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Association of osteoporosis risk and polymorphisms of osteoprotegerin gene T950C in postmenopausal Chinese women

A PRISMA-compliant meta-analysis

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Abstract

Background: This study aimed to assess the association between the T950C polymorphism and osteoporosis in postmenopausal Chinese women to further reduce the influence of different genetic backgrounds by meta-analysis and subgroup analysis.

Methods: Through November 2022, a systematic online investigation was performed with the aid of the Cochrane Library, EMBASE, PubMed, Web of Science and the Chinese National Knowledge Infrastructure to find case-control studies looking into the correlation between the osteoprotegerin gene (OPG) T950C polymorphism and postmenopausal osteoporosis susceptibility.

Results: This study included 6 studies with a total of 1669 postmenopausal osteoporosis cases and 2992 controls. In the recessive model, postmenopausal women with the CC genotype (mutant homozygote at the T950C locus) had a lower risk of osteoporosis, indicating that the CC genotype of OPG T950C might show a preventive effect on osteoporosis after menopause. In a stratified analysis by geographic area, the population from South China had a significantly higher risk under the dominant model [CC + TC (heterozygote at the T950C locus) vs TT (wild-type homozygotes at the T950C locus): odds ratio = 1.34, 95% confidence interval = 1.17–1.54, $P < .01$], while the population from South China had a significantly lower risk under the recessive model (CC vs TC + TT: odds ratio = 0.79, 95% confidence interval = 0.69–0.95, $P = .02$).

Conclusions: Together, the OPG T950C polymorphism may be associated with osteoporosis risk in postmenopausal Chinese women, according to this meta-analysis. Because of the study's limitations, more large-scale research is needed to corroborate these findings.

Abbreviations: BMD = bone mineral density, CI = confidence interval, OPG = osteoprotegerin gene, OR = odds ratio, RANKL = the receptor activator of nuclear factor (NF)- KB ligand.

Keywords: meta-analysis, osteoporosis, osteoprotegerin, polymorphism, postmenopausal

1. Introduction

Postmenopausal osteoporosis, the most common metabolic bone disease, is characterized by low bone mineral density (BMD) that causes susceptibility to fragility fracture.[1–3] Approximately 50% of women experience at least 1 fracture after menopause,[4] and osteoporosis-related fractures are a significant cause of death and disability in the elderly.[5]

With the aging of Chinese population, the prevalence of osteoporosis is increasing rapidly. Currently the number of people at risk for osteoporotic fractures in China is reported to be 83.9 million. By 2050, it will increase to 212 million people.[6] However, the number of people currently screened who are at high risk for fracture is much smaller than the number of people who actually cause fractures.[4] Therefore, more risk factors are still needed to more accurately identify people at high risk of fracture, and a positive family history is an important risk factor for the development of the disease.[4]

Altered immune status in postmenopausal women is associated with persistent bone destruction. Under estrogen-deficient conditions, B lymphocytes regulate osteoclastogenesis through the receptor activator of nuclear factor (NF)-B ligand (RANKL)/Osteoprotegerin gene (OPG) signaling pathway, which plays an important role in bone loss.[7] OPG levels are significantly increased after treatment in postmenopausal osteoporosis patients. This suggests an important role of OPG in bone loss.[8]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The conducted research is not related to either human or animals use.

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Research on OPG gene polymorphisms has also been carried out extensively, but there is still controversy about the effect of T950C on osteoporosis.

Previous meta-analyses showed no significant effect of rs2073617 (T950C) of the OPG gene on osteoporotic fractures in men and women.[9,10] In multiethnic population meta-analyses, T950C also did not show a significant effect on fracture risk in postmenopausal women.[11,12] However, T950C is associated with BMD at the lumbar spine in postmenopausal Asian women.[13] However, the applicability of the above result remains controversial due to differences in estrogen, sex, race, region, and lifestyle habits. In the meta-analysis of Chinese people, no relationship was found in general. However, in the subgroup analysis of southern China and the postmenopausal population, it is believed that there is a relationship between T950C and osteoporosis.[14] Unfortunately, there is still insufficient research on the interaction of regional differences and estrogen status. The current meta-analysis was performed on the relationship of the OPG T950C polymorphism with osteoporosis risk and the participants were all postmenopausal Chinese women, so that there was no variation in genetic background.

2. Materials and methods

The Preferred Reporting Items of Systematic Reviews Meta-Analysis (PRISMA) guidelines were followed for this study.

2.1. Identifying research that is eligible

From inception of the databases to November 2022, public databases, including EMBASE, the Chinese National Knowledge Infrastructure, Web of Science, PubMed and the Cochrane Library were systematically searched. The search term and Boolean strategy were performed as "Osteoporosis AND (osteoprotegerin odds ratio [OR] TNFRSF11B OR OPG) AND (Chinese OR China) AND polymorphism." No date or language restrictions were applied. A manual search of relative topic reviews was performed to avoid omissions. The following research met the inclusion criteria: Papers reporting the association between the polymorphism of OPG T950C and postmenopausal osteoporosis; Studies having enough genotype data to compute the OR; Studies performed a case-control design or cohort design with a control group; All of the contestants were Chinese people. The following criteria were used as exclusion standards: Research with missing data; Case reports; Editorial papers; Reviews; and Meeting abstracts.

2.2. Data extraction

Two reviewers independently extracted data from all eligible papers in accordance with the eligibility criteria. First, all possibly relevant papers titles and abstracts were reviewed. If the title and abstract were confusing, the full-text articles were examined. If the 2 reviewers could not reach an agreement, disagreements were resolved by discussion. The first author's name, year of publication online, source of controls, geographic location, sample size, and accessible genetic data for OPG T950C were all gathered for each included study. The 9-stars Newcastle-Ottawa scale was used to assess the methodological quality of the study.

2.3. Statistical analysis

Pooled ORs combined from individual ORs were used to evaluate the association of the polymorphism of OPG T950C and postmenopausal osteoporosis. CC mutant homozygote at the T950C locus; CT indicated heterozygote at the T950C locus; and TT indicated wild-type homozygotes at the T950C locus. The meta-analysis looked at the general association of the C allele with the risk of osteoporosis compared to the T allele, as well as the homozygotes CC versus TT, CC vs (TC + TT), and (CC + TC) versus TT. We adopted the Chi-square-based Q test to evaluate the heterogeneity between studies and Hardy-Weinberg equilibrium expectations in control groups.[15] According to the findings of the heterogeneity test, the random-effect model (DerSimonian and Laird) or fixed-effect model (Mantel-Haenszel) was chosen to conclude the combined ORs and their 95% confidence intervals (CIs). Geographical subgroup analyses and sensitivity analyses were also carried out. Stata, version 12 was used to perform all statistical analyses (StataCorp LP, College Station, TX). P value of <.05 was defined as statistically significant.

3. Results

3.1. Description of included studies

Using the search approach given above, a total of 123 relevant publications were found after duplicates were removed. Six case-control studies[9,16–20] satisfied our inclusion criteria, and 117 were eliminated from our meta-analysis based on the eligibility criteria. Figure 1 depicts a flow chart of the research selection procedure as well as particular reasons for exclusion. This meta-analysis included 1669 instances of postmenopausal osteoporosis and 2992 healthy controls. The included studies were published between 2005 and 2017. Table 1 shows the features of the studies that were included. In the included studies, 2 studies had low risk of bias, with an 8 score (Table 1). Since all the included studies were case-control designs, the overall methodological quality was medium.

3.2. Meta-analysis results

Table 2 summarizes the findings of the study on the polymorphism of OPG T950C and the risk of osteoporosis development. Under the recessive model, postmenopausal women with the CC genotype had a lower risk of osteoporosis, indicating that the CC genotype of OPG T950C might be predictive of the prevention of osteoporosis development after menopause (CC vs TC + TT: OR = 0.78, 95% CI = 0.64–0.94, P = .01) (Fig. 2). In the stratified analysis by geographic area, the population from South China had a significantly higher risk under the dominant model (CC + TC vs TT: OR = 1.34, 95% CI = 1.17–1.54, P < .01) (Fig. 3), whereas the population from South China had a significantly lower risk under the recessive model (CC vs TC + TT: OR = 0.79, 95% CI = 0.69–0.95, P = .02) (Fig. 2). In sensitivity analysis, 1 study was found to have a large impact on the pooling results of recessive and dominant models.[19]

4. Discussion

Osteoporosis is a complex disease with a recognized hereditary component. The OPG gene is considered a promising osteoporosis potential risk factor. T950C is one of the most important polymorphic loci of the OPG gene. Research on OPG gene polymorphisms has also been carried out extensively, but there is still controversy about the effect of T950C on osteoporosis.

A previous study found that there is a difference in fracture risk across regions of China.[21] This difference is not only in China, but also has a north-south gradient in Europe and the United States.[22] This may be due to potential differences in lifestyle, occupational category, and dietary habits. Therefore, we performed subgroup analysis of the southern and northern Chinese populations. In the southern subgroup, opposite results were observed in the recessive and dominant models. This is mainly due to a higher incidence of osteoporosis in TC carriers.

In the sensitivity analysis, 1 study was found to have a large impact on the pooling results of recessive and dominant models.[19] This study was well-designed with a large sample size.

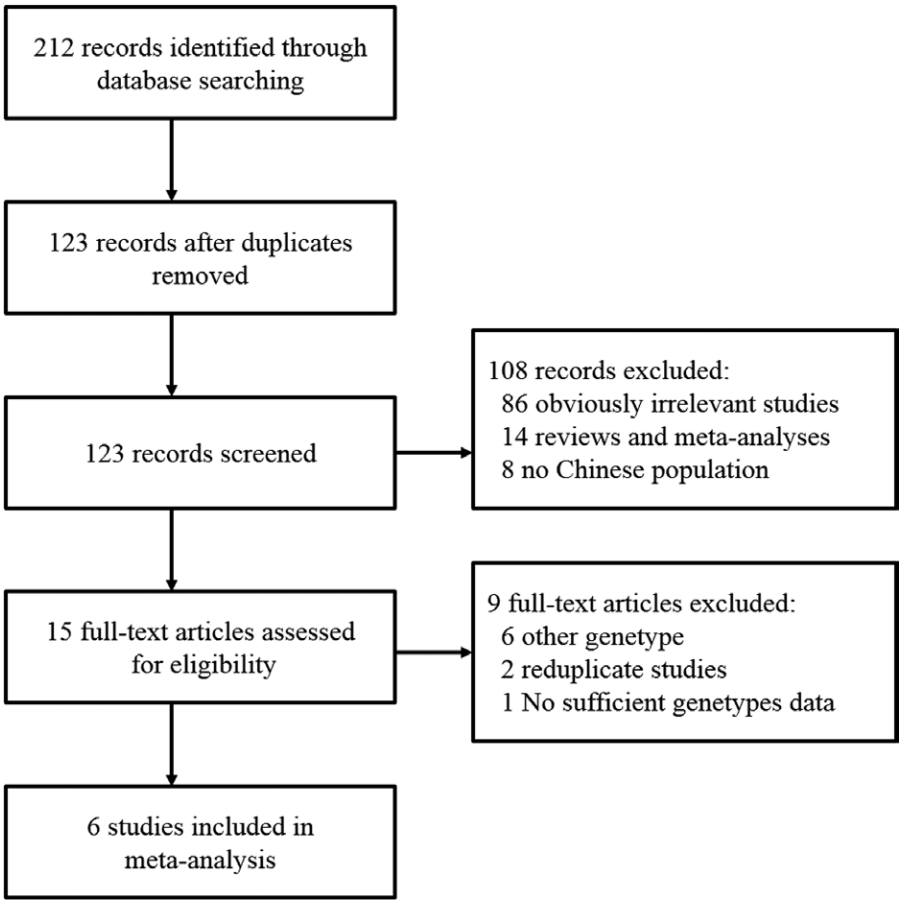

Figure 1. Flow diagram of the literature search.

Table 1

Characteristics of studies included in the meta-analysis.

						Cases			Controls			HWE	
References	Control source	Geographic area	NOS	Case number	Control number	TT	TC	CC	TT	TC	CC	χ^2	*P* value
Geng 2008	Hospital-based	Chongqing	6	186	214	70	76	40	72	100	42	0.47	.495
Liu 2010	Hospital-based	Beijing	5	50	50	18	23	9	9	28	13	0.81	.368
Tao 2011	Hospital-based	Fujian	7	77	54	22	45	10	20	30	4	2.57	.109
Wang 2012	Hospital-based	Shanghai	8	1094	2386	350	624	120	954	1074	358	3.79	.052
Wu 2005	Hospital-based	Guangdong	6	73	61	28	39	6	29	29	3	1.60	.206
Sheng 2017	Population-based	Zhejiang	8	189	227	T: 220; C: 158			T: 267; C: 187			NA	.193

Abbreviations: HWE = Hardy-Weinberg equilibrium, NA = not available, NOS = Newcastle-Ottawa Scale.

Table 2

Association of the OPG T950C polymorphism on postmenopausal osteoporosis risk.

	Analysis model	n	ORr (95% CI)	ORf (95% CI)	P_h
C vs T	Total analysis	6	1.05 (0.92–1.20)	1.06 (0.98–1.16)	0.258
	South China	5	1.08 (0.99–1.18)	1.08 (0.99–1.18)	0.698
CC vs TT	Total analysis	5	0.96 (0.66–1.38)	0.93 (0.76–1.15)	0.220
	South China	4	0.96 (078–1.19)	0.97 (0.78–1.19)	0.412
CC vs TC + TT	Total analysis	5	0.90 (0.62–1.29)	0.78 (0.64–0.94)	0.165
	South China	4	0.98 (0.63–1.53)	0.79 (0.65–0.95)	0.098
CC + TC vsTT	Total analysis	5	1.08 (0.74–1.59)	1.30 (1.14–1.49)	0.015
	South China	4	1.24 (0.93–1.66)	1.34 (1.17–1.54)	0.133

South China including Fujian, Guangdong, Zhejiang, Chongqing and Shanghai.

CI = confidence interval, OPG = osteoprotegerin gene, ORf = odd ratio for fixed-effects model, ORr = odd ratio for random-effects model, P_h = *P* value for heterogeneity test.

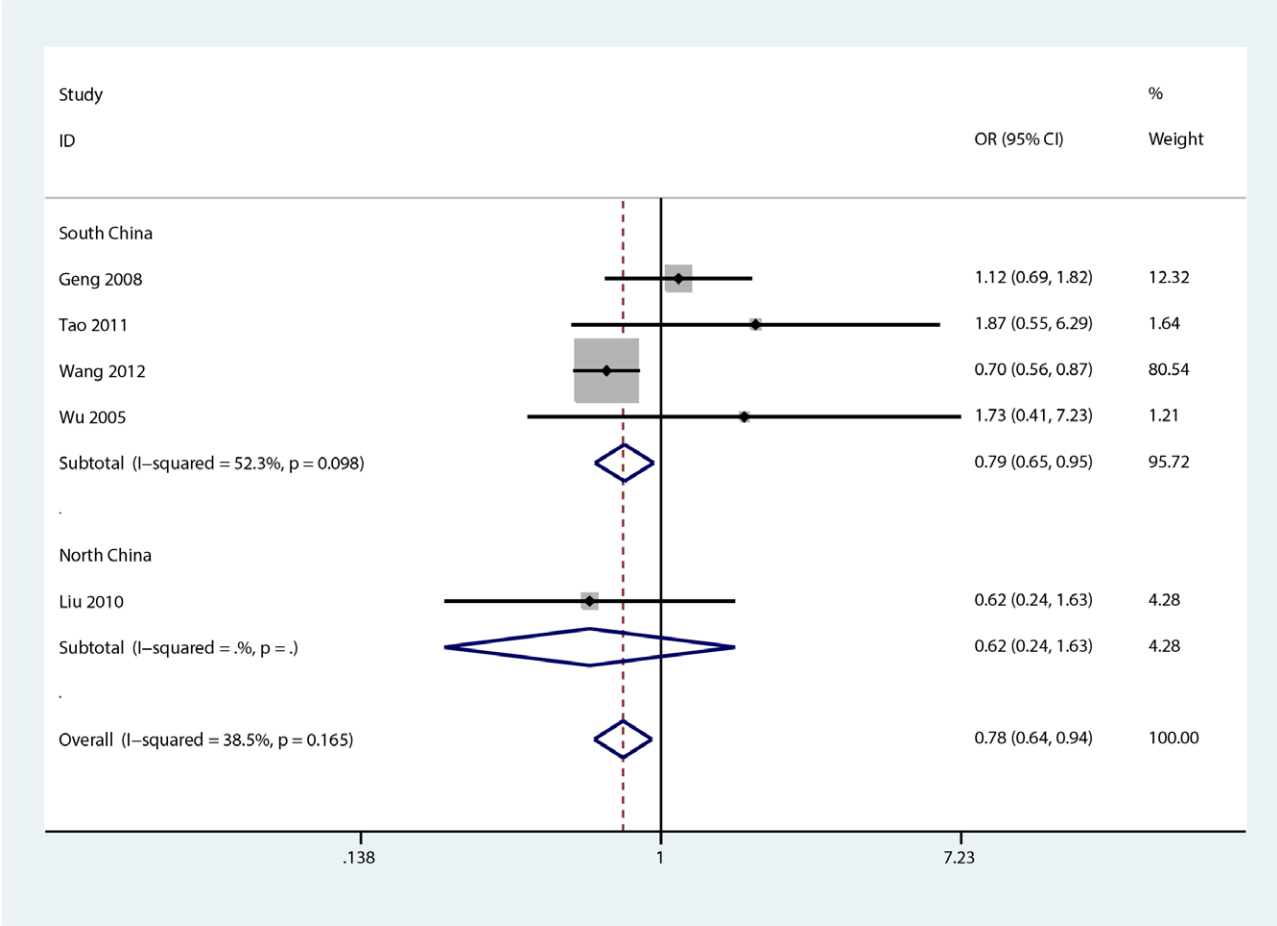

Figure 2. Forest plot of the association between the OPG T950C polymorphism and postmenopausal osteoporosis risk in the recessive model. OPG = osteoprotegerin gene.

There is no sufficient reason to ignore the findings of this study. The incidence of osteoporosis was higher in the TC carrier population in this study, which could not be further interpreted and needs to be confirmed by basic research.

Several meta-analyses on the polymorphism of T950C and osteoporosis risk have been published in the past decade. However, the association between the T950C polymorphism and BMD remains unclear,[13,23] and the association between T950C and osteoporotic fractures in Chinese individuals is also controversial.[11,12,14] This study supports the finding that there is a relationship between the T950C polymorphism and osteoporosis risk in postmenopausal Chinese women. In particular, there is a high incidence of osteoporosis in TC carriers.

This updated meta-analysis was performed to determine the connection between polymorphisms of OPG T950C and postmenopausal osteoporosis susceptibility in a population of Chinese postmenopausal women. This study comprised 6 trials with a total of 1669 postmenopausal osteoporosis patients and 2992 controls. The OPG T950C polymorphism was shown to be associated with osteoporosis risk in postmenopausal Chinese women, according to the findings of this study. In recessive and dominant models, different pooled findings were observed.

Mechanistically, OPG acts as a decoy receptor for RANKL that binds RANKL to prevent the receptor activator of nuclear factor (NF)- KB-RANKL interaction and inhibit osteoclastogenesis. Therefore, OPG is considered an effective inhibitor of osteoclast bone resorption, while a low level of OPG leads to osteoporosis.[24–26] The T950C site is located in the 5'UTR of the OPG gene. Clinical studies showed that the serum OPG level of TT genotype carriers was lowest, followed by TC genotype carriers, and the highest level was found in CC carriers.[27,28] However, the aforementioned study also found that the OPG level was higher in the intervertebral disc degeneration population than in healthy controls regardless of the T950C genotype.[27]This suggests that the T950C genotype has an influence on the OPG levels, but OPG levels are still subject to disease status and that the influence of other OPG mutant loci also cannot be ignored. In addition, the current basic research suggests that the OPG/RANKL ratio may be more meaningful than the OPG levels alone during osteoclast formation.[29]

There are still some limitations in this study. First, only published studies were included, which may lead to publication bias. Second, the sensitivity analysis suggested that the pooled results were influenced by a single study, which may have contributed to the nonrobustness of the results. Third, although the present population source was restricted to Chinese postmenopausal women, the association of T950C with osteoporosis may still be influenced by confounding factors such as comorbidities, other polymorphic loci, lifestyle habits, etc. Fourth, all the included studies were case-control designs, and the overall methodological quality was medium. More well-designed research is still needed to confirm this result.

5. Conclusion

This study adds evidence to show that polymorphisms in OPG T950C are associated with the risk of postmenopausal osteoporosis in Chinese women. Due to the limitations of the study,

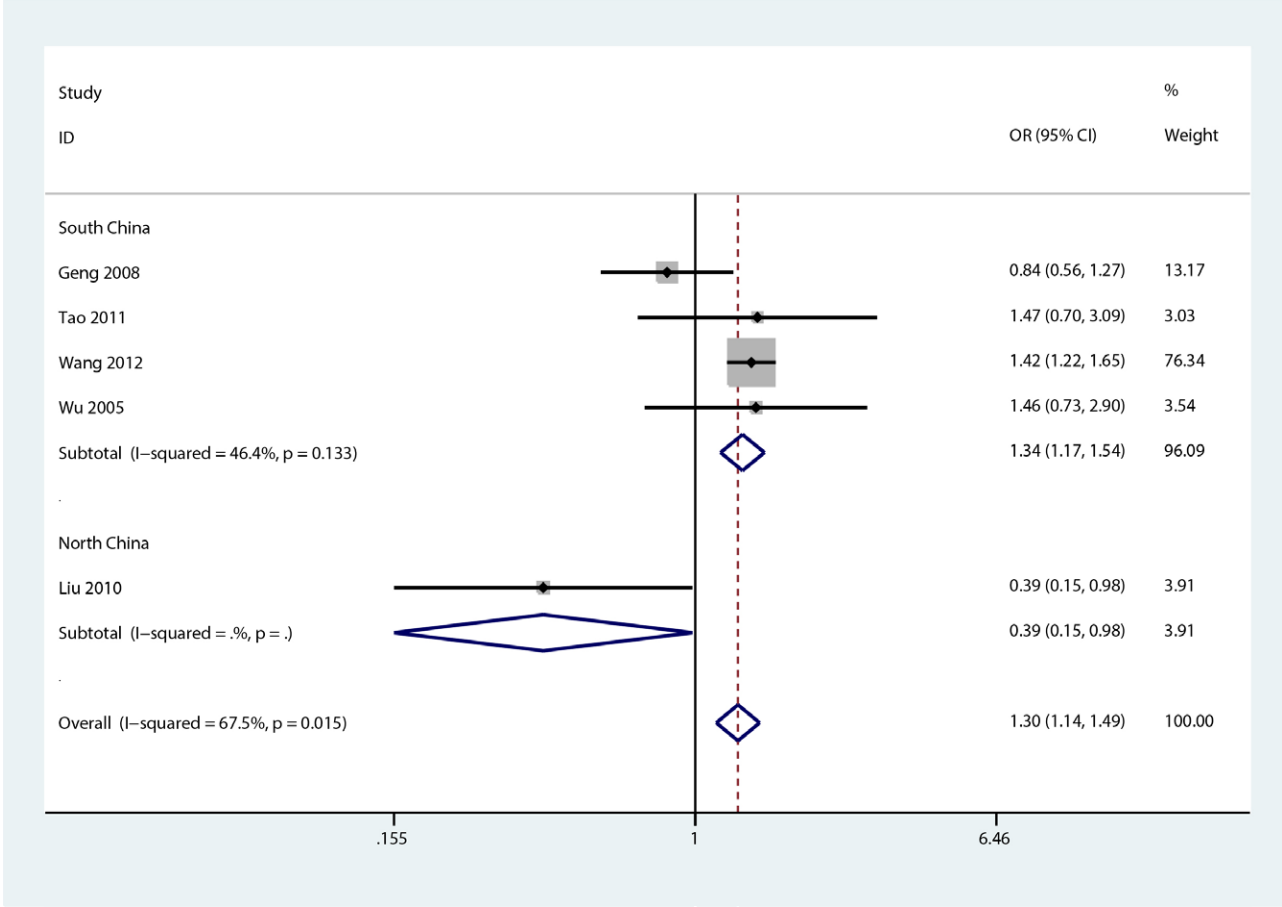

Figure 3. Forest plot of the association between the OPG T950C polymorphism and postmenopausal osteoporosis risk in the dominant model. OPG = osteoprotegerin gene.

the findings should be treated with caution, and a larger-scale investigation is needed.

Author contribution

Conceptualization: Yuansheng Xia, Huiyan Chen.
Data curation: Huiyan Chen.
Investigation: Huiyan Chen.
Methodology: Yuansheng Xia.
Writing – original draft: Huiyan Chen.
Writing – review & editing: Yuansheng Xia.

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