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ORIGINAL ARTICLE

Polymorphisms in the CYP2A6 and ABCC4 genes are associated with a protective effect on chronic myeloid leukemia in the Brazilian Amazon population

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Abstract

Background: Susceptibility to Chronic Myeloid Leukemia (CML) may be modulated by genetic variables. However, the majority of previous investigations have focused on genetically homogeneous populations, resulting in a lack of evidence on how genetic factors may influence the development of CML in miscegenated populations. We analyzed 30 polymorphisms in genes related to DNA repair, folate metabolism, transmembrane transport, xenobiotic metabolism, and pyrimidine synthesis in relation to their potential role in the susceptibility of the individual to CML.

Methods: This case-control study included 126 healthy individuals and 143 patients diagnosed with CML from the admixed population of the Brazilian Amazon. The samples were genotyped by real-time PCR and the genetic ancestry analysis was based on a panel of 61 ancestry informative markers.

Results: The results indicated a protective effect against the development of CML in carriers of the C allele of the rs28399433 (*CYP2A6*) gene and the CC genotype of the rs3742106 (*ABCC4*) gene.

Conclusion: Our findings suggest that the rs3742106 (*ABCC4*) and rs28399433 (*CYP2A6*) polymorphisms may modulate susceptibility to CML in a population of the Brazilian Amazon region.

KEYWORDS

ABCC4, ancestry, chronic myeloid leukemia, *CYP2A6*, genetic susceptibility

1 | INTRODUCTION

The carcinogenesis of Chronic Myeloid Leukemia (CML) is complex and multifactorial (Li et al., 2014). The principal genetic hallmark of CML is the *BCR-ABL1* oncogene, originated by the t(9;22) translocation, which fuses *ABL1* on chromosome 9q34 to *BCR* on chromosome 22q11 (Langabeer, 2013). This encodes the chimeric protein BCR-ABL, a constitutively active tyrosine kinase that drives the pathogenesis of CML (Egan & Radich, 2016).

The etiology of CML is still not completely elucidated. Some studies have reported that environmental factors may be involved

The authors Natasha Monte and Karla B C C Pantoja share the first authorship.
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in the development of the disease, but this is not conclusive (Bispo et al., 2020; Musselman et al., 2013). The importance of the expression of *BCR-ABL* in the onset and progression of CML is well established, however, although other genes may also be involved in its development. For example, Ferri et al., (2019) found an association with CML risk in the case of the A allele of the rs12573787 polymorphism of the phosphatase and tensin homolog gene (*PTEN*), a tumor suppressor gene involved in the modulation of cell proliferation and apoptosis.

To better understand the genetic factors involved in the etiology of CML, we investigated 30 polymorphisms in genes of the carcinogenic metabolism involved in susceptibility to different types of cancer, including CML (Campa et al., 2012; Özten et al., 2012; Weich et al., 2016). These genes encode DNA repair proteins (Coskunpinar et al., 2015; Damineni et al., 2014), transmembrane carriers (Campa et al., 2012; Pereira et al., 2016), and endogenous and xenobiotic-metabolizing enzymes (He et al., 2014; Islam et al., 2013; Zhao et al., 2016).

The genetic variability of the target population is an important consideration for susceptibility studies, given that groups with distinct ancestry may present substantial differences in their allelic frequencies. Given this, the findings on a specific population may not be applicable to other groups that have a distinct genetic composition (Carvalho et al., 2015; Yu & Chen, 2012;). One clear example here is the Brazilian population, which is one of the most genetically heterogeneous groups found anywhere in the world, with principal contributions from three parental groups: Europeans, Amerindians, and Africans (Carvalho et al., 2015). The study of highly admixed populations is paramount to the comprehension of the influence of genetic polymorphisms on the predisposition of the individual to develop complex diseases, such as CML.

Given these considerations, the present study evaluated the association between the polymorphisms of key genes (in the transport and metabolism pathways) and susceptibility to CML in a population with a high degree of genetic admixture from the Brazilian Amazon. The key genes evaluated in this study and their OMIM access numbers are: FPGS (136510), ABCC2 (601107), ABCC4 (605250), ABCB1 (171050), ABCG2 (603756), SLC29A1 (602193), SLC22A7 (604995), DPYD (612779), CYP2A6 (122720), UMPS (613891), MTHFR (607093), GGH (601509), RRM1 (180410), and TP53 (191170).

2 | MATERIAL AND METHODS

2.1 | Ethical compliance

The present study was approved by the Research Ethics Committees of the Oncology Research Nucleus, under protocol number 3.354.571/2019, and the Ophir Loyola Hospital, under protocol number 1.575.920/2016. All the participants signed a statement of informed consent.

2.2 | Case and controls

The participants in the present study were selected based on a retrospective case-control study design. Data and samples were collected from 269 individuals, of which, 143 were patients diagnosed with CML (case group) and 126 were cancer-free individuals (control group), both from the city of Belém, located in the Amazon region of Brazil.

The CML patients had been treated for a minimum of 5 years and a maximum of 15 years, and they all had well-documented laboratory and clinical data. These patients were being treated in the onco-hematology sector of the Ophir Loyola Hospital in Belém (Pará, Brazil). The control group consisted of elderly individuals (ages of between 60 and 75 years) with no clinical reports of any type of cancer. Some of these individuals had been diagnosed with chronic conditions, such as hypertension or diabetes.

2.3 | Selection of markers

Thirty Single Nucleotide Polymorphisms (SNPs) of 14 genes were chosen through a search of two databases, *The Human Gene Mutation Database* (www.hgmd.cf.ac.uk/) and *PharmGKB* (www.pharmgkb.org/). The markers were selected based on two principal criteria: (1) polymorphisms involved in pivotal intracellular metabolic activities, and (2) previous reports of the marker in associative studies found in the *Pubmed* (www.ncbi.nlm.nih.gov/) database, which identify the marker as a potential predictor of susceptibility to different types of cancer. The polymorphisms presented in Table 1 met these prerequisites, and were thus selected for the analyses presented here.

2.4 | Extraction and quantification of the DNA

The DNA was extracted using the commercial Axy Prep™ Blood Genomic DNA Miniprep kit (Axygen Biotechnology), according to the manufacture's recommendations. The concentration and purity of the DNA were measured with a NanoDrop 1000 spectrophotometer (Thermo Scientific NanoDrop 1000; NanoDrop Technologies).

2.5 | Genotyping

The polymorphisms were genotyped by allelic discrimination using the TaqMan OpenArray Genotyping technology, which was run in a QuantStudio™ 12K Flex Real-Time PCR system (Applied Biosystems, Life Technologies), according to the manufacture's protocol.

TABLE 1 Polymorphisms chosen after applying the criteria of selection of markers

Gene	Pathway	Reference sequence (RefSeq)	SNP
TP53	DNA repair	NG_017013.2	rs1042522
RRM1	DNA repair	NG_027992.2	rs1042927
RRM1			rs12806698
MTHFR	Folate metabolism	NG_013351.1	rs1801131
MTHFR			rs1801133
GGH	Folate metabolism	NG_028126.1	rs3758149
FPGS	Folate metabolism	NG_023245.1	rs4451422
ABCG2	Transmembrane transporter	NG_032067.2	rs2231142
ABCB1	Transmembrane transporter	NG_011513.1	rs1045642
ABCB1			rs1128503
ABCC2	Transmembrane transporter	NG_011798.2	rs717620
ABCC4	Transmembrane transporter	NG_050651.2	rs4148551
ABCC4			rs3741206
ABCC4			rs9524885
SLC29A1	Transmembrane transporter	NG_042893.1	rs747199
SLC29A1			rs760370
SLC22A7	Transmembrane transporter	NC_000006.12	rs2270860
SLC22A7			rs4149178
DPYD	Xenobiotic-metabolizing	NG_008807.2	rs17116806
DPYD			rs1801159
DPYD			rs1801265
DPYD			rs3918290
DPYD			rs4970722
DPYD			rs55886062
DPYD			rs67376798
DPYD			rs17376848
DPYD-AS1	Xenobiotic-metabolizing	NC_000001.11	rs1760217
CYP2A6	Xenobiotic-metabolizing	NG_008377.1	rs28399433
CYP2A6			rs8192726
UMPS	Pyrimidine synthesis	NG_017037.1	rs1801019

2.6 | Quality control

The polymorphisms that were not in Hardy-Weinberg equilibrium or had at least 15% of missing genotypes were excluded from subsequent statistical analyses. Of the 30 markers selected initially, then only 13 polymorphisms met all the criteria for analysis (see Table S1 in the Appendix).

2.7 | Analysis of genetic ancestry

Genetic ancestry was analyzed according to Ramos et al., (2016), using 61 autosomal ancestry informative markers in three multiplex PCR reactions. The amplicons were analyzed by electrophoresis using the ABI Prism 3130 sequencer and the Gene Mapper ID v.3.2 software. The individual proportions of European, African, and Amerindian genetic ancestry were estimated using STRUCTURE v.2.3.3, assuming the contribution of three parental populations.

2.8 | Statistical analysis

The statistical analyses were run in RStudio v.3.6.1 (SNPassoc library). Differences in the categorical variable (sex) were tested using Pearson's Chi-square, while the quantitative variable (mean age) was evaluated using Student's *t*. The ancestry indices were compared between case and control groups using the Mann-Whitney test. Multiple logistic regressions were used to assess possible associations between the polymorphisms and susceptibility to CML, by estimating the odds ratios (ORs) and their 95% confidence intervals (CIs).

Sex and age were controlled for in this multivariate analysis, to avoid confounding associations. A significance level of $p < 0.05$ was considered for all the statistical analyses.

3 | RESULTS

3.1 | Description of the study population

The results of the epidemiological analyses are presented in Table 2. Women predominated in the control group, accounting for 66.7% of all individuals, whereas men dominated the CML patients, with 63.7% of the total. There was a significant difference ($p < 0.001$) between the case and control groups in the distribution of the sexes. The mean age of the case group (47.5 years) was also significantly lower ($p < 0.001$) than that of the control group (66.0 years). Given these differences between the two groups, both age and sex were controlled for in the subsequent analyses, in order to minimize their interference in the assessment of the genetic data.

The analysis of the genetic ancestry of the participants revealed a mostly European ancestry in both groups, being 46.3% in the case group and 44.2% in the control group, followed by Amerindian (31.0% in patients and 30.5% in the control individuals), and African ancestry (22.6% in the case group and 25.4% in the control). There was no significant variation ($p > 0.05$) in the ancestral makeup of the two groups.

3.2 | Genotype distribution and risk estimates

Table 3 shows the distribution of the genotypes that varied significantly between the case and control groups, in in addition to their ORs, with regard to the potential susceptibility to CML. Significant differences were found in the cases of the rs28399433 polymorphism of the *CYP2A6* gene and the rs3742106 polymorphism of the *ABCC4* gene.

Individuals with the C allele of the rs28399433 polymorphism of the *CYP2A6* gene, either homozygously or heterozygously, presented a significant protective effect against the development of CML ($p = 0.008$; OR = 0.33; 95% CI = 0.14–0.78). Similarly, carriers of the CC genotype of the rs3742106 variant of the *ABCC4* gene also presented a significantly reduced susceptibility to CML ($p = 0.020$; OR = 0.30; 95% CI = 0.10–0.88), in comparison with the other genotypes.

None of the other polymorphisms presented any significant variation between case and control groups. The distribution of the genotypes in the case and control groups is shown in the Appendix (Table S2).

TABLE 2 Epidemiological data of the CML patients and the control group

Variable	CML (%)	Control (%)	*p*-value
Total	143	126	
Age (years)	47.41 ± 14.93	66.02 ± 4.45	<0.001
Sex (%)			
Men	79 (63.7)	42 (33.3)	<0.001
Women	45 (36.3)	84 (66.7)	
Ancestry mean			
European	0.463 ± 0.149	0.442 ± 0.161	0.268
Amerindian	0.310 ± 0.138	0.305 ± 0.147	0.572
African	0.226 ± 0.097	0.254 ± 0.147	0.517

4 | DISCUSSION

Carcinogenesis is a multistep process that involves both genetic and environmental risk factors. The presence of genetic polymorphisms in pivotal genes may affect the structure, function, stability or folding of the encoded proteins, which may initiate a carcinogenic event (Frikha et al., 2020; Zhang & Zhu, 2020). The present study evaluated the possible association of SNPs in genes of key cellular pathways, such as the transport of substances across cell membranes, DNA repair, the folate and xenobiotic metabolisms, and pyrimidine synthesis, with a predisposition to the development of CML.

Over the years, these polymorphisms have been associated with different cancers and other complex diseases. The *RRM1* gene, for example, has been related to a high degree of sensitivity to oncological chemotherapy (Yang et al., 2019; Zhao et al., 2012) and has been identified as a predictive factor in gemcitabine therapy in oncology patients (Jordheim et al., 2011). The *ABCG2* gene has also been associated with resistance to chemotherapy in the treatment of many types of cancer (Amawi et al., 2019; Robey et al., 2018). Polymorphisms of the *CYP* gene family are also known to modulate susceptibility to a number of different complex diseases (Daly, 2015). Up to now, however, there has been little research into possible associations between these variants and susceptibility to CML.

The results of the present study indicated that carriers of the C allele (whether homozygous or heterozygous) of the rs28399433 polymorphism of the *CYP2A6* gene are significantly less susceptible to the development of CML in comparison with the AA genotype. Previous studies have shown that the rs28399433 polymorphism, which is common in Asian populations, is located in the TATA box region, and is responsible for reducing gene transcription (Rodriguez-Antona et al., 2010).

TABLE 3 Odds Ratios and genotype distribution of the statistically significant polymorphisms in the CML patients and the control group

Genotype	Control (%)	CML (%)	*p*-value	OR (95% CI)[a]
CYP2A6[b] rs28399433				
AA	107 (66.5)	95 (83.3)	0.008	AC + CC vs. AA[c]: 0.33 (0.14–0.78)
AC	45 (28.0)	17 (14.9)		
CC	9 (5.6)	2 (1.8)		
Allele A	107 (66.5)	95 (83.3)		
Allele C	54 (33.5)	19 (16.7)		
ABCC4[e] rs3742106				
AA	43 (29.7)	43 (37.1)	0.020	CC vs. AA + AC[d]: 0.30 (0.10–0.88)
AC	71 (49.0)	55 (47.4)		
CC	31 (21.4)	18 (15.5)		
Allele A	114 (78.6)	98 (84.5)		
Allele C	31 (21.4)	18 (15.5)		

[a]Multiple logistic regression adjusted by age and gender.
[b]*CYP2A6* RefSeq: NG_008377.1.
[c]Heterozygous genotype + mutant homozygous genotype *vs*. Wild homozygous genotype.
[d]Mutant homozygous genotype *vs*. Wild homozygous genotype + heterozygous genotype.
[e]*ABCC4* RefSeq: NG_050651.2.

The only previous study that has linked this variant to predisposition to cancer was that of Ezzeldin et al., (2018), who attempted to establish a relationship between this polymorphism and the risk of lung cancer in the population of Egypt. However, this variant occurred at a prohibitively low frequency in the study group (3.7%) to support the statistical analyses.

The association between other polymorphisms of the *CYP2A6* gene and cancer has also been evaluated in a number of other studies. For example, Song et al., (2009) found that the deletion of the entire *CYP2A6* gene (CYP2A6*4) resulted in a reduced risk of bladder cancer in Chinese smokers, while Coskunpinar et al., (2015) found that this same variant was linked to a decreased risk of lung cancer in a population from Bangladesh.

The present study also showed that the homozygous CC genotype of the rs3742106 polymorphism of the *ABCC4* gene confers a decreased susceptibility to the development of CML. It is important to note here that *ABCC4*, also known as the multi-drug resistance-associated protein 4, is an important member of the ATP-binding cassette transporter family, and is responsible for transporting a variety of endogenous and exogenous organic anions, of varying composition, out of the cell (Wen et al., 2015). Given its chemotherapeutic drug efflux capacity, *ABCC4* has been studied extensively in relation to drug resistance, in various types of cancer cells. Previous research has also shown that this gene influences the biology of the cancer cell.

For example, Zhao et al., (2014) found a high level of expression of ABCC4 in different lung cancer cell lines. In this study, the authors reported that the suppression of the expression of the ABCC4 messenger RNA (mRNA) resulted in a decrease in cell proliferation, probably due to the ability of ABCC4 to transport the molecules involved in cell signaling. Corroborating these findings, Chen et al., (2017) demonstrated in cell culture that the presence of the T allele of the rs3742106 polymorphism affects the regulatory role of the mRNA and thus decreases the expression of the ABCC4 protein.

A high level of ABCC4 expression has also been observed in aggressive primary neuroblastoma (Murray et al., 2017), the blast cells of adult patients with acute myeloid leukemia, and in acute childhood lymphoblastic leukemia (Copsel et al., 2011; Mesrian Tanha et al., 2017). Pereira et al., (2014) also found an association between other variants of the *ABCC4* gene, which were not evaluated in the present study, and colorectal carcinogenesis. Despite the existence of previous studies linking polymorphisms of the *ABCC4* gene with certain types of cancer, there has been no research on the relationship between the rs3742106 variant and a predisposition to neoplasms or other diseases.

As shown in the present study, the proteins expressed by these genes can be modulated by SNPs, which modifies their function. In the case of the *ABBC4* gene, this would affect the cell's efflux, while in the *CYP2A6* gene, the effect would be on the metabolizing activity of potential carcinogens (Ezzeldin et al., 2018; Rodriguez-Antona et al., 2010), which would contribute to the carcinogenic process.

In addition to the variation in the genotype frequencies of the study polymorphisms and their association with the risk

of CML, significant differences were also found in the mean age and the sexes of the case and control groups, but not in their ancestral makeup.

These findings indicate that CML occurs more frequently in men than in women, which is consistent with the findings of two studies in Bangladesh and Pakistan (Bhatti et al., 2012; Mottalib et al., 2014). It remains unclear, however, while there is a higher frequency of CML in men, with different studies suggesting social, behavioral, or even biological factors (Bortolheiro & Chiattone, 2008). Radivoyevitch et al., (2014) raised the hypothesis that men have more target cells at risk of developing CML than women.

The mean ages of the two groups were significantly different ($p < 0.001$; case = 47.41 ± 14.93 years; control = 66.02 ± 4.45 years). As the incidence of CML is known to increase with age, peaking between 55 and 60 years of age, the control group was selected specifically to include individuals of an older age.

5 | CONCLUSIONS

The results of the present study demonstrated that the rs28399433 (CYP2A6) and the rs3742106 (ABCC4) polymorphisms are associated with a protective effect against the development of CML in a highly miscegenated population from the Brazilian Amazon. This is the first study to associate genetic polymorphisms with a susceptibility to CML in an admixed population from the Brazilian Amazon region, which has a unique genetic background and may thus deviate from the patterns found in more genetically homogeneous populations.

The present study is the first to show an association between polymorphisms of the ABCC4 and CYP2A6 genes with a decreased predisposition for the development of CML. The findings of this study may provide important insights into the genetic predisposition of individuals to develop CML, although further research will be required to provide a more conclusive interpretation of the observed patterns.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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