Received: 25 December 2019 | Revised: 7 February 2020 | Accepted: 24 February 2020

DOI: 10.1002/mgg3.1247

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

Genetic polymorphisms of *IL1RN* were associated with lumbar disk herniation risk in a Chinese Han population

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Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background: Interleukin (IL)-1 is a cytokine superfamily, which involved in the inflammatory process and immune response in human body. IL-1 receptor antagonist (*IL1RN*) has been found to be associated with risk of lumbar disk herniation (LDH) in Finland samples. However, to date, there was no investigation focus on the polymorphisms of *IL1RN* in Chinese Han LDH patient.

Materials and Methods: We conducted a case–control study based on 498 LDH patients and 463 controls. Five single-nucleotide polymorphisms (SNPs) in *IL1RN* were genotyped.

Results: As a result, we found that the AG and GG genotypes of rs3181052 were associated with decreased risk LDH under the dominant model (OR = 0.74, 95%CI: 0.57–0.96, p = .025). In the stratification analysis, the frequency of the "A" allele of rs17042888 was significantly lower in elder LDH cases than in controls (OR = 0.723, 95%CI: 0.544–0.961, p = .025). In addition, the AG and AA genotypes of rs17042888 were associated with decreased risk of LDH in elder group under the dominant model (OR = 0.69, 95%CI: 0.49–0.98, p = .038). The GG genotype of rs315919 was identified have correlation with decreased risk of LDH in elder group under the recessive model (OR = 0.60, 95%CI: 0.37–0.97, p = .034).

Conclusions: Our data showed that *IL1RN* may be a susceptibility gene for risk of LDH in Chinese Han population.

KEYWORDS

case–control study, gene polymorphisms, IL-1 receptor antagonist (*IL1RN*), Lumbar disk herniation (LDH)

1 | INTRODUCTION

Lumbar disk herniation (LDH) is one of the most common orthopedic disorders. LDH is mainly caused by the degenerative changes in various parts of the lumbar disk, including central nucleus pulposus, ring annulus fibrosus, and cartilage (Mio et al., 2007). Under the action of external factors, annulus fibrosus may be disrupted, and nucleus pulposus may further protrude or prolapse from the rupture to the rear or spinal canal. These situations will lead to the stimulation or oppression of adjacent spinal nerve root, and resulting in backaches, numbness of lower extremity, and a series of clinical symptoms (Vialle, Vialle, Henao, & Giraldo, 2010). LDH make patients suffer from low living quality and high health care costs (Eskola et al., 2012). Although several risk factors associated with LDH have been reported in epidemiologic studies (Andersson, 1998), the pathogenesis and etiology of LDH is still unclear. However, twins studies showed that more than 70% of the LDH patients have a positive family history (Battié, Videman, Levälahti, Gill, & Kaprio, 2008), which arouse researchers' interest to identify genes associated with development of LDH.

Previous literatures have reported several types of susceptibility genes for LDH, including structural, catabolic, and inflammatory-related genes (Mayer et al., 2013). The nucleus pulposus and annulus fibrosus of lumbar disk are mainly composed of type I and type II collagen (Le, Freemont, & Hoyland, 2005; Sive et al., 2002). Some researchers believed that excessive degradation and fibrosis of type I and type II collagen will lead to LDH, and the catabolic processes are actually regulated by a series of cytokines (Watanabe et al., 2003). Interleukin (IL)-1 is a cytokine superfamily, which has been reported that involved in the inflammatory process and immune response in human body (Balasubramanian et al., 2006). IL-1 cytokine family included IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra), which encoded by *IL1A*, *IL1B*, and *IL1RN*, respectively. The level of IL-1β has been found increased in the collagen of LDH patients (Attur et al., 2002). Moreover, polymorphisms of *IL1B* and *IL1RN* were associated with risk of LDH in a Finland population (Solovieva et al., 2004). However, to date, little information is found about the correlation of *IL1RN* (OMIM:147679) polymorphisms and LDH risk in the Chinese population.

Age was a major risk factor for LDH. Therefore, in this study, the individuals were divided to two groups based on their age. We attempted to investigate the candidate SNPs and their interaction with age that may have correlation with LDH risk in Chinese Han samples.

2 | MATERIALS AND METHODS

2.1 | Subjects

All subjects in our study were unrelated Han Chinese individuals and coming from Shaanxi Province of China. The overall number of 498 LDH patients and 463 healthy individuals were recruited between September 2015 and September 2017 at the Xi'an Jiaotong University Hospital Medical College Red Cross Hospital. All the patients were recently diagnosed with LDH according to the magnetic resonance imaging (sagittal and axial images obtained with a 1.5-T imaging system), and a history of unilateral pain from the femoral or sciatic nerve to the corresponding dermatome of the nerve root for more than 3 months. Patients with trauma-related LDH, rheumatic, spinal tumor, or spondylitis were excluded. The controls were randomly recruited healthy individuals. We excluded those with known disease or cancers.

All subjects were at least 18 years old and were in good mental condition. The Human Research Committee for Approval of Research Involving Human Subjects, Xi'an Jiaotong University Hospital Medical College Red Cross Hospital, approved the use of human blood samples in this study. The written informed consent was signed by all of them.

2.2 | SNP genotyping

Candidate SNPs were selected from DisGenet database (http://www.disgenet.org/). First, we selected SNPs in *IL1RN* that associated with other types of disease. Then, we excluded those SNPs with minor allele frequencies under 5% in the CHB population of 1,000 genome project (http://www.internationalgenome.org/). Finally, five SNPs (rs17042888, rs315919, rs928940, rs3181052, and rs452204) in *IL1RN* were selected for our study. To date, these SNPs have not been reported for LDH susceptibility. Genomic DNA was prepared from peripheral blood samples using the GoldMag-Mini Purification Kit (GoldMag Co. Ltd.), following the manufacturer's instructions. DNA concentrations were measured by NanoDrop 2000 (Thermo Scientific) at a wavelength value of A260 and A280 nm. Primers for amplification process and single base extension reactions were designed using the Sequenom MassARRAY Assay Design 3.0 software. SNP genotyping was performed by Sequenom MassARRAY RS1000 (Sequenom) (Thomas et al., 2007). Finally, Sequenom Typer 4.0 software (Sequenom) was used to perform data management and analyses (Gabriel, Ziaugra, & Tabbaa, 2009).

2.3 | Statistical analyses

All of the statistical analyses were performed with Microsoft Excel (Microsoft Corporation) and the SPSS 21.0 statistical package (SPSS, Chicago, IL, USA). The Hardy–Weinberg Equilibrium (HWE) test was used for the controls before analysis. Differences between the cases and controls in the distributions of gender, age, and allele frequencies of the SNPs were evaluated using χ^2 tests and Welch's *t* tests. The subjects were divided into two groups: younger group and elder group based on their age. Associations between the genotypes of SNPs and LDH susceptibility were evaluated by odds ratios (ORs) and 95% confidence intervals (CIs). Four genetic models (codominant, dominant, recessive, and log-additive) were used to assess the associations. All *p* values were two sided, and *p* values under .05 were considered to be statistical significance.

3 | RESULTS

The overall number of 498 LDH patients and 463 healthy individuals were included in the study. The gender and age of two groups are described in Table 1. The mean age of the participants was 50.27 ± 12.53 years in the case group and 50.65 ± 11.8 years in the control group. No significant difference in the distribution of gender and age was observed between two groups ($p > .05$).

The basic information of the *IL1RN* polymorphisms (rs17042888, rs315919, rs928940, rs3181052, and rs452204) is shown in Table 2, including gene, band, position, role, alleles, and minor allele frequency (MAF). We compared the difference in frequency distributions of alleles between LDH cases and controls by Chi-squared test. However, no associations were observed between the alleles and LDH risk.

The subjects were divided into two groups based on their age: younger group and elder group. The MAFs of SNPs in younger and elder groups are listed in Table 3. We found one significant SNP was associated with LDH risk in elder group. The frequency of the "A" allele of rs17042888 was significantly lower in elder LDH cases than in controls (0.219 versus. 0.279), which suggested that "A" allele of rs17042888 was a protective allele against LDH risk (OR = 0.72, 95%CI: 0.54–0.96, $p = .025$).

Next, we assumed that the major allele of each SNP was a reference allele and calculated the OR and 95%CI between each variant and LDH risk under four genetic models (Table 4). We found that rs3181052 was associated with LDH risk under the dominant model. Compared with rs3181052

TABLE 1 Distributions of age and gender in LDH patients and controls

Variables	cases($N = 498$)	%	Controls ($N = 463$)	%	*p*	
Gender						.413
Female	200	40.2	198	42.8		
Male	298	59.8	265	57.2		
Age						.978
Mean ± *SD*	50.27 ± 12.53		50.65 ± 11.8			.964
≤50	233	46.8	216	46.7		
>50	265	53.2	247	53.3		

Note: *p* values were calculated from χ^2 test/student's *t* test.

TABLE 2 Basic information of candidate SNPs in this study

						MAF				
SNP ID	Gene	Band	Position	Role	Alleles A/B	Case	Control	*p*-HWE	OR(95% CI)	p^a
rs17042888	*IL1RN*	2q13	113862173	Intron	A/G	0.239	0.261	.47	0.89 (0.72–1.09)	.257
rs315919	*IL1RN*	2q13	113876213	Intron	T/G	0.391	0.411	.63	0.92 (0.77–1.10)	.370
rs928940	*IL1RN*	2q13	113877495	Intron	T/G	0.375	0.393	<.05[b]	0.93 (0.77–1.12)	.428
rs3181052	*IL1RN*	2q13	113886049	Intron	G/A	0.377	0.406	.25	0.88 (0.74–1.06)	.185
rs452204	*IL1RN*	2q13	113889061	Intron	G/A	0.335	0.348	1	0.95 (0.78–1.14)	.555

Abbreviations: Alleles A/B, Minor/major alleles; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] *p* values were calculated using two-sided Chi-squared test.

[b] *p*-HWE < .05 was excluded from the study.

TABLE 3 Minor allele frequency of SNPs in younger and elder groups

SNP ID	Alleles A/B	Younger group (≤50)					Elder group (>50)				
		MAF case	MAF control	*p*-HWE	OR (95% CI)	p^a	MAF case	MAF control	*p*-HWE	OR (95% CI)	p^a
rs17042888	A/G	0.262	0.241	.47	1.12 (0.83–1.51)	.467	0.219	0.279	.75	0.72 (0.54–0.96)	.025*
rs315919	T/G	0.391	0.39	.89	1.01 (0.77–1.31)	.991	0.391	0.429	.60	0.86 (0.67–1.10)	.217
rs928940	T/G	0.363	0.377	.01[b]	0.94 (0.72–1.24)	.663	0.386	0.407	<.05[b]	0.92 (0.71–1.18)	.503
rs3181052	G/A	0.363	0.398	.79	0.86(0.66–1.13)	.274	0.389	0.413	.25	0.90 (0.70–1.16)	.428
rs452204	G/A	0.33	0.322	.53	1.03 (0.78–1.37)	.816	0.340	0.370	.78	0.88 (0.68–1.138)	.312

Abbreviations: Alleles A/B, Minor/major alleles; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] *p* values were calculated using two-sided Chi-squared test.

[b] *p*-HWE < .05 was excluded from the study.

* *p* value < .05 indicates statistical significance.

AA genotype, carriers of AG and GG exhibited a lower risk of LDH (OR = 0.74, 95%CI: 0.57–0.96, $p = .025$).

In the stratified analysis by age, we found two susceptibility SNPs were associated with LDH risk in elder group (Table 5). The AG and AA genotypes of rs17042888 were associated with decreased risk of LDH under the dominant model (OR = 0.69, 95%CI: 0.49–0.98, $p = .038$). The GG genotype of rs315919 was identified have correlation with decreased risk of LDH under the recessive model (OR = 0.60, 95%CI: 0.37–0.97, $p = .034$).

4 | DISCUSSION

Even to this day, the pathogenesis of degeneration of lumbar disk retained poorly investigated. LDH is a very complicated disease, understanding the molecular genetics leading to susceptibility to LDH is very helpful to designing novel targets for clinical prevention and treatment. In the present study, we investigated the associations between five selected *IL1RN* SNPs and LDH risk, and found that the minor alleles of rs17042888, rs315919, and rs3181052 are significantly associated with decreased risk of LDH in a Chinese Han population. The current data suggested that genetic polymorphisms of *IL1RN* may play a protective role against risk of LDH.

It is noteworthy that rs17042888 and rs315919 were associated with risk of LDH in elder group whose age is over 50; but it is not significant in younger group whose age is less than 50. It is widely accepted that degenerative change of collagen types II in nucleus pulposus and collagen I in annulus fibrosus have close correlation with intervertebral disk degeneration (Nerlich, Boos, Wiest, & Aebi, 1998). Intervertebral disk degeneration is actually a process of aging (Boos et al., 2002). There is a significant difference in the collagenous matrix in the disks between younger and elder (Nerlich et al., 1998), which may explain our results and that is also why we divided the subjects into two groups. The results identified here also suggested that age as an important factor need to be considered in the clinical personalized treatment.

According to the report, SNPs can affect gene function through similar or different molecular mechanisms at gene transcription level, posttranscription level, translation level, posttranslation protein folding, and protein cell localization level (Rose, 2008). For example, Japanese scholars have discovered through in vivo and in vitro experiments that the transition of an snp(g/a) allelic site on Duchenne muscular dystrophy (dmd) gene from G to A can completely inactivate the splice donor site(Tran et al.). This study investigated five SNPs in *IL1RN*, which have been reported have correlation with several disease in previous literatures. Hosgood et al. reported that rs17042888 and two other SNPs in *IL1RN* (rs2637988, rs315949) were in high linkage disequilibrium

TABLE 4 Genotypes frequencies of the SNPs and their associations with risk of LDH

Model	Genotype	Control	Case	OR (95% CI)	*p* value
rs17042888					
Codominant	G/G	249 (53.8%)	280 (56.2%)	1	.310
	A/G	186 (40.2%)	198 (39.8%)	0.95 (0.73–1.23)	
	A/A	28 (6%)	20 (4%)	0.63 (0.34–1.14)	
Dominant	G/G	249 (53.8%)	280 (56.2%)	1	.440
	A/G-A/A	214 (46.2%)	218 (43.8%)	0.91 (0.70–1.17)	
Recessive	G/G-A/G	435 (94%)	478 (96%)	1	.140
	A/A	28 (6%)	20 (4%)	0.64 (0.36–1.16)	
Log-additive	—	—	—	0.88 (0.71–1.09)	.230
rs315919					
Codominant	T/T	162 (35.3%)	175 (35.1%)	1	.160
	G/T	217 (47.3%)	257 (51.6%)	1.10 (0.83–1.45)	
	G/G	80 (17.4%)	66 (13.2%)	0.76 (0.52–1.13)	
Dominant	T/T	162 (35.3%)	175 (35.1%)	1	.960
	G/T-G/G	297 (64.7%)	323 (64.9%)	1.01 (0.77–1.31)	
Recessive	T/T-G/T	379 (82.6%)	432 (86.8%)	1	.070
	G/G	80 (17.4%)	66 (13.2%)	0.72 (0.51–1.03)	
Log-additive	—	—	—	0.92 (0.76–1.10)	.360
rs3181052					
Codominant	A/A	157 (33.9%)	204 (41%)	1	.034
	A/G	236 (51%)	213 (42.8%)	0.70 (0.53–0.92)	
	G/G	70 (15.1%)	81 (16.3%)	0.89 (0.61–1.31)	
Dominant	A/A	157 (33.9%)	204 (41%)	1	.025*
	A/G-G/G	306 (66.1%)	294 (59%)	0.74 (0.57–0.96)	
Recessive	A/A-A/G	393 (84.9%)	417 (83.7%)	1	.620
	G/G	70 (15.1%)	81 (16.3%)	1.09 (0.77–1.55)	
Log-additive	—	—	—	0.89 (0.74–1.06)	.190
rs452204					
Codominant	A/A	195 (42.4%)	230 (46.3%)	1	.270
	A/G	210 (45.6%)	201 (40.4%)	0.81 (0.62–1.07)	
	G/G	55 (12%)	66 (13.3%)	1.02 (0.68–1.53)	
Dominant	A/A	195 (42.4%)	230 (46.3%)	1	.230
	A/G-G/G	265 (57.6%)	267 (53.7%)	0.86 (0.66–1.10)	
Recessive	A/A-A/G	405 (88%)	431 (86.7%)	1	.540
	G/G	55 (12%)	66 (13.3%)	1.13 (0.77–1.65)	
Log-additive	—	—	—	0.95 (0.79–1.14)	.570

Abbreviations: CI, confidence interval; ORs, odds ratios.

*p value < .05 indicates statistical significance.

(LD) and may involve in lymphomagenesis (Iii et al., 2011). Bensen (Bensen et al., 2003) and Buckham(Buckham et al., 2010) reported that rs315919 and rs452204 variants have a close correlation with end-stage renal disease in Caucasians. It is worth noting that rs928940 and rs3181052 have been associated with orthopedic disorders. Jung et al. (Jung et al., 2010) reported that rs928940 polymorphism was associated with risk rheumatoid arthritis in a Korean population. Wu et al. (Wu et al., 2013) reported that haplotype ACAGATACTGCC constructed by rs3181052 and other SNPs in *IL1RN* was significantly associated with increased risk of knee osteoarthritis in Caucasians. In our study, we have shown that polymorphisms of rs17042888, rs315919, and rs3181052 were related to decreased risk of LDH in our

TABLE 5 Association between SNPs and risk of LDH in younger and elder groups

		younger group(≤50)				elder group (>50)			
Model	**Genotype**	**Control**	**Case**	**OR (95% CI)**	***p* value**	**Control**	**Case**	**OR (95% CI)**	***p* value**
rs17042888									
Codominant	G/G	122 (56.5%)	120 (51.5%)	1	.46	127 (51.4%)	160 (60.4%)	1	.063
	A/G	84 (38.9%)	104 (44.6%)	1.26 (0.86–1.85)		102 (41.3%)	94 (35.5%)	0.73 (0.51–1.05)	
	A/A	10 (4.6%)	9 (3.9%)	0.91 (0.36–2.32)		18 (7.3%)	11 (4.2%)	0.47 (0.21–1.03)	
Dominant	G/G	122 (56.5%)	120 (51.5%)	1	.29	127 (51.4%)	160 (60.4%)	1	.038*
	A/G-A/A	94 (43.5%)	113 (48.5%)	1.22 (0.84–1.77)		120 (48.6%)	105 (39.6%)	0.69 (0.49–0.98)	
Recessive	G/G-A/G	206 (95.4%)	224 (96.1%)	1	.68	229 (92.7%)	254 (95.8%)	1	.1
	A/A	10 (4.6%)	9 (3.9%)	0.83 (0.33–2.07)		18 (7.3%)	11 (4.2%)	0.53 (0.25–1.15)	
Log-additive	—	—	—	1.13 (0.82–1.56)	.44	—	—	0.71 (0.53–0.95)	.02
rs315919									
Codominant	T/T	80 (37.4%)	84 (36%)	1	.86	82 (33.5%)	91 (34.3%)	1	.096
	G/T	101 (47.2%)	116 (49.8%)	1.09 (0.72–1.63)		116 (47.4%)	141 (53.2%)	1.10 (0.74–1.61)	
	G/G	33 (15.4%)	33 (14.2%)	0.95 (0.54–1.69)		47 (19.2%)	33 (12.4%)	0.63 (0.37–1.08)	
Dominant	T/T	80 (37.4%)	84 (36%)	1	.79	82 (33.5%)	91 (34.3%)	1	0.83
	G/T-G/G	134 (62.6%)	149 (64%)	1.05 (0.72–1.55)		163 (66.5%)	174 (65.7%)	0.96 (0.67–1.39)	
Recessive	T/T-G/T	181 (84.6%)	200 (85.8%)	1	.71	198 (80.8%)	232 (87.5%)	1	.034*
	G/G	33 (15.4%)	33 (14.2%)	0.91 (0.54–1.53)		47 (19.2%)	33 (12.4%)	0.60 (0.37–0.97)	
Log-additive	—	—	—	1.00 (0.76–1.31)	1	—	—	0.85 (0.65–1.09)	.2
rs3181052									
Codominant	A/A	77 (35.6%)	100 (42.9%)	1	.24	80 (32.4%)	104 (39.2%)	1	.12
	A/G	106 (49.1%)	97 (41.6%)	0.70 (0.47–1.06)		130 (52.6%)	116 (43.8%)	0.68 (0.46–1.00)	
	G/G	33 (15.3%)	36 (15.4%)	0.85 (0.48–1.48)		37 (15%)	45 (17%)	0.93 (0.55–1.58)	
Dominant	A/A	77 (35.6%)	100 (42.9%)	1	.12	80 (32.4%)	104 (39.2%)	1	.099
	A/G-G/G	139 (64.3%)	133 (57.1%)	0.74 (0.50–1.08)		167 (67.6%)	161 (60.8%)	0.74 (0.51–1.06)	
Recessive	A/A-A/G	183 (84.7%)	197 (84.5%)	1	.94	210 (85%)	220 (83%)	1	.53
	G/G	33 (15.3%)	36 (15.4%)	1.02 (0.61–1.71)		37 (15%)	45 (17%)	1.16 (0.72–1.87)	
Log-additive	—	—	—	0.87 (0.66–1.13)	.29	—	—	0.90 (0.70–1.16)	.42
rs452204									
Codominant	A/A	96 (44.9%)	111 (47.8%)	1	.15	99 (40.2%)	119 (44.9%)	1	.56
	A/G	98 (45.8%)	89 (38.4%)	0.78 (0.52–1.16)		112 (45.5%)	112 (42.3%)	0.83 (0.57–1.21)	
	G/G	20 (9.3%)	32 (13.8%)	1.39 (0.75–2.59)		35 (14.2%)	34 (12.8%)	0.81 (0.47–1.39)	
Dominant	A/A	96 (44.9%)	111 (47.8%)	1	.51	99 (40.2%)	119 (44.9%)	1	.29
	A/G-G/G	118 (55.1%)	121 (52.2%)	0.88 (0.61–1.28)		147 (59.8%)	146 (55.1%)	0.83 (0.58–1.17)	
Recessive	A/A-A/G	194 (90.7%)	200 (86.2%)	1	.14	211 (85.8%)	231 (87.2%)	1	.63
	G/G	20 (9.3%)	32 (13.8%)	1.56 (0.86–2.83)		35 (14.2%)	34 (12.8%)	0.88 (0.53–1.47)	
Log-additive	—	—	—	1.03 (0.78–1.36)	.83	—	—	0.88 (0.68–1.13)	.32

Abbreviations: CI, confidence interval; ORs, odds ratios.

*p value < .05 indicates statistical significance.

Chinese Han individuals, which provided new evidence for the correlation between these SNPs and orthopedic disorders.

Some intrinsic drawback need to be stated in our study. LDH is a complex disease that influenced by multiple genes and its interaction with a lot of environmental factors. The present study only investigated the associations between *IL1RN* SNPs and LDH risk; hence, the results may be partial and need to be replicated in other populations. In addition, the variables of body mass index and occupation were not taken into consideration due to a lack of data from participants.

Therefore, the significant SNPs need to be further demonstrated in a larger sample size composed of different populations and contained specific clinical information.

In summary, the present study demonstrated a close correlation of polymorphic markers in *IL1RN* with the risk of LDH. We have shown that rs17042888, rs315919, and rs3181052 in *IL1RN* may have protective role against risk of LDH, which may be further used for targets of clinical prevention and treatment. Further study will focus on the functional role of *IL1RN* involved in the development of LDH.

ACKNOWLEDGMENT

We thank all of the participants for their involvement in this study. We are very grateful to the clinicians and other hospital staff for providing blood samples and data collection for this study.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHORS CONTRIBUTION

Tianbo Jin conceived and designed the experiments; Mingzhu and Hanqilimuge: performed the experiments; Hao Rong collected data; Xue He analyzed the data; Mei Bai contributed reagents/materials/analysis tools; Arigatai wrote the paper.

DATA DEFAULT STATEMENT

Research data are not shared.

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How to cite this article: Tai A, Zhu M, Qilimuge H, et al. Genetic polymorphisms of *IL1RN* were associated with lumbar disk herniation risk in a Chinese Han population. *Mol Genet Genomic Med*. 2020;8:e1247. https://doi.org/10.1002/mgg3.1247