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TP53 codon 72 polymorphism predicts chronic myeloid leukemia susceptibility and treatment outcome

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ABSTRACT

BCR-ABL1 gene is a key molecular marker of chronic myeloid leukemia (CML), but it is still unclear which molecular factors may influence CML risk or lead to variable responses to tyrosine kinase inhibitors (TKIs). The aim of this study was to investigate the impact of *TP53* c.213 G > C(Arg72Pro; rs1042522) polymorphism on CML risk and its correlation with clinical outcome. Peripheral blood samples from 141 treated CML patients and 141 sex- and age-matched healthy individuals were genotyped by PCR-RFLP. Standard genetic models for disease penetrance were evaluated by logistic regression analysis and Kaplan-Meier method was performed to estimate survival curves. Our study suggests that *TP53* c.213 G > C polymorphism may be involved in CML development considering a recessive model ($p = 0.01$; OR: 0.19; CI: 0.06–0.68). In addition, a non-homogenous distribution was found for this polymorphism in males and patients youngers than 50 years ($p = 0.02$). According to clinical response, *TP53-GG* genotype was associated with higher levels of *BCR-ABL1* transcripts ($p = 0.04$) and shorter event free survival ($p = 0.04$). Moreover, a trend toward significance was found for failure free survival ($p = 0.06$) and time to imatinib failure ($p = 0.08$). In conclusion, our data suggest that a; *TP53* c.213 G > C may be a potential biomarker of CML susceptibility and clinical outcome.

1. Introduction

Chronic myelogenous leukemia (CML) is driven by the expression of *BCR-ABL1* tyrosine kinase, which results in increased cell proliferation and inhibition of apoptosis, generating genomic instability [1,2]. Although, CML pathogenesis is strongly associated to the *BCR-ABL1* oncogene, it still remains unclear which molecular mechanism drive the translocation or initiates leukemogenesis [3,4]. Ancestral or additional genetic events necessary for CML to develop have long been hypothesized but never really demonstrated [5]. Previous association studies have identified polymorphic variants in various critical genes associated with CML susceptibility, albeit results are still inconsistent [6].

Current treatments with Tyrosine kinase inhibitors (TKIs), imatinib, nilotinib and dasatinib have significantly improved survival. However, several studies have reported the emergence of resistance or intolerance during TKIs treatment. Point mutations within the *ABL* kinase domain are the major cause of TKI resistance in 30%–50% of CML resistance cases [7]. Moreover, TKI failure has been also linked to *BCR-ABL1* gene amplification, transcript overexpression, alterations in drug transporters and upregulation of other kinase pathways [8]. However, all these mechanisms do not explain many cases of clinical resistance [9]. Patients with drug resistance or intolerance may develop disease progression to blast phase [1,10]. Most genetic changes associated with progression occur during the transformation to advanced stages [11], but they do not in and of themselves cause progression [12]. CML progression has been associated with the phenomenon of genomic instability and abnormal DNA repair that results in additional cytogenetic abnormalities and mutations. Among these, genetic or functional inactivation of the tumor suppressor *TP53* gene has been reported in 25%–30% of myeloid CML-BCs [1,13].

TP53 gene (encoding p53) has been called the "guardian of the genome", given its crucial role in maintaining genetic stability and the prevention of cancer formation [14]. Subsequent to a range of stress stimuli, p53 may induce a variety of processes, such as transcription regulation, DNA damage response, control of cell cycle progression and apoptosis, metabolism, stem cell differentiation and as a translational regulator,

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Table 1
Association study between polymorphisms and CML risk.

		Patients 141 (%)	Controls 141 (%)	p	OR (95%CI)*
Genotypes[a]	GG	83 (58.8)	74 (52.5)		1 (ref)
	GC	53 (37.6)	50 (35.4)	0.89	1.06 (0.64–1.75)
	CC	5 (3.6)	17 (12.1)	**0.012**	**0.26 (0.09–0.74)**
Alleles[a]	G	219 (77.7)	198 (70.2)		1 (ref)
	C	63 (22.3)	84 (29.8)	0.05	0.67 (0.46–1)
Genetic models[b]					
Dominant	GG	83 (58.8)	74 (52.5)		1 (ref)
	GC/CC	58 (41.1)	67(47.5)	0.79	1.08 (0.69–1.97)
Recessive	GG/GC	136 (96.4)	124 (87.9)		1 (ref)
	CC	5 (3.6)	17 (12.1)	**0.01**	**0.19 (0.06–0.68)**
Additive		–		0.17	0.72 (0.15–1.15)

[a] Univariate analysis by Fisher's exact test.
[b] Logistic regression adjusted by sex and age.

among other processes [15-17]. *TP53* is one of the most frequently mutated genes in human cancers and has been reported to be a significant determining factor in carcinogenesis. Many mutant p53 proteins gain novel functions, often with deleterious effects acquire new activities that indeed, encompass oncogenic roles [18] or impairs radiotherapy and chemotherapy promoting cancer aggression [17]. Numerous single nucleotide polymorphisms (SNPs) have been identified on *TP*53 gene. A functional SNP *TP53* c.213 G > C (rs1042522) at exon 4 codon 72 has been shown to result in an arginine (Arg) to proline (Pro) substitution (Arg72Pro) [19,20]. The Pro72 variant has a markedly reduced capacity to induce apoptosis [20]. Hence, much attention has been paid to address the influence of this polymorphism in the susceptibility of various cancers and treatment outcomes [21,22]. However, scarce studies have been performed in CML showing contradictory results [23–27].

Taken together, these findings suggest that genetic variability of *TP53* gene could be an important factor both in CML development and disease progression by modulating TKI treatment. However, the exact significance of *TP53* codon 72 polymorphism in CML remains largely unknown and few studies have been undertaken. The aim of the present study was to evaluate its influence on CML susceptibility and to correlate with clinical outcome in CML Argentinean patients treated with TKIs.

2. Materials and methods

2.1. Patients

Peripheral blood samples were obtained from 141 patients (68 females and 73 males; mean age 51.33 ± 1.33; range 17–85 years) diagnosed with CML and under different TKIs treatment (imatinib, dasatinib, nilotinib) with a mean of follow up of 67.6 months. In particular, 71 patients were in chronic phase and TKIs responders (54 were in optimal response with imatinib, 12 with nilotinib and 5 with dasatinib). In patients failing TKI treatment (n = 70), direct sequencing of the *ABL1*kinase domain of *BCR-ABL1*was carried out. In this group, 25 patients had mutations in the tyrosine kinase domain. The remaining 45 cases, 29 of them were in chronic phase (CP) with suboptimal response either to dasatinib or nilotinib and 16 progressed to accelerated phase/blast phase (AP/BP). *BCR-ABL1* transcripts were measured in whole blood using reverse transcription quantitative PCR (RT-qPCR) with *ABL1* as a reference gene, according to log reduction international scale. Response to TKI treatment was defined using the update criteria of the European LeukemiaNet [28]. In addition, 141 sex- and age-matched unrelated healthy individuals (68 females and 73 males; mean age 51.03 ± 1.23; range 20-85 years) without medical history of leukemia or other chronic diseases, were analyzed. Patients and controls were Argentineans from Buenos Aires city and surrounding urban areas, and had the same ethnicity. All individuals provided their informed consent according to institutional guidelines. The study was approved by the Institutional Ethical Committee and complies with the International Declaration of Helsinki.

2.2. Genotyping

Genomic DNA was isolated using DNAzol (Invitrogen) according to the manufactures' guidelines. *TP53* c.213 G > C (rs1042522; p.72Arg > Pro) genotyping was performed by a similar PCR-RFLP previously reported method [29]. Briefly, primers sequences were: 5′-GAAGACCCAGGTCCAGATGA-3′ (forward) and 5′-CTGCCCTGGTAGG TTTTCTG-3′ (reverse). The amplification reaction was done with 50 ng of genomic DNA and 0.4 uM of each primer. Cycling conditions were as follows: 32 cycles each of 30 s at 94 °C, 30 s at 54 °C, and 30 s at 72 °C. The 152 bp PCR products were digested overnight with *Bsh1236I* (Thermo Fisher) and analyzed by electrophoresis on 4% (3:1) NuSieve/agarose gels. Enzyme digestion gave 2 electrophoretic fragments (50 and 102 pb) for the *TP53*-GG genotype (Arg/Arg) and a 152 pb band for *TP53*-CC genotype (Pro/Pro). Samples were randomly reanalyzed, yielding identical results.

2.3. Statistical analysis

Statistical analysis were performed using PLINK software and SPSS statistical package (version 15.0) (IBM, SPSS Inc., Chicago, USA). The associations between *TP53* polymorphisms with CML were performed by univariate Fisher's exact test and multivariable logistic regression analysis. The estimating odds ratios (OR) and their corresponding 95% confidence intervals (CIs) were calculated. Hardy–Weinberg equilibrium (HWE) was tested using a goodness-of-fit Chi-square test. Standard genetic models (additive, recessive and dominant) for disease penetrance were evaluated. The Kaplan-Meier method was performed to estimate survival curves, and the log-rank test was used to compare the stratified genotype subgroups. The following outcomes were undertaken: 1. Event free survival (EFS): an event was defined as either loss of complete hematologic, cytogenetics or molecular response, progression to AP or BC, death, discontinuation due to adverse effects. 2. Failure free survival (FFS): an event was the treatment failure with all the three TKIs. 3. Time to treatment failure (TTF): an event was a change of treatment because either unsatisfactory or intolerance to treatment. All statistical tests were two-sided and values of $p \leq 0.05$ were considered statistically significant.

3. Results

3.1. Case-control study

Genotype and allele frequencies distributions for *TP53* codon 72 SNP in cases and controls is shown in Table 1. No deviation from HWE was found either for controls or patients ($p > 0.05$). The genotype comparison (GG vs. CC) showed that *TP53*-CC was significantly

Table 2
Distribution of *TP53* genotypes stratified by sex and age groups.

		Genotypes			p
		GG	GC	CC	
Gender					
Males	Patients (n = 73)	42 (58)	30 (41)	1 (1)	
	Controls (n = 73)	39 (53)	23 (32)	11 (15)	0.02
Females	Patients (n = 68)	41 (60)	23 (34)	4 (6)	
	Controls (n = 68)	35 (51)	27 (40)	6 (9)	0.4
Age*					
< 50	Patients (n = 63)	38 (60)	24 (38)	1 (2)	
	Controls (n = 63)	31 (49)	22 (35)	10 (16)	0.02
> 50	Patients (n = 78)	45 (58)	29 (37)	4 (5)	
	Controls(n = 78)	43 (55)	28 (36)	7 (9)	0.55

* Mean age either for patients and controls.

underrepresented in patients (3.6%) compared to controls (12.1%) (p = 0.012; OR: 0.26; CI: 0.09–0.74). No significant association was found for the (GG vs. GC) comparison (p = 0.89; OR: 1.06; CI: 0.64–1.75). *TP53*-C allele frequency was also significantly decreased in patients (22.3%) compared to controls (29.8%) (p = 0.05; OR: 0.67; CI: 0.46–1). Multivariate analysis adjusted for age and gender for various genetic models were performed. A recessive model (GG/GC vs. CC) is significantly involved in CML development (p = 0.01; OR: 0.19; CI: 0.06–0.68).

TP53 genotype frequencies were also analyzed comparing patients and controls according to sex and age stratification (Table 2). A non-homogenous distribution of the *TP53*-CC was shown in males (p = 0.02), but not in females (p = 0.4). Moreover, according to mean age of the study populations (50 years), two age strata were defined to analyze the genotype distribution. Frequencies of *TP53 GG* and *CG* genotypes in the two age groups were similar between cases and controls; however, *TP53*-CC genotype in the younger group was significantly lower in patients (2%) compared to controls (16%) (p = 0.02).

3.2. Association between TP53 SNP and TKI treatment outcome

The main clinical parameters of our CML population stratified according two genotypes groups (*TP53-GG and TP53*-CG/CC) is summarized in Table 3. The Sokal score was homogeneously distributed among evaluated groups and the majority of patients were in chronic phase. According the European LeukemiaNet criteria, 70 patients were non-responders to TKIs. In these cases, the study of *BCR-ABL1* mutation was carried out. Twenty five patients presented mutation in *ABL1*, being the most common: T315I, G250E, F359V (data not shown). The mean levels of *BCR-ABL1* (%) were significantly increased in patients carrying the *TP53*-GG genotype compared to *TP53*-CG/CC (p = 0.04). No significant differences were found for molecular and cytogenetic responses among different groups (p = 0.7; p = 0.5 respectively), however the majority of patients without Major Molecular (57%) and cytogenetic responses (62%) were carriers of *TP53*-GG genotype did not reach molecular and cytogenetic responses. Disease progression was observed in 16 cases but no differences were found according genotype groups.

Three endpoints were undertaken in order to evaluate the association between *TP53* polymorphism and treatment response by Kaplan-Meier plots. The analysis of EFS revealed that 87 events had occurred, the majority of them (52/87, 60%) were observed in patients carrying the *TP53*-GG genotype, while 40% (35/87) events had occurred in patients with *TP53* CG/CC genotypes. The long-rank test revealed that the EFS was significantly shorter for patients with *TP53*-GG genotypes compared to *TP53*-CG/CC (p = 0.04) (Fig. 1A). According to FFS, a nearly

Table 3
Main clinical parameters stratified according *TP53* genotypes.

Clinical parameters	Genotypes		p
	GG n (%)	CG/CC n (%)	
Sokal			
High (n = 32)	21 (21)	11 (11)	
Intermediate (n = 32)	15 (15)	17 (17)	0.3
Low (n = 36)	20 (20)	16 (16)	
Phase			
Chronic (n = 76)	44 (47)	32 (34)	
Accelerated (n = 9)	6 (6)	3 (3)	0.7
Blast crisis (n = 9)	6 (6)	3 (3)	
Treatment outcome			
TKIs responders (n = 71)	42 (30)	29 (21)	0.58
TKIs non-responders (n = 70)*	47 (33)	23 (16)	
***BCR-ABL1*mutation**			
Yes (n = 25)	16 (23)	9 (13)	0.6
No (n = 45)	31 (44)	14 (20)	
Mean of *BCR-ABL1* (%)	(12.95 ± 2.2)	(6.4 ± 2.1)	0.04
Molecular response			
Major/4.5/5.0 (n = 63)	38 (27)	25 (18)	0.7
Minor/minimal/null (n = 76)	43 (57)	33(43)	
Cytogenetic response			
Major (n = 78)	46 (39)	32 (27)	0.5
Minimal/minor/null (n = 40)	25 (62)	15 (37)	
Progression			
Yes (n = 16)	9 (7)	7 (6)	0.8
No (n = 110)	65 (51)	45 (36)	

* Non-responder patients were considered when had at least one TKI change.

significant association was found for *TP53*-GG genotype and treatment failure with all the TKI ($p = 0.06$) (Fig. 1B). Regarding TTF, patients carrying *TP53*-GG genotype were most likely to fail earlier to imatinib treatment compared to *TP53*-CG/CC genotypes, however, did not reach statistical significance ($p = 0.08$) (Fig. 1C).

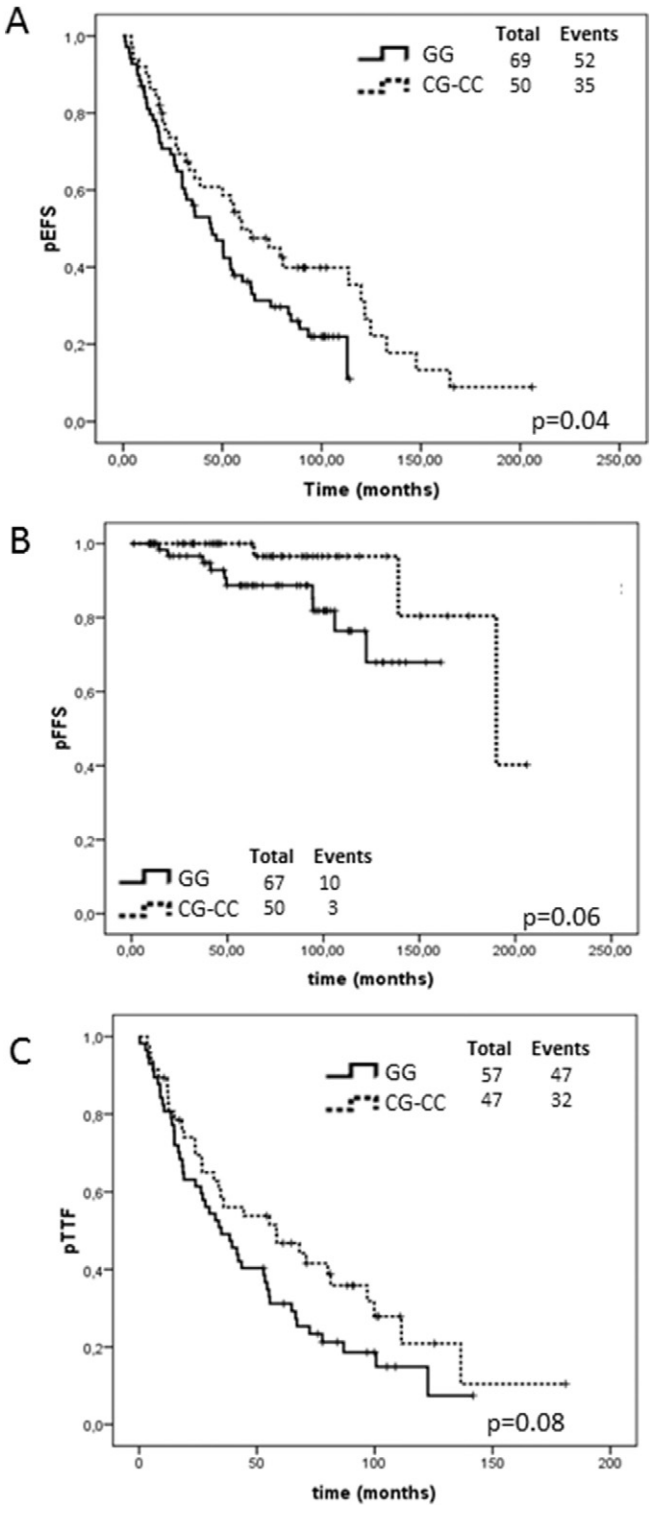

Fig. 1. Kaplan-Meier Log-rank plots stratified by *TP53* genotypes: GG (solid black line) vs. CG-CC (dashed black line). A) Probability of event free survival during treatment. B) Probability of failure free survival with imatinib, dasatinib and nilotinib treatment. C) Probability to time to imatinib failure.

4. Discussion

Germline polymorphisms can determine cancer susceptibility and the response to a given therapy. *TP53* codon 72 polymorphism has been extensively studied in order to determine its role as a cancer risk biomarker and treatment response on a wide variety of cancers. However, concerning CML, scarce and inconclusive studies have been reported [25]. Therefore, this is the first case-control study of TP53 c.213 G > C in an Argentinean population to evaluate the associations with the susceptibility of CML and clinical outcome.

In the current study we found that *TP53* polymorphism may be related to CML susceptibility considering a recessive model suggesting that homozygosity for *TP53*-C (Pro) allele has a protective role in CML. Contradictory results were previously reported by Bergamashi et al. [23], who showed that *TP53*-C (Pro) allele is a risk factor for development of CML. On the other hand, a recent meta-analysis performed on hematological malignancies, reported no significant association in the overall analysis between leukemia risk and T*P53*c.213 G > C polymorphism [30]. Nevertheless, a protective effect of the *TP53*-CC (Pro/Pro) genotype was also found for acute leukemia [31], as well as for others cancer types [32–36]. Therefore, in case-control studies, the role of *TP53 c.213 G > C*on hematological or cancer susceptibility remains controversial rather than conclusive. However, in vitro studies have reported that this polymorphism may influence the biological gene functions affecting the induction pathways that lead to either apoptosis or cell cycle arrest. *TP53*-G (Arg) allele has been reported to induce apoptosis more efficiently than the *TP53*-C (Pro) allele [20]. Several studies have suggested that the *TP53*-CC (Pro/Pro) genotype and its association with CML risk may be explained by the reduced apoptotic capacity of leukemic cells expressing the Pro72 protein [20, 23, 24]. However, the *TP53*-CC (Pro/Pro) variant was reported to be stronger inducer of cell cycle arrest and DNA repair [37,38], suggesting that the increased apoptotic capacity of the T*P53*-GG (Arg/Arg) actually represents a default mechanism due to the fact that it is less efficient at inducing cell growth arrest [37]. On the other hand, it was also shown that TP53-CC (Pro/Pro) expressing-cells are more able to remove micronuclei, a chromosomal aberration which has been used to measure chromosome damage. This evidence suggests that *TP53*-C (Pro) might be more potent in reducing genomic instability, and perhaps cancer predisposition [38]. In line with this hypothesis, our finding that *TP53*-CC (Pro/Pro) genotype has a protective role, could be explained by the fact that the Pro variant is involved in the maintenance of genome integrity, decreasing the probability of occurring the *BCR-ABL1* translocation.

A decreased frequency distribution was found for the *TP53*-CC (Pro/Pro) protective genotype in our CML cohort. It has been suggested that the incidence of CML increases by age and is more common in males than females [39]. Different genetic and non-genetic factors that may have influence on CML risk. Among these, we propose that *TP53* genetic variability may be involved because a significantly reduce of protective *TP53*-CC (Pro/Pro) genotype in males and youngers than 50 years. However, we can speculate that in older patients, longer time of exposure to environmental factors and carcinogens may have a more powerful effect on CML susceptibility than the *TP53* genetic variability.

In order to study in detail how germline polymorphisms on TP53 gene could potentially cause TKI resistance, *TP53* codon 72 polymorphism has been linked with different CML clinico-pathological parameters. Bergamaschi et al., [23] found significant association between *TP53*-C (Pro) allele and poor cytogenetic response in CML patients. Moreover, patients with advanced phase and cytogenetic poor responders exhibited a higher frequency of proline genotype [24]. In discordance with these previous studies, a significant risk to high Sokal score and failure to imatinib treatment has been reported for the *TP53-GG* (Arg/Arg) genotype [25]. In our study, a significant association was found for the *TP53-GG* (Arg/Arg) genotype with higher levels of *BCR-ABL1* transcripts, suggesting that this genotype may be related to worse clinical outcome.

In this study we also assessed for first time the association between the genetic polymorphism in *TP53* with three different clinical endpoints. Significant differences were found for EFS, showing that patients carrying the *TP53*-GG genotype were more likely to have an adverse event compared to those cases with other genotypes (GC/CC). Moreover, a trend toward for significance was also found for *TP53*-GG carriers concerning FFS and TTF analysis. Therefore, we demonstrated that patients with *TP53*-GG genotype may have a worse clinical prognosis. The introduction of treatment with TKI significantly improves the CML patients' outcome; however some patients do not respond to TKI treatment or have to discontinue due to adverse effects. Thus, it is important to define new predictive markers in order to identify those patients with worse clinical outcome.

In conclusion, we demonstrate that CML susceptibility and TKI outcome can be determined by germline polymorphisms on *TP53* gene. *TP53*-CC (Pro/Pro) genotype was found to have a protective role in the susceptibility to CML in Argentinean population. Moreover, *TP53-GG* (Arg/Arg) genotype was associated with a worse clinical outcome. This suggest that genotyping of TP53 codon 72 polymorphism could be a useful routine to predict the response of CML patients to tyrosine kinase inhibitor therapy. Despite the unquestionable improvement achieved by the use of TKIs in CML treatment, inter-individual variability in drug responses and the development of resistance or intolerance in a substantial proportion of patients, support the need for new genetic markers to individualize the treatment.

Conflicts of interest

Authors declare no conflict of interests.

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