with heterozygous *SCN9A* gene (AG) and similar intraoperative and postoperative consumption of analgesics had significantly lower pain severity according to NRS scale within 3 days after surgery (p<0.05). In particular, patients with homozygous carriage (GG) experienced moderate-to-severe pain syndrome (NRS score 3—7). Patients with heterozygous carriage (AG) had mild pain syndrome (NRS score 1—5) **(Table 3)**.

Patients with hemophilia and genotypes AA and AG in the *OPRM1* gene were characterized by similar intraoperative and postoperative consumption of narcotic analgesics and NRS score of pain syndrome (p>0.05; **Table 3**). However, hemophilia patients with AG genotype in the *OPRM1* gene experienced more intense pain according to McGill scale, overexertion and stress according to PSS scale in comparison with carriers of homozygous AA genotype (p<0.05). Moreover, these patients had significantly lower SF-36 scores (physical and mental health, vital activity) and FSS score (fatigue level) (p<0.05). Patients with AG genotype had more severe pain syndrome according to McGill scale and lower quality of sleep within 10 days after surgery (p<0.05).

Consumption of narcotic analgesics was similar in patients with different genotypes and approximately the same duration of surgery and intraoperative blood loss. However, similar intraoperative and postoperative consumption of analgesics was associated with different scores of pain syndrome.

Chronic postoperative pain (CPP) was observed in 3 out of 21 patients with hemophilia after total knee arthroplasty. Approximately the same intraoperative and postoperative consumption of opioids (fentanyl 0.6 mg and morphine 20 mg) was associated with more severe pain syndrome in patients with chronic postoperative pain within 3 days after surgery **(Table 4)**. Thus, CPP patients had extremely severe pain syndrome within the first postoperative day (NRS score 10) compared to the patients without CPP after knee replacement (NRS score 4—8 on the 1st postoperative day). On the 3rd postoperative day, pain severity was similar in all patients. At the same time,

Table 2. **Descriptive statistics of polymorphisms in the COMT, OPRM1, and SCN9A genes**

Gene	SNP	Chromosome	Genotype	*n* (%)	Minor allele, incidence	HWE*, *p*
COMT	rs4818	22	CC	12 (57,1)	G, 0,34	0,29
—	—	—	CG	6 (28,6)	—	—
—	—	—	GG	3 (14,3)	—	—
COMT	rs4680	22	GG	6 (28,6)	A, 0,46	0,65
—	—	—	AG	9 (42,8)	—	—
—	—	—	AA	6 (28,6)	—	—
OPRM1	rs1799971	6	AA	16 (76,2)	G, 0,19	1
—	—	—	AG	5 (23,8)	—	—
—	—	—	GG	0	—	—
SCN9A	rs6746030	2	GG	18 (85,7)	A, 0,12	1
—	—	—	AG	3 (14,3)	—	—
—	—	—	AA	0	—	—

Note. * — test for deviation from the Hardy-Weinberg equilibrium and *p*-value.

Table 3. **Phenotypic characteristics of patients with hemophilia and various genotypes of polymorphisms in the COMT, OPRM1 and SCN9A genes**

PSS scores	OPRM1 AA (*n*=16)	OPRM1 AG (*n*=5)	SCN9A GG (*n*=18)	SCN9A AG (*n*=3)	COMT rs4818 CC (*n*=12)	COMT rs4818 CG (*n*=6)	COMT rs4818 GG (*n*=3)	COMT rs4680 GG (*n*=6)	COMT rs4680 AG (*n*=9)	COMT rs4680 AA (*n*=6)
Surgery time, min	130 (90—205)	150 (120—170)	135 (95—185)	107 (90—205)	135 (90—185)	117,5 (95—205)	140 (130—150)	145 (100—205)	120 (95—160)	142,5 (90—170)
Intraoperative consumption of opioids (fentanyl), mg	0,6 (0,4—0,8)	0,7 (0,5—0,9)	0,6 (0,4—0,9)	0,5 (0,5—0,8)	0,65 (0,5—0,9)	0,5 (0,5—0,7)	0,7 (0,4—0,7)	0,6 (0,4—0,8)	0,6 (0,5—0,7)	0,7 (0,5—0,9)
Postoperative consumption of opioids (morphine), mg	20 (6,6—40)	20 (6,6—20)	20 (6,6—40)	20 (20—23,3)	20 (6,6—23,3)	21,65 (6,6—40)	20 (6,6—23,3)	21,65 (6,6—40)	20 (6,6—23,3)	20 (6,6—23,3)
Blood loss, ml	375 (175—1150)	650 (150—1150)	400 (150—1150)	200 (175—350)	400 (175—1150)	350 (150—650)	400 (200—600)	375 (200—1150)	400 (150—650)	425 (175—1150)
Drainage output within a day after surgery, ml	455 (200—900)	300 (150—650)	425 (150—900)	460 (250—650)	430 (200—900)	350 (150—650)	510 (280—770)	365 (200—770)	550 (150—900)	430 (260—650)
Hemoglobin, g/l	154,5 (121—200)	150 (134—180)	154,5 (121—200)	135 (134—157)	158 (134—200)	145 (134—165)	129 (121—149)	142 (121—167)	154 (134—200)	158 (134—180)
White blood cells, thousand/µl	7,15 (4,8—35)	6,7 (4—9)	6,8 (4—35)	16 (4,8—19)	7,545 (4—35)	6,45 (4,8—9,5)	7,4 (6,4—8,4)	7,795 (4,8—9,5)	6,7 (4,8—35)	7,15 (4—19)
Platelets, thousand/µl	292 (169—877)	159 (148—447)	265,5 (148—877)	232 (207—291)	216 (148—409)	323 (159—877)	300 (220—322)	311 (220—877)	293 (159—447)	207,5 (148—232)
Glucose, mmol/l	5,55 (5—9,4)	6 (5—6,3)	5,55 (5—9,4)	5,7 (5,4—6,4)	5,55 (5—9,4)	5,85 (5—6,3)	5,2 (5—6,1)	5,65 (5—6,2)	5,5 (5—9,4)	6,05 (5—6,4)
Lactate, mmol/l	1,5 (0,9—2,8)	1,8 (1,4—2,1)	1,65 (0,9—2,8)	1,2 (1,2—1,5)	1,7 (1,2—2,8)	1,6 (1,2—1,7)	1,1 (0,9—1,4)	1,3 (0,9—2,3)	1,6 (1,4—2,6)	1,8 (1,2—2,8)
PH	7,37 (7,3—7,5)	7,4 (7,3—7,4)	7,37 (7,3—7,5)	7,4 (7,4—7,4)	7,4 (7,3—7,4)	7,385 (7,3—7,4)	7,3 (7,3—7,5)	7,335 (7,3—7,5)	7,37 (7,3—7,4)	7,4 (7,3—7,4)
NRS score within the first postoperative day	6,5 (2—10)	4 (3—5)	5 (3—10)*	5 (2—5) *	5 (2—9)	5 (3—10)	5 (*n*=1)**	7 (5—10)	5 (7,3—7,4)	5 (2—8)
	6 (1—10)	4,5 (3—6)	6 (3—10)*	2 (1—4)*	5 (2—9)	6 (1—10)	5 (*n*=1)	7 (1—9)	6 (3—10)	4 (2—8)
	7 (2—10)	4,5 (3—7)	7 (3—10)*	3 (2—4)*	6 (2—10)	5 (3—10)	6 (*n*=1)	7,5 (3—9)	5 (4—10)	4 (2—10)
NRS score within the second postoperative day	5,5 (2—10)	5,5 (4—7)	6 (4—10)*	3 (2—4)*	5 (3—9)	7 (2—10)	7 (*n*=1)	8 (2—9)	5 (3—10)	5 (3—6)
	5 (2—7)	6 (5—7)	6 (3—7)*	2 (2—3)*	5,5 (2—7)	7 (2—7)	5 (*n*=1)	5 (2—7)	6,5 (4—10)	5 (2—6)
	5 (0—8)	5 (4—6)	5 (0—8)*	2 (2—3)*	4,5 (0—8)	5 (2—6)	7 (*n*=1)	6 (2—7)	5 (3—7)	4 (2—6)
	4 (2—8)	6 (5—7)	6 (3—8)*	2 (2—2)*	5,5 (2—8)	5 (2—7)	4 (*n*=1)	4 (2—6)	5 (0—8)	6 (2—8)
NRS score within the third postoperative day	5 (1—10)	6 (6—6)	6 (2—10)*	1 (1—2)*	5,5 (1—10)	6 (1—6)	5 (*n*=1)	5 (1—5)	6 (3—7)	6 (1—6)
	5 (1—8)	4 (4—6)	5 (3—8)*	1 (1—2)*	4,5 (1—8)	5 (1—6)	6 (*n*=1)	6 (1—6)	5 (2—10)	4 (1—6)
	5 (1—8)	4 (4—4)	5 (3—8)*	1 (1—2)*	4 (1—8)	4 (1—5)	5 (*n*=1)	5 (1—5)	4,5 (3—8)	4 (1—6)
	3 (0—8)	3 (3—4)	3 (0—8)*	2 (1—2)*	3 (0—8)	3 (1—4)	5 (*n*=1)	5 (1—6)	3 (3—8)	3 (2—8)
LANSS score	11 (0—21)	16 (1—17)	11 (1—19)	14 (0—21)	12 (1—21)	10 (0—17)	6 (*n*=1)	6 (0—13)	10,5 (0—4)	16 (1—21)
McGill scores										
Sum of sensory applicable descriptors	5 (1—13)	13 (8—14)	8 (1—14)	5 (1—13)	6 (1—13)	13 (1—14)	10 (*n*=1)	13 (10—13)	4,5 (5—17)	5 (1—13)
Sensory pain rank index	6 (1—31)*	28 (21—36)*	19 (1—36)	6 (3—31)	10 (1—28)	31 (1—36)	19 (*n*=1)	19 (19—31)	9 (1—14)	6 (2—28)

Continuation of Table 3. see on the next page.

Table 3. **Phenotypic characteristics of patients with hemophilia and various genotypes of polymorphisms in the COMT, OPRM1 and SCN9A genes**

PSS scores	OPRM1 AA (*n*=16)	OPRM1 AG (*n*=5)	SCN9A GG (*n*=18)	SCN9A AG (*n*=3)	COMT rs4818 CC (*n*=12)	COMT rs4818 CG (*n*=6)	COMT rs4818 GG (*n*=3)	COMT rs4680 GG (*n*=6)	COMT rs4680 AG (*n*=9)	COMT rs4680 AA (*n*=6)
Sum of affective applicable descriptors	5 (1—6)	5 (5—6)	5 (1—6)	5 (5—5)	5 (1—6)	5 (1—5)	4 (*n*=1)	5 (4—6)	3,5 (1—36)	5 (1—6)
Affective pain rank index	7 (1—13)	9 (8—9)	7 (1—11)	12 (6—13)	8 (1—13)	8 (3—12)	7 (*n*=1)	10 (7—12)	5 (1—5)	9 (1—13)
Total sum of applicable descriptors	10 (2—19)	19 (13—19)	13 (2—19)	10 (6—18)	11 (2—19)	18 (2—19)	14 (*n*=1)	18 (14—19)	7,5 (1—11)	10 (2—19)
Total pain rank index	16 (3—43)*	37 (30—44)*	26 (3—44)	16 (12—43)	20,5 (3—37)	43 (4—44)	26 (*n*=1)	29 (26—43)	15 (2—19)	16 (3—37)
Von Korff scores										
Pain intensity score	12 (4—21)	15 (10—19)	14,5 (5—21)	6,5 (4—9)	13 (5—21)	11 (4—15)	16 (*n*=1)	10 (4—16)	14,5 (4—44)	11 (9—19)
Social maladjustment, scores	7 (0—20)	14 (9—20)	9,5 (0—20)	4 (4—4)	8,5 (4—20)	4 (0—14)	20 (*n*=1)	12 (4—20)	7,5 (5—21)	9,5 (4—20)
Duration of disability, days	10 (3—100)	7 (7—180)	7 (3—180)	12,5 (10—15)	8,5 (3—180)	7 (5—10)	100 (*n*=1)	55 (10—100)	6 (0—17)	12,5 (7—180)
WOMAC scores										
Pain intensity	5 (3—9)	8 (7—11)	7,5 (3—11)	5,5 (4—7)	6 (3—8)	9 (4—11)	9 (*n*=1)	6,5 (4—9)	5 (3—50)	7,5 (7—8)
Stiffness	4 (3—6)	5 (4—6)	4 (3—6)	3,5 (3—4)	4 (3—6)	4 (4—5)	3 (*n*=1)	3,5 (3—4)	4 (3—11)	4,5 (3—6)
Knee joint function	14 (5—21)	28 (16—46)	17,5 (5—46)	13 (9—17)	18 (9—46)	9 (5—28)	14 (*n*=1)	11,5 (9—14)	16,5 (3—6)	18 (16—46)
Physical health	52,5 (25—75)*	25 (5—35)*	50 (5—75)	25 (*n*=1)	50 (5—75)	25 (25—65)	55 (*n*=1)	40 (25—55)	57,5 (5—28)	35 (5—50)
Role activity determined by physical health	62,5 (0—100)	25 (0—75)	37,5 (0—100)	75 (*n*=1)	50 (0—100)	75 (25—100)	0 (*n*=1)	37,5 (0—75)	62,5 (25—75)	0 (0—75)
Pain intensity	52 (22—90)	32 (20—45)	45 (20—90)	77 (*n*=1)	45 (20—90)	57 (32—77)	22 (*n*=1)	49,5 (22—77)	52 (0—100)	45 (20—45)
General health	65 (25—80)	45 (35—80)	65 (35—80)	25 (*n*=1)	55 (45—80)	35 (25—80)	75 (*n*=1)	50 (25—75)	65 (32—90)	55 (45—80)
Vital activity	70 (55—80)*	50 (20—50)*	62,5 (20—80)	65 (*n*=1)	60 (20—80)	65 (50—75)	80 (*n*=1)	72,5 (65—80)	70 (35—80)	50 (20—55)
Social activity	81 (50—100)	62 (37—75)	75 (37—100)	62 (*n*=1)	75 (50—87)	62 (37—100)	50 (*n*=1)	56 (50—62)	87 (50—80)	62 (50—75)
Role activity determined by emotional state	100 (0—100)	33 (33—66)	66 (0—100)	100 (*n*=1)	66 (0—100)	66 (33—100)	100 (*n*=1)	100 (100—100)	83 (37—100)	33 (0—66)
Mental health	74 (60—84)*	44 (36—64)*	68 (36—84)	64 (*n*=1)	64 (36—84)	64 (44—76)	72 (*n*=1)	68 (64—72)	78 (33—100)	64 (36—64)
HADS scores										
Anxiety	5 (2—10)	9 (4—11)	6 (2—11)	6,5 (4—9)	7 (2—11)	4 (4—9)	3 (*n*=1)	4 (3—9)	5 (44—84)	8 (4—11)
Depression	3 (1—13)	6 (0—8)	3 (0—8)	6 (2—13)	4,5 (0—13)	2 (1—8)	2 (*n*=1)	2 (2—7)	3 (2—10)	6 (0—13)
PSS scores										
Overexertion	13 (10—19)*	18 (16—21)*	16 (10—21)	13 (12—13)	16 (11—21)	12 (10—18)	11 (*n*=1)	11,5 (11—12)	14,5 (1—8)	16 (13—21)
Stress resistance	6 (4—9)*	10 (9—10)*	8 (4—10)	4,5 (4—5)	7,5 (4—10)	5 (4—10)	9 (*n*=1)	7 (5—9)	6,5 (10—19)	8,5 (4—10)

Continuation of Table 3. see on the next page.

Table 3. **Phenotypic characteristics of patients with hemophilia and various genotypes of polymorphisms in the COMT, OPRM1 and SCN9A genes**

PSS scores	OPRM1 AA (*n*=16)	OPRM1 AG (*n*=5)	SCN9A GG (*n*=18)	SCN9A AG (*n*=3)	COMT rs4818 CC (*n*=12)	COMT rs4818 CG (*n*=6)	COMT rs4818 GG (*n*=3)	COMT rs4680 GG (*n*=6)	COMT rs4680 AG (*n*=9)	COMT rs4680 AA (*n*=6)
Perceived stress score	19 (14—27)*	28 (25—31)*	23,5 (14—31)	16,5 (16—17)	23,5 (17—31)	16 (14—28)	20 (*n*=1)	18 (16—20)	21 (4—10)	24,5 (17—31)
FSS score	32 (15—63)*	21 (18—47)*	30 (15—48)	33 (31—63)	33 (21—63)	18 (15—31)	27 (*n*=1)	29 (27—31)	30 (14—28)	47 (21—63)
Pain catastrophizing score										
Hopelessness	4 (0—18)	4 (0—4)	4 (0—10)	11,5 (5—18)	4 (0—10)	4 (4—18)	0 (*n*=1)	9 (0—18)	4 (15—48)	4,5 (0—10)
Exaggeration	4 (0—9)	5 (1—6)	4,5 (0—9)	5 (2—8)	5 (0—9)	5 (1—8)	0 (*n*=1)	4 (0—8)	4,5 (1—6)	4 (1—7)
Permanent thinking	3 (0—12)	4 (0—7)	3 (0—12)	4,5 (3—6)	3,5 (0—12)	6 (2—7)	0 (*n*=1)	3 (0—6)	4 (0—9)	3,5 (0—12)
Sleep quality	15 (12—21)	18 (14—18)	15 (12—19)	15 (12—21)	14,5 (12—21)	16 (15—18)	12 (*n*=1)	15 (12—19)	14,5 (6—19)	15 (12—21)
Algometry										
Pain threshold	3 (1,8—4,5)	3,3 (2,4—3,9)	3 (1,8—3,9)	3,3 (2,7—4,5)	2,85 (1,8—3,9)	3,5 (3,3—4,5)	2,1 (*n*=1)	3,2 (2,1—4,5)	3,15 (12—19)	2,7 (2,4—3,9)
Pain tolerance	3,8 (2,5—6,8)	3,7 (3,2—4,6)	3,8 (2,5—5,8)	3,5 (3,5—6,8)	3,65 (2,5—5,8)	4,5 (3,7—6,8)	2,5 (*n*=1)	4,2 (2,5—6,8)	3,9 (1,8—3,5)	3,5 (3,1—4,6)
LANSS score in 10 days after surgery	7,5 (5—17)	14 (2—16)	10 (2—17)	6 (*n*=1)	6 (2—14)	16 (6—17)	9 (*n*=1)	7,5 (6—9)	9 (5—17)	11 (2—14)
McGill scores in 10 days after surgery										
Sum of sensory applicable descriptors	2,5 (1—13)*	10 (8—13)*	3,5 (1—13)	13 (*n*=1)	4 (1—13)	10 (1—13)	1 (*n*=1)	7 (1—13)	3,5 (5—17)	8 (2—13)
Sensory pain rank index	3 (2—30)	21 (11—28)	3,5 (2—28)	30 (*n*=1)	3 (2—28)	11 (2—30)	4 (*n*=1)	17 (4—30)	3 (1—10)	21 (2—28)
Sum of affective applicable descriptors	1,5 (1—6)	5 (2—6)	2 (1—6)	6 (*n*=1)	2 (1—6)	2 (1—6)	2 (*n*=1)	4 (2—6)	1,5 (2—11)	5 (1—6)
Affective pain rank index	3 (1—11)	9 (2—9)	3 (1—9)	11 (*n*=1)	3 (1—9)	3 (2—11)	2 (*n*=1)	6,5 (2—11)	3 (1—3)	9 (1—9)
Total sum of applicable descriptors	2,5 (2—19)*	13 (12—19)*	3 (2—19)	19 (*n*=1)	3 (2—19)	12 (2—19)	2 (*n*=1)	10,5 (2—19)	2,5 (2—3)	13 (3—19)
Total pain rank index	5 (3—41)	30 (13—37)	5,5 (3—37)	41 (*n*=1)	5 (3—37)	13 (5—41)	6 (*n*=1)	23,5 (6—41)	5 (2—12)	30 (3—37)
HADS scores in 10 days after surgery										
Anxiety	9 (2—12)	4 (2—11)	9 (2—12)	4 (*n*=1)	10 (2—12)	4 (2—9)	2 (*n*=1)	4 (2—9)	8,5 (3—14)	11 (4—12)
Depression	7 (1—10)	4 (0—6)	6 (0—10)	2 (*n*=1)	7 (0—10)	4 (2—4)	2 (*n*=1)	2 (2—7)	5,5 (2—12)	6 (0—10)
Sleep quality	19 (15—21)*	14 (14—17)*	18 (14—21)	20 (*n*=1)	19 (14—21)	18 (17—20)	15 (*n*=1)	19 (15—20)	18,5 (1—9)	14 (14—19)

Note. * — $p<0,05$, Mann-Whitney test; ** — data for only one patient were obtained, and statistical analysis is impossible.

Table 4. **Phenotypic and genotypic characteristics of patients with hemophilia undergoing total knee replacement**

Variable	Patients without CPP (*n*=18)	Patients with CPP (*n*=3)
Age, years	37,5 (25—48)	37 (30—43)
Genotypes rs1799971, OPRM1	AA, AG	AA
Genotypes rs6746030, SCN9A	GG, GA	GG
Genotypes rs4818, COMT	CC, CG, GG	CC, CG, GG
Genotypes rs4680, COMT	AA, AG, GG	AA, AG, GG
Surgery time, min	130 (90—205)	140 (115—145)
Postoperative opioid consumption (morphine), mg	20 (6,6—40)	20 (20—23,3)
Blood loss, ml	375 (150—1150)	400 (300—500)
Drainage output within the first postoperative day, ml	425 (150—900)	510 (400—550)
Hemoglobin, g/l	152 (121—200)	155 (149—159)
White blood cells, thousand/μl	7,15 (4—35)	6,1 (5,9—8,4)
Platelets, thousand/μl	261,5 (148—877)	238 (224—300)
PH	7,39 (7,3—7,4)	7,4 (7,34—7,5)
Glucose, mmol/l	5,65 (5—9,4)	5,5 (5,2—6,1)
Lactate, mmol/l	1,55 (0,9—2,6)	1,7 (1,1—2,8)
NRS score within the first postoperative day	5 (2—10)	9 (8—10)
	5 (1—9)	9 (8—10)
	5 (2—9)*	10 (10—10)*
NRS score within the second postoperative day	5 (2—9)	8 (6—10)
	5 (2—7)	6,5 (6—7)
	4,5 (0—8)	5,5 (5—6)
	4,5 (2—7)*	7,5 (7—8)*
NRS score within the third postoperative day	5 (1—10)	6 (6—6)
	4,5 (1—8)	5,5 (5—6)
	4 (1—8)	5,5 (5—6)
	3 (0—6)	5,5 (3—8)
McGill scores		
Sum of sensory applicable descriptors	9 (1—14)	1 (1—1)
Sensory pain rank index	19 (1—36)	1,5 (1—2)
Sum of affective applicable descriptors	5 (1—6)*	1 (1—1)*
Affective pain rank index	8,5 (1—13)	2 (1—3)
Total sum of applicable descriptors	13,5 (3—19)*	2 (2—2)*
Total pain rank index	27,5 (4—44)*	3,5 (3—4)*
LANSS score	11 (0—21)	14,5 (10—19)
Von Korff scores		
Pain intensity score	14,5 (4—21)	11,5 (11—12)
Duration of disability, days	8,5 (3—180)	7,5 (5—10)
Social maladjustment, scores	8,5 (4—20)	5 (0—10)
WOMAC scores		
Pain intensity	6 (3—11)	8,5 (8—9)
Stiffness	4 (3—6)	4,5 (4—5)
Knee joint function	16,5 (9—46)	12 (5—19)
Physical health	45 (5—75)	57,5 (50—65)
Role activity determined by physical health	50 (0—100)	50 (0—100)
Pain intensity	45 (20—90)	51 (45—57)
General health	55 (25—80)	67,5 (55—80)
Vital activity	65 (20—80)	65 (55—75)
Social activity	75 (37—87)	75 (50—100)
Role activity determined by emotional state	100 (33—100)	33 (0—66)
Mental health	64 (36—84)	70 (64—76)
HADS scores		
Anxiety	6 (2—11)	5,5 (4—7)
Depression	4,5 (0—13)	1,5 (1—2)
PSS scores		
Overexertion	13 (11—21)	13 (10—16)
Stress resistance	7,5 (4—10)	6 (4—8)

Continuation of Table 4. see on the next page.

Table 4. **Phenotypic and genotypic characteristics of patients with hemophilia undergoing total knee replacement**

Variable	Patients without CPP (n=18)	Patients with CPP (n=3)
Perceived stress score	21,5 (16—31)	19 (14—24)
FSS score	31 (18—63)	31 (15—47)
Pain catastrophizing score		
Permanent thinking, score	3,5 (0—7)	7 (2—12)
Exaggeration, scores	4,5 (0—9)	4 (1—7)
Hopelessness, scores	4 (0—18)	7 (4—10)
Sleep quality, score	14,5 (12—21)	15,5 (15—16)
Algometry		
Pain threshold	3,1 (1,8—4,5)	3 (2,5—3,5)
Pain tolerance	3,75 (2,5—6,8)	3,8 (3,1—4,5)
LANSS score in 10 days after surgery	6 (2—16)	14 (11—17)
McGill score in 10 days after surgery		
Sum of sensory applicable descriptors	4 (1—13)	1,5 (1—2)
Sensory pain rank index	11 (2—30)	2 (2—2)
Sum of affective applicable descriptors	2 (1—6)	1 (1—1)
Affective pain rank index	3 (2—11)	2 (1—3)
Total sum of applicable descriptors	6 (2—19)	2,5 (2—3)
Total pain rank index	13 (3—41)	4 (3—5)
HADS score in 10 days after surgery		
Anxiety	6 (2—12)	10,5 (9—12)
Depression	5 (0—9)	7 (4—10)
Sleep quality in 10 days after surgery, score	18,5 (14—21)	18,5 (18—19)

Note. * — p<0,05, Mann-Whitney test.

CPP patients demonstrated more severe pain syndrome in preoperative period according to the McGill scale. Pain thresholds and pain tolerance were approximately the same in both groups. Preoperative LANSS score was similar. However, re-assessment after 10 days showed a slightly increased value. Thus, preoperative score was 11 (5—15) in patients without CPP, in 10 days after surgery — 6 (5—12) points by the neuropathic pain scale. In patients with CPP this value remained intact (14 points) that points to neuropathic pain. There were no other between-group differences (Table 4). There were no between-group differences in Von Korff scores (duration of disability and social maladjustment) and WOMAC scores (similar stiffness and dysfunction of the knee joint). There were no significant between-group differences in HADS scores (anxiety and depression). Normal and borderline psychological states were recorded. Similar PSS scores were associated with a tendency towards an increased anxiety and depression in postoperative period. Overall FSS score <36 suggests no fatigue in a patient. Upon admission, overall score of sleep quality was 14. Some deterioration was noted (18 points) after 10 days. Nevertheless, these values are within the reference points (up to 19 points).

Discussion

According to the literature data, this study is the first research devoted to phenotypic profiles of hemophilia patients with different genotypes of polymorphisms in the *COMT*, *OPRM1* and *SCN9A* genes.

The basic premise was that genes can contribute to pain-related psychosocial (e.g., mood, sleep, and mimicking behavior) and psychophysical (different characteristics of pain sensation, pain threshold and pain tolerance) characteristics. Therefore, the totality of these characteristics can be considered as mean pain phenotypes in genetic pain studies.

The main hypothesis of this study was that genes and psychosocial factors can influence postoperative outcomes independently or in interaction with each other, as well as via interaction with environmental factors (e.g., demographic and clinical parameters). To confirm this hypothesis, we performed genotyping of patients for various genes associated with pain, analyzed clinical data, pain data (pain questionnaires and algometry), and psychosocial data of each patient.

Hemophilic arthropathy is accompanied by chronic pain syndrome that significantly impedes physical activity and reduces quality of life. Total knee arthroplasty is the only treatment for most people with hemophilia. Recent studies show that only 70% of patients after total knee arthroplasty for knee joint osteoarthritis (patients without hemophilia) are satisfied with postoperative outcome (normalized joint function and reduced pain syndrome). Other 30% of patients still experience pain syndrome and impaired joint function. In available literature, we did not find similar data for patients with hemophilia. According to our data, chronic pain occurred in 3 (14%) out of 21 patients after total knee arthroplasty.

It is known that various people can suffer different postoperative pain intensity, and different consumption of analgesics may be observed [4, 5, 25]. Pain sensitivity and analgesics consumption can depend on sociodemographic and genetic characteristics of patients, psychoemotional status, duration and characteristics of baseline pain syndrome, and previous surgeries. In routine practice, we are often unable to ensure adequate postoperative pain relief on demand due to inability to organize hourly monitoring and documentation of pain intensity, a lack of staff and inadequate training of staff. Preventive multimodal approach significantly improves these outcomes. However, risk of side effects of analgesics is increased if these drugs will be administered in standard daily doses in a patient with mild pain syndrome. These adverse events can significantly reduce patients' quality of life and their satisfaction with

postoperative pain relief, complicate early mobilization and increase duration and cost of treatment. In this regard, prediction of postoperative pain intensity and the need for analgesics considering individual pain sensitivity seems perspective. Probably, this could be valuable for selection of patients for surgical treatment, as well as development of differentiated protocols for intraoperative and postoperative pain relief, treatment and rehabilitation. For example, medication may be preferable in patients with high pain sensitivity. At the same time, advanced analgesic technologies will be advisable if surgery is inevitable. In case of low pain sensitivity, less aggressive and simple methods of postoperative analgesia will be desirable.

Analysis of postoperative pain shows that certain risk factors are correlated with pain. Recent studies have shown an importance of psychosocial, psychophysical and clinical factors affecting the development of chronic postoperative pain syndrome (chronic preoperative pain, depression, high body mass index, young age, female sex, X-ray signs of severe osteoarthritis) [28]. However, these factors do not explain all cases of "inadequate" pain syndrome.

Numerous studies have shown that pain severity is influenced by various genes controlling the functions of nociceptive sensory system [6, 8, 10, 12, 14, 18, 20, 28]. Presumably, contribution of genetic factors into formation of pain sensitivity is 25-50% [35, 36]. Some genetic variants alter occurrence, transmission and processing of nociceptive information or local availability of active analgesics and their pharmacodynamic effect. Each individual genetic variant has a moderate effect on pain perception, but together they form a variety of pain sensitivity in the world population [6]. Associations with CPP and different requirements for opioids are most often noted for the *COMT*, *OPRM1* and *SCN9A* genes [7-12].

COMT gene encodes the main degrading enzyme in metabolic pathways of catecholaminergic neurotransmitters. For this gene, associations between minor alleles, pain intensity and need for opioids were most often noted [7–12]. The most common polymorphisms in this gene are rs4680 and rs4818. Some authors found their joint contribution [7, 17, 19, 23]. However, we did not observe significant influence of the alleles c. 1947G>A (rs4680) and c. 408C>G (rs4818) on pain intensity and need for analgesics. Nevertheless, clear relationship with these polymorphisms has been previously found only in some reports [19, 20, 23]. Perhaps, *COMT* gene is involved in the development of not all types of pain.

M-opioid receptor (*OPRM1*) is the main target for endogenous and exogenous opioids. Therefore, functional polymorphisms in the encoding gene can cause different incidence, intensity or duration of chronic pain and response to opioids [15, 16]. In particular, minor allele G SNP rs1799971 has been shown to influence these parameters, especially increased pain intensity and need for opioids [37]. In this research, we did not find significant effect of minor G allele in the *OPRM1* gene on intraoperative and postoperative consumption of opioids and NRS score in patients with hemophilia. Carriers of this allele tended to have higher McGill score of pain syndrome, higher overexertion, perception and resistance to stress, worse physical and mental health, vitality, stress tolerance and sleep quality.

SCN9A gene encodes alpha subunits of closed sodium channel NaV1.7. This gene is responsible for human pain perception disturbances. Rare point-nonsense mutations cause a lifelong complete analgesia, while rare activating mutations cause severe pain. Thus, *SCN9A* gene mutations are associated with syndromes of decreased and increased pain perception [10]. In this study, we found significantly lower NRS scores within 3 days after surgery in the same intraoperative and postoperative consumption of analgesics in patients with heterozygous genotype in the *SCN9A* gene (AG, rs6746030). It has been previously shown that rs6746030 polymorphism is significantly associated with pain perception in various diseases. Clinical and experimental studies confirmed an additive effect model, i.e. AA genotype carriers experience the most severe pain while GG genotype carriers — the weakest pain syndrome [10, 13]. Nevertheless, an absolutely opposite effect was observed in this research that requires further study.

Consumption of opioids was similar in patients with different genotypes if surgery time and intraoperative blood loss were approximately the same. However, similar intraoperative and postoperative consumption of analgesics was accompanied by different pain scores. In this regard, intraoperative and postoperative pain scores should be considered for correction of analgesia. As a rule, non-opioid analgesics and adjuvants were used to enhance pain relief in these cases which could insignificantly change pain intensity.

According to the International Association for the Study of Pain (IASP), chronic pain lasts beyond the normal healing period, typically over 3–6 months [38]. One of the main differences from acute pain is difficult treatment of chronic pain. Chronic pain seriously influences quality of life (mood, daily activity, sleep, cognitive function, and social life). In this regard, it is very important to distinguish individual characteristics of patients who are at risk of such adverse effects of total knee arthroplasty.

In this study, chronic postoperative pain was observed in 3 out of 21 hemophilia patients after total knee arthroplasty. Postoperative pain within 3 days after surgery was more intense in patients with chronic pain despite similar intraoperative and postoperative opioid consumption. In these patients, a tendency to increased postoperative anxiety and depression was observed.

It should be noted that this study is the first one devoted to relationship between phenotypic and genotypic characteristics of pain in patients with hemophilia. However, there are some limitations of this study.

Research limitations

It is important to note the limitations of this study. These are small sample size and small number of genes. Small sample size is partially explained by small incidence of hemophilia. Probably, further research will identify new clinical and genetic factors associated with the risk of severe acute and chronic pain. These data will be valuable to create individual pain treatment regimens, develop of individual approach and reduce chronic pain.

Despite an inclusion of various psychosocial, psychophysical, genetic, clinical and demographic factors influencing pain perception, other unrecognized factors may be also essential. In particular, analysis of the determinants of chronic pain after total knee arthroplasty is difficult due to various environmental and personal factors which can influence pain syndrome over many months.

Another limitation is determined by potential deficiency of several factors in some patients. This event is extremely rare. However, more complex examination algorithm is required to diagnose and exclude these patients from the study.

Conclusion

Certain demographic, psychological, and clinical factors predict the development of pain after total knee arthroplasty. However, all spectrum of risk factors of chronic postoperative pain is currently unknown. There is a knowledge gap about genetic mechanisms underlying severe postoperative and/or chronic pain after standard surgery.

Influence of certain genes controlling functions of the components of nociceptive sensory system on pain syndrome is confirmed in patients with hemophilia. Each individual genetic variant has a moderate effect on pain perception. However, together they form a variety of pain sensitivity in the global population. Probably, analysis of *OPRM1* genotype can ensure more information about genetic predisposition to pain in patients with hemophilia compared to *COMT* and *SCN9A* genotypes and induce a differentiated approach to analgesic therapy. Influence of functional polymorphisms in the *COMT* and *SCN9A* genes on psychophysiological profile of pain requires additional studies with larger samples. Moreover, effects of other genes should also be studied, since different genetic factors can influence different types of pain.

According to this study, chronic postoperative pain syndrome occurs in 14% of patients with hemophilia who underwent total knee arthroplasty. Neuropathic postoperative pain and severe early postoperative pain may be predictors of chronic postoperative pain.

The authors declare no conflicts of interest.

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