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The Relationship Between COMT and MAO-B Gene Polymorphisms with Levodopa in Parkinson's Disease Patients; *A Review*

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Abstract

Parkinson's disease is a degenerative nervous system disorder caused by the death of dopamine-producing cells in the substantia nigra. Dopaminergic treatment could alleviate motor symptoms for a period. One of the effective dopaminergic medications for symptomatic relief was Levodopa and dopamine agonists. Clinically, Levodopa was always combined with Dopa Decarboxylase (DDC) inhibitors, which redirected Levodopa metabolism towards the COMT pathway, increasing its bioavailability in the central nervous system. The purpose of this article was to investigate the relationship between COMT and MAO-B gene polymorphisms and Levodopa in Parkinson's disease patients, starting by gathering literature on the association between COMT and MAO-B polymorphisms and Levodopa in Parkinson's disease patients using various databases. Reviewed literature revealed that the most frequent polymorphism in the COMT gene was rs4680. Some polymorphisms significantly impacted the treatment of Parkinson's disease patients. However, despite efforts to identify genetic factors influencing the risk of side effects or treatment ineffectiveness, the role of pharmacogenetics in Parkinson's disease has not been fully explored and lacks consistent clinical recommendations. Further research was needed to tailor treatment to individual polymorphisms so that pharmacogenomic approaches could be applied more consistently

Keywords: *DNA Polymorphism, Levodopa, Pharmacogenomic*

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INTRODUCTION

Parkinson's Disease, also known as Tremor Paralysis, is a neurodegenerative condition resulting from the demise of neurons responsible for dopamine production in the substantia nigra. The substantia nigra is located above the spinal cord within the midbrain region (Opara et al. 2017). The most significant risk factor for developing Parkinson's disease is age. The disease predominantly affects the elderly, with an average age of ≥65 (Fan et al. 2020; Vuletić et al. 2021). Parkinson's disease is the second most common neurodegenerative disease globally, affecting over 6 million individuals, and its incidence is projected to rise alongside the aging demographic. Moreover, males are more vulnerable to this condition than females, with an approximate prevalence ratio of 3:2 (Tolosa et al. 2021). Information regarding Parkinson's disease patients in Indonesia remains scarce, but it is estimated that there are 200,000 to 400,000 patients with Parkinson's disease (Setiarini and Subagya, 2018).

The disease's clinical progression is gradual and characterized by motor manifestations like tremors, bradykinesia, and rigidity. Alongside these motor symptoms, non-motor manifestations such as impaired sense of smell, sleep disruptions, cognitive impairments, pain, fatigue, and alterations in behavior are also observed (Ng 2018). These symptoms arise from alterations occurring at various brain levels. The central pathological alteration primarily involves the gradual deterioration of neurons situated in the substantia nigra, which is one of the core components of the basal ganglia. These neurons play a role in conveying dopamine to other nuclei within the basal ganglia and the striatum. The degeneration of these neurons results in motor dysfunction, ultimately leading to movement disorders and impacting the individual's quality of life (Lotankar et al., 2017).

There are numerous treatment options available for Parkinson's disease at present. Unfortunately, no treatment can halt the pathological mechanisms driving the disease's progression, meaning that most treatments are focused on replacing or increasing the availability of dopamine (Vuletić et al. 2021). Dopaminergic treatment can alleviate motor symptoms for a period. One of the effective dopaminergic medications for symptomatic relief is Levodopa and dopamine agonists (Dietrichs and Odin 2017).

Levodopa Metabolism

Levodopa is a pro-drug to increase dopamine levels in Parkinson's disease patients (Elroby et al. 2012). Following oral administration, Levodopa is absorbed in the duodenum and proximal jejunum, entering the bloodstream and gaining access to the brain by crossing the Blood-Brain Barrier (BBB) through a carrier-mediated process. The question arises: why isn't dopamine directly administered as therapy to raise dopamine levels in the brain? This is because dopamine itself cannot traverse the BBB, necessitating the use of another compound that can be converted into dopamine, like Levodopa. Once Levodopa makes its way into the central nervous system, it undergoes metabolism into dopamine through the action of aromatic-L-amino-acid decarboxylase (AAAD), an enzyme widely distributed in catecholaminergic neurons, the gastrointestinal tract, liver, plasma, and even the Blood-Brain Barrier (Hanson and Gálvez-Jiménez 2001). Levodopa

can be metabolized through four different pathways: decarboxylation, O-methylation, transamination, and oxidation. The primary route for Levodopa metabolism is decarboxylation, which converts it into dopamine by the enzyme AAAD. Decarboxylation plays a central role in Levodopa metabolism. Since widespread decarboxylation of Levodopa can also occur in peripheral tissues, enzyme inhibitors like Carbidopa and Benserazide are commonly combined with Levodopa. Carbidopa and Benserazide are administered in low doses to prevent them from crossing the blood-brain barrier (BBB). Consequently, it is assumed that most of the Levodopa transported to the brain is predominantly converted into dopamine by central AAAD, and this process remains unaffected by Carbidopa or Benserazide.

Another notable metabolic route includes the transformation of Levodopa into 3-O-methyldopa and dopamine into 3-O-methyldopamine, a process facilitated by Catechol-O-Methyltransferase (COMT). This pathway gains significance, especially when decarboxylation is restrained. The O-methylation of Levodopa yields metabolites that cannot be converted into dopamine within the brain. COMT is present not only in the brain but also in various peripheral tissues. This pathway may account for approximately 10% of Levodopa's metabolism when administered without an AAAD inhibitor. Tolcapone and Entacapone are two COMT inhibitors in competition, employed in treating Parkinson's disease. Entacapone functions peripherally by obstructing COMT, consequently elevating the amount of Levodopa that can reach the brain as Levodopa (Aldred and Nutt 2010).

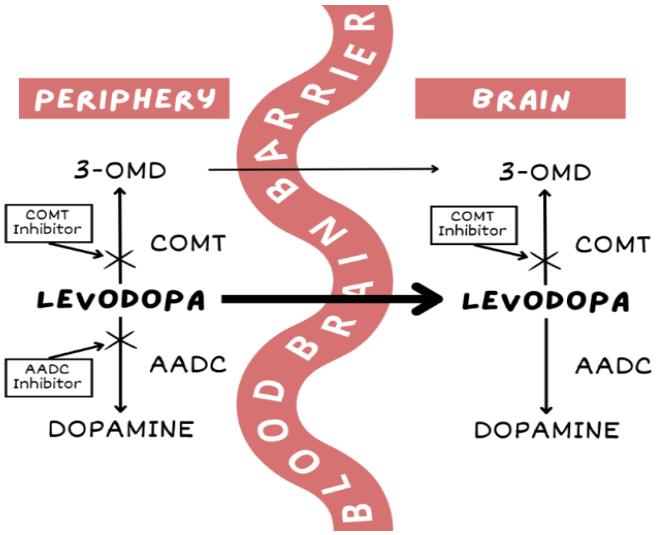

Figure 1. Metabolic pathway of Levodopa

METHOD

This article explores the connection between COMT and MAO-B gene variations and their impact on Levodopa treatment in individuals with Parkinson's disease. The investigation commences by compiling pertinent literature that examines the correlation between COMT and MAO-B genetic variations and the response to Levodopa in Parkinson's disease patients. Databases like PubMed, Springer Link, and Google Scholar

were utilized in this endeavor. The search terms or keywords utilized include 1) COMT, 2) MAO-B, 3) Parkinson's disease, 4) Levodopa, and 5) polymorphism. These keywords are also combined to generate more search results. Inclusion criteria encompass: 1) case-control or cohort studies describing the connection between COMT and MAO-B gene polymorphisms and Parkinson's disease; and 2) Research should evaluate the link between genetic variations in the COMT and MAO-B genes and the occurrence of Parkinson's disease. The data gathered from various reference sources are then synthesized into a review article that provides insights into the influence of COMT and MAO-B gene polymorphisms on Parkinson's disease.

RESULTS AND DISCUSSION

Pharmacogenomics of Levodopa Therapy

Over the past decade, pharmacogenomics has been extensively studied to understand how genetic variations among individuals might impact their responses to drugs. Pharmacogenomics aims to identify patients with a genetically determined heightened susceptibility to drug side effects, leading to tailored dosing and ultimately improving the efficacy and safety of pharmacotherapy (Droździk et al., 2013). One of the diseases recently associated with its treatment and gene polymorphisms is Parkinson's disease, particularly concerning levodopa therapy.

A consistently effective approach to improving the plasma profile of levodopa has been using enzyme inhibitors that control the activity of the main catabolic pathway, determining levodopa's efficacy. A few of these inhibitors consist of dopamine decarboxylase inhibitors like benserazide and carbidopa, which shift Levodopa's metabolic pathway towards the COMT route, enhancing Levodopa's presence in the central nervous system. Furthermore, MAO-B inhibitors like selegiline and rasagiline prolong the presence of endogenous dopamine and dopamine generated from levodopa in the brain (Jenner et al. 2021). COMT inhibitors like entacapone are frequently combined with levodopa to protect it from its primary peripheral metabolic route governed by COMT enzyme because 3-OMD competes with levodopa to cross the BBB. By inhibiting the transformation of L-dopa into 3-OMD, entacapone enhances levodopa's ability to enter the brain (Yamamoto et al. 2021). Variations in these genes are frequently linked to Parkinson's disease, influencing enzyme activity or leading to undesirable effects like dyskinesia.

Table 1. The Impact of COMT and MAO-B Gene Polymorphisms in Various Populations

Reference	Study Design	Population	Gene
(Sampaio et al., 2018)	Evaluating the genetic response of levodopa metabolism enzymes (MAO-B and COMT) to levodopa and developing its side effects after treatment.	One hundred sixty-two patients from Brazil were diagnosed with Parkinson's disease and underwent Levodopa treatment. The participants were separated into two categories: group 1,	MAO-B (rs1799836) G/G; G/A; A/A COMT (rs4680) L/L; H/L; H/H

		consisting of 76 individuals who received a daily dosage of 600 mg, and group 2, comprising 86 individuals who were administered a dose exceeding 600 mg.	
(Yamamoto et al. 2021)	Assessing the influence of COMT Val158Met polymorphism on the concentrations of Levodopa and 3-OMD when utilized alongside entacapone.	In Japan, 54 individuals have been diagnosed with Parkinson's disease.	COMT Val158Met L/L, H/L, H/H
(dos Santos et al. 2020)	Investigating the impact of polymorphisms in several genes, one of which is the COMT gene (rs4680), on the development of Levodopa-induced dyskinesia (LID)	In Brazil, 220 Parkinson's disease patients. Patients were classified as those who have experienced Levodopa-induced dyskinesia (LID) before (51 individuals) and those who have never reported LID (169 individuals)	COMT (rs4680) H/H; H/L; L/L
(Ivanova et al. 2018)	Investigating the potential connection between SNPs in the COMT gene and the development of LID	Two hundred thirty-two Parkinson's disease patients were of Caucasian ethnicity, and 56 individuals experienced dyskinesia.	The genes that are potentially related are rs165774, rs4818, rs4633, and rs4680
(Michałowska et al. 2020)	Evaluating the relationship between SNPs in several genes, including the COMT gene, MLIC in Parkinson's disease	Seventy-six Parkinson's disease patients based on the UK PDS Brain Bank criteria and 60 controls	COMT rs4680 AA, AG, GG
(Cheshire et al. 2014)	Evaluating the impact of SNPs in several genes, including the COMT gene, on the phenotype of increased risk of Levodopa-induced dyskinesia (LID).	Two hundred eighty-five cases of Parkinson's disease from the Australian Brain Bank tissue	COMT rs4680
(De Lau et al. 2012)	Assessing the correlation between the COMT Val158Met genetic variation and the	A total of 219 Parkinson's disease patients in the Netherlands	COMT Val158Met genotipe AA, AG, GG

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	emergence of dyskinesia.		
(Cui et al. 2022)	Investigating the relationship between MAO-B gene polymorphisms and the development of Parkinson's disease in China.	A total of 30 Parkinson's disease patients from China and PPMI	MAOB rs1799836 Gene
(Löhle et al. 2022)	Investigating the relationship between MAO-B gene polymorphisms and the risk of LID.	Thirty Parkinson's disease patients	MAOB (rs1799836) genotype CC/CT/TT

The development of Parkinson's disease seems to be heavily influenced by genetic tendencies related to dopamine metabolism. One crucial enzyme involved in this process is COMT, which deactivates dopamine (Chuan et al. 2015). Among the reviewed literature, the most common polymorphism occurrence in the COMT gene is rs4680. Located on chromosome 22, the COMT gene undergoes a substitution at codon 158, where methionine replaces valine due to a G to A transition, also referred to as Val158Met or (rs4680), representing the extensively studied polymorphism. The COMT haplotype offers a more comprehensive description of enzymatic activity. The three primary haplotypes are composed of four COMT SNP combinations: in the S-COMT promoter region (rs6269: A>G), a synonymous change (rs4633 C>T, His62His), and (rs4818: C>G, Leu136Leu), along with a non-synonymous change (rs4680: A>G, Val158Met). These three common haplotypes, determined by the four SNPs mentioned above, dictate enzymatic activity levels: A_C_C_G for low, A_T_C_A for medium, and G_C_G_G for high.(Drożdzik et al. 2013).

The COMT Val158Met gene polymorphism manifests in different genotypes, namely H/H, H/L, and L/L. Individuals with the H/H genotype typically exhibit heightened enzyme activity, while those with the L/L genotype show diminished enzyme activity. The non-synonymous SNP rs4680 within the COMT gene involves a G→A transition, resulting in a valine-methionine substitution at codon 148 (exon 4) of the transmembrane transcript variant. This substitution has been associated with the regulation of enzyme activity. The A allele is linked to a substantial 3-4 fold decrease in enzyme activity, designated as L (indicating low activity). Conversely, the G allele is labeled as H due to its association with increased enzymatic activity. In a study conducted by Sampaio et al. (2018), individuals with Parkinson's disease who had the COMT H/H genotype tended to require higher levodopa doses. From a clinical perspective, heightened COMT enzyme activity leads to a more rapid metabolism of L-DOPA, necessitating increased or more frequent Levodopa administration (Cheshire et al. 2014).

Recent investigations suggest that Single Nucleotide Polymorphisms (SNPs) in COMT and MAO-B can influence the risk of developing Parkinson's disease and its pharmacological treatment. There is a splicing enhancer created by a single-strand conformation polymorphism in intron 13 (rs1799836) of the MAO-B gene. This

polymorphism causes an adenine (A) to guanine (G) transition, which also alters the enzymatic activity (Sampaio et al. 2018).

Therefore, does the presence of polymorphism in a gene, when treated with an inhibitor such as entacapone, impact Levodopa, the primary therapy for Parkinson's disease? This query corresponds to the investigation conducted by Yamamoto et al. (2020), which explored the influence of COMT polymorphism on the pharmacokinetic effects of levodopa when administered alongside entacapone in the Japanese population. In this study, most patients had either H/L or H/H genotypes. The findings suggest that the Val158Met polymorphism can impact plasma levodopa levels when combined with entacapone, especially in patients with the H/H genotype with the highest plasma levodopa concentrations. As such, the Val158Met polymorphism is a valuable biomarker for determining the appropriate COMT inhibitor dosage.

Functional polymorphisms in dopamine metabolism genes, specifically COMT, can impact the development of LID in Parkinson's patients over time. Research has shown that individuals with the COMT LL genotype are more susceptible to developing LID due to the genotype's correlation with significant dopaminergic denervation and decreased enzymatic activity. These elements have the potential to interfere with the dopaminergic pathway, causing an accumulation of dopamine in the synaptic cleft, consequently leading to the initiation of LID (Dos Santos et al. 2020). Ivanova et al. reported that several COMT SNPs related to levodopa, such as rs165774, rs4818, rs4633, and rs4680, among these four SNPs, COMT Val158Met (rs46680) have an influence on the prevalence of LID in Parkinson's disease, but the impact is relatively small.

MAO inhibitors utilized in the treatment of Parkinson's disease primarily target the MAO-B enzyme, responsible for dopamine breakdown (Vuletić et al., 2021). MAO inhibitors utilized in the treatment of Parkinson's disease primarily target the MAO-B enzyme, responsible for dopamine breakdown (Vuletić et al., 2021). According to Cui et al., the MAOB rs1799836 variant is associated with Parkinson's disease development, particularly in non-motor symptoms such as cognitive impairment, and the emergence of a combination of motoric and non-motoric symptoms within the Chinese population. Conversely, in a study by Löhle et al., (2022) individuals with the MAOB CC/(C)/CT genotype, indicative of moderate to low enzymatic activity, exhibited a reduced risk of developing LID (levodopa-induced dyskinesia) compared to those with the MAOB TT/(T) genotype, which denotes high enzymatic activity.

Therapeutic Approaches and Future Perspectives

Levodopa frequently considered the benchmark therapy to manage Parkinson's disease, doesn't appear to reach optimal therapeutic effectiveness in every patient. Multiple factors contribute to the drug's therapeutic outcomes including disease progression, higher individual doses of Levodopa, drug combination, and genetic factors (Freitas et al., 2017). Several instances of genetic variations substantially impact the treatment outcomes for Parkinson's disease patients. Nevertheless, despite numerous attempts to pinpoint genetic factors that influence the risk of side effects or the ineffectiveness of therapy, the role of pharmacogenomics in Parkinson's disease remains largely unexplored and lacks uniform clinical guidelines. Pharmacogenomics in the modern era still needs to be emphasized

and further researched to draw conclusive findings, especially in long-term Levodopa treatment, which can result in adverse reactions like dyskinesia.

CONCLUSION

In some research reports, genetic polymorphisms of COMT and MAO-B have been linked to the administration of levodopa therapy in Parkinson's disease patients. However, the treatment with a pharmacogenomic approach in Parkinson's disease needs further investigation to provide conclusive findings regarding its therapeutic application.

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