**MIR31HG** polymorphisms are related to steroid-induced osteonecrosis of femoral head among Chinese Han population

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**Abstract**

**Backgrounds:** *MIR31* host gene (*MIR31HG*) polymorphisms play important roles in the occurrence of osteonecrosis. However, the association of *MIR31HG* polymorphisms with the risk of steroid-induced osteonecrosis of the femoral head (SONFH) remains unclear. In this study, we aimed to investigate the correlation between *MIR31HG* polymorphisms and SONFH susceptibility in the Chinese Han population.

**Methods:** A total of 708 volunteers were recruited to detect the effect of seven single nucleotide polymorphisms (SNPs) in the *MIR31HG* gene on SONFH risk in the Chinese Han population. Genotyping of *MIR31HG* polymorphisms was performed using the Agena MassARRAY platform. The odds ratio (OR) and 95% confidence interval (95% CI) were used to evaluate the correlation between *MIR31HG* polymorphisms and SONFH risk using logistic regression model.

**Results:** According to the results of genetic model, rs10965059 in *MIR31HG* was significantly correlated with the susceptibility to SONFH (OR = 0.56, *p* = 0.002). Interestingly, the stratified analysis showed that rs10965059 was associated with the reduced risk of SONFH in subjects aged > 40 years (OR = 0.30, *p* < 0.001) and male populations (OR = 0.35, *p* < 0.001). Moreover, rs10965059 was associated with the reduced risk of bilateral SONFH (OR = 0.50, *p* = 0.002). Finally, multi-factor dimension reduction (MDR) results showed that the combination of rs1332184, rs72703442, rs2025327, rs55683539, rs2181559, rs10965059 and rs10965064 was the best model for predicting SONFH occurrence (*p* < 0.0001).

**Conclusion:** The study indicated that rs10965059 could be involved in SONFH occurrence in the Chinese Han population, which might provide clues for investigating the role of *MIR31HG* in the pathogenesis of SONFH.

**Keywords:** *MIR31HG*, Osteonecrosis, Polymorphism, Steroid, Gene

**Introduction**

Osteonecrosis of the femoral head (ONFH) is a progressive rupture of the femoral head caused by the death of bone cells from various causes. The main characteristics of ONFH are the differentiation and the damage of bone marrow mesenchymal cells, enhanced cytotoxicity and destruction of vascular blood flow [1].

Osteonecrosis can be summarized into two categories: traumatic and non-traumatic femoral head necrosis. The steroid-induced osteonecrosis of the femoral head (SONFH), a non-traumatic femoral head necrosis, is a devastating disease, which is often result in devastating and crippled health conditions following steroid therapy [2]. In China, there were approximately 8 million patients with non-traumatic ONFH, which may be closely related to their frequent use of high-dose hormone therapy [3]. The pathogenesis is likely multifactorial, with genetic and environmental factors playing a role. Corticosteroid use, alcohol consumption,
smoking, and infection and metabolic disease are all risk factors for SONFH [4]. Furthermore, genetics appears to play an important role in the development of SONFH. Previous studies have suggested that some genes play a role in SONFH occurrence including eNOS, PAI-1, VEGF, and ApoA [5]. However, there are still a large number of potential osteonecrosis-related genes and loci that have not been fully explored.

Long non-coding RNA (LncRNA) is a non-protein coding RNA molecule with a structure size of 200 nucleotides [6, 7]. Yuan and Sun’s studies showed that, LncRNA can regulate the development of immune diseases and affect immune function and autoimmunity, such as osteosarcoma and IgA nephropathy (IgAN) [8, 9]. The LncRNA MIR31 host gene (MIR31HG) is an crucial regulator of malignant tumors [10]. MIR31HG located on chromosome 9 with the length of 2166 bp, is an LncRNA that acts on the progression of cancers, such as osteosarcoma, lung cancer, breast cancer and cervical cancer [9, 11, 12]. For example, recent studies have mentioned that MIR31HG is also involved in the development and regeneration of bone, and the pathogenesis of numerous orthopaedic conditions [13]. MIR31HG was up-regulated in osteosarcoma (OS) tissues and OS cell lines. In the case of bone loss, it was usually inflamed in the defective or injured tissue. A previous research has demonstrated that knock-down of MIR31HG not only affects the enhancement of osteogenic differentiation, but also limits the inhibitory effect of osteogenic in an inflammatory environment [14]. Studies have found that the interference with MIR31HG can improve osteogenesis in bone marrow stromal cells in patients with cleidocranial dysplasia (BMSCs-CCD), possibly through by promoting osteogenic differentiation and improving the aging-related properties of BMSCs-CCD [15]. MIR31HG can regulate the tumor suppressor miR-361 and its target genes, and promote tumor progression in osteosarcoma acting as an oncogene [9]. These studies have shown that MIR31HG may play an important role in SONFH. At present, the connection between MIR31HG gene polymorphism and the susceptibility to SONFH was not reported.

In the case-control study, the MassARRAY platform was used to select seven single nucleotide polymorphisms (SNPs) in MIR31HG for genotyping. We further investigated the effect of MIR31HG genetic polymorphisms on SONFH risk and conducted the stratified analysis to identify the contribution of confounding factors to the association between SNPs and the risk of SONFH. Our research will provide a new perspective to study the role of MIR31HG on the susceptibility to SONFH.

Methods

Subjects

A total of 708 unrelated participants were recruited, embracing 200 SONFH cases (41.15 ± 12.90 years) and 508 healthy controls (42.70 ± 13.01 years) geographically and ethnically matched. Exclusion criteria were as follows: (1) Patients who did not meet the diagnostic criteria of SONFH and patients with traumatic ONFH, hip dislocation and other hip diseases; and (2) Patients without major family genetic diseases. The histopathological diagnosis was based on X-rays and/or magnetic resonance imaging (MRI) examination of the hip and frog positions. The research protocol was in compliance with the Declaration of Helsinki and was approved by the ethics committee of Affiliated Hospital of Weifang Medical University and Second Affiliated Hospital of Inner Mongolia Medical University. All experimental subjects signed a written informed consent. Demographic and blood biochemical indicators of each subject were collected from standardized questionnaires and medical records by trained research staff.

Selection and genotyping for MIR31HG polymorphisms

Seven functional SNPs in MIR31HG (rs1332184, rs72703442, rs2025327, rs55683539, rs10965059 and rs10965064) were selected from the 1000 Genomes Project (http://www.1000genomes.org/), with the minor allele frequency (MAF) of each SNP greater than 0.05. Peripheral blood genomic DNA was extracted from all subjects according to the operating procedures of Whole Blood Genomic DNA Isolation Kit (Xi’an GoldMag Biotechnology, China). Agena MassARRAY iPLEX platform was used for genotyping. Agena Bioscience Assay was used to design PCR primers for amplification (Supplementary Table 1). Finally, Agena Biosciences TYPER application software 4.0 was performed to analyze the genetic data.

Statistical analysis

The differences in demographic or clinical characteristics between the case and the control groups were compared by \( \chi^2 \) tests for the categorical variables and Student’s t-tests for continuous variables. PLINK software was used to detect four genetic models (co-dominant, dominant, recessive, and log-additive). Hardy-Weinberg equilibrium (HWE) of all SNPs from control individuals was evaluated by \( \chi^2 \) test. Multi-factor dimension reduction (MDR) is suitable for detecting the interaction between SNP-SNP and SONFH risk. Analysis of variance (ANOVA) was performed to determine differences in clinical characteristics among SNPs genotypes. By calculating the odds ratio (OR) and 95% confidence interval (CI), logistic regression results were adjusted for age and
gender to assess the impact of MIR31HG polymorphism on SONFH risk. HaploView software version 4.2 and logistic regression were carried out to assess the correlation of MIR31HG haplotypes with SONFH susceptibility. All statistics were two-tailed, and a $p < 0.05$ was considered statistically significant. SPSS 20.0 software (Chicago, IL, USA) was used for statistical analysis in this study.

**Results**

**Basic conventional characteristics**

were consisted. The basic characteristics of 200 patients with SONFH and 508 healthy participants are summarized in Table 1, including age, gender, necrosis, and course. The mean age was $41.15 \pm 12.90$ years in the case group and $42.70 \pm 13.01$ years in control group. There were no significant differences in age ($p = 0.152$) and gender ($p = 0.706$) characteristics between cases and controls.

**Association analysis of MIR31HG and SONFH risk**

In this study, seven SNPs (rs1332184, rs72703442, rs2025327, rs55683539, rs2181559, rs10965059, and rs10965064) were successfully genotyped. The minor allele frequencies are record in Table 2. All SNP distribution of controls were in line with HWE ($p > 0.05$). The rs10965059-T allele frequency in the case group (0.103) was lower than that in the control group (0.169), and the reduced risk of SONFH was found (OR = 0.56, $p = 0.002$).

The correlation between the risk of SONFH and the MIR31HG polymorphisms was assessed after adjusting for age and gender in the four genetic models (co-dominant, dominant, recessive, and log-addition models). Our analysis results showed that rs10965059 was significantly related to the risk of SONFH (Table 3). In addition, rs10965059 was associated with the reduced susceptibility to SONFH in the co-dominant (T/C vs. C/C, OR = 0.50, $p = 0.002$), dominant (T/T-T/C vs. C/C, OR = 0.54, $p = 0.004$) and log-additive (OR = 0.63, $p = 0.016$) models.

**Stratification analyses**

To further investigate the effect of confounding factors on the association of MIR31HG variants with SONFH occurrence, we conducted a stratified analysis based on age, gender, disease course, and bilateral. The age-stratified analysis of the relationship between SNPs and SONFH risk is presented in Table 4. In subjects aged >40 years, rs10965059 was related to a reduced risk of SONFH (T allele: OR = 0.30, $p < 0.001$; C/T genotype: OR = 0.34, $p < 0.001$; C/T-T/T genotype: OR = 0.33, $p < 0.001$). Conversely, no significant relationship of

### Table 1 Basic characteristic of SONFH patients and healthy subjects in this study

| Characteristics | Cases ($n = 200$) | Controls ($n = 508$) | $p$     |
|-----------------|------------------|----------------------|--------|
| Age, years (mean ± SD) | 41.15 ± 12.90 | 42.70 ± 13.01 | 0.152$^a$ |
| > 40            | 100 (50%)       | 290 (57%)           |        |
| ≤ 40            | 100 (50%)       | 218 (43%)           | 0.706$^b$ |
| Gender          |                  |                      |        |
| Male            | 117 (59%)       | 425 (84%)           |        |
| Female          | 83 (41%)        | 83 (16%)            |        |
| Necrosis        |                  |                      |        |
| Bilateral       | 143 (72%)       |                      |        |
| Missing         | 55 (28%)        |                      |        |
| Course (months) |                  |                      |        |
| > 29            | 61 (31%)        |                      |        |
| ≤ 29            | 139 (69%)       |                      |        |

$SD$ Standard deviation

$p^a$ values were calculated from student’s t test

$p^b$ values were calculated from χ² test

### Table 2 Basic information for MIR31HG SNPs

| SNP ID       | Chromosome position | Role   | Alleles A/B | MAF       | O (HET) | E (HET) | $P^a$-HWE | OR (95% CI) | $P^b$  |
|--------------|---------------------|--------|-------------|-----------|---------|---------|-----------|-------------|--------|
| rs1332184    | chr9:21504203       | Intron | A/G         | 0.245     | 0.264   | 0.383   | 0.732     | 0.90 (0.69–1.18) | 0.456  |
| rs72703442   | chr9:21515795       | Intron | A/C         | 0.143     | 0.163   | 0.286   | 0.328     | 0.86 (0.62–1.19) | 0.347  |
| rs2025327    | chr9:21531629       | Intron | C/T         | 0.108     | 0.122   | 0.217   | 0.999     | 0.87 (0.60–1.25) | 0.445  |
| rs55683539   | chr9:21542134       | Intron | T/C         | 0.230     | 0.244   | 0.341   | 0.093     | 0.92 (0.71–1.22) | 0.590  |
| rs2181559    | chr9:21543938       | Intron | A/T         | 0.332     | 0.359   | 0.443   | 0.387     | 0.89 (0.69–1.13) | 0.328  |
| rs10965059   | chr9:21544062       | Intron | T/C         | 0.103     | 0.169   | 0.299   | 0.281     | 0.204       | 0.56 (0.39–0.81) | 0.002* |
| rs10965064   | chr9:21553538       | Intron | G/C         | 0.358     | 0.370   | 0.461   | 0.466     | 0.776       | 0.94 (0.74–1.21) | 0.658  |

SNP Single nucleotide polymorphism, MAF Minor allele frequency, HWE Hardy-Weinberg equilibrium

$p^a$-values were calculated by exact test $p^a < 0.05$ are excluded

$p^b$-values were calculated by two-sided χ². $p^b < 0.05$ indicates statistical significance

* indicates statistical strongly significance ($p < 0.01$)
Table 3  Association analysis between MIR31HG SNPs and SONFH risk

| SNP ID  | Model      | Genotype | Case | Control | With Adjustment | OR (95% CI)  | Pp  |
|---------|------------|----------|------|---------|----------------|--------------|-----|
|         |            |          |      |         |                |              |     |
| rs1332184 | Codominant | G/G      | 109  | 276     | 1              | 1            |     |
|         |            | A/A      | 7    | 37      | 0.49 (0.20–1.14) | 0.099        |     |
|         |            | A/G      | 84   | 194     | 1.05 (0.74–1.50) | 0.770        |     |
|         | Dominant   | G/G      | 109  | 276     | 1              | 1            |     |
|         |            | A/A-A/G  | 91   | 231     | 0.96 (0.68–1.36) | 0.837        |     |
|         | Recessive  | A/G-G/G  | 193  | 470     | 1              |              |     |
|         |            | A/A      | 7    | 37      | 0.47 (0.20–1.11) | 0.084        |     |
|         | Log-additive | –     | –    | –       | 0.88 (0.67–1.17) | 0.391        |     |
| rs72703442 | Codominant | C/C      | 145  | 352     | 1              | 1            |     |
|         |            | A/A      | 2    | 10      | 0.52 (0.11–2.49) | 0.414        |     |
|         |            | A/C      | 53   | 145     | 0.85 (0.58–1.25) | 0.417        |     |
|         | Dominant   | C/C      | 145  | 352     | 1              | 1            |     |
|         |            | A/A-A/C  | 55   | 155     | 0.83 (0.57–1.22) | 0.342        |     |
|         | Recessive  | A/C-C/C  | 198  | 497     | 1              |              |     |
|         |            | A/A      | 2    | 10      | 0.54 (0.11–2.59) | 0.446        |     |
|         | Log-additive | –     | –    | –       | 0.82 (0.58–1.17) | 0.285        |     |
| rs2025327 | Codominant | T/T      | 159  | 391     | 1              | 1            |     |
|         |            | C/C      | 2    | 7       | 0.61 (0.12–3.13) | 0.557        |     |
|         |            | C/T      | 39   | 110     | 0.84 (0.55–1.28) | 0.407        |     |
|         | Dominant   | T/T      | 159  | 391     | 1              | 1            |     |
|         |            | C/C-C/T  | 41   | 117     | 0.82 (0.54–1.25) | 0.354        |     |
|         | Recessive  | C/T-T/T  | 198  | 501     | 1              |              |     |
|         |            | C/C      | 2    | 7       | 0.64 (0.13–3.24) | 0.588        |     |
|         | Log-additive | –     | –    | –       | 0.82 (0.56–1.21) | 0.324        |     |
| rs55683539 | Codominant | C/C      | 116  | 297     | 1              | 1            |     |
|         |            | T/T      | 8    | 37      | 0.57 (0.25–1.29) | 0.176        |     |
|         |            | T/C      | 76   | 173     | 1.12 (0.78–1.60) | 0.536        |     |
|         | Dominant   | C/C      | 116  | 297     | 1              | 1            |     |
|         |            | T/T-T/C  | 84   | 210     | 1.02 (0.73–1.45) | 0.893        |     |
|         | Recessive  | T/C-C/C  | 192  | 470     | 1              |              |     |
|         |            | T/T      | 8    | 37      | 0.54 (0.24–1.22) | 0.139        |     |
|         | Log-additive | –     | –    | –       | 0.93 (0.71–1.24) | 0.629        |     |
| rs2181559 | Codominant | T/T      | 87   | 213     | 1              | 1            |     |
|         |            | A/A      | 20   | 70      | 0.64 (0.36–1.15) | 0.135        |     |
|         |            | A/T      | 92   | 225     | 1.05 (0.73–1.50) | 0.804        |     |
|         | Dominant   | T/T      | 87   | 213     | 1              | 1            |     |
|         |            | A/A-A/T  | 112  | 295     | 0.95 (0.67–1.33) | 0.746        |     |
|         | Recessive  | A/T-T/T  | 179  | 438     | 1              |              |     |
|         |            | A/A      | 20   | 70      | 0.63 (0.36–1.09) | 0.097        |     |
|         | Log-additive | –     | –    | –       | 0.87 (0.68–1.12) | 0.292        |     |
| rs10965059 | Codominant | C/C      | 164  | 340     | 1              | 1            |     |
|         |            | T/T      | 5    | 10      | 1.12 (0.36–3.49) | 0.842        |     |
|         |            | T/C      | 31   | 149     | 0.50 (0.32–0.78) | 0.002*       |     |
|         | Dominant   | C/C      | 164  | 340     | 1              |              |     |
|         |            | T/T-T/C  | 36   | 159     | 0.54 (0.35–0.82) | 0.004*       |     |
|         | Recessive  | T/C-C/C  | 195  | 489     | 1              |              |     |
|         |            | T/T      | 5    | 10      | 1.31 (0.42–4.07) | 0.644        |     |
|         | Log-additive | –     | –    | –       | 0.63 (0.43–0.92) | 0.016*       |     |
**Table 3 (continued)**

| SNP ID     | Model       | Genotype | Case | Control | With Adjustment | OR (95% CI) | p |
|------------|-------------|----------|------|---------|----------------|-------------|---|
| rs10965064 | Codominant  | C/C      | 80   | 203     | 1              |             |   |
|            |             | G/G      | 23   | 71      | 0.82 (0.47–1.42) | 0.474       |   |
|            |             | G/C      | 97   | 234     | 1.00 (0.70–1.45) | 0.989       |   |
|            | Dominant    | C/C      | 80   | 203     | 1              |             |   |
|            |             | G/G-G/C  | 120  | 305     | 0.96 (0.68–1.36) | 0.818       |   |
|            | Recessive   | G/C-C/C  | 177  | 437     | 1              |             |   |
|            |             | G/G      | 23   | 71      | 0.81 (0.48–1.37) | 0.440       |   |
|            | Log-additive| –        | –    | –       | –              | 0.93 (0.72–1.20) | 0.580 |

*SNP* Single nucleotide polymorphism, CI Confidence interval, OR Odds ratio
*indicates statistical significance (p < 0.05)

**Discussion**

SONFH is multi-layered and intricate disease with femoral neck fracture or bone tissue disorder, whose symptoms and signs are diverse, and the time and degree of pain attack are different. However, SONFH still has the basis of pathological evolution. There are no specific clinical manifestations of ONFH, so it is difficult to make a diagnosis of ONFH from the patient's symptoms and clinical examination [16]. With the development of modern precision medicine in recent years, an in-depth research on stem cells, molecular biology, and the exact pathogenesis of SONFH has been analyzed. A large number of experiments have shown that the increase in reactive oxygen species (ROS) caused by hormone use is related to the occurrence and development of SONFH.
Table 4  Correlation between MIR31HG SNPs and SONFH risk stratified by age

| SNP   | Allele/Genotype | Case Control OR (95% CI) | p   | Case Control OR (95% CI) | p   |
|-------|-----------------|--------------------------|-----|--------------------------|-----|
| Age   | > 40            |                          |     |                          |     |
| rs1332184 | G 149 | 426 1 153 | 320 1 | 0.96 (0.67–1.39) | 0.825 | 47 116 0.85 (0.58–1.25) | 0.413 |
|        | A 51 | 152 1 | 47 116 | 0.96 (0.67–1.39) | 0.825 |
|        | G/G 53 | 154 1 | 56 122 | 0.96 (0.67–1.39) | 0.825 |
|        | G/A 43 | 118 1 | 41 76 | 1.02 (0.62–1.68) | 0.937 |
|        | A/A 4 17 | 0.70 (0.22–2.31) | 0.564 | 3 20 | 0.33 (0.09–1.15) | 0.080 |
|        | G/A-A/A 47 | 135 1 | 0.98 (0.61–1.59) | 0.939 | 44 96 | 1.00 (0.62–1.61) | 0.995 |
| rs72703442 | C 169 481 1 | 174 368 1 | 0.89 (0.57–1.38) | 0.608 | 26 66 | 0.83 (0.51–1.36) | 0.466 |
|        | A 31 99 | 0.89 (0.57–1.38) | 0.608 | 26 66 | 0.83 (0.51–1.36) | 0.466 |
|        | G/G 70 195 1 | 75 157 1 | 0.89 (0.57–1.38) | 0.608 |
|        | G/A 29 91 | 0.79 (0.47–1.34) | 0.386 | 24 54 | 0.93 (0.53–1.62) | 0.799 |
|        | A/A 1 4 | 0.70 (0.07–6.83) | 0.764 | 1 6 | 0.35 (0.04–2.95) | 0.334 |
|        | G/A-A/A 30 | 95 1 | 0.79 (0.47–1.33) | 0.371 | 25 60 | 0.87 (0.51–1.50) | 0.621 |
| rs2025327 | C 176 511 1 | 181 381 1 | 1.01 (0.62–1.66) | 0.969 | 19 55 | 0.73 (0.42–1.26) | 0.255 |
|        | T 24 69 | 0.86 (0.47–1.56) | 0.618 | 19 47 | 0.83 (0.46–1.51) | 0.549 |
|        | T/T 78 224 1 | 81 167 1 | 0.86 (0.47–1.56) | 0.618 |
|        | C/C 20 63 | 1.16 (0.17–7.90) | 0.882 | 0 4 | / | 0.999 |
|        | C/A 2 3 | 0.88 (0.49–1.56) | 0.657 | 19 51 | 0.77 (0.43–1.39) | 0.381 |
| rs55683539 | C 155 429 1 | 153 338 1 | 0.82 (0.56–1.21) | 0.320 | 47 96 | 1.08 (0.73–1.59) | 0.706 |
|        | T 45 151 | 0.82 (0.56–1.21) | 0.320 | 47 96 | 1.08 (0.73–1.59) | 0.706 |
|        | C/C 58 162 1 | 58 135 1 | 0.82 (0.56–1.21) | 0.320 |
|        | C/T 39 105 | 1.07 (0.65–1.76) | 0.790 | 37 68 | 1.27 (0.76–2.10) | 0.359 |
|        | T/T 22 66 | 0.32 (0.09–1.17) | 0.885 | 5 14 | 0.83 (0.29–2.42) | 0.734 |
|        | T/C-C/C 42 | 128 1 | 0.93 (0.57–1.50) | 0.753 | 42 82 | 1.19 (0.74–1.93) | 0.475 |
| rs2181559 | T 132 362 1 | 134 289 1 | 0.86 (0.61–1.20) | 0.364 | 64 147 | 0.94 (0.67–1.33) | 0.739 |
|        | A 68 218 | 0.86 (0.61–1.20) | 0.364 | 64 147 | 0.94 (0.67–1.33) | 0.739 |
|        | T/T 41 113 | 1.08 (0.65–1.81) | 0.746 | 42 89 | 1.03 (0.62–1.70) | 0.921 |
|        | C/C 50 136 | 1.08 (0.65–1.81) | 0.746 | 42 89 | 1.03 (0.62–1.70) | 0.921 |
|        | C/T 4 11 | 0.49 (0.21–1.16) | 0.105 | 11 29 | 0.83 (0.38–1.79) | 0.627 |
|        | T/T-T/T 59 | 177 1 | 0.93 (0.57–1.52) | 0.774 | 53 118 | 0.98 (0.61–1.57) | 0.922 |
| rs10965059 | C 186 451 1 | 173 378 1 | 0.30 (0.17–0.54) | <0.001* | 27 56 | 1.05 (0.66–1.67) | 0.845 |
|        | T 14 113 | 0.30 (0.17–0.54) | <0.001* | 27 56 | 1.05 (0.66–1.67) | 0.845 |
|        | C/C 86 174 1 | 78 166 1 | 0.30 (0.17–0.54) | <0.001* |
|        | C/T 14 103 | 0.34 (0.18–0.65) | <0.001* | 17 46 | 0.79 (0.42–1.46) | 0.446 |
|        | T/T 0 5 | 0.34 (0.18–0.65) | 0.79 (0.42–1.46) | 0.446 |
|        | C/T-T/T 14 | 108 1 | 0.33 (0.18–0.62) | <0.001* | 22 51 | 0.92 (0.52–1.62) | 0.768 |
| rs10965064 | C 126 350 1 | 131 290 1 | 0.89 (0.64–1.25) | 0.507 | 69 146 | 1.05 (0.74–1.47) | 0.807 |
|        | G 74 230 | 0.89 (0.64–1.25) | 0.507 | 69 146 | 1.05 (0.74–1.47) | 0.807 |
|        | C/C 37 103 1 | 43 100 1 | 0.89 (0.64–1.25) | 0.507 |
|        | C/G 52 144 | 0.96 (0.57–1.62) | 0.884 | 45 90 | 1.16 (0.70–1.93) | 0.559 |
|        | G/G 11 43 | 0.96 (0.57–1.62) | 0.884 | 45 90 | 1.16 (0.70–1.93) | 0.559 |
|        | C/G-G/G 63 | 187 1 | 0.90 (0.55–1.47) | 0.662 | 57 118 | 1.12 (0.70–1.81) | 0.633 |

SNP: Single nucleotide polymorphism, CI: Confidence interval, OR: Odds ratio
p-Values were calculated by logistic regression adjusted by age and gender
*indicates statistical strongly significance (p<0.01)
Table 5 Correlation between SNPs and SONFH susceptibility stratified by gender

| SNP          | Allele/Genotype | Case | Control | OR (95% CI) | p      | Case | Control | OR (95% CI) | p      |
|--------------|-----------------|------|---------|-------------|--------|------|---------|-------------|--------|
| rs1332184    | G               | 174  | 630     | 0.98 (0.70–1.37) | 0.904  | 38  | 48      | 0.72 (0.44–1.18) | 0.187  |
|              | A               | 60  | 220     | 1.39 (0.91–2.13) | 0.123  | 30  | 40      | 0.59 (0.31–1.11) | 0.100  |
|              | G/G             | 60  | 238     | 0.35 (0.10–1.18) | 0.089  | 4   | 4       | 0.77 (0.18–3.30) | 0.729  |
|              | G/A             | 54  | 154     | 1.21 (0.80–1.82) | 0.375  | 34  | 44      | 0.60 (0.33–1.12) | 0.108  |
|              | G/A-A/A         | 57  | 187     | 0.98 (0.70–1.37) | 0.904  | 38  | 48      | 0.72 (0.44–1.18) | 0.187  |
| rs72703442   | C               | 202  | 712     | 0.82 (0.54–1.26) | 0.363  | 25  | 29      | 0.84 (0.47–1.50) | 0.552  |
|              | A               | 32  | 136     | 1.39 (0.91–2.13) | 0.123  | 30  | 40      | 0.59 (0.31–1.11) | 0.100  |
|              | G/G             | 60  | 238     | 0.35 (0.10–1.18) | 0.089  | 4   | 4       | 0.77 (0.18–3.30) | 0.729  |
|              | G/A             | 54  | 154     | 1.21 (0.80–1.82) | 0.375  | 34  | 44      | 0.60 (0.33–1.12) | 0.108  |
|              | G/A-A/A         | 57  | 187     | 0.98 (0.70–1.37) | 0.904  | 38  | 48      | 0.72 (0.44–1.18) | 0.187  |
| rs2025327    | T               | 207  | 753     | 0.99 (0.63–1.57) | 0.975  | 16  | 27      | 0.55 (0.28–1.06) | 0.072  |
|              | T/T             | 91   | 333     | 1.04 (0.63–1.71) | 0.892  | 14  | 23      | 0.52 (0.24–1.10) | 0.085  |
|              | C/C             | 25   | 87      | 0.68 (0.08–5.92) | 0.275  | 1   | 2       | 0.40 (0.03–6.63) | 0.463  |
|              | C/A             | 44   | 144     | 1.13 (0.73–1.74) | 0.587  | 32  | 29      | 1.16 (0.61–2.20) | 0.658  |
|              | T/T             | 4    | 32      | 0.46 (0.16–1.34) | 0.152  | 4   | 5       | 0.83 (0.21–3.27) | 0.785  |
|              | C/T-T/T         | 48   | 176     | 1.00 (0.66–1.53) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
| rs55683539   | C               | 182  | 640     | 0.90 (0.64–1.26) | 0.535  | 40  | 39      | 1.03 (0.62–1.71) | 0.898  |
|              | T               | 52   | 208     | 1.04 (0.63–1.71) | 0.892  | 14  | 23      | 0.52 (0.24–1.10) | 0.085  |
|              | C/C             | 69   | 248     | 0.68 (0.08–5.92) | 0.275  | 1   | 2       | 0.40 (0.03–6.63) | 0.463  |
|              | C/T             | 44   | 144     | 1.13 (0.73–1.74) | 0.587  | 32  | 29      | 1.16 (0.61–2.20) | 0.658  |
|              | T/T             | 4    | 32      | 0.46 (0.16–1.34) | 0.152  | 4   | 5       | 0.83 (0.21–3.27) | 0.785  |
| rs2181559    | T               | 155  | 551     | 0.95 (0.70–1.29) | 0.725  | 53  | 66      | 0.72 (0.46–1.14) | 0.159  |
|              | T/T             | 46   | 183     | 1.42 (0.92–2.19) | 0.117  | 29  | 40      | 0.53 (0.27–1.04) | 0.064  |
|              | T/A             | 63   | 185     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
|              | T/A-A/A         | 71   | 242     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
| rs10965059   | C               | 210  | 691     | 0.95 (0.70–1.29) | 0.725  | 53  | 66      | 0.72 (0.46–1.14) | 0.159  |
|              | T               | 79   | 299     | 1.42 (0.92–2.19) | 0.117  | 29  | 40      | 0.53 (0.27–1.04) | 0.064  |
|              | C/C             | 46   | 183     | 1.42 (0.92–2.19) | 0.117  | 29  | 40      | 0.53 (0.27–1.04) | 0.064  |
|              | C/T             | 63   | 185     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
|              | T/T             | 71   | 242     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
| rs10965064   | T               | 210  | 691     | 0.95 (0.70–1.29) | 0.725  | 53  | 66      | 0.72 (0.46–1.14) | 0.159  |
|              | C               | 79   | 299     | 1.42 (0.92–2.19) | 0.117  | 29  | 40      | 0.53 (0.27–1.04) | 0.064  |
|              | C/C             | 46   | 183     | 1.42 (0.92–2.19) | 0.117  | 29  | 40      | 0.53 (0.27–1.04) | 0.064  |
|              | C/T             | 63   | 185     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |
|              | T/T             | 71   | 242     | 1.20 (0.79–1.83) | 0.986  | 36  | 34      | 1.11 (0.60–2.05) | 0.747  |

SNP Single nucleotide polymorphism, CI Confidence interval, OR Odds ratio

*p values were calculated by logistic regression adjusted by age and gender

*indicates statistical strongly significant (p < 0.01)
Table 6  Relationships of MIR31HG SNPs with SONFH risk stratified by course and bilateral

| SNP          | Allele/Genotype | Case 1 (course > 29 month) | Case 2 (course ≤ 29 month) | OR (95% CI) | p       | Cases with bilateral | Control OR (95% CI) | p       |
|--------------|-----------------|----------------------------|----------------------------|-------------|---------|----------------------|---------------------|---------|
| rs1332184    | G               | 95                         | 207                        | 1           | 216     | 746                  | 1                   |         |
|              | A               | 27                         | 71                         | 0.83 (0.50–1.37) | 0.466   | 70                   | 268                 | 0.90 (0.67–1.22) | 0.506   |
|              | G/G             | 35                         | 74                         | 1           | 77      | 276                  | 1                   |         |
|              | G/A             | 25                         | 59                         | 0.10 (0.53–1.88) | 0.987   | 62                   | 194                 | 1.10 (0.74–1.63) | 0.650   |
|              | A/A             | 1                          | 6                          | 0.27 (0.03–2.45) | 0.246   | 4                    | 37                  | 0.38 (0.13–1.14) | 0.084   |
|              | G/A-A/A         | 26                         | 65                         | 0.91 (0.49–1.70) | 0.764   | 66                   | 231                 | 0.98 (0.67–1.45) | 0.935   |
| rs72703442   | C               | 106                        | 237                        | 1           | 244     | 849                  | 1                   |         |
|              | A               | 16                         | 41                         | 0.87 (0.47–1.62) | 0.667   | 42                   | 165                 | 0.89 (0.61–1.28) | 0.517   |
|              | C/C             | 45                         | 100                        | 1           | 102     | 352                  | 1                   |         |
|              | C/A             | 16                         | 37                         | 0.98 (0.48–1.97) | 0.949   | 40                   | 145                 | 0.93 (0.60–1.43) | 0.727   |
|              | A/A             | 0                          | 2                          | /           | 1       | 10                   | 0.40 (0.05–3.27) | 0.393   |
|              | C/A-A/A         | 16                         | 39                         | 0.90 (0.45–1.81) | 0.764   | 41                   | 155                 | 0.90 (0.59–1.37) | 0.610   |
| rs2025327    | T               | 105                        | 252                        | 1           | 259     | 892                  | 1                   |         |
|              | C               | 17                         | 26                         | 1.57 (0.82–3.01) | 0.173   | 27                   | 124                 | 0.75 (0.48–1.16) | 0.197   |
|              | T/T             | 44                         | 115                        | 1           | 117     | 391                  | 1                   |         |
|              | T/C             | 17                         | 22                         | 2.14 (1.01–4.53) | 0.046*  | 25                   | 110                 | 0.70 (0.43–1.16) | 0.164   |
|              | C/C             | 0                          | 2                          | /           | 1       | 7                    | 0.49 (0.06–4.09) | 0.506   |
|              | T/C-C/C         | 17                         | 24                         | 1.93 (0.92–4.02) | 0.081   | 26                   | 117                 | 0.69 (0.42–1.13) | 0.136   |
| rs55683539   | C               | 92                         | 216                        | 1           | 220     | 767                  | 1                   |         |
|              | T               | 30                         | 62                         | 1.14 (0.69–1.87) | 0.617   | 66                   | 247                 | 0.93 (0.68–1.27) | 0.654   |
|              | C/C             | 33                         | 83                         | 1           | 82      | 297                  | 1                   |         |
|              | C/T             | 26                         | 50                         | 1.35 (0.71–2.57) | 0.355   | 56                   | 173                 | 1.16 (0.77–1.73) | 0.481   |
|              | T/T             | 2                          | 6                          | 0.80 (0.15–4.37) | 0.796   | 5                    | 37                  | 0.52 (0.19–1.41) | 0.198   |
|              | C/T-T/T         | 28                         | 56                         | 1.29 (0.69–2.41) | 0.422   | 61                   | 210                 | 1.05 (0.71–1.55) | 0.812   |
| rs2181559    | T               | 75                         | 191                        | 1           | 193     | 651                  | 1                   |         |
|              | A               | 45                         | 87                         | 1.37 (0.84–2.06) | 0.228   | 91                   | 365                 | 0.84 (0.64–1.11) | 0.225   |
|              | T/T             | 22                         | 65                         | 1           | 63      | 213                  | 1                   |         |
|              | T/A             | 31                         | 61                         | 1.68 (0.85–3.31) | 0.135   | 67                   | 225                 | 1.04 (0.69–1.56) | 0.854   |
|              | A/A             | 7                          | 13                         | 1.54 (0.53–4.48) | 0.427   | 12                   | 70                  | 0.53 (0.27–1.07) | 0.078   |
|              | T/A-A/A         | 38                         | 74                         | 1.65 (0.87–3.15) | 0.128   | 79                   | 295                 | 0.91 (0.62–1.35) | 0.640   |
| rs10965059   | C               | 108                        | 251                        | 1           | 257     | 829                  | 1                   |         |
|              | T               | 14                         | 27                         | 1.21 (0.61–2.39) | 0.592   | 29                   | 169                 | 0.56 (0.36–0.84) | 0.005*  |
|              | C/C             | 48                         | 116                        | 1           | 119     | 340                  | 1                   |         |
|              | C/T             | 12                         | 19                         | 1.54 (0.68–3.50) | 0.301   | 19                   | 149                 | 0.43 (0.25–0.74) | 0.002*  |
|              | T/T             | 1                          | 4                          | 0.87 (0.09–8.29) | 0.900   | 5                    | 10                  | 1.55 (0.49–4.89) | 0.452   |
|              | C/T-T/T         | 13                         | 23                         | 1.45 (0.66–3.16) | 0.357   | 24                   | 159                 | 0.51 (0.31–0.83) | 0.007*  |
| rs10965064   | C               | 78                         | 179                        | 1           | 184     | 640                  | 1                   |         |
|              | G               | 44                         | 99                         | 1.02 (0.66–1.59) | 0.931   | 102                  | 376                 | 0.94 (0.72–1.24) | 0.677   |
|              | C/C             | 21                         | 59                         | 1           | 55      | 203                  | 1                   |         |
|              | C/G             | 36                         | 61                         | 1.53 (0.79–2.97) | 0.212   | 74                   | 234                 | 1.11 (0.76–1.68) | 0.612   |
|              | G/G             | 4                          | 19                         | 0.52 (0.15–1.76) | 0.290   | 14                   | 71                  | 0.73 (0.37–1.43) | 0.359   |
|              | C/G-G/G         | 40                         | 80                         | 1.29 (0.68–2.45) | 0.440   | 88                   | 305                 | 1.03 (0.69–1.53) | 0.896   |

SNP: Single nucleotide polymorphism, CI: Confidence interval, OR: Odds ratio
p values were calculated by logistic regression adjusted by age and gender
*indicates statistical significance (p < 0.05)
The frequent collapse of the femoral head and hip joint dysfunction makes the treatment of SONFH difficult [4, 19]. LncRNA consists of non-protein coding transcripts with approximately 200 nucleotides [6], which are drawn into various cellular processes such as chromatin remodelling, post-transcriptional processing and transcription process [20], involved in the occurrence, progression, and metastasis of human cancers, and played corresponding roles. Among those cancers, lncRNAs are more widely researched in osteosarcoma, including lncRNA-21A, UCA1, MEG3, HULC, and MIR31HG [21]. MIR31HG acts as an oncogene in osteosarcoma to promote tumor progression via regulation of tumor suppressor miR-361 and its target genes [9, 21]. Taken together, studying SONFH in the field of exploring lncRNAs is highly needed and promising. Moreover, according to our current research results, there is a significant correlation between MIR31HG polymorphism and SONFH susceptibility in the Chinese Han population.

### Table 7: Analysis of SNP-SNP interaction models using MDR method

| Model | Training Bal. Acc. | Testing Bal. Acc. | CVC | OR (95% CI) | p     |
|-------|-------------------|------------------|-----|-------------|-------|
| rs10965059 | 0.578            | 0.574            | 10/10 | 2.46 (1.61–3.77) | <0.0001 |
| rs2181559, rs10965059 | 0.598            | 0.577            | 7/10  | 2.60 (1.76–3.83) | <0.0001 |
| rs2025327, rs2181559, rs10965059 | 0.609            | 0.555            | 5/10  | 3.07 (2.03–4.65) | <0.0001 |
| rs1332184, rs2181559, rs10965059, rs10965064 | 0.634            | 0.523            | 7/10  | 2.93 (2.07–4.16) | <0.0001 |
| rs1332184, rs72703442, rs2181559, rs10965059, rs10965064 | 0.652            | 0.521            | 7/10  | 3.34 (2.37–4.72) | <0.0001 |
| rs1332184, rs72703442, rs55683539, rs2181559, rs10965059, rs10965064 | 0.666            | 0.542            | 7/10  | 3.79 (2.68–5.36) | <0.0001 |
| rs1332184, rs72703442, rs2025327, rs55683539, rs2181559, rs10965059, rs10965064 | 0.671            | 0.543            | 10/10 | 4.39 (3.01–6.40) | <0.0001 |

Bal. Acc. Balanced accuracy, CVC Cross-validation consistently, CI Confidence interval, OR Odds ratio

*p values were calculated by χ² test

*p < 0.01 indicates statistical strongly significant

Fig. 1 The tree diagram analysis among SNP interaction

Fig. 2 The linkage disequilibrium structure of seven SNPs in the MIR31HG gene. The numbers in squares are $D'$ values
Our research is the first to find a significant risk connection between \textit{MIR31HG} genetic variations and SONFH susceptibility in the Han population in China. The locus in \textit{MIR31HG} has only been reported in IgAN currently [8]. In future studies, if SNP assessment is used as a type of risk marker, patients with high risk of ONFH can be identified through screening, and the dosage of steroids then can be differentiated based on individual differences, which can prevent the development of SONFH [1].

Therefore, we are committed to investigating the association between the \textit{MIR31HG} gene polymorphism and the risk of SONFH disease. Our study results of genotyping showed that rs10965059-T allele frequency in the case group (0.103) was lower than that in the control group (0.169), and the reduced risk of SONFH was found. The stratified analysis results showed that rs10965059 was associated with the reduced risk of SONFH in subjects aged >40 years ($p < 0.001$), and males ($p < 0.001$). Consequently, we speculated that age and gender may interact with \textit{MIR31HG} genetic polymorphisms on SONFH occurrence. Moreover, rs10965059 was associated with the reduced risk of bilateral SONFH ($p = 0.002$).

However, there are other candidate genes in the research on SONFH, and the research on \textit{MIR31HG} is relatively rare. Nonetheless, our current work has some limitations. First of all, the relationship between SNPs and SONFH risk was investigated in the early stage, and the relationship among gene-environment interactions needs to be studied in the later work. Second, we have successfully demonstrated the relationship between \textit{MIR31HG} polymorphisms and SONFH, and the molecular mechanism of SONFH will be studied in the future work. Patients were all from Shandong, Inner Mongolia and adjacent areas, which are in low population mobility. It is easy to carry out population-based research. As is known to all, this is the first study to probe into the effect of \textit{MIR31HG} mutation on SONFH, which may provide a scientific basis for future research of \textit{MIR31HG} on the molecular mechanism of SONFH.

\textbf{Conclusion}
Our study indicates that rs10965059 in \textit{MIR31HG} is a protective SNP for SONFH, which offers a new insight for the molecular mechanism and provides a new major candidate gene in the study progression of SONFH. In the future, we will continue to collect samples to expand the sample size for confirming our results in a larger cohort of subjects.

\textbf{Supplementary Information}
The online version contains supplementary material available at https://doi.org/10.1186/s12891-022-05785-w.

\textbf{Additional file 1: Supplementary Table 1. Primers used for this study}

\begin{table}[h!]
\centering
\caption{Relationships of \textit{MIR31HG} haplotypes with SONFH risk}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Blocks & SNPs & Haplotype & Frequency & Crude analysis & Adjusted by age and gender \\
& & & & & \\
& & & & OR (95\% CI) & $p$ & OR (95\% CI) & $p$ \\
\hline
Block 1 & rs72703442|rs2025327|rs55683539 & ATT & 0.138 & 0.159 & 0.84 (0.60–1.18) & 0.305 & 0.82 (0.58–1.17) & 0.271 \\
& rs72703442|rs2025327|rs55683539 & CTT & 0.093 & 0.084 & 1.11 (0.75–1.65) & 0.607 & 1.16 (0.76–1.75) & 0.497 \\
& rs72703442|rs2025327|rs55683539 & CCC & 0.108 & 0.122 & 0.86 (0.60–1.25) & 0.435 & 0.82 (0.56–1.21) & 0.319 \\
& rs72703442|rs2025327|rs55683539 & CTC & 0.343 & 0.369 & 0.89 (0.70–1.14) & 0.360 & 0.88 (0.68–1.12) & 0.300 \\
\hline
\end{tabular}
\end{table}

\textit{MIR31HG} polymorphism and SONFH susceptibility.

\textit{MIR31HG} haplotypes with SONFH risk.

\begin{table}[h!]
\centering
\caption{Relationships of \textit{MIR31HG} haplotypes with SONFH risk}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Blocks & SNPs & Haplotype & Frequency & Crude analysis & Adjusted by age and gender \\
& & & & & \\
& & & & OR (95\% CI) & $p$ \\
\hline
Block 1 & rs72703442|rs2025327|rs55683539 & ATT & 0.138 & 0.159 & 0.84 (0.60–1.18) \\
& rs72703442|rs2025327|rs55683539 & CTT & 0.093 & 0.084 & 1.11 (0.75–1.65) \\
& rs72703442|rs2025327|rs55683539 & CCC & 0.108 & 0.122 & 0.86 (0.60–1.25) \\
& rs72703442|rs2025327|rs55683539 & CTC & 0.343 & 0.369 & 0.89 (0.70–1.14) \\
\hline
\end{tabular}
\end{table}

\textit{SNP} Single nucleotide polymorphism, CI Confidence interval, OR Odds ratio $p$ values were calculated by logistic regression adjusted by age and gender.

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\textbf{Authors’ contributions}
Yuan Wang: drafting and revising important content; Yexin Wang, Da Liang, and Hongtao Hu: performed the experiments; Guangwei Li, Xiaoguang Meng and Bing Zhu: analyzed the data; Wei Zhong: conceived and designed the experiments. All authors have read and approved the manuscript.

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\textbf{Availability of data and materials}
The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

\textbf{Declarations}
Ethics approval and consent to participate
The protocol for this study was approved by the Ethics Committee of the Affiliated Hospital of Weifang Medical University and Second Affiliated Hospital of Inner Mongolia Medical University, and was in line with the Helsinki declaration. And the participant’s signature informed consent was received.
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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