



The Role of Catechol-O-Methyl-Transferase Gene Variants in Modulating Labor Analgesia and Anxiety—A Prospective Observational Study

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Abstract

Background Women experiencing labor pain undergo significant psychological and physiological challenges, often leading to increased rates of cesarean sections.

Epidural analgesia has proven effective in managing labor pain, but its efficacy varies among individuals, partly due to genetic differences, including variations in the COMT gene, which influences pain perception pathways.

Methodology Fifty-three hospitalized patients provided informed consent to participate in this study. Peripheral venous blood samples were collected in EDTA tubes for DNA isolation and Polymerase Chain Reaction (PCR) analysis to investigate COMT gene polymorphisms. Epidural analgesia (Fentanyl with Ropivacaine) was administered upon reaching regular uterine contractions and cervical dilation of 4–5 cm. Pain and anxiety levels were assessed using the Visual Analog Scale (VAS) and State Anxiety Inventory (SAI) at predetermined intervals post-administration. Data analysis focused on exploring associations between COMT gene variants and outcomes related to pain perception and anxiety during labor.

Results Of the 53 participants, 35 were homozygous for the wild-type genotype (Val/Val). Approximately 33.9% displayed COMT gene polymorphisms: 14 women were heterozygous (Met/Val) and 4 were homozygous for the Met allele (Met/Met). Women with the Met/Met and Met/Val genotypes reported significantly higher scores on the State Anxiety Inventory (SAI) and Visual Analog Scale (VAS) compared to those with the Val/Val genotype ($p < 0.005$). These women also required more supplementary analgesia during labor.

Conclusion The presence of the Val158Met mutation in the COMT gene correlates with increased labor anxiety and reduced effectiveness of analgesia in pregnant women. Understanding the genetic factors influencing pain perception could improve analgesic strategies tailored to specific genetic profiles, potentially promoting higher rates of vaginal deliveries and better birth experiences for women. Further research into genetic markers of labor analgesia is crucial for refining pain management approaches in obstetrics.

Keywords COMT polymorphism · Labor pain · Labor Anxiety · Epidural Analgesia

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Introduction

Childbirth, or labor, is a fundamental aspect of human existence. Often described as one of the most intense and excruciating pains a woman may experience, the perception of this pain can vary greatly. Although the physiological process of labor and delivery is consistent across all women, individual childbirth experiences differ widely [1].

During labor, pain triggers a neuroendocrine stress response, which heightens sympathetic activity and releases catecholamines. Pain and anxiety, hence, become abnormal reactions that become detrimental to the adaptation of the mother and fetus. Excessive maternal distress may adversely affect fetal well being. This may lead to complications such as obstructed or prolonged labor, which in turn leads to increased rates of cesarean section [2].

Furthermore, women have begun to request cesarean sections because they feel afraid or anxious during labor. The worldwide incidence of cesarean sections has been rising owing to the growing demand for cesarean deliveries on maternal request (CDMR) [3]. Even with the most effective type of labor analgesia—epidural analgesia, some women still report experiencing severe pain and fear while giving birth.

Longitudinal assessment of pain scores demonstrates considerable inter-individual variability, independent of parity or cervical dilatation. The notion that genetic variability may be a significant influence has recently come to light as a possible explanation for the reported disparities in pain perception and analgesic requirements during labor and delivery between women. Several studies have linked polymorphisms at specific gene loci to the sense of pain, a field known as “Functional Pain Genomics.”[4].

Among the most extensively studied genes are catechol-O-methyltransferase (COMT), human opioid receptor 1 (OPRM1), guanosine triphosphate cyclohydrolase 1 (GCH1), and melanocortin-1 receptor (MC1R). Advances in understanding the genetic basis of pain are opening new possibilities for predicting individual pain sensitivity and tailoring treatments based on specific genetic variation patterns.

COMT enzyme is a crucial regulator of adrenergic, noradrenergic, and dopaminergic neurotransmission, primarily involved in the degradation of catecholamines [5]. The most extensively researched COMT genetic variation is “p.158Val/Met (c.472G/A),” linked to several pain phenotypes and sensitivity.

When Valine is replaced by Methionine at codon 158, it causes a multifold decrease in the activity of COMT [2]. This decreased COMT activity results in higher levels of epinephrine and norepinephrine, which may increase pain sensitivity by activating receptors in peripheral nerves. It also increases dopamine availability, which blocks the production of enkephalins and endorphins, depriving the individual

of endogenous opioids and, hence, more pain or analgesic requirements.

However, it is yet unknown whether the COMT gene polymorphism could impact pregnant women’s labor anxiety and analgesia. Our research will help to clarify this conundrum and contribute to the body of the literature already in existence.

Materials and Methods

The study included pregnant women admitted to the Labor Room at Shri B.M. Patil Medical College, Hospital and Research Centre, from April 2023 to April 2024. It was a prospective observational study with an intervention component. Participants were primiparous women with singleton, term pregnancies (37–41 weeks) who were in the latent phase of labor and had consented to epidural analgesia. Women were excluded if they had cephalopelvic disproportion, placental abnormalities, any pathological obstetric conditions, a history of mental illness such as anxiety or depression, or any contraindications to epidural analgesia.

Genetic Analysis for COMT Gene

After hospitalization, we collected 1 mL of peripheral venous blood from each participant in K2 EDTA vials and stored it at 4° Celsius. From 200 µl of peripheral blood, genomic DNA was isolated with the help of a commercial DNA isolation kit. Web-based, freely available program—Primer3, which is widely accepted, was used to develop PCR primers [6]. Screening of the forward primer for the C.O.M.T. polymorphism 5'-ACTGGCTACTCAGCTGTG-3' and the reverse primer 5'-CCTTTTCCAGGTCTGACAA-3' was done. (Primers were designed with reference for genome—NG_001526.1; Reference for mRNA—NM_000754.4; Reference for Protein—NP_001128634.1.)

PCR was carried out in a 20 µl reaction with 1 µl genomic DNA, 0.4 µl of each primer, 0.4 µl dNTPs, 10 µl Master Mix (Takara, Japan), and 8.2 µl water. Amplification involved an initial denaturation at 95 °C for 5 min, followed by 35 cycles of 95 °C for 30 s, 56 °C for 30 s, and 72 °C for 1 min, with a final extension at 72 °C for 5 min. PCR products were verified by gel electrophoresis using a 100-bp ladder.

For sequencing, PCR products were processed with Big-Dye Terminator v3.1 and analyzed on an ABI 3730 genetic analyzer, with sequence quality assessed using Sequencing Analysis software.

Epidural Analgesia

At our institution, epidural analgesia is routinely offered to all eligible women in labor as part of standard obstetric

care. All participants received epidural analgesia using an identical standardized drug protocol, administered by the same anesthesiology team following uniform institutional guidelines.

When cervical dilatation reached 4–5 cm, the parturient was made to sit, back painted, and draped. Epidural analgesia was performed at the L2/L3 intervertebral space using an 18 G Tuohy epidural needle to insert an epidural catheter 3–4 cm into the epidural space. After administering a test dose of 3 mL of 2% lidocaine, the parturient received 2 µg/mL of Fentanyl together with 0.1% Ropivacaine as the loading dose. The further top-up dose was given based on the patient’s need and pain scores.

Study Parameters

The patient’s pain and anxiety were assessed by Visual Analog Scale (VAS) and State Anxiety Inventory (SAI), respectively, along with other vital parameters (pulse rate,

blood pressure). The VAS score and SAI score were evaluated before epidural placement (baseline) and at 5, 10, 20, 30, 60, and 90 min after the administration of the drug and 10 min post-delivery to ensure consistency in measurements. All assessments were performed at predetermined standardized intervals for every participant to ensure uniformity of measurement and minimize variability across genotype groups.

Statistical Processing

Data were entered into Microsoft Excel and analyzed using SPSS (version 20). Continuous variables were tested for normality. Normally distributed variables were expressed as mean ± standard deviation and compared using one-way ANOVA. Non-normally distributed variables were analyzed using the Kruskal–Wallis test. Categorical variables were compared using Chi-square or Fisher’s exact test, as appropriate. A *p* value < 0.05 was considered statistically significant. All tests were two-tailed.

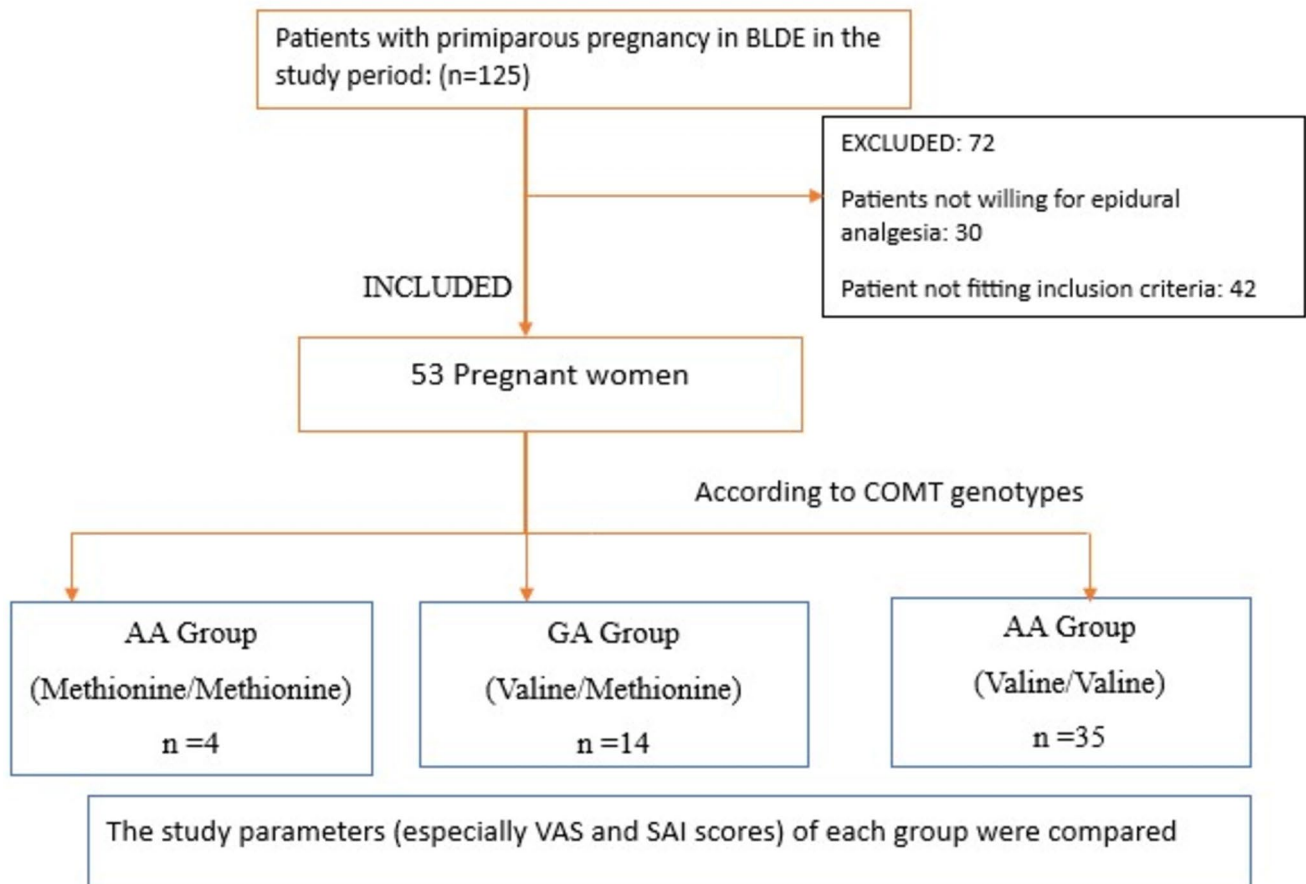


Fig. 1 A flowchart of the study

Results

Fifty-three individuals who met the inclusion criteria were enrolled in the study and administered epidural analgesia. The anxiety and pain levels were assessed using SAI and VAS scores, respectively. These were then compared with their respective COMT genotype (see Fig. 1). There were no difficulties or failed follow-up cases in this study. Patients who underwent emergency cesarean section (4 cases) were also included for pain analysis.

Out of 53 patients, 35 were categorized into the GG (Valine/Valine; wild type) group, showing no mutations. Approximately 33.9% had single nucleotide polymorphisms (SNPs): Four women with a homozygous mutation were assigned to the AA (Methionine/Methionine) group (see Fig. 2a), while fourteen women with a heterozygous mutation were classified into the GA (Valine/Methionine) group (see Fig. 2b), as detailed in Table 1.

Descriptive statistics and Kruskal–Wallis's test results for age, gestation period, height, weight, and BMI showed

Table 1 Distribution of COMT genotype in the study population

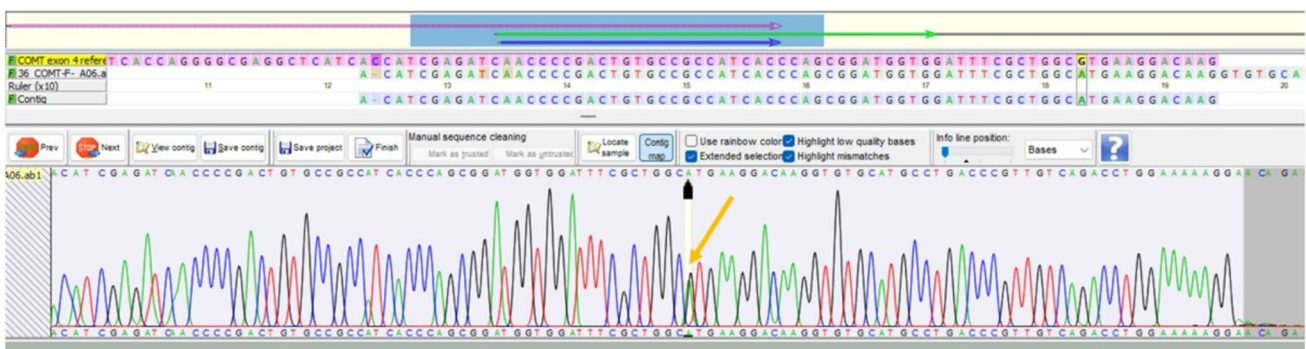
COMT gene analysis	Frequency	Percent
AA	4	7.5
GA	14	26.4
GG	35	66
Total	53	100

no statistically significant differences among genotypes (all $p > 0.05$). Vital parameters such as maternal heart rate, blood pressure, and fetal heart rate measured at baseline and various intervals (5, 10, 20, 30, 60, 90 min, and 10 min post-delivery) also showed no significant differences among the genotypes.

Significant differences in VAS scores were observed at all time intervals (VAS 0 min: $p = 0.005$; 5 min: $p = 0.012$; 10 min: $p < 0.001$; 20 min: $p < 0.001$; 30 min: $p < 0.001$; 60 min: $p < 0.001$; 90 min: $p < 0.001$; post-delivery: $p = 0.004$),



(a)



(b)

Fig. 2 Chromatograph of patients showing mutation in COMT gene: **a)** Homozygous mutation **b)** Heterozygous mutation

Table 2 The association between Visual Analog Score and COMT genotypes

Variables	Group	N	Mean	STD. deviation	P Value
VAS 0 min	AA	4	8	0	0.005*
	GA	14	7.64	0.497	
	GG	35	7.29	0.458	
VAS 5 min	AA	4	5.5	0.577	0.012*
	GA	14	5.79	0.426	
	GG	35	5.31	0.471	
VAS 10 min	AA	4	4.75	0.5	0.001*
	GA	14	4.14	0.663	
	GG	35	3.46	0.561	
VAS 20 min	AA	4	3.75	0.5	0.001*
	GA	14	3.5	0.519	
	GG	35	2.63	0.598	
VAS 30 min	AA	4	4	0	0.001*
	GA	14	3.43	0.514	
	GG	35	2.26	0.443	
VAS 60 min	AA	4	5.75	0.5	0.001*
	GA	14	4.93	0.917	
	GG	35	2.71	0.825	
VAS 90 min	AA	4	4.75	0.5	0.001*
	GA	14	4.21	0.579	
	GG	35	2.89	0.631	
VAS POST-DELIVERY (10 mins)	AA	4	3.5	0.577	0.004*
	GA	14	2.71	0.611	
	GG	35	2.37	0.547	

Statistically significant (p values <0.05) are highlighted in bold

indicating that pain perception varies significantly based on COMT gene variants, as seen in Table 2. SAI scores differed significantly at all intervals (SAI 0 min to SAI 90 min: $p < 0.001$), except post-delivery (Table 3). It was observed that women with AA and GA genotypes had higher anxiety scores compared to those with the GG genotype. Most participants with the GG genotype mostly (85.7%) did not require a top-up dose, whereas 71.4% of those with the GA genotype and all with the AA genotype did, indicating reduced pain tolerance and higher analgesic needs (Table 4). The Chi-square test revealed a significant association between COMT gene variants and the need for a top-up dose (Chi-square = 21.941, $p = 0.001$).

Discussion

Labor pains is widely recognized as one of the most excruciating experiences a woman can have in her lifetime. Neuraxial analgesia, often regarded as the gold standard of labor pain treatment, has redefined labor pain management. However, despite the use of epidural analgesia, some women do

Table 3 The association between State Anxiety Inventory Score and COMT genotypes

Variables	Group	N	Mean	Standard deviation	P Value
SAI 0 min	AA	4	54.25	0.957	0.001*
	GA	14	52.5	0.855	
	GG	35	46.23	0.973	
SAI 5 min	AA	4	49.75	0.957	0.001*
	GA	14	49.21	0.579	
	GG	35	41.54	1.915	
SAI 10 min	AA	4	49.00	2.45	0.001*
	GA	14	46.71	4.38	
	GG	35	40.60	2.09	
SAI 20 min	AA	4	43	6.218	0.001*
	GA	14	44.36	3.855	
	GG	35	34.34	2.141	
SAI 30 min	AA	4	43.25	2.754	0.001*
	GA	14	43.36	2.205	
	GG	35	30.8	2.688	
SAI 60 min	AA	4	47.25	2.062	0.001*
	GA	14	43.07	3.43	
	GG	35	29.43	2.019	
SAI 90 min	AA	4	45.25	1.258	0.001*
	GA	14	42.36	2.53	
	GG	35	30.6	2.44	
SAI POST-DELIVERY (10 mins)	AA	4	26	2.449	0.185
	GA	14	26.36	3.201	
	GG	35	24.69	2.285	

Statistically significant (p values <0.05) are highlighted in bold

not achieve sufficient pain relief with standard dosages of analgesic drugs. This study aimed to explore the reasons for this variation, focusing mainly on genetic factors.

Research on the genetics of pain is still in its early stages. While there are likely numerous genes contributing to the human experience of pain, only a select few with functional polymorphisms may prove clinically significant. Extensive research is presently being done on genes like COMT, GCH1, and OPRM1 to determine whether they may be used for genetic screening as potential diagnostics. The COMT gene, noted for its sensitivity in pain modulation, has been a primary focus of this study.

This study highlights the pivotal role of catechol-O-methyltransferase (COMT) in modulating pain sensitivity through the degradation of catecholamines. A critical SNP, rs4680, introduces a Val158Met substitution, altering COMT activity by reducing its enzymatic function. This change potentially augments dopaminergic neurotransmission and diminishes endogenous enkephalin levels, thereby heightening pain sensitivity.

Table 4 The association between the need for top-up dose and COMT genotypes

		COMT gene analysis			Total	Chi-square value	<i>P</i> value	
		AA	GA	GG				
Need for top-up dose	No	Count	0	4	30	34	21.941	0.001*
		%	0%	28.6%	85.7%	64.2%		
	Yes	Count	4	10	5	19		
		%	100%	71.4%	14.3%	35.8%		
Total		Count	4	14	35	53		
		%	100%	100%	100%	100%		

Statistically significant (p value <0.05) is highlighted in bold

In our study, we assessed the distribution and impact of COMT gene variants among 53 participants, identifying three genotypes: AA (mutant homozygote), GA (mutant heterozygote), and GG (wild type). The genotype distribution in our sample was AA (7.5%), GA (26.4%), and GG (66%). This distribution closely mirrors the findings of Xiaohui Ren et al. [2] Conversely, Jadranka Šanjug et al. [7] found a different distribution: AA (25%), GA (53%), and GG (22%). As this was a prospective observational study, participants were enrolled based on clinical criteria, and genotyping was performed subsequently. Therefore, the genotype distribution reflected the natural population frequency of the COMT Val158Met polymorphism rather than predefined stratification. The relatively smaller AA subgroup represents the lower incidence of this genotype in the population.

Our study population had a mean age of 22.34 years and a mean gestational age of 39.04 weeks, with no statistically significant differences in these parameters among the genotypes ($p > 0.05$). This is consistent with results from Xiaohui Ren et al.

There was significant variability in anxiety levels, with higher State Anxiety Inventory (SAI) scores for AA (54.25) and GA (52.5) genotypes compared to GG (46.23), indicating increased anxiety among the former groups. This aligns with Xiaohui Ren et al., who also found higher anxiety levels in carriers of the COMT Val158Met mutation (AA and GA).

In terms of labor pain, our study used Visual Analog Scale (VAS) scores to evaluate pain perception associated with COMT genotypes. Participants with the AA genotype reported higher pain scores compared to those with GA and GG genotypes, consistent with Jadranka Šanjug et al.'s findings and previous research by Zubieta et al. and Xiaohui Ren et al., which attributed increased pain sensitivity to reduced COMT activity.

Li-Jia Tang et al. [8] found that dexmedetomidine reduced VAS scores more effectively in GG genotypes (mean VAS = 3.6) than in AA (4.8) and GA (4.2) genotypes. Our study, focusing on top-up dose requirements, found a significant association with COMT variants (Chi-square = 21.941,

$p = 0.001$). GG genotypes required no top-up, while 71.4% of GA and all AA genotypes did.

This study adds to the limited body of literature and represents one of the few studies from India exploring this association. However, the study's limitations include its focus solely on the COMT gene, not considering other genetic factors, its confinement to a single healthcare center, and a relatively small sample size of 53 participants, particularly the limited number of participants in the AA genotype group. Although appropriate nonparametric statistical methods were used to account for unequal group sizes, larger multi-center studies are required to validate these findings.

Current research projects look at portable instruments for on-site genotyping as well as analgesic dosage prediction equations based on genetic polymorphisms. By better customizing analgesic treatments to individual genetic profiles, these developments may improve the efficacy of pain control during childbirth.

Conclusion

Pregnant women with the Val158Met mutation in the COMT gene experience severe labor anxiety and reduced analgesic efficacy. Further research into the genetics of labor analgesia is essential to enhance the effectiveness of analgesic drugs for specific populations and to improve labor analgesia and maternal experience.

These findings add to the expanding corpus of research on targeted obstetric care. Although routine genotyping is not currently part of standard obstetric practice, our findings contribute to the growing field of precision obstetrics. In the future, if rapid and cost-effective genetic testing becomes feasible, individualized counseling and tailored analgesic strategies may be considered for women at risk of heightened anxiety or increased analgesic requirements.

Author Contributions All authors have made significant contributions to the conception, design, execution, and interpretation of this research.

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data Availability The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest The authors declare no conflicts of interest related to this study. There are no financial or personal relationships that could influence the outcomes or interpretations of this research.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration. This study was approved by the Institutional Ethical Committee (IEC) at BLDE (Deemed to be University) with Number: BLDE(DU)/IEC/775/2022–23 and registered in the Central Trial Registry of India—CTRI/2023/03/051123. Informed consent was obtained from all individual participants included in the study.

Informed Consent Informed consent was obtained from all participants involved in the study. Written consent was obtained from each participant before their inclusion in the study, and all participants were fully informed of the study's objectives and procedures.

References

1. Whitburn LY, Jones LE, Davey M-A, McDonald S. The nature of labour pain: an updated review of the literature. *Women Birth*. 2019;32(1):28–38. <https://doi.org/10.1016/j.wombi.2018.03.004>.
2. Ren X, Zhang L, Xiao Q, Huang D, Liu Q, Zhang Y. Association between C.O.M.T. polymorphism, labor anxiety, and analgesia in pregnant women. *J Pain Res*. 2019;12:779–85.
3. Puramban P, Ravula PC, Aziz N. Maternal request caesarean sections: fear tops the list. *Int J Reprod Contracept Obstet Gynecol*. 2024;13(1):125–30.
4. Kringel D, Malkusch S, Kalso E, Lötsch J. Computational functional genomics-based AmpliSeq™ panel for next-generation sequencing of key genes of pain. *Int J Mol Sci*. 2021;22(2):878.
5. Vetterlein A, Monzel M, Reuter M. Are catechol-O-methyltransferase gene polymorphisms genetic markers for pain sensitivity after all?—a review and meta-analysis. *Neurosci Biobehav Rev*. 2023;1(148):105112.
6. Primer3Web [Internet]. [cited 2022 July 27th]; Available from <https://primer3.ut.ee/>
7. Šanjug J, Kuna K, Goldštajn MŠ, Dunkić LF, Carek A, Negovetić VD. Relationship between COMT gene polymorphism, anxiety, and pain perception during labour. *J Clin Med*. 2023;12(19):6298.
8. Tang L, Han J, Feng Y, Pu C, Zhang Y. Comparative study of the efficacy of dexmedetomidine and fentanyl on anxiety and pain of parturients with different COMTva1158met genotypes. *BMC Anesthesiol*. 2022. <https://doi.org/10.1186/s12871-022-01628-2>.

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