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ORIGINAL PAPER

# Genetic polymorphisms of interleukin-1 beta and osteosarcoma risk

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**Abstract**
*Purpose* Osteosarcoma is the most common childhood bone cancer. Interleukin-1 beta (*IL-1B*) is crucially involved in osteosarcoma carcinogenesis. Whether genetic polymorphisms of *IL-1B* also influence osteosarcoma risk is unknown. The aim of this study was to investigate the association between *IL-1B* gene polymorphisms and osteosarcoma risk in Chinese Han patients.
*Methods* A hospital-based case–control study involving 120 osteosarcoma patients and 120 controls was conducted. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis was performed to detect three *IL-1B* gene polymorphisms (−31 T/C, −511 C/T and +3954 C/T) in these patients.
*Results* Patients with osteosarcoma had a significantly lower frequency of −31 CC genotype [odds ratio (OR) = 0.40, 95 % confidence interval (CI)=0.17–0.92; *P*=0.03] and −31 C allele (OR=0.67, 95 % CI=0.46–0.99; *P*=0.04) than controls. Patients with osteosarcoma had a significantly lower frequency of −511 TT genotype (OR=0.40, 95 % CI=0.17–0.95; *P*=0.04) than controls. The +3954 C/T gene polymorphisms were not associated with a risk of osteosarcoma. When stratified by Enneking stage, tumour location, histological type, tumour metastasis of osteosarcoma and family history of cancer, no statistically significant results were found.
*Conclusions* This is the first study to provide evidence for an association of *IL-1B* gene polymorphisms with osteosarcoma risk.

**Keywords** Osteosarcoma · Interleukin-1 beta · Gene polymorphism · Hospital-based case–control study

**Abbreviations**

| | |
|---|---|
| IL-1B | Interleukin-1 beta |
| PCR-RFLP | Polymerase chain reaction restriction fragment length polymorphism |
| OR | Odds ratio |
| CI | Confidence interval |
| SNPs | Single-nucleotide polymorphisms |
| UTR | Untranslated region |
| NSCLC | Non-small-cell lung cancer |

## Introduction

Osteosarcoma is the most commonly diagnosed primary malignancy of bone, particularly among children and adolescents, but there is a second incidence peak among individuals >60 years [1, 2]. Osteosarcoma is a complex, multistep and multifactorial process in which many factors are implicated [3–5]. Several research groups are investigating cancer stem cells and their potential to cause tumours [6, 7]. Bone dysplasias, Li–Fraumeni syndrome and Rothmund–Thomson syndrome are associated with increased risk of osteosarcoma [8, 3, 4, 6, 5]. Previous studies suggest a genetic predisposition for osteosarcoma [9–13].

The interleukin-1 (*IL-1*) gene cluster on chromosome 2q contains three related genes within a 430-kilobase (kb) region,

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*IL-1A*, *IL-1B* and *IL-1RN* [14]. The *IL-1B* gene, encoding IL-1beta cytokine, contains several single-nucleotide polymorphisms (SNPs). Three di-allelic polymorphisms in *IL-1B* have been reported, all representing C-T base transitions, at positions −511, −31 and +3954 base pairs (bp) from the transcriptional start site [14]. These polymorphisms have been associated with increased risk of developing a number of inflammatory diseases and cancer [15–20].

*The IL-1B* is crucially involved in osteosarcoma carcinogenesis [21–23]. Whether genetic polymorphisms of *IL-1B* also influence osteosarcoma risk is unknown. The aim of this study was to investigate the association between *IL-1B* gene polymorphisms and osteosarcoma risk in Chinese Han patients.

## Materials and methods

### Study participants

A hospital-based case–control study involving 120 osteosarcoma patients and 120 controls was conducted between January 2009 to January 2014 in the Union Hospital of Tongji Medical College and Cancer Hospital of Wuhan University (Wuhan, China). The healthy controls, who were free from any cancer and matched by gender and age, were recruited when they were attending a clinic for routine examination. These controls were genetically unrelated to the patients. Osteosarcoma patients were newly diagnosed and histopathologically confirmed independently by two gynaecologic pathologists. For the cases, clinical and pathological information was extracted, including Enneking stage (I–III), tumour location (extremities and other), histological type (osteoblastic, chondroblastic, fibroblastic and mixed), tumour metastasis and family history of cancer. The Chinese Han population was collected from the same geographic region. Written informed consents were obtained according to the Declaration of Helsinki from both groups. The Ethical Committee of the Union Hospital of Tongji Medical College and Cancer Hospital of Wuhan University approved the study protocols.

### Genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells of study participants using the QIAamp DNA blood minikit (QIAGEN Inc., Valencia, CA, USA). The *IL-1B* −31 T/C, −511 C/T and +3954 C/T gene polymorphisms were then determined using a polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. Based on the GenBank reference sequence, the PCR primers designed for *IL-1B* −31 T/C, −511 C/T and +3954 C/T were 5′- TCT TTT CCC CTT TCC TTT AAC T -3′ (forward) and 5′- GAG AGA CTC CCT TAG CAC CTA GT -3′ (reverse); 5′- CTG CAT ACC GTA TGT TCT CTG CC -3′ (forward) and 5′- GGA ATC TTC CCA CTTA CAG ATG G -3′ (reverse); 5′- GAC TTT GAC CGT ATA TGC TCA G -3′ (forward) and 5′- ATG GAC CAG ACA TCA CCA AGC -3′ (reverse), respectively. Reaction conditions were: ten minutes at 95 °C, 40 cycles of 30 seconds at 72 °C, 20 seconds at 95 °C, 30 seconds at 59 °C. PCR products were digested overnight with the appropriate restriction enzymes (New England Biolabs, Beverly, MA, USA), which were *Alu*I for the −31 T/C, *Dde*I for the −511 C/T and *Nco*I and *Taq*I for the +3954 C/T polymorphisms. The digested PCR products were resolved on a 3 % agarose gel and stained with ethidium bromide for visualization under ultraviolet (UV) light. For quality control, the genotyping analysis was done blind as regards participants. The selected PCR-amplified DNA samples were also examined by DNA sequencing to confirm genotyping results.

### Statistical analysis

The Statistical Analysis System software (Version 11; SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses. Comparisons between groups were made using the $x^2$ test (nominal data) or Student's $t$ test (interval data). Comparison of genotypes of *IL-1B* variants between cases and controls was evaluated using the chi-square test. Crude odds ratios (OR) and adjusted ORs for sex and age, with 95 % confidence interval (CI), were calculated by logistic regression analysis. The Hardy–Weinberg equilibrium was tested for goodness-of-fit chi-square test with one degree of freedom to compare the observed genotype frequencies among individuals with the expected genotype frequencies. $P$ value < 0.05 was considered statistically significant.

## Results

### Participant characteristics

Clinicopathological characteristics in patients with osteosarcoma and in controls are presented in Table 1. Cases and controls did not differ regarding gender ($P$=0.60) or age ($P$=0.81). Nine (7.5 %) cases Enneking stage I osteosarcoma, 56 (46.7 %) were stage II osteosarcoma and 55 (45.8 %) were stage III osteosarcoma. Tumour location of these cases were 91 (75.8 %) in extremities and 29 (24.2 %) other osteosarcoma. Histological types were 38 (31.6 %) osteoblastic osteosarcoma, 41 (34.2 %) were chondroblastic osteosarcoma, 15 (12.5 %) were fibroblastic osteosarcoma and 26 (21.7 %) were mixed osteosarcoma. Tumour metastasis were positive osteosarcoma in 55 (45.8 %) and negative osteosarcoma in 65

**Table 1** Clinicopathological characteristics in patients with osteosarcoma and controls

| Variable | Cases ($n$=120) | Controls ($n$=120) | $P$ value |
|---|---|---|---|
| Gender (%) | | | 0.60 |
| Male | 68 (56.7) | 64 (53.3) | |
| Female | 52 (43.3) | 56 (46.7) | |
| Age; mean (SD) year | 23.7 (12.8) | 24.1 (13.0) | 0.81 |
| Enneking stage (%) | | | |
| I | 9 (7.5) | | NA |
| II | 56 (46.7) | | NA |
| III | 55 (45.8) | | NA |
| Tumour location (%) | | | |
| Extremities | 91 (75.8) | | NA |
| Other | 29 (24.2) | | NA |
| Histological type (%) | | | |
| Osteoblastic | 38 (31.6) | | NA |
| Chondroblastic | 41 (34.2) | | NA |
| Fibroblastic | 15 (12.5) | | NA |
| Mixed | 26 (21.7) | | NA |
| Tumour metastasis (%) | | | |
| Positive | 55 (45.8) | | NA |
| Negative | 65 (54.2) | | NA |
| Family history of cancer | | | |
| Positive | 11 (9.2) | | NA |
| Negative | 109 (90.8) | | NA |

*SD* standard deviation, *NA* not applicable

(54.2 %). Family history of cancer in these cases showed 11 (9.2 %) were positive and 109 (90.8 %) were negative.

### *IL-1B* −31 T/C polymorphism and osteosarcoma

Patients with osteosarcoma had a significantly lower frequency of −31 CC genotype (OR =0.40, 95 % CI=0.17–0.92; $P$= 0.03) and −31 C allele (OR=0.67, 95 % CI=0.46–0.99; $P$= 0.04) than controls (Table 2). When stratified by Enneking stage, tumour location, histological type, tumour metastasis of osteosarcoma and family history of cancer, no statistically significant results was found (Table 3).

### *IL-1B* −511 C/T polymorphism and osteosarcoma

Patients with osteosarcoma had a significantly lower frequency of −511 TT genotype (OR=0.40, 95 % CI=0.17–0.95; $P$= 0.04) than controls (Table 2). When stratified by Enneking stage, tumour location, histological type, tumour metastasis of osteosarcoma and family history of cancer, no statistically significant results were found (Table 3).

### *IL-1B* +3954 C/T polymorphism and osteosarcoma

The +3954 C/T polymorphisms were not associated with a risk of osteosarcoma (Table 2). When stratified by Enneking stage, tumour location, histological type, tumour metastasis of osteosarcoma and family history of cancer, no statistically significant results were found (Table 3).

## Discussion

There is increasing evidence of the association between genetic polymorphisms and risk of osteosarcoma. A case–control study found that polymorphisms of *ITGA3* gene rs2230392 may affect incidence, metastasis and survival in patients with osteosarcoma and have prognostic value [24]. Another study provided the first evidence for the association between collagen type I alpha-1 polymorphism and osteosarcoma risk in Chinese [9]. A case–control study suggested that *IL-12* gene polymorphisms were associated with the risk of osteosarcoma [25]. A meta-analysis of seven studies suggested that the rs231775 polymorphism of cytotoxic T-lymphocyte antigen-4 may play an important role in osteosarcoma carcinogenesis [26, 13, 27]. A hospital-based case–control study suggested that bisphenol A exposure interacts with the −22 G/C polymorphism of the lysyl oxidase gene to increase the risk of osteosarcoma [11]. A case–control study suggested that genotype CC in *PIK3CA* locus rs7646409 may increase the risk of osteosarcoma in the Chinese population [10]. A case–control study suggested that *MDM2* genetic variants are potentially related to osteosarcoma susceptibility in Chinese Han population [28]. A case–control study suggested that the +1057G/A polymorphism of the *CD86* gene was associated with increased susceptibility to osteosarcoma [29]. Another study concluded that Int7G24A was a polymorphism of *TGFBR1* that is associated with the susceptibility and distant metastasis of osteosarcoma [30]. A case–control study suggested that *PON1* 192 wild-type genotypes may be associated with a risk of developing osteosarcoma [31]. A case–control study suggested an association between Fas exon 3 A>G polymorphism and osteosarcoma risk [32].

The association between *IL-1B* gene polymorphisms and other cancer types was much studied [33]. A case–control study demonstrated that genotype CC or CT of *IL-1B* −31, TT or CT of *IL-1B* −511 increased the risk of gastric cancer in this Chinese population, and the risk was further enhanced by *Helicobacter pylori* [34]. A meta-analysis of 39 studies, which compared 6,863 gastric cancer cases and 8,434 controls, suggested that *IL-1B* −511 genetic polymorphisms were associated with an increased risk of developing gastric cancer [35]. A case–control study suggested that *IL-1B* −511 C/T gene polymorphisms were associated with cervical cancer risk in

**Table 2** *IL-1B* gene polymorphisms among osteosarcoma patients and controls

| Genotype | Cases *n* (%) | Controls *n* (%) | OR (95 % CI) | *P* value |
|---|---|---|---|---|
| −31 TT | 60 (50.0) | 50 (41.7) | 1.00 (reference) | |
| −31 TC | 50 (41.7) | 49 (40.8) | 0.85 (0.49,1.47) | 0.56 |
| −31 CC | 10 (8.3) | 21 (17.5) | 0.40 (0.17,0.92) | 0.03 |
| −31 T allele frequency | 170 (70.8) | 149 (62.1) | 1.00 (reference) | |
| −31 C allele frequency | 70 (29.2) | 91 (37.9) | 0.67 (0.46,0.99) | 0.04 |
| −511 CC | 59 (49.2) | 52 (43.3) | 1.00 (reference) | |
| −511 CT | 52 (43.3) | 48 (40.0) | 0.96 (0.56,1.64) | 0.87 |
| −511 TT | 9 (7.5) | 20 (16.7) | 0.40 (0.17,0.95) | 0.04 |
| −511 C allele frequency | 170 (70.8) | 152 (63.3) | 1.00 (reference) | |
| −511 T allele frequency | 70 (29.2) | 88 (36.7) | 0.71 (0.49,1.04) | 0.08 |
| +3954 CC | 77 (64.2) | 79 (65.8) | 1.00 (reference) | |
| +3954 CT | 30 (25.0) | 32 (26.7) | 0.96 (0.53,1.73) | 0.90 |
| +3954 TT | 13 (10.8) | 9 (7.5) | 1.48 (0.60,3.67) | 0.40 |
| +3954 C allele frequency | 184 (76.7) | 190 (79.2) | 1.00 (reference) | |
| +3954 T allele frequency | 56 (23.3) | 50 (20.8) | 1.16 (0.75,1.78) | 0.51 |

*OR* odds ratio, *CI* confidence interval

Egyptian women [36]. Another study provided evidence of an association between *IL-1B* +3953 polymorphism and risk of cervical cancer [37]. A case–control study demonstrated that the *IL-1B* −31 T allele was positively associated with a risk for non-small-cell lung cancer (NSCLC), and the carriers of *IL-1B* −31 T/T or −511C/C would have a higher risk of developing NSCLC if they drank alcohol or smoked heavily [38]. A case–control study demonstrated that *IL-1B* gene polymorphisms influenced survival rates in patients with pancreatic cancer [39].

Some shortcomings of this study should be noted. Firstly, although our study suggested statistically significant interactions between *IL-1B* gene polymorphisms and osteosarcoma risk, more biological background data are needed to explain our results. Secondly, this study only considers a Chinese population, which may limit the application of these findings

**Table 3** Stratification analysis of *IL-1B* gene polymorphisms among osteosarcoma patients

| Variable | Cases | −31 TT | | −31 TC | | −31 CC | | −511 CC | | −511 CT | | −511 TT | | +3954 CC | | +3954 CT | | +3954 TT | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* | *n* | *P* |
| Enneking stage | 120 | 60 | | 50 | | 10 | | 59 | | 52 | | 9 | | 77 | | 30 | | 13 | |
| I | 9 | 5 | 0.86 | 3 | 0.75 | 1 | 0.79 | 4 | 0.87 | 4 | 0.97 | 1 | 0.72 | 6 | 0.94 | 2 | 0.88 | 1 | 0.98 |
| II | 56 | 25 | 0.69 | 26 | 0.71 | 5 | 0.90 | 27 | 0.95 | 25 | 0.92 | 4 | 0.94 | 35 | 0.92 | 15 | 0.85 | 6 | 0.98 |
| III | 55 | 30 | 0.75 | 21 | 0.78 | 4 | 0.82 | 28 | 0.90 | 23 | 0.91 | 4 | 0.96 | 36 | 0.94 | 13 | 0.88 | 6 | 0.99 |
| Tumour location | 120 | 60 | | 50 | | 10 | | 59 | | 52 | | 9 | | 77 | | 30 | | 13 | |
| Extremities | 91 | 46 | 0.96 | 37 | 0.92 | 8 | 0.91 | 45 | 0.98 | 39 | 0.97 | 7 | 0.96 | 60 | 0.90 | 22 | 0.92 | 9 | 0.84 |
| Other | 29 | 14 | 0.92 | 13 | 0.85 | 2 | 0.81 | 14 | 0.96 | 13 | 0.93 | 2 | 0.92 | 17 | 0.79 | 8 | 0.83 | 4 | 0.69 |
| Histological type | 120 | 60 | | 50 | | 10 | | 59 | | 52 | | 9 | | 77 | | 30 | | 13 | |
| Osteoblastic | 38 | 19 | 1.00 | 16 | 0.98 | 3 | 0.94 | 18 | 0.91 | 17 | 0.92 | 3 | 0.94 | 25 | 0.93 | 9 | 0.90 | 4 | 0.96 |
| Chondroblastic | 41 | 20 | 0.94 | 17 | 0.99 | 4 | 0.80 | 20 | 0.98 | 18 | 0.97 | 3 | 0.97 | 26 | 0.97 | 10 | 0.95 | 5 | 0.83 |
| Fibroblastic | 15 | 7 | 0.89 | 7 | 0.82 | 1 | 0.84 | 8 | 0.86 | 6 | 0.88 | 1 | 0.91 | 10 | 0.93 | 4 | 0.91 | 1 | 0.65 |
| Mixed | 26 | 14 | 0.84 | 10 | 0.85 | 2 | 0.92 | 13 | 0.96 | 11 | 0.95 | 2 | 0.98 | 16 | 0.91 | 7 | 0.88 | 3 | 0.93 |
| Tumor metastasis | 120 | 60 | | 50 | | 10 | | 59 | | 52 | | 9 | | 77 | | 30 | | 13 | |
| Yes | 55 | 28 | 0.95 | 23 | 0.99 | 4 | 0.82 | 28 | 0.90 | 23 | 0.91 | 4 | 0.96 | 35 | 0.98 | 14 | 0.96 | 6 | 0.99 |
| No | 65 | 32 | 0.95 | 27 | 0.99 | 6 | 0.85 | 31 | 0.91 | 29 | 0.92 | 5 | 0.97 | 42 | 0.98 | 16 | 0.96 | 7 | 0.99 |
| Family history of cancer | 120 | 60 | | 50 | | 10 | | 59 | | 52 | | 9 | | 77 | | 30 | | 13 | |
| Yes | 11 | 4 | 0.60 | 6 | 0.61 | 1 | 0.94 | 5 | 0.89 | 5 | 0.93 | 1 | 0.86 | 7 | 0.99 | 3 | 0.90 | 1 | 0.87 |
| No | 109 | 56 | 0.91 | 44 | 0.90 | 9 | 0.99 | 54 | 0.97 | 47 | 0.98 | 8 | 0.97 | 70 | 0.99 | 27 | 0.98 | 12 | 0.97 |

to other ethnic populations. Thirdly, this is a hospital-based case –control study, so selection bias may not be avoidable, and participants may not be representative of the general population. Finally, findings might involve gene-to-environment interactions, which are not explored here.

In conclusion, to the best of our knowledge, this is the first study to provide evidence for an association between *IL-1B* gene polymorphisms and osteosarcoma risk. Our study suggests that patients with osteosarcoma have a significantly lower frequency of *IL-1B* −31 CC genotype, *IL-1B* −511 TT genotype and *IL-1B* −31 C allele than controls. We also found that *IL-1B* +3954 C/T gene polymorphisms are not associated with a risk of osteosarcoma. However, it is highly desirable that our findings are validated through replication in other case–control series.

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**Competing interest** None.

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