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The influence of COMT gene functional polymorphism on formation of chronic pain

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Abstract

Introduction and purpose

The prevalence of chronic pain is estimated at around 30% of the world's population. The risk of developing chronic pain depends, among others, on from genetic factors. Considering that chronic pain is a serious diagnostic and therapeutic problem, and if treated inadequately constitutes a serious threat to public health, focus should be on identifying the risk factors for its occurrence in order to establish an effective treatment. The aim of the work is to summarize the latest knowledge about the influence of functional polymorphism of the COMT gene on the formation of chronic pain.

Material and methods

The material for this literature review were publications on the subject of research from the last 5 years. Relevant articles have been identified by two authors using PubMed, Google Scholar and Researchgate publishing bases using key words: "gene COMT", "headache", "chronic pain", "chronic back pain", "fibromyalgia", "temporomandibular

disorder", "postoperative pain" according to Medical Subject Headings. The review of articles consisted of 3 stages. Finally, 19 works were qualified for the review.
Results

Functional polymorphism of the COMT gene is one of the factors affecting the modulation of pain. Its single genetic variants will positively correlate with the occurrence of temporomandibular disorders and chronic lower back pain. Differences in genetic variants of the COMT gene will also affect the susceptibility to fibromyalgia and increase the severity of clinical symptoms. The COMT gene polymorphism does not seem to correlate with chronic headaches.
Conclusions

Research to determine the effect of COMT gene polymorphism can significantly affect the diagnosis and treatment of chronic pain.

Keywords: COMT gene; chronic pain; genetics; functional polymorphism

Introduction and purpose

Pain is defined as an unpleasant emotional or sensory experience related to actual or potential tissue damage or described in the category of such damage (1). When the pain persists beyond 3 months, it is considered chronic (2). Its prevalence is estimated at around 30% of the world's population (3). The incidence of chronic pain increases with age and over 85, affects up to 55% of the population (4). The etiology of chronic pain is broad and includes both biological and psychosocial factors (5). The risk of developing chronic pain depends to a large extent on genetic factors, among others, polymorphism of COMT, OPRM1, SLC6A4 genes (3). Considering that chronic pain is a serious diagnostic and therapeutic problem, and if treated inadequately constitutes a serious threat to public health, focus should be on determining the risk factors for its occurrence and accurate diagnosis (5).

The COMT gene is found on the long arm of the 22th chromosome encoding catechol-O-methyltransferase (COMT) (6). It is an enzyme of the central nervous system that inactivates catecholamines - dopamine, adrenaline and noradrenaline (6,7). Therefore, he takes part in such body functions as feeling pain, reaction to stress or modifying mood (8). COMT is a highly polymorphic gene with multiple functional single nucleotide polymorphisms (SNPs) (9). The different genetic variants of the COMT gene will have different effects on the activity of catechol-O-metolotransferase (8). Reduced activity increases the sensitivity to harmful stimuli and the increased risk of chronic pain (8). The effect of COMT on the formation of chronic pain is explained by the enzyme modulation of such processes in the body as inflammation, autonomic response, nociceptive sensitivity or the influence of this gene on the mental state (9). So far, the studies have checked how the COMT gene polymorphism affects such pain dysfunctions as fibromyalgia, chronic back pain (CBP), postoperative pain, chronic headaches, temporomandibular disorders (TMD) (3). The aim of this publication is to summarize the current knowledge about the effect of COMT gene polymorphism on the formation of chronic pain.

Material and methods

The material for the literature review were works found in PubMed, ResearchGate and Google Scholar publications bases and published over the last 5 years (2014-2019). Various combinations of key words were used to find appropriate works: "gene COMT", "chronic pain", "chronic back pain", "fibromyalgia", "temporomandibular joint disorders", "headache", "postoperative pain" (according to Medical Subject Headings - MeSH). The literature review consisted of three stages. At the beginning, the two independent authors analyzed the publication titles found using the key words. In the second stage, the authors reviewed the abstracts of the works initially included in the review. The next stage included works in the

Polish or English language version, the aim of which was to investigate the influence of COMT gene polymorphism on the occurrence of chronic pain. The exclusion criterion from the study was the lack of English or Polish language version, articles older than 5 years, conference summaries. Finally, 19 works were qualified for the review.

Table 1. Publications qualified for the review (authors, title, year, aim of the study, materials and methods).

Authors, year	Title	Aim of the study, materials and methods
Rut M. et al. 2014	Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: a report on 176 cases.	Aim of the study: to evaluate the relationship between genetic COMT polymorphisms and susceptibility to pain after lumbar discectomy. Materials and methods: 176 patients operated on because of single-level, symptomatic intervertebral disc herniation at level L3 to S1; visual analogue pain scale (VAS); Oswestry Disability Index (ODI); SNP genotyping of the COMT gene.
Omair A. et al. 2015	Catechol-O-methyltransferase (COMT) gene polymorphisms are associated with baseline disability but not long-term treatment outcome in patients with chronic low back pain.	Aim of the study: to evaluate the relationship between COMT and OPRM1 gene polymorphism and pain and disability in patients treated for chronic lower back pain (CLBP). Materials and methods: 371 patients with CLBP; the scale of "function and working disability"; Oswestry Disability Index (ODI); SNP genotyping (rs6269, rs4633, rs4818 and rs4680, rs2075507 and rs1799971); observation method.
Michelotti A. et al. 2014	Catechol-O-methyltransferase (COMT) gene polymorphisms as risk factor in temporomandibular disorders patients from Southern Italy.	Aim of the study: to assess the role of COMT gene variants as potential risk factors in the group of patients affected by chronic temporomandibular pain (TMD). Materials and methods: sequencing the COMT gene in 50 people with TMD and 132 people in the control group; diagnostic criteria for Research Diagnostic Criteria Temporomandibular Disorders (RDC / TMD).
Meloto CB et al. 2015	COMT gene locus: new functional variants.	Aim of the study: to identificate the functional SNP within the COMT gene (locus-rs165774). Materials and methods: group of Caucasian women aged 18-55, 200 women with TMD, 198 people from the control group, quantitative sensory tests (QST); a group of Caucasian women, 106 women with TMD, 859 people from the control group, QST; genotyping.
Fernández-de-Las-Peñas C. et al.	Catechol-O-Methyltransferase (COMT) rs4680 Val158Met	Aim: To investigate the relationship between val158Met rs4680 polymorphism in frequent episodic (FETTH) and chronic (CTTH) tension headache and analysis of the relationship between val158Met rs4680

2019	Polymorphism is Associated with Widespread Pressure Pain Sensitivity and Depression in Women with Chronic, but not Episodic, Tension Type Headache.	polymorphism and clinical, psychological or psychophysical variables. Materials and methods: 50 women with FETTH, 50 women with CTTH, 50 healthy women; SNP genotyping in the COMT gene; keeping a headache diary; Oswestry Disability Index (ODI); Pittsburgh sleep quality index (PSQI); hospital scale of anxiety and depression (HADS); pressure pain thresholds (PPT).
Wang L. et al. 2019	Influences of COMT rs4680 and OPRM1 rs1799971 Polymorphisms on Chronic Postsurgical Pain, Acute Pain, and Analgesic Consumption After Elective Cesarean Delivery.	Aim of the study: to assess the effect of COMT rs4680 and receptor polymorphism rs1799971 separately or in combination of genotypes for chronic post-surgical pain (CPSP), acute pain and consumption of analgesics after scheduled cesarean section (CS) in the Chinese population. Materials and methods: 266 patients with scheduled CS ; genotyping (rs4680 and rs1799971); State Trait Anxiety Inventory (STAI); VAS scale.
Rydman E. et al. 2017	COMT genotype and non-recovery after a whiplash injury in a Northern European population.	Aim of the study: to assess whether the patient reported improvement after injury, including pain, is associated with the COMT genotype and whether environmental factors, including mental health, are associated with the genotype and lack of improvement reported by the patient. Materials and methods: patients after cervical spine injury; questionnaire on sociodemographic data; Health Related Quality of Life (HRQoL) scale; Short Form-36 (SF-36) Health Survey; VAS; HADS; Posttraumatic Stress Disorder questionnaires (PTSD-10); genotyping - rs6269, rs4633, rs4818, rs4680.
Mladenovic I. et al. 2016	Genetic Polymorphisms of Catechol-O-Methyltransferase: Association with Temporomandibular Disorders and Postoperative Pain.	Aim of the study: to evaluate the relationship between COMT and TMD gene polymorphism, TMD pain, psychosocial disorders associated with TMD and CPSP. Materials and methods: 90 TMD patients with pain, 92 matched patients without TMD; RDC / TMD; genotyping - rs4680, rs6269 and rs165774.
Takigawa H., Kowa H,	No associations between five polymorphisms in	Aim of the study: to examine the correlation of COMT polymorphism and chronic headaches. Materials and methods:

Nakashima K. 2017	COMT gene and migraine.	71 patients with migraine with aura, 152 patients with migraine without aura, 86 patients with tension headache, 191 healthy controls; genotyping for rs4633, rs6267, rs4680, rs6270, rs740602.
Martire LM et al. 2016	COMT and OPRM1 Genotype Associations with Daily Knee Pain Variability and Activity Induced Pain.	Aim of the study: to examine the correlation between COMT and OPRM1 polymorphisms and the variability of knee pain in patients with osteoarthritis (OA) of the knee joints. Materials and methods: 120 patients with OA; accelerometer, activity diary; genotyping for rs1799971, rs4680.
De Marchis ML et al. 2016	Look beyond Catechol-O-Methyltransferase genotype for cathecolamines derangement in migraine: the BioBIM rs4818 and rs4680 polymorphisms study.	Aim of the study: to examine the role of genetic variant COMT rs4818 and rs4680 in migraine. Materials and methods: 380 patients with migraine, 132 people from the control group; genotyping of COMT-rs4680, 4818 polymorphisms
Inanir A. et al. 2014	Clinical symptoms in fibromyalgia are associated to catechol-O-methyltransferase (COMT) gene Val158Met polymorphism.	Aim: to determine the relationship between the genetic variant COMT rs4680 and the occurrence of fibromyalgia. Materials and methods: 379 patients with fibromyalgia, 290 without fibromyalgia from the control group; VAS scale; BDI; Beck Anxiety Inventory (BAI); FMS Impact Questionnaire; algometry; genotyping for rs4680.
Bjorland S. et al. 2016	Genes associated with persistent lumbar radicular pain; a systematic review.	Aim of the study: to present a review of the literature on the role of genetic factors and biomarkers predicting pain improvement in patients with root pain in the lumbar region of the spine. Materials and methods: review of Medline OVID, Embase, PsycInfo, Web of Science publication databases from 2004-2015.
Gruber HE et al. 2014	A novel catechol-O-methyltransferase variant associated with human disc degeneration.	Aim of the study: to search for new SNPs related to the degeneration of the intervertebral disc. Materials and methods: DNA genotyping; MRI.
Slade GD et al. 2015	COMT Diplotype Amplifies Effect of Stress on Risk of Temporomandibular Pain.	Aim of the study: to check if temporary escalation of the stress and genetic variants of the COMT gene affect TMD. Materials and methods: 2707 adults without TMD during recruitment for the

		study; Perceived Stress Scale (PSS); COMT genotyping; observation method.
Park DJ et al. 2016	Association between catechol-O-methyl transferase gene polymorphisms and fibromyalgia in a Korean population: A case-control study.	Aim of the study: to evaluate the relationship between SNP COMT and the risk of fibromyalgia and the severity of its symptoms. Materials and methods: 409 patients with fibromyalgia, 423 patients in the control group; COMT-rs6269 genotyping, rs4633, rs4818, rs4680 and rs165599.
Zhang L. et al. 2014	Meta-analysis reveals a lack of association between a common catechol-O-methyltransferase (COMT) polymorphism Val158Met and fibromyalgia.	Aim of the study: to evaluate the relationship between SNP COMT rs4680 and the risk of fibromyalgia. Materials and methods: meta-analysis of 8 case-control studies involving 589 cases of fibromyalgia and 527 subjects of the control group.
Lee YH, Kim JH, Song GG 2015	Association between the COMT Val158Met polymorphism and fibromyalgia susceptibility and fibromyalgia impact questionnaire score: a meta-analysis.	Aim of the study: to investigate whether the COMT Val158Met polymorphism (rs4680) is associated with susceptibility to fibromyalgia and the outcome of Fibromyalgia Impact Questionnaire (FIQ) in patients with fibromyalgia. Materials and methods: meta-analysis: 993 patients with fibromyalgia and 778 controls from 10 studies evaluating the effects of rs4680 on fibromyalgia and 538 patients with fibromyalgia from 5 studies on the outcome of FIQ and fibromyalgia.
Chen H. et al. 2015	Association Between Polymorphisms of DRD2, COMT, DBH, and MAO-A Genes and Migraine Susceptibility: A Meta-Analysis.	Aim of the study: to evaluate the relationship between genetic polymorphisms DRD2, COMT, DBH and MAO-A and susceptibility to migraine. Materials and methods: a meta-analysis of 11 case-control studies, including 3138 patients with migraine and 4126 subjects in the control group.

Results

Table 2. Results of surveys included in the review (autors, results).

Authors	Results
Rut M. et al.	The severity of pain was related to COMT polymorphism. Carriers rs6269 AA, rs4633 TT, rs4818 CC and rs4680 AA were characterized by the lowest pain scores before and after surgery. People with genotype rs4633 CC, rs4680 GG showed significant clinical improvement on the VAS scale one year after surgery. Patients with COMT haplotype associated with the low metabolic activity of the COMT enzyme showed better scores on the ODI scale and VAS scale one year after surgery. There was no correlation between leg pain and SNP of the COMT gene.
Omair A. et al.	Disability checked at the beginning of the study was associated with SNP COMT rs4818, rs6269, rs4633, rs2075507, smoking, age and sex. There was no significant association with clinical variables for OPRM1 or COMT in long-term follow-up.
Michelotti A. i in.	Trzy SNP, wszystkie zlokalizowane w rejonach promotorowych były częściej obecne u osób z TMD niż u osób z grupy kontrolnej. Genetyczny polimorfizm rs165656 i r4646310 odgrywa rolę w podatności na TMD.
Meloto CB. et al.	The presence of the A gene allele A of rs165774 correlates with lower COMT activity, suggesting a contribution to reduced pain sensitivity through increased dopaminergic activity rather than decreased adrenergic activity that is characteristic of other COMT isoforms.
Fernández-de-Las-Peñas C et al.	The distribution of the Val158Met rs4680 genotype was not significantly different between women with / without headache. There were no differences in the features of headache, disability, anxiety and sleep quality depending on the genotype r1546Mr158Met. Women with CTTH, but not with FETTH, with the Met / Met genotype had lower PPT prevalence and higher depressive symptoms than those with the Val / Val or Val / Met genotype.
Wang L. et al.	In 29 women, 3 months after the operation, CPSP developed. Risk factors for CPSP included earlier cesarean section and higher analgesic use 24 and 48 hours after surgery. No relationship was found between CPSP and SNP rs4680 and rs1799971 or combinations thereof. However, patients with rs1799971 GG required more analgesics 24 hours and 48 hours after surgery compared to other genotypes (GG> AG> AA). However, no significant effect of the second SNP on analgesic consumption was observed.
Rydman E. et al.	The frequency of reporting a lack of improvement by patients after 12 months of spinal damage was 44%, with no significant differences in the distribution of COMT haplotypes. The high level of reported pain and anxiety after the accident was related to the reported lack of improvement, but not related to haplotypes. None of the other factors were associated with the haplotype of the COMT gene or the reported lack of improvement.
Mladenovic I. et al.	Carriers of the homozygous AA genotype and heterozygous carriers of the variant A allele (genotype AG / AA) for rs165774 polymorphism had an increased risk of developing TMD compared to the GG genotype. In addition, the AA genotype was associated with an increased risk of myofascial pain, joint pain and chronic pain in the course of TMD. The AA genotype for rs6269 polymorphism was associated with smaller postoperative acute and chronic pain. There was no association with somatization and depression.
Takigawa H.,	No significant differences were found in genotypes, allele frequencies or

Kowa H, Nakashima K.	haplotypes among patients with chronic headaches and in the control group.
Martire LM Et al.	Patients with the Val / Val genotype (COMT rs4680 (Val158Met)) showed the highest variability of pain, they also experienced the highest increase in pain as a result of physical activity. According to previous studies, there were no significant differences in daily pain when comparing patients with COMT rs4680 or OPRM1 rs1799971.
De Marchis ML et al.	The COMT genotype does not affect the susceptibility to migraine or its phenotype, even taking into account the rs4818 polymorphism and the clinical subtypes of migraine.
Inanir A. et al.	The frequencies of the Val158Met polymorphism genotypes showed a slight difference between patients with fibromyalgia and those in the control group. The Met / Met genotype was significantly more common in patients with fibromyalgia than in healthy controls. There was no difference in the frequency of alleles between the two groups. The weight, result of the FMS Impact Questionnaire, algometry and Raynaud's syndrome are related to the Val158Met polymorphism. The pain sensitivity measured by algometry was lower in patients with the Val / Val and Val / Met genotypes than in patients with the Met / Met genotype.
Bjorland S. et al.	Five genetic variants; i.e., OPRM1 allele rs1799971 G, COMT allele rs4680 G, MMP1 allele rs1799750 2G, IL1α allele rs1800587 T, IL1RN rs2234677 A were associated with reduced pain improvement in LRP. Three biomarkers; i.e. TNFα, IL6 and IFNα were associated with chronic LRP.
Gruber HE et al.	Analysis of the results confirmed the previous association between COMT SNP rs4633 and degeneration of the intervertebral disc. Two new SNPs related to disc degeneration were also discovered (rs2095019 and rs470859).
Slade GD et al.	Psychological stress will have a greater impact on the formation of TMD in people whose genetic variants of the COMT gene increase the body's response to catecholamine neurotransmitters.
Park DJ et al.	The COMT rs4818 gene polymorphism was significantly associated with increased susceptibility to fibromyalgia. The rs4818 GG genotype was more strongly associated with fibromyalgia than the CC genotype. Although allele and genotype frequencies did not differ between groups, the rs4633 CT genotype was not associated with the presence of fibromyalgia after age and gender adjustment. There was no relationship between individual SNPs of the COMT gene and clinical measurements.
Zhang L. et al.	Carrier of rs4680 does not involve a greater risk of fibromyalgia.
Lee YH, Kim JH, Song GG	The meta-analysis demonstrated the relationship between the COMT Met / Met + Val / Met genotype and fibromyalgia in all subjects. Analysis using other genetic models did not show a correlation between COMT Val158Met polymorphism and fibromyalgia. It was also shown that the FIQ score was significantly higher in people with the COMT Met / Met genotype than in those with the Val / Val genotype.
Chen H. et al.	The studied polymorphisms of the DRD2, DBH and MAO-A genes may not be related to migraine susceptibility. COMT rs4680 polymorphism can, on the other hand, reduce the risk of migraines, especially in Caucasians.

Studies of Rut M. et al. (10), Meloto CB et al. (8), Wang L. et al. (11), Bjorland S. et al. (12), Lee YH, Kim JH, Song GG (13) and Martire LM et al. (14) evaluate the effect of SNP COMT on pain modulation. In these studies, the COMT gene polymorphism was most often associated with lower pain scores before and after surgery, lower COMT enzyme activity, and no improvement in pain management. Only the work of Wang L. et al. suggests the lack of effect of the rs4680 gene on the development of chronic postoperative pain in women after caesarean section (11).

Works of Inanir A. et al. (15), Park DJ et al. (16), Lee YH, Kim JH, Song GG (13) showed a relationship between individual SNPs of the COMT gene and the occurrence and more severe symptoms of fibromyalgia. In opposition to this research, there is the work of Zhang L. et al. in which the rs4680 gene was not correlated with fibromyalgia (17).

The results of research carried out by Michelotti A. et al. (18), Mladenovic I. et al. (19), Meloto CB et al. (8) suggest the effect of SNP COMT on TMD formation and increased pain sensation in the course of these disorders. However, the work of Slade GD et al. draws attention to the significant influence of psychological stress on the occurrence of TMD in people who carry the genetic variants of the COMT gene that increase the body's response to catecholamine neurotransmitters (20).

Studies by Fernández-de-Las-Peñas C. et al. (22), Takigawa H., Kowa H, Nakashima K. (23), De Marchis ML et al. (24) indicate that SNP COMT is not associated with the occurrence of chronic headache. The only research confirming the influence of SNP COMT on the risk of migraine is the work of Chen H. et al. (21).

The association of COMT polymorphism with the formation and persistence of chronic back pain is assessed by Gruber HE et al. (25), Bjorland S. et al. (12), Omair A. et al. (26) and Rydman E. et al. (27). This relationship is explained by the influence of SNP COMT on increased degeneration of the intervertebral discs (25), reduced improvement in symptoms of root pain (12) and increased disability in people with CLBP (26). The only work not binding the polymorphism of this gene with chronic pain of the spine was the work of Rydman E. et al. (27).

Discussion

Chronic pain are considered multifactorial pathologies with overlapping etiologies (3). Nociceptive activity, hypothalamic-pituitary-adrenal gland, psychosocial and socio-economic factors contribute to their development (28). Chronic pain affects a large part of society (3). In spite of many known methods of their treatment, no treatment option has been defined that does not cause side effects or will not lead to further complications (3,29). Chronic pain cannot be considered solely as a symptom of disease (30). It is a team characterized by annoying physical pain, disability, emotional disorders and social withdrawal (30). These dysfunctions affect each other, being able to undergo progression (30). Due to the fact that chronic pain affects physical, psychological, cognitive and behavioral aspects, their treatment should be based on an interdisciplinary approach, including pharmacotherapy, physiotherapy, physical rehabilitation, psychotherapy, lifestyle change, surgical treatment and alternative methods (29). Considering that the heredity of chronic pain is estimated at 16-50%, and the heredity of individual pain syndromes was determined at 50% for migraines, tension headaches and fibromyalgia, 35% for chronic back and neck pain, 27% for TMD in determining treatment strategies, consider genetic factors as one of many possible causes of chronic pain (31). Therefore, the purpose of this literature review was to summarize the knowledge of recent years regarding the functional polymorphism of the COMT gene on the occurrence of chronic pain. A review of current research on this topic suggests that the COMT gene polymorphism will affect the modulation of pain and disorders such as fibromyalgia, TMD and CBP.

Catechol-O-methyltransferase is responsible for the metabolism of ketechol neurotransmitters and its activity will lead to the strengthening or inhibition of nociceptive signaling (32). The COMT gene coding for this enzyme will therefore be responsible for the mechanism of pain perception (3). This is confirmed by the results of the works of Rut M. et al. (10), Meloto CB et al. (8), Wang L. et al. (11), Bjorland S. et al. (12), Lee YH, Kim JH, Song GG (13) and Martire LM et al. (14).

Fibromyalgia is defined as a disorder characterized by chronic pain and tenderness often associated with fatigue, sleep disorders and memory problems (33, 34). It affects 2 to 8% of the population (34). In the course of fibromyalgia, among others to reduce the concentration of catecholamine metabolites in the cerebrospinal fluid, which reduces the sympathetic nervous system pressure and, as a result, reduces the inhibition of pain (33). This mechanism may play a significant role in the COMT gene, which is responsible for the metabolism of catecholamines (6), which would agree with the results of Inanir A. et al. (15), Park DJ et al. (16), Lee YH, Kim JH, Song GG (13). Moreover, considering that the COMT gene affects the modulation of pain, we can conclude that it may have an effect on increasing the pain symptoms of fibromyalgia, which is additionally confirmed by studies by Lee YH, Kim JH, Song GG and Inanir A. et al. (13,15).

Temporomandibular disorders are the most common cause of pain in the craniofacial region, with a prevalence reaching 3-12% of the world's population (35). The etiology of these dysfunctions is multifactorial and so far ambiguous (36). As in the case of fibromyalgia, the catecholamine system will be involved in the formation of TMD - the COMT gene polymorphism will affect the decrease of the COMT enzyme activity causing the increase of the adrenaline level and the increase of nociceptive signaling (36). The correlation of some genotypes of the COMT gene with the formation of TMD is confirmed by studies of Michelotti A et al. (18) and Mladenovic I. et al. (19). However, in Meloto CB studies, some SNP COMTs cause increased dopaminergic rather than adrenergic effects resulting in reduced sensitivity to pain (8). This suggests that not all genetic variants of this gene will affect the increase of pain symptoms in the course of TMD. It is worth mentioning that the carriage of the SNP of the COMT gene responsible for increasing the susceptibility to TMD does not guarantee the occurrence of these disorders (3). Only appropriate environmental factors in people genetically predisposing to temporomandibular disorders can cause their initiation (3). This is confirmed by the results of Slade GD et al. suggesting that genetic variants that increase the body's response to catecholamine neurotransmitters do not induce TMD formation until psychological stress (20). This underlines the importance of psychosocial factors in the mechanism of this disease.

Chronic back pain and surrounding tissues are a big medical and social problem. Their prevalence reaches even 80% of the society being the second cause of disability in the world (37.38). Chronic low back pain (CLBP) is considered to be a major clinical problem, with annual prevalence estimated from 22 to 65% (39). One of the many possible causes of these ailments is degenerative changes in the intervertebral discs (40). Their degeneration will involve, among others, enzymes mediating cell degradation which are building blocks and proinflammatory cytokines (3). These substances will affect the occurrence of inflammation and pathological tissue remodeling, which in turn will cause excessive nociceptive signaling and pain formation (3). As noted in the studies of Gruber HE et al. some SNPs of the COMT gene affect increased disc degeneration (24).

In the studies of Bjoland S. et al. genetic variants of the COMT gene caused a reduced improvement in the root pain of the lumbar spine, while the work of Omair A. discusses the impact of this gene on increasing the disability of people with CLBP (12.25). Therefore, it can be concluded that the SNP of the COMT gene, apart from the direct impact on the mechanics of spine pain, will also cause an increase in the symptoms of dysfunction and the progression

of disability occurring in its course. Considering that in the pathophysiology of CBP, not only biological factors but also psychosocial factors are distinguished, the examined gene will influence components of chronic spine pain, increasing dysfunction (41).

Migraine is defined as a cycle of pain signaling and interpretation of non-nociceptive stimuli as pain stimuli (42). Its estimated prevalence is around 15% (43). It is believed that despite many genes involved in the aetiology of this disease, genetic factors do not play a significant role in it (44). In the course of migraine, pathologies of the dopaminergic neurotransmission pathway occur (42). This suggests that the COMT gene should be associated with migraine due to its effect on dopamine metabolism (8). This is in conflict with the results of the work of De Marchis ML et al. in which the SNP of the COMT gene was not related to this dysfunction. This gene probably will not also affect the formation of chronic tension headaches (45), which is confirmed in the work of Fernández-de-Las-Peñas C. et al. and Takigawa H., Kowa H, Nakashima K. (22.23,45). This may be explained by the fact that many genes will affect the metabolism of dopamine (45). It is worth mentioning that in the work of Fernández-de-Las-Peñas C. SNP of the COMT gene will correlate with a higher sensitivity to pressure pain and higher depressive levels (21). This shows that the functional polymorphism of a single nucleotide of the COMT gene does not affect the disease itself, but its components are exacerbated.

In conclusion, individual COMT genetic variants will predispose their carriers to TMD, chronic back pain and fibromyalgia. In addition, the functional polymorphism of this gene by affecting the activity of the COMT enzyme will affect the modulation of pain and, consequently, the alleviation or exacerbation of pain in the course of the above-mentioned disorders. Apart from affecting the intensity of pain, SNP of the COMT gene will cause longer recovery time and increase of other symptoms of dysfunction or progression of disability.

Knowledge about the influence of genetic factors on the formation of chronic pain can significantly increase the effectiveness of treatment of these disorders. Thanks to the development of research to determine the mechanisms of the formation of these dysfunctions, we can implement specific treatment, including drugs targeted at the metabolic pathway causing the disorder (3). In addition, knowledge about risk factors and mechanisms of chronic pain will allow for a multidisciplinary approach to their treatment, including the implementation of appropriate rehabilitation, psychotherapy or prophylaxis, which is currently the most effective method of treating chronic pain (28). In connection with the above, it would be worthwhile to undertake research in the future to determine the effect of functional polymorphism of the COMT gene and other genes on the formation of chronic pain.

Conclusions

Functional polymorphism of the COMT gene will play an important role in the formation and course of chronic pain by modulation of pain. The SNP of the COMT gene seems to play an important role in disorders such as fibromyalgia, temporomandibular disorders and chronic back pain.

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