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ORIGINAL PAPER

Association of the *GPX1* rs1050450 single nucleotide variant and identification of the novel variant rs771425412 in patients with primary osteoporosis from Baghdad, Iraq

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ABSTRACT

Introduction and aim. Osteoporosis is a multifactorial bone disorder driven by genetic and environmental factors, with oxidative stress implicated in its pathogenesis. Glutathione peroxidase 1 (GPX1), a key antioxidant enzyme, modulates bone homeostasis by regulating reactive oxygen species. To our knowledge, this is the first study to report the rs771425412 variant of the GPX1 gene in association with primary osteoporosis. This study investigated the association between the single nucleotide variant (rs1050450 C>T and rs771425412 C>A) and the risk of primary osteoporosis in Iraqi patients.

Material and methods. A case-control study was conducted involving 105 patients with primary osteoporosis and 105 age-/sex-matched healthy controls recruited from Baghdad Hospital. Peripheral blood genomic DNA was genotyped by PCR and direct sequencing.

Results. The rs1050450-T allele was significantly more frequent in patients than in controls (25.7% vs. 10.95%; OR=2.68, 95% CI: 1.58–4.55, p<0.001), with the CT genotype increasing the risk (dominant model: OR=3.77, 95% CI: 2.08–6.86). Similarly, the rs771425412-A allele was enriched in patients compared to controls (17.1% vs. 2.9%; OR=7.03, 95% CI: 2.93–16.92, p<0.001), and the CA genotype increased risk (OR=8.61, 95% CI: 3.47–21.3). Haplotype analysis revealed a protective C-C haplotype (OR=0.31, 95% CI: 0.19–0.51), while the T-A (OR=23.2, 95% CI: 3.09–174.3) and C-A (OR=3.15, 95% CI=1.12–8.8) haplotypes were associated with increased susceptibility.

Conclusion. The CT genotype of rs1050450 and the CA genotype of rs771425412 in the *GPX1* gene are significantly associated with an increased susceptibility to primary osteoporosis in the Iraqi population, likely through mechanisms involving impaired oxidative stress regulation.

Keywords. GPX1, osteoporosis, oxidative stress, rs1050450, rs771425412, SNV

Introduction

Osteoporosis is a bone disorder characterized by weakened bone structure that increases the risk of fractures. This condition arises from various factors, including age, genetics, sex, environmental influences, and lifestyle choices.[1] Primary osteoporosis, the most common form of the disease, develops because of age-related changes or hormonal deficiencies, particularly estrogen decline during menopause.[2] This condition differs from secondary osteoporosis, which results from underlying medical conditions or medications.[3] The pathophysiology of primary osteoporosis involves complex interactions between genetic factors, environmental influences, hormonal changes, and lifestyle choices, with genetic components contributing approximately 70% of bone mineral density variation.[4,5]

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Oxidative stress plays a crucial role in bone homeostasis by disrupting the balance between bone formation and resorption.[6] The accumulation of reactive oxygen species (ROS) leads to increased osteoclast activity and enhanced bone resorption while simultaneously inducing apoptosis in osteoblasts and osteocytes, resulting in net bone loss.[7] This oxidative imbalance significantly contributes to the pathogenesis of osteoporosis by altering key signaling pathways, including the upregulation of RANKL and downregulation of osteoprotegerin (OPG), which favors osteoclast differentiation and bone resorption.[8,9]

Glutathione peroxidase 1 (GPX1) stands as a principal contributor to the cellular antioxidant system. Functioning as a selenium-dependent enzyme, its primary role involves the catalytic reduction of harmful hydroperoxides, including hydrogen peroxide, into inert products like water and alcohols.[10] The gene encoding GPX1 is situated on chromosome 3p21.31, spans 1,183 base pairs, and features a two-exon structure interrupted by one intron.[11,12] *GPX1* is the most copious isoform of its kind in human cells, with widespread expression and a predominantly cytoplasmic distribution.[13] A critical aspect of its function is the presence of selenocysteine at the active site. This unique amino acid is encoded by a UGA codon, which typically terminates translation but is co-opted for selenocysteine insertion when guided by SECIS elements in the 3' UTR.[14] Among these variants, a single nucleotide variant (SNV) with a missense mutation, considered the most studied polymorphism in the *GPX1* gene, is rs1050450, which is correlated with various diseases.[15,16]

SNV rs1050450, located in exon 2 of the *GPX1* gene at position 198, is a single substitution from cytosine to thymine, which alters the function of the synthesized protein by changing the amino acid from proline to leucine.[17] The role of *GPX1* and its variants in osteoporosis may vary across different populations owing to genetic diversity, environmental factors, and lifestyle choices.[18] Population-specific studies are essential for understanding how SNVs such as rs1050450 (Pro198Leu) affect *GPX1* activity and its association with bone health. For example, the frequency of the T allele of rs1050450 may differ between populations, potentially influencing the prevalence of osteoporosis in these groups.[15,19] In contrast to the well-characterized rs1050450 variant, rs771425412 appears to be a less commonly studied polymorphism in GPX1. This C>A transversion results in a missense mutation, changing the codon from CCA to CAA, which leads to an amino acid substitution of proline to glutamine at codon 198 (p.Pro198Gln). This non-conservative change, replacing a rigid proline with a polar glutamine, could potentially alter the local protein structure and stability of the GPX1 enzyme, thereby impacting its antioxidant function. The limited literature specifically addressing this variant suggests that it may represent a rarer genetic variation with potentially different functional implications compared to the more prevalent Pro198Leu polymorphism.[20] Crucially, the variant rs771425412 remains poorly characterized in osteoporosis, with no population-specific data from Iraq or similar regions. This study aimed to investigate the association between two GPX1 variants (rs1050450 and rs771425412) and primary osteoporosis in Iraqi patients, introducing rs771425412 as a newly identified variant in this context.

Material and methods

Ethical Approval

The study protocol received ethical sanction from the Ethics Committee of the Department of Biotechnology, College of Science, University of Baghdad (Reference: CSEC/1023/0069 on October 30, 2023). All procedures conformed to the ethical standards of the Declaration of Helsinki. Prior to any study procedures, written informed consent was secured from every participant. From November 2023 to August 2024, a total of 210 subjects within the age range of 32–75 years were recruited. The study population consisted of 105 patients diagnosed with primary osteoporosis (75 females, 30 males) and 105 healthy controls matched for age and sex. Patients were recruited from those attending the Baghdad Teaching Hospital and Al-Wasit Hospital in Baghdad Province.

Dual energy X-ray absorptiometry (DEXA) scan

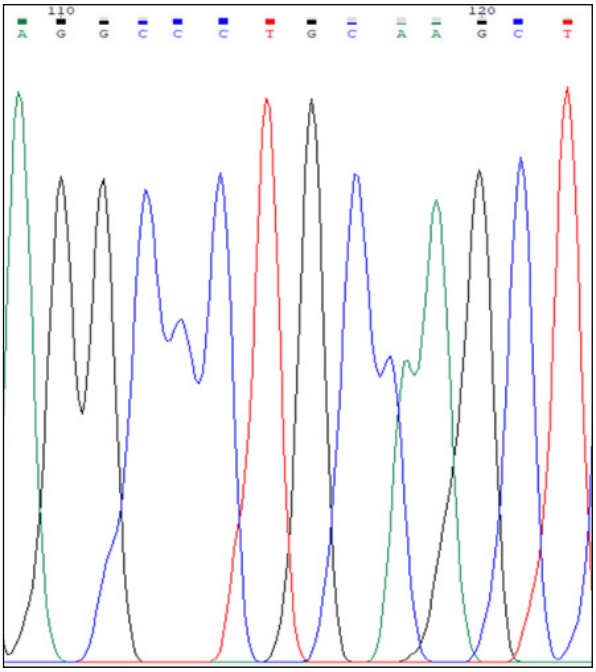
Each participant was examined by a physician, and bone mineral density (BMD) was measured via a DEXA scan of the hip and spine. Participants were classified as healthy controls (T-score ≥ -1.0 SD) or osteoporosis patients (T-score ≤ -2.5 SD), according to the World Health Organization (WHO) criteria.[1]

Including and exclusion criteria for blood samples

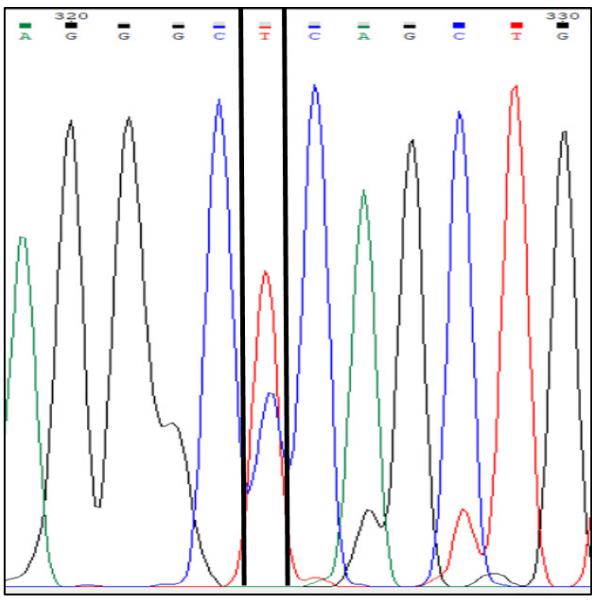
Patients aged 32–75 years were confirmed to have primary osteoporosis. Individuals with medical conditions known to affect bone metabolism, such as chronic diseases or other systemic and metabolic bone disorders, were excluded. None of the participants had recently taken medications that could influence bone metabolism. All participants completed a questionnaire to provide clinical data, including BMI, comorbidities, lifestyle factors (alcohol consumption, smoking, physical activity), and medication history.

Blood samples collection

Approximately 5 mL of venous blood was collected from each participant. Of this, 2 mL was transferred to an EDTA-containing tube for the analysis of GPX1 variants using polymerase chain reaction (PCR) and direct DNA sequencing.



(rs771425412 C>A)



(rs1050450 C>T)

Fig. 1. DNA sequence chromatograms of *GPX1* gene single nucleotide polymorphisms (rs1050450 and rs rs771425412). ChromasPro software was used to generate the chromatogram

Genetic analysis of GPX1

Genomic DNA was extracted from blood samples using the EasyPure® Blood Genomic DNA Kit (TransGen Biotech, Cat. No. EE121-01), and its purity and concentration were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific, USA). A 665 bp region of exon 2 of the GPX1 gene, containing the SNV rs1050450, was amplified using newly designed primers (Forward: 5′-CGCCAAGAACGAAGAGATTC-3′; Reverse: 5′-CCTGGGCAATAGAGCAAAAA-3′) from Alpha DNA Ltd. (Montreal, QC, Canada). PCR was performed in a 25 µL reaction volume containing 12.5 µL of 2xEasyTaq® PCR SuperMix, 1 µL of each primer, 6 µL of gDNA, and 4.5 µL of nuclease-free water. The thermal cycling conditions were as follows: initial denaturation at 94°C for 5 minutes; 35 cycles of 94°C for 30 seconds, 56°C for 30 seconds, and 72°C for 30 seconds; and a final extension at 72°C for 5 minutes.

Sequencing and aata analysis

Genotyping of the GPX1 exon 2 SNVs was performed by Sanger sequencing (Macrogen Corporation, Seoul, South Korea). The resulting sequences were analyzed with ChromasPro software and aligned to the GPX1 reference sequence using the Basic Local Alignment Search Tool (BLAST).

The sequence chromatograms of the GPX1 SNVs rs1050450 and rs771425412 were analyzed, as shown in Figure 1. Primers were designed to amplify a region within exon 2 of GPX1 gene, specifically targeting the known SNV rs1050450 (Pro198Leu). However, upon sequencing and alignment of the amplified products using the NCBI reference sequence, an additional SNV, rs771425412 was consistently detected within the same amplified region. This variant was observed in multiple samples with a high frequency in premenopausal women. The NCBI GenBank accession numbers (PV656547, PQ793280, and PQ768535).

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Sample size power was calculated using G*Power, Version 3.1.9.7.[21] Allele and genotype frequencies were calculated and assessed for Hardy-Weinberg equilibrium (HWE). Associations between genotypes and disease risk were estimated using odds ratios (ORs) with 95% confidence intervals (CIs) computed via multinomial logistic regression. The significance of categorical data was assessed using Fisher's exact test (two-sided), with the Bonferroni correction applied for multiple testing. Linkage disequilibrium (LD) and haplotype frequencies were analyzed using the SHEsis web platform.[22]

Results

This case-control study included 105 primary osteoporotic patients and 105 age-/sex-matched healthy controls. A post hoc power analysis confirmed the statistical validity of the sample size (power=0.95). The proportion of women with primary osteoporosis was significantly higher than that of men ($p<0.0001$). Among patients with osteoporosis, 30 men (28.6%) and 75 women (71.4%) were affected, reflecting the same proportions observed in the healthy control (HC) group. According to menopausal status for women, 30 women (28.6%)

were premenopausal, while 45 women (42.9%) were postmenopausal.

The quality of the extracted DNA was confirmed using gel electrophoresis, as shown in Figure 2. Gel electrophoresis results show the PCR products. The bands had a molecular size of approximately 700 bp. As shown in Figure 3.

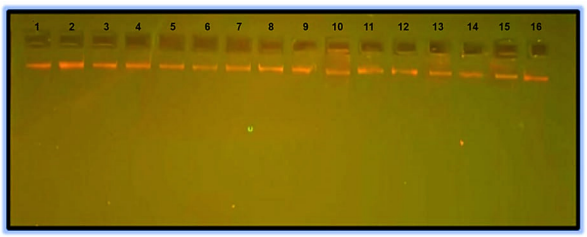


Fig. 2. Genomic DNA electrophoresis; chromosomal DNA bands extracted from human blood samples were visualized under the short wave UV light after staining with the ethidium bromide (EtBr) on (1%) of agarose gel at (70 volts for 30 min), lanes (1-8): healthy controls, lanes (9-16): osteoporosis patients

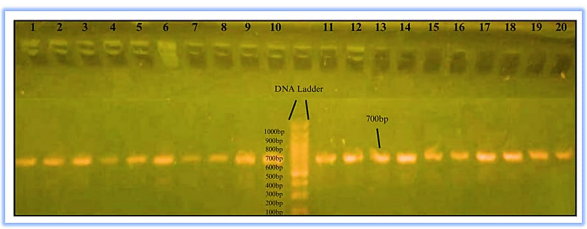


Fig. 3. Agarose gel electrophoresis of PCR products amplified from exon 2 of the *GPX1* gene. Clear bands around 700 bp were observed in both control and patient samples, the gel was run on 1.5% agarose stained with ethidium bromide, lane (1-10): exon2 products for healthy controls, DNA ladder (1000 bp), lanes (11-20): exon2 products for primary osteoporosis patients

Genotype frequencies were notably assessed for HWE, and the genotype distributions of rs1050450 significantly deviated from HWE in the osteoporosis group (p=0.0004), whereas controls showed equilibrium (p=0.2076). Conversely, rs771425412 also deviated slightly in patients (p=0.034) but was in equilibrium among controls (p=0.763), this is presented in Table 1. For rs1050450, the T allele showed a significantly higher frequency in patients (25.7%) than in controls (10.95%), and was associated with an increased risk of osteoporosis (OR=2.68; 95% CI: 1.58–4.55; p<0.001). The dominant model (CT+TT vs. CC) further supported this association (OR=3.77; 95% CI: 2.08–6.86). Similarly, the overdominant and codominant models yielded statistically significant results.

For rs771425412, the A allele was significantly enriched in patients (17.1%) compared with controls (2.9%), corresponding to an increased risk of osteoporosis (OR=7.03; 95% CI: 2.93–16.92; p<0.001). In the dominant model (CA + AA vs. CC), the risk remained substantial (OR=8.61; 95% CI: 3.47–21.3).

Table 1. Multinomial logistic regression analysis combined with HWE analysis of SNVs ((rs1050450-rs771425412) of the *GPX1* gene in primary osteoporosis patients (controls were the reference group))*

SNV/ genetic model	Allele/ genotype/	Pt, n=105		HC, n=105		OR (95% CI)	p
		n	%	n	%		
rs1050450 C/T							
Allele	C	156	74.3	178	89.1	Reference; 1.0	
	T	54	25.7	23	10.95	2.68 (1.58–4.55)	p<0.001
Recessive	CC+CT	105	100.0	105	100.0	Reference; 1.0	
	TT	ND	ND	ND	ND	7.39 (0.15–372.3)	p>0.999
Dominant	CC	51	48.6	82	78.1	Reference; 1.0	
	CT+TT	54	51.4	23	21.9	3.77 (2.08–6.86)	p<0.001
Over-dominant	CC+TT	51	48.6	82	78.1	Reference; 1.0	
	CT	54	51.4	23	21.9	3.77 (2.08–6.86)	p<0.001
Co-dominant	CC	51	48.6	82	78.1	Reference; 1.0	
	CT	54	51.4	23	21.9	3.77 (2.08–6.86)	p<0.001
	TT	ND	ND	ND	ND	4.16 (0.06-301.3)	p>0.999
HWE p		0.0004		0.2076			
rs771425412 C/A							
Allele	C	174	82.9	204	97.1	Reference; 1.0	
	A	36	17.1	6	2.9	7.03 (2.93–16.92)	p<0.001
Recessive	CC+CA	105	100.0	105	100.0	Reference; 1.0	
	AA	ND	ND	ND	ND	7.39 (0.15–372.4)	p>0.999
Dominant	CC	69	65.7	99	94.3	Reference; 1.0	
	CA+AA	36	34.3	6	5.7	8.61 (3.47–21.3)	p<0.001
Over-dominant	CC+AA	69	65.7	99	94.3	Reference; 1.0	
	CA	36	34.3	6	5.7	8.61 (3.47–21.3)	p<0.001
Co-dominant	CC	69	65.7	99	94.3	Reference; 1.0	
	CA	36	34.3	6	5.7	8.61 (3.47–21.3)	p<0.001
	AA	ND	ND	ND	ND	0.06 (0.01-0.52)	p = 0.049
HWE p		0.034		0.763			

* SNV – single nucleotide variant, HWE – Hardy-Weinberg equilibrium, Pt – patients, HC – healthy controls, OR – odds ratio, CI – confidence interval, p – two-tailed probability; pc – Bonferroni correction probability, ND – not detected

Haplotype analysis (in the order rs1050450-rs771425412) identified four haplotypes (C-C, T-C, T-A, C-A) with frequencies of 67.1, 15.7, 1.0%, and 7.1%, respectively, in osteoporosis patients. Compared with the control, the expression of the C-C haplotype (OR=0.31; 95% CI: 0.19–0.5; p=2.06). The T-A haplotype was expressed (OR=23.2; 95% CI: 3.09–174.3; p=1.19). The expression of the C-A haplotype was significantly different (OR=3.15, 95% CI=1.12-8.8; p=0.2). The results are illustrated in Table 2.

Analysis of linkage disequilibrium (LD) revealed that *GPX1* rs1050450 and rs771425412 SNVs: D' (D-prime) measures the degree of LD (non-random association) between the two SNVs Figure 4. A value of 0.41 indicates

moderate LD, meaning that the SNVs are not completely independent, but do not always segregate. Additionally, R^2 (RS) quantifies the correlation between allele frequencies of the two SNVs. A low R^2 (0.08).

Table 2. Haplotype analysis for SNVs (rs1050450-rs771425412) located in the second exon of *GPX1* gene*

Haplotype (rs1050450-rs771425412)						
	Pt, n=105		HC, n=105		OR (95% CI)	p
	n	%	n	%		
C-C	141	67.1	182	86.6	0.31 (0.19-0.51)	p=2.06
T-C	33	15.7	22	10.4	1.59 (0.89-2.84)	p=0.11
T-A	21	1.0	1	0.4	23.2 (3.09-174.3)	p=1.19
C-A	15	7.1	5	2.3	3.15 (1.12-8.8)	p=0.02

* SNV – single nucleotide variant, Pt – patients, HC – healthy controls, OR – odds ratio, CI – confidence interval, p – two-tailed probability

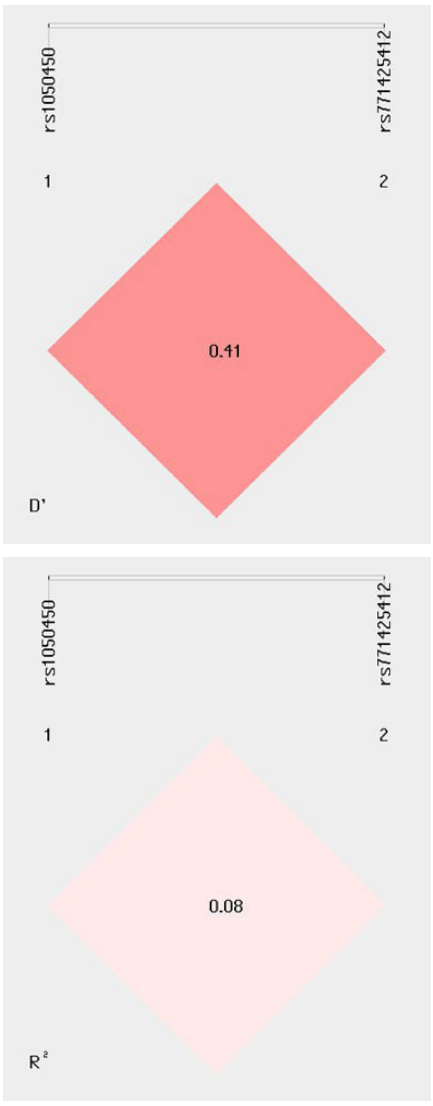


Fig. 4. Pairwise analysis depicting linkage disequilibrium plot coefficient (D') and RS between two SNVs (rs1050450 and rs771425412) for the gene showing the LD coefficient (D'; 0.41) and RS (R2; 0.08)

Discussion

A key finding was a discrepancy in the rs771425412 variant. While dbSNP annotates it as a Pro→Leu substitution, our sequencing identified a Pro→Gln change (CCA→CAA) in the Iraqi cohort. This suggests we may have detected a rare, previously unannotated sub-variant or a novel SNV at the same position, primarily observed in premenopausal women, which would currently be classified as a variant of uncertain significance (VUS). VUS variants are mostly missense; therefore, they are difficult to classify as either pathogenic or benign based on the guidelines set by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[23] VUS are especially prevalent in the context of rare variants because they lack sufficient population frequency or functional data to be confidently classified as pathogenic or benign.[23,24] Despite ongoing advancements in genomics and data sharing, some rare variants, particularly those in underrepresented populations or with limited functional evidence, will likely remain uncertain by 2030.[25] Continued innovation and global collaboration are essential to reduce this uncertainty in rare disease diagnostics. The importance of global data sharing underscores the resolution of VUS classifications in the future.[25]

HWE analysis revealed that both rs1050450 and rs771425412 significantly deviated from equilibrium in patients but not in controls. This observed deviation in patients indicates a potential pathogenic role of these variants in susceptibility to osteoporosis. The deviations are characterized primarily by an increase in heterozygotes along with significant associations observed in dominant and over dominant genetic models.[26] These findings may suggest that heterozygosity at this locus disrupts the normal balance of antioxidant defense, thereby contributing to increased oxidative stress that induces bone loss.[19] Importantly, the presence of HWE in the control group supports the reliability of the genotyping process that reflects true biological differences associated with disease status.[26]

Haplotype analysis revealed significant differences in haplotype distribution between patients and controls. Among the identified haplotypes, the C-C haplotype was significantly more frequent in controls and conferred a protective effect (OR=0.31; p=2.06). This finding may be explained by its potential to maintain normal GPX1 activity, thereby enhancing antioxidant defenses and reducing bone loss. Conversely, the T-A and C-A haplotypes were more frequent in patients and showed strong and moderate associations with disease risk, respectively. These results indicate that the combination of alleles may be utilized to obtain more effective results not captured by single SNV analysis.

Regarding rs1050450, this SNV has been previously associated with various diseases, such as cancer and

bone diseases, such as arthritis, osteopenia, and osteoporosis.[27–29] *GPX1* activity is negatively influenced by substituting the amino acid Lue with the T variant instead of the amino acid Pro with the C variant.[30] The CT genotype was significantly more prevalent in the patient group. This suggests that this polymorphism may contribute to disease susceptibility by impairing antioxidant defense mechanisms in bone tissue. Conversely, individuals with the CC genotype exhibited protective effects against the disease. This protective effect may be attributed to the higher enzymatic activity of *GPX1*, which encodes glutathione peroxidase 1. Previous studies have demonstrated that individuals carrying the CC genotype tend to have more efficient oxidative stress responses than those carrying the CT or TT genotypes.[31,32] The functional variant SNV rs1050450 may alter the activity of glutathione peroxidase 1, an enzyme critical in detoxifying reactive oxygen species. The present results are consistent with prior reports of sex-specific metabolic dysfunction linked to the Leu allele and found that in men, the T (Leu) allele was linked to metabolic syndrome, elevated insulin levels, and hypertension. At the same time, in women, it correlates with morbid obesity, hyperinsulinemia, and insulin resistance.[33–35] These findings suggest that the Leu allele may impair metabolic function in a sex-dependent manner, possibly due to hormonal influences on oxidative stress pathways.[33–35] However, the stronger association in women could reflect the synergistic effects of estrogen decline, especially in post-menopausal women, and reduce *GPX1* activity, further amplifying oxidative damage.[29,35] *GPX1* polymorphic variants may influence disease susceptibility through mechanisms involving oxidative stress regulation, potentially due to linkage disequilibrium effects within specific ethnic groups. A recent study provided valuable evidence that the *GPX1* rs1050450 polymorphism influences oxidative stress markers, supporting the biological plausibility of these findings.[36] However, contrasting results were reported in studies that found no significant association between the *GPX1* Pro198Leu (rs1050450) variant and T2D.[37,38] The functional impact of the T allele on *GPX1* may be more pronounced in conditions such as osteoporosis, in which oxidative stress directly affects tissue integrity (such as bone) rather than peripheral nerves. While the CT genotype association aligns with *GPX1* reduced antioxidant capacity, the tissue-specific selenoprotein regulation demonstrated by Ogino et al. suggests that osteoporosis risk in Leu carriers may be modifiable by selenium status environment interaction, warranting further study.[39]

The identification of rs771425412 within exon 2 of *GPX1* raises the possibility that it may affect protein structure and function, potentially influencing redox regulation. Individuals carrying the heterozygous CA genotype were found to be at higher risk, suggesting this variant may impair the *GPX1* enzyme's function through an amino acid change, independently of the known rs1050450 polymorphism. While direct evidence for this specific variant is limited, its location in an exon indicates a potential mechanism affecting redox regulation, underscoring the need for further functional studies to confirm its role. Schembri et al. highlighted the importance of investigating rare variants, which are essential for uncovering the full spectrum of genetic contributions to complex diseases such as osteoporosis.[40] These findings highlight the potential of exon variants such as rs771425412 to compromise *GPX1* antioxidant function.[30] The findings indicated that *GPX1* polymorphisms may similarly influence the susceptibility to primary osteoporosis, supporting the value of population genetic specific investigations. The results of the current study are in line with several studies that linked *GPX1* variants to oxidative stress with osteoporosis.[19,40] To our knowledge, this is the first study to demonstrate an association between the *GPX1* rs771425412 SNV and patients with osteoporosis. The lack of literature on this SNV across bone-related and systemic diseases highlights it as a potentially overlooked locus in *GPX1* and oxidative stress.

The modest sample size may have limited the ability to confidently detect rare genotypes. This study did not assess the correlation between genotype and densitometry-based osteoporosis severity, which represents an important direction for future research, thereby enabling more reliable and clinically relevant conclusions. Future research should combine the incorporation of environmental and lifestyle factors, such as dietary selenium, vitamin D intake, and smoking, which are known to influence oxidative stress and bone metabolism.

Conclusion

This study established a significant association between specific genotypes of the *GPX1* gene and susceptibility to primary osteoporosis in an Iraqi population. The findings indicate that individuals carrying the CT genotype of the rs1050450 variant and the CA genotype of the rs771425412 variant are at a significantly higher risk of developing primary osteoporosis. Conversely, the CC genotype for both variants appears to confer a protective effect. Haplotype analysis further reinforced these findings, revealing that the combination of alleles constituting the C-C haplotype was protective, while the T-A and C-A haplotypes were associated with significantly increased risk. Collectively, these results suggest that specific genetic constitutions, particularly the heterozygous genotypes CT and CA of GPX1, contribute to osteoporosis pathogenesis likely by disrupting the enzyme's ability to regulate oxidative stress, thereby tipping the balance towards bone resorption.

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Declarations

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Author contributions

Conceptualization, S.S.A. and R.K.M.; Methodology, S.S.A.; Software, S.S.A.; Validation, S.S.A. and R.K.M.; Formal Analysis, S.S.A.; Investigation, S.S.A.; Resources, S.S.A.; Data Curation, S.S.A.; Writing – original draft preparation, S.S.A.; writing – Review & Editing, S.S.A.; Visualization, R.K.M.; Supervision, R.K.M.; Project Administration, S.S.A.; Funding Acquisition, R.K.M..

Conflicts of interest

The authors declare that there are no conflicts of interest related to this study.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval

This case-control study was approved by the Ethics Committee of the Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq [Ref. CSEC/1023/0069) on October 30, 2023].

References

1. Aibar-Almazán A, Voltes-Martínez A, Castellote-Caballero Y, Afanador-Restrepo DF, Carcelén-Fraile MDC, López-Ruiz E. Current Status of the Diagnosis and Management of Osteoporosis. *Int J Mol Sci*. 2022;23(16):9465. doi:10.3390/ijms23169465
2. Amarnath SS, Kumar V, Das SL. Classification of Osteoporosis. *Indian J Orthop*. 2023;57(1):49-54. doi:10.1007/s43465-023-01058-3
3. Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P, Milat F. Secondary osteoporosis. *Endocr Rev*. 2022;43(2):240-313. doi:10.1210/endrev/bnab028.
4. Sobh MM, Abdalbary M, Elnagar S, et al. Secondary osteoporosis and metabolic bone diseases. *J Clin Med*. 2022;11(9):2382. doi:10.3390/jcm11092382.
5. Al Anouti F, Taha Z, Shamim S, Khalaf K, Al Kaabi L, Alsafar H. An insight into the paradigms of osteoporosis: From genetics to biomechanics. *Bone Rep*. 2019;11:100216. doi:10.1016/j.bonr.2019.100216.
6. Kimball JS, Johnson JP, Carlson DA. Oxidative stress and osteoporosis. *JBJS*. 2021;103(15):1451-1461. doi:10.2106/JBJS.20.00989.
7. Domazetovic V, Marcucci G, Iantomasi T, Brandi ML, Vincenzini MT. Oxidative stress in bone remodeling: role of antioxidants. *Clin Cases Miner Bone Metab*. 2017;14(2):209. doi:10.11138/ccmbm/2017.14.1.209.
8. Alshaikhli RJ, Alkazaz AA, Aljanabi AA. Association of PARP1 Gene Single Nucleotide Polymorphisms with Papillary Thyroid Carcinoma in The Iraqi population. *Iraqi J Sci*. 2024:108-118. doi.org/10.24996/ijs.2024.64.1.10.
9. Zhu C, Shen S, Zhang S, Huang M, Zhang L, Chen X. Autophagy in Bone Remodeling: A Regulator of Oxidative Stress. *Front Endocrinol (Lausanne)*. 2022;13:898634. doi:10.3389/fendo.2022.898634
10. Zhao Q, Tang Y, Zhang L, Sun N, Liu Q, Zhang R. Biological functions of selenoprotein glutathione peroxidases (Gpxs) and their expression in osteoarthritis. *J Inflamm Res*. 2023:183-196. doi:10.2147/JIR.S388934.
11. Zhao Y, Wang H, Zhou J, Shao Q. Glutathione peroxidase GPX1 and its dichotomous roles in cancer. *Cancers (Basel)*. 2022;14(10):2560. doi:10.3390/cancers14102560.
12. Laribi A, Aouf S, Gabbouj S, Bouaouinaa N, Zakhama A, Harizi H. Human glutathione peroxidase codon 198 variant increases nasopharyngeal carcinoma risk and progression. *Eur Arch Oto-Rhino-Laryngology*. 2021;278(10):1-8. doi:10.1007/s00405-021-06628-5.
13. Dawood HH, Mohammed RK. The Association between Single Nucleotide Polymorphisms rs1042522 and rs1642785 in the TP53 gene and Acute Myeloid leukemia in a sample of the Baghdad/Iraq population. *Baghdad Sci J*. 2024;21(3):909. doi:10.21123/bsj.2023.8207.
14. Handy DE, Loscalzo J. The role of glutathione peroxidase-1 in health and disease. *Free Radic Biol Med*. 2022;188:146-161. doi:10.1016/j.freeradbiomed.2022.06.004.
15. Buraczynska M, Buraczynska K, Dragan M, Ksiazek A. Pro198Leu polymorphism in the glutathione peroxidase 1 gene contributes to diabetic peripheral neuropathy in type 2 diabetes patients. *Neuromolecular Med*. 2017;19:147-153. doi:10.1007/s12017-016-8438-2.
16. Ściskalska M, Milnerowicz H. Association of genetic variants in the GPX1 and GPX4 genes with the activities of glutathione-dependent enzymes, their interaction with smoking and the risk of acute pancreatitis. *Biomed Pharmacother*. 2022;146:112591. doi:10.1016/j.biopha.2021.112591.
17. Wang C, Zhang R, Chen N, et al. Association between glutathione peroxidase-1 (GPX1) Rs1050450 polymorphisms and cancer risk. *Int J Clin Exp Pathol*. 2017;10(9):9527.
18. Bani-Wais DFN, Ad'hiah AH. The 5'untranslated region variant rs3811050 C/T of the interleukin-38 encoding gene is associated with susceptibility to rheumatoid arthritis in Iraqi women. *Mol Biol Rep*. 2024;51(1):589. doi:10.1007/s11033-024-09529-y.
19. Jiménez-Ortega RF, Aparicio-Bautista DI, Becerra-Cervera A, et al. Association Study between Antioxidant Nutrient Intake and Low Bone Mineral Density with Oxidative Stress-Single Nucleotide Variants: GPX1 (rs1050450 and rs17650792), SOD2 (rs4880) and CAT (rs769217)

in Mexican Women. *Antioxidants*. 2023;12(12):2089. doi:10.3390/antiox12122089.
20. Barbosa P, Abo El-Magd NF, Hesketh J, Bermano G. The role of rs713041 glutathione peroxidase 4 (GPX4) single nucleotide polymorphism on disease susceptibility in humans: a systematic review and meta-analysis. *Int J Mol Sci*. 2022;23(24):15762. doi:10.3390/ijms232415762.
21. Bashi MA, Ad'hiah AH. Susceptibility to acute myeloid leukemia: Influence of genetic variants of interleukins 37 and 38. *Clin Chim Acta*. 2025;576:120386. doi:10.1016/j.cca.2025.120386
22. Yong Y, He L. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res*. 2005;15(2):97. doi:10.1038/sj.cr.7290272.
23. Fayer S, Horton C, Dines JN, et al. Closing the gap: Systematic integration of multiplexed functional data resolves variants of uncertain significance in BRCA1, TP53, and PTEN. *Am J Hum Genet*. 2021;108(12):2248-2258. doi:10.1016/j.ajhg.2021.11.001
24. Tabet D, Parikh V, Mali P, Roth FP, Claussnitzer M. Scalable Functional Assays for the Interpretation of Human Genetic Variation. *Annu Rev Genet*. 2022;56:441-465. doi:10.1146/annurev-genet-072920-032107
25. Fowler DM, Rehm HL. Will variants of uncertain significance still exist in 2030? *Am J Hum Genet*. 2024;111(1):5-10. doi:10.1016/j.ajhg.2023.11.005
26. Chen B, Cole JW, Grond-Ginsbach C. Departure from Hardy Weinberg Equilibrium and Genotyping Error. *Front Genet*. 2017;8:167. doi:10.3389/fgene.2017.00167
27. Ferreira RR, Carvalho RV, Coelho LL, et al. Current understanding of human polymorphism in selenoprotein genes: a review of its significance as a risk biomarker. *Int J Mol Sci*. 2024;25(3):1402. doi:10.3390/ijms25031402
28. Iantomasi T, Romagnoli C, Palmini G, et al. Oxidative stress and inflammation in osteoporosis: molecular mechanisms involved and the relationship with microRNAs. *Int J Mol Sci*. 2023;24(4):3772. doi:10.3390/ijms24043772
29. Janowska M, Potocka N, Paszek S, et al. An assessment of GPX1 (rs1050450), DIO2 (rs225014) and SEPP1 (rs7579) gene polymorphisms in women with endometrial cancer. *Genes (Basel)*. 2022;13(2):188. doi:10.3390/genes13020188
30. Iqbal MW, Shahab M, Zheng G, et al. Analysis of damaging non-synonymous SNPs in GPx1 gene associated with the progression of diverse cancers through a comprehensive in silico approach. *Sci Rep*. 2024;14(1):28690. doi:10.1038/s41598-024-78232-6
31. Irfan S, Rani A, Sameem M, Nawaz SK, Liaqat I, Arshad M. Association of rs1800668 polymorphism in glutathione peroxidase-1 gene and risk of rheumatoid arthritis in Pakistani population. *Pakistan J Med Sci*. 2016;32(5):1204. doi:10.12669/pjms.325.10325
32. Goričar K, Debevec T, Dolžan V, et al. Antioxidant and neurodevelopmental gene polymorphisms in prematurely born individuals influence hypoxia-related oxidative stress. *Sci Rep*. 2024;14(1):14956. doi:0.1038/s41598-024-65647-4
33. Hernández Guerrero CÁ, Hernández Chávez P, Martínez Castro N, Parra Carriedo A, García del Río SL, Pérez Lizaur AB. Glutathione peroxidase-1 Pro200Leu polymorphism (rs1050450) is associated with morbid obesity independently of the presence of prediabetes or diabetes in women from Central Mexico. 2015;32(4):1516-1525. doi:10.3305/nh.2015.32.4.9500
34. Donadio JLS, Guerra-Shinohara EM, Rogero MM, Cozzolino SMF. Influence of gender and SNPs in GPX1 gene on biomarkers of selenium status in healthy Brazilians. *Nutrients*. 2016;8(5):81. doi:10.3390/nu8050081
35. Tarhonska K, Raimondi S, Specchia C, et al. Association of allelic combinations in selenoprotein and redox related genes with markers of lipid metabolism and oxidative stress–multimarkers analysis in a cross-sectional study. *J Trace Elem Med Biol*. 2022;69:126873. doi:10.1016/j.jtemb.2021.126873
36. Mansoor MA, Stea TH, Slettan A, et al. Impact of single nucleotide polymorphisms (SNPs) in antioxidant-enzyme genes on the concentrations of folate, homocysteine and glutathione in plasma from healthy subjects after folic acid supplementation–a randomized controlled crossover trial. *Genes Nutr*. 2025;20(1):1. doi:10.1186/s12263-024-00761-6
37. Kasznicki J, Sliwinska A, Kosmalski M, Merecz A, Majsterek I, Drzewoski J. Genetic polymorphisms (Pro197Leu of Gpx1,+ 35A/C of SOD1,– 262C/T of CAT), the level of antioxidant proteins (GPx1, SOD1, CAT) and the risk of distal symmetric polyneuropathy in Polish patients with type 2 diabetes mellitus. *Adv Med Sci*. 2016;61(1):123-129. doi:10.1016/j.advms.2015.10.006
38. Buraczynska M, Buraczynska K, Dragan M, Ksiazek A. Pro198Leu polymorphism in the glutathione peroxidase 1 gene contributes to diabetic peripheral neuropathy in type 2 diabetes patients. *Neuromolecular Med*. 2017;19:147-153. doi:10.1007/s12017-016-8438-2
39. Ogino H, Murano K, Okuno T, Ueno H. Relationship between Serum Concentrations and Muscular Expressions of Selenoproteins on Selenium-Supplemented Insulin Resistance Mouse Model. *Biol Pharm Bull*. 2024;47(5):1000-1007. doi:10.1248/bpb.b23-00662
40. Schembri M, Formosa MM. Identification of osteoporosis genes using family studies. *Front Endocrinol (Lausanne)*. 2024;15:1455689. doi:10.3389/fendo.2024.1455689