Association of IL-6 174G/C (rs1800795) and 572C/G (rs1800796) polymorphisms with risk of osteoporosis: a meta-analysis

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Abstract

Background: Several studies have been performed to investigate association between IL-6 174G/C (rs1800795) and 572C/G (rs1800796) gene polymorphisms and osteoporosis predisposition. However, the results were conflicting. So, we performed a meta-analysis designed to provide more reliable results for the association between IL-6 gene polymorphisms and osteoporosis.

Methods: Studies were searched using PubMed, EMBASE, the Cochrane Library and Wanfang electronic databases. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the association between IL-6 174G/C (rs1800795) and 572C/G (rs1800796) gene polymorphisms and osteoporosis risk. The false-positive report probabilities (FPRP) test and the venice criteria were used to assess the credibility of statistically significant associations.

Results: A total of 9 studies with 1891 osteoporosis patients and 2027 healthy controls were included in current meta-analysis. Overall, The IL-6 174G/C (rs1800795) gene polymorphism was insignificantly associated with osteoporosis vulnerability. For IL-6 572C/G (rs1800796), statistically significant elevated osteoporosis vulnerability was found in IL-6 572C/G additive model (OR = 2.25, 95% CI: 1.55–3.26), dominant model (OR = 1.42, 95% CI: 0.78–2.56) and recessive model (OR = 1.96, 95% CI: 1.36–2.83). However, the IL-6 572C/G C allele was found to be associated with reduced susceptibility to osteoporosis (OR = 0.76, 95% CI: 0.56–1.04). When excluding studies that did not conform to HWE, the results did not change significantly. Further, when we evaluated the credibility of the positive results of the current meta-analysis, we identified less credible positive results in IL-6 572C/G recessive and additive model.

Conclusion: In conclusion, IL-6 572C/G GG genotype may be associated with increased risk of osteoporosis.

Keywords: IL-6, Single nucleotide polymorphism, Osteoporosis, Meta-analysis

Background

Osteoporosis, one of the most common disorder, which is characterized by low bone mineral density (BMD) and degradation of bone microstructure, leading to an increased risk of fractures [1]. According to WHO standard, osteoporosis was defined as bone mineral density below 2.5 standard deviation of the average level of healthy adults. With the extension of human lifespan, more and more elderly people suffer from osteoporosis. Approximately 1.5 million new cases of osteoporotic fractures were reported every year worldwide, placing a huge financial burden on patient families [2]. It has become a public health problem in the world.

Several factors contribute to the pathogenesis of osteoporosis, such as exercise, age, sex, diet etc. [3]. In addition, genes and gene polymorphisms may also play an important
role in osteoporosis predisposition [4]. Such as, In a study of familial diseases, bone mineral density was found to be highly heritables: 60–90% of BMD in the population is genetically determined [5]. Many genes were thought to be linked to osteoporosis and bone density. Those genes include estrogen receptor (ESR), calcitonin receptor (CTR), vitamin D receptor (VDR) and interleukin 6 (IL-6), etc. [6–8]. However, these risk genes can only explain part of the heritability of osteoporosis, and more variants have yet to be identified.

IL-6 gene is a multifunctional cytokine, located on human chromosome 7p21, which can stimulate the formation and absorption of bone cells [9–11]. Clinical studies had shown that the expression of IL-6 mRNA in bone explants of patients with osteoporotic vertebral fractures is enhanced [12]. Furthermore, some studies had found that IL-6 and other inflammatory cytokines can potentially up regulate the expression of RANKL on osteoblasts, accelerate the signal transduction of RANKL, and directly lead to bone destruction [13]. Recently, it has been discovered that functional polymorphisms of the IL-6 promoter, such as the C allele of the G-174C polymorphism, were associated with reduced promoter activity and plasma IL-6 levels, leading to reduced bone density [14–16]. Since Nordstrom first reported the link between IL-6 and susceptibility to osteoporosis [8], many related studies had also been published, but their results were conflicting. Such as, research by Ji Y F et al. revealed that G allele of rs1800796 was associated with increased risk of osteoporosis, while IL-6 174G/C was not significantly associated with osteoporosis [17]. However, the study of Magana et al. suggested that the increase of BMD is related to IL-6 174G/C, but not rs1800796 [18]. We consider that it may be related to the size of the sample size, the quality of the study, and whether the study conform to HWE. In view of this, we performed a meta-analysis in the hope of providing more reliable results for this association.

**Methods**

**Search strategy**

We performed the meta-analysis according to the guidelines of the PRISMA group [19]. Literature search was performed using PubMed, EMBASE, the Cochrane Library and Chinese Wanfang Data Knowledge Service Platform. The following search terms were applied in PubMed: (Interleukin-6 or IL-6) and (variant or variation or polymorphism) and (osteoporosis or osteoporoises). Language was not restricted in the current meta-analysis. The search deadline is March, 2020.

**Inclusion and exclusion criteria**

Eligible publications were selected according to the following criteria: (1) case–control study; (2) case and

| Table 1 | Scale for quality assessment of molecular association studies |
|--------|-------------------------------------------------------------|
| **Criterion** | **Score** |
| Source of case | |
| Selected from population | 2 |
| Selected from hospital | 1 |
| Not described | 0 |
| Source of control | |
| Population-based | 3 |
| Blood donors or volunteers | 2 |
| Hospital-based | 1 |
| Not described | 0 |
| Ascertainment of osteoporosis | |
| WHO | |
| Diagnosis of osteoporosis by patient medical record | 1 |
| Not described | 0 |
| Ascertainment of control | |
| Controls were tested to screen out | 2 |
| Controls were subjects who did not report osteoporosis, no objective testing | 1 |
| Not described | 0 |
| Matching | |
| Controls matched with cases by age and sex | 2 |
| Controls matched with cases only by age or sex | 1 |
| Not matched or not described | 0 |
| Genotyping examination | |
| Genotyping done blindly and quality control | 2 |
| Only genotyping done blindly or quality control | 1 |
| Unblinded and without quality control | 0 |
| Specimens used for determining genotypes | |
| Blood cells or normal tissues | 1 |
| Tumor tissues or exfoliated cells of tissue | 0 |
| HWE | |
| HWE in the control group | 1 |
| Hardy-Weinberg disequilibrium in the control group | 0 |
| Association assessment | |
| Assess association between genotypes and osteoporosis with appropriate statistics and adjustment for confounders | 2 |
| Assess association between genotypes and osteoporosis with appropriate statistics without adjustment for confounders | 1 |
| Inappropriate statistics used | 0 |
| Total sample size | |
| > 500 | 3 |
| 200–500 | 2 |
| < 200 | 1 |
| HWE: Hardy-Weinberg equilibrium | |
control groups provide detailed genotype frequencies; (3) study must assess the association between IL-6 polymorphism and osteoporosis predisposition. Study excluded if it is a case report, duplicate or incomplete data, animal experiments, meta-analysis, and so on.

Data extraction
According to the established inclusion and exclusion criteria, information was collected independently by two investigators. Potential differences were judged by a third system reviewers if necessary. The information collected was as follows: first author’s surname, year of publication, country, ethnicity, age, menopausal status, matching, diagnostic criteria of osteoporosis, sample size, and genotype frequencies.

Quality assessment
The quality of individual studies was assessed independently by two researchers. We designed a study quality assessment criteria by referring to two previous meta-analyses [20, 21]. The total score of the scoring standard is 20 points. They were considered as high quality studies if quality scores were ≥12, while scores of ≤10 were regarded as low quality. The score between them is regarded as medium quality. Detailed scoring criteria were listed in Table 1.

Statistical analysis
The crude odds ratios (ORs) and their 95% confidence intervals (CIs) were applied to evaluate the association between IL-6 polymorphisms and osteoporosis risk. Genotypes were assessed by the following models: allele

Table 2 General characteristics and quality scores of studies included in current meta-analysis

| First author/Year | Country  | Race        | Gender     | Cases | Menopause  | BMD site | Age (Mean ± SD yrs (min-max)) | Diagnosis | Matching | N | Healthy | Age (Mean ± SD yrs (min-max)) | Menopause  | BMD site | Controls | score |
|-------------------|----------|-------------|------------|-------|------------|----------|-------------------------------|-----------|----------|---|---------|-------------------------------|------------|----------|----------|-------|
| Ji Y F, 2019      | China    | East Asia   | Female     | 758   | PSM        | LS-fn    | 65.5 ± 16.1                  | Ne        | age, sex | 766 | Yes     | 66.7 ± 17.0                  | PSM        | LS-fn    | 14       |
| Eftekhari H, 2018 | Iran     | West Asia   | Female/Male| 181   | PSM        | LS-fn    | 68 ± 7.21                    | WHO       | age, sex | 116 | Yes     | 64 ± 5.44                   | PSM        | LS-fn    | 17       |
| Deveci D, 2012    | Turkey   | Caucasian   | Female     | 201   | PSM        | LS-fn    | 57 ± 7                       | WHO       | age, sex | 155 | Yes     | 57 ± 6                     | PSM        | LS-fn    | 14       |
| Czerny B, 2010    | Poland   | Caucasian   | Female     | 226   | PSM        | LS-fn    | 63.3 ± 5.1                   | WHO       | age, sex | 224 | Yes     | 64.8 ± 6.3                 | PSM        | LS-fn    | 14       |
| Breuil V, 2009    | France   | Caucasian   | Female     | 92    | PSM        | LS-fn    | 70 ± 7.4                     | WHO       | age, sex | 69  | Yes     | 64.1 ± 7.7                 | PSM        | LS-fn    | 11       |
| Magaña JJ, 2008   | Mexico   | Caucasian   | Female     | 70    | Pre        | LS       | 34.3 ± 10.2                  | BMD values| age, sex | 70  | Yes     | 34.3 ± 10.2                | Pre        | LS       | 11       |
| Dincel E, 2008    | Turkey   | Caucasian   | Female/Male| 21    | Ne         | Fn       | 74.47 ± 8.91                 | BMD values| age     | 21  | Yes     | 75.47 ± 7.44               | Ne         | Fn       | 10       |
| Kusek J, 2008     | Poland   | Caucasian   | Female     | 110   | PSM        | LS       | 58.5 ± 5.9                   | WHO       | sex      | 62  | Yes     | 58.5 ± 5.9                 | PSM        | LS       | 11       |
| Nordstrom A, 2004 | Sweden   | Caucasian   | Female     | 232   | LS-fn      | BMD values| 75 ± 0                       | BMD values| age, sex | 544 | Yes     | 75 ± 0                     | PSM        | LS-fn    | 16       |

Ne not available, PSM Postmenopausal, Pre Premenopausal, LS Lumbar spine, Fn Femoral neck

Table 3 Characteristics of the studies examining the effects of IL-6 174G/C genes on osteoporosis risk

| First author/Year | Ethnicity | Menopause | Case | Control | HWE Chi-square test | HWE P |
|-------------------|-----------|-----------|------|---------|---------------------|-------|
| Ji Y F, 2019      | East Asia | PSM       | GG   | 399     | 440                 | 2.613 | 0.106   |
| Deveci D, 2012    | Caucasian | PSM       | GC   | 285     | 31                  | 42.528| 0       |
| Czerny B, 2010    | Caucasian | PSM       | CC   | 74      | 93                  | 0.872 | 0.3503  |
| Breuil V, 2009    | Caucasian | PSM       | 12   | 93      | 31                  | 0.12  | 0.7293  |
| Magaña JJ, 2008   | Caucasian | Pre       | 126  | 76      | 42                  | 0.09  | 0.7645  |
| Dincel E, 2008    | Caucasian | Ne        | 0    | 0       | 7                   | 1.143 | 0.2851  |
| Kusek J, 2008     | Caucasian | PSM       | 34   | 30      | 3                   | 1.637 | 0.2007  |
| Nordstrom A, 2004 | Caucasian | PSM       | 68   | 167     | 246                 | 4.565 | 0.0326  |
model, additive model, dominant model and recessive model. Heterogeneity between studies assessed by $Q$ test and $I^2$ metric. Statistically significant heterogeneity between studies was considered, if $P < 0.10$ and $I^2 > 50\%$ [22]. Meantime, the random-effects model were selected to pool results [23], if not, a fixed-effects model was used [24]. The source of heterogeneity was estimated by meta-regression analysis. Sensitivity analysis was performed according to two methods: first, a single study was removed each time, second, studies that do not

| First author/ Year | Ethnicity | Menopause | IL-6 572 C/G (rs1800796) genotype distribution | HWE |
|--------------------|-----------|-----------|-----------------------------------------------|-----|
| Ji Y F, 2019       | East Asia | PSM       | Case | Control |
|                    |           |           | CC  | CG   | GG  | CC  | CG   | GG  | Chi-square |
|                    |           |           | 377 | 300  | 81  | 469 | 255  | 42  | 0.888       |
| Eftekhari H, 2018  | West Asia | Ne        | 152 | 27   | 2   | 96  | 18   | 2   | 1.071       |
| Magaña JJ, 2008    | Caucasian | Pre       | 33  | 30   | 7   | 36  | 30   | 4   | 0.489       |

Table 4 Characteristics of the studies evaluating the effects of IL-6 572 C/G genes on osteoporosis risk

Fig. 1 Flow diagram of the literature search
conform to HWE and unmatched were removed [25]. Publication bias was determined based on Begg’s funnel plot [26] and Egger’s test (significant publication bias was considered if \( P < 0.05 \) ) [27]. Furthermore, the false-positive report probabilities (FPRP) test [28] and the Venice criteria [29] was used to evaluate the credibility of statistically significant associations. All statistical analyses were conducted using Stata 12.0 software.

**Results**

**Description of included studies**

According to the pre-designed search strategy, 336 potential related studies were retrieved. Among them, 297 articles were excluded by reading titles or abstracts. Further, 30 studies that were irrelevant or did not provide genotypic data were excluded by detailed evaluation. Finally, 9 studies met inclusion and exclusion criteria (involving 1891 osteoporosis patients and 2027 healthy controls) [8, 17, 18, 30–35], of which 8 studies explored the relationship between IL-6 174G/C (rs1800795) and osteoporosis, 3 studies reported IL-6 572C/G (rs1800796) and osteoporosis predisposition. In addition, according to the quality evaluation criteria of our design, five studies were found to be of high quality, while the other four were of medium quality (as shown in Table 2).

**Quantitative synthesis**

At the overall analysis, The IL-6 174G/C (rs1800795) gene polymorphism was insignificantly associated with osteoporosis vulnerability in four genetic model comparisons (allele model: \( \text{OR} = 1.09, 95\% \text{ CI: } 0.90–1.33 \), additive model: \( \text{OR} = 0.89, 95\% \text{ CI: } 0.64–1.24 \), dominant model: \( \text{OR} = 1.03, 95\% \text{ CI: } 0.83–1.28 \) and recessive model: \( \text{OR} = 0.81, 95\% \text{ CI: } 0.60–1.09 \), (as shown in Table 5 and Figs. 2, 3). For IL-6 572C/G (rs1800796), statistically significant elevated osteoporosis vulnerability was found in IL-6 572C/G additive model (\( \text{OR} = 2.25, 95\% \text{ CI: } 1.55–3.26 \), dominant model (\( \text{OR} = 1.42, 95\% \text{ CI: } 0.78–2.56 \)) and recessive model (\( \text{OR} = 1.96, 95\% \text{ CI: } 1.36–2.83 \)). However, the IL-6 572C/G C allele was found to be associated with reduced susceptibility to osteoporosis (\( \text{OR} = 0.76, 95\% \text{ CI: } 0.56–1.04 \), (as shown in Table 5 and Figs. 4, 5).

**Heterogeneity and sensitivity analyses**

The obvious heterogeneity between studies was observed in the current meta-analysis. Then, we evaluated the sources of heterogeneity by means of meta regression analysis. In IL-6 174G/C, the results suggested that menopause was the source of heterogeneity (\( p = 0.034 \) for Menopause vs Non-menopausal). Regrettably, we did not find the source of IL-6 572C/G dominant model heterogeneity.

Sensitivity analysis was estimated by applying two methods. First, the pool ORs did not change significantly when removing one study at a time to evaluate the robustness of the current meta-analysis. Furthermore, the results have not changed significantly when we restricted HWE and matching studies (as shown in Table 6).

**Publication bias diagnosis**

The publication bias was confirmed by Begg’s funnel plot and Egger’s test. No significant funnel asymmetry was found in all genetic models (Fig. 6). Similarly, There was no statistical evidence of publication bias based on
Egger’s test results ($P > 0.05$ in all genetic models, as shown in Table 5).

**Credibility of the identified genetic associations**

Genetic associations were classified as “positive results” when they met the following criteria [36]: (1) $P$ value < 0.05 in at least two of the genetic models; (2) FPRP < 0.2; (3) statistical power > 0.8; (4) $I^2 < 50\%$. Associations were considered to be “less-credible positive results” if they met the following criteria: (1) $p$ value < 0.05 in at least one of the genetic models; (2) FPRP > 0.2 or their statistical power was between 50 and 79% or $I^2 > 50\%$. Associations with $P$ value > 0.05 were classified as “null” or “negative”. After credibility assessment, we identified “less-credible positive results” for IL-6 572C/G recessive and additive model in Overall. The credibility assessment results for the current meta-analyses were listed in Table 7.

**Discussion**

With the increasing aging of society, osteoporosis is becoming a serious social health problem, and have caused
severe physical, psychological and economic burden to patients. Several factors contribute to the pathogenesis of osteoporosis. Among them, genetic factors play an important role in the histogenesis and development of osteoporosis [4]. Identification of potential pathogenic genes and their polymorphisms enables us to predict disease risk and take corresponding preventive measures. Interleukin-6 is one of the candidate genes due to it can potentially up regulate the expression of RANKL on osteoblasts, accelerate the signal transduction of RANKL, and directly lead to bone destruction [13]. There are some studies trying to figure out the association between IL-6 gene polymorphism and osteoporosis risk, while these results acquired were conflicting. The limited sample size of a single study is considered as one of the reasons. To overcome this shortcoming, meta-analysis is a competent alternative [37].

A total of 9 studies involving 1891 osteoporosis patients and 2027 healthy controls were included in the current meta-analysis, of which 8 studies evaluated the association between IL-6 174G/C polymorphism and osteoporosis, 3 studies related to IL-6 572C/G (rs1800796). Overall, We
observed the higher osteoporosis risk in IL-6 572C/G additive, dominant and recessive model. However, the IL-6 572C/G C allele was associated with reduced osteoporosis risk. For IL-6 174G/C, the pooled odds ratios indicate it was insignificantly associated with risk of developing osteoporosis in four genetic model comparisons. Furthermore, the current meta-analysis were performed by applying different genetic models, at the cost of multiple comparisons, in which case, the pooled $P$-value must be adjusted [37]. In the Venice criteria, statistical power and $I^2$ were important indicator [38]. Hence, the false-positive report probabilities (FPRP) test [28] and the Venice criteria [29] were used to evaluate the credibility of statistically significant associations. Finally, we identified “less credible positive results” in IL-6 572C/G recessive and additive model. Heterogeneity was also observed in IL-6 174G/C allele model and IL-6 572C/G dominant model. We explore the source of heterogeneity using meta regression analysis. The results suggested that menopause was the source of heterogeneity. In addition, in molecular epidemiological studies, small sample studies are more likely to generate random errors and biases, and are more likely to produce false positive results [29]. Positive research results are more likely to be published, which can lead to publication bias. As shown in Fig. 6 in the current meta-analysis, the slight asymmetry of the funnel plot is caused by the study of small samples. However, due to the limited number of studies on IL-6 572C/G and osteoporosis risk, Begg’s funnel plot was not performed to explored publication bias.

It is worth noting that two previous meta-analyses of IL-6 174G/C and osteoporosis risk have been published [39, 40]. Ni Y et al’s meta-analysis included 4 articles

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**Fig. 4** The forest plots on the association between IL-6 572C/G polymorphism and osteoporosis risk in overall (a: allele model, b: additive model)
including 800 case groups and 900 control groups, and the results showed that the IL-6 CC genotype was significantly associated with a reduced risk for osteoporosis [39]. The examination of 12 studies by Fajar et al. indicated that 174G/C C allele and CC genotype may significantly decreased osteoporosis risk [40]. However, when we carefully examined these two meta-analyses, we found that 6 articles [41–46] were incorrectly included in the study of Fajar et al. Such as Garnero et al. explored the relationship between IL-6 and BMD in premenopausal and postmenopausal healthy people. There was no osteoporosis in the case group [41]. Similarly, the case group in the Lee j et al. study was adolescents with idiopathic scoliosis [45], and Korvala et al. studied stress fractures in military personnel, not osteoporotic or

**Table 6** Pooled estimates of association of IL-6 174G/C and osteoporosis risk, only studies with matching, and studies conforming to HWE

| Genetic Model | Test of association | Tests for heterogeneity |
|---------------|---------------------|------------------------|
| OR (95%CI)    | \( P_\chi^2 \)     | \( P \) \text{ value} \| \( I^2 \) |
| IL-6 174G/C   |                     |                        |
| G VS C        | 1.07 (0.82–1.39)    | 0.618                  | 0.018    | 63.30%   |
| CC VS GG      | 1.05 (0.71–1.57)    | 0.805                  | 0.217    | 30.60%   |
| GC + CC VS GG | 1.01 (0.73–1.41)    | 0.942                  | 0.05     | 57.80%   |
| CC VS GG + GC | 0.93 (0.65–1.34)    | 0.692                  | 0.194    | 32.20%   |
osteoporotic fracture [44]. The other three studies did not provide detailed case and control genotype data [42–44]. So the results are not credible. In the meta-analysis of Ni Y et al., we found that the quality of the literature was not evaluated, no statistical power was calculated, and p-value was not adjusted after multiple comparisons. In order to overcome these shortcomings, the current meta-analysis was performed.

The advantages of current meta-analysis as follows: (1) this is the first meta-analysis to investigate the association between IL-6 572C/G polymorphisms and osteoporosis predisposition; (2) we performed a quality assessment of the literature to ensure the credibility of the pool results; (3) p-value was adjusted after multiple comparisons; (4) we conducted sensitivity analysis to test the stability of the current meta-analysis; (5) compared with previous meta-analysis, the current meta-analysis has a larger sample size. However, the current meta-analysis still has some defects. First, we have only investigated the relationship between the individual gene polymorphism of IL-6 and osteoporosis. In order to fully elucidate the pathogenesis of osteoporosis, it is necessary to study the combined role of these related genes. Second, the limited sample size of IL-6 572C/G may be the reason for the weak statistical power, so a larger sample size is needed to verify our results. Finally, due to the limited number of studies, we did not perform subgroup analysis.

**Conclusion**

In conclusion, IL-6 572C/G GG genotype may be associated with increased risk of osteoporosis. The question of whether and how rs1800795 affect osteoporosis in post-menopausal women requires further investigation.

**Table 7** False-positive report probability values for the current meta-analysis

| Variables          | OR (95% CI) | p (%)  | P_h | Statistical power | Prior probability of 0.01 |
|--------------------|-------------|--------|-----|-------------------|--------------------------|
|                    |             |        |     | OR = 1.2 | OR = 1.5 | OR = 1.2 | OR = 1.5 |
| IL-6 572C/G        |             |        |     |                   |                         |
| C VS G             | 0.76 (0.56–1.04) | 45.60% | 0.083 | 0.282 | 0.794 | 0.968 | 0.915 |
| GG VS CC           | 2.25 (1.55–3.26) | 0.00%  | 0    | 0     | 0.016 | 0.801 | 0.101 |
| CG + GG VS CC      | 1.42 (0.78–2.56) | 77.00% | 0.253 | 0.288 | 0.572 | 0.988 | 0.977 |
| GG VS CC + CG      | 1.96 (1.36–2.83) | 0.00%  | 0    | 0.004 | 0.077 | 0.881 | 0.298 |

Fig. 6 Beggs funnel plot to assess publication bias on IL-6 174G/C polymorphism in overall population (a: allele model, b: additive model, c: dominant model, d: recessive model)
Abbreviations
HWE: Hardy-Weinberg equilibrium; IL-6: Interleukin-6; OR: Odds ratio; 95% CI: 95% confidence interval; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses; FPPR: False-positive report probabilities; BMD: Bone mineral density; PSMI: Postmenopausal; Pre: Premenopause; LS: Lumbar spine; Fr: Femoral neck

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Authors' contributions
BC designed research, performed research, collected data, analyzed data and wrote paper. HZL designed research, collected data and revised article. The author(s) read and approved the final manuscript.

Authors' information
The author information can be found in the title page.

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References
1. Raftery TD, Khlosa S, Hofbauer LC. Osteoporosis: now and the future. Lancet. 2011;377(9733):1276–87.
2. Wiktorowicz ME, et al. Economic implications of hip fracture: health service use, institutional care and cost in Canada. Osteoporos Int. 2001;12(4):271–8.
3. Havill LM, et al. Effects of genes, sex, age, and activity on BMC, bone size, and areal and volumetric BMD. J Bone Miner Res. 2007;22(5):377–46.
4. Xie W, et al. Identification of transcriptional factors and key genes in primary osteoporosis by DNA microarray. Med Sci Monit. 2015;21:1333–44.
5. Clark GR, Duncan EL. The genetics of osteoporosis. Br Med Bull. 2015;113(1):73–81.
6. Bandres E, et al. Association between bone mineral density and polymorphisms of the VDR, ERalpha, COL1A1 and CTR genes in Spanish postmenopausal women. J Endocrinol Invest. 2005;28(4):312–21.
7. Kishimoto T, et al. The molecular biology of interleukin 6 and its receptor. Ciba Found Symp. 1992;167:5–16 discussion 16–23.
8. Ishimi Y, et al. IL-6 is produced by osteoblasts and induces bone resorption. J Immunol. 1990;145(10):3297–303.
9. Littlewood AJ, et al. The modulation of the expression of IL-6 and its receptor in human osteoblasts in vitro. Endocrinology. 1991;129(3):1513–20.
10. Ralston SH. Do genetic markers aid in risk assessment? Osteoporos Int. 1998;8(Suppl 1):S37–42.
11. Arron JR, Choi Y. Bone versus immune system. Nature. 2000;408(6812):535–6.
12. Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. J Biol Chem. 2002;275(51):41838–48.
13. Fishman D, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic- onset juvenile chronic arthritis. J Clin Investig. 1998;102(7):1369–76.
14. Ferrari SL, et al. A functional polymorphic variant in the interleukin-6 gene promoter associated with low bone resorption in postmenopausal women. Arthritis Rheum. 2001;44(1):196–201.
15. Ji YF, et al. Impact of interleukin-6 gene polymorphisms and its interaction with obesity on osteoporosis risk in Chinese postmenopausal women. Environ Health Prev Med. 2019;24(1):48.
16. Ferrari SL, et al. A functional polymorphic variant in the interleukin-6 gene promoter associated with low bone resorption in postmenopausal women. Arthritis Rheum. 2001;44(1):196–201.
17. Ji YF, et al. Association of interleukin-6 gene polymorphisms with bone mineral density in Mexican women. Arch Med Res. 2008;39(6):618–24.
18. Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
19. Moher D, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
20. Xue WQ, et al. Association of BRCA2 N372H polymorphism with cancer susceptibility: a comprehensive review and meta-analysis. Sci Rep. 2014;4:6791.
21. Thakkinstian A, et al. Systematic review and meta-analysis of the association between complement 3 and age-related macular degeneration: a HuGE review and meta-analysis. Am J Epidemiol. 2011;173(12):1365–79.
22. Higgins JP, et al. Measuring inconsistency in meta-analyses. Br J. 2003;327(7414):557–60.
23. DerSimonian, R. and N. Laird, Meta-analysis in clinical trials revisited. Contemp Clin Trials, 2015. 45(5 Pt A): p. 139–45.
24. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719–48.
25. Klug SJ, et al. TP53 codon 72 polymorphism and cervical cancer: a pooled analysis of individual data from 49 studies. Lancet Oncol. 2009;10(8):772–84.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1089–101.
27. Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. Br J. 1997;315(7109):629–34.
28. Wacholder S, et al. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst. 2004;96(6):454–62.
29. Ioannidis JP, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol. 2008;37(1):120–32.
30. Eftekhari H, et al. Association of interleukin-6 (rs1800796) but not transforming growth factor beta 1 (rs1800469) with serum calcium levels in osteoporotic patients. Gene. 2018;671:21–7.
31. Deveci D, Ozkan ZS, Yuce H. Is there any relation between IL-6 gene polymorphism and osteoporosis? Eur J Obstet Gynecol Reprod Biol. 2012;164(1):108–101.
32. Czerney B, et al. The association of IL-1beta, IL-2, and IL-6 gene polymorphisms with bone mineral density and osteoporosis in postmenopausal women. Eur J Obstet Gynecol Reprod Biol. 2010;149(1):82–5.
33. Breuil V, et al. Gene polymorphisms and osteoporotic fractures: a study in postmenopausal French women. Joint Bone Spine. 2009;76(3):317–9.
34. Oncel E, et al. Hip fracture risk and different gene polymorphisms in the Turkish population. Clinics (Sao Paulo). 2008;63(5):645–50.
35. Kusek J, et al. The influence of interleukin-6 and tumor necrosis factor alpha in patients with osteoporosis. Bone. 2019;123:8.
36. Montazeri, Z., et al., Assessment of the evidence of genetic association studies in colorectal cancer. Gut, 2019: p. gutjnl-2019-319313.
37. Attia J, Thakkinstian A, D’Este C. Meta-analyses: interim guidelines. Int J Epidemiol. 2008;37(1):120–32.
38. Ioannidis JP, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. Int J Epidemiol. 2008;37(1):120–32.
39. Eftekhari H, et al. Association of interleukin-6 (rs1800796) but not transforming growth factor beta 1 (rs1800469) with serum calcium levels in osteoporotic patients. Gene. 2018;671:21–7.
40. Montazeri, Z., et al., Assessment of the evidence of genetic association studies in colorectal cancer. Gut, 2019: p. gutjnl-2019-319313.
41. Garnero P, et al. Association between a functional interleukin-6 gene polymorphism and peak bone mineral density and postmenopausal bone loss in women: the OFELY study. Bone. 2002;31(1):43–50.
42. Ferrari SL, et al. Interactions of interleukin-6 promoter polymorphisms with dietary and lifestyle factors and their association with bone mass in men and women from the Framingham osteoporosis study. J Bone Miner Res. 2004;19(4):552–9.
43. Moffett SP, et al. Association of the G-174C variant in the interleukin-6 promoter region with bone loss and fracture risk in older women. J Bone Miner Res. 2004;19(10):1612–8.
44. Kovala J, et al. Genetic predisposition for femoral neck stress fractures in military conscripts. BMC Genet. 2010;11:95.
45. Lee JS, Suh KT, Eun IS. Polymorphism in interleukin-6 gene is associated with bone mineral density in patients with adolescent idiopathic scoliosis. J Bone Joint Surg Br. 2010;92(8):1118–22.
46. Mendez JP, et al. Impact of genetic variants of IL-6, IL6R, LRP5, ESR1 and SP7 genes on bone mineral density in postmenopausal Mexican-mestizo women with obesity. Gene. 2013;528(2):216–20.

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