



# **Neuropsychology and Genetics of Psychotropic Drug Users - Lithuanian COMT Gene Polymorphisms Frequencies**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Addiction is increasing worldwide, so there is a need to study the neuropsychology and genetics of the emergence of this process. In our study, we have focused on the characteristics of the COMT gene in psychotropic drug users.

**Aim of the Study:** Investigation of the frequency of COMT gene polymorphisms in psychotropic drug users in Lithuania as well to review literature of addiction neuropsychology and genetics.

**Materials and Methods:** The study involved 73 patients aged 18 to 75 years from InMedica Santariškės clinics who were tested for A (adenine), G (guanine) alleles and A/A, A/G and G/G COMT genotypes.

**Results:** The study analyzed the frequency of comt gene polymorphisms in 73 psychotropic drug users. It was identified A/A genotypes in 17, A/G in 37, G/G in 19 participants.

**Conclusion:** In studied cohort we detected high rates of more rare A/A genotype, which is related to lower amount of COMT enzyme and in result higher catecholamines level.

*Keywords: Neuropsychology; genetics; polymorphic frequencies; addiction; COMT gene.*

## 1. INTRODUCTION

Neuropsychology is a borderline area between psychology and neuroscience that focuses on mental, behavioral, and brain disorders. Addiction is one of the areas of research in neuropsychology. Drugs in addiction alters the brain system in such a way that quitting is difficult even for those who want to [1-3]. Addiction is a disease characterized by drug seeking and use that is compulsive or controllable regardless of harmful consequences [4,5]. "Sometimes it is difficult to understand why some individuals are more susceptible to developing addictive behavior than others. An individual's background, moral principles and social status determine whether someone may become an addict, but also a person's genetics is one of the most important factors in the development of addiction as far as modern medicine dictates. Heritability is responsible for 40-60% of the population's variability in developing an addiction., [6,7]. "There has been proof of both genetic factors that influence the susceptibility of developing an addiction in general, and other genes and sets of genes more specific for one substance or type of addiction., [6].

"Metabolic degradation of catecholamines such as dopamine, epinephrine, norepinephrine is an essential step in the regulation of neurotransmitters with specific enzymes contributing to the degradation process. The Catechol-o-methyl transferase enzyme encoded by the COMT gene is involved in dopamine degradation" [8]. This enzyme catalyzes the transfer of a methyl group from Sadenosylmethionine to catecholamines. This O-methylation is one of the major degradative pathways of the endogenous catecholamine transmitters. If this enzyme is low in activity it results in higher level of triggering neuromediators – catecholamines.

Genes are regulated in a very complex way, especially mRNA genes. Which gene and when is active and which is inactive depends on other nucleotide sequences present in the (regulatory) part of the mark [9]. These sequences are recognized by proteins called transcription factors encoded by special regulatory genes. There are several groups of transcription factors that interact with DNA in different ways: the gene is activated or repressed [2]. Genes encoding activating transcription factors are called activators, suppressing transcription factors - epistatic genes, suppressors, inhibitors. Many

genes are inactive in the cell; this is mainly due to changes in the chromatin structure in the chromosomes. Chromatin structure is regulated by special genes and environmental factors. All genes that affect the activity of genes that determine a particular trait are called modifier genes [10].

Constitutive genes are always active in the cell. They include the so-called housekeeping genes, which are necessary for the vital activity of the cell. Other genes that determine the adaptation of the organism to changing conditions (eg, high temperatures, light duration and intensity) are collectively called adaptation genes, according to the adaptation - with a specific name, for example, heat shock genes. Developmental, tissue-specific genes are active only at a certain time of development or only in certain cells, tissues; they determine cell differentiation, organ development. These and adaptive genes are also called luxury genes [11].

"Until genome-wide association studies (GWASs), genetic variant associations were not substantially established. GWASs compare the DNA of individuals that have different phenotypes for a specific trait or medical condition with a control group formed by similar individuals without the disease. Thus, GWASs identify single nucleotide polymorphisms (SNPs), as well as other DNA variants, that are associated with a disease' (Jacqueline, 2016). Unfortunately, SNPs explain only a part of the variance in substance addiction and further research is required. The first GWAS conducted on the subject of addiction was regarding nicotine dependence., [6].

"The relationship between genetic influences and environmental factors took center stage in terms of new findings. It has been pointed out that these two factors can modulate each other. More so, childhood adversity, stressful life events and lower levels of education seem to have an effect over alcohol-metabolizing, dopaminergic and serotonin transporter genes., [12].

"Epigenetics studies the heritable changes in phenotype that do not occur after DNA sequence alterations. DNA methylation and modifications of histones are the most studied epigenetic alterations. There are also epigenetic enzymes that mediate DNA demethylation and have important roles in learning, memory, neurodevelopment, but also in some psychiatric and neurologic disorders., [12]. "There are

studies regarding epigenetic changes in the molecular processes that result in addiction to psychostimulants. Repeated stressful life events are capable of causing epigenetic changes. Given that addicts are individuals with stressful lives, this may explain why these individuals are more vulnerable to neuroplastic changes induced by drugs, changes that constitute the substrate of addiction, [5].

Mental, neurological, and drug-related illnesses can cause brain dysfunction and are a major cause of the global disease burden. The burden of disease associated with neurological disorders also increases with increasing life expectancy. The societal demands on the cognitive functions of both working and studying people are high, and adolescents with cognitive impairments may lose their ability to work or study [5].

Analysis of biological fluids, electrophysiological examinations contribute to the clarification, confirmation or refutation of the diagnosis [3]. Despite the high level of modern technology, not all areas of the brain necessary for diagnosis can be adequately examined. Both neurological and mental illnesses differ in that technology-based research does not always show objective change, especially in the early stages of illness. In such cases, changes are recorded based on the patient's subjective complaints by performing cognitive function tests and observing the patient. There are also cases where obvious changes in the brain are seen and the patient's complaints are minor [3]. Each case is individual, requiring thorough investigation.

## 2. METHODOLOGY

The study involved 73 patients from InMedica Santariškės clinics who were tested for A/A, A/G and G/G COMT genotypes during 2000 January till 2022 May. All patients, aged from 18 till 75 years of age were users of psychotropic drugs (at least one of these: haloperidol, alprazolam, bromazepam, mirtazapin, diazepam, quetiapin).

### 2.1 Genetic Analysis

Primers sequences for rs165774 are as follows:

PCR Primer 1:  
ACGTTGGATGGCCCTACCTAGCCAGGCAT;

PCR Primer 2:  
ACGTTGGATGTCCCAGAACTGGACTGC;

Extension Primer: cgct CCTCGTGCTCCTAGTC.

## 3. RESULTS

A study of the frequency of COMT gene polymorphisms in addictive neuropsychology and genetics in 73 patients. Rare genotype A/A, which results in reduced COMT enzyme level was quite high: 23.29% (Table 1).

**Table 1. COMT gene polymorphism frequency**

| Comt gene | Frequency | Percentage |
|-----------|-----------|------------|
| A/A       | 17        | 23.29%     |
| A/G       | 37        | 50.68%     |
| G/G       | 19        | 26.03%     |

All alleles are in pairs, so 73 patients (genotypes) results in total 146 alleles. After calculation the frequency of A allele was 71 (48.63%), and A allele was 75 (51.37%).

## 4. DISCUSSION

We have found that A/A genotype is detected in 23.29% of psychotropic drug users.

This genotype enables COMT enzyme to be low in activity. It results, that epinephrine and other catecholamines are not so quickly removed from synapses. This may cause increases anxiety and irritability.

Several studies have shown association of Val158 with impulsive behaviour and substance abuse [2]. Met158 has been reported to be associated with low activity of enzyme and literature suggests Asian population in which risk appears to be associated with Met158 [8].

There are also studies implicated COMT polymorphism conferring risk and GABRA polymorphism as a protective genotype for addiction [13].

“Sometimes it is difficult to understand why some individuals are more susceptible to developing addictive behavior than others. An individual's background, moral codes and social status determine whether someone may become an addict, but also a person's genetics is one of the most important factors in the development of addiction as far as modern medicine dictates. Heritability is responsible for 40-60% of the population's variability in developing an addiction, [9].

There has been proof of both genetic factors that influence the susceptibility of developing an addiction in general, and other genes and sets of genes more specific for one substance or type of addiction.

“COMT gene is associated with different psychiatric conditions. It is well established that COMT is a strong candidate gene for substance use disorder and schizophrenia. Recently we identified two SNPs in COMT (rs4680 and rs165774) that are associated with schizophrenia in an Australian cohort, [7].

“Until genome-wide association studies (GWASs), genetic variant associations were not substantially established. GWASs compare the DNA of individuals that have different phenotypes for a specific trait or medical condition with a control group formed by similar individuals without the disease. Thus, GWASs identify single nucleotide polymorphisms (SNPs), as well as other DNA variants, that are associated with a disease. Unfortunately, SNPs explain only a part of the variance in substance addiction and further research is required. The first GWAS conducted on the subject of addiction was regarding nicotine dependence, [14].

“The relationship between genetic influences and environmental factors took center stage in terms of new findings. It has been pointed out that these two factors can modulate each other. For example, one study concluded that genetic influences were decreased in adolescent smoking twins when the parental monitoring increased’ [1]. More so, childhood adversity, stressful life events and lower levels of education seem to have an effect over alcohol-metabolizing, dopaminergic and serotonin transporter genes, [15].

“Epigenetics studies the heritable changes in phenotype that do not occur after DNA sequence alterations. DNA methylation and modifications of histones are the most studied epigenetic alterations. There are also epigenetic enzymes that mediate DNA demethylation and have important roles in learning, memory, neurodevelopment, but also in some psychiatric and neurologic disorders. There are studies regarding epigenetic changes in the molecular processes that result in addiction to psychostimulants. Repeated stressful life events are capable of causing epigenetic changes. Given that addicts are individuals with stressful lives, this may explain why these individuals are more vulnerable to neuroplastic changes induced

by drugs, changes that constitute the substrate of addiction, [7].

Mental, neurological, and drug-related illnesses can cause brain dysfunction and are a major cause of the global disease burden. The burden of disease associated with neurological disorders also increases with increasing life expectancy. The societal demands on the cognitive functions of both working and studying people are high, and adolescents with cognitive impairments may lose their ability to work or study [16].

The development of clinical neuropsychology has accelerated significantly over the last decade. It is driven by the growing knowledge of the links between various diseases / conditions and brain activity, cognitive processes and behavior. Neuroscopy (such as computed tomography of the brain, magnetic resonance imaging (MRI), positron emission testing) and functional testing (such as functional MRI) and other new technologies make it possible not only to diagnose more quickly, to prescribe treatment, but also to see what is going on in the patient’s brain, the extent to which individual structures are active, how those structures interact [10].

Analysis of biological fluids, electrophysiological examinations contribute to the clarification, confirmation or refutation of the diagnosis. Despite the high level of modern technology, not all areas of the brain necessary for diagnosis can be adequately examined. Both neurological and mental illnesses differ in that technology-based research does not always show objective change, especially in the early stages of illness. In such cases, changes are recorded based on the patient's subjective complaints by performing cognitive function tests and observing the patient. There are also cases where obvious changes in the brain are seen and the patient’s complaints are minor. Each case is individual, requiring thorough investigation [11].

When a teen comes to a neurologist, the examination begins with an assessment of the state of consciousness. Detailed neurological clinical examination requires considerable time and skill, so only superficial orientation assessment or short tests of cognitive function are usually used to assess mental status. This is often not enough. Comprehensive neuropsychological assessment requires precise work and knowledge. Subtle mental and behavioral disorders and their possible etiology are assessed, excluding factors that could

mislead or otherwise distort the results, as well as the diagnosis. Therefore, a neuropsychological evaluation should be performed by a qualified neuropsychologist. The practice of the neuropsychologist profession requires a high degree of general competence of a clinical psychologist, specific methodological knowledge, and the ability to collaborate [17,18]. During counselling of people with addiction, some organic diseases of central nervous system must be excluded. Neuroscopy (such as computed tomography of the brain, magnetic resonance imaging (MRI), positron emission testing) and functional testing (such as functional MRI) and other new technologies make it possible not only to diagnose more quickly, to prescribe treatment, but also to see what is going on in the patient's brain, the extent to which individual structures are active, how those structures interact [19].

People with mental illness also often have cognitive difficulties [20]. Cognitive and emotional symptoms are often interrelated, so it is very important to properly assess these symptoms and determine their causes. Thus, health services for people with both neurological and mental illness should include consultation with a neuropsychologist [13].

Although the evidence is mixed, some research has linked catechol-O-methyltransferase (COMT) rs4680 (or COMT Val158Met) to the development of gambling or drinking problems; however, no molecular genetic study has jointly examined gambling and drinking problems [17]. Similar to our results the investigators in Turkey have found, that COMT A/A genotypes frequencies in synthetic cannabinoid users were 20.4% [21]. This number is higher comparing to controls – 16% [21]. Other study tried to explain why COMT A allele maybe related to psychotropic drug use. They have found that COMT Met/Val genotype (that includes A allele) was more common among depressed individuals than among controls [22].

From the analysis of the obtained data, we can see that the mechanisms of addiction are complex due to the disruption of neurotransmitters, environmental and genetic factors.

## 5. CONCLUSION

In studied cohort we detected high rates of more rare A/A genotype, which is related to lower

amount of COMT enzyme. Elevated epinefrine due to these changes may be risk factor related to anxiety and probably to addiction. These findings show the importance of sympatholitic agents usage in these patients especially plant based (*Passiflora incarnata*, *Melissa officinalis*, *Crataegus oxycanta* etc.).

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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