**IL1R1 Polymorphisms are Associated with Lumbar Disc Herniation Risk in the Northwestern Chinese Han Population**

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**Background**: The aim of this study was to assess the association of single-nucleotide polymorphisms (SNPs) in *IL1R1* with the risk of lumbar disc herniation (LDH) in the Han population in northwest China.

**Material/Methods**: To estimate the association of *IL1R1* polymorphisms with LDH risk, Agena MassARRAY was used to determine the genotypes of 498 LDH patients and 463 controls. The association between *IL1R1* variants and LDH risk was examined by logistic regression analysis with adjustments for age and gender. Stratification analysis was observed between gender and age with polymorphisms of *IL1R1*. Haplotype construction and analysis in *IL1R1* were also applied to detect the potential association.

**Results**: The mutant homozygous genotype in codominant model (AA versus GG, OR=2.37, 95% CI: 1.08–5.21, \( P = 0.001 \)) and in recessive model (AA versus GG/GA, OR=2.82, 95% CI: 1.30–6.12, \( P = 0.005 \)) of rs956730 were associated with an increased LDH risk in males, while rs956730 heterozygous genotype under codominant model (AG versus GG, OR=0.65, 95% CI: 0.46–0.92, \( P = 0.001 \)) was a protective genotype in males. In addition, the recessive model (CT/CC versus TT, OR=3.43, 95% CI: 1.11–10.57, \( P = 0.020 \)) of rs10490571 was associated with an increased LDH risk among people older than 50 years of age.

**Conclusions**: This study demonstrated that genetic variants in the *IL1R1* genes were associated with LDH risk in the Han population of northwestern China.

**MeSH Keywords**: Lumbar Vertebrae • Polymorphism, Genetic • Receptors, Interleukin-1

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Background

Lumbar disc herniation (LDH) is a primary cause of low-back pain and unilateral leg pain, which is a degeneration and herniation of the nucleus pulposus of intervertebral disc [1]. It is the most common cause of activity limitation in individuals under 45 years of age [2]. With the clinical symptoms of lumbarcausal pain, it occurs 18% of the normal population on average in China [3]. Furthermore, more than 20% of patients need surgery to relieve prolonged or aggravated leg pain. Although some risk factors associated with LDH have been reported, its pathogenesis and etiology for the most part unclear. Objective epidemiological evidence suggests that the most determining individual factor in intervertebral disc degeneration is a family history [4]. Variotta et al. [5] showed that the risk of LDH is estimated to be approximately 5 times greater in patients who have a positive family history.

The intervertebral disc is a fibrocartilaginous tissue, which provides stability and flexibility to the spinal column. It is composed of a central nucleus pulposus and a ring-like fibrous annulus fibrosus mainly composed of type I collagen, type II collagen, and proteoglycan, and providing tensile strength [6,7]. Several researchers have reported that the excessive degradation and fibrosis of type I and type II collagen are the main causes of disc degeneration [8]. These catabolic processes are thought to be mediated by soluble factors such as the pleiotropic cytokine interleukin-1 (IL1).

Interleukin-1 (IL1) is involved in the inflammatory process of LDH. IL-1β is an active form of IL1 during the inflammatory response, and its expression is increased in LDH patients [9]. IL1R1 encodes cytokine receptor for IL1, through combining with IL-1 on the cell surface affects NF-κB signaling and upregulates inflammation [10,11]. Millward-Sadler and others have suggested the expression of IL1R1 and associated receptors in disc degeneration and shown that the IL1R1 is expressed by normal disc cells, with upregulation of IL1R1, during degeneration [12]. Christine et al. [7] confirmed that IL1 gene cluster mutation plays an important role in the pathogenesis of LDH. Nakki and colleagues [13] found that the genetic variation rs2287047 in IL1R1 gene was associated with severe hand osteoarthritis. Osteoarthritis and LDH can be seen as having a similar etiological pathway, both of which involve the degeneration of collagen [14]. There has been little research on IL1R1 gene polymorphism and LDH.

For the IL1R1 gene, Ren et al. [15] explored the association of the IL1R1 polymorphism (rs10490571, rs956730, and rs3917225) with tuberculosis risk. Xie et al. [16] revealed the association between the IL1R1 gene (rs10490571, rs12712127, rs956730, rs3917225, and rs3917318) and IgA nephropathy. Na et al. [17] analyzed the association between the IL1R1 gene and knee arthritis. However, the relationship between IL1R1 and LDH has not been reported, so this study aimed to investigate the association between 5 SNPs (rs10490571, rs12712127, rs956730, rs3917225, and rs3917318) within IL1R1 gene and LDH susceptibility in a Chinese Han population from north-west China. Our study will provide more significant evidence for further understanding of the LDH pathogenesis.

Material and Methods

Study participants

A case-control study involving a Chinese study population of 498 LDH patients and 463 controls was conducted at the Second Affiliated Hospital of Inner Mongolia Medical University and the Hohhot First Hospital. Inclusion criteria for LDH patients were: patients with typical clinical symptoms who were diagnosed with LDH by imaging studies such as computed tomography (CT), or magnetic resonance imaging (MRI). Symptoms of LDH included: 1) low back pain; 2) partial lumbar spine pain and local typical sciatica; 3) differences in straight leg elevation test and protuberance test; 4) range of LDH. Exclusion criteria for LDH patients were: patients with blood diseases, autoimmune diseases, tumors, trauma, rheumatoid arthritis, and related lumbar spine diseases, including lumbar spinal stenosis, congenital dysplasia of the spine, intraspinal tumor, spondylolisthesis, etc. [18].

The control group enrolled healthy volunteer with no physical history of sciatica and low back pain. The inclusion criteria of the control group were: 1) no history of waist and leg pain, family history; 2) no trauma, scoliosis, spondylolisthesis, osteoarthritis, rheumatism, rheumatoid arthritis, spinal instability; 3) no history of infection or cancer. All the participants were genetically unrelated ethnic Han Chinese and provided written informed consent for their participation in the present study. The protocols for this study were approved by the ethics committee of the Institutional Review Board of the Second Affiliated Hospital of Inner Mongolia Medical University.

SNP genotyping

We selected 5 candidate polymorphisms (rs10490571, rs12712127, rs956730, rs3917225, and rs3917318) in IL1R1 with minor allele frequency (MAF) more than 0.05 based on the global population from 1000 Genome Projects (https://www.internationalgenome.org/). Then we used Regulome DB (http://www.regulomedb.org/) and HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to predict SNP function [19]. Genomic DNA was prepared from peripheral blood samples using the Whole Blood Genomic DNA Extraction Kit (GoldMag Co. Ltd., Xi’an city, Shaanxi, China).
Table 1. Distributions of age and gender in LDH patients and controls.

| Variable | Cases | %   | Controls | %   | P   |
|----------|-------|-----|----------|-----|-----|
|          | 498   |     | 463      |     |     |
| Gender   |       |     |          |     |     |
| Female   | 200   | 40.2| 198      | 42.8| 0.413|
| Male     | 298   | 59.8| 265      | 57.2|     |
| Age      |       |     |          |     |     |
| ≤50      | 233   | 46.8| 216      | 46.7|     |
| >50      | 265   | 53.2| 247      | 53.3|     |
| Mean ±SD | 50.27 ± 12.53 |     | 50.65 ± 11.80 |     |     |

P<0.05 indicates statistical significance.

Results

Demographic characteristics

The study included 498 LDH patients (200 female and 298 male) and 463 controls (198 female and 265 male). No significant difference in gender and age was observed between the patient and control groups (P>0.05). The mean age ± standard deviation of 498 patients (age ≤50 years, 233 cases; age >50 years, 265 cases) was 50.27±12.53 years, and the average age of control group (age ≤50 years, 216 cases; age >50 years, 247 cases) was 50.65±11.8 years (Table 1).

Basic information and allele frequencies of IL1R1 polymorphisms are shown in Table 2. The genotype distribution of all SNPs in control participants met the HWE (P>0.05). To evaluate the function of the selected SNPs, we use Regulome DB Score and HaploReg for database analysis, results in Table 2 show that Regulome DB score of rs10490571 loci was 2b, and show that the SNP might affected the binding; the score of rs956730 was 4 and other 3 SNPs (rs12712127, rs3917225, and rs3917318) had Regulome DB score of 5, which were classified as “minimal binding evidence”. HaploReg function annotation results revealed that SNPs associated with LDH risk were successfully predicted to have biological functions, the results showed that rs10490571 might be a functional loci of DNAse, proteins bound, motifs changed, and selected eQTL hits; rs12712127 had the potential function of selected eQTL hits; rs956730 might have the function of DNAse and motifs changed; rs3917225 had the potential motifs changed and selected eQTL hits functions; and rs3917318 might have the function of DNAse and Motifs changed. Genotype frequencies of the IL1R1 polymorphisms were described in Supplementary Table 1. Unfortunately, there were no differences between SNPs in the IL1R1 gene and LDH risk (all P>0.05).

Controls

The study included 498 LDH patients (200 female and 298 male) and 463 controls (198 female and 265 male). No significant difference in gender and age was observed between the patient and control groups (P>0.05). The mean age ± standard deviation of 498 patients (age ≤50 years, 233 cases; age >50 years, 265 cases) was 50.27±12.53 years, and the average age of control group (age ≤50 years, 216 cases; age >50 years, 247 cases) was 50.65±11.8 years (Table 1).

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Table 2. Basic characteristics and allele frequencies of the 5 SNPs.

| SNP_ID   | Genes | Chr. | Allele (A/B) | MAF            | OR (95%CI)       | P      | Regulome DB Score | Function                                      |
|----------|-------|------|--------------|----------------|-----------------|--------|------------------|-----------------------------------------------|
| rs10490571 | IL1R1 | 2q12.1 | T/C          | 0.186          | 0.165           | 1.15   | (0.91–1.45)      | 0.238                                         |
|          |       |       |              |                |                 |        |                  | DNAse, Proteins bound, Motifs changed, Selected eQTL hits |
| rs12712127 | IL1R1 | 2q12.1 | G/A          | 0.234          | 0.210           | 1.15   | (0.93–1.43)      | 0.197                                         |
|          |       |       |              |                |                 |        |                  | Selected eQTL hits                           |
| rs956730  | IL1R1 | 2q12.1 | A/G          | 0.258          | 0.261           | 0.98   | (0.80–1.20)      | 0.889                                         |
|          |       |       |              |                |                 |        |                  | DNAse, Motifs changed                         |
| rs3917225 | IL1R1 | 2q12.1 | G/A          | 0.350          | 0.342           | 1.03   | (0.86–1.25)      | 0.699                                         |
|          |       |       |              |                |                 |        |                  | Motifs changed, Selected eQTL hits            |
| rs3917318 | IL1R1 | 2q12.1 | G/A          | 0.491          | 0.485           | 1.02   | (0.86–1.22)      | 0.789                                         |
|          |       |       |              |                |                 |        |                  | DNAse, Motifs changed                         |

SNP – single nucleotide polymorphism; Chr. – chromosome; A/B – minor/major; MAF – minor allele frequency; OR – odds ratio; 95%CI – 95% confidence interval. Score 2b indicated the SNP loci is likely to affect binding; score 4 and 5 indicated minimal binding evidence. P<0.05 indicates statistical significance.

Table 3. Stratified analysis between IL1R1 SNPs and gender associated with LDH risk.

| Model     | Genotype | Male | Adjusted by age OR (95%CI) | P     | Female | Adjusted by age OR (95%CI) | P     |
|-----------|----------|------|---------------------------|-------|--------|---------------------------|-------|
|           |          | Control | Case                     |       | Control | case                     |       |
| rs956730  | Codominant | GG      | 139                       | 176   | 1.00   | 107                       | 104   | 1.00                          |
|           |          | AG      | 116                       | 95    | 0.65   | (0.46–0.92)               | 0.001 | 0.580                         |
|           |          | AA      | 9                         | 27    | 2.37   | (1.08–5.21)               |       |                               |
|           | Dominant | GG      | 139                       | 176   | 1.00   | 107                       | 104   | 1.00                          |
|           |          | AG/AA   | 125                       | 122   | 0.77   | (0.55–1.08)               |       | 1.07                          |
|           |          |         | 91                        | 96    | 0.72   | (0.33–1.56)               |       |                               |
|           | Recessive | GG/AG   | 255                       | 271   | 1.00   | 182                       | 188   | 1.00                          |
|           |          | AA      | 9                         | 27    | 2.82   | (1.30–6.12)               | 0.005 | 0.400                         |
|           | Log-additive | AA      | 9                         | 27    | 0.98   | (0.75–1.28)               | 0.880 |                               |

OR – odds ratio; CI – confidence interval. P<0.05 indicates statistical significance. Bold values indicate a significant difference.

SNPs and the risk of LDH

In stratified analysis by gender, we found that the SNP IL1R1 rs956730 was not significant in females, while it was statistically significant in males (Table 3). The frequency of “AA” genotype in IL1R1 rs956730 was significantly different between patients and controls in males (9.1% versus 3.4%). Further, IL1R1 rs956730 was related to an increased risk of LDH based on the mutant homozgyous genotype “AA” in the codominant model (adjusted by age, AA versus GG, OR=2.37, 95% CI: 1.08–5.21, P=0.001) and in the recessive model (adjusted by age, GG/GA versus AA, OR=2.82, 95% CI: 1.30–6.12, P=0.005) in males. While the heterozygous genotype “AG” in the codominant model (adjusted by age, AG versus GG, OR=0.65, 95% CI: 0.46–0.92, P=0.001) of rs956730 was associated with a reduced risk of LDH in males. There was no significant association between polymorphisms in the remaining 4 loci (rs10490571, rs12712127, rs3917225, and rs3917318) and LDH susceptibility in gender-stratified analysis (all P>0.05, Supplementary Table 2).

In stratified analysis by age, we found that the SNP rs10490571 was not significant among people under 50 years of age, but was statistically significant in people older than 50 years of age (Table 4). The frequency of “TT” genotype in IL1R1 rs10490571 was differed significantly between patients and controls in people older than 50 years of age (5.3% versus 1.6%). And rs10490571 was correlated with an increased risk of LDH based on the results of the recessive model (adjusted by gender and age, CC/CT versus TT, OR=3.43, 95% CI: 1.11–10.57, P=0.020) in people older than 50 years of age. There was no significant association between polymorphisms in the other 4 loci (rs12712127, rs956730, rs3917225, and rs3917318) on the IL1R1 gene and susceptibility to LDH in age-stratified analysis (all P>0.05, Supplementary Table 3).
Finally, 2 *IL1R1* polymorphisms (rs10490571-rs12712127) mapped to a 9kb LD block and showed 2 haplotypes with frequencies of more than 0.05 in our study participants (Table 5). The red squares of the *IL1R1* LD block presented significant linkage between the 2 SNPs in Figure 1. Unfortunately, there was no significant difference among any of the *IL1R1* haplotype frequencies in patients and controls.

**Table 4.** Stratified analysis between *IL1R1* SNPs and age associated with LDH risk.

| Model     | Genotype | ≤50 Control | Case | Adjusted by age OR (95%CI) | P    | >50 Control | Case | Adjusted by age OR (95%CI) | P  |
|-----------|----------|-------------|------|---------------------------|------|-------------|------|---------------------------|----|
| rs956730  | Codominant | CC          | 153  | 157 | 1.00                   | 170  | 182 | 1.00                   | 0.054|
|           |          | CT          | 54   | 64  | 1.16 (0.76–1.77)       | 0.700| 73   | 69 | 0.89 (0.60–1.31)       | 0.0054|
|           |          | TT          | 9    | 12  | 1.31 (0.54–3.20)       | 4    | 14  | 3.31 (1.07–10.26)      | 0.0054|
| Dominant  |          | CC          | 153  | 157 | 1.00                   | 170  | 182 | 1.00                   | 0.095|
|           |          | CT/TT       | 63   | 76  | 1.18 (0.79–1.76)       | 77   | 83  | 1.01 (0.70–1.47)       | 0.095|
| Recessive |          | CC/CT       | 207  | 221 | 1.00                   | 243  | 251 | 1.00                   | 0.019|
|           |          | TT          | 9    | 12  | 1.26 (0.52–3.05)       | 4    | 14  | 3.43 (1.11–10.57)      | 0.019|
| Log-additive | --        | --          | ---  | ---  | 1.15 (0.83–1.60)       | 0.400| ---  | ---  | 1.14 (0.83–1.57)       | 0.410|

OR = odds ratio; CI = confidence interval. *P*<0.05 indicates statistical significance. Bold values indicate a significant difference.

**Table 5.** *IL1R1* haplotype frequencies and the association with LDH risk.

| rs10490571 | rs12712127 | Freq | Adjusted by age and gender OR (95%CI) | P-value |
|------------|------------|------|--------------------------------------|---------|
| C          | A          | 0.778|                                      | 1.00    |
| T          | G          | 0.175| 1.15 (0.91–1.45)                     | 0.230   |
| C          | G          | 0.047| 1.01 (0.68–1.52)                     | 0.940   |

OR = odds ratio; CI = confidence interval. *P*<0.05 indicates statistical significance.

**LDH and haplotypes at chromosome 2q12.1**

Finally, 2 *IL1R1* polymorphisms (rs10490571-rs12712127) mapped to a 9kb LD block and showed 2 haplotypes with frequencies of more than 0.05 in our study participants (Table 5). The red squares of the *IL1R1* LD block presented significant linkage between the 2 SNPs in Figure 1. Unfortunately, there was no significant difference among any of the *IL1R1* haplotype frequencies in patients and controls.

**Discussion**

It is well known that genetic factors play an important role in the development of LDH. However, only a few genetic risk factors for LDH have been identified in Chinese population. In our case-control study, we genotyped 5 SNPs of the *IL1R1* gene and evaluated their association with LDH risk in the Han population.

**Figure 1.** Haplotype block map for part of the SNPs in the *IL1R1* gene. LD is displayed by standard color schemes with bright red for very strong LD (LOD >2, D'=1), pink red (LOD >2, D' <1) and rose pink (LOD <2, D'=1) for partial linkage, and white (LOD <2, D' <1) for complete recombination.
population of northwest China. Our data showed that the SNPs rs956730 and rs10490571 were significantly associated with LDH susceptibility.

LDH is a degenerative disease that can cause neuropathic symptoms of spinal cord pain syndrome and nerve root ischemia. In addition, a variety of inflammatory related factors can also induce lumbar disc degeneration and nerve root pain, further accelerate inflammation and intervertebral disc formation, this vicious circle will deepen the lumbar disc degeneration and pain. IL1 is a protein coding gene, the protein encoded by this gene is a member of the interleukin 1 (IL1) cytokine family. This cytokine is a pleiotropic cytokine involved in various immune responses [23], inflammatory processes [24], and hematopoiesis [25]. Inflammation is regulated by a series of corresponding receptors, downstream signaling pathways and cytokines. It has been suggested that the polymorphism of IL1 genes is associated with rheumatoid arthritis [26]. Moen et al. [27] indicated that IL1 was associated with chronic lumbar radicular pain. IL1R1 belongs to IL1 family, and IL1R1 has reported to be involved in inflammatory reactions [13]. Latiano et al. [28] indicated that the genetic polymorphism of IL1R1 was correlated with inflammatory bowel disease. Na et al. [17] revealed that IL1R1 gene polymorphisms are associated with knee osteoarthritis risk. Therefore, we present a reasonable hypothesis related to IL1R1 in the pathogenesis of LDH. And in this study, we found that 2 SNPs (rs956730 and rs10490571) mutations in the IL1R1 gene are associated with susceptibility to LDH, validating our hypothesis.

In addition, there was a meaningful finding in our research that gender and age play important roles in the development of LDH. Within the disc structure, collagen is essential for the biomechanical stability and the overall property. Zhang et al. [29] found that age was inversely correlated with collagen synthesis, suggested that with the increase of age, the decreased collagen synthesis will affect the stability of intervertebral disc structure and lead to the occurrence of related diseases such as LDH. Boos et al. [30] reported that intervertebral disc degeneration is part of aging process. Compared with young people, the collagenous matrix in the discs of the elderly was significant changed [31]. Our studies showed that the recessive model of rs10490571 in the IL1R1 gene was associated with an increased LDH risk among people older than 50 years of age. It was consistent with previous research that hinted that people older than 50 years of age with rs10490571 mutations in IL1R1 were more likely to develop LDH. Moreover, according to the results of the Regulome DB database, it was speculated that rs10490571 is a binding site for various proteins such as HNF4A, MYBL2 and CDX2. CDX2 has been found to be involved in the body's immune response [32], and differences in CDX2 expression might lead to disease. Thus, we hypothesized that the rs10490571 mutation might affect the binding of CDX2 to cause differential expression of the protein, leading to the occurrence of LDH. Furthermore, our research indicated that the “AA” genotype model and recessive model of rs956730 in the IL1R1 gene was associated with increased LDH risk in males. This was similar to the research Miller et al. [33] conducted, who found that disc degeneration occurred significantly more often in males. Min et al. [34] proved that LDH was more likely to occur in males. The reason might be that males tend to perform heavier work and have a higher body weight than females. In addition, the Regulome DB database suggested that rs956730 is a binding site for the POLR2A protein, and it has been reported that POLR2A is involved in neuroinflammatory responses [35,36]. Therefore, we speculated that the pathogenesis of LDH might be related to the change of POLR2A expression caused by rs956730 locus variation.

Unfortunately, we did not find a significant association between the other 3 SNPs (rs12712127, rs3917225, and rs3917318) on the IL1R1 gene and susceptibility to LDH. Na et al. [17] also found that they were not significantly associated with knee arthritis. The reason for this phenomenon might be the limitations of the sample size of this study. In future studies, we will increase the sample size for further verification.

Conclusions

Our study demonstrated a significant association between the IL1R1 gene polymorphism and susceptibility to LDH in the Han population of northwestern China, especially the mutations of rs956730 and rs10490571 were found to be significantly associated with the susceptibility of LDH, which might provide new insights into therapeutic targets for LDH.

Ethics approval and consent to participate

This study was approved by the ethics committee of The Second Affiliated Hospital of Inner Mongolia Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants were informed both in writing and verbally to the procedures and purpose of the study and signed informed consent documents.

Acknowledgements

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Conflicts of interest

None.
### Supplementary Table 1. *IL1R1* SNP genotypes and the risk of LDH.

| Model     | Genotype | Control | Case | Crude OR (95%CI) | P-value | Adjust by gender and age OR (95%CI) | P-value |
|-----------|----------|---------|------|------------------|---------|------------------------------------|---------|
| rs10490571 | Codominant | CC      | 323 (69.8%) | 339 (68.1%) | 1.00 | 1.00 |
|           |          | CT      | 127 (27.4%) | 133 (26.7%) | 1.00 (0.75–1.33) | 0.160 | 1.00 (0.75–1.34) | 0.160 |
|           |          | TT      | 13 (2.8%) | 26 (5.2%) | 1.91 (0.96–3.77) | 0.990 | 1.90 (0.96–3.77) | 0.990 |
| Dominant  | CC      | 323 (69.8%) | 339 (68.1%) | 1.00 | 1.00 |
|           | CT/TT   | 140 (30.2%) | 159 (31.9%) | 1.08 (0.82–1.42) | 0.570 | 1.08 (0.83–1.43) | 0.560 |
| Recessive | CC/CT   | 450 (97.2%) | 472 (94.8%) | 1.00 | 1.00 |
|           | TT      | 13 (2.8%) | 26 (5.2%) | 1.91 (0.97–3.76) | 0.056 | 1.90 (0.97–3.75) | 0.056 |
| Log-additive |        |        |        | 1.04 (0.86–1.24) | 0.710 | 1.04 (0.86–1.24) | 0.700 |
| rs12712127 | Codominant | AA      | 314 (68.3%) | 322 (65.0%) | 1.00 | 1.00 |
|           |          | AG     | 99 (21.5%) | 114 (23%) | 1.12 (0.82–1.53) | 0.540 | 1.12 (0.83–1.55) | 0.530 |
|           |          | GG     | 47 (10.2%) | 59 (11.9%) | 1.22 (0.81–1.85) | 0.010 | 1.22 (0.81–1.84) | 0.010 |
| Dominant  | AA      | 314 (68.3%) | 322 (65%) | 1.00 | 1.00 |
|           | AG/GG   | 146 (31.7%) | 173 (35.0%) | 1.16 (0.88–1.51) | 0.290 | 1.16 (0.89–1.52) | 0.280 |
| Recessive | AA/AG   | 413 (89.8%) | 436 (88.1%) | 1.00 | 1.00 |
|           | GG     | 47 (10.2%) | 59 (11.9%) | 1.19 (0.79–1.78) | 0.530 | 1.18 (0.79–1.78) | 0.510 |
| Log-additive |        |        |        | 1.04 (0.86–1.24) | 0.710 | 1.04 (0.86–1.24) | 0.700 |
| rs956730  | Codominant | GG      | 246 (53.2%) | 280 (56.2%) | 1.00 | 1.00 |
|           |          | AG     | 191 (41.3%) | 179 (35.9%) | 0.82 (0.63–1.07) | 0.120 | 0.82 (0.63–1.08) | 0.120 |
|           |          | AA     | 25 (5.4%) | 39 (7.8%) | 1.37 (0.81–2.33) | 0.350 | 1.38 (0.81–2.34) | 0.360 |
| Dominant  | GG      | 246 (53.2%) | 280 (56.2%) | 1.00 | 1.00 |
|           | AG/AA   | 216 (46.8%) | 218 (43.8%) | 0.89 (0.69–1.14) | 0.890 | 0.89 (0.69–1.15) | 0.890 |
| Recessive | GG/AG   | 437 (94.6%) | 459 (92.2%) | 1.00 | 1.00 |
|           | AA     | 25 (5.4%) | 39 (7.8%) | 1.49 (0.88–2.50) | 0.360 | 1.49 (0.89–2.50) | 0.360 |
| Log-additive |        |        |        | 0.99 (0.80–1.21) | 0.890 | 0.99 (0.80–1.21) | 0.900 |
| rs3917225 | Codominant | AA      | 204 (44.2%) | 219 (44.0%) | 1.00 | 1.00 |
|           |          | AG     | 200 (43.3%) | 209 (42.0%) | 0.97 (0.74–1.28) | 0.780 | 0.98 (0.75–1.29) | 0.800 |
|           |          | GG     | 58 (12.6%) | 70 (14.1%) | 1.12 (0.76–1.67) | 0.120 | 1.12 (0.75–1.67) | 0.120 |
| Dominant  | AA      | 204 (44.2%) | 219 (44.0%) | 1.00 | 1.00 |
|           | AG/GG   | 258 (55.8%) | 279 (56.0%) | 1.01 (0.78–1.30) | 0.960 | 1.01 (0.78–1.31) | 0.930 |
| Recessive | AA/AG   | 404 (87.5%) | 428 (85.9%) | 1.00 | 1.00 |
|           | GG     | 58 (12.6%) | 70 (14.1%) | 1.14 (0.78–1.66) | 0.490 | 1.13 (0.78–1.65) | 0.510 |
| Log-additive |        |        |        | 0.99 (0.80–1.21) | 0.890 | 0.99 (0.80–1.21) | 0.900 |
### Supplementary Table 2. Stratified analysis between *IL1R1* SNPs and gender associated with LDH risk.

| Model       | Genotype       | Male          | Adjusted by age | Female          | Adjusted by age | P     |
|-------------|----------------|---------------|-----------------|-----------------|-----------------|-------|
|             | Control        | Case          |                 | OR (95%CI)      | Male            | Case  | OR (95%CI) | P     |
|             | Control        | Case          |                 |                 |                 |       |            |       |
| rs10490571  | Codominant     |               |                 |                 |                 |       |            |       |
|             | C/C            | 193           | 198             | 1.00            | 130             | 141   | 1.00       | 0.084 |
|             | C/T            | 63            | 64              | 1.31 (0.90–1.93)| 0.230           | 64    | 68         | 0.70 (0.52–1.09) | 0.047 |
|             | T/T            | 9             | 15              | 1.62 (0.69–3.80)| 0.047           | 4     | 11         | 2.58 (0.80–8.30) | 0.060 |
| Dominant    | C/C            | 193           | 198             | 1.00            | 130             | 141   | 1.00       | 0.064 |
|             | C/T-T/T        | 72            | 100             | 1.35 (0.94–1.94)| 0.320           | 68    | 59         | 0.81 (0.53–1.23) | 0.060 |
| Recessive   | C/C-T/T        | 256           | 282             | 1.00            | 124             | 180   | 1.00       | 0.060 |
|             | T/T            | 9             | 15              | 1.51 (0.65–3.51)| 0.088           | 4     | 11         | 2.87 (0.90–9.17) | 0.088 |
| Log-additive| ---            | ---           | ---             | ---             | ---             | ---   | ---        | ---   |

| rs12712127  | Codominant     |               |                 |                 |                 |       |            |       |
|             | A/A            | 186           | 189             | 1.00            | 128             | 133   | 1.00       | 0.730 |
|             | A/G            | 49            | 72              | 1.43 (0.94–2.17)| 0.180           | 20    | 22         | 1.06 (0.55–2.03) | 0.060 |
|             | G/G            | 27            | 37              | 1.35 (0.79–2.30)| 0.100           | 20    | 22         | 1.06 (0.55–2.03) | 0.060 |
| Dominant    | A/A            | 186           | 189             | 1.00            | 128             | 133   | 1.00       | 0.620 |
|             | A/G-G/G        | 76            | 108             | 1.40 (0.98–2.00)| 0.620           | 70    | 65         | 0.90 (0.59–1.37) | 0.620 |
| Recessive   | A/A-G/G        | 235           | 260             | 1.00            | 178             | 176   | 1.00       | 0.760 |
|             | G/G            | 27            | 37              | 1.24 (0.73–2.10)| 0.760           | 20    | 22         | 1.11 (0.58–2.10) | 0.760 |
| Log-additive| ---            | ---           | ---             | ---             | ---             | ---   | ---        | ---   |

| rs3917225   | Codominant     |               |                 |                 |                 |       |            |       |
|             | A/A            | 126           | 126             | 1.00            | 78              | 93    | 1.00       | 0.310 |
|             | A/A-G/G        | 104           | 127             | 1.22 (0.85–1.75)| 0.310           | 96    | 82         | 0.72 (0.47–1.10) | 0.070 |
|             | G/G            | 34            | 45              | 1.32 (0.80–2.20)| 0.310           | 24    | 25         | 0.87 (0.46–1.64) | 0.070 |
| Dominant    | A/A            | 126           | 126             | 1.00            | 78              | 93    | 1.00       | 0.160 |
|             | A/G-G/G        | 138           | 172             | 1.25 (0.89–1.74)| 0.160           | 120   | 107        | 0.75 (0.50–1.12) | 0.160 |
| Recessive   | A/A-G/G        | 138           | 172             | 1.00            | 120             | 107   | 1.00       | 0.930 |
|             | G/G            | 34            | 45              | 1.20 (0.74–1.94)| 0.930           | 24    | 25         | 1.03 (0.56–1.87) | 0.930 |
| Log-additive| ---            | ---           | ---             | ---             | ---             | ---   | ---        | ---   |

OR – odds ratio; CI – confidence interval. P<0.05 indicates statistical significance.
### Supplementary Table 3. Stratified analysis between IL1R1 SNPs and age associated with LDH risk.

| Model      | Genotypes | Male Adjusted by age OR (95%CI) | Female Adjusted by age OR (95%CI) | P   |
|------------|------------|----------------------------------|-----------------------------------|-----|
|            |            | Control                          | Case                              |     |
|            |            |                                  |                                   |     |
| rs3917318  | Codominant | G/G 76 68 1.00                   | 61 46 1.00                        |     |
|            |            | A/G 113 150 1.48 (0.99–2.23)    | 91 105 1.53 (0.95–2.46)           | 0.200|
|            |            | A/A 75 80 1.19 (0.76–1.88)      | 46 49 1.41 (0.81–2.45)            |     |
| Dominant   |            | G/G 76 68 1.00                   | 61 46 1.00                        |     |
|            |            | A/G-A/A 188 230 1.37 (0.94–2.00) | 137 154 1.49 (0.95–2.33)          | 0.079|
| Recessive  |            | G/G-A/G 189 218 1.00            | 152 151 1.00                      |     |
|            |            | A/A 75 80 0.92 (0.64–1.34)      | 46 49 1.07 (0.67–1.69)            | 0.780|
| Log-additive |          | 1.09 (0.87–1.36)                | 1.19 (0.91–1.58)                  | 0.210|

OR – odds ratio; CI – confidence interval. P<0.05 indicates statistical significance.
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| Genotypes | ≤50 Control | <50 Case | Adjusted by age OR (95%CI) | P | ≥50 Control | ≥50 Case | Adjusted by age OR (95%CI) | P |
|-----------|-------------|---------|---------------------------|---|-------------|---------|---------------------------|---|
| Codominant | A/A         | 66      | 53                        | 1.00 | 0.16       | 70      | 73                        | 1.00 | 0.140       |
|           | A/G         | 94      | 117                       | 1.55 (0.98–2.43) | 110 | 138       | 1.21 (0.80–1.83)       |
|           | G/G         | 56      | 63                        | 1.40 (0.84–2.33) | 66 | 54       | 0.78 (0.48–1.27)       |
| Dominant  | A/A         | 66      | 53                        | 1.00 | 0.064      | 70      | 73                        | 1.00 | 0.810       |
|           | A/G-G/G     | 150     | 180                       | 1.49 (0.98–2.27) | 176 | 192       | 1.05 (0.71–1.54)       |
| Recessive | A/A-A/G     | 160     | 170                       | 1.00 | 0.800      | 180     | 211                       | 1.00 | 0.078       |
|           | G/G         | 56      | 63                        | 1.06 (0.69–1.61) | 66 | 54       | 0.69 (0.46–1.04)       |

Log-additive --- --- --- --- 1.18 (0.91–1.53) 0.200 --- --- --- 0.90 (0.70–1.14) 0.370

OR = odds ratio; CI = confidence interval. P<0.05 indicates statistical significance.
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