Association Between Genetic Polymorphisms of MIR3142HG and the Risk of Steroid-induced Osteonecrosis of the Femoral Head in the Population of Northern China

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Abstract

Background: Steroid-induced osteonecrosis of the femoral head (ONFH) is aseptic necrosis of the femoral head caused by glucocorticoid use. Once necrotic femoral head necrosis occurs, it irreversibly affects the quality of life seriously. Studies have shown that the susceptibility to steroid-induced ONFH is likely to be related to the variation of miRNA coding genes. Therefore, this study aimed was to investigate the effect of MIR3142HG on steroid-induced ONFH.

Methods: Agena MassARRAY was used to genotype MIR3142HG gene rs1582417, rs2431689, rs7727155 and rs17057846 in 199 patients and 506 healthy people. A genetic model and haplotype analysis were used to evaluate the relationship between the MIR3142HG polymorphism and the risk of steroid-induced ONFH. The odds ratio (OR) and 95% confidence intervals (CIs) were obtained through logistic regression to assess the influence of gene polymorphisms on the occurrence of steroid-induced ONFH.

Results: The consequences show that rs7727115(OR=0.76,p=0.036) is a protective factor, it could reduce the risk of steroid-induced ONFH, rs1582417(OR=1.28, p=0.041) could increase the risk of steroid-induced ONFH. Stratified analysis, according to each clinical index shows that MIR3142HG TC-CC genotype facilitated the risk of steroid-induced ONFH in male ($p<0.05$). In addition, rs2431689 is related to HDL-C($p=0.012$) and ApoA1 ($p=0.010$) levels, and rs17057846 ($p=0.024$) is related to ApoB levels. The linkage analysis indicated that three SNPs (rs2431689, rs7727115 and rs17057846) in MIR3142HG with significant chain imbalance. In addition, haplotype “GGG” of MIR3142HG was found out is harmful for steroid-induced ONFH.

Conclusion: Our results firstly confirm that the genetic polymorphism of MIR3142HG is associated with steroid-induced ONFH susceptibility in Chinese Han population.

1. Introduction

With the widespread, clinical use of hormone drugs, the reports of steroid-induced ONFH at home and abroad are gradually increasing. Steroid-induced ONFH is a serious concomitant hormone widely recognized in clinical practice disease, high disability rate, and seriously affect the physical and mental health of patients. In China, long-term or high-dose corticosteroids are the most common cause of non-traumatic femoral head necrosis[1]. The pathogenesis is currently unclear, and studies have shown that the genome Changes in epigenetics are closely related to its occurrence and development, including genetic polymorphism and methylation changes.

Neuroimmune diseases and rheumatic diseases often need to be treated with glucocorticoids. Glucocorticoids can cause adverse reactions such as oedema, high sodium and low potassium, high blood sugar, centripetal obesity, and infection. Steroid-induced ONFH is the most common one of the severe adverse reactions. Abnormal glucocorticoid metabolism, transporter receptor and target, lipid metabolism disorder, coagulation and fibrinolysis dysfunction, inflammatory response and osteoporosis are the important pathogenesis of steroid-induced ONFH. Glucocorticoids act on osteoblasts, osteoclasts, and osteocytes, reducing fluid in the interstitial tubules of bone, blood supply and strength of bone, and causing damage [2]. However, not all glucocorticoids are used for treatment. All patients had femoral head necrosis, suggesting that there may be other risk factors or individual differences in the occurrence of steroid-induced ONFH. Current research has shown that the pathogenesis and genes of the disease SNPs are related to gene mutations. Steroid-induced ONFH may be a polygenic disease, such as lipid metabolism-related genes (ApoA, ApoB), drug metabolizing enzymes (CYP), drug transporters (ABCB1, ABCG2) and drug target molecules (NR3C1), etc.[3–5] For example, MMP-8, MMP-9, MMP-14 and TIMP4[6–9] have been confirmed to be associated with steroid-induced ONFH risk.

MiRNAs are regulatory short - stranded non-coding RNAs found in eukaryotes.[9]. MiRNAs have been shown to participate in many biological and pathological processes, as well as tissue development[10]. The primary targeted pathways of miRNA with differential expression are mostly related to osteogenic differentiation, bone metabolism and vascular pathways. SNPs in miRNAs-encoding genes may alter the expression or function of their host miRNAs, thus associated with cancer-related risks [11–12].

To our knowledge, the contact between MIR3142HG polymorphism and the risk of steroid-induced ONFH has not been studied previously. Therefore, we designed a study to evaluate the MIR3142HG gene polymorphism at the allele, genotplotype and haplotype interface for the development of the steroid-induced ONFH in the population of northern China.

2. Materials And Methods

2.1. Study Participants.

From 2018 to 2020, a total of 705 subjects including 199 consecutive recruited steroid-induced ONFH and 506 healthy controls at the Second Affiliated Hospital of Inner Mongolia Medical University. The control is based on the physical examination enrollment group, without steroid-induced ONFH or other related diseases. This study was approved by the Hospital Ethics Committee. Informed consent of all participants.

All patients were diagnosed with hormonal femoral head necrosis in accordance with the relevant standards established by the International Bone Circulation Research Association. Inclusion criteria for the case group were long-term use of steroids, more than 16 mg per day or high-dose steroid impulsive treatment appears after more than 1 week; The patient presented with relevant clinical manifestations; such as hip pain, lower limb muscle atrophy, claudication, etc.[6] All outcome measures were confirmed as femur head necrosis by MRI X-ray bone scan or MRI. None of the patients had a history of alcohol consumption, chronic metabolic history, tumour history, hip trauma history or infection history. The patient had complete clinical data and no history of other treatments. Our exclusion criteria are patients who did not strictly meet the diagnostic criteria for hormonal cerebral haemorrhage and the diagnostic criteria for traumatic cerebral haemorrhage compared to other hip diseases; those with weekly alcohol intake of more than 400 ml Patients. The healthy control group is defined according to the following criteria: No symptoms of hip-joint disease, no history of thromboembolism. People with severe chronic diseases and other significant family genetic diseases will be excluded.

2.2. Genotyping assay

In our study, blood samples of steroid-induced ONFH patients and normal control group were collected to analyze the difference of miR3142HG SNP in the blood of steroid-induced ONFH patients and normal control group and its correlation with clinical data, so as to study the application of miR3142HG in the diagnosis of steroid-induced ONFH. Rs1582417,rs2431689, rs7727115, and rs17057846 in the MIR3142HG gene were further selected. Blood samples were taken in EDTA tubes and centrifuged at 2000 rpm for 10 minutes. Blood samples are stored at -80 °C for future experiments. Genomic DNA was extracted from whole blood of steroid-induced ONFH patients and healthy controls, using the GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xian City, China). The genotyping of four SNPs (rs1582417, rs2431689, rs7727115,rs17057846) was put into practice on the Agena MassARRAY platform (San Diego, CA). And data management and analysis using the Sequenom TYPER software.

2.3. Statistical Analyses.

Results were presented as the mean $\pm$ SD (standard deviation). All data were statistically analyzed using SPSS19.0. The difference in age between the two groups was analyzed by T-test or T 'test, and the functional analysis of SNP on SONFH susceptibility was performed by Logistic regression analysis. We used the Chi-squared test/Fisher's exact tests to compare the allelic and genotypic frequencies of cases and controls. ORs and 95% CIs were determined using logistic regression analysis with adjustments for age and gender. Associations between the genotype polymorphisms and the risk of steroid-induced ONFH were evaluated under different genetic models using PLINK version 1.07 software. Finally, linkage disequilibrium among polymorphic sites was assessed with Haploview software package (version 4.2). With P values < 0.05 was considered statistically significant.

3. Result

A total of 705 people participated in this study of 199 patients (83 female,116 male) and 506 healthy controls (83 female, 423 male). The mean ages were 42.58 ± 13.154 years for the cases and 41.21 ± 12.900 years for the controls. The information of the steroid-induced ONFH patients and healthy participants were shown in Table 1. There was no gender match between the patients and healthy participants in this study, and we will adjust this factor in the subsequent analysis.

Table 1
Characteristics of the participants

Variables	Cases (n = 199)	Controls (n = 506)	<i>p</i> value
Sex N			
Male	116	423	< 0.001 ^a
Female	83	83	
Age, years (mean $\pm$ SD)	42.58 ± 13.154	41.21 ± 12.900	0.212 ^b
Clinical stages			
Stage I and II	46		
Stage III and IV	153		
Hip lesions			
unilateral	142		
bilateral	55		
Course of disease(month)			
More than 25 months	67		
25 months or less	132		
^a <i>p</i> value was calculated by chi-squared test			
^b <i>p</i> value was calculated by independent samples t test			
<i>p</i> < 0.05 indicates statistical significance			

Four SNPs (rs1582417, rs2431689, rs7727115 and rs17057846) of MIR3142HG gene were selected for this case-control study. The basic information about all the SNPs, including alleles, MAF, OR, 95% CI and HWE results are presented in Table 2. It was found that rs1582417 (OR = 1.28, 95%CI = 1.01–1.62, $p = 0.041$) were related to an increased risk of steroid-induced ONFH. On the other hand, rs7727115 (OR = 0.76, 95% CI = 0.58–0.98, $p = 0.036$) was related to a reduced risk of steroid-induced ONFH.

Table 2
Basic information of candidate SNPs of MIR3142HG gene in this study

SNP ID	Alleles A/B	MAF		HWE- p	OR (95% CI)	Pvalue
		Case	Control			
rs1582417	C/T	0.427	0.368	0.504	1.28(1.01–1.62)	0.041*
rs2431689	A/G	0.126	0.156	1.000	0.78(0.56–1.10)	0.162
rs7727115	G/T	0.260	0.317	0.918	0.76(0.58–0.98)	0.036*
rs17057846	A/G	0.214	0.205	1.000	1.05(0.79–1.40)	0.719
SNP single-nucleotide polymorphism, HWE Hardy–Weinberg equilibrium, OR odds ratio, 95% CI 95% confidence interval, MAF minor allele frequency						
p were calculated by chi-squared test						
* $p < 0.05$ indicates statistical significance						

Subsequently, genetic models were used to compare the relationship between SNP genotypes and steroid-induced ONFH risk. As illustrated in Table 3, rs1582417 in the MIR3142HG gene was showed an increased risk of steroid-induced ONFH in the dominant model (OR = 1.44, 95% CI: 1.01–2.07, $p = 0.046$). At the same time, rs1582417 showed a negative effect on steroid-induced ONFH under the Log-additive model (OR = 1.28, 95% CI: 1.00–1.64, $p = 0.049$). Moreover, rs7727115 was found to be associated with a reduced risk of steroid-induced ONFH under the Log-additive model (OR = 0.75, 95% CI: 0.57–0.99, $p = 0.039$).

Table 3
Genotypic model analysis of relationship between SNPs and steroid-induced ONFH.

SNP ID	Model	Genotype	Control	Case	OR (95% CI)	Pvalue
rs1582417	Codominant	TT	205	63	1	
		TC	228	102	1.40(0.96–2.06)	0.08
		CC	72	34	1.58(0.94–2.64)	0.085
	Dominant	TT	205	63	1	
		TC-CC	300	136	1.44(1.01–2.07)	0.046*
	Recessive	TT-TC	433	165	1	
		CC	72	34	1.3(0.81–2.06)	0.274
	Log-additive				1.28(1.00-1.64)	0.049*
rs7727115	Codominant	TT	235	107	1	
		TG	221	79	0.76(0.53–1.08)	0.126
		GG	50	12	0.55(0.28–1.10)	0.091
	Dominant	TT	235	107	1	
		TG-GG	271	91	0.72(0.51–1.01)	0.06
	Recessive	TT-TG	456	186	1	
		GG	50	12	0.63(0.32–1.23)	0.172
	Log-additive				0.75(0.57–0.99)	0.039*
SNP single-nucleotide polymorphism, OR odds ratio, 95% CI 95% confidence interval						
p value adjusted for age was calculated by logistic regression						
*p< 0.05 indicates statistical significance						

Stratified analysis by age, hip lesions classification and gender. The results show that in male group the MIR3142HG rs1582417 TC-CC genotype accelerated the risk of steroid-induced ONFH in the dominant model(OR = 2.12, 95% CI 1.15–3.36, $p = 0.001$)and in the codominant model risk of steroid-induced ONFH (TC:OR = 2.09, 95% CI 1.29–3.38, $p = 0.012$;CC:OR = 2.28, 95% CI 1.16–2.09, $p = 0.003$) .We observed that rs17057846 shows association with unilateral and bilateral lesion of the hip joint ($p = 0.049$)(Table 4). In the Age(Older than 45), rs1582417 CC genotype and in the MIR3142HG gene are danger factors, increasing the risk of steroid-induced ONFH in the codominant model (OR = 2.57, 95% CI 1.13–5.86, $p = 0.024$)and recessive model (OR = 2.10, 95% CI 1.03–4.32, $p = 0.043$) ,log-additive model(OR = 1.59, 95% CI 1.05–2.39, $p = 0.028$).In addition, in the Age(Older than 45), rs7727115 TG genotype in the MIR3142HG gene are protect factors, reducing the risk of steroid-induced ONFH under the recessive model (OR = 0.43, 95% CI 0.23–0.82, $p = 0.010$)and dominant model TG-GG (OR = 0.44, 95% CI 0.24–0.81, $p = 0.008$)and log-additive model(OR = 0.55, 95% CI 0.33–0.90, $p = 0.019$).

Table 4

Analysis of the relationship between MIR3142HG gene polymorphism and steroid-induced ONFH subgroups

Subgroup analysis	SNP	Model	Genotype	Control	Case	OR (95% CI)	p
Male	rs1582417	Codominant	TT	181(42.8%)	30(25.9%)	1	
			TC	182(43.0%)	64(55.1%)	2.09(1.29–3.38)	0.012*
			CC	60(14.2%)	22(19%)	2.28(1.19–4.16)	0.003*
		Dominant	TT	181(42.8%)	30(26%)	1	
			TC-CC	242(57.2%)	86(74%)	2.12(1.34–3.36)	0.001*
		Recessive	TT-TC	363(85.8%)	94(81%)	1	
			CC	60(14.2%)	22(19.0%)	1.44(0.84–2.47)	0.187
		Log-additive	...	...	...	1.55(1.16–2.09)	0.330*
Hip lesions	rs17057846	Codominant	GG	81(57.0%)	40(72.7%)	1	
			GA	55(38.7%)	12(21.8%)	2.41(1.14–5.09)	0.021*
			AA	6(4.2%)	3(5.5%)	0.88(0.19–4.04)	0.872
		Dominant	GG	81(57.0%)	40(72.7%)	1	
			GA-AA	61(43%)	15(27.3%)	2.11(1.05–4.26)	0.037*
		Recessive	GG-GA	136(95.8%)	52(94.5%)	1	
			AA	6(4.2%)	3(5.5%)	0.65(0.15–2.91)	0.574
		Log-additive	...	...	...	1.63(0.89–2.99)	0.111
Age(Older than 45)	rs1582417	Codominant	TT	96(41.7%)	19(27.1%)	1	
			TC	102(44.3%)	34(48.6%)	1.42(0.73–2.77)	0.305
			CC	32(13.9%)	17(24.3%)	2.57(1.13–5.86)	0.024*
		Dominant	TT	96(41.7%)	19(27.1%)	1	
			TC-CC	134(58.3%)	51(72.9%)	1.68(0.90–3.14)	0.103

p values were calculated by logistic regression**p* < 0.05 indicates statistical significance

Subgroup analysis	SNP	Model	Genotype	Control	Case	OR (95% CI)	p
		Recessive	TT-TC	198(86.1%)	53(75.7%)	1	
			CC	32(13.9%)	17(24.3%)	2.10(1.03–4.32)	0.043*
		Log-additive	...	...	...	1.59(1.05–2.39)	0.028*
	rs7727115	Codominant	TT	107(46.3%)	45(65.2%)	1	
			TG	103(44.6%)	20(29.0%)	0.43(0.23–0.82)	0.010*
			GG	21(9.1%)	4(5.8%)	0.50(0.15–1.63)	0.249
		Dominant	TT	107(46.3%)	45(65.2%)	1	
			TG-GG	124(53.7%)	24(34.8%)	0.44(0.24–0.81)	0.008*
		Recessive	TT-TG	110(90.9%)	65(94.2%)	1	
			GG	21(9.1%)	4(5.8%)	0.69(0.21–2.22)	0.535
		Log-additive	...	...	...	0.55(0.33–0.90)	0.019*
<i>p</i> values were calculated by logistic regression							
* <i>p</i> < 0.05 indicates statistical significance							

Effect on lipid metabolism level in patients, we found that the HDL-C and ApoA1 levels of the AA genotype carriers in rs 2431689 were higher than the GG genotype carriers, and the ApoB ratio of the GG genotype carriers in rs17057846 was significantly lower than that of the AA genes. For genotype carriers, TC level AA genotype is significantly lower than GG genotype carrier. (Table 5)

Table 5
The association of genotypes in MIR3142HG genes with the clinical phenotypes

SNP	Genotype	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1(mmol/L)	ApoB(mmol/L)
rs1582417	TT(n = 63)	4.46 ± 0.95	2.04 ± 1.71	1.08 ± 0.27	2.54 ± 0.79	1.24 ± 0.21	0.98 ± 0.78
	TC(n = 102)	4.52 ± 0.91	1.74 ± 1.35	1.05 ± 0.26	2.69 ± 0.76	1.23 ± 0.25	0.93 ± 0.24
	CC(n = 34)	4.54 ± 0.91	1.75 ± 1.22	1.09 ± 0.30	2.67 ± 0.71	1.26 ± 0.25	0.98 ± 0.42
	<i>p</i>	0.897	0.416	0.726	0.485	0.868	0.736
rs2431689	GG(n = 151)	4.47 ± 0.93	1.89 ± 1.54	1.04 ± 0.25	2.62 ± 0.76	1.21 ± 0.22	0.96 ± 0.56
	GA(n = 44)	4.62 ± 0.91	1.67 ± 1.16	1.17 ± 0.31	2.69 ± 0.880	1.33 ± 0.27	0.92 ± 0.24
	AA(n = 3)	5.18 ± 0.28	2.33 ± 0.73	1.05 ± 0.15	3.21 ± 0.56	1.32 ± 0.29	1.13 ± 0.01
	<i>p</i>	0.288	0.580	0.012*	0.388	0.010*	0.756
rs7727115	TT(n = 12)	4.79 ± 0.95	2.81 ± 2.54	1.01 ± 0.25	2.66 ± 0.87	1.24 ± 0.24	0.95 ± 0.22
	TG(n = 79)	4.50 ± 0.95	1.76 ± 1.38	1.06 ± 0.26	2.67 ± 0.78	1.22 ± 0.24	0.90 ± 0.24
	GG(n = 107)	4.47 ± 0.90	1.78 ± 1.33	1.08 ± 0.28	2.61 ± 0.75	1.26 ± 0.23	0.99 ± 0.65
	<i>p</i>	0.542	0.056	0.699	0.838	0.472	0.515
rs17057846	GG(n = 123)	4.52 ± 0.88	1.88 ± 1.53	1.07 ± 0.28	2.66 ± 0.74	1.24 ± 0.26	0.93 ± 0.29
	GA(n = 67)	4.56 ± 1.02	1.80 ± 1.35	1.05 ± 0.25	2.67 ± 0.81	1.23 ± 0.19	0.95 ± 0.26
	AA(n = 9)	3.93 ± 0.45	1.52 ± 1.24	1.16 ± 0.27	2.10 ± 0.44	1.33 ± 0.25	1.40 ± 2.03
	<i>p</i>	0.151	0.742	0.518	0.094	0.495	0.024*
<i>p</i> values were calculated by logistic regression							
* <i>p</i> < 0.05 indicates statistical significance							

Table 6

The haplotype frequencies of MIR3142HG polymorphisms and their association with the risk of steroid-induced ONFH.

Haplotype			Freq	Without adjustment		With adjustment	
rs2431689	rs7727115	rs17057846		OR (95% CI)	p^a	OR (95% CI)	p^b
1	G	A	0.2157	1.10(0.82–1.46)	0.531	1.03(0.77–1.40)	0.806
2	G	T	0.2614	0.77(0.59–1.00)	0.050	0.76(0.58–1.00)	0.055
3	A	G	0.1269	0.82(0.58–1.16)	0.267	0.81(0.57–1.16)	0.244
4	G	G	0.3959	1.33(1.04–1.70)	0.024*	1.40(1.08–1.81)	0.010*
p^a values were calculated by unconditional logistic regression.							
p^b values were calculated by unconditional logistic regression adjusted for age and gender.							
$p < 0.05$ indicates statistical significance.							

In haplotype model analysis, one linkage disequilibrium (LD) block was detected in the MIR3142HG SNPs (rs2431689, rs7727115, rs17057846; Fig. 1). The “GGG” sequence was associated with an increased risk of steroid-induced ONFH (OR = 1.33, 95% CI 1.04–1.70, $p = 0.021$; adjusted OR = 1.40, 95% CI 1.08–1.81, $p = 0.010$).

4. Discussion

Despite the introduction of many new treatment methods, and the rapid development of surgical techniques, the therapeutic effect of osteonecrosis has not improved significantly. Because many patients have reached the early stage of diagnosis, the final hip replacement is an inevitable choice. Therefore, researching the underlying mechanism of femoral head necrosis and development, and searching for more accurate biomarkers, are crucial for clinicians to formulate precise treatment strategies.

We assessed the relationship between the four SNPs in MIR3142HG and steroid-induced ONFH susceptibility in Han Chinese. The frequencies of 4 allelic SNPs of MIR3142HG genotype and haplotype in cases and control group were compared and further stratified. Among them, the rs1582417 polymorphism is associated with increased risk of steroid-induced ONFH, while the rs7727115 mutation is associated with reduced risk. For all we know, this is the first case-control study to examine the relationship between MIR3142HG gene polymorphism and the risk of steroid-induced ONFH. This research provides evidence for the biological significance of genetic variation in miRNA-coding genes, suggesting that it may affect the pathogenesis of steroid-induced ONFH.

MiRNA is highly conservative in evolution and its expression is tissue-specific. MiRNA has the following characteristics: Highly conserved; The order of time and space; Some MiRNAs are tissue-specific. Studies have shown that miRNAs play a crucial role in different physiological and pathological processes via regulating gene expression post-transcriptionally, that is, it specifically binds to the untranslated region (3' UTR) at the 3' end of the mRNA of the target gene through base complementary pairing, inhibits the translation process of the mRNA or directly mediates the degradation of the mRNA, so as to achieve the purpose of regulating the expression of the target gene [13–15]. Recently, more and more miRNAs have been studied in orthopaedic diseases. Increasing evidence also indicates that miRNAs can directly play a role in the pathogenesis of many orthopedic diseases, regulating bone development and bone regeneration, such as disc degeneration, osteoarthritis, osteoporosis, and osteosarcoma. [16–19]. In recent years,

MiRNAs have gradually become a research hotspot in the field of non-coding RNA, and some miRNAs have been proved to be closely related to the pathogenesis of steroid-induced ONFH.[20–21].

MIR3142HG, also known as the MIR146A host gene, is located on human chromosome 5q33.3. However, it is reported that MIR3142HG can produce miR-146a[22]. MiR-146a is abnormal in lung cancer, breast cancer, colorectal cancer, glioma and other cancers.[23–26]. MiR-146a may participate in ONFH and other physiological processes such as inflammation.[27]. The study showed that MIR3142HG knockdown observably decreased the release of IL-8 and CCL2, and partially reduced the release of il-6 in control fibroblasts, suggesting that the decreased expression of MIR3142HG might be the reason for the decreased inflammatory reaction of IPF fibroblasts stimulated by IL-1[28]. It was found that MIR3142HG regulates the inflammatory response, and it is proved that the reduction of the inflammatory response of IPF fibroblasts is related to the decreased expression of MIR3142HG/miR-146a[28]. Yuan et al. designed a study to compare miRNA expression profiles in 9 ONFH patients and 6 femoral neck fractures. It was confirmed that the expression of Mir-146a was up-regulated in ONFH.[29]. So we doped out that MIR3142HG polymorphism might affect the expression or function of MiR-146a during the steroid-induced ONFH process. At present, the mechanism of MIR3142HG in steroid-induced ONFH has not been reported and remains to be studied.

We suggest that the induction age-related steroid-induced ONFH may relevance with rs1582417 and rs7727115 polymorphism in MIR3142HG. Further studies through gender stratification found that that rs1582417 polymorphism increases steroid-induced ONFH susceptibility, suggesting that the polymorphism risk association may be gender-related. We found that the HDL-C and ApoA1 levels of the AA genotype carriers in rs2431689 were higher than the GG genotype carriers, and the ApoB ratio of the GG genotype carriers in rs17057846 was well below that of the AA genes. For genotype carriers, TC level AA genotype is significantly lower than GG genotype carrier. These results further illustrate the correlation between rs2431689, rs17057846, HDL-C levels, ApoA1 levels, ApoB levels, metabolic disorders, and osteonecrosis. At present, few functional studies have been reported. Understanding the function of miRNAs is crucial, which will provide new ideas for future treatment.

Some important findings were revealed in our study, but in interpreting these results, some limitations of this study should be considered. First, the sample size of hormonal femoral head necrosis is too small and lacks representativeness, while the large sample study takes time and effort; second, the relationship between genetic polymorphisms of different regions and races and the incidence of hormonal femoral head necrosis is inconsistent, and further analysis is needed. Reduce the variation within the interval and reduce the impact of the sampling error; again, the combination of large sample size aetiology and SNP analysis has become the direction of future research on steroid-related femoral head necrosis, but the credibility of the experimental results needs to be further improved, such as application of statistical methods such as multivariate analysis of variance and avoidance of confounding factors in case-control intervals.

5. Conclusions

In a word, This is the first evidence that two polymorphisms(rs1582417rs7727115) in MIR3142HG might contribute to the susceptibility to steroid-induced ONFH in the Chinese Han population. However, It is not clear whether these changes in MIR3142HG are consistent with the onset of ONFH, or simply reflect the terminal stage of the disease.

Declarations

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References

1. Zhao Jie, Ma Xin-Long, Ma Jian-Xiong et al. TET3 Mediates Alterations in the Epigenetic Marker 5hmC and Akt pathway in Steroid-Associated Osteonecrosis.[J] .J. Bone Miner. Res., 2017, 32: 319-332.
2. Weinstein Robert S, Glucocorticoid-induced osteonecrosis.[J] .Endocrine, 2012, 41: 183-90.
3. Hirata Tetsuro, Fujioka Mikihiro, Takahashi Kenji A et al. Low molecular weight phenotype of Apo(a) is a risk factor of corticosteroid-induced osteonecrosis of the femoral head after renal transplant.[J] .J. Rheumatol., 2007, 34: 516-22.
4. Hirata Tetsuro, Fujioka Mikihiro, Takahashi Kenji A et al. ApoB C7623T polymorphism predicts risk for steroid-induced osteonecrosis of the femoral head after renal transplantation.[J] .J Orthop Sci, 2007, 12: 199-206.
5. Kuribayashi Masaaki, Fujioka Mikihiro, Takahashi Kenji A et al. Combination analysis of three polymorphisms for predicting the risk for steroid-induced osteonecrosis of the femoral head.[J] .J Orthop Sci, 2008, 13: 297-303.
6. Du Jieli, Jin Tianbo, Cao Yuju et al. Association between genetic polymorphisms of MMP8 and the risk of steroid-induced osteonecrosis of the femoral head in the population of northern China.[J] .Medicine (Baltimore), 2016, 95: e4794.
7. Du Jieli, Liu Wanlin, Jin Tianbo et al. A single-nucleotide polymorphism in MMP9 is associated with decreased risk of steroid-induced osteonecrosis of the femoral head.[J] .Oncotarget, 2016, 7: 68434-68441.
8. Qi Yuxin, Wang Jiaqi, Sun Mingqi et al. MMP-14 single-nucleotide polymorphisms are related to steroid-induced osteonecrosis of the femoral head in the population of northern China.[J] .Mol Genet Genomic Med, 2019, 7: e00519.
9. Mendell Joshua T, Olson Eric N, MicroRNAs in stress signaling and human disease.[J] .Cell, 2012, 148: 1172-87.
10. Ambros Victor, The functions of animal microRNAs.[J] .Nature, 2004, 431: 350-5.
11. Króliczewski Jarosław, Sobolewska Aleksandra, Lejnowski Dawid et al. microRNA single polynucleotide polymorphism influences on microRNA biogenesis and mRNA target specificity.[J] .Gene, 2018, 640: 66-72.
12. Preskill Carina, Weidhaas Joanne B, SNPs in microRNA binding sites as prognostic and predictive cancer biomarkers.[J] .Crit Rev Oncog, 2013, 18: 327-40.
13. Li Zheng, Yu Xin, Shen Jianxiong et al. MicroRNA in intervertebral disc degeneration.[J] .Cell Prolif., 2015, 48: 278-83.
14. Wang Yuan, Jia Lian-Shun, Yuan Wen et al. Low miR-34a and miR-192 are associated with unfavorable prognosis in patients suffering from osteosarcoma.[J] .Am J Transl Res, 2015, 7: 111-9.
15. Lv Cai, Bai Zhiming, Liu Zhenxiang et al. MicroRNA-495 suppresses human renal cell carcinoma malignancy by targeting SATB1.[J] .Am J Transl Res, 2015, 7: 1992-9.
16. Jing Wanli, Jiang Wenxue, MicroRNA-93 regulates collagen loss by targeting MMP3 in human nucleus pulposus cells.[J] .Cell Prolif., 2015, 48: 284-92.
17. Jackson Miriam T, Moradi Babak, Smith Margaret M et al. Activation of matrix metalloproteinases 2, 9, and 13 by activated protein C in human osteoarthritic cartilage chondrocytes.[J] ., 2014, 66: 1525-36.
18. Li Zheng, Shen Jianxiong, Chan Matthew T V et al. MicroRNA-379 suppresses osteosarcoma progression by targeting PDK1.[J] .J. Cell. Mol. Med., 2017, 21: 315-323.

19. He Xiaoning,Zhang Wenkai,Liao Li et al. Identification and characterization of microRNAs by high through-put sequencing in mesenchymal stem cells and bone tissue from mice of age-related osteoporosis.[J] .PLoS ONE, 2013, 8: e71895.
20. Hao Cheng,Yang Shuhua,Xu Weihua et al. MiR-708 promotes steroid-induced osteonecrosis of femoral head, suppresses osteogenic differentiation by targeting SMAD3.[J] .Sci Rep, 2016, 6: 22599.
21. Gu Chenxi,Xu Yan,Zhang Shanfeng et al. miR-27a attenuates adipogenesis and promotes osteogenesis in steroid-induced rat BMSCs by targeting PPAR γ and GREM1.[J] .Sci Rep, 2016, 6: 38491.
22. Paterson Mark R,Kriegel Alison J,MiR-146a/b: a family with shared seeds and different roots.[J] .Physiol. Genomics, 2017, 49: 243-252.
23. Iacona Joseph R,Lutz Carol S,miR-146a-5p: Expression, regulation, and functions in cancer.[J] .Wiley Interdiscip Rev RNA, 2019, 10: e1533.
24. Iacona Joseph R,Monteleone Nicholas J,Lutz Carol S,miR-146a suppresses 5-lipoxygenase activating protein (FLAP) expression and Leukotriene B4 production in lung cancer cells.[J] .Oncotarget, 2018, 9: 26751-26769.
25. Si Chengshuai,Yu Qiao,Yao Yufeng,Effect of miR-146a-5p on proliferation and metastasis of triple-negative breast cancer via regulation of SOX5.[J] .Exp Ther Med, 2018, 15: 4515-4521.
26. Bleau Anne-Marie,Redrado Miriam,Nistal-Villan Estanislao et al. miR-146a targets c-met and abolishes colorectal cancer liver metastasis.[J] .Cancer Lett., 2018, 414: 257-267.
27. Guo Xiaoye,Zhang Ming,Li Qi et al. Evaluation of Genetic Variants in MIR3142HG in Susceptibility to and Prognosis of Glioma.[J] .Am. J. Clin. Oncol., 2020, 43: 1-8.
28. Hadjicharalambous Marina R,Roux Benoit T,Feghali-Bostwick Carol A et al. Long Non-coding RNAs Are Central Regulators of the IL-1 β -Induced Inflammatory Response in Normal and Idiopathic Pulmonary Lung Fibroblasts.[J] .Front Immunol, 2018, 9: 2906.
29. Yuan Heng-feng,Von Roemeling Christina,Gao Hui-di et al. Analysis of altered microRNA expression profile in the reparative interface of the femoral head with osteonecrosis.[J] .Exp. Mol. Pathol., 2015, 98: 158-63.

Figures

Figure 1

Linkage disequilibrium (LD) analysis of the SNPs on MIR3142HG. Red squares display statistically significant associations between a pair of SNPs, as measured by D' ; darker shades of red indicate higher D' .