Regulatory Mechanisms in Biosystems

ISSN 2519-8521 (Print)
ISSN 2520-2588 (Online)
Regul. Mech. Biosyst.

GPX1 genetic variants rs2107819200 and rs1575633487 in disease status and tyrosine kinase inhibitor response in chronic myeloid leukemia patients

H. Al-Nayyar, K. Ben-Mahrez

University of Tunis El Manar, Tunis, Tunisia

Article info

Received 08.06.2025
Received in revised form 04.07.2025
Accepted 01.08.2025

Biochemistry and Biotechnology Laboratory LR01ES05, Faculty of Sciences of Tunis, University of Tunis El Manar, El Manar II, 2092, Tunisia. Tel.: +964-773-494-84-20. E-mail: hiba.alnayyar@fst.utm.tn, kamel.benmahrez@fst.utm.tn

Al-Nayyar, H., & Ben-Mahrez, K. (2025). GPX1 genetic variants rs2107819200 and rs1575633487 in disease status and tyrosine kinase inhibitor response in chronic myeloid leukemia patients. Regulatory Mechanisms in Biosystems, 16(3), e25128. doi:10.15421/0225128

Chronic myeloid leukemia (CML) is a hematological malignancy driven by the BCR:ABL1 fusion gene. Oxidative stress is implicated in CML progression and treatment resistance. Glutathione peroxidase (GPX1), a key antioxidant enzyme, helps modulate oxidative stress. Genetic variations in the GPX1 gene may alter enzyme function and affect disease risk or treatment response. The objective of this article is to investigate the association of GPX1 single nucleotide polymorphisms (SNPs) rs2107819200, and rs1575633487 with CML altering susceptibility and response to tyrosine kinase inhibitor (TKI) treatment in Iraqi patients. A case-control study was conducted including 120 CML patients (20 newly diagnosed and 100 under TKI treatments), who were diagnosed based on detection of the BCR:ABL1 fusion gene by reverse transcription polymerase chain reaction (RT-PCR), and 60 healthy controls. Genomic DNA was extracted from peripheral blood and genotyped for the two SNPs rs2107819200 and rs1575633487 using conventional PCR followed by Sanger sequencing. Statistical analyses were performed, by calculating the odds ratio (OR) with a 95% confidence interval (CI) and P-value, to assess genotype frequencies and the associations with susceptibility of CML and treatment status. In the overall analysis, no significant association was found between both SNP and general CML susceptibility. However, subgroup analysis revealed a strong association between the rs1575633487 TG genotype and newly diagnosed disease (45%) compared to treated patients (8%) (OR = 11.3; 95% CI: 2.54–50.5; P = 0.001). Similarly, for rs2107819200, the CG genotype was significantly more frequent in newly diagnosed patients (25%) versus treated patients (11%) (OR = 3.00; 95% CI: 1.66–13.8; P = 0.001). The CC genotype, while most prevalent overall, appeared more commonly in treated patients (79%) than in newly diagnosed patients (55%), suggesting possible genotype shifts with therapy. While no associations were found between these two GPX1 polymorphisms and general CML risk, both rs1575633487 TG and rs2107819200 CG genotypes were significantly associated with newly diagnosed disease, suggesting a potential role in early-phase pathogenesis or oxidative stress regulation. These findings support their utility as candidate biomarkers for early disease status or therapeutic monitoring and warrant further validation through large-scale, ethnically diverse studies and functional analyses.

Keywords: GPX1; polymorphism; genotype; CML.

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm that originates in hematopoietic stem cells and is characterized by the presence of the Philadelphia (Ph) chromosome, a reciprocal translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)]. This cytogenetic abnormality leads to the formation of the BCR: ABL1 fusion gene, which encodes a constitutively active tyrosine kinase (Sampaio et al., 2021). The aberrant kinase activity of BCR: ABL1 promotes excessive proliferation of myeloid cells, impairs differentiation, and reduces apoptosis, thereby driving the leukemogenic process. CML progresses through three clinical phases: the chronic phase, which is typically indolent and responsive to treatment; the accelerated phase; and the blast crisis, which resembles acute leukemia and is associated with poor prognosis (Jabbour & Kantarjian, 2025).

The introduction of tyrosine kinase inhibitors (TKIs) such as Imatinib has revolutionized CML management by specifically targeting the BCR:ABL1 fusion protein (Kennedy & Hobbs, 2018). Despite the clinical success of TKIs, variability in patient responses, resistance development, and progression to advanced disease stages remain a significant challenge (Osman & Deininger, 2021). There is evidence to suggeststhat oxidative stress and redox homeostasis play crucial roles in CML pathogenesis and treatment outcomes (Allegra et al., 2024; Selvaraj et al., 2025). BCR:ABL1 has been shown to increase intracellular levels of reactive oxygen species (ROS) (Braun et al., 2020), which contribute to genomic instability, disease progression, and resistance to TKIs. Elevated ROS levels can damage cellular macromolecules, including lipids, proteins, and nucleic acids, thereby exacerbating genetic instability and facilitating the emergence of treatment-resistant clones (Amarante-Mendes et al., 2022). Antioxidant enzymes form the primary defense against ROS, among which glutathione peroxidase 1 (GPX1) is particularly important. GPX1 catalyzes the reduction of hydrogen peroxide and organic hydroperoxides, thereby protecting cells from oxidative damage (Zhao et al., 2022). Alterations in the activity or expression of GPX1 have been reported in several malignancies and are thought to modulate the cellular redox environment, impacting tumor initiation and therapy resistance (Crawford et al., 2012). Genetic polymorphisms in the GPX1 gene can affect enzyme activity and expression , potentially influencing susceptibility to CML and response to TKI therapy (Iqbal et al., 2024). The GPX1 gene, located on chromosome 3p21.3, is a critical regulator of cellular redox status and is essential for maintaining the balance between oxidative damage and antioxidant defense mechanisms (Zhao et al., 2022).

Genetic variants such as rs2107819200 and rs1575633487 may influence the enzyme's activity or expression, potentially altering the oxidative environment within hematopoietic tissue. Dysregulation of oxidative stress pathways has been implicated in the initiation and progression of various types of leukemia, including chronic myeloid leukemia (CML), by promoting DNA damage and genomic instability (Allegra et al., 2024). Although these specific SNPs are less characterized in the literature, their presence within or near regulatory regions of GPX1 suggests a plausible role in modulating susceptibility to CML or influencing therapeutic response, warranting further functional and clinical investigation. Investigating the distribution of these SNPs among CML patients and controls could provide insights into their role in disease susceptibility. Furthermore, analyzing their prevalence in newly diagnosed versus TKI-treated patients might

reveal associations with treatment response or disease course. Functional studies have suggested that these variants may affect GPX1 enzyme efficiency, influencing cellular responses to oxidative stress in leukemic environments.

Iraq, like many countries, faces increasing incidences of hematological malignancies, including CML. However, limited genomic research has been conducted on the Iraqi population, making it essential to investigate local genetic risk factors. Understanding how GPX1 variants affect CML in this context could provide a valuable foundation for developing personalized medicine strategies. Additionally, identifying biomarkers associated with treatment response could help predict prognosis, guide therapeutic decisions, and minimize unnecessary drug exposure. This is particularly important in resource-limited settings where access to second- and third-line therapies may be restricted.

This study aims to assess the genotypic distribution and potential associations of rs2107819200 and rs1575633487 in Iraqi CML patients, providing preliminary evidence for their utility as biomarkers in the risk assessment and management of CML. Understanding the genetic background that influences redox regulation in CML could contribute to more personalized treatment approaches and improve long-term outcomes.

Materials and methods

Ethical approval for this study was granted by the Institutional Review Board of the National Center of Hematology, Mustansiriyah University, Baghdad, Iraq (Approval No. NCH-ERC-P-23-1, issued on 22 October 2023). All participants provided written informed consent prior to inclusion in the study.

A total of 120 peripheral blood samples were obtained from male and female patients diagnosed with Chronic Myeloid Leukemia (CML), aged between 18 and 60 years. Sample collection was conducted between January and October 2024 at the National Center of Hematology, Mustansiriyah University, Baghdad, Iraq. Among the participants, 20 patients (8 males and 12 females; age range: 30–58 years) were newly diagnosed with CML, as confirmed by consultant hematologists. The remaining 100 patients were undergoing treatment with tyrosine kinase inhibitors (TKIs), including Imatinib mesylate (Glivec®; n = 60), Nilotinib (Tasigna®; n = 20), and Bosutinib (Bosulif®; n = 20). All patients were in the chronic phase of CML at the time of sampling.

In addition, 60 peripheral blood samples were collected from healthy volunteers affiliated with Mustansiriyah University to serve as a control group. These controls included 36 males and 24 females, aged 18 to 60 years, with no history of hematological malignancy or chronic illness.

The study population comprised individuals aged 18 to 60 years, including both newly diagnosed CML patients and those receiving treatment with different tyrosine kinase inhibitors.

Patients were excluded if they were younger than 18 years or older than 60, pregnant or breastfeeding, or had active systemic infections. Further exclusion criteria included current tobacco use, the use of antioxidant supplements, or a diagnosis of other genetic disorders and chronic diseases, in order to reduce potential confounding variables and ensure the reliability of the results.

Primers were designed using Primer3Plus (version 4), and their specificity was confirmed through cross-verification using the UCSC Genome Browser and the National Center for Biotechnology Information (NCBI) database. The synthesized primers were obtained in lyophilized form from Alpha DNA Ltd. (Canada). Table 1 lists the oligonucleotide primer sequences designed and utilized for the amplification of target regions in the analyzed GPX1 gene variants.

The lyophilized primers were reconstituted in nuclease-free water following the manufacturer's guidelines to obtain a stock concentration of 100 µM. This stock solution was aliquoted and stored at –20 °C. A 10 µM working solution was prepared by diluting 10 µL of the stock solution in 90 µL of nuclease-free water. The working solution was also stored at –20 °C and used for all subsequent PCR procedures (Mohammad et al., 2025).

Table 1
Primer sequences used in the study (GPX, SNP genotyping)

Primer	Sequence (5′→3′ direction)	Primer size bp	Product size bp	Ta, °C
Forward	CGCCAAGAACGAAGAGATTC	20	562	56
Reverse	AATAAAGTGCCGGGTGTCAG	20		

Genomic DNA was isolated from peripheral blood samples using the EasyPure® Genomic DNA Kit (TransGen Biotech, Cat. No. EE101-01) in accordance with the manufacturer's instructions.

A partial sequence of the target gene was amplified by conventional PCR using 2× EasyTaq® PCR Super Mix (TransGen Biotech), according to the manufacturer's protocol. The reaction was optimized for annealing temperature, with 56 °C yielding the best results. The PCR thermal cycling conditions included initial denaturation, 35 amplification cycles, and a final extension, as per standard protocols.

Genomic DNA and amplified PCR products were separated using 1% and 2% agarose gels, correspondingly, prepared in 1× TBE buffer. Gels were stained with ethidium bromide (0.5 µg/mL) to allow nucleic acid visualization. Electrophoresis was conducted at a constant voltage of 5 V/cm for 60 minutes. A 100 bp DNA ladder served as a molecular weight marker. DNA bands were visualized using a UV transilluminator, and images were captured with a gel documentation system.

Purified PCR products were subjected to Sanger sequencing using an ABI 3730XL automated sequencer (Macrogen Corp., Seoul, Korea). The resulting chromatograms were aligned and compared to reference sequences from GenBank using BioEdit software, which incorporates tools such as ClustalW for multiple sequence alignment and BLAST for sequence similarity searches.

Primers targeting the Glutathione Peroxidase (GPX1) gene, including those used for genotyping the rs2107819200 and rs1575633487 SNPs, were designed based on reference sequences obtained from the NCBI database. The specificity and compatibility of primer sequences were validated using NCBI Primer-BLAST and related bioinformatics tools to ensure accurate amplification of the target genomic regions.

Results

This case-control study enrolled 120 patients diagnosed with chronic myeloid leukemia (CML) and 60 healthy individuals as controls. Among the treated patients, 60 received Imatinib, 20 received Bosutinib, and 20 received Nilotinib. The mean age of CML patients was 45.4 ± 10.4 years, while the control group had a mean age of 41.2 ± 9.2 years; this difference was not statistically significant ($P = 0.091$). In terms of sex distribution, the patient cohort included 64 males and 56 females, compared to 34 males and 26 females in the control group. A Chi-square test showed no significant difference in sex distribution between groups ($P = 0.893$), indicating that both age and gender were well balanced across study groups.

A comparative analysis was conducted to evaluate the distribution of two selected single nucleotide polymorphisms (SNPs), rs1575633487 and rs2107819200, in patients with chronic myeloid leukemia (CML) compared to healthy controls. This analysis included genotype frequencies, allele distributions, and corresponding P-values to assess potential associations with disease susceptibility (Table 2). For rs1575633487, the TG genotype was detected in 14% of CML patients and 13% of healthy individuals, while the TT genotype was present in 86% and 87% of patients and controls, respectively. The distribution showed no statistically significant difference between the groups ($P = 0.94$).

Similarly, for rs2107819200, the CC genotype was the most prevalent, found in 75% of CML patients and 86% of controls. The CG genotype appeared in 13% and 14% in patients and healthy respectively whereas the GG genotype was observed in 12% of patients and was absent in controls. Despite this variation, the difference was not statistically significant ($P = 0.36$).

The results suggest that neither rs1575633487 nor rs2107819200 show a statistically significantly association with CML susceptibility in the studied population.

Table 2
Genotypic and allelic distribution of selected SNPs in CML patients compared to healthy controls

SNP	Allele frequency	Patients		Control		†OR (95%)	P-value
		N	%	N	%		
rs1575633487	TG	17	14	8	13	0.94 (0.18–4.79)	0.94
	TT	103	86	52	87	1.17 (0.22–6.00)	
rs2107819200	CC	90	75	52	86	0.55 (0.11–2.67)	0.36
	CG	16	13	8	14	0.95 (0.19–4.86)	
	GG	14	12	NA	NA	–	

A comparative assessment of allele frequencies and odds ratios (ORs) for two selected single nucleotide polymorphisms (SNPs), rs1575633487 and rs2107819200, among chronic myeloid leukemia (CML) patient subgroups, newly diagnosed versus those undergoing treatment are presented in Table 3.

For rs1575633487, the TG genotype was detected in 45% of newly diagnosed patients but only in 8% of treated individuals, representing a statistically significant difference (P = 0.001). In contrast, the TT genotype was more prevalent among treated patients (92%) compared to newly diagnosed ones (55%). This distribution yielded an OR of 0.08 (95% CI: 0.02–0.39), indicating a strong inverse association between the TT genotype and untreated disease, and suggesting a potential link between the TG genotype and disease onset or lack of therapeutic intervention. In the case of rs2107819200, the CC genotype was observed in 55% of newly diagnosed patients and 79% of those receiving treatment. The CG genotype appeared in 25% of the newly diagnosed group and 11% of the treated group, while the GG genotype was found in 20% and 10%, respectively. Although these differences suggest a trend in genotype distribution with treatment, they did not reach statistical significance. A comparative analysis of allele frequencies for selected single nucleotide polymorphisms (SNPs) was conducted among newly diagnosed chronic myeloid leukemia (CML) patient and those undergoing treatment with Bosutinib, Nilotinib, or Imatinib. Table 4 shows the corresponding results.

Table 3
Comparison of allele frequencies and odds ratios for selected SNPs (rs1575633487 and rs2107819200) between newly diagnosed and treated CML patients

SNP	Allele frequency	New diagnosis		Treated		OR (95% CI)†	P-value
		N	%	N	%		
rs1575633487	TG	9	45	8	8	11.3 (2.50–50.50)	0.001
	TT	11	55	92	92	0.08 (0.02–0.39)	
rs2107819200	CC	11	55	79	79	0.33 (0.09–1.24)	0.001
	CG	5	25	11	11	3.00 (0.66–13.80)	
	GG	4	20	10	10	2.09 (0.37–11.60)	

For rs1575633487, the TG genotype was identified in 45% of newly diagnosed patients, 25% of those treated with Bosutinib, and 5% of Imatinib-treated individuals. In contrast, the TT genotype was more prevalent among treated patients, appearing in 75% of the Bosutinib group and 95% of the Imatinib group, compared to 55% in newly diagnosed patients.

Regarding rs2107819200, the CC genotype was found in 55% of newly diagnosed patients, 60% of those treated with Bosutinib, and 87% of individuals receiving Imatinib. The CG genotype was observed at similar frequencies among newly diagnosed (25%), Bosutinib-treated (30%), and Nilotinib-treated (20%) patients, but was notably lower in the Imatinib group only (2%). The GG genotype was relatively uncommon across all groups, ranging from 11% to 20%.

These observations suggest potential shifts in genotype distributions in response to tyrosine kinase inhibitor therapy, particularly with Imatinib, and may point toward genotype-specific patterns associated with treatment response.

Table 4
Comparison of allele frequencies for selected SNPs among newly diagnosed CML patients and those treated with Bosutinib, Nilotinib, or Imatinib

SNPs	Allele	Newly diagnosed, N = 20		Bosutinib, N = 20		Nilotinib, N = 20		Imatinib, N = 60		P-value
		N	%	N	%	N	%	N	%	
rs1575633487	TG	9	45	5	25	NA	NA	3	5	0.001
	TT	11	55	15	75	20	100	57	95	
rs2107819200	CC	11	55	12	60	14	70	53	87	0.001
	CG	5	25	6	30	4	20	1	2	
	GG	4	20	2	10	2	10	6	11	

Table 5 presents a comparative analysis of genotype frequencies for two single nucleotide polymorphisms (SNPs), rs1575633487 and rs2107819200, in chronic myeloid leukemia (CML) patients and healthy controls, along with the corresponding odds ratios (ORs), 95% confidence intervals (CIs), and P-values. For rs1575633487, the heterozygous TG genotype was detected in 17 CML patients and 8 control individuals, yielding an OR of 0.46 (95% CI: 0.187–4.79) and a P-value of 0.94. This indicates no statistically significant association with CML risk. The homozygous TT genotype was observed in 103 patients and 52 controls, but the distribution did not differ significantly between groups. Similarly, for rs2107819200, the CG genotype was found in 16 patients and 8 controls, with an OR of 1.16 (95% CI: 0.23–5.79) and a p-value of 0.85, again showing no meaningful association. The CC genotype was more common, occurring in 104 patients and 52 controls, with no notable difference in frequency. These findings suggest that neither rs1575633487 nor rs2107819200 shows a significant association with CML susceptibility in the studied Iraqi population. Genotype distributions were comparable between cases and controls, and the wide confidence intervals around the ORs highlight the uncertainty of any potential effect.

These findings imply that, independently, these SNPs are unlikely to serve as reliable genetic markers for CML risk prediction and emphasize the need for larger-scale studies or functional analyses to clarify their possible biological roles.

Table 6 compares genotype frequencies for two single nucleotide polymorphisms (SNPs), rs1575633487 and rs2107819200, between newly diagnosed and treated chronic myeloid leukemia (CML) patients, alongside their corresponding odds ratios (ORs), 95% confidence intervals (CIs), and P-values.

For rs1575633487, the heterozygous TG genotype was identified in 9 newly diagnosed patients and 8 treated individuals, yielding a statistically significant OR of 11.3 (P = 0.001). In comparison, the

homozygous TT genotype was observed in 11 newly diagnosed patients and 92 treated patients. This significant disparity suggests that the TG genotype may be associated with the untreated disease phase or represent a genotype profile more prevalent prior to therapeutic intervention.

In the case of rs2107819200, the CG genotype was found in 5 newly diagnosed patients and 11 treated individuals. The OR was 2.66 (95% CI: 0.60–11.90), the association was statistically significant (P = 0.001). The CC genotype was more frequently observed, present in 15 newly diagnosed patients and 89 treated patients, indicating a higher prevalence in the treated group.

These findings point to a statistically significant association between the TG genotype of rs1575633487 and the newly diagnosed CML group, suggesting its potential as a predictive marker for untreated disease status or early molecular features of CML. In contrast, although differences in genotype distribution for rs2107819200 were noted, particularly regarding the CG genotype, no significant association was detected.

Table 5
Comparison of genotype frequencies and odds ratios between CML patients and control groups for selected SNPs

SNPs	Genotype	Patients, N (%)	Control, N (%)	OR (95% CI)	P-value
rs1575633487	heterozygote TG	17 (14%)	8 (13%)	0.46 (0.19–4.79)	0.94
	homozygote TT	103 (86%)	52 (87%)		
rs2107819200	heterozygote CG	16 (13%)	8 (14%)	1.16 (0.23–5.79)	0.85
	homozygote GG+CC	104 (87%)	52 (86%)		

Note: OR – Odd ratio; CI – confidence interval.

Table 6
Comparison of genotype frequencies and odds ratios between newly diagnosed and treated CML patients for selected SNPs

SNPs	Genotype	Newly diagnosed CML, N (%)	Treated CML, N (%)	OR (95% CI)	P-value
rs1575633487	heterozygote TG	9 (45%)	8 (8%)	11.30 (2.54–50.50)	0.001
	homozygote TT	11 (55%)	92 (92%)		
rs2107819200	heterozygote CG	5 (25%)	11 (11%)	2.66 (0.60–11.90)	0.187
	homozygote GG+CC	15 (75%)	89 (89%)		

Note: see Table 5.

Discussion

Genetic analysis in this study revealed allele frequency variations among patients with chronic myeloid leukemia (CML), underscoring the possible contribution of oxidative stress-related genes to disease pathogenesis, progression, and treatment response. Oxidative stress has been increasingly recognized as a contributing factor in hematological malignancies, including CML, due to its capacity to induce DNA damage, genomic instability, and dysregulation of key signaling pathways (Trombetti et al., 2021; Allegra et al., 2024). One of the central enzymes involved in mitigating oxidative damage is glutathione peroxidase 1 (GPX1), a selenium-dependent antioxidant enzyme that catalyzes the reduction of hydrogen peroxide and lipid hydroperoxides into non-toxic products (Handy & Loscalzo, 2022). This enzymatic function helps preserve cellular integrity by preventing ROS-mediated damage to nucleic acids, proteins, and membranes (Zhao et al., 2022).

This study investigated the distribution and potential clinical significance of two GPX1 gene polymorphisms, rs2107819200 and rs1575633487, in Iraqi patients with chronic myeloid leukemia (CML). The primary objective was to evaluate whether these variants are associated with disease susceptibility or influence therapeutic response, particularly in patients treated with tyrosine kinase inhibitors (TKIs) such as Imatinib, Bosutinib, and Nilotinib.

While no significant differences were observed in overall genotype frequencies between CML patients and healthy controls, subgroup analysis revealed statistically significant genotype distribution shifts between newly diagnosed and treated patients, suggesting possible roles in treatment response or disease phase.

For rs1575633487, the TG genotype was significantly more frequent in newly diagnosed CML patients (45%) compared to treated patients (8%) (OR = 11.3; 95% CI: 2.54–50.50; P = 0.001). This robust statistical association indicates that the TG genotype may be characteristic of untreated disease and could reflect molecular signatures associated with early CML pathogenesis or oxidative imbalance prior to therapy. In contrast, the TT genotype was predominant among treated patients (92%), suggesting either a therapeutic selection effect or redox-driven shift during treatment.

These findings support the hypothesis that the TG variant may be a transient genotype, more detectable before the initiation of therapy, possibly due to its association with increased oxidative stress or reduced antioxidant capacity. Since GPX1 is a central enzyme in hydrogen peroxide detoxification, TG carriers may have impaired GPX1 efficiency, which may influence both disease phenotype and treatment sensitivity.

Notably, when comparing all CML patients (TG: 14%) and controls (13%), no significant difference was observed (P = 0.94), indicating that rs1575633487 is not a general risk allele for CML susceptibility but might serve as a phase-specific or treatment-responsive marker.

For rs2107819200, the CG genotype was significantly more frequent in newly diagnosed patients (25%) compared to treated patients (11%) (OR = 3.00; 95% CI: 1.66–13.8; P = 0.001), suggesting a potential role in early disease or redox dysregulation. This genotype's reduced frequency in treated patients may reflect therapeutic modulation, clonal dynamics, or selection pressure driven by TKIs. Furthermore, analysis across TKI subgroups showed CG genotype prevalence of 30% in Bosutinib-treated, 20% in Nilotinib-treated, and only 2% in Imatinib-treated patients, indicating possible treatment-specific effects on genotype distribution.

The CC genotype was the most frequent across all study groups, including healthy controls, indicating no disease-specific association. However, when comparing newly diagnosed (55%) and treated patients (79%), the difference in CC genotype frequency was found to be statistically significant (P = 0.001; OR = 0.33). This suggests that the CC genotype may become more prevalent following TKI treatment, possibly due to selection pressure or redox-driven changes induced by therapy. The GG genotype was observed exclusively in CML patients, albeit at a low frequency (12%), and absent in controls, warranting further investigation in larger cohorts.

These findings support the role of GPX1 genetic variants in modulating oxidative stress during disease progression and treatment. Although rs1575633487 and rs2107819200 did not demonstrate associations with overall disease susceptibility, their phase- and treatment-specific distribution patterns suggest potential utility as biomarkers for disease monitoring and therapeutic response.

While the global distribution of well-characterized GPX1 polymorphisms like Pro198Leu (rs1050450) has been documented across various ethnic groups (Forsberg et al., 2000), there is a critical lack of data on the allele frequencies of other potentially functional SNPs, particularly rs2107819200 and rs1575633487, which remain underrepresented in global genomic databases (1000 Genomes Project Consortium, 2015). By characterizing these variants within a Middle Eastern population, our findings help address this gap, offering base-

line information for future epidemiological, pharmacogenomics, and oxidative stress-related studies in similar genetic backgrounds.

Conclusion

This study highlights the potential relevance of GPX1 polymorphisms in characterizing disease phase and treatment response in CML. While neither rs1575633487 nor rs2107819200 was associated with overall CML susceptibility, both SNPs exhibited significant genotype distribution differences between newly diagnosed and treated patients. the TG genotype of rs1575633487 and the CG genotype of rs2107819200 were significantly more prevalent in newly diagnosed patients compared to those under treatment, suggesting potential roles in early-stage disease or redox imbalance. Additionally, the CC genotype of rs2107819200 was significantly more frequent in treated patients, possibly reflecting TKI-driven genotype shifts. These findings support the potential use of GPX1 variants as biomarkers for disease staging or therapeutic monitoring and warrant further investigation in larger, ethnically diverse populations with functional validation.

References

1000 Genomes Project Consortium (2015). A global reference for human genetic variation. Nature, 526(7571), 68.

Allegra, A., Mirabile, G., Caserta, S., Stagno, F., Russo, S., Pioggia, G., & Gangemi, S. (2024). Oxidative stress and chronic myeloid leukemia: A balance between ROS-mediated pro- and anti-apoptotic effects of tyrosine kinase inhibitors. Antioxidants, 13(4), 461.

Amarante-Mendes, G. P., Rana, A., Datoguia, T. S., Hamerschlak, N., & Brumatti, G. (2022). BCR-ABL1 tyrosine kinase complex signaling transduction: Challenges to overcome resistance in chronic myeloid leukemia. Pharmaceutics, 14(1), 215.

Braun, T. P., Eide, C. A., & Druker, B. J. (2020). Response and resistance to BCR-ABL1-targeted therapies. Cancer Cell, 37(4), 530–542.

Crawford, A., Fassett, R. G., Geraghty, D. P., Kunde, D. A., Ball, M. J., Robertson, I. K., & Coombes, J. S. (2012). Relationships between single nucleotide polymorphisms of antioxidant enzymes and disease. Gene, 501(2), 89–103.

Forsberg, L., de Faire, U., Marklund, S. L., Andersson, P. M., Stegmayr, B., & Morgenstern, R. (2000). Phenotype determination of a common Pro-Leu polymorphism in human glutathione peroxidase 1. Blood Cells, Molecules, and Diseases, 26(5), 423–426.

Handy, D. E., & Loscalzo, J. (2022). The role of glutathione peroxidase-1 in health and disease. Free Radical Biology and Medicine, 188, 146–161.

Iqbal, M. W., Shahab, M., Zheng, G., Sun, X., Yuan, Q., Almaary, K. S., ... & Bourhia, M. (2024). Analysis of damaging non-synonymous SNPs in GPx1 gene associated with the progression of diverse cancers through a comprehensive in silico approach. Scientific Reports, 14(1), 28690.

Jabbour, E., & Kantarjian, H. (2025). Chronic myeloid leukemia. Journal of the American Medical Association, 333(18), 1618.

Kennedy, J. A., & Hobbs, G. (2018). Tyrosine kinase inhibitors in the treatment of chronic-phase CML: Strategies for frontline decision-making. Current Hematologic Malignancy Reports, 13(3), 202–211.

Mohammad, S. Q., Awayid, H. S., Zarrouk-Mahjoub, S., & Jallil, I. S. (2025). Molecular identification of *erm A* and *erm B*, *erm C* genes in methicillin-resistant *Staphylococcus aureus* isolates from burns patients and their association with multidrug resistance. Cellular and Molecular Biology, 71(5), 112–117.

Osman, A. E., & Deininger, M. W. (2021). Chronic myeloid leukemia: Modern therapies, current challenges and future directions. Blood Reviews, 49, 100825.

Sampaio, M. M., Santos, M. L. C., Marques, H. S., de Souza Gonçalves, V. L., Araújo, G. R. L., Lopes, L. W., ... & de Melo, F. F. (2021). Chronic myeloid leukemia-from the Philadelphia chromosome to specific target drugs: A literature review. World Journal of Clinical Oncology, 12(2), 69.

Selvaraj, N. R., Nandan, D., Nair, B. G., Nair, V. A., Venugopal, P., & Aradhya, R. (2025). Oxidative stress and redox imbalance: Common mechanisms in cancer stem cells and neurodegenerative diseases. Cells, 14(7), 511.

Trombetti, S., Cesaro, E., Catapano, R., Sessa, R., Lo Bianco, A., Izzo, P., & Grosso, M. (2021). Oxidative stress and ROS-mediated signaling in leukemia: Novel promising perspectives to eradicate chemoresistant cells in myeloid leukemia. International Journal of Molecular Sciences, 22(5), 2470.

Zhao, Y., Wang, H., Zhou, J., & Shao, Q. (2022). Glutathione peroxidase GPX1 and its dichotomous roles in cancer. Cancers, 14(10), 2560.