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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 lumbocrural 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]. Varlotta 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 *IL1* 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 *IL-1R1* 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 northwest 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 (*http://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)

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Table 1. Distributions of age and gender in LDH patients and controls.

Variable	Cases	%	Controls	%	*P*
Total	498		463		
Gender					0.413
Female	200	40.2	198	42.8	
Male	298	59.8	265	57.2	
Age					0.978
≤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.

according to the manufacturer's instructions. DNA concentrations were measured by NanoDrop 2000 (Thermo Scientific, Waltham, MA, USA). Primers for amplification process and single base extension reactions were designed using the Assay Design Suite V2.0 (*https://agenacx.com/online-tools/*). SNP genotyping was performed by Agena MassARRAY iPLEX (Agena Bioscience, San Diego, CA, USA) [20]. Genotyping results were output by Agena Bioscience TYPER version 4.0 software [21].

Statistical analysis

We used Microsoft Excel 2016 and SPSS 21.0 (SPSS, Chicago, IL, USA) for statistical analyses. the Student's *t*-test and χ^2 test were applied to assess the differences in the distribution of age and gender between cases and controls. Allele frequencies of each SNP were analyzed by χ^2 test to evaluate whether these polymorphisms departures from Hardy-Weinberg equilibrium (HWE). The χ^2 test was used to compare the differences in SNPs allele and genotype frequencies between patients and controls. Multiple genetic model analyses (codominant, dominant, recessive and log-additive) were applied using SNPStats software (*http://bioinfo.iconcologia.net/snpstats/start.htm*) to appraise the link between SNPs and LDH risk. Then we conducted the stratification analysis according to age and gender to estimate the association between SNPs genotype and LDH risk. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression analyses, the wild-type allele was used as a reference. Finally, we used Haploview software (version 4.2) to construct haplotype and to estimate the pairwise linkage disequilibrium, the SHEsis software platform (*http://analysis.bio-x.cn/myAnalysis.php*) was used to estimate the association between haplotype and LDH risk [22]. All *P*-values were 2-sided, and *P*<0.05 was considered to have significant differences. All of the aforementioned statistical analyses were performed on 5 SNPs (rs10490571, rs12712127, rs956730, rs3917225, and rs3917318) of the *IL1R1* gene.

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).

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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
				Case	Control				
rs10490571	*IL1R1*	2q12.1	T/C	0.186	0.165	1.15 (0.91–1.45)	0.238	2b	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	4	Selected eQTL hits
rs956730	*IL1R1*	2q12.1	A/G	0.258	0.261	0.98 (0.80–1.20)	0.889	5	DNAse, Motifs changed
rs3917225	*IL1R1*	2q12.1	G/A	0.350	0.342	1.03 (0.86–1.25)	0.699	5	Motifs changed, Selected eQTL hits
rs3917318	*IL1R1*	2q12.1	G/A	0.491	0.485	1.02 (0.86–1.22)	0.789	5	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**	75	84	1.14 (0.75–1.73)	0.580
		AA	9	27	**2.37 (1.08–5.21)**		16	12	0.76 (0.34–1.69)	
	Dominant	GG	139	176	1.00	0.130	107	104	1.00	0.720
		AG/AA	125	122	0.77 (0.55–1.08)		91	96	1.07 (0.72–1.60)	
	Recessive	GG/AG	255	271	1.00	**0.005**	182	188	1.00	0.400
		AA	9	27	**2.82 (1.30–6.12)**		16	12	0.72 (0.33–1.56)	
	Log-additive	---	---	---	0.98 (0.75–1.28)	0.880	---	---	0.99 (0.72–1.36)	0.950

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 homozygous 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).

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

	Model	Genotype	≤50		Adjusted by age OR (95%CI)	*P*	>50		Adjusted by age OR (95%CI)	*P*
			Control	Case			Control	case		
rs956730	Codominant	CC	153	157	1.00		170	182	1.00	
		CT	54	64	1.16 (0.76–1.77)	0.700	73	69	0.89 (0.60–1.31)	0.054
		TT	9	12	1.31 (0.54–3.20)		4	14	3.31 (1.07–10.26)	
	Dominant	CC	153	157	1.00		170	182	1.00	
		CT/TT	63	76	1.18 (0.79–1.76)	0.420	77	83	1.01 (0.70–1.47)	0.950
	Recessive	CC/CT	207	221	1.00		243	251	1.00	
		TT	9	12	1.26 (0.52–3.05)	0.610	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 (rs10450571-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.

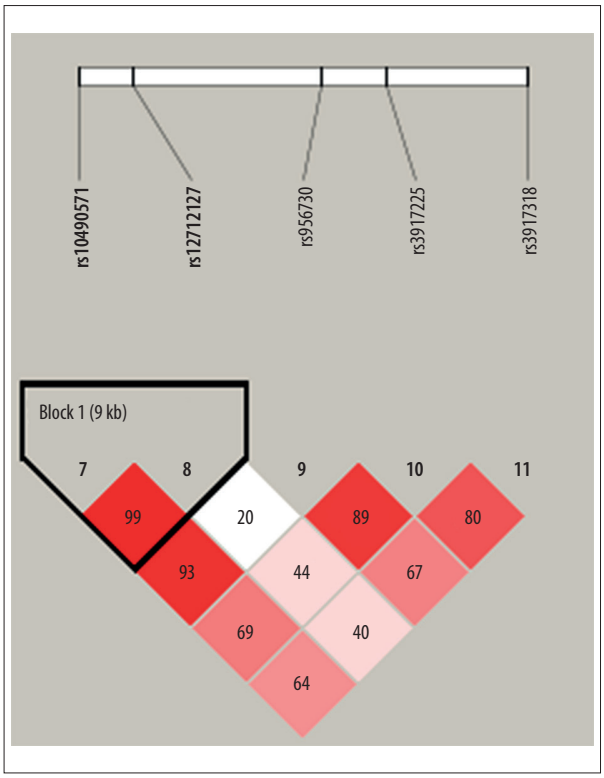

Figure 1. Haplotype block map for part of the SNPs in the *IL1R1* gene. LD is displayed by standard color schemes with bright red for very strong LD (LOD >2, D'=1), pink red (LOD >2, D' <1) and rose pink (LOD <2, D'=1) for partial linkage, and white (LOD <2, D' <1) for complete recombination.

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

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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.

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Conflicts of interest

None.

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Supplementary Tables

Supplementary Table 1. *IL1R1* SNP genotypes and the risk of LDH.

	Model	Genotype	Control	Case	Crude		Adjust by gender and age	
					OR (95%CI)	*P*-value	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)		1.90 (0.96–3.77)	
	Dominant	CC	323 (69.8%)	339 (68.1%)	1.00	0.570	1.00	0.560
		CT/TT	140 (30.2%)	159 (31.9%)	1.08 (0.82–1.42)		1.09 (0.83–1.43)	
	Recessive	CC/CT	450 (97.2%)	472 (94.8%)	1.00	0.056	1.00	0.056
		TT	13 (2.8%)	26 (5.2%)	1.91 (0.97–3.76)		1.90 (0.97–3.75)	
	Log-additive	---	---	---	1.14 (0.91–1.44)	0.250	1.15 (0.91–1.44)	0.250
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	1.13 (0.83–1.55)	0.530
		GG	47 (10.2%)	59 (11.9%)	1.22 (0.81–1.85)		1.22 (0.81–1.84)	
	Dominant	AA	314 (68.3%)	322 (65%)	1.00	0.290	1.00	0.280
		AG/GG	146 (31.7%)	173 (35.0%)	1.16 (0.88–1.51)		1.16 (0.89–1.52)	
	Recessive	AA/AG	413 (89.8%)	436 (88.1%)	1.00	0.400	1.00	0.420
		GG	47 (10.2%)	59 (11.9%)	1.19 (0.79–1.78)		1.18 (0.79–1.78)	
	Log-additive	---	---	---	1.11 (0.92–1.34)	0.270	1.11 (0.92–1.34)	0.260
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)		1.38 (0.81–2.34)	
	Dominant	GG	246 (53.2%)	280 (56.2%)	1	0.350	1	0.360
		AG/AA	216 (46.8%)	218 (43.8%)	0.89 (0.69–1.14)		0.89 (0.69–1.15)	
	Recessive	GG/AG	437 (94.6%)	459 (92.2%)	1.00	0.130	1.00	0.130
		AA	25 (5.4%)	39 (7.8%)	1.49 (0.88–2.50)		1.49 (0.89–2.50)	
	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)		1.12 (0.75–1.67)	
	Dominant	AA	204 (44.2%)	219 (44.0%)	1.00	0.960	1.00	0.930
		AG/GG	258 (55.8%)	279 (56.0%)	1.01 (0.78–1.30)		1.01 (0.78–1.31)	
	Recessive	AA/AG	404 (87.5%)	428 (85.9%)	1.00	0.490	1.00	0.510
		GG	58 (12.6%)	70 (14.1%)	1.14 (0.78–1.66)		1.13 (0.78–1.65)	
	Log-additive	---	---	---	1.04 (0.86-1.24)	0.710	1.04 (0.86–1.24)	0.700

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	Model	Genotype	Control	Case	Crude		Adjust by gender and age	
					OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
rs3917318	Codominant	AA	136 (29.4%)	126 (25.3%)	1.00		1.00	
		AG	204 (44.2%)	255 (51.2%)	1.35 (1.00–1.83)	0.090	1.35 (1.00–1.83)	0.087
		GG	122 (26.4%)	117 (23.5%)	1.04 (0.73–1.47)		1.03 (0.73–1.47)	
	Dominant	AA	136 (29.4%)	126 (25.3%)	1.00	0.150	1.00	0.150
		AG/GG	326 (70.6%)	372 (74.7%)	1.23 (0.93–1.64)		1.23 (0.93–1.64)	
	Recessive	AA/AG	340 (73.6%)	381 (76.5%)	1.00	0.300	1.00	0.290
		GG	122 (26.4%)	117 (23.5%)	0.86 (0.64–1.15)		0.85 (0.64–1.14)	
	Log-additive	---	---	---	1.02 (0.86–1.22)	0.790	1.02 (0.86–1.22)	0.800

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

Supplementary Table 2. Stratified analysis between *IL1R1* SNPs and gender associated with LDH risk.

	Model	Genotypes	Male		Adjusted by age OR (95%CI)	*P*	Female		Adjusted by age OR (95%CI)	*P*
			Control	Case			Control	Case		
rs10490571	Codominant	C/C	193	198	1.00		130	141	1.00	
		C/T	63	85	1.31 (0.90–1.93)	0.230	64	48	0.70 (0.45–1.09)	0.047
		T/T	9	15	1.62 (0.69–3.80)		4	11	2.58 (0.80–8.30)	
	Dominant	C/C	193	198	1.00	0.100	130	141	1.00	0.320
		C/T-T/T	72	100	1.35 (0.94–1.94)		68	59	0.81 (0.53–1.23)	
	Recessive	C/C-C/T	256	283	1.00	0.330	194	189	1.00	0.060
		T/T	9	15	1.51 (0.65–3.51)		4	11	2.87 (0.90–9.17)	
	Log-additive	---	---	---	1.30 (0.96–1.75)	0.088	---	---	0.96 (0.67–1.38)	0.830
rs12712127	Codominant	A/A	186	189	1.00		128	133	1.00	
		A/G	49	71	1.43 (0.94–2.17)	0.180	50	43	0.84 (0.52–1.35)	0.730
		G/G	27	37	1.35 (0.79–2.30)		20	22	1.06 (0.55–2.03)	
	Dominant	A/A	186	189	1.00	0.064	128	133	1.00	0.620
		A/G-G/G	76	108	1.40 (0.98–2.00)		70	65	0.90 (0.59–1.37)	
	Recessive	A/A-A/G	235	260	1.00	0.430	178	176	1.00	0.760
		G/G	27	37	1.24 (0.73–2.10)		20	22	1.11 (0.58–2.10)	
	Log-additive	---	---	---	1.22 (0.96–1.56)	0.100	---	---	0.97 (0.73–1.30)	0.840
rs3917225	Codominant	A/A	126	126	1.00		78	93	1.00	
		A/G	104	127	1.22 (0.85–1.75)	0.410	96	82	0.72 (0.47–1.10)	0.310
		G/G	34	45	1.32 (0.80–2.20)		24	25	0.87 (0.46–1.64)	
	Dominant	A/A	126	126	1.00	0.200	78	93	1.00	0.160
		A/G-G/G	138	172	1.25 (0.89–1.74)		120	107	0.75 (0.50–1.12)	
	Recessive	A/A-A/G	230	253	1.00	0.450	174	175	1.00	0.930
		G/G	34	45	1.20 (0.74–1.94)		24	25	1.03 (0.56–1.87)	
	Log-additive	---	---	---	1.17 (0.92–1.48)	0.200	---	---	0.86 (0.65–1.15)	0.320

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	Model	Genotypes	Male		Adjusted by age OR (95%CI)	P	Female		Adjusted by age OR (95%CI)	P
			Control	Case			Control	Case		
rs3917318	Codominant	G/G	76	68	1.00		61	46	1.00	
		A/G	113	150	1.48 (0.99–2.23)	0.150	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)	0.110	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)	0.670	46	49	1.07 (0.67–1.69)	0.780
	Log-additive	---	---	---	1.09 (0.87–1.36)	0.480	---	---	1.19 (0.91–1.58)	0.210

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	≤50		Adjusted by age OR (95%CI)	P	>50		Adjusted by age OR (95%CI)	P
			Control	Case			Control	Case		
rs12712127	Codominant	A/A	147	149	1.00		167	173	1.00	
		A/G	36	52	1.43 (0.88–2.32)	0.340	63	62	0.96 (0.63–1.44)	0.370
		G/G	30	32	1.06 (0.61–1.83)		17	27	1.54 (0.81–2.94)	
	Dominant	A/A	147	149	1.00		167	173	1.00	
		A/G-G/G	66	84	1.26 (0.85–1.87)	0.250	80	89	1.08 (0.75–1.57)	0.680
	Recessive	A/A-A/G	183	201	1.00		230	235	1.00	
		G/G	30	32	0.98 (0.57–1.67)	0.930	17	27	1.56 (0.83–2.94)	0.160
	Log-additive	---	---	---	1.10 (0.85–1.42)	0.480	---	---	1.13 (0.86–1.49)	0.360
rs956730	Codominant	G/G	112	125	1.00		134	155	1.00	
		A/G	91	90	0.89 (0.60–1.32)	0.550	100	89	0.77 (0.53–1.11)	0.180
		A/A	12	18	1.36 (0.62–2.94)		13	21	1.40 (0.68–2.91)	
	Dominant	G/G	112	125	1.00		134	155	1.00	
		A/G-A/A	103	108	0.95 (0.65–1.37)	0.770	113	110	0.84 (0.59–1.20)	0.340
	Recessive	G/G-A/G	203	215	1.00		234	244	1.00	
		A/A	12	18	1.42 (0.67–3.03)	0.350	13	21	1.56 (0.76–3.18)	0.220
	Log-additive	---	---	---	1.02 (0.76–1.38)	0.890	---	---	0.96 (0.73–1.27)	0.780
rs3917225	Codominant	A/A	93	105	1.00		111	114	1.00	
		A/G	89	95	0.95 (0.64–1.43)	0.920	111	114	1.01 (0.69–1.46)	0.410
		G/G	33	33	0.89 (0.51–1.55)		25	37	1.45 (0.82–2.57)	
	Dominant	A/A	93	105	1.00		111	114	1.00	
		A/G-G/G	122	128	0.94 (0.64–1.36)	0.730	136 (55.1%)	151	1.09 (0.77–1.54)	0.640
	Recessive	A/A-A/G	182	200	1.00		222	228	1.00	
		G/G	33	33	0.91 (0.54–1.54)	0.720	25	37	1.44 (0.84–2.48)	0.180
	Log-additive	---	---	---	0.95 (0.73–1.23)	0.680	---	---	1.14 (0.88–1.47)	0.320

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	Model	Genotypes	≤50		Adjusted by age OR (95%CI)	P	>50		Adjusted by age OR (95%CI)	P
			Control	Case			Control	Case		
rs3917318	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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