ejpmr, 2024, 11(5), 04-12

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

IMPLICATIONS OF GENETIC VARIANTS RS2515641 AND RS20700672 OF *CYP2E1* GENE AND RS4680 OF THE *COMT* GENE IN PATHOGENESIS OF LYMPHOMAS

Júlia de Dio Carvalho[1]*, Thaís Mitie Ogasawara[1*], Laila Zolin Tominaga[1], Mirela De Lima Dias[1], Carlos Eduardo Coral de Oliveira[2]

[1]Medical Academics of Pontifical Catholic University of Paraná.
[2]PhD of Pontifical Catholic University of Paraná.

***Corresponding Author: Júlia de Dio Carvalho**

Medical Academics of Pontifical Catholic University of Paraná.

Article Received on 01/03/2024 **Article Revised on 22/03/2024** **Article Accepted on 11/04/2024**

ABSTRACT

Introduction: Lymphoma is a neoplasm that affects the lymphoid tissue, classified into Hodgkin's lymphoma and non-Hodgkin's lymphoma. Its pathophysiology is still unclear, indicating the involvement of genetic mechanisms. Therefore, changes in the polymorphism of the *COMT* gene and the CYP2E1 enzyme may be related to the pathogenesis of lymphoma. **Objectives:** Investigate the allele and genotype frequency of the polymorphism rs4680 of the *COMT* gene and rs2515641 and rs2070672 of the *CYP2E1* gene in individuals with lymphomas and controls. M**ethodology:** Peripheral blood samples from 165 volunteers were submitted to analysis of polymorphisms by PCR. **Results:** No association was observed between the presence of the A allele *COMT* gene and susceptibility to lymphomas, whereas the recessive genotype (OR= 2.91; 95%CI= 1.06-7.41; p=0.05) and the recessive genetic model (OR= 2.81; 95%CI= 1.09-7.10; p=0.04) were associated with a higher risk of developing lymphoma in this population. The CYP2E1 rs251561 polymorphism is not associated with the development of lymphomas. However, the presence of the allelic variant (OR= 0.38; CI95%= 0.20-0.69; p= 0.002) as well as the recessive genotypes (OR= 0.19; CI95%= 0.06-0, 63; p= 0.008) and dominant (OR= 0.38; 95%CI= 0.17-0.87; p= 0.03), recessive (OR= 0.25; 95%CI= 0.08) genetic models -0.81; p= 0.02) and additive (OR= 0.32; 95%CI= 0.15-0.67; p= 0.004) of CYP2E1 variant rs2070672 were significantly related to protection against lymphoma. **Conclusion:** The COMT rs4680 genetic polymorphism appears to influence susceptibility to Hodgkin's and non-Hodgkin's disease. The CYP2E1 rs2070672 genotypes, on the other hand, demonstrate its function as a molecular marker for lymphomas.

KEYWORDS: Lymphomas, Polymorphism, CYP2E1, COMT.

1. INTRODUCTION

Lymphomas are neoplasms originating from lymphoid cells that are found in lymphoid tissues.[1] It is divided into two main groups: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Lymphomas is considered the third most common neoplasm that mainly affects the head and neck region.[2]

It is known the onset of lymphoma involves changes in the adaptive and innate immune system, significantly reducing cytotoxic T lymphocytes. Thus, there is an imbalance of T-cell stimulating and inhibitory signals.[3] Furthermore, the exact etiology correlation is unknown, there are indications that environmental, hereditary, occupational factors, exposure to certain chemical agents and even infectious agents are related with the onset of lymphomas.[4]

Faced with the challenge of the best therapeutic approach for lymphoma and understanding its pathophysiology, genetic studies on oxidative stress in the context of inflammation, DNA repair and induction of the NF-κB pathway are relevant.[5] Therefore, several studies suggest a relationship between the loss of function of catechol-O-methyltransferase enzymes (*COMT*) and the occurrence and development of cancer.[6] Because it is an enzyme that influences the metabolism of catecholamines and consequently the intensity of metabolic processes, an imbalance between the amount of pro-inflammatory cytokines and growth factors can cause the appearance of tumors.[7]

The *COMT*, gene located on chromosome 22, band q11.2 composed of six exons, is responsible for catalyzing the O-methylation of catechol substrates by transferring the methyl of S-adenosyl-I-methionine (SAM) to a hydroxyl group of catechol substrates via Mg^2. The alteration of the *COMT* gene was described by Lotta et al. who reported the occurrence of the polymorphism, resulting in the change of amino acids from valine (Val) to methionine (Met) at codon 158.[8,9]

The presence of the Val158Met polymorphism influences the enzymatic activity, in individuals homozygous for the amino acid Val (GG) the enzymatic activity is high. On the other hand, the presence of Met/Met (AA) the enzymatic activity is low and carriers of heterozygous genotypes Val/Met (GA) have intermediate enzymatic activity.[10]

Allelic variations involving the *COMT* gene modify estrogen metabolism, which contributes to increased B cells and factors associated with the risk of NHL.[4,11] Other studies have also analyzed this mechanism with the development of pathologies such as gastric cancer, schizophrenia, pain, depression and chronic fatigue, due to the process of dysregulation of sympathetic function and DNA methylation.[12-14] In addition, the presence of the polymorphism also had an impact on certain side effects during chemotherapy in patients with breast cancer and lymphoma, resulting in cognitive impairment and consequently damage to their life.[15,16]

In this context, other polymorphic variants also seem to be related to the development of neoplasms, such as genes involved in carbon metabolism and oxidative stress. One of them would be the genetic variants of enzymes related to phase I metabolism of cytochrome P450, being prevalent in patients with lymphomas.[4,17]

The cytochrome P450 (CYP450) enzymes carry out the oxidative metabolism of numerous exogenous and endogenous compounds and turn them into reactive metabolites. In particular, the CYP2E1 enzyme is responsible for activating low molecular weight compounds such as ethanol, benzene, vinyl chloride and N-nitrosamines. Compared to other enzymes, CYP2E1 has a high redox potential and can induce lipid peroxidation, and consequently, increase the production of reactive oxygen species leading to increased susceptibility to carcinogenesis.[18]

In view of this, there is strong experimental evidence that polymorphisms of the *CYP2E1* gene, located on chromosome 10 in the 10q24.3 region, are related to the activation of carcinogenic compounds, with interactions of these polymorphisms being observed with lung cancers, head and neck squamous cell and colorectal cancer.[18,19]

A relevant polymorphism described in this gene is the *CYP2E1 RsaI*, in which the replacement of a cytosine by thymine in the 5' regulatory region can give rise to 3 distinct genotypic profiles: CC as wild-type genotype, heterozygous CT genotype and TT genotype, with the presence of homozygous mutation, in which it promotes lower basal activity of the CYP2E1 enzyme and, thus, has been identified by studies as a genotype with a lower risk for developing lung cancer.[20] Furthermore, carriers of the rs2070672 polymorphism, which presents wild genotype GG, heterozygosity GA and mutated genotype AA, had a higher risk of developing nasopharyngeal carcinoma.[21]

Therefore, there is evidence of the association of polymorphisms of the *COMT* gene and the *CYP2E1* gene with greater susceptibility to cancerous diseases and influence on the prognosis of these patients using chemotherapy. Regarding these mechanisms, the present study aimed to elucidate the impact of the Val158Met polymorphism of the *COMT* gene, and the potential risk of the rs2515641 and rs2070672 variants of the *CYP2E1* gene on the susceptibility and progression of lymphomas.

2. OBJECTIVE

Analyze the allele and genotype frequency of the rs4680 polymorphism of the *COMT* gene and rs2515641 and rs2070672 polymorphisms of the *CYP2E1* gene in individuals with lymphoma and in control individuals. In addition, evaluate possible implications of polymorphic variants in the susceptibility and prognosis of these patients.

3. METHOD

The research is a retrospective case-control study, with a total sample number (n) of 165 subjects. Of these samples, 86 individuals were diagnosed with lymphoma (40 are HL and 46 are NHL); the other 79 subjects are controls, without neoplasia. The study participants were aged between 18 and 86 years, regardless of gender.

The project was approved by the Research Ethics Committee Involving Human Beings of the Pontifical Catholic University of Paraná with protocol number 3.372.788 and also by the Research Ethics Committee Involving Human Beings of the State University of Londrina with opinion 189/2013; both being in agreement with the resolution 466/12, of the Ministry of Health, in its ethical questions. Also has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

The blood extraction was carried out at Hospital do Câncer de Londrina, Paraná, during the years 2014 to 2019. Peripheral blood samples were collected in two EDTA tubes, DNA extraction from total leukocytes was performed, using the Salting Out technique, described by Miller et al. For the study of genetic variants, the reaction primers were designed according to the gene sequence deposited in GeneBank (NCBI).

With the synthesized primers, dilution and concentration quantification were performed, followed by polymerase chain reaction (PCR), performed in an Applied Biosystems 2720 thermocycler (Thermo Scientific™, USA), using a negative and a positive control, in the sense of identify contaminants and the success of reactions, respectively. The amplified fragments were analyzed by electrophoresis in agarose gel (2%) for 90 minutes at 100V and stained with Sybr Safe.

All statistical analyzes were performed using SPSS® Statistics 20 (IBM®, Armonk, New York, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) softwares. All tests were two-tailed and the significance level adopted was 5%, they were also based on non-parametric variables, as the data did not show normal distribution through the Shapiro-Wilk test ($p>0.05$). Absolute and relative values were used to show the distribution of alleles and genotypes.

Genotypes were tested for Hardy-Weinberg equilibrium using an electronic tool (Bińkowski and Miks, 2018). In cases where the observed number of individuals in one of the cells was less than 5, the chi-square test and the p-value were analyzed with Yates' correction for continuity.

To assess differences in genotype and allele distributions between groups, Chi-square ($\chi 2$) and Fisher's exact tests were applied, respectively. To test the additive genetic association model, the $\chi 2$ test for trend (Cochran-Armitage test) was applied.

Binary logistic regression models were tested to obtain odds ratios (ORs) and 95% confidence intervals (95% CI) in case-control analyses. The association models tested in these analyzes were: genotypic (heterozygotes or variant homozygotes vs wild-type homozygotes), dominant (heterozygotes and variant homozygotes as a single group vs wild-type homozygotes), recessive (variant homozygotes vs heterozygotes and wild-type homozygotes as a single group) and additive. (variant homozygotes multiplied by 2 and heterozygotes as a single group vs wild-type homozygotes).

4. RESULTS

4.1. ANALYSIS OF THE GENOTYPE FREQUENCY OF THE *COMT* GENE

Table 1: Quantity and percentage of genotypic frequencies of the rs4680 polymorphism.

COMT rs4680	Case	Control
GG	25 (33,78%)	30 (41,01%)
GA	32 (43,24%)	36 (49,3%)
AA	17 (22,97%)	7 (9,59%)

To assess possible deviations from the Hardy-Weinberg equilibrium, the frequency observed for the COMT rs4680 polymorphism was consulted using the chi-square test. Note that the distribution of alleles and genotypes is consistent with equilibrium.

4.2. ANALYSIS OF THE GENOTYPE FREQUENCY OF THE *CYP2E1* GENE

Table 2: Quantity and percentage of genotypic frequencies of the rs2515641 polymorphism.

CYP2E1 rs251561	Case	Control
CC	57 (73,08%)	40 (50,7%)
CT	17 (21,80%)	25 (37,32%)
TT	4 (5,12%)	2 (2,98%)

Table 3: Quantity and percentage of genotypic frequencies of the rs2070672 polymorphism.

CYP2E1 rs2070672	Case	Control
AA	27 (61.36%)	21 (37,50%)
AG	13 (29,36%)	19 (33,50%)
GG	4 (9,10%)	16 (28,58%)

From the allelic and genotypic frequencies, it was observed that the data established in the chi-square test with Yates correction, the distributions are consistent with the Hardy Weinberg equilibrium at the 0.05 significance level.

4.3. *COMT* GENE ASSOCIATION STUDY ANALYSIS

The analysis of the case-control association study showed the allele frequency of variant A was not associated with lymphoma (p= 0.12) (Table 4). Likewise, the heterozygous genotype and the dominant and additive genetic models were also not associated with susceptibility to lymphoma in this population ($p>0.05$).

On the other hand, the AA variant homozygous genotype was associated with a higher risk for the development of lymphomas (p= 0.05), where patients with lymphomas had a 2.91 times greater chance of developing these neoplasms (95%CI= 1. 06-7.41). Also, the recessive genetic model was associated with increased risk for susceptibility to lymphomas (OR= 2.81; 95%CI= 1.09-7.10; p=0.04).

Table 4: Association between COMT rs4680 polymorphism and susceptibility to develop lymphoma.

		Case		Control				
		n	%	n	%	p value*	OR	IC (95%)
Allele Frequency								
	Allele G	82	56.16	96	65.75	0.12	1.45	0.94-2.40
	Allele A	64	43.84	50	34.25			
Genotypes								
Wild Homozygous	GG	25	33.78	30	41.10	-	-	-
Heterozygous	GA	32	43.24	36	49.32	0.99	1.07	0.51-2.23
Variant Homozygous	AA	17	22.97	7	9.59	**0.05**	**2.91**	**1.06-7.41**
Dominant Model								
	GA+AA vs GG	49 vs 25		43 vs 30		0.4	1.37	0.70-2.63
Recessive Model	AA vs GG+GA	17 vs 57		7 vs 66		**0.04**	**2.81**	**1.09-7.10**
Additive Model	2.(AA)+GA vs GG	66 vs 25		50 vs 30		0.19	1.58	0.83-3.10

*Fisher's Exact Test. OR= Odds ratio. CI= confidence interval. In bold, the statistically significant results are highlighted.

4.4. *CYP2E1* GENE ASSOCIATION STUDY ANALYSIS

For the CYP2E1 rs2515641 polymorphism, the study revealed there was no association between the presence of the allele and the risk of developing lymphomas in the studied population. Beyond that, the genotypic analysis and the dominant, recessive and additive genetic models showed no association with the risk of lymphoma (Table 5).

On the other hand, the case-control association study for the CYP2E1 rs2070672 polymorphism revealed the presence of the G allele (variant) represents a protective factor for the development of lymphoma in this population (OR= 0.38, 95%CI= 0.20 – 0.69; p= 0.002). Likewise, the GG variant homozygous genotype and dominant, recessive, and additive genetic models were also associated with protection against lymphoma in this population ($p<0.05$; Table 6).

Table 5: Association between CYP2E1 rs2515641 polymorphism and susceptibility to develop lymphoma.

		Case		Control				
		n	%	n	%	p value*	OR	IC (95%)
Allele Frequency								
	Allele C	131	83.97	105	78.36	0.23	0.69	0.39-1.26
	Allele T	25	16.03	29	21.64			
				134				
Genotypes								
Wild Homozygous	CC	57	73.08	40	59.70	-	-	-
Heterozygous	CT	17	21.79	25	37.31	0.06	0.48	0.23-102
Variant Homozygous	TT	4	5.13	2	2.99	0.99	1.4	0.31-7.63
Dominant Model								
	CT+TT vs CC	21 vs 57		27 vs 40		0.11	0.55	0.26-1.09
Recessive Model	TT vs CC+CT	4 vs 74		2 vs 65		0.69	1.76	0.40-9.44
Additive Model	2.(TT)+CT vs CC	25 vs 57		29 vs 40		0.17	0.61	0.31-1.27

*Fisher's Exact Test. OR= Odds ratio. CI= confidence interval.

Table 6: Association between CYP2E1 rs2070672 polymorphism and susceptibility to develop lymphoma.

		Case		Control				
		n	%	n	%	p value*	OR	IC (95%)
Allele Frequency								
	Allele A	67	76.14	61	57.43	**0.002**	**0.38**	**0.20-0.69**
	Allele G	21	23.86	51	45.54			
Genotypes								
Wild Homozygous	AA	27	61.36	21	37.50	-	-	-
Heterozygous	AG	13	29.55	19	33.93	0.25	0.53	0.22-1.37
Variant Homozygous	GG	4	9.09	16	28.57	**0.008**	**0.19**	**0.06-0.63**
Dominant Model								
	AG+GG vs AA	17 vs 27		35 vs 21		**0.03**	**0.38**	**0.17-0.87**
Recessive Model	GG vs AA+AG	4 vs 40		16 vs 40		**0.02**	**0.25**	**0.08-0.81**
Additive Model	2.(GG)+AG vs AA	21 vs 27		51 vs 21		**0.004**	**0.32**	**0.15-0.67**

*Fisher's Exact Test. OR= Odds ratio. CI= confidence interval. In bold, the statistically significant results are highlighted.

5. DISCUSSION

It is known lymphomas are in a heterogeneous group of cancers, which does not have a widely known etiology, but there is an association with genetic mutations and the involvement of risk factors, such as infections and immunodeficiency.[22] Therefore, the study of genetic variants has been widely carried out in recent research, due to the possible interaction between inherited genetic components (polymorphisms) and environmental exposure factors.[4,6,17]

In the case of lymphomas, low penetrance variants, such as COMT rs4680, may represent a possible molecular marker for evaluation in the disease.[8,9] And among the metabolizing enzymes of the CYP450 family, CYP2E1 has an important particularity because it is involved in the activation of more than 85 xenobiotics and carcinogenic substances.[19]

In this study, the variant homozygous genotype and the recessive genetic model of the *COMT* gene were associated with greater susceptibility to the disease, with just over 2.8 times more chance of developing lymphoma in this group. This finding suggests a possible participation of this variant in the lymphomagenesis of Hodgkin's and non-Hodgkin's disease.

In a case report of a patient with B-cell chronic lymphocytic leukemia, described by Sak K. et al (2017), it was demonstrated the presence of the Val158Met polymorphism has an implication in carcinogenesis. The results obtained associated the greater enzymatic activity with a protective factor mechanism against chronic lymphocytic leukemia.[9]

This result was different from that found in individuals with HL and NHL in the analysis of the genotypic frequency of the rs4680 polymorphism in this study. It was observed that the heterozygous genotype was not associated with susceptibility to lymphomas. However, the recessive genotype was associated with a higher risk for developing lymphomas compared to the homozygous wild-type genotype.

In addition, evidence suggests genetic susceptibility to the development of lymphomas is associated with the individual's response to exposure to exogenous compounds with consequent interaction with the pathogenesis of the studied disease, and these *CYP2E1* gene polymorphisms are associated with the diagnosis of patients with non-Hodgkin's lymphoma.[23]

Furthermore, the geographical variation CYP2E1 polymorphisms has being shown around the world is an important point for analysis, since there are numerous variants and one of its main functioning polymorphisms is the *CYP2E1* RsaI (or rs2515641), which evince the G allele mutated which its frequency in Caucasians is 1% to 5%; and in Asians it is around 28%.[24]

From this analysis, it is possible to observe that the catalytic activity of the CYP2E1 enzyme presents individual changes which are related to exposure to environmental factors, genetic polymorphisms and other determinants, such as obesity, fasting and liver dysfunction. In addition to the expression of such enzyme being altered by other compounds, which promotes different risks in each individual for the appearance of tumors.[19,25]

The presence of the variant in rs2515641 modifies the peptide sequence of the CYP2E1 protein, as it represents a missense variant. Thus, it is expected there is an influence on the role of this enzyme in biotransformation, as it has less catalytic activity in the presence of the T variant allele.[26] However, studies are

needed to evaluate the variation in protein expression in experimental models subjected to exposure to carcinogenic xenobiotics or even the antitumor chemotherapy itself, in order to demonstrate its role in protecting against lymphomas.

Moreover, the CYP2E1 rs2515641 polymorphism is related to lower gene expression both at the level of messenger RNA and for the protein itself, meaning that the mutation affects transcription and translation of the gene. Due to this effect, it was associated with a greater risk for the development of breast and bladder cancer.[26-28]

Importantly, in this study, the variant allele for the rs2070672 polymorphism was associated with a lower risk for developing lymphomas. Although other variants have been related to altered CYP2E1 expression[29], this polymorphism is located in the promoter region, upstream of the gene. The function of this variant has not yet been demonstrated in other studies.

The rs2070672 variant is strongly associated with the incidence of nasopharyngeal carcinoma[29], on the other hand, in this study the presence of the variant allele, as well as the homozygous genotype, and the dominant, recessive and additive genetic models showed a protective role for the allele and variant genotypes in lymphomagenesis. It can be suggested there are indications of the influence of this polymorphism on carcinogenesis and enzymatic dysregulation that need to be analyzed in models of expression or even function of this enzyme.

Besides, in this study, evidence for a higher risk of developing lymphomas was associated with the presence of the AA variant homozygous genotype for the COMT rs4680 polymorphism. As this polymorphism is of the missense type, there is a substitution of a codon in the sequence of the transcribed RNA, which results in the exchange of a valine for a methionine at amino acid 158.[13,14]

This alteration modifies the site of interaction between COMT and its ligands and results in changes in the enzymatic activity profile in relation to the metabolism of endogenous and exogenous compounds. Notably, the rs4680 variant of COMT was associated with a lower need for opioid analgesics, such as morphine, in cancer patients[30], although it was associated with a greater tendency to side effects in the central nervous system.[31]

Possibly the influence of these genetic polymorphisms on susceptibility to Hodgkin's and non-Hodgkin's disease is partial, as well as other low penetrance variants, and depends on the modulation that occurs with *COMT* and *CYP2E1*. It is suggested that further studies be carried out with the possibility of covering a larger sample, in addition to searching for other variants of the same gene, so that it is possible to assess the impact of haplotypic structures of *COMT* and *CYP2E1* on the pathogenesis of the disease.

6. CONCLUSION

Given the above, there are strong indications that the COMT rs4680 polymorphism and the CYP2E enzyme may influence the risk of developing lymphomas, especially in the Brazilian population. Furthermore, as it is a functional genetic polymorphism, it is expected that the altered activity of the COMT enzyme may influence the response to pharmacological therapy used in patients with lymphomas.

Another consideration of this present study concerns the rs2070672 polymorphism, which showed a strong protective relationship against the studied neoplasm, both for Hodgkin lymphomas and for non-Hodgkin lymphomas. Finally, it is imperative to recruit a larger sample to expand the study of the impact of this gene on the development of malignant hematological neoplasms.

7. ACKOWLEDGEMENTS

First of all, we would like to thank the technician from the PUCPR Campus Londrina laboratory, Claudia, who guided us on the necessary processes to carry out this project. We are especially grateful to the patients in this study, who were willing to help science and thus improve our knowledge on the topic addressed. Furthermore, we would like to thank the Pontifical Catholic University of Paraná, an institution that encourages scientific initiation and successfully provides us with the necessary knowledge for the formation of an excellent medical professional.

Finally, our special acknowledgements to our supervisor Prof. Carlos Eduardo Coral de Oliveira, who guided us with affection and knowledge throughout this project. We are immensely grateful for all the time and attention provided by Prof. Carlos Eduardo, the existence of this work would not be the same without such help.

8. REFERENCES

1. Wang L, Qin W, Huo YJ, et al. Advances in targeted therapy for malignant lymphoma. Signal Transduct Target Ther., 2020; 5: 1–45.
2. Singh R, Shaik S, Negi B, Rajguru J, Patil P, Parihar A, et al. Non-Hodgkin's lymphoma: A review. J Fam Med Prim Care., 2020; 9(4): 1834.
3. Joshi M, Ansell SM. Activating the Antitumor Immune Response in Non-Hodgkin Lymphoma Using Immune Checkpoint Inhibitors. J Immunol Res., 2020; 2020.
4. Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. Haematologica, 2007; 92: 960–969.
5. Wang SS. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. Carcinogenesis, Apr. 5, 2006; 27(9): 1828–34.
6. Rai V, Yadav U, Kumar P. Impact of catechol-O-methyltransferase val 158Met (rs4680)

polymorphism on breast cancer susceptibility in Asian population. Asian Pacific J Cancer Prev., 2017; 18(5): 1243–50.
7. Ivanova TI, Potapov AL, Zemskova D V., Khorokhorina VA, Shegai P V., Ivanov SA, et al. Evaluation of the Association of rs4680 COMT Polymorphism and Clinical Parameters of the Tumor in Colorectal Cancer (a Pilot Study). Bull Exp Biol Med., 2020; 170(2): 254–7.
8. Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I, et al. Kinetics of Human Soluble and Membrane-Bound Catechol O-Methyltransferase: A Revised Mechanism and Description of the Thermolabile Variant of the Enzyme. Biochemistry [Internet], Apr. 4, 1995; 34(13): 4202–10.
9. Sak K. Polymorphisms in COMT and SULT1A1 Genes and Chronic Lymphocytic Leukemia Risk in Estonia. Eurasian J Med Oncol, 2019; 3(4): 281–8.
10. Sak K. Change of COMT Val158Met Genotype in Tumoral B Cells of a Chronic Lymphocytic Leukemia Patient: A Case Report. Ann Hematol Oncol, 2017; 4(1): 0–3.
11. Skibola CF. Polymorphisms and Haplotypes in the Cytochrome P450 17A1, Prolactin, and Catechol-O-Methyltransferase Genes and Non-Hodgkin Lymphoma Risk. Cancer Epidemiol Biomarkers Prev., Oct. 1, 2005; 14(10): 2391–401.
12. Tahara T, Shibata T, Arisawa T, Nakamura M, Yamashita H, Yoshioka D, et al. Impact of catechol-O-methyltransferase (COMT) gene polymorphism on promoter methylation status in gastric mucosa. Anticancer Res., 2009; 29(7): 2857–61.
13. Hoenemeyer TW, Baidwan NK, Hall K, Kaptchuk TJ, Fontaine KR, Mehta TS. An Exploratory Analysis of the Association Between Catechol-O-Methyltransferase and Response to a Randomized Open-Label Placebo Treatment for Cancer-Related Fatigue. Front Psychiatry, June 2021; 12: 1–8.
14. Sak K. The Val158Met polymorphism in COMT gene and cancer risk: role of endogenous and exogenous catechols. Drug Metab Rev., 2017; 49(1): 56–83.
15. Li WB, Zhao JB, Ding KE, Chao BC HH, Li AG C-SR, Cheng HA, et al. Catechol-O-Methyltransferase Gene Polymorphisms and the Risk of Chemotherapy-Induced Prospective Memory Impairment in Breast Cancer Patients with Varying Tumor Hormonal Receptor Expression, 2020.
16. Janelsins MC, Mohamed M, Peppone LJ, Magnuson A, Belcher EK, Melnik M, et al. Longitudinal Changes in Cognitive Function in a Nationwide Cohort Study of Patients With Lymphoma Treated With Chemotherapy. JNCI J Natl Cancer Inst., 2022; 114(1): 47–59.
17. de Sousa Mesquita A, Zamora-Obando HR, Neves dos Santos F, et al. Volatile organic compounds analysis optimization and biomarker discovery in urine of Non-Hodgkin lymphoma patients before and during chemotherapy. Microchem J., 2020; 159: 105479.
18. Wang L, Ren G, Le J, et al. Genetic polymorphism analysis of cytochrome P4502E1 (CYP2E1) in a Chinese Tibetan population. Med; 96. Epub ahead of print, 2017. DOI: 10.1097/MD.0000000000008855.
19. Trafalis DT, Panteli ES, Grivas A, et al. CYP2E1 and risk of chemically mediated cancers. Expert Opin Drug Metab Toxicol, 2010; 6: 307–319.
20. He Q, Wang L, Zhang J, et al. CYP2E1 and GSTM1 gene polymorphisms, environmental factors, and the susceptibility to lung cancer. J Clin Lab Anal, 2018; 32: 1–7.
21. Ahmed S, Altaf N, Ejaz M, et al. Genetic variations in the drug metabolizing enzyme, CYP2E1, among various ethnic populations of Pakistan. Peer J., 2020; 8: 1–12.
22. Thandra KC, Barsouk A, Saginala K, et al. Epidemiology of Non-Hodgkin' s Lymphoma, 2021; 1–9.
23. Kelly RS, Vineis P. Biomarkers of susceptibility to chemical carcinogens: The example of non-Hodgkin lymphomas. Br Med Bull, 2014; 111: 89–100.
24. Neafsey P, Ginsberg G, Hattis D, et al. Genetic polymorphism in CYP2E1: Population distribution of CYP2E1 activity. J Toxicol Environ Heal - Part B Crit Rev., 2009; 12: 362–388.
25. Danko IM, Chaschin NA. Association of CYP2E1 gene polymorphism with predisposition to cancer development. Exp Oncol, 2005; 27: 248–256.
26. Chen K, Guo R, Wei C. Synonymous mutation rs2515641 affects CYP2E1 mRNA and protein expression and susceptibility to drug-induced liver injury. Pharmacogenomics, 2020; 21: 459–470.
27. Lu Y, Zhu X, Zhang C, et al. Role of CYP2E1 polymorphisms in breast cancer: A systematic review and meta-analysis. Cancer Cell Int., 2017; 17: 1–10.
28. Yin X, Xiong W, Wang Y, et al. Association of CYP2E1 gene polymorphisms with bladder cancer risk: A systematic review and meta-analysis. Med; 97. Epub ahead of print, 2018. DOI: 10.1097/MD.0000000000011910.
29. Yao K, Qin H, Gong L, et al. CYP2E1 polymorphisms and nasopharyngeal carcinoma risk: a meta-analysis. Eur Arch Oto-Rhino-Laryngology, 2017; 274: 253–259.
30. Rakvåg TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan HE, Skorpen F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain, Jul. 2005; 116(1-2): 73-8.
31. Ross JR, Riley J, Taegetmeyer AB, Sato H, Gretton S, du Bois RM, Welsh KI. Genetic variation and response to morphine in cancer patients: catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. Cancer, Mar. 15, 2008; 112(6): 1390-403.

ETHICAL MATTERS

Universidade Estadual de Londrina

PARANÁ

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS
Universidade Estadual de Londrina
Registro CONEP 5231

Parecer CEP/UEL:	189/2013
CAAE:	17123113.4.0000.5231
Data da Relatoria:	30/09/2013
Pesquisador(a):	Maria Angelica Ehara Watanabe
Unidade/Órgão:	Programa de PG em Patologia Experimental

Prezado(a) Senhor(a):

O "**Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina**" (Registro CONEP 5231) – de acordo com as orientações da Resolução 466/12 do Conselho Nacional de Saúde/MS e Resoluções Complementares, avaliou o projeto:

"Estudo de marcadores genéticos, epigenéticos, moleculares e imunológicos em câncer."

Situação do Projeto: **Aprovado**

Informamos que deverá ser comunicada, por escrito, qualquer modificação que ocorra no desenvolvimento da pesquisa, bem como deverá apresentar ao CEP/UEL, via Plataforma Brasil, relatório final da pesquisa.

Londrina, 30 de setembro de 2013.

Profa. Dra. Alexandrina Aparecida Maciel Cardelli
Coordenadora do Comitê de Ética em Pesquisa Envolvendo Seres Humanos
Universidade Estadual de Londrina

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: POLIMORFISMO DE GENES DO SISTEMA GLUTATIONA E SUSCEPTIBILIDADE AO ESTRESSE OXIDATIVO EM PACIENTES COM LINFOMA HODGKIN E NÃO-

Pesquisador: Carlos Eduardo Coral de Oliveira

Área Temática:

Versão: 1

CAAE: 14415119.3.0000.0020

Instituição Proponente: Pontifícia Universidade Católica do Parana - PUCPR

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.372.788

Apresentação do Projeto:
análises de polimorfismos genéticos, perfil redox e citometria de
fluxo para identificação de possíveis marcadores de prognóstico. Assim, este projeto poderá contribuir na determinação de marcadores genéticos e
bioquímicos de enzimas reguladoras do estado redox implicados na linfomagênese e resistência à quimioterapia. A análise da associação entre
estes marcadores do estado oxidativo poderá auxiliar no melhor entendimento das complicações relacionadas ao tratamento dos linfomas.

Objetivo da Pesquisa:
Analisar o polimorfismo de genes do sistema glutationa e susceptibilidade ao estresse oxidativo em pacientes com Linfoma Hodgkin e não-Hodgkin

Avaliação dos Riscos e Benefícios:
O participante da pesquisa não terá nenhum benefício direto em participar da pesquisa, apenas contribuirá para um melhor entendimento da temática estudada.

Comentários e Considerações sobre a Pesquisa:
não ha

Considerações sobre os Termos de apresentação obrigatória:
termos apresentados em conformidade

Endereço: Rua Imaculada Conceição 1155
Bairro: Prado Velho **CEP:** 80.215-901
UF: PR **Município:** CURITIBA
Telefone: (41)3271-2103 **Fax:** (41)3271-2103 **E-mail:** nep@pucpr.br

Página 01 de 02

Recomendações:

não ha

Conclusões ou Pendências e Lista de Inadequações:

O projeto esta em acordo com a resolução 466/12 em suas questões éticas. Sendo aprovado a realização da pesquisa com seres humanos.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1336827.pdf	23/05/2019 20:54:35		Aceito
Folha de Rosto	FolhaRosto.pdf	23/05/2019 20:54:11	Carlos Eduardo Coral de Oliveira	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	16/04/2019 22:47:55	Carlos Eduardo Coral de Oliveira	Aceito
Declaração de Pesquisadores	TCUD.jpeg	16/04/2019 22:47:41	Carlos Eduardo Coral de Oliveira	Aceito
Declaração de Instituição e Infraestrutura	Autorizacao.pdf	16/04/2019 22:47:10	Carlos Eduardo Coral de Oliveira	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoCEP.pdf	16/04/2019 22:46:57	Carlos Eduardo Coral de Oliveira	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

CURITIBA, 05 de Junho de 2019

Assinado por:
NAIM AKEL FILHO
(Coordenador(a))

Endereço: Rua Imaculada Conceição 1155
Bairro: Prado Velho **CEP:** 80.215-901
UF: PR **Município:** CURITIBA
Telefone: (41)3271-2103 **Fax:** (41)3271-2103 **E-mail:** nep@pucpr.br