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Assessment of *MIR3142HG* genetic polymorphisms and the susceptibility of lumbar disc herniation in the Chinese population

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Lumbar disc herniation (LDH) is a common degenerative disease of the lumbar spine, which is related to host genetic factors. Our study aimed to explore the association between *MIR3142HG* polymorphisms and LDH susceptibility. Six SNPs in *MIR3142HG* from 504 LDH patients and 500 healthy individuals were genotyped by the Agena MassARRAY platform. The relationship between SNPs and LDH susceptibility was evaluated with logistic regression analysis by calculating odds ratios (ORs) and 95% confidence intervals (CIs). The interactions between SNP and SNP were analyzed using the multifactor dimensionality reduction (MDR) method. Our study showed that rs7727115 was related to a decreased susceptibility to LDH. Rs2961920 and rs58747524 were significantly associated with an increased risk of LDH. Stratified analysis showed that rs7727115 reduced the risk of LDH in patients aged > 49 years. Rs17057846, rs2961920, and rs58747524 had a risk-increasing influence on patients aged > 49 years and women. Besides, rs7727115 decreased susceptibility in cases of disc prolapse, while rs2961920 and rs58747524 increased the risk. Rs2431689 increased susceptibility in patients with a single hernia, and rs58747524 correlated with an increased risk in cases of multiple hernias. Moreover, MDR analysis indicated that the combination of rs1582417, rs2431689, rs7727115, rs17057846, rs2961920, and rs58747524 was the best predictive model for LDH. Our study showed that *MIR3142HG* polymorphisms were significantly associated with LDH risk, which suggests that *MIR3142HG* polymorphisms play some potential roles in diagnosing LDH.

Keywords Lumbar disc herniation, Genetic risk, *MIR3142HG*, Single nucleotide polymorphisms, Stratified analysis

Lumbar disc herniation (LDH) is a common lumbar degenerative disease caused by degeneration and displacement of the nucleus pulposus or the annulus fibrosus outside the intervertebral disc space [1]. Pains in the leg or lower back are the main clinical features of LDH, which affect approximately 90% of the world's population at some point during their life [2]. At present, surgery is the most common treatment for LDH, but a large number of patients still suffer persistent low back and leg pain after surgical treatment [3,4]. Thus, it is necessary to find new therapeutic targets for LDH. Several studies have shown that LDH is related to various inflammatory and immune responses. Among them, hematological indicators such as the neutrophil ratio (NEU), mean platelet volume (MPV), mononuclear cell ratio (MON), lymphocyte count (LYM), red blood cell distribution width (RDW), indirect bilirubin (IBIL) are closely related to the inflammation level and immune response of patients with LDH [5,6]. As a common and multifactorial spinal disease, LDH is affected by multifactorial interactions, such as age, gender, height, smoking habits, trauma, and cold or humid environment as well as genetic factors. It has been reported that genetic factors such as gene polymorphisms play a more important role than environmental factors in the progression of LDH [7]. To date, many susceptibility genes such as Storkhead Box1 (*STOX1*), CollagenType IX (*COL9*), Metallopeptidase Inhibitor 1 (*TIMP1*), Interleukin 4 (*IL4*), and Interleukin 6 (*IL6*), and *MIR31HG*

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polymorphisms were identified to be associated with LDH [8–10]. However, the specific pathogenesis of LDH is still unclear.

Long non-coding RNAs (lncRNAs), non-coding transcripts of longer than 200 nucleotides, participate in the regulation of crucial biological processes. Growing evidence has indicated that lncRNAs are involved in numerous diseases, including intervertebral disc degeneration, and osteoarthritis [11–13]. *MIR3142HG*, located at chromosome 5q33.3, can influence the transcription of MIR146A (the host gene of miR-146a), and then regulate the expression of miR-146a [14]. *MIR3142HG* is involved in the occurrence of a variety of human diseases by affecting the inflammatory reaction, including lipopolysaccharide-induced acute lung injury and idiopathic pulmonary fibrosis [14,15]. Previous studies have shown that inflammatory response plays an important role in the occurrence and development of intervertebral disc degeneration [16]. There is evidence revealed that *MIR3142HG* can directly target miR-146a to regulate the inflammatory response in fibroblasts [14]. Additionally, a recent study has shown that miR-146a can mediate the IL6/Signal Transducer And Activator Of Transcription 3 (STAT3) signaling pathway to regulate the occurrence of lumbar intervertebral disc degeneration [17]. The above studies suggest that *MIR3142HG* has a crucial role in the occurrence of LDH. Single nucleotide polymorphisms (SNPs), the most common type of human heritable variants, are likely to be biomarkers for human disease [18]. Several studies have indicated that *MIR3142HG* SNPs are significantly associated with human diseases. For instance, Cao et al. showed that rs17057846 and rs58747524 in *MIR3142HG* contributed to the elevated risk for IgA nephropathy [19]. What's more, a study has indicated that *MIR3142HG* rs1582417 and rs7727115 were significantly associated with osteonecrosis of the femoral head [20]. However, the association between *MIR3142HG* genetic polymorphisms and LDH remains unclear.

Thus, we performed the case–control study (including 504 LDH patients and 500 healthy controls) to investigate the impact of *MIR3142HG* genetic variants on LDH susceptibility in the Chinese Han population. Our study will provide a new perspective on the molecular mechanism, prevention, and diagnosis of LDH.

Materials and methods

Study population

Before the study, G* Power (version 3.1.9.7) software was used to calculate the sample size. First, we selected the statistical method (*t*-test) and then chose classification (Difference between two independent means (two groups)). Then set the parameters: tail = 2, effective size = 0.2, $\alpha = 0.05$, power = 0.884, and allocation ratio = 1. Finally, the calculated sample size of the case group and the control group was 499 cases respectively. A total of 1004 participants including 504 patients with LDH and 500 ethnicity, age, and gender-matched healthy controls were randomly recruited from the First Affiliated Hospital of Xi'an Jiaotong University. Patients were newly diagnosed as LDH by imaging examination and typical clinical symptoms and signs. Symptoms of LDH included: (1) partial lumbar pain and local typical sciatica; (2) low back pain; and (3) difficulty in straight leg elevation test and enhancement test. All controls were selected the healthy volunteers who were admitted to the hospital for physical examination at the same period as the cases and had no history of sciatica and low back pain. The controls showed to meet the following inclusion criteria: (1) subjects without any medical and family history of lumbosacral pain; (2) without any history of tumors; and (3) without spondylolisthesis, scoliosis, from trauma, osteoarthritis, rheumatism and rheumatoid arthritis. All participants with trauma, tumors, autoimmune diseases, and related lumbar diseases were excluded. We were informed about the purpose of the study and obtained an informed consent form from each subject before starting the study. The basic characteristics of each subject including age, gender, complication, blood indicators (NEU, (MPV), mononuclear MON, LYM, RDW, IBIL), degree, and level of herniation were obtained by medical records and standard questionnaires. This study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

SNP screening and DNA extracting

The SNPs in *MIR3142HG* were selected based on the following standards. First, we obtained the physical position of *MIR3142HG* on chromosome 5:160438594-160487426 by the human Ensembl database (release 110) [21]. In the VCF to PED Converter window, we entered *MIR3142HG*'s physical location, selected the Chinese Han population in Beijing (CHB) population, and downloaded the ped and info file for *MIR3142HG* SNPs. We obtained 103 SNPs within *MIR3142HG* from the database. Second, Haploview v4.2 software was performed for quality control (min genotype > 75%, Hardy–Weinberg equilibrium (HWE) > 0.05, minor allele frequency (MAF) > 5%, and $r^2 < 0.8$). The linkage disequilibrium plot for the SNPs is shown in Figure S1. Finally, six candidate SNPs (rs1582417, rs2431689, rs7727115, rs17057846, rs2961920, and rs58747524) in the *MIR3142HG* gene were selected for investigation. The Gold Mag-Mini Purification Kit (Gold Mag Co. Ltd) was used to extract DNA from peripheral blood samples of study subjects. The extracted DNA was cryopreserved in ethylene diamine tetra acetic acid (EDTA) tubes. The DNA concentration was measured using NanoDrop2000, and the SNP was genotyped using Agena MassARRAY RS1000. The genotyping data was analyzed by Agena Typer Software (version 4.0). The primer sequences for PCR amplification are shown in Table S1.

Bioinformatic analysis

The possible functions of the six selected SNPs were predicted using HaploReg v4.2 online software (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). Additionally, we explored the effects of SNPs on the expression of *MIR3142HG* through the expression quantitative trait loci (eQTL) analysis of the Genotype-Tissue Expression (GTEx) database (http://www.gtexportal.org/).

Statistical analysis

SPSS 20.0 software was used to perform all statistical analyses. The *t-test* and chi-square test were used to assess the continuous variables (age, NEU, MPV, MON, LYM, RDW, and IBIL) and non-continuous variables (gender) between the case and control groups, respectively. The association between *MIR3142HG* polymorphisms and LDH susceptibility was determined by calculating 95% confidence interval (CI) and relative odds ratio (OR) with logistic regression analysis under multiple genetic models. The Benjamini and Hochberg's false discovery rate (FDR) method was used to correct for multiple testing. The SNP-SNP interactions were analyzed by open-source Java software multifactor dimensionality reduction (MDR), version 3.0.2 [22], and generalized multifactor dimensionality reduction (GMDR) (version 0.7). The one-way ANOVA method was used for index analysis.

Results

Characteristics of the study population

A total of 504 LDH patients (294 males and 210 females) and 500 healthy controls (293 males and 207 females) are included in this study (Table 1). The mean ages of cases and controls were 49.24 ± 14.88 years and 49.06 ± 14.47 years, respectively. There was no significant difference between the two groups in terms of gender ($p = 0.642$), age ($p = 0.644$), and RDW ($p = 0.165$). Statistically significant differences in NEU ($p < 0.001$), MPV ($p < 0.001$), MON ($p = 0.042$), LYM ($p = 0.001$), and IBIL ($p < 0.001$) were observed between the case and control groups. Additionally, the degree of herniation included disc herniation (110 cases), disc prolapse (388 cases), disc displacement (1 case), and others.

Association of *MIR3142HG* polymorphisms and LDH risk

The basic information and allele frequency distribution of the six SNPs in *MIR3142HG* are shown in Table 2. All SNPs in the control groups conformed to HWE (all $p > 0.05$). The relationship between *MIR3142HG* polymorphisms and the risk of LDH was analyzed by logistic regression analysis adjusted for gender and age. As shown in Fig. 1, rs7727115 was associated with a reduced risk of LDH (OR = 0.79, 95%CI = 0.65–0.96, *p*

Characteristics	Cases (n = 504)	Control (n = 500)	*p*-value
Age	49.24 ± 14.88	49.06 ± 14.47	0.849[a]
≤ 49	254(50%)	248(50%)	
> 49	250(50%)	252(50%)	
Gender			0.949[b]
Male	294(58%)	293(59%)	
Female	210(42%)	207(41%)	
Complication			
yes	221(44%)		
no	283(56%)		
NEU (%)	68.93 ± 14.75	57.64 ± 8.44	**< 0.001[a]**
MPV (fL)	11.46 ± 1.36	10.85 ± 1.28	**< 0.001[a]**
MON (%)	6.69 ± 2.33	6.98 ± 1.95	**0.042[a]**
LYM (10^9/L)	1.66 ± 0.71	1.95 ± 1.58	**0.001[a]**
RDW (%)	13.33 ± 1.41	13.88 ± 7.81	0.165[a]
IBIL (umol/L)	7.48 ± 7.53	11.90 ± 4.73	**< 0.001[a]**
Degree of herniation			
Disc herniation	110 (21.8%)		
Disc prolapse	388 (77.0%)		
Disc displacement	1 (0.2%)		
Others	5 (1%)		
Level of herniation			
L5-S1	98		
L4-L5 and L5-S1	160		
L3-L4 and L4-L5	30		
L4-L5	80		
L3-L4, L4-L5, and L5-S1	50		
L2-L3, L3-L4,L4-L5, and L5-S1	12		
others	74		

Table 1. Basic characteristics of the LDH patients and the controls. LDH: Lumbar disc herniation; NEU: Neutrophil ratio; MPV: Mean platelet volume; MON: Mononuclear cell ratio; LYM: Lymphocyte count; RDW: Red blood cell distribution Width; IBIL: Indirect Bilirubin. [a]*p* value was calculated by independent samples *t*-test. [b]*p* value calculated by χ^2-test. $p < 0.05$ indicates statistical significance. The highlighted in bold represent statistical significance.

SNP ID	Position	Alleles A/B	Callrate	MAF		HWE-*p*	HaploReg v4.2
				Case	Control		
rs1582417	5:159897501	A/G	99.9%	0.374	0.381	0.343	Promoter histone marks, Enhancer histone marks, DNAse, Proteins bound, Motifs changed, Selected eQTL hits
rs2431689	5:159899122	A/G	99.5%	0.164	0.151	1.000	Promoter histone marks, Enhancer histone marks, DNAse, Proteins bound, Motifs changed
rs7727115	5:159901739	T/G	99.5%	0.279	0.328	0.479	Promoter histone marks, Enhancer histone marks, DNAse, Motifs changed, Selected eQTL hits
rs17057846	5:159902313	A/G	99.9%	0.217	0.190	0.663	Promoter histone marks, Enhancer histone marks, DNAse, Selected eQTL hits
rs2961920	5:159911506	A/C	99.9%	0.465	0.397	0.926	Enhancer histone marks, Proteins bound, Motifs changed, GRASP eQTL hits
rs58747524	5:159911584	C/T	99.4%	0.275	0.231	0.614	Enhancer histone marks, Proteins bound

Table 2. Basic information of the selected SNPs in *MIR3142HG*. SNP: Single nucleotide polymorphism; HWE: Hardy–Weinberg equilibrium. $p < 0.05$ indicates statistical significance.

(FDR) = 0.047). Rs2961920 (OR = 1.76, 95%CI = 1.22–2.53, *p* (FDR) = 0.014) and rs58747524 (OR = 1.27, 95%CI = 1.03–1.55, *p* (FDR) = 0.044) showed an increased susceptibility to LDH.

Stratified analysis by age

We further analyzed the correlation between LDH susceptibility and *MIR3142HG* polymorphisms under age stratification analysis (Table 3). We observed that rs7727115 had protective effects on the risk of LDH in patients aged ˃ 49 years (OR = 0.71, 95% CI = 0.54–0.93, *p* (FDR) = 0.025) *MIR3142HG* polymorphism rs17057846 (OR = 1.59, 95% CI = 1.10–2.30, *p* (FDR) = 0.029) and rs58747524 (OR = 1.69, 95% CI = 1.18–2.42, *p* (FDR) = 0.025) were associated with an increased risk of LDH in people aged > 49 years.

Stratified analysis by gender

As shown in Table 3, gender-based stratification analysis found that rs17057846, rs2961920, and rs58747524 in *MIR3142HG* were associated with an increased risk of LDH in women. Specifically, rs17057846 had a higher risk probability to LDH (OR = 1.51, 95% CI = 1.06–2.15, *p* (FDR) = 0.044). We also found rs2961920 (OR = 1.82, 95% CI = 1.20–2.76, *p* (FDR) = 0.028) and rs58747524 (OR = 1.54, 95% CI = 1.12–2.13, *p* (FDR) = 0.023) had an increased risk of LDH.

Stratified analysis by severity of LDH

When stratified by the severity of LDH (Table 4), we found that rs7727115 was linked with decreased susceptibility to LDH among disc prolapse individuals (OR = 0.79, 95%CI = 0.64–0.97, *p* (FDR) = 0.044). Besides, rs2961920 (OR = 1.86, 95%CI = 1.26–2.74, *p* (FDR) = 0.010) and rs58747524 (OR = 1.32, 95%CI = 1.05–1.65, *p* (FDR) = 0.047) were related to an increased risk of LDH in patients with disc prolapse.

Stratified by hernia levels

As demonstrated in Table 4, it was found that rs2431689 was significantly associated with increased susceptibility to patients with single hernia (OR = 1.50, 95%CI = 1.03–2.18, *p* (FDR) = 0.207). Besides, rs58747524 demonstrated an increased risk correlation with LDH within multiple hernias (OR = 1.51, 95%CI = 1.11–2.05, *p* (FDR) = 0.048).

SNP–SNP interaction analysis using GMDR and MDR

GMDR analysis (Table 5) showed that the six-locus model with a combination of rs1582417, rs2431689, rs7727115, rs17057846, rs2961920, and rs58747524 was the best predictive model for LDH (test balanced accuracy = 0.5149, CVC = 10/10). Additionally, the six-locus model was associated with increased susceptibility to LDH (OR = 1.8899, 95%CI = 1.3227–2.7003, *p* = 0.0004). We further used the information gain theory to explain the relationship between six SNPs and drew a tree diagram. As shown in Fig. 2, the interaction map with low entropy values or negative entropy values (plotted in orange, blue, or green) indicated the independence or redundancy of each pairwise combination of attributes.

The relationship between SNP genotypes and clinical indicators in LDH

By analyzing the relationship between SNP genotypes and clinical parameters in LDH (Table 6), we found that rs1582417 and rs7727115 different genotypes had significantly different IBIL levels ($p = 0.026$, $p = 0.048$, respectively). Similarly, the genotypes of rs17057846, rs2961920, and rs58747524 in LDH patients showed significantly different MON levels ($p = 0.004$, $p = 0.026$, and $p = 0.021$, respectively). Rs7727115 genotypes were significantly associated with RDW levels ($p = 0.007$). Besides, AA (2.094 ± 0.300 10^9/L) and AG genotypes (1.719 ± 0.069 10^9/L) in rs2431689 were related to an increased concentration of LYM in LDH patients compared with GG genotype (0.624 ± 0.035 10^9/L) ($p = 0.042$).

Impact of SNPs on gene expression (eQTLs)

We further evaluated each SNP's expression loci (eQTLs) by GTEx. As shown in Fig. 3, we found that rs7727115 (Fig. 3C) and rs2961920 (Fig. 3E) were significantly associated with mRNA expression of *MIR3142HG*. Whereas there were no significant associations between rs1582417, rs2431689, rs17057846, rs58747524 and *MIR3142HG* expression (Fig. 3A, B, D, F).

Model	Genotype	Case(n, %)	Control(n, %)	OR(95% CI)	p	p (FDR)
rs1582417						
Allele	G	631 (63%)	618 (62%)	1		
	A	377 (37%)	380 (38%)	0.97(0.81-1.06)	0.755	0.755
Codominant	G/G	198 (39%)	186 (37%)	1		
	G/A	235 (47%)	246 (49%)	0.90(0.69-1.71)	0.431	0.431
	A/A	71 (14%)	67 (14%)	0.99(067-1.47)	0.979	0.979
Dominant	G/G	198 (39%)	186 (37%)	1		
	G/A-A/A	306 (61%)	313 (63%)	0.92(0.71-1.19)	0.513	0.513
Recessive	G/G-G/A	433 (86%)	432 (87%)	1		
	A/A	71 (14%)	67 (13%)	1.06(0.74-1.51)	0.765	0.918
Log-additive	--	--	--	0.97(0.81-1.17)	0.752	0.752
rs2431689						
Allele	G	841 (84%)	842 (85%)	1		
	A	165 (16%)	150 (15%)	1.10(0.87-1.40)	0.432	0.519
Codominant	G/G	350 (70%)	357 (72%)	1		
	G/A	141 (18%)	128 (26%)	1.13(0.85-1.49)	0.413	0.495
	A/A	12 (2%)	11 (2%)	1.11(0.48-2.55)	0.802	0.962
Dominant	G/G	350 (70%)	357 (72%)	1		
	G/A-A/A	153 (30%)	139 (28%)	1.12(0.86-1.48)	0.402	0.483
Recessive	G/G-G/A	491 (98%)	485 (98%)	1		
	A/A	12 (2%)	11 (2%)	1.08(0.47-2.47)	0.860	0.860
Log-additive	--	--	--	1.10(0.87-1.41)	0.426	0.512
rs7727115						
Allele	G	721 (72%)	672 (67%)	1		
	T	279 (28%)	328 (33%)	0.79(0.65-0.96)	**0.017**	0.052
Codominant	G/G	256 (51%)	222 (44%)	1		
	G/T	209 (42%)	228 (46%)	0.80(0.61-1.03)	0.084	0.168
	T/T	35 (7%)	50 (10%)	0.61(0.38-0.97)	**0.036**	0.109
Dominant	G/G	256 (51%)	222 (44%)	1		
	G/T-T/T	244 (49%)	278 (56%)	0.76(0.59-0.98)	**0.032**	0.063
Recessive	G/G-G/T	465 (93%)	450 (90%)	1		
	T/T	35 (7%)	50 (10%)	0.68(0.43-1.06)	0.090	0.270
Log-additive	--	--	--	0.79(0.65-0.96)	**0.016**	**0.047**
rs17057846						
Allele	G	788 (78%)	810 (81%)	1		
	A	218 (22%)	190 (19%)	1.18(0.95-1.47)	0.137	0.206
Codominant	G/G	306 (61%)	326 (65%)	1		
	G/A	176 (35%)	158 (32%)	1.19(0.91-1.55)	0.206	0.309
	A/A	21 (4%)	16 (3%)	1.40(0.72-2.73)	0.327	0.491
Dominant	G/G	306 (61%)	326 (65%)	1		
	G/A-A/A	197 (39%)	174 (35%)	1.21(0.93-1.56)	0.153	0.229
Recessive	G/G-G/A	482 (96%)	484 (97%)	1		
	A/A	21 (4%)	16 (3%)	1.32(0.68-2.56)	0.415	0.623
Log-additive	--	--	--	1.19(0.95-1.48)	0.133	0.199
rs2961920						
Allele	C	538 (53%)	603 (60%)	1		
	A	468 (47%)	397 (40%)	1.32(1.11-1.58)	**0.002**	**0.012**
Codominant	C/C	144 (29%)	181 (36%)	1		
	C/A	250 (50%)	241 (48%)	1.31(0.99-1.73)	0.063	0.188
	A/A	109 (21%)	78 (16%)	1.76(1.22-2.53)	**0.002**	**0.014**
Dominant	C/C	144 (29%)	181 (36%)	1		
	C/A-A/A	359 (71%)	319 (64%)	1.42(1.09-1.85)	**0.010**	0.060
Recessive	C/C-C/A	394 (78%)	422 (84%)	1		
	A/A	109 (22%)	78 (16%)	1.50(1.09-2.07)	**0.014**	0.083
Log-additive	--	--	--	1.32(1.11-1.58)	**0.002**	**0.012**
rs58747524						
Allele	T	726 (72%)	766 (77%)	1		
	C	276 (28%)	230 (23%)	1.27(1.03-1.55)	**0.022**	**0.044**
Codominant	T/T	259 (52%)	292 (57%)	1		
	T/C	208 (42%)	182 (37%)	1.29(0.99-1.67)	0.056	0.334
	C/C	34 (6%)	24 (6%)	1.60(0.92-2.77)	0.093	0.187
Dominant	T/T	259 (52%)	292 (57%)	1		
	T/C-C/C	242 (48%)	206 (43%)	1.33(1.03-1.70)	**0.027**	0.082
Recessive	T/T-T/C	467 (93%)	474 (94%)	1		
	C/C	34 (7%)	24 (6%)	1.44(0.84-2.47)	0.184	0.368
Log-additive	--	--	--	1.28(1.04-1.57)	**0.020**	**0.040**

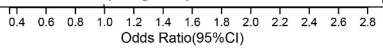

Fig. 1. Association of *MIR3142HG* polymorphisms with LDH susceptibility. SNP: Single nucleotide polymorphism; OR: Odds ratio; 95% CI: 95% confidence interval. *p*-values were calculated by logistic regression analysis with adjustments for age and gender. $p < 0.05$ indicates statistical significance.

Discussion

LDH is a degenerative disease that can lead to neuropathic symptoms such as spinal cord pain syndrome and nerve root ischemia [23]. Evidence has shown that inflammation-related factors play an important role in LDH, can accelerate inflammation and disc formation, and ultimately deepen lumbar disc degeneration and pain [24]. *MIR3142HG*, also known as the MIR3142 host gene, is located on human chromosome 5q33.3. Studies showed

SNP ID	Model	Genotype	≤ 49 years			> 49 years			Male			Female		
			OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)
rs1582417	allele	G	1			1			1			1		
		A	1.02 (0.79–1.31)	0.910	0.910	0.93 (0.72–1.20)	0.580	0.698	1.13 (0.89–1.43)	0.325	0.649	0.79 (0.60–1.05)	0.100	0.151
	codominant	G/G	1			1			1			1		
		G/A	0.98 (0.67–1.43)	0.907	1.089	0.82 (0.56–1.21)	0.322	0.386	1.10 (0.78–1.57)	0.577	0.153	0.66 (0.43–1.01)	0.054	0.108
		A/A	1.06 (0.60–1.86	0.837	0.837	0.96 (0.56–1.65)	0.876	0.876	1.30 (0.77–2.20)	0.320	0.640	0.69 (0.38–1.24)	0.214	0.321
	dominant	G/G	1			1			1			1		
		G/A-A/A	0.99 (0.69–1.43)	0.977	0.977	0.85 (0.60–1.23)	0.391	0.469	1.14 (0.82–1.59)	0.428	0.642	0.67 (0.45–1.00)	0.047	0.071
	recessive	G/G-G/A	1			1			1			1		
		A/A	1.07 (0.64–1.81)	0.788	0.945	1.07 (0.65–1.76)	0.804	0.804	1.23 (0.76–2.01)	0.396	0.792	0.87 (0.51–1.49)	0.617	0.740
	log-additive	–	1.02 (0.78–1.32)	0.909	0.909	0.94 (0.73–1.21)	0.630	0.756	1.13 (0.89–1.44)	0.318	0.636	0.79 (0.60–1.05)	0.099	0.148
rs2431689	allele	G	1			1			1			1		
		A	1.25 (0.89–1.75)	0.199	0.597	0.96 (0.68–1.36)	0.832	0.832	1.06 (0.78–1.45)	0.708	0.849	1.16 (0.80–1.70)	0.436	0.436
	codominant	G/G	1			1			1			1		
		G/A	0.15 (0.77–1.70)	0.497	1.490	1.12 (0.74–1.68)	0.593	0.593	1.02 (0.71–1.47)	0.898	0.898	1.30 (0.83–2.03)	0.254	0.304
		A/A	2.73 (0.71–10.47)	0.143	0.430	0.50 (0.15–1.71)	0.272	0.407	1.40 (0.44–4.48)	0.573	0.860	0.86 (0.26–2.88)	0.806	0.806
	dominant	G/G	1			1			1			1		
		G/A-A/A	1.21 (0.83–1.78)	0.322	0.644	1.05 (0.71–1.55)	0.827	0.827	1.05 (0.73–1.49)	0.805	0.966	1.25 (0.81–1.92)	0.314	0.314
	recessive	G/G-G/A	1			1			1			1		
		A/A	2.62 (0.69–10.01)	0.158	0.475	0.49 (0.15–1.66)	0251	0.376	1.39 (0.44–4.43)	0.580	0.870	0.80 (0.24–2.69)	0.724	0.724
	log-additive	–	1.26 (0.89–1.78)	0.192	0.577	0.97 (0.69–1.37)	0.874	0.874	1.06 (0.77–1.46)	0.706	0.847	1.16 (0.80–1.68)	0.443	0.443
rs7727115	allele	G	1			1			1			1		
		T	0.89 (0.68–1.17)	0.392	0.783	**0.71 (0.54–0.93)**	**0.013**	**0.025**	0.77 (0.60–0.99)	0.042	0.249	0.82 (0.61–1.11)	0.203	0.244
	codominant	G/G	1			1			1			1		
		G/T	0.81 (0.56–1.17)	0.267	1.603	0.77 (0.53–1.12)	0.166	0.249	0.79 (0.56–1.11)	0.169	1.014	0.81 (0.54–1.20)	0.292	0.292
		T/T	0.89 (0.45–1.77)	0.746	0.895	**0.44 (0.23–0.84)**	**0.014**	0.081	0.57 (0.31–1.03)	0.064	0.383	0.68 (0.32–1.44)	0.311	0.373
	dominant	G/G	1			1			1			1		
		G/T-T/T	0.82 (0.58–1.17)	0.281	0.843	**0.70 (0.49–0.99)**	**0.046**	0.069	0.74 (0.54–1.03)	0.076	0.455	0.79 (0.53–1.16)	0.219	0.263
	recessive	G/G-G/T	1			1			1			1		
		T/T	0.98 (0.51–1.91)	0.963	0.963	**0.50 (0.26–0.93)**	**0.029**	0.177	0.64 (0.36–1.13)	0.124	0.373	0.75 (0.36–1.55)	0.441	0.661
	log-additive	–	0.88 (0.67–1.17)	0.380	0.761	**0.70 (0.54–0.93)**	**0.012**	**0.024**	0.77 (0.60–0.99)	0.040	0.240	0.82 (0.60–1.11)	0.193	0.231
rs17057846	allele	G	1			1			1			1		
		A	0.96 (0.71–1.30)	0.809	0.971	**1.46 (1.07–2.01)**	**0.018**	**0.026**	1.01 (0.76–1.34)	0.942	0.942	**1.47 (1.04–2.06)**	**0.027**	0.054
	codominant	G/G	1			1			1			1		
		G/A	0.90 (0.62–1.30)	0.560	1.121	**1.58 (1.08–2.33)**	**0.019**	0.058	1.04 (0.74–1.48)	0.812	0.975	1.43 (0.95–2.15)	0.090	0.135
		A/A	1.18 (0.45–3.08)	0.731	1.096	1.63 (0.64–4.17)	0.307	0.368	0.93 (0.40–2.16)	0.861	0.861	2.92 (0.89–9.55)	0.077	0.154
	dominant	G/G	1			1			1			1		
		G/A-A/A	0.92 (0.64–1.32)	0.645	0.967	**1.59 (1.10–2.30)**	**0.014**	**0.029**	1.03 (0.74–1.44)	0.863	0.863	**1.51 (1.02–2.26)**	**0.042**	0.085
	recessive	G/G-G/A	1			1			1			1		
		A/A	1.23 (0.48–3.18)	0.665	0.997	1.40 (0.55–3.56)	0.475	0.570	0.91 (0.40–2.11)	0.833	0.833	2.56 (0.79–8.32)	0.117	0.234
	log-additive	–	0.96 (0.70–1.31)	0.798	0.957	**1.46 (1.06–2.01)**	**0.020**	**0.030**	1.01 (0.76–1.35)	0.940	0.940	**1.51 (1.06–2.15)**	**0.022**	**0.044**

Continued

SNP ID	Model	Genotype	≤ 49 years			> 49 years			Male			Female		
			OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)
rs2961920	allele	C	1			1			1			1		
		A	1.25 (0.97–1.60)	0.081	0.484	**1.40 (1.09–1.80)**	**0.009**	**0.028**	1.22 (0.97–1.54)	0.088	0.264	**1.48 (1.12–1.95)**	**0.006**	**0.034**
	codominant	C/C	1			1			1			1		
		C/A	1.12 (0.75–1.69)	0.575	0.862	**1.50 (1.02–2.23)**	**0.042**	0.084	1.07 (0.74–1.55)	0.723	1.084	**1.73 (1.11–2.67)**	**0.015**	0.087
		A/A	1.62 (0.97–2.71)	0.065	0.393	**1.87 (1.11–3.14)**	**0.018**	0.055	1.53 (0.96–2.43)	0.073	0.218	**2.15 (1.19–3.88)**	**0.011**	0.067
	dominant	C/C	1			1			1			1		
		C/A-A/A	1.25 (0.85–1.83)	0.261	1.566	**1.59 (1.10–2.31)**	**0.014**	**0.041**	1.19 (0.84–1.68)	0.330	0.989	**1.82 (1.20–2.76)**	**0.005**	**0.028**
	recessive	C/C–C/A	1			1			1			1		
		A/A	1.51 (0.96–2.36)	0.072	0.433	1.48 (0.93–2.35)	0.102	0.305	1.47 (0.98–2.21)	0.064	0.387	**1.54 (0.91–2.61)**	**0.105**	0.316
	log-additive	–	1.26 (0.97–1.62)	0.078	0.471	**1.39 (1.08–1.79)**	**0.011**	**0.032**	1.22 (0.97–1.53)	0.093	0.280	**1.51 (1.13–2.01)**	**0.005**	**0.030**
rs58747524	allele	T	1			1			1			1		
		C	1.06 (0.80–1.41)	0.677	1.015	**1.53 (1.14–2.05)**	**0.004**	**0.027**	1.11 (0.85–1.44)	0.442	0.663	**1.54 (1.12–2.13)**	**0.008**	**0.023**
	codominant	T/T	1			1			1			1		
		T/C	1.00 (0.70–1.44)	0.992	0.992	**1.66 (1.14–2.41)**	**0.008**	**0.049**	1.13 (0.81–1.59)	0.470	1.411	**1.55 (1.04–2.32)**	**0.033**	0.099
		C/C	1.30 (0.61–2.79)	0.499	0.998	1.95 (0.88–4.33)	0.100	0.199	1.19 (0.60–2.33)	0.619	0.742	**2.85 (1.06–7.68)**	**0.038**	0.114
	dominant	T/T	1			1			1			1		
		T/C–C/C	1.04 (0.73–1.47)	0.845	1.014	**1.69 (1.18–2.42)**	**0.004**	**0.025**	1.14 (0.82–1.58)	0.428	0.855	**1.65 (1.12–2.44)**	**0.012**	**0.036**
	recessive	T/T-T/C	1			1			1			1		
		C/C	1.30 (0.62–2.74)	0.491	0.981	1.60 (0.73–3.49)	0.242	0.484	1.13 (0.58–2.18)	0.724	0.869	2.38 (0.90–6.32)	0.082	0.491
	log-additive	–	1.07 (0.80–1.42)	0.667	1.000	**1.53 (1.14–2.07)**	**0.005**	**0.031**	1.11 (0.85–1.45)	0.434	0.651	**1.60 (1.15–2.24)**	**0.006**	**0.018**

Table 3. The association between SNPs and LDH after stratification by age and gender under different genotypic models. SNP: Single nucleotide polymorphism; OR: Odds ratio; 95% CI: 95% confidence interval; FDR: False discovery rate. $p < 0.05$ indicates SNP with statistical significance. The highlighted in bold represent significant association.

that *MIR3142HG* is abnormally expressed in lung fibroblasts induced by interleukin 1β (*IL-1β*), which plays an important role in inflammation regulation [14]. Studies have reported that SNP can significantly influence gene expression [25,26]. We speculate that *MIR3142HG* polymorphisms have some possible roles in the occurrence of LDH. In this study, we explored the relationship between the *MIR3142HG* polymorphism and LDH susceptibility in the Chinese Han population. We found that individuals carrying the T and TT genotype of rs7727115 in *MIR3142HG* had a reduced risk of developing LDH compared to the other genotypes, whereas rs17057846 (G > A), rs2961920 (C > A), and rs58747524 (T > C) were associated with an increased susceptibility to LDH. To the best of our knowledge, this is the first study of *MIR3142HG* polymorphism in LDH, which can serve as potential genetic markers for LDH risk assessment, which may contribute to early diagnosis, personalized treatment strategies, and preventive measures for LDH patients.

Our study indicated that rs7727115 was associated with a reduced risk of LDH, and rs17057846, rs2961920, and rs58747524 were associated with an increased susceptibility to LDH. According to the present results, a previous study has demonstrated that rs17057846, rs2961920, and rs58747524 are significantly associated with an increased risk of glioma [27]. Besides, rs7727115 could reduce the risk of steroid-induced osteonecrosis of the femoral head [20]. These findings suggest that *MIR3142HG* polymorphisms have a crucial role in the progression of human diseases including LDH. Several studies have provided more and more evidence that intron SNPs can confer human diseases susceptibility by affecting gene expression [28–30]. Here, we evaluated the impact of SNPs on the mRNA expression of *MIR3142HG*, we found that rs17057846 and rs2961920 were significantly associated with *MIR3142HG* expression. Besides, the possible functions of *MIR3142HG* SNPs were predicted and we found that rs17057846 could influence Promoter histone marks, Enhancer histone marks, DNAse, and Selected eQTL hits. Rs2961920 might be involved in Enhancer histone marks, Proteins bound, Motifs changed, and GRASP eQTL hits. Taken above, we speculated that *MIR3142HG* SNPs, especially rs17057846 and rs2961920 may affect gene expression and function, and then contribute to LDH development, which needs further study and confirmation.

Previously published studies have revealed that age is the risk factor for LDH, and the number of individuals diagnosed with symptomatic cervical and lumbar disc herniation increased with age [31–33]. In this study, the mean age was 49 years in the case and control groups, thus we stratified by 49 years. Age-stratified analysis showed that rs7727115 reduced the risk of LDH in patients aged > 49 years, and rs17057846, rs2961920, and rs58747524 had a risk-increasing influence on the patients aged > 49 years, but not in aged ≤ 49 years. Similar to our results, rs9450607 in the Eyes Shut Homolog (*EYS*) gene was related to an increased risk of LDH in people aged ≥ 49 years, but not in those aged < 49 years [34]. Additionally, rs6265, rs11030104, and rs10767664 in Brain-Derived Neurotrophic Factor (BDNF) could significantly increase the risk of LDH in those aged > 50 years, but not in those aged ≤ 50 years [35]. Rs77681114 polymorphism in Gasdermin C (*GSDMC*) protected LDH risk at age ≥ 49 years, but not at age < 49 years [36]. To sum up, these findings indicated that the association between genetic polymorphisms and LDH susceptibility may depend on age. Gender is also another risk factor for LDH, and the incidence of LDH was higher in women than in men [32]. When stratified by gender, we observed that rs17057846, rs2961920, and rs58747524 had a risk-increasing influence on LDH in females, but not in males. In consistent with our results, Zhu et al. found that Interleukin 1 Receptor Type 1 (*IL1R1*) rs956730 was statistically significant in LDH among males, but not in females [24]. The MMP-3 gene rs591058 was related to an increased susceptibility to LDH in females, but not in males [37]. Besides, rs1008993 was associated with increased LDH risk in males, but not in females [38]. These results suggest that genetic susceptibility to LDH is influenced by gender. Besides, we found that rs7727115, rs2961920, rs2431689, and rs58747524 also were associated with the risk of severity of LDH and hernia levels. Taken above, our study given that the association of *MIR3142HG* polymorphisms and LDH risk may rely on age, gender, severity of LDH, and hernia levels, highlights the importance of considering heterogeneity in studies of the association between genetics and LDH.

MPV and RDW are important indicators for evaluating the inflammatory state and immune response of the body. Dagistan et al. found that MPV and RDW may be related to the occurrence of LDH [5]. Our study showed that rs7727115 genotypes were significantly associated with RDW levels. Besides, AA and AG genotypes in rs2431689 were related to an increased concentration of LYM in LDH patients. We speculate that certain genotypes (such as rs 7727115 and rs 2431689) may influence the levels of these indicators, thereby affecting the immune response in LDH, which needed to be further validated.

Inevitably, the current study has some limitations. First, the present study focuses on the Chinese Han population, the association is needed to be verified in another ethnicity. Second, some potential risk factors, such as activity status and occupation, were not included in our analysis due to the limited information, which should be further evaluated in future studies. Third, our study is the basic research, the association between *MIR3142HG* polymorphisms and the expression of *MIR3142HG* need to be further investigated. Despite the above limitations, this is the first study to determine the impact of *MIR3142HG* polymorphisms on LDH risk.

Conclusion

This study indicated that rs2431689, rs7727115, rs17057846, rs2961920, and rs58747524 in *MIR3142HG* were significantly associated with LDH susceptibility in the Chinese population, which may serve as a new biomarker for prevention and diagnosis of LDH.

SNP ID	Model	Genotype	Disc herniation			Disc prolapse			Single hernia			Multiple hernias		
			OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)
rs1582417	allele	G	1			1			1			1		
		A	1.04 (0.77–1.41)	0.779	0.779	0.96 (0.79–1.17)	0.678	0.678	1.05 (0.82–1.35)	0.677	0.677	0.94 (0.76–1.18)	0.605	0.726
	codominant	G/G	1			1			1			1		
		G/A	0.97 (0.62–1.52)	0.886	0.886	0.88 (0.65–1.18)	0.394	0.394	0.85 (0.58–1.24)	0.385	0.577	0.98 (0.71–1.36)	0.916	0.916
		A/A	1.17 (0.62–2.20)	0.626	0.939	0.97 (0.64–1.47)	0.888	0.888	1.26 (0.75–2.10)	0.383	0.460	0.85 (0.52–1.40)	0.531	0.637
	dominant	G/G	1			1			1			1		
		G/A-A/A	1.01 (0.66–1.55)	0.962	0.962	0.90 (0.69–1.18)	0.455	0.455	0.93 (0.65–1.33)	0.698	0.837	0.95 (0.70–1.31)	0.771	0.771
	recessive	G/G-G/A	1			1			1			1		
		A/A	1.19 (0.67–2.13)	0.551	0.827	1.04 (0.71–1.53)	0.841	1.009	1.38 (0.86–2.20)	0.181	0.542	0.86 (0.54–1.37)	0.527	0.632
	log-additive	–	1.05 (0.78–1.43)	0.735	0.882	0.96 (0.79–1.17)	0.664	0.664	1.06 (0.82–1.36)	0.677	0.677	0.94 (0.75–1.18)	0.596	0.715
rs2431689	allele	G	1			1			1			1		
		A	1.06 (0.71–1.59)	0.769	0.922	1.12 (0.87–1.45)	0.377	0.452	1.35 (0.98–1.85)	0.062	0.123	0.95 (0.70–1.29)	0.744	0.744
	codominant	G/G	1			1			1			1		
		G/A	1.04 (0.65–1.67)	0.874	1.048	1.16 (0.86–1.57)	0.324	0.389	**1.50 (1.03–2.18)**	**0.034**	0.207	0.89 (0.63–1.28)	0.541	0.649
		A/A	1.27 (0.34–4.67)	0.720	0.864	1.09 (0.45–2.68)	0.845	1.014	1.19 (0.37–3.85)	0.771	0.771	1.17 (0.44–3.08)	0.751	0.751
	dominant	G/G	1			1			1			1		
		G/A-A/A	1.06 (0.67–1.67)	0.811	0.973	1.16 (0.86–1.55)	0.326	0.391	**1.48 (1.02–2.13)**	**0.038**	0.113	0.92 (0.65–1.29)	0.623	0.747
	recessive	G/G-G/A	1			1			1			1		
		A/A	1.26 (0.34–4.60)	0.730	0.876	1.05 (0.43–2.56)	0.917	0.917	1.05 (0.33–3.39)	0.929	0.929	1.20 (0.46–3.15)	0.708	0.708
	log-additive	–	1.07 (0.71–1.59)	0.754	0.754	1.13 (0.87–1.46)	0.366	0.439	1.37 (0.99–1.89)	0.059	0.119	0.95 (0.70–1.29)	0.750	0.750
rs7727115	allele	G	1			1			1			1		
		T	0.80 (0.58–1.11)	0.184	1.102	**0.79 (0.64–0.97)**	**0.022**	**0.044**	**0.75 (0.57–0.99)**	**0.039**	0.117	**0.78 (0.61–0.98)**	**0.036**	0.071
	codominant	G/G	1			1			1			1		
		G/T	0.80 (0.52–1.23)	0.308	0.923	0.80 (0.60–1.05)	0.108	0.216	0.75 (0.52–1.08)	0.122	0.244	0.80 (0.58–1.10)	0.162	0.323
		T/T	0.63 (0.28–1.40)	0.254	0.762	**0.59 (0.35–0.98)**	**0.042**	0.126	0.56 (0.28–1.12)	0.101	0.302	**0.54 (0.29–0.98)**	**0.043**	0.130
	dominant	G/G	1			1			1			1		
		G/T-T/T	0.77 (0.51–1.16)	0.210	0.632	**0.76 (0.58–0.99)**	**0.042**	0.085	0.72 (0.51–1.02)	0.061	0.122	0.75 (0.55–1.02)	0.064	0.128
	recessive	G/G-G/T	1			1			1			1		
		T/T	0.70 (0.32–1.52)	0.365	1.095	0.66 (0.40–1.08)	0.094	0.282	0.64 (0.32–1.26)	0.193	0.290	0.60 (0.33–1.07)	0.085	0.510
	log-additive	–	0.79 (0.57–1.10)	0.170	1.020	**0.78 (0.63–0.96)**	**0.020**	**0.041**	**0.75 (0.57–0.99)**	**0.042**	0.127	**0.76 (0.60–0.97)**	**0.028**	0.083
rs17057846	allele	G	1			1			1			1		
		A	1.19 (0.83–1.70)	0.340	0.509	1.18 (0.94–1.49)	0.159	0.239	1.09 (0.80–1.47)	0.584	0.700	1.25 (0.96–1.62)	0.099	0.149
	codominant	G/G	1			1			1			1		
		G/A	1.25 (0.81–1.93)	0.320	0.640	1.17 (0.88–1.56)	0.280	0.420	1.02 (0.70–1.48)	0.923	0.923	1.29 (0.93–1.78)	0.122	0.365
		A/A	1.20 (0.39–3.72)	0.751	0.751	1.47 (0.73–2.97)	0.284	0.426	1.50 (0.62–3.62)	0.369	0.554	1.48 (0.67–3.29)	0.331	0.496
	dominant	G/G	1			1			1			1		
		G/A-A/A	1.24 (0.81–1.90)	0.314	0.627	1.20 (0.91–1.58)	0.199	0.298	1.06 (0.74–1.52)	0.745	0.745	1.31 (0.96–1.79)	0.091	0.137
	recessive	G/G-G/A	1			1			1			1		
		A/A	1.11 (0.36–3.40)	0.855	0.855	1.39 (0.69–2.79)	0.352	0.704	1.49 (0.62–3.57)	0.372	0.446	1.36 (0.62–2.98)	0.447	0.671
	log-additive	–	1.19 (0.83–1.71)	0.350	0.700	1.19 (0.94–1.05)	0.157	0.235	1.10 (0.80–1.49)	0.563	0.676	1.26 (0.97–1.65)	0.088	0.132

Continued

SNP ID	Model	Genotype	Disc herniation			Disc prolapse			Single hernia			Multiple hernias		
			OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)	OR (95%CI)	*p*	*p* (FDR)
rs2961920	allele	C	1			1			1			1		
		A	1.20 (0.89–1.61)	0.230	0.689	**1.36 (1.12–1.64)**	**0.002**	**0.010**	**1.44 (1.13–1.83)**	**0.004**	**0.022**	**1.27 (1.02–1.57)**	**0.033**	0.099
	codominant	C/C	1			1			1			1		
		C/A	1.31 (0.82–2.10)	0.263	1.580	1.32 (0.97–1.79)	0.075	0.226	1.49 (0.99–2.25)	0.054	0.163	1.28 (0.91–1.81)	0.161	0.323
		A/A	1.40 (0.76–2.59)	0.286	0.571	**1.86 (1.26–2.74)**	**0.002**	**0.010**	**2.07 (1.25–3.43)**	**0.005**	**0.030**	**1.63 (1.04–2.53)**	**0.032**	0.193
	dominant	C/C	1			1			1			1		
		C/A-A/A	1.33 (0.85–2.08)	0.211	0.632	**1.45 (1.09–1.94)**	**0.011**	**0.033**	**1.63 (1.11–2.40)**	**0.013**	0.080	1.37 (0.99–1.90)	0.061	0.184
	recessive	C/C–C/A	1			1			1			1		
		A/A	1.19 (0.69–2.05)	0.528	1.057	**1.58 (1.12–2.21)**	**0.009**	0.053	**1.61 (1.05–2.48)**	**0.031**	0.184	1.40 (0.95–2.08)	0.090	0.271
	log-additive	–	1.20 (0.89–1.62)	0.230	0.689	**1.36 (1.12–1.64)**	**0.002**	**0.010**	**1.44 (1.12–1.85)**	**0.004**	**0.025**	**1.03 (1.03–1.59)**	**0.029**	0.057
rs58747524	allele	T	1			1			1			1		
		C	1.18 (0.84–1.65)	0.336	0.673	**1.29 (1.04–1.61)**	**0.019**	0.057	1.21 (0.92–1.60)	0.173	0.259	**1.36 (1.07–1.73)**	**0.013**	0.079
	codominant	T/T	1			1			1			1		
		T/C	0.96 (0.61–1.50)	0.842	1.263	**1.41 (1.07–1.86)**	**0.014**	0.087	1.14 (0.79–1.64)	0.480	0.576	**1.49 (1.08–2.05)**	**0.014**	0.084
		C/C	1.93 (0.87–4.25)	0.104	0.623	1.46 (0.80–2.65)	0.221	0.441	1.70 (0.82–3.49)	0.152	0.303	1.69 (0.87–3.27)	0.119	0.238
	dominant	T/T	1			1			1			1		
		T/C–C/C	1.07 (0.70–1.63)	0.756	1.134	**1.42 (1.09–1.85)**	**0.011**	0.063	1.20 (0.85–1.71)	0.296	0.445	**1.51 (1.11–2.05)**	**0.008**	**0.048**
	recessive	T/T-T/C	1			1			1			1		
		C/C	1.96 (0.91–4.24)	0.087	0.523	1.26 (0.70–2.26)	0.447	0.671	1.61 (0.79–3.26)	0.187	0.374	1.42 (0.75–2.71)	0.283	0.567
	log-additive	–	1.17 (0.84–1.64)	0.357	0.535	**1.32 (1.05–1.65)**	**0.016**	**0.047**	1.22 (0.92–1.62)	0.172	0.259	**1.40 (1.09–1.79)**	**0.009**	0.057

Table 4. The association between SNPs and LDH stratified by severity of lumbar disc herniation and hernia levels. SNP: Single nucleotide polymorphism; OR: Odds ratio; 95% CI: 95% confidence interval; FDR: False discovery rate. $p < 0.05$ indicates SNP with statistical significance. The highlighted in bold represent significant association.

Model	Training Bal. Acc	Testing Bal. Acc.[b]	CVC
rs2961920	0.5391	0.5159	6/10
rs2431689, rs58747524	0.5487	0.5145	7/10
rs2431689, rs2961920, rs58747524	0.5568	0.5034	5/10
rs1582417,rs7727115, rs2961920, rs58747524	0.5660	0.4880	4/10
rs1582417, rs7727115, rs17057846, rs2961920, rs58747524	0.5754	0.5036	5/10
rs1582417, rs2431689, rs7727115, rs17057846, rs2961920, rs58747524	0.5802	0.5149	10/10

Table 5. SNP–SNP interaction models of the *MIR3142HG* gene analyzed by the GMDR[a]. a Whole dataset statistics: Training Balanced Accuracy, 0.5782; Training Accuracy, 0.5782; Training Sensitivity, 0.5302; Training Specificity, 0.6261; Training Odds Ratio, 1.8899 (1.3227, 2.7003); Training χ2 (P), 12.3300 ($p = 0.0004$); Training Precision, 0.5860; Training Kappa, 0.1563; Training F-Measure, 0.5567. GMDR: Generalized Multifactor dimensionality reduction; Bal. Acc: Balanced accuracy; CVC: Cross-validation consistency.

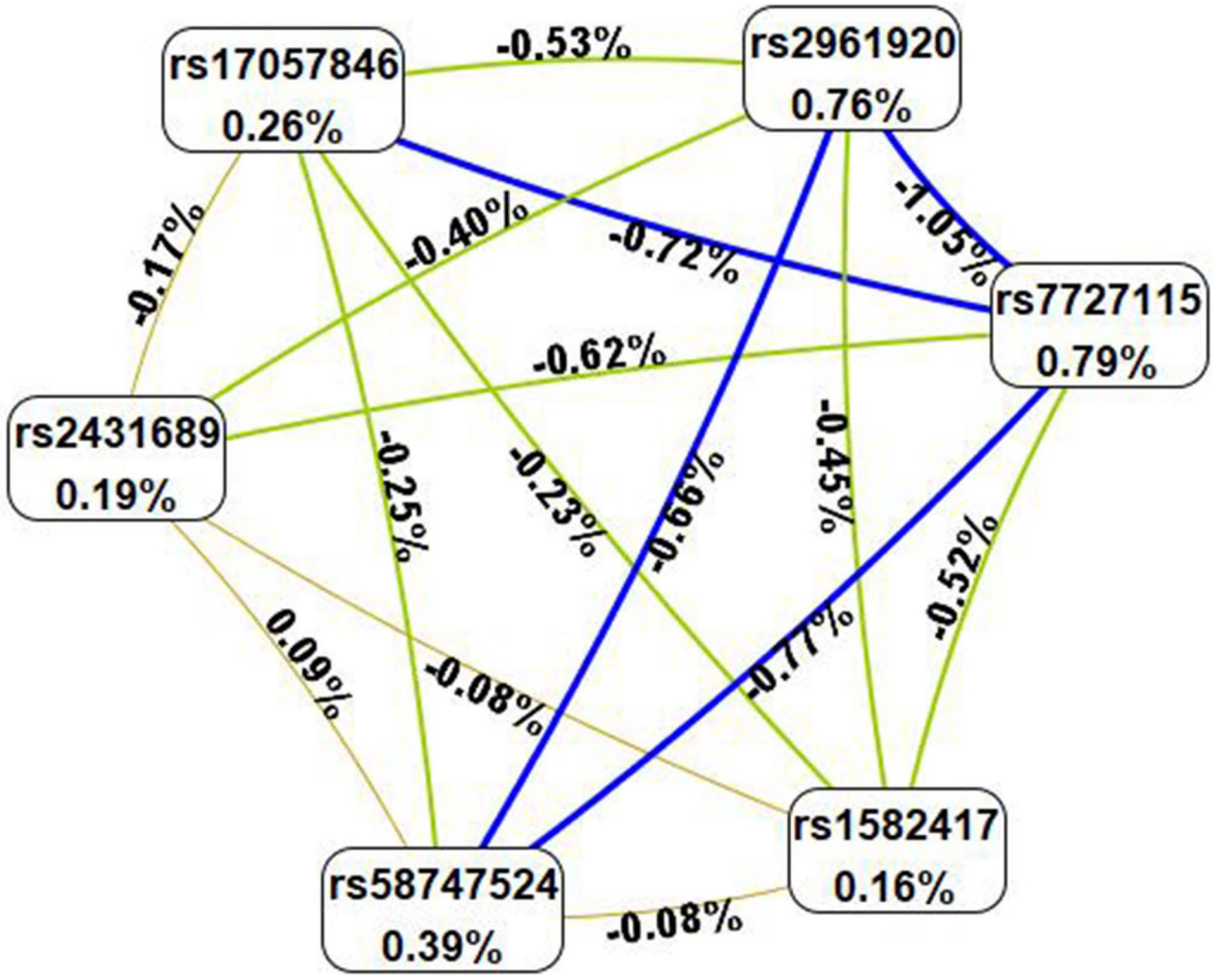

Fig. 2. The tree diagram analysis of SNP interaction. Values in nodes represent the information gains of individual attribute (main effects). Values between nodes are information gains of each pair of attributes (interaction effects). The brown with positive percent entropy represents a moderate level of synergy on the phenotype. The green and blue with negative values indicate redundancy or lack of synergy between the SNPs.

	rs1582417				rs2431689				rs7727115			
Characteristics	**AA**	**GA**	**GG**	***p***	**AA**	**AG**	**GG**	***p***	**TT**	**GT**	**GG**	***p***
NEU	67.688 ± 1.729	68.121 ± 1.050	70.326 ± 0.940	0.229	66.940 ± 3.402	67.655 ± 1.405	69.484 ± 0.756	0.419	71.469 ± 1.937	68.780 ± 1.078	68.593 ± 0.915	0.564
MPV	11.594 ± 0.141	11.477 ± 0.095	11.398 ± 0.094	0.568	11.483 ± 0.332	11.506 ± 0.106	11.443 ± 0.076	0.897	11.153 ± 0.221	11.408 ± 0.104	11.553 ± 0.077	0.201
MON	6.884 ± 0.275	6.788 ± 0.151	6.506 ± 0.169	0.343	6.403 ± 0.422	6.829 ± 0.197	6.647 ± 0.127	0.673	6.464 ± 0.320	6.724 ± 0.172	6.668 ± 0.142	0.830
LYM	1.810 ± 0.108	1.653 ± 0.044	1.615 ± 0.047	0.138	2.094 ± 0.300	1.719 ± 0.069	0.624 ± 0.035	**0.042**	1.604 ± 0.093	1.643 ± 0.051	1.686 ± 0.045	0.718
RDW	13.352 ± 0.148	13.358 ± 0.106	13.291 ± 0.087	0.880	13.583 ± 0.358	13.338 ± 0.135	13.320 ± 0.072	0.817	13.147 ± 0.159	13.575 ± 0.121	13.173 ± 0.070	**0.007**
IBIL	9.800 ± 1.958	6.991 ± 0.318	7.262 ± 0.399	**0.026**	6.908 ± 0.725	7.482 ± 0.381	7.485 ± 0.467	0.967	5.821 ± 0.405	6.800 ± 0.267	8.299 ± 0.642	**0.048**
	rs17057846				**rs2961920**				**rs58747524**			
Characteristics	**AA**	**GA**	**GG**	***p***	**AA**	**CA**	**CC**	***p***	**TT**	**CT**	**CC**	***p***
NEU	75.164 ± 2.854	69.032 ± 1.067	68.391 ± 0.873	0.125	68.873 ± 1.495	68.646 ± 0.914	69.583 ± 1.245	0.831	68.510 ± 0.951	68.892 ± 1.014	71.639 ± 2.121	0.520
MPV	11.457 ± 0.215	11.508 ± 0.967	11.443 ± 0.080	0.880	11.422 ± 0.118	11.567 ± 0.080	11.321 ± 0.132	0.214	11.408 ± 0.091	11.544 ± 0.086	11.309 ± 0.229	0.457
MON	5.033 ± 0.444	6.789 ± 0.183	6.740 ± 0.130	**0.004**	6.242 ± 0.222	6.943 ± 0.144	6.575 ± 0.203	**0.026**	6.734 ± 0.143	6.802 ± 0.166	5.607 ± 0.367	**0.021**
LYM	1.375 ± 0.131	1.639 ± 0.048	1.696 ± 0.043	0.116	1.684 ± 0.070	1.686 ± 0.047	1.594 ± 0.054	0.431	1.682 ± 0.481	1.654 ± 0.045	1.547 ± 0.116	0.581
RDW	13.143 ± 0.270	13.206 ± 0.090	13.421 ± 0.088	0.228	13.159 ± 0.118	13.325 ± 0.087	13.479 ± 0.133	0.208	44.502 ± 0.375	43.961 ± 0.244	44.000 ± 0.648	0.125
IBIL	10.395 ± 2.851	7.317 ± 0.415	7.367 ± 0.474	0.209	8.032 ± 0.662	7.240 ± 0.317	7.481 ± 0.939	0.673	7.392 ± 0.551	7.327 ± 0.371	9.175 ± 1.811	0.423

Table 6. The relationship between genotypes at different loci and clinical parameters. NEU: Neutrophil ratio; MPV: Mean platelet volume; MON: Mononuclear cell ratio; LYM: Lymphocyte count; RDW: Red blood cell distribution Width; IBIL: Indirect Bilirubin. $p < 0.05$ indicates statistical significance. The highlighted in bold represent statistical significance.

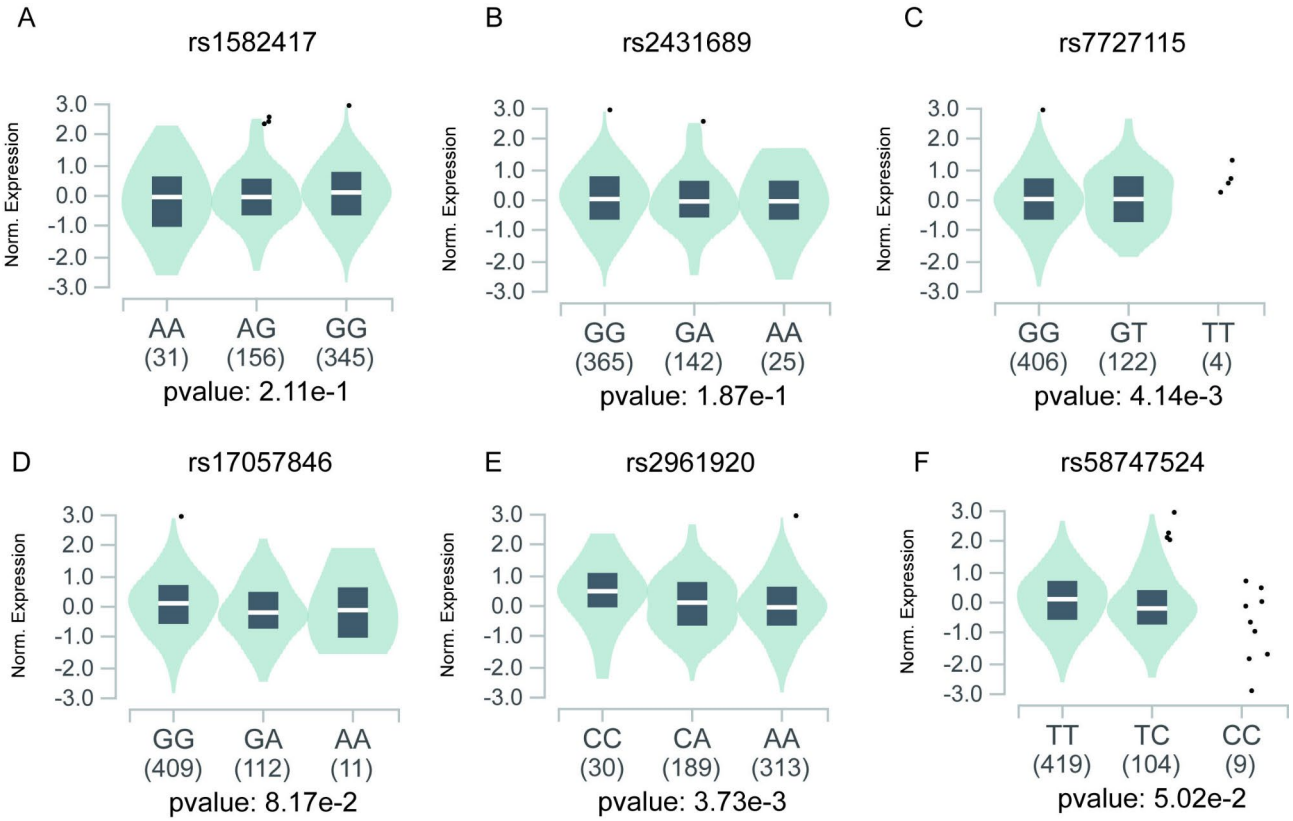

Fig. 3. Functional relevance of each SNP on gene expression of *MIR3142HG* in GTEx database. (**A**) rs1582417, (**B**) rs2431689, (**C**) rs7727115, (**D**) rs17057846, (**E**) rs2961920, and (**F**) rs58747524.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Qi Dong contributed to methodology, formal analysis, software, validation, and writing. Guoxia Ren contributed to methodology, formal analysis, and interpretation. Dingjun Hao contributed to conceiving the study and revising the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. The participants provided their written informed consent to participate in this study.

Additional information

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