Significant association between \textit{RETN} genetic polymorphisms and alcohol-induced osteonecrosis of femoral head

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**Abstract**

**Background:** Alcohol-induced osteonecrosis of femoral head (ONFH) is a complex disease and genetic factors are one of the causes. The purpose of this study is to investigate the effects of \textit{RETN} (resistin; OMIM: 605565) and \textit{LDLR} (low density lipoprotein receptor; OMIM: 606945) polymorphisms on the risk of alcohol-induced ONFH in Chinese Han population.

**Methods:** A case–control study including 201 patients and 201 controls was designed. Seven single nucleotide polymorphisms (SNPs) in \textit{RETN} gene and four SNPs in \textit{LDLR} gene were genotyped using Agena MassARRAY platform. In allele model and genetic model, chi-square test and logistic regression were used to study the associations between these SNPs and ONFH susceptibility. In addition, the relationships between these SNPs, clinical phenotypes, and blood lipid level with one-way analysis of variance were analyzed.

**Results:** In the allele model, rs7408174 and rs3745369 in \textit{RETN} were associated with increased risk of alcohol-induced ONFH, whereas rs34861192 and rs3219175 in \textit{RETN} showed reduced risk of alcohol-induced ONFH. In the genetic model, rs7408174 was associated with increased risk of alcohol-induced ONFH in dominant model and log-additive model. Rs3745369 showed an increased risk in codominant model, recessive model, and log-additive model. Rs34861192 showed a decreased risk in codominant model, dominant model, and log-additive model, and rs3219175 showed a decreased risk in dominant model and log-additive model. The rs3745368 in \textit{RETN} was associated with the clinical stage of the disease.

**Conclusion:** These results suggest that \textit{RETN} genetic polymorphisms are associated with the susceptibility of alcohol-induced ONFH in Chinese Han population.

**KEYWORDS**  
alcohol-induced osteonecrosis of femoral head, \textit{LDLR}, \textit{RETN}, single nucleotide polymorphisms
1 | INTRODUCTION

Osteonecrosis of femoral head (ONFH) is a complicated disease in clinic and is usually divided into traumatic and non-traumatic types. Alcohol-induced ONFH caused by excessive alcohol intake over a long period of time is a type of non-traumatic ONFH. The etiology of alcohol-induced ONFH is complicated. Early diagnosis of this disease is difficult, and the complex pathological process is often manifested due to abnormal lipid metabolism and inflammation. Excessive alcohol drinking may result in dyslipidemia, abnormal differentiation of bone marrow mesenchymal stem cells (BMSCs) and bone metabolic disorders. Moreover, alcohol has a significant dose effect on bone homeostasis (Gaddini, Turner, Grant, & Iwaniec, 2016). However, we found in clinical work that only a portion of people who drank similar amounts of alcohol developed ONFH.

Some studies have suggested that the ONFH disease is caused by the interaction between genetic and environmental factors (Song et al., 2017; Wang, Azeddine, et al., 2018; Zhou, Qu, Lv, & Zhu, 2018). Therefore, genetic polymorphisms involved in alcohol metabolism, lipid metabolism, bone and circulatory homeostasis may lead to differences in susceptibility to alcohol-induced ONFH (Cui, Kaisaierjiang, Cao, Wu, & Lv, 2014; Hadjiegiorgiou et al., 2008).

RETN (resistin; OMIM: 605565), located on chromosome 19, encodes resistin. Resistin affects bone metabolism and in vitro studies have shown that it can promote bone remodeling (Thommesen et al., 2006). Some scholars believe that there is a negative correlation between resistin content and bone density (Oh et al., 2005; Pedone et al., 2013; Zhang et al., 2010). Plasma resistin is also correlated with insulin resistance, lower HDL-C, and high hs-CRP (Osawa et al., 2007). Studies have shown that the polymorphisms of RETN have significant effect on plasma resistin concentration (Asano et al., 2010). In recent years, some scholars have found that the polymorphism of human RETN is also associated with osteoarthritis and rheumatoid arthritis (Hamalainen, Solovieva, Vehmas, Hirvonen, & Leino-Arjas, 2018; Junker et al., 2017; Wang, Tang, et al., 2018).

LDLR (low density lipoprotein receptor; OMIM: 606945) is located on chromosome 19, which plays a critical role in regulating the plasma cholesterol level. Mutations in LDLR result in elevated cholesterol (Hobbs, Brown, Russell, Davignon, & Goldstein, 1987). Cholesterol is one of the risk factors for osteoporosis and cholesterol metabolic disorders is detrimental to bone health (Li et al., 2018; Mandal, 2015). Alterations in the function of the LDLR affected bone development and homeostasis (Yang & Williams, 2017).

There are few studies on the association of RETN and LDLR with alcohol-induced ONFH. This work studies the association between RETN and LDLR genetic polymorphisms and the susceptibility of alcohol-induced ONFH in Chinese Han population, which can guide the identification of high-risk alcohol-induced ONFH patients.

2 | MATERIALS AND METHODS

2.1 | Ethics approval and consent to participate

This study was conducted under the approval of the Second Affiliated Hospital of Inner Mongolia Medical University of Inner Mongolia, China and Zhengzhou Traditional Chinese Medicine (TCM) Traumatology Hospital of Henan Province, China. Blood samples were collected at the time of initial diagnosis after informed consent was obtained from all participants.

2.2 | Subjects

All the 402 individuals including 201 cases and 201 controls were male and members of Chinese Han population living in Henan Province in China. Individuals who disagree to participate in this study were excluded.

The cases in our research satisfy the following criteria: (a) Patients should have a history of alcohol intake >400 ml/week (320 g/week, any type of alcoholic beverage) of pure ethanol for more than 6 months; (b) ONFH should be diagnosed within 1 year after the alcohol intake with this dose; (c) Patients should not have direct trauma and other risk factors (such as history of taking corticosteroids, cardiovascular diseases, congenital diseases, human immunodeficiency virus infection, diabetes mellitus, renal dysfunction, cancers, and familial hereditary diseases); (c) The diagnosis and staging of alcohol-induced ONFH was evaluated by X-ray, computed tomography (CT), nuclear magnetic resonance imaging (MRI); The selection criteria for control: (a) The age of the control group was matched with that of the case group; (b) The controls should have a history of alcohol intake >400 ml/week (320 g/week, any type of alcoholic beverage) of pure ethanol for more than 6 months; (c) No ONFH occurred; (d) Other factors were excluded (history of taking corticosteroids, cardiovascular diseases, congenital diseases, human immunodeficiency virus infection, diabetes mellitus, renal dysfunction, cancers, and familial hereditary diseases).

2.3 | SNP selection and genotyping

The GenBank reference sequence and version number: RETN (Reference Sequence and version number: NG_023447.1; accession: NG_023447), LDLR (Reference Sequence and version number: NG_009060.1; accession: NG_009060). All eleven SNPs in RETN and LDLR with minor allele...
frequencies >5% were selected from the 1,000 Genomes Project databases (http://www.internationalgenome.org/). Blood samples were collected in tubes containing ethylene diaminetetraacetic acid (EDTA) and stored at −80°C after centrifuging at 2,000 rpm for 10 min. Genomic DNA was extracted from the peripheral blood of the participants using the GoldMag whole blood genomic DNA purification kit (GoldMag Co. Ltd., Xi’an, China). DNA concentration was determined by using a NanoDrop 2000C spectrophotometer (Thermo Scientific, Waltham, MA). The genotyping primers were designed with the Agena MassARRAY Assay Design 3.0 Software. Agena Typer 4.0 Software was used for managing the related data and the Agena MassARRAY RS1000 was used for genotyping.

TABLE 1 Characteristics of the participants

| Variables | Mean ± SD | Controls (n = 201) | p value |
|-----------|-----------|-------------------|---------|
| Age (years) | 42.68 ± 12.88 | 43.80 ± 8.38 | 0.302 |
| TC (mmol/L) | 4.65 ± 0.92 | 4.66 ± 0.88 | 0.938 |
| TG (mmol/L) | 1.89 ± 1.28 | 2.10 ± 1.12 | 0.084 |
| HDL-C (mmol/L) | 1.04 ± 0.24 | 1.08 ± 0.19 | 0.099 |
| LDL-C (mmol/L) | 2.73 ± 0.85 | 2.71 ± 0.74 | 0.869 |
| TC/HDL-C | 4.62 ± 1.15 | 4.38 ± 0.81 | 0.017* |
| TG/HDL-C | 1.98 ± 1.58 | 2.02 ± 1.14 | 0.759 |
| LDL-C/HDL-C | 2.70 ± 0.86 | 2.56 ± 0.72 | 0.086 |

Clinical stages
- Stage II: 54
- Stage III: 89
- Stage IV: 58

Hip lesions
- Unilateral: 44
- Bilateral: 157

Note: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

TABLE 2 Basic information of candidate SNPs in this study

| SNP | Gene | Chromosome | alleles A/B | MAF case | MAF control | p value for HWE | ORs | 95% CI | p value |
|-----|------|------------|-------------|----------|-------------|----------------|------|--------|---------|
| rs7408174 | RETN | 19 | C/T | 0.271 | 0.206 | 1.000 | 1.43 | 1.03 | 1.98 | 0.032* |
| rs34861192 | RETN | 19 | A/G | 0.135 | 0.199 | 0.826 | 0.63 | 0.43 | 0.92 | 0.016* |
| rs3219175 | RETN | 19 | A/G | 0.144 | 0.201 | 0.826 | 0.67 | 0.46 | 0.97 | 0.032* |
| rs3745367 | RETN | 19 | A/G | 0.373 | 0.423 | 0.885 | 0.81 | 0.61 | 1.08 | 0.150 |
| rs3745368 | RETN | 19 | A/G | 0.173 | 0.138 | 0.547 | 1.30 | 0.88 | 1.91 | 0.181 |
| rs3745369 | RETN | 19 | C/G | 0.381 | 0.313 | 0.254 | 1.35 | 1.01 | 1.81 | 0.045* |
| rs1477341 | RETN | 19 | A/T | 0.526 | 0.463 | 0.887 | 1.29 | 0.97 | 1.71 | 0.075 |
| rs12611067 | LDLR | 19 | T/G | 0.319 | 0.321 | 0.194 | 0.99 | 0.74 | 1.34 | 0.951 |
| rs14158 | LDLR | 19 | A/G | 0.400 | 0.388 | 0.882 | 1.05 | 0.79 | 1.40 | 0.718 |
| rs2738464 | LDLR | 19 | G/C | 0.278 | 0.294 | 0.125 | 0.93 | 0.68 | 1.26 | 0.630 |
| rs2738465 | LDLR | 19 | G/A | 0.485 | 0.495 | 0.480 | 0.96 | 0.73 | 1.27 | 0.778 |

Note: Reference Sequence and version number (RETN: NG_023447.1; LDLR: NG_009060.1).

Abbreviations: SNP, single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; MAF, minor allele frequency.

*p was calculated by Chi-squared test.

*p < 0.05 indicates statistical significance.
In this research, online database (http://www.gtexportal.org/) was used to investigate the association between the 11 selected SNPs and the expression of two genes.

### RESULTS

This study involved 402 male subjects as shown in Table 1, including 201 cases and 201 controls. The mean ages were 42.68 ± 12.88 years for the cases and 43.80 ± 8.38 years for the controls. In the case group, there were 54 cases of stage II, 89 cases of stage III, 58 cases of stage IV, 44 cases of unilateral side and 157 cases of bilateral side. No significant differences in the distributions of age, TC, TG, HDL‐C, LDL‐C, TG/HDL‐C, and LDL‐C/HDL‐C between the cases and the controls were observed from the statistical analysis. However, there was a significant difference in TC/HDL‐C between the cases and the controls.

The basic information of all SNPs is shown in Table 2. The genotype distributions were in Hardy–Weinberg
equilibrium for the case and control groups ($p > 0.05$). Two SNPs, rs7408174 and rs3745369 in \textit{RETN}, were associated with the increased risk of alcohol-induced ONFH (OR = 1.43, 95% CI: 1.03–1.98, $p = 0.032$; OR = 1.35, 95% CI: 1.01–1.81, $p = 0.045$). On the other hand, rs34861192 and rs3219175 in \textit{RETN} showed reduced risk (OR = 0.63, 95% CI: 0.43–0.92; $p = 0.016$; OR = 0.67, 95% CI: 0.46–0.97; $p = 0.032$) of alcohol-induced ONFH.

Genetic models were used to compare the SNP genotypes and the risk of alcohol-induced ONFH. The results of logistic regression analysis for each genetic model are shown in Table 3. Four SNPs in \textit{RETN} had strong associations with alcohol-induced ONFH in genetic models after they were adjusted by age. It was discovered that rs7408174 was associated with increased risk of alcohol-induced ONFH in dominant model (OR = 1.57, 95% CI: 1.05–2.34, $p = 0.028$) and log-additive

| Table 4 | The association of genotypes in \textit{RETN} and \textit{LDLR} genes with the clinical phenotypes |
|---------|---------------------------------------------------------------|
| Gene    | SNP               | genotype | Hip lesions | Clinical stages | |
|         |                   |          | Unilateral | Bilateral | $p$ | Stage II | Stage III | Stage IV | $p$ |
| \textit{RETN} | rs7408174 | CC      | 5          | 8        | 0.268 | 2        | 7         | 4        | 0.884 |
|         | CT      | 19      | 64         | 22       | 36     | 25       |           |          |      |
|         | TT      | 20      | 85         | 30       | 46     | 29       |           |          |      |
|         | rs34861192 | AA    | 0          | 3        | 0.436 | 1        | 2         | 0        | 0.698 |
|         | AG      | 8       | 39         | 14       | 18     | 15       |           |          |      |
|         | GG      | 34      | 112        | 38       | 68     | 40       |           |          |      |
|         | rs3219175 | AA   | 0          | 3        | 0.543 | 1        | 2         | 0        | 0.489 |
|         | AG      | 10      | 42         | 14       | 19     | 19       |           |          |      |
|         | GG      | 34      | 112        | 39       | 68     | 39       |           |          |      |
|         | rs3745367 | AA    | 3          | 23       | 0.217 | 7        | 11        | 8        | 0.338 |
|         | AG      | 20      | 78         | 32       | 38     | 28       |           |          |      |
|         | GG      | 21      | 56         | 15       | 40     | 22       |           |          |      |
|         | rs3745368 | AA   | 3          | 4        | 0.396 | 5        | 1         | 1        | 0.022* |
|         | AG      | 12      | 43         | 10       | 31     | 14       |           |          |      |
|         | GG      | 29      | 109        | 39       | 56     | 43       |           |          |      |
|         | rs3745369 | CC    | 5          | 29       | 0.547 | 10       | 14        | 10       | 0.976 |
|         | CG      | 19      | 61         | 20       | 35     | 25       |           |          |      |
|         | GG      | 18      | 62         | 22       | 36     | 22       |           |          |      |
|         | rs1477341 | AA    | 14         | 40       | 0.243 | 13       | 21        | 20       | 0.125 |
|         | AT      | 15      | 76         | 31       | 39     | 21       |           |          |      |
|         | TT      | 12      | 32         | 7        | 21     | 16       |           |          |      |
| \textit{LDLR} | rs12611067 | GG | 20         | 68       | 0.739 | 27       | 40        | 21       | 0.306 |
|         | TG      | 19      | 72         | 19       | 41     | 31       |           |          |      |
|         | TT      | 5       | 12         | 6        | 5      | 6        |           |          |      |
|         | rs14158 | AA      | 9          | 20       | 0.409 | 9        | 8         | 12       | 0.158 |
|         | AG      | 20      | 83         | 23       | 49     | 31       |           |          |      |
|         | GG      | 15      | 54         | 22       | 32     | 15       |           |          |      |
|         | rs2738464 | CC    | 27         | 72       | 0.19  | 28       | 40        | 31       | 0.784 |
|         | GC      | 14      | 71         | 23       | 38     | 24       |           |          |      |
|         | GG      | 2       | 10         | 3        | 7      | 2        |           |          |      |
|         | rs2738465 | AA    | 13         | 37       | 0.489 | 15       | 18        | 17       | 0.621 |
|         | GA      | 24      | 83         | 26       | 50     | 31       |           |          |      |
|         | GG      | 7       | 37         | 13       | 21     | 10       |           |          |      |

Note: Reference Sequence and version number (\textit{RETN}: NG_023447.1; \textit{LDLR}: NG_009060.1). $p$ value was calculated by Chi-squared test. *$p < 0.05$ indicates statistical significance.
TABLE 5  Comparison of lipids levels between each genotype

| SNP          | TC (mmol/L) | TG (mmol/L) | HDL-C (mmol/L) | LDL-C (mmol/L) | TC/HDL-C | TG/HDL-C | LDL-C/HDL-C |
|--------------|-------------|-------------|----------------|----------------|----------|----------|-------------|
| rs7408174    |             |             |                |                |          |          |             |
| CC (n = 13)  | 4.49 ± 0.88 | 1.76 ± 0.89 | 1.02 ± 0.26    | 2.66 ± 0.87    | 4.52 ± 0.85 | 1.88 ± 1.12 | 2.61 ± 0.74 |
| CT (n = 83)  | 4.66 ± 0.95 | 2.07 ± 1.60 | 1.03 ± 0.22    | 2.75 ± 0.94    | 4.64 ± 1.08 | 2.19 ± 1.99 | 2.74 ± 0.90 |
| TT (n = 105) | 4.66 ± 0.91 | 1.77 ± 1.01 | 1.06 ± 0.25    | 2.72 ± 0.78    | 4.61 ± 1.25 | 1.82 ± 1.21 | 2.68 ± 0.85 |
| p            | 0.821       | 0.247       | 0.688          | 0.923          | 0.934    | 0.289    | 0.828       |
| rs34861192   |             |             |                |                |          |          |             |
| AA (n = 3)   | 4.68 ± 0.48 | 1.37 ± 0.42 | 1.08 ± 0.14    | 2.30 ± 0.85    | 4.36 ± 0.23 | 1.32 ± 0.56 | 2.22 ± 1.01 |
| AG (n = 47)  | 4.67 ± 1.02 | 2.02 ± 1.73 | 1.07 ± 0.26    | 2.78 ± 0.91    | 4.52 ± 1.25 | 2.08 ± 2.08 | 2.67 ± 0.92 |
| GG (n = 146) | 4.65 ± 0.91 | 1.86 ± 1.12 | 1.04 ± 0.23    | 2.73 ± 0.84    | 4.64 ± 1.14 | 1.94 ± 1.38 | 2.72 ± 0.85 |
| p            | 0.992       | 0.59        | 0.619          | 0.627          | 0.765    | 0.68     | 0.589       |
| rs3219175    |             |             |                |                |          |          |             |
| AA (n = 3)   | 4.68 ± 0.48 | 1.37 ± 0.42 | 1.08 ± 0.14    | 2.30 ± 0.85    | 4.36 ± 0.23 | 1.32 ± 0.56 | 2.22 ± 1.01 |
| AG (n = 52)  | 4.68 ± 1.00 | 1.96 ± 1.59 | 1.07 ± 0.26    | 2.74 ± 0.89    | 4.58 ± 1.26 | 2.01 ± 1.89 | 2.65 ± 0.89 |
| GG (n = 146) | 4.64 ± 0.90 | 1.88 ± 1.17 | 1.04 ± 0.23    | 2.73 ± 0.84    | 4.63 ± 1.13 | 1.98 ± 1.47 | 2.73 ± 0.85 |
| p            | 0.952       | 0.718       | 0.720          | 0.677          | 0.886    | 0.760    | 0.546       |
| rs3745368    |             |             |                |                |          |          |             |
| AA (n = 7)   | 4.53 ± 1.00 | 1.46 ± 0.73 | 1.02 ± 0.40    | 2.67 ± 0.89    | 4.85 ± 1.47 | 1.72 ± 1.31 | 2.79 ± 0.79 |
| AG (n = 55)  | 4.51 ± 0.81 | 1.74 ± 1.09 | 1.03 ± 0.18    | 2.70 ± 0.82    | 4.50 ± 1.02 | 1.81 ± 1.30 | 2.67 ± 0.76 |
| GG (n = 138) | 4.72 ± 0.96 | 1.97 ± 1.37 | 1.05 ± 0.25    | 2.75 ± 0.87    | 4.65 ± 1.19 | 2.05 ± 1.69 | 2.70 ± 0.91 |
| p            | 0.326       | 0.355       | 0.727          | 0.940          | 0.628    | 0.578    | 0.931       |
| rs3745369    |             |             |                |                |          |          |             |
| CC (n = 34)  | 4.53 ± 0.68 | 1.60 ± 0.87 | 1.04 ± 0.26    | 2.74 ± 0.63    | 4.56 ± 1.08 | 1.68 ± 1.03 | 2.74 ± 0.71 |
| CG (n = 80)  | 4.58 ± 1.00 | 1.96 ± 1.30 | 1.02 ± 0.22    | 2.65 ± 0.89    | 4.61 ± 1.17 | 2.09 ± 1.66 | 2.64 ± 0.83 |
| GG (n = 80)  | 4.76 ± 0.94 | 1.84 ± 1.20 | 1.07 ± 0.25    | 2.77 ± 0.92    | 4.64 ± 1.20 | 1.90 ± 1.42 | 2.72 ± 0.96 |
| p            | 0.364       | 0.345       | 0.548          | 0.662          | 0.942    | 0.366    | 0.798       |

Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.
model (OR = 1.47, 95% CI: 1.05–2.06, \( p = 0.024 \)). On the other hand, rs3219175 showed a decreased risk in dominant model (OR = 0.64, 95% CI: 0.42–0.97, \( p = 0.036 \)) and log-additive model (OR = 0.65, 95% CI: 0.44–0.95, \( p = 0.025 \)). In the other two SNPs, rs34861192 showed a reduced risk in codominant model (AG: OR = 0.62, 95% CI: 0.39–0.96, \( p = 0.032 \)), dominant model (OR = 0.59, 95% CI: 0.38–0.91, \( p = 0.017 \)), and log-additive model (OR = 0.61, 95% CI: 0.41–0.90, \( p = 0.013 \)). Rs3745369 showed an increased risk in codominant model (CC: OR = 2.50, 95% CI: 1.28–4.90, \( p = 0.007 \)), recessive model (CC: OR = 2.55, 95% CI: 1.35–4.81, \( p = 0.004 \)), and log-additive model (OR = 1.36, 95% CI: 1.01–1.82, \( p = 0.042 \)).

Correlation analysis between the genotypes and hip lesions, as well as clinical stages are shown in Table 4. The rs3745368 in RETN shows association with the clinical stages (\( p = 0.022 \)). Comparisons of lipid levels between each genotype are compared by Analysis of Variance (ANOVA), but no difference was found.
The Linkage analysis showed that two SNPs (rs34861192, rs3219175) in RETN (Figure 1) and three SNPs (rs14158, rs2738464, rs2738465) in LDLR exhibited significant linkage disequilibrium (Figure 2).

In Table 6, the risk alleles of rs34861192 \( (p = 4.0 \times 10^{-14}, p = 6.4 \times 10^{-5}) \) and rs3219175 \( (p = 1.6 \times 10^{-14}, p = 1.9 \times 10^{-9}) \) were associated with increased expression of RETN gene in the whole-blood and muscle-skeletal. In contrast, rs2738464 \( (p = 3.4 \times 10^{-5}) \) was associated with decreased expression of LDLR gene in muscle-skeletal.

4 | DISCUSSION

In this research, it was discovered that RETN genetic polymorphisms were associated with alcohol-induced ONFH risk among Chinese Han individuals. The rs3745368 was associated with the stages of the disease, and more patients with AA genotype were in Stage II than those in Stage III and Stage IV. However, more patients with AG and GG genotypes were in stage III. The SNPs (rs7408174, rs34861192, and rs3219175) are located in the upstream of RETN and rs3745369 is located in the downstream. The rs34861192 is associated with the level of serum insulin, glycemic index and cholesterol (Zhou, Chen, Ji, Luo, & Luo, 2018). The cholestrol of the case group was measured but no association with this SNP was found. In orthopedic diseases, individuals with the C allele of the SNP rs7408174 and the AG or A allele of the SNP rs3219175 are at a higher risk of developing rheumatoid arthritis compared with wild-type (Wang, Tang, et al., 2018). Plasma resistin level is strongly affected by rs34861192, rs3219175, and rs3745368 (Asano et al., 2010; Nakatochi et al., 2015). Using GTEx portal, RETN and LDLR expressions in different genotype individuals were compared and it was found that the risk alleles of rs34861192 and rs3219175 were associated with increased expression of RETN gene in the whole-blood and muscle-skeletal. We observed from Tables 2 and 3 that the number of GG genotypes in rs34861192 and rs3219175 in the case group was significantly higher than that in the control group, while the number of AG/AA genotypes was lower than that in the control group. This study provides new insights to facilitate early diagnosis and early prevention of ONFH, as well as for new candidate gene studies. The sample size will be increased to study the mechanism of RETN action in our future research.

5 | CONCLUSION

In summary, this study suggested that polymorphisms of RETN were associated with the alcohol-induced ONFH. The SNPs (rs7408174, rs34861192, rs3219175, and rs3745369) in RETN were associated with the risk of alcohol-induced ONFH. The rs3745368 was associated with the stage of the disease. The levels of TC/HDL-C in the case group was significantly lower than that in the control group. This study provides new insights to facilitate early diagnosis and early prevention of ONFH, as well as for new candidate gene studies. The sample size will be increased to study the mechanism of RETN action in our future research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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