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Original Article

Effect of gene polymorphism of COMT and OPRM1 on the preoperative pain sensitivity in patients with cancer

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Abstract: Objectives: To evaluate the effect of COMT and OPRM1 gene polymorphisms on the preoperative pain sensitivity in tumor patients. Methods: 300 cases of cancer patients undergoing elective surgery were included, and the Val158 Met loci of COMT gene and OPRM1 loci of A118 G gene were genotyped by PCR-RFLP. Pain threshold and pain tolerance threshold were measured using electrical stimulation to investigate the preoperative pain sensitivity in patients with different genotypes. Results: For the COMT gene, the pain threshold and pain tolerance threshold of patients with M allele both decreased (both $P < 0.001$); for PPRM1 gene, pain threshold and pain tolerance threshold of patients with G allele decreased (both $P < 0.001$). We also found that there was an interaction between the two genes. Conclusion: Gene polymorphisms of COMT and OPRM1 were correlated with the preoperative pain sensitivity of cancer patients. The patients with M allele of COMT and G allele of OPRM1 had higher preoperative pain sensitivity.

Keywords: Pain measurement, COMT, Opioid receptors; SNP, pre-operative care

Instruction

Surgery is an important therapeutic measure for cancer patients, but the sensitivity of preoperative pain has a significant effect on the cooperation in operation and quality of life after surgery [1]. Preoperative pain sensitivity has significant individual differences, which related to the genetic factors of patients [2]. Previous studies have shown that various genetic polymorphisms were correlated with pain sensitivity, such as KCNJ6 gene [3], opioid receptor μ1 gene [4], COMT gene [5], OPRM1 [6] and 5-serotonin receptor gene [7]. But the findings are inconsistent, and most studies only focused on the effect of a single gene, paying little attention to the combined roles of genes. Research confirmed that the impact of gene polymorphisms on the disease trait was minor, so the gene-gene interaction could achieve a more comprehensive understanding of the relationships between genetics and complex traits. Previous studies showed that, gene polymorphisms of OPRM1 and COMT were associated with pain sensitivity [5, 6]. Therefore, this study focused on the effects of OPRM1 and COMT polymorphisms on the preoperative pain sensitivity in cancer patients and the interactions between the two genes.

Materials and methods

The study was approved by the Medical Ethics Committee of Shengjing Hospital of China Medical University, and all patients had signed informed consent.

Case selection

300 cases of cancer patients undergoing surgery in the departments of oncology, gynecology or general surgery of Shengjing Hospital of China Medical University from February 2010 to December 2013 were selected, without previous surgery, aged from 22 to 57 years, with a mean age of 41.3±12.4 years old, including 218 cases of male and 82 cases of female. The mean body mass index (BMI) was 25kg/m^2; ASA grade: 178 cases of grade I, 122 cases of grade II. There were no history of smoking and alcohol abuse, no abnormity in liver and kidney

Table 1. Primer sequences and PCR products

SNPs	Primer sequence	PCR product	Annealing temperature	Endonuclease
Val158Met	upstream:5'-GGATGGTGGATTTCGCTCGC-3'	117	55	Bsh1236I
	downstream:5'CTGGTGGGGAGGACAAAGTGC-3'			
A118G	upstream:5'-GGTCAACqTGTCCCACTI'AGATCGC-3'	193	58	Bsh1236I
	downstream:5'-AATCACATACATGACCAGGAAGTTT-3'			

Table 2. Genotype and allele frequency of these two SNPs

SNPs	Genotype			Allele	
A118G	AA	AG	GG	A	G
	144 (48.0%)	114 (38.0%)	42 (14.0%)	0.67	0.33
V158M	VV	VM	MM	V	M
	138 (46.0%)	115 (38.3%)	47 (15.7%)	0.65	0.35

function, no history of diabetic, spiritual and neurological diseases, no complications of acute and chronic pain, no recent application of sedative and analgesic drugs.

Genetic testing

5 ml peripheral blood was collected before surgery and anticoagulated by EDTA; phenol-chloroform extraction method was used to extract DNA. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for the genotyping of Val158Met loci in COMT gene and A118G loci in OPRM1gene. PCR primer sequences and PCR-RFLP conditions were shown in **Table 1**.

Determination of the pain threshold and pain tolerance

Patients calmed for 10 min after burglary; using MEB-5100 type electric stimulator (Nihon Kohden Corporation, Japan), pain threshold and pain tolerance threshold were measured. Patients were in supine position, and the electrodes were fixed to the deltoid muscle of right upper arm; two electrodes were both 5 mm × 5 mm, with an electrode spacing of 1.5 cm, stimulation frequency of 50 Hz and pulse width of 0.5 ms [8]. Current intensity started from 0, increasing 0.2 mA each time; when gradually turning up the output current, we observed and inquired the reaction of the objects, and respectively recorded the current intensity when a slight tingling began and the pain cannot be tolerated (pain threshold and pain tolerance threshold). The test was repeated three times, with an interval of 3 min; the mean value was calculated.

Statistical analysis

SPSS 16.0 statistical software was used for analysis; Measurement data were presented as mean ± standard deviation (Mean ± SD); factorial analysis of two factors and three levels was performed; a weighted analysis of variance was performed between groups. Count data were compared using the chi-square test. Hardy-Weinberg equilibrium was tested by chi-square test. $P < 0.05$ was considered statistically significant.

Results

Hardy-Weinberg equilibrium test

Genotyping results of A118G and Val158Met were shown in **Table 2**; the distribution of genotypes was consistent with Hardy-Weinberg equilibrium (all $P > 0.05$).

Comparison of patients with different genotypes in general

According to different genotypes, the age, gender, BMI and other indicators were compared, and there were no significant differences between genotypes (**Table 3**).

Comparison of pain threshold and pain tolerance among different genotypes

For both OPRM1 and COMT genes, compared to wild homozygote, the pain threshold and pain tolerance threshold of mutant homozygote carriers were significantly lower (**Table 4**).

Gene-gene interaction analysis

Factorial analysis showed that there was an interaction between COMT gene and OPRM1 gene ($P < 0.05$). Patients with the two kinds of

Table 3. General comparison of different genotypes

Genotype	N	Sex (M/F)	Age (Year)	BMI (Kg/m^2)
OPRM1 gene				
AA	144	104/40	41.1±12.1	18.4±2.8
AG	114	85/29	40.8±12.0	18.2±2.4
GG	42	29/13	41.6±12.4	18.3±2.4
P value		0.122	0.887	0.433
COMT gene				
VV	138	106/32	40.9±11.9	18.1±2.7
VM	115	85/30	41.7±12.1	18.4±2.2
MM	47	32/15	41.4±12.2	18.2±2.1
P value		0.683	0.342	0.338

Table 4. Comparison of pain threshold and pain tolerance among different genotypes

Genotype	N	Pain threshold (Mean ± SD, mA)	Pain tolerance (Mean ± SD, mA)
OPRM1 gene			
AA	144	2.2±0.8	5.4±1.2
AG	114	1.6±0.7	4.3±1.1
GG	42	1.5±0.6	4.2±1.4
P value		< 0.001	< 0.001
COMT gene			
VV	138	2.1±0.7	5.4±1.2
VM	115	1.5±0.8	4.4±1.0
MM	47	1.4±0.6	4.3±0.9
P value		< 0.001	< 0.001

mutant alleles had a more significant decrease in the pain threshold and pain tolerance threshold (**Table 5**).

Discussion

The study found that, polymorphisms of OPRM1 gene and COMT gene were correlated with pain sensitivity in cancer patients, and there was an interaction between the two genes.

Although pain threshold and pain tolerance threshold have different forming mechanisms and asynchronous changes, they are both the specific and sensitive indicators of pain sensitivity in clinical, which can accurately reflect the changes in pain sensitivity [9]. Continuous electrical stimulation at the same point in the deltoid muscle can objectively assess the body's pain threshold and pain tolerance threshold [9]; therefore this study chose to stimulate the central part of the deltoid muscle of right forearm and used electrical stimulator to assess the preoperative pain threshold and pain tolerance threshold, thus ensuring the reliability of the observed indicators.

Table 5. Interaction analysis between OPRM1 and COMT genes

Genotype combinations	N	Pain threshold	Pain tolerance
AA-VV	74	2.3±0.9	5.5±1.3
AA-VM	44	2.2±1.0	5.4±1.2
AA-MM	26	2.0±1.1	5.0±1.1
AG-VV	51	2.2±0.9	5.3±1.2
AG-VM	49	1.7±0.9	4.5±1.3*
AG-MM	14	1.6±0.9*	4.4±1.2*
GG-VV	13	2.0±0.9	4.8±1.6
GG-VM	22	1.6±0.8*	4.4±1.2*
GG-MM	7	1.5±0.8*	4.3±1.2*

*$P < 0.05$, compared to AA-VV group.

Factorial analysis showed that there was a interaction between polymorphisms of COMT gene and OPRM1 in pain sensitivity; one factor was fixed in the further weighted analysis of variance, and the difference of another factor between different levels was analyzed, indicating that pain sensitivity was increased in mutant homozygote group and the pain sensitivity of patients carrying mutations in both alleles increased more apparent.

Some studies showed that GOMT-V158M gene affected the pain by changing COMT activity and regulating psychology, stress and other factors [10-11]. Studies have also indicated that with respect to COMT single nucleotide polymorphism, low activity state of COMT was an important regulator of pain sensitivity [12, 13]. But the factors that affect the state of COMT activity are various; on the COMT gene, the polymorphisms of multiple loci may affect COMT activity. In this study, only the common V158M polymorphisms were studied, and the pain sensitivity was not fully explained; so further research remains to be conducted.

In summary, gene polymorphisms of COMT-V158 M and OPRM1-A118 G were correlated with the preoperative pain sensitivity in cancer patients. Patients carrying double mutant homozygote of COMT and OPRM genes had higher pain sensitivity before surgery.

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Disclosure of conflict of interest

None

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References

[1] Chirila M, Muresan M, Bolboaca SD. Study of preoperative predictive signs in management of facial nerve in parotid tumors. Maedica (Buchar) 2014; 9: 39-43.

[2] Terkawi AS, Jackson WM, Hansoti S, Tabassum R, Flood P. Polymorphism in the ADRB2 gene explains a small portion of intersubject variability in pain relative to cervical dilation in the first stage of labor. Anesthesiology 2014; 121: 140-8.

[3] Nishizawa D, Fukuda K, Kasai S, Ogai Y, Hasegawa J, Sato N, Yamada H, Tanioka F, Sugimura H, Hayashida M, Ikeda K. Association between KCNJ6 (GIRK2) gene polymorphism rs2835859 and post-operative analgesia, pain sensitivity, and nicotine dependence. J Pharmacol Sci 2014; 126: 253-63.

[4] Solak Ö, Erdoğan MÖ, Yıldız H, Ulaşlı AM, Yaman F, Terzi ES, Ulu S, Dündar Ü, Solak M. Assessment of opioid receptor μ1 gene A118G polymorphism and its association with pain intensity in patients with fibromyalgia. Rheumatol Int 2014; 34: 1257-61.

[5] Kambur O, Kaunisto MA, Tikkanen E, Leal SM, Ripatti S, Kalso EA. Effect of catechol-o-methyltransferase-gene (COMT) variants on experimental and acute postoperative pain in 1,000 women undergoing surgery for breast cancer. Anesthesiology 2013; 119: 1422-33.

[6] Gong XD, Wang JY, Liu F, Yuan HH, Zhang WY, Guo YH, Jiang B. Gene polymorphisms of OPRM1 A118G and ABCB1 C3435T may influence opioid requirements in Chinese patients with cancer pain. Asian Pac J Cancer Prev 2013; 14: 2937-43.

[7] Heddini U, Bohm-Starke N, Grönbladh A, Nyberg F, Nilsson KW, Johannesson U. Serotonin Receptor Gene (5HT-2A) Polymorphism is Associated with Provoked Vestibulodynia and Comorbid Symptoms of Pain. J Sex Med 2014; 11: 3064-71.

[8] Liebmann PM, Lehofer M, Moser M, Legl T, Pernhaupt G, Schauenstein K. Nervousness and pain sensitivity: II. Changed relation in ex-addicts as a predictor for early relapse. Psychiatry Res 1998; 79: 55-8.

[9] Staahl C, Drewes AM. Experimental human pain models a review of standardized methods for preclinical testing of analgesics. Basic Clin Pharmacol Toxicol 2004; 95: 97-111.

[10] Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. Pain 2011; 152: 300-7.

[11] Slade GD, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim RB, Belfer I, Max MB, Goldman D, Maixner W. Influence of psychological factors on risk of temporomandibular disorders. J Dent Res 2007; 86: 1120-5.

[12] Tammimki A, Mannisto PT. Cateehol-O-methyhransferase gene polymorphism and chronic human pain a systematic review and meta-analysis. Pharmaeogenet Genomics 2012; 22: 673-691.

[13] Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 2004; 75: 807-21.

[14] Dempster EL, Mill J, Craig IW. The quantification of COMT mRNA in post mortem cerebellum tissue: diagnosis, genotype, methylation and expression. BMC Med Genet 2006; 7: 10-16.