Arh. farm. 2024; 74: 23 – 37 *Review article/Pregledni rad*

Association of catechol-O-methyltransferase gene polymorphisms with treatment response and levodopa-induced complications in Parkinson's disease: A summary of current knowledge

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Abstract

Catechol-O-methyltransferase (COMT) is one of the cardinal enzymes in the degradation of catecholamines and levodopa. Genetic variants of the *COMT* gene may affect COMT enzyme activity. The most examined *COMT* gene polymorphism is the nonsynonymous single nucleotide polymorphism (SNP) in exon 4 (Val108/158Met; rs4680). This highly functional polymorphism is responsible for fourfold variations in enzyme activity and dopamine catabolism. Recent data suggested that even synonymous SNPs of the *COMT* gene can lead to changes in enzyme activity. Genetically determined COMT activity can affect an individual's response to levodopa therapy and carries the risk of complications from prolonged levodopa use in Parkinson's disease (PD) patients. Identifying at-risk individuals through genetic susceptibility markers could help to prevent the development of levodopa-induced complications in PD.

Key words: Parkinson's disease, levodopa-induced dyskinesia, hallucinations, *COMT* gene, single nucleotide polymorphisms, Val158Met (rs4680)

doi.org/10.5937/arhfarm74-45472

Introduction

Parkinson's disease (PD) is a progressive disabling disorder caused by the degeneration of dopaminergic nigrostriatal pathways. It is clinically manifested by the presence of motor (bradykinesia, resting tremor, rigidity, and postural instability) and non-motor symptoms (cognitive decline, behavioral disturbances, autonomic dysfunction, sleep disorders) (1). The dopamine precursor, levodopa, has remained the most effective symptomatic therapy in PD since its introduction (2). Acute side effects of levodopa, such as nausea, vomiting, anorexia, and hypotension, commonly recede after 2 to 3 weeks of drug use (2). However, prolonged treatment with levodopa and disease progression lead to several motor and non-motor complications (2). About 40-50% of PD patients medicated with levodopa develop motor complications, such as motor fluctuations and dyskinesias, 4-6 years following the introduction of levodopa (3). Psychotic symptoms occur in about one-third of PD patients on dopaminergic therapy, usually ten or more years after diagnosis, and significantly impair the quality of life of these patients (4).

Disease progression parameters and clinical variables do not explain inter-individual heterogeneity in response to levodopa, suggesting a complex pathomechanism involving genetic factors. Pharmacogenetics aims to identify genetic factors that could be responsible for variability in treatment response, as well as for the occurrence of complications of chronic dopaminergic therapy. Polymorphisms in various genes implicated in dopamine metabolism and transport have been studied concerning the side effects of prolonged use of levodopa in PD patients, and the *COMT* gene is one of the most examined genes.

Thus, we performed this review to critically discuss current findings and how polymorphisms of the *COMT* gene may affect the treatment response and levodopa-induced complications such as motor fluctuations, dyskinesias, hallucinations, and psychosis in PD patients. An extensive literature search for English-language clinical trials was performed using MEDLINE (through PubMed up to April 2023) and EMBASE databases. The search terms were: "Parkinson's disease," "levodopa-induced dyskinesia," "hallucinations," "catechol-O-methyltransferase" or "*COMT* polymorphism," "single nucleotide polymorphisms," and "Val158Met (rs4680)". We have also searched manually to identify any studies potentially omitted by the database search. We (BR and MS) independently reviewed the titles and abstracts. The inclusion criteria were cross-sectional or longitudinal, the study group were idiopathic PD patients, genetic factors were any SNPs of the *COMT* gene, outcomes were dose-response, motor fluctuation, dyskinesia, hallucinations, and psychosis, and patients were treated with chronic dopaminergic agents (levodopa, dopamine agonists, MAO-B inhibitors and COMT inhibitors). References of reviewed articles and meta-analyses were also checked. The systematic search procedures used are shown in Figure 1.

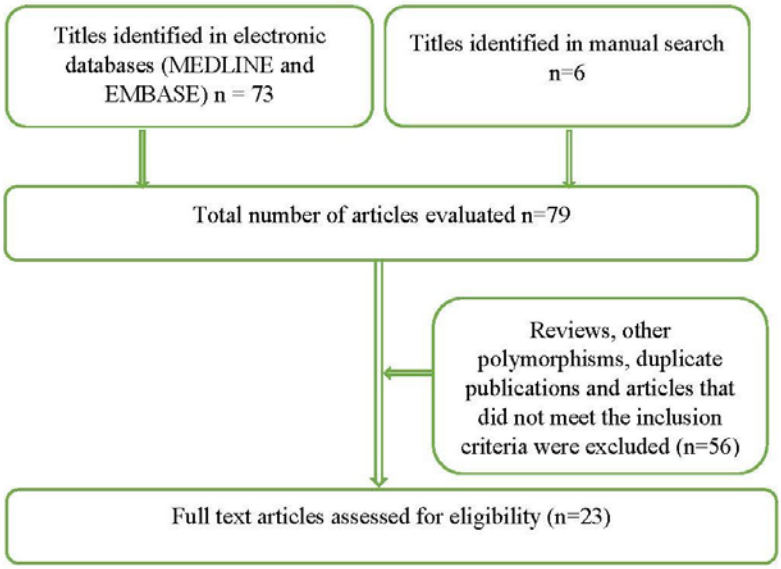

Figure 1. The methodology used
Slika 1. Korišćena metodologija

COMT gene

The human *COMT* gene is localized on the long arm chromosome 22 at the gene map locus of 22q11.2. It consists of six exons (the first two non-coding) and two promoters, P1 and P2, which control expression and are located in exon 3 (5). The *COMT* gene encodes two known isoforms of the COMT enzyme: the shorter, soluble, or cytosolic isoform (S-COMT) and the membrane-associated isoform (MB-COMT) (5, 6). MB-COMT is located in almost all parts of the human central nervous system (CNS). At the same time, S-COMT predominates in most other tissues except the brain (7). COMT enzyme degrades catecholamines, including dopamine and levodopa.

SNP rs4680 polymorphism is the most considered *COMT* gene polymorphism found in the 4th exon of the *COMT* gene. The substitution of valine (Val) to methionine (Met) at position 158, i.e., the replacement of G>A (Val158Met), leads to greater thermolability of the enzyme, resulting in approximately 30% lower enzyme activity. Val with Met can be replaced in the S-COMT but at position 108 (8, 9). COMT genotype distribution varies by ethnic origin. About 25% of Caucasians are homozygous for the low activity variant (Met/Met; AA), 25% are homozygous for the high activity variant (Val/Val; GG), and the remaining ones have the intermediate activity variant (Val/Met; AG) (7). AA genotype COMT is present in only 10% of the Asian population. The SNP rs4680 *COMT* gene has been linked to differences in cognitive abilities (specifically in tasks involving executive functions), mood, pain perception, and response to physical or

emotional stress (8-10). It has been shown that carriers of the GG genotype have an increased risk of developing schizophrenia (6) and a weaker response to olanzapine therapy (11).

However, it has been recognized that the haplotype formed by the four SNPs of the *COMT* gene (rs6269, rs4633, rs4818, and rs4680) has been affected to a greater extent on enzyme activity compared to a single rs4680 polymorphism (12). Therefore, the ACCG, ATCA, and GCGG haplotype carriers have low, medium, and high COMT activity, respectively (12).

Recent data suggested that synonymous SNPs of the *COMT* gene (i.e., rs165728 and rs174699) impact mRNA structure and stability and decrease COMT activity (13).

The association of therapeutic response to levodopa treatment and *COMT* gene SNPs

There are appreciable inter-patient and intra-personal distinctions in the response to levodopa. Genetic variations in the COMT activity contribute to different individual levodopa responses. It could be expected that carriers of the low COMT activity genotype would show a more significant response to levodopa than those with other genotypes. However, studies have shown that different COMT genotypes (14, 15) did not affect the duration or extent of response to a single levodopa dose in PD patients. Bialecka et al. found that daily doses of levodopa were significantly higher for GCGG *COMT* haplotype carriers (rs6269-rs4633-rs4818-rs4680) (16). A recent case-control study investigated the association of eleven SNPs in the *COMT* gene and levodopa response in Chinese PD patients and found that patients with the TT genotype of rs165728 and TT of rs174699 required higher daily levodopa equivalent doses (LEDs) than the patients with CC and CT genotypes (13). Replacement of the T allele with C has been hypothesized to reduce COMT enzymatic activity, decreasing the needed levodopa doses (13). Though rs165728 is located in the 3'-UTR, and rs174699 is located in intron 5, they possibly alter mRNA structure and stability, decreasing COMT activity. In addition, Xiao et al. found that carriers of the T allele of rs4633 and A allele of rs4680 used higher daily LEDs (17).

The association of motor complications of prolonged levodopa treatment and *COMT* gene SNPs

PD patients frequently develop severe and often debilitating motor complications (motor fluctuations and dyskinesia) due to their prolonged therapy. The "wearing off" phenomenon is the predictable recurrence of PD symptoms ahead of the scheduled levodopa dose. The "on-off" phenomenon refers to sudden, sometimes unpredictable changes in PD symptoms, varying between the "on" state (phase of optimal drug action and motor improvement) and the "off" state (phase of returning PD symptoms after the expiration of therapy). Motor fluctuations most likely occur due to pharmacokinetic and pharmacodynamic factors associated with chronic levodopa use in the presence of severe nigrostriatal degeneration (1, 18).

The impact of COMT genotype on the risk of motor fluctuations has been investigated in several studies, with conflicting results (16, 19). A cross-sectional study among Chinese PD patients found that AA homozygotes had a lower risk of developing "wearing-off," suggesting that the rs4680 *COMT* gene might affect susceptibility to "wearing off" (20). However, a meta-analysis showed that allele A of rs4680 increased the risk of "wearing off" (21).

COMT inhibitors are considered the medication of choice for treating motor fluctuation by increasing the "on" state, decreasing the "off" state, and improving motor response (22, 23). Administration of levodopa with a COMT inhibitor maintains a permanent level of levodopa in the plasma and obtains uniform availability of levodopa in the brain. Few trials have examined the potential contribution of the COMT genotype in the clinical response to COMT inhibitors. Corvol et al. have shown that *COMT* polymorphism rules the acute response to COMT inhibitors (24). In this study, the GG rs4680 *COMT* gene genotype was associated with a prolonged entacapone-induced "on" state (24). However, other studies did not show variations in the therapeutic response and toxicity of COMT inhibitors among PD patients with different COMT genotypes. One longitudinal study found no association between rs4680 *COMT* and the duration of "on" and "off" states and disease severity in PD patients during two months of entacapone treatment (25). After entacapone therapy, the mean reduction in daily levodopa dose in each patient was significant in GG and AG carriers, but not in those with the AA genotype of the *COMT* gene (25). Kim et al. also showed that entacapone's efficacy and side effects did not differ among PD patients with different *COMT* genotypes (26).

Levodopa-induced dyskinesia (LID) or involuntary movements are usually clinically manifested as choreiform or dystonic movements and less frequently in ballistic movements and myoclonus. The most common LIDs are "peak dose," which occur when the concentration of levodopa in the blood is at its highest. Dyskinesias present during the entire duration of the levodopa effect are referred to as square wave dyskinesias (1, 18). Biphasic dyskinesias are less frequent and occur when plasma levodopa concentrations fall below or rise above the threshold for therapeutic efficacy. Finally, "off" dyskinesias happen when the concentration of levodopa in plasma is low and manifest through pain and cramps in the legs or foot dystonia. Clinical risk factors for LID include younger age at PD onset, greater severity, longer disease duration, length of levodopa treatment, and higher total levodopa dose (27, 28). However, it is still difficult to explain why dyskinesias do not appear in all patients medicated with high doses of levodopa for an extended period and sometimes occur in those exposed to relatively low levodopa daily doses in a short period (1).

The role of *COMT* gene polymorphisms as a vulnerability factor in LID onset has been explored to a great extent. Previous studies regarding the association of the rs4680 *COMT* gene polymorphism and LID have shown conflicting results. A prospective study conducted in the Netherlands found a twice higher risk among heterozygous PD patients and a 2.81 times higher risk of developing dyskinesia during levodopa therapy among AA carriers of the rs4680 *COMT* gene (19). A possible interpretation of this

result was that a higher incidence of dyskinesia occurred in patients with lower COMT activity due to exposure to higher doses of levodopa. In one study, the AA genotype was more common in patients with motor fluctuations (p = 0.045, OR= 3.82) or dyskinesia (p = 0.030, OR = 4.80) than in controls. Still, this finding was insignificant after Bonferroni's correction (29). Sampaio et al. found that the *COMT* AA genotype (rs4680) was associated with the risk of LID after adjusting for sex and age (OR=5.53; 95%CI 1.5-20.1; p=0.0009) (30). A recent study that included 220 Brazilian PD patients found that AA genotype *COMT* had a 3.8-fold increased risk for LID development after Bonferroni's correction (HR=3.841; 95% CI 1.29–11.37; p=0.012) (31). However, several other clinical studies have not verified the findings that a low-activity allele will have an increased risk of dyskinesia (14, 16, 32-35). The cross-sectional studies with Polish (16) and Italian PD patients (14) found no significant association between *COMT* polymorphism and LID, as well as the extensive survey of 1087 Chinese PD patients (30). The reviewed studies regarding the association between *COMT* polymorphism and LID demonstrated inconsistent results, which may be due to different ethnic groups, methodology used, and outcome definitions. The study with Chinese patients found that the GG genotype was more common in patients with motor fluctuations than in those without them (30). However, a meta-analysis involving 2385 PD patients implied that the AA rs4680 *COMT* may increase the risk of LID in a recessive genetic model for PD patients (36). Pooled ORs and 95% CIs suggested that the AA rs4680 *COMT* was associated with LID (OR=1.39, 95%CI:1.02–1.89, p=0.039) in the recessive model, and this correlation was more evident in Brazilian samples in the analysis stratified by ethnicity. Another recent meta-analysis on ethnicity showed that allele A rs4680 *COMT* is a risk factor for LID development in Asian PD patients. At the same time, using different genetic models, the GG genotype is a risk factor for LID development in non-Asian PD patients (37). Study design and small sample sizes led to the following essential limitations of the reviewed studies. Most of the studies are cross-sectional or retrospective, so they cannot be used to determine causality. Longitudinal studies with large samples would be preferable to provide insight into cause-and-effect relationships.

Ivanova et al. reported an association between four COMT SNPs (rs165774, rs4818, rs4633, and rs4680) and LID in 232 Caucasian PD patients (33). The rare allele of rs165774 was associated with an increased risk of dyskinesia (OR = 1.75; 95%CI 1.14-2.72), while in the case of rs4818, rs4633 and rs4680, the rare allele or homozygote genotype for the rare allele were protective against LID (OR = 0.57; 95%CI 0.34-0.92, OR=0.45; 95%CI 0.23-0.89 and OR=0.46; 95% CI 0.23-0.91, respectively), although the results did not reach statistical significance after adjusting for disease duration (33). No associations were found between combined *BDNF* (Brain-Derived Neurotrophic Factor) Val66Met, *COMT* Val158Met, and T941G *MAO-A* (Monoamine oxidase-A) SNPs and the prevalence or time to onset of LID in PD patients (32). A recent study found no individual associations of *BDNF* Val66Met, *DAT* (Dopamine Transporter) rs397595, and *COMT* rs4680 SNPs, but a potential combined impact of these polymorphisms on the occurrence of levodopa-induced motor complications (38). This

result implicated that a single SNP does not drive the event of motor complications. In addition, the phenotypic expressions of SNPs are probably affected by gene-gene interactions.

The association of non-motor complications of prolonged levodopa treatment and *COMT* gene SNPs

Hallucinations occur in about 8-40% of PD patients on chronic dopaminergic therapy, most often as visual hallucinations with preserved introspection in the initial stages and less frequently as auditory hallucinations (4). Besides hallucinations, the clinical range of psychotic symptoms in PD encompasses minor hallucinations (illusions, presence hallucinations, passage hallucinations) and delusions (4). The pathophysiology of psychotic symptoms in PD is complex and still insufficiently known. Prolonged dopaminergic therapy was long considered to be the primary risk factor for hallucinations in PD. Still, recent studies have shown that antiparkinsonian drugs alone are neither necessary nor sufficient to explain the onset of psychotic symptoms in all patients (39, 40). The appearance of psychotic symptoms in PD was related to older age, disease duration, cognitive disorders, depression, and sleep disorders (4).

Thus far, several attempts have assessed the impact of genetic factors on developing hallucinations in PD. A recent cross-sectional study, which included 234 PD patients, found no association between rs4680 of the *COMT* gene and psychotic symptoms in PD (41). This finding follows a retrospective postmortem study by Camicioli et al. (42) and another study by Creese et al. (43), which included demented PD patients. However, the survey by Radojević et al. showed that, in addition to well-established clinical risk factors for psychosis in PD (dopaminergic drugs, motor status, depression, and anxiety), the GG rs2734849 of the *ANKK1* gene was a potential contributing factor (41). These results suggested that dopamine probably has a limited role in developing psychotic symptoms in PD compared to other neurotransmitters. Besides *COMT*, other genes might increase the risk of treatment complications (43). Moreover, the occurrence of levodopa nonmotor complications could be the result of gene-gene interactions. Namely, haplotypes of *COMT* and *SLC6A3* were associated with the occurrence of visual hallucinations (AT *vs*. GC: OR=0.34; 95%CI=0.16-0.72; p=0.005) (44).

Table I summarizes studies examining the association of *COMT* gene polymorphisms with treatment response and levodopa-induced complications in PD patients.

Table I Studies examining the association of catechol-O-methyltransferase (*COMT*) gene polymorphisms with treatment response and levodopa-induced complications in Parkinson's disease (PD) patients presented in chronological order

Tabela I Studije o udruženosti polimorfizama gena za katehol-O-metiltransferazu *(COMT)* sa terapijskim odgovorom i komplikacijama izazvanim levodopom kod pacijenata sa Parkinsonovom bolesti prikazane hronološki

Study (Year)	Study design/sample	Genes (SNPs)	Outcomes	Main findings
Lee et al. (2001)[15]	Cross-sectional study with 73 Korean PD patients	*COMT* (rs4680)	Motor response after a single levodopa dose challenge test	No association
Lee et al. (2002)[25]	A longitudinal study with 65 Korean PD patients with end-of-dose deterioration	*COMT* (rs4680)	The therapeutic efficacy of entacapone was assessed using the UPDRS score, the daily levodopa dosage, and the patients' diary card.	No association The mean of the percentage reduction of daily levodopa dose for each individual after entacapone treatment was significant in patients with GG and GA rs4680 *COMT*, but not in those with AA genotype.
Watanabe et al. (2003)[29]	Cross-sectional enrolled 121 Japanese PD patients	*COMT* (rs4680)	PD susceptibility Wearing-off Dyskinesia	AA rs4680 *COMT* may be related to an increased risk of wearing-off (p=0.045, OR=3.82) or dyskinesia (p=0.030, OR=4.80) compared with controls, although these differences were not significant after Bonferroni's correction.
Bialecka et al. (2004)[45]	The retrospective study enrolled 95 patients diagnosed with idiopathic PD and treated with levodopa.	*COMT* (rs4680) *MAO-B* (A>G, Intron13)	Levodopa dose	AA rs4680 *COMT* was associated with using doses of levodopa below 500mg during the first five years of treatment.
Contin et al. (2005)[14]	Cross-sectional that included 104 Italian PD patients	*COMT* (rs4680)	Levodopa pharmacokinetic and pharmacodynamic variables and the presence of dyskinesias after standard oral levodopa/benserazide test	No association
Camicioli et al. (2005.)[42]	Retrospective study in 47 autopsy-confirmed cases of PD	COMT (rs4680)	Hallucinations	No association
Bialecka et al. (2008)[16]	Case-control study that included 322 Poland PD patients	*COMT* (rs6269, rs4633, rs4818, rs4680)	Levodopa dose Motor complications	Levodopa doses prescribed for carriers of the high activity haplotype (604.2±261.9mg) were significantly higher than those for noncarriers (512.2±133.5mg, p<0.05).

Corvol et al. (2011)[24]	A randomized cross-over clinical trial with 33 French PD patients	*COMT* (rs4680)	The primary endpoint was the effect of entacapone on the motor response to levodopa. Secondary endpoints were the peak motor response, time to peak, levodopa pharmacokinetics, and COMT activity in red blood cells.	GG rs4680 *COMT* genotype in PD patients enhanced the effect of entacapone on the levodopa pharmacodynamics and pharmacokinetics.
Kim et al. (2011)[26]	Longitudinal study with168 Korean PD patients who had daily "off" duration of ≤2 hours	*COMT* (rs4680)	The efficacy and side effects of entacapone	No association
De Lau et al. (2012)[19]	A longitudinal study among a hospital-based cohort of 219 Dutch PD patients	*COMT* (rs4680)	Dyskinesia	AA rs4680 *COMT* carriers had an increased risk of developing dyskinesias during follow-up in a dose-dependent manner (adjusted hazard ratios for the AG and AA genotypes [compared to GG]: 2.09 [95% confidence interval (CI) 1.07–4.06] and 2.81 [CI, 1.43–5.54], respectively.
Torkaman-Boutorabi et al. (2012)[46]	Cross-sectional study that enrolled 103 Iranian PD patients	*COMT* (rs4680) *MAO-B* (rs1799836)	Levodopa doses	There are no significant differences in genotype distributions when comparing those receiving daily doses of levodopa above 500 mg and below 500 mg in the fifth year of treatment.
Yin et al. (2013)[36]	A case-control study that involved 97 Chinese patients with PD	*COMT* (rs74745580, rs4633, rs6267, rs3838146)	PD susceptibility Severity of disease Levodopa dose Duration of levodopa	The polymorphisms rs4633, rs6267, and rs3838146 were associated with the severity of PD disease, but not with levodopa medication.
Wu et al. (2014)[20]	Cross-sectional study with 259 Chinese PD patients	*COMT* (rs4680)	Wearing off	AA rs4680 *COMT* was related to a decreased risk of wearing off. GG vs. AA rs4680 *COMT* carried a higher risk factor for the wearing-off ($p < 0.001$) [OR=8.84, CI: 4.74-16.39]. GA vs. AA genotype had a higher risk for wearing off (p=0.013) [OR=6.54, CI:1.49-28.57].
Cheshire et al. (2014)[32]	A longitudinal study that involved 285 pathologically confirmed PD cases	*COMT* (rs4680) *MAO-A* (rs6323) *BDNF* (rs6265)	Dyskinesias	No association

Xiao et al. (2017)[17]	A case-control study with 143 outpatient Chinese PD patients	*COMT* (rs4680, rs6269 rs4633, rs4818)	PD severity Levodopa treatment response Wearing-off	TT rs4633, AA rs4680, and the two linked TT/AA rs4633-rs4680 were more frequent in patients with wearing-off, longer disease duration, higher LED, and higher UPDRS scores ($p < 0.05$).
Sampaio et al. (2018)[30]	A retrospective study with 162 PD Brazilian patients on levodopa	*COMT* (rs4680) *MAO-B* (rs1799836)	Therapeutic response to levodopa Dyskinesia	AA rs4680 *COMT* was associated with a risk of dyskinesia after adjusting for sex and age.
Michałowska et al. (2018)[38]	Cross-sectional study with 76 PD patients on chronic levodopa therapy lasting at least three years	*COMT* (rs4680) *DAT* (rs397595) *BDNF* (rs6265)	Motor levodopa-induced complications (on-off and dyskinesias)	There is no association between individual *BDNF*, *DAT*, and *COMT* polymorphisms. The genotype combination of AG *BDNF*, AG *DAT*, and GG *COMT* was correlated with motor complications, and the genotype combination of GG *BDNF*, AA *DAT*, and AA *COMT* showed a lack of motor complications in PD patients.
Kakinuma et al. (2018)[34]	Retrospective study with 110 Asian patients with PD	*COMT* (rs4680) *MAO-B* (rs1799836)	Dyskinesia	No association between COMT and dyskinesia Patients with AG or GG rs1799836 were more likely to have dyskinesia than those with an AA genotype (HR=3.41; 95% CI 1.28–9.10).
Ivanova et al. (2019)[33]	Cross-sectional study with 232 Russian PD patients	*COMT* gene (rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696)	Dyskinesia	The rare allele of rs165774 was associated with an increased risk of dyskinesia (OR = 1.75 [95% CI 1.14-2.72]). The rare allele or homozygote genotype for the rare allele of rs4818, rs4633, and rs4680 were protective against dyskinesia (OR = 0.57 [0.34-0.92], 0.45 [0.23-0.89] and 0.46 [0.23-0.91], respectively).
Redenšek et al. (2019)[44]	A retrospective cohort study that enrolled 231 PD on levodopa and DAs treatment duration at least three months	*COMT* (rs4680, rs165815) *DRD2* (rs1799732, rs1801028) *DRD3* (rs6280) *SLC22A1* (rs628031) *DDC* (rs921451, rs3837091) *MAOB* (rs1799836), *SLC6A3*	Motor fluctuations Dyskinesia Excessive daytime sleepiness and sleep attacks Visual hallucinations (VHs) Nausea/vomiting Orthostatic hypotension Peripheral edema Impulse control disorders	Carriers of at least one *COMT* rs165815 C allele had lower odds for VHs (OR = 0.34; 95% CI = 0.16–0.72; p = 0.004); Heterozygotes for *SLC22A1* rs628031 and carriers of at least one *SLC22A1* rs628031 A allele had lower odds for dyskinesia (OR = 0.48; 95% CI = 0.24–0.98, p = 0.043 and OR = 0.48;

		(rs393795, rs6347, rs104209) *SLC7A5* (rs1060253, rs1060257) *SLC18A2* (rs14240) SV2C SNP (rs1423099)		95% CI = 0.25–0.92; p = 0.027, respectively) Haplotypes of *COMT* and *SLC6A3* were associated with the occurrence of VHs (AT vs. GC: OR = 0.34; 95% CI = 0.16–0.72; p = 0.005).
Dos Santos et al. (2020)[31]	220 Brazilian PD patients	*COMT* (rs4680) *DRD1* (rs4532), *DRD2* (rs1800497), *DAT1* (rs28363170)	Dyskinesias	AA rs4680 *COMT* had a3.84–fold increased risk for dyskinesia development (HR=3.841; 95% CI 1.29–11.37; p=0.012).
Zhao et al. (2020)[13]	73 Chinese PD patients	*COMT* (rs4680, rs4633, rs769224, rs4646316, rs174699, rs737865, rs4646312, rs933271, rs174675, rs2020917, rs165728	Dyskinesia	TT rs165728 and rs174699 had larger LED than CC and CT genotypes (p=0.01421 for rs165728 and p=0.02302 for rs174699). GG rs4680 had a lower occurrence of dyskinesia than AA and AG (p=0.0196). CC rs4633 had a lower occurrence of dyskinesia than TT and TC (p=0.0429)
Radojević et al. (2021)[41]	A cross-sectional study that included 234 Serbian PD patients on levodopa therapy for at least two years and age at onset > 40 years	*COMT* (rs4680) *DRD2* (rs6277, rs1076560, and rs2283265) *ANKK1* (1800497, rs2734849) *DAT* (VNTR)	Psychosis	TT rs6277 *DRD2* carriers had 2.3 times higher risk (0R=2.302; CI 1.100-4.816, p=0.027) and GG rs2734849 *ANKK1* 2.2 times higher risk (OR=2.203, CI1.073-4.522, p=0.031) for developing psychosis.

PD - Parkinson's disease, COMT – catechol-O-methyltransferase, SNP – single nucleotide polymorphisms, OR -odds ratio, CI- confidence interval, MAO – monoamine-oxidase, DRD2- dopamine receptor 2, BDNF – brain-derived neurotrophic factor, DAT – dopamine transporter, UPDRS – Unified Parkinson's Disease Rating Scale, LED – levodopa equivalent doses, VHs=visual hallucinations

Conclusion

SNP rs4680 of the *COMT* gene has been considered the main reason for individual variation in human COMT activity. However, several studies have failed to demonstrate the relationship between treatment response, long-term levodopa complications, and rs4680 of the *COMT* gene, implying that a single SNP does not drive the event of difficulties. Additionally, interactions between SNPs likely affect mRNA structure and protein translation efficiency, all leading to changes in enzyme activity. Besides *COMT*, other genes affect individual response to dopaminergic drugs and the risk of treatment complications. Increased insight into how genetic variants affect response to levodopa could contribute to personalized antiparkinsonian therapy to maximize symptom control while minimizing severe side effects.

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Udruženost polimorfizama gena za katehol-O-metiltransferazu sa terapijskim odgovorom i komplikacijama izazvanim levodopom kod Parkinsonove bolesti: Rezime sadašnjih saznanja

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Kratak sadržaj

Katehol-O-metiltransferaza (engl. *catechol-O-methyltransferase*, COMT) je jedan od glavnih enzima u razgradnji kateholamina i levodope. Genetske varijante *COMT* gena mogu uticati na aktivnost COMT enzima. Polimorfizam *COMT* gena koji je najviše proučavan je nesinonimni jednonukleotidni polimorfizam (engl. *single nucleotide polymorphism*, SNP) u egzonu 4 (Val108/158Met; rs4680). Ovaj visoko funkcionalni polimorfizam odgovoran je za četvorostruke varijacije u aktivnosti enzima i katabolizmu dopamina. Nedavni podaci sugerišu da čak i sinonimni SNP *COMT* gena mogu da dovedu do promena u aktivnosti enzima. Genetski određene razlike u COMT aktivnosti mogu uticati na odgovor pojedinca na terapiju levodopom i nose rizik od komplikacija dugotrajne primene levodope kod pacijenata sa Parkinsonovom bolešću (PB). Identifikacija osoba u riziku putem markera genetske osetljivosti može pomoći u prevenciji komplikacija izazvanih levodopom kod PB.

Ključne reči: Parkinsonova bolest, levodopa indukovane diskinezije, halucinacije, *COMT* gen, jednonukleotidni polimorfizmi, Val158Met (rs4680)