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Identification of m7G RNA Methylation Regulators in Osteoarthritis and its Prognostic Markers

Zhenhui Huo[1†], Kuo Hao[1†], Xingkai Wang[1], Chongyi Fan[1], Yingzhen Niu[1*] and Fei Wang[1*]

Abstract

Background: Osteoarthritis (OA) is a multifactorial disease that places an increasing burden on modern society. Synovial inflammation plays an important role in osteoarthritis. 7-methylguanosine (m7G) is one of the most common forms of base modification in post-transcriptional regulation. However, the function of m7G RNA methylation regulators in synovial tissue remains unclear, and the expression and predictive value of m7G RNA methylation regulators are rarely reported. So new studies are needed to fill this gap.

Methods: Firstly, 40 m7G RNA methylation-related genes were selected from the four pathways and compared with the GSE55457 dataset to obtain gene expression profiles and clinical information. And 25 related genes were obtained. Six differential genes were also selected after the differential analysis of the 25 m7G RNA methylation-related regulators in OA and normal patients. Finally, the areas under the curve (AUC) were used to evaluate the diagnostic efficacy of m7G related genes in distinguishing OA patients from healthy population.

Results: We found these genes are mainly involved in RNA metabolism, RNA cap binding, and the formation of RNA cap-binding complexes and the regulation of RNA cap formation had a strong impact on gene regulation. Then we identified 6 differentially expressed genes (DEGs), confirming for the first time that SNUPN and NUDT11 were associated with early diagnosis and prediction of OA.

Conclusions: The regulators of m7G RNA methylation play a crucial role in the advancement of OA and hold promise in terms of prognosis. However, the clinical effects of these biomarkers on OA need further study.

Keywords: m7G; Osteoarthritis; Biomarker; RNA modification; Expressed genes; Bioinformatics analysis.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and the most common degenerative joint disease, accompanied by pain, joint deformity and disability [1]. It is the main cause of the lower quality of life and life expectancy in the elderly. The combined effects of global population aging, the increase in the incidence of obesity and the increase in the number of joint injuries have led to an increasing incidence of the disease. By 2020, osteoarthritis affects more than 500 million people around the world. This disease has brought huge burdens and pressures to personal health, medical systems and social economy [2-4]. At present, the treatment strategies for OA mainly focus on relieving pain, reducing swelling and improving joint

Affiliation:

[1]Department of Orthopaedic Surgery, Third Hospital of Hebei Medical University, 139 Ziqiang Road, Shijiazhuang 050051, Hebei, People's Republic of China

[†]Zhenhui Huo and Kuo Hao have contributed equally to this work

***Corresponding author:**
Fei Wang. Department of Orthopaedic Surgery, Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China 050051.

Yingzhen Niu. Department of Orthopaedic Surgery, Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China 050051.

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function. As a multifactorial disease, the potential risk factors for OA appear to be related to metabolism, mechanical overload, trauma, inflammation, and genetic sensitivity [5]. At present, there is no effective treatment for OA. The typical management of OA is palliative and reactive, and knee replacement surgery can be the only option for OA patients who progress to terminal partial motor function. But joint replacement is often accompanied by high mortality, multiple complications and poor recovery risks [2, 6-9]. Therefore, clarifying the pathogenesis of OA is important for the prevention and radical cure of diseases. Although several studies have been conducted on the formation and development of OA, due to the unclear pathogenesis and etiology, no effective method has been found to cure OA. Considering the increasing number of patients affected by OA, there is still a lack of early diagnosis and effective treatment of OA. Therefore, new methods or techniques are urgently needed to diagnose OA. At the present stage, the studies on the pathogenesis of OA have mainly focused on the cartilage [2]. As a complex whole joint disease, its pathological changes involve a range of joint tissues, including cartilage, subchondral bone, ligaments, meniscus, fat pads, and synovial membrane [10]. Abnormalities can occur in the synovium at the onset of OA and even before the visual observation of cartilage damage, and the degree of synovitis is closely related to the progression of the disease, causing the destruction of bone and cartilage [11]. Synovial inflammation present in the OA joints is associated with radiological and pain progression [12, 13]. Studies have shown that genetic markers associated with apoptosis and senescence in the synovial tissue of OA promote OA progression [13, 14]. Scientists have found that OA synoviocytes produce some inflammatory regulators and matrix-degrading enzymes that promote the progression of OA [15, 16]. Dysregulation of lncRNAs and mRNA expression in synovial tissues is often associated with the pathogenesis of OA [17]. More research is needed on the important role of synovial tissue in OA.

Epigenetic modifications play an important role in guiding and maintaining unique cellular phenotypes [18]. More and more studies have identified the link between the pathogenesis of the disease and abnormal modification. RNA modification is a post-transcriptional modification widely found in eukaryotes and has become a hot field in recent years. RNA methylation is considered to be a key regulator of disease progression. It has important effects on many aspects of RNA metabolism, such as RNA splicing and subcellular localization, RNA degradation, mRNA stability and translation [19-21]. The important role of RNA methylation in the development of various diseases such as various cancers, cardiovascular diseases, metabolic diseases, and mitochondrial-related defects has been elucidated [22]. Studies have suggested that inflammatory diseases including OA may be related to RNA modification [23]. Therefore, it is important to investigate the epigenetic factors and mechanisms associated with OA progression and treatment response. N6-methyladenosine (m6A) was widely studied in recent years [24]. On the basis of whole transcriptome sequencing, six more internal modifications were found widely found on mammalian mRNA: pseudouridine (Ψ), N1methyladenosine (m1A), ribose methylations (Nm), 5methylcytidine (m5C), N7-methylguanosine (m7G) and N4-acetylcytidine (ac4C) [25]. Among them, m6A and m7G are the two most common types of RNA methylation [26-28]. But relatively few studies on m7G. Under the action of methyltransferase, the nitrogen-containing base at the 7th position of RNA guanine is methylated. m7G is a highly conserved RNA modification found in the 5 ' cap structure of tRNA, rRNA and mRNA and in the mRNA region. It plays an important role in regulating RNA processing, metabolism and function [29, 30]. The modification of m7G was also observed in OA-related mRNA and contributed to the translation of OA-related mRNA [31]. Therefore, m7G, as a transcriptional marker, is important for protein translation and can be used as a basis for a predictive model for OA diagnosis. However, little is known about the m7G RNA methylation characteristics in OA synovial tissues. And the expression and prognosis of m7G RNA methylation regulators are rarely reported, so new studies are needed to fill this gap. In this study, we used bioinformatics methods to analyze the expression pattern of m7G RNA methylation regulators in OA. To further analyze the relationship between differential m7G RNA methylation-related genes and OA prediction and early diagnosis. We identified 6 differentially expressed genes (DEGs) and established an OA prediction model based on them. We found that the expression of m7G RNA methylation-related genes plays a key role in the process of OA and identified two genes as potential biomarkers for the first time.

Methodology

Data acquisition and processing

The GSE55457 dataset was acquired from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), which included the mRNA sequencing data and sample information from the normal synovial tissues and OA synovial tissues. All the datasets were obtained from the GPL96 sequencing platform (Affymetrix Human Genome U133A Array). Inclusion criteria included (1) Datasets involving human synovial tissue, (2) Homo sapiens Expression Profiling by array, (3) datasets containing complete information on the samples. The R software was used for the preprocessing and transformation of the genes.

Selection of m7G RNA methylation regulators

We downloaded m7G RNA methylation-related genes from the Gene Set Enrichment Analysis (GSEA, https://www.gsea-msigdb.org/gsea/index.jsp) database. 40 m7G

RNA methylation-related genes were downloaded in the four related pathways (GOMF_RNA_CAP_BINDING, GOMF_RNA_7_METHYLGUANOSINE_CAP_BINDING, GOMF_M7G_5_PPPN_DIPHOSPHATASE_ACTIVITY, GOBP_7_METHYLGUANOSINE_RNA_CAPPING). Then, we systematically compared their expression in OA and normal tissues. Finally, a total of 25 m7G RNA methylation regulators were extracted in this study, including WDR4, TGS1, SNUPN, RNMT, RNGTT, NUDT7, NUDT4, NUDT3, NUDT11, NUDT1, NCBP2, NCBP1, METTL1, LSM1, LARP1, IFIT5, EIF4G3, EIF4E2, EIF4E, EIF3D, DCPS, DCP2, CYFIP2, CYFIP1 and CMTR1.

Bioinformatics Analysis

In this study, the relationship between the expression of these 25 genes and the disease and the relationship between the expressions of m7G RNA methylation regulators themselves were studied. Convert the OA dataset into expression estimates. Then, background correction, quartile data normalization and probe summary were performed through the Robust multi-array averaging algorithm in the R software "affy" package [32]. The protein-protein interaction (PPI) network between 25 m7G RNA methylation regulators was constructed using the STRING (https://string-db.org/) database, and the results were visualized using Cytoscape software. Cytoscape was software used to sort and extract the central elements of biological networks according to various network characteristics. The correlation of m7G RNA methylation regulators expression in OA patients was determined by Spearman's correlation. The chromosomal localization of the m7G RNA methylation-related genes was visualized using the R software "circus" package [33]. GO and KEGG pathway analysis were performed using the R software "clusterProfiler" and "enrichedplot". The maximum gene set was set to 500 genes and the minimum set to 5 genes and analysis results with $P < 0.05$ were considered meaningful. Differentially expressed m7G RNA methylation regulators between OA and normal patients were selected using the R software "limma" package and DEGs screening cutoff criterion was $P < 0.05$. The Wilcoxon rank-sum test was used to assess difference in gene expression between the two groups. The volcano plot was drawn with function ggplot of the R software "ggplot2" package. The differential expression heatmap of genes associated with m7G RNA methylation regulators was generated using the "heatmap" package, and correlations between genes associated with m7G RNA methylation regulators were analyzed using the "Corrplot" package. Univariate logistic regression was used to find the m7G RNA methylation regulators related to the occurrence of OA, and the results were combined with the differential genes to determine the predictive value. To determine the predictive value of m7G RNA methylation regulators, we performed receiver operating characteristics (ROC) analysis and calculated the area under the curve (AUC), as well as the corresponding sensitivity and specificity [32]. ROC analysis was carried out by using R software "pROC" package to obtain AUC, and the ci function of "pROC" package was used to evaluate AUC and confidence interval to obtain the final AUC result.

Statistical analysis

The data were processed and analyzed using R software (version 4.3.1) and related software packages ($P < 0.05$). We used the Wilcoxon rank-sum test to assess the significance of the differences between the two groups, with the adjusted $P < 0.05$ considered as a statistically significant difference. Univariate logistic regression analysis was analyzed using SPSS (R26.0.0), and $P < 0.1$ was considered statistically significant. For all data: * represented $P < 0.05$, * * represented $P < 0.01$, * * * represented $P < 0.001$.

Result

Identifying important m7G RNA methylation regulators in OA

We calculated the Spearman correlation coefficient between these 25 regulators, and correlation analysis demonstrated that LSM1 had the strongest positive relationship with EIF4E2 ($r = 0.95$), while RNGTT exhibited the strongest negative relationship with CMTR1 ($r = -0.73$) (Figure. 1A). The PPI network was then constructed to reveal the interaction relationships of these 25 regulators (Figure. 1B). The PPI network of 25 regulators consisted of 25 nodes and 58 edges. The heatmap showed the expression levels of these 25 regulators (Figure. 1C). The chromosome mapping map showed the relative positions of m7G RNA methylation regulators (Figure. 1D).

Function enrichment analyses in the m7G-Related Genes in OA

To identify different biological functions of the 25 m7G RNA methylation regulator genes, we performed GO and KEGG enrichment analysis on 25 methylation regulators (Table 1). GO enrichment analysis showed that they are mainly involved in complex catabolic process, RNA cap binding, and mRNA cap binding complexes, including biological process (BP), cell component (CC) and molecular function (MF), respectively. The BP analysis of GO terms showed that these genes were significantly enriched in the nucleobase-containing compound catabolic process, heterocycle catabolic process, cellular nitrogen compound catabolic process, regulation of translation, aromatic compound catabolic process, and organic cyclic compound catabolic process (Figure 2A, 2B). With regards to the MF, analysis showed that mainly with RNA cap binding, RNA 7-methylguanosine cap binding, catalytic activity, and action on RNA (Figure 3A, 3B). For the CC of GO terms, regulator genes were mainly associated with mRNA cap

Huo Z., et al., Fortune J Rheumatol 2024
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binding complex, RNA cap binding complex, cytoplasmic ribonucleoprotein granule, and ribonucleoprotein granule (Figure 4A, 4B). The KEGG results showed that the regulator genes were mainly correlated with mRNA surveillance pathway, RNA degradation, and nucleocytoplasmic transport (Figure 5A, 5B). These findings may reveal a regulatory network of gene expression mediated by m7G modification patterns.

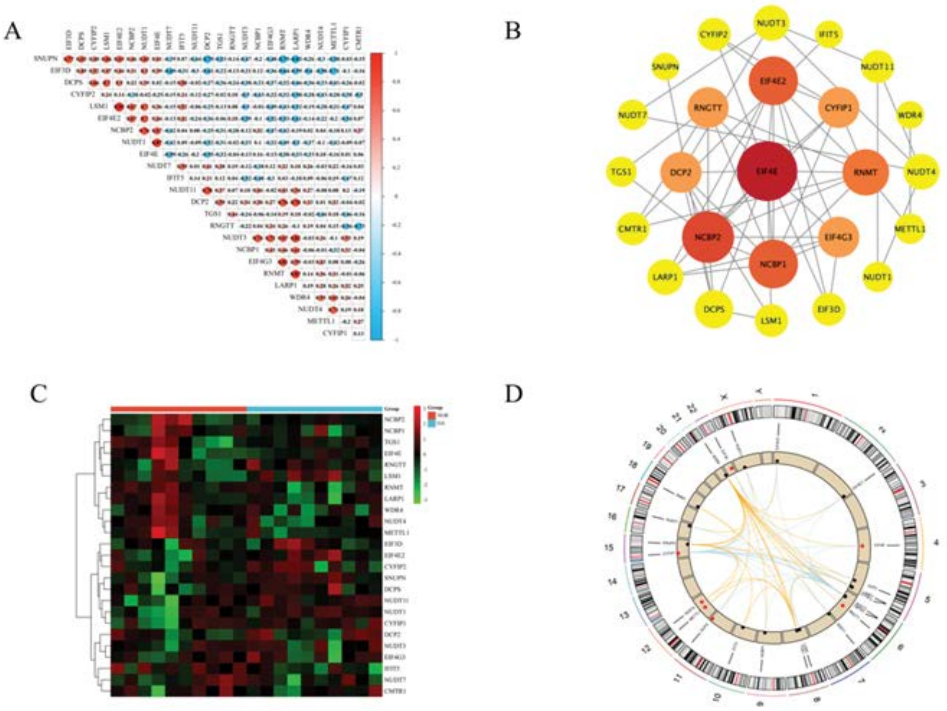

Figure 1: Expression characteristics and gene localization of m7G RNA methylation regulators. A Spearman correlation analysis of m7G methylation regulators. B The PPI network of the 25 m7G methylation regulators. C Heat map showing the expression characteristics of m7G methylation regulators in OA and normal patients. D The position of m7G regulator genes on the chromosome. *, P < 0.05; **, P < 0.01; ***, P < 0.001; NOR, normal; OA, Osteoarthritis.

Table 1: The top 10 GO terms and top 3 of m7G RNA methylation-related genes

Category	ID	Description	*P* value	Count
BP	GO:0034655	nucleobase-containing compound catabolic process	2.73E-10	11
	GO:0046700	heterocycle catabolic process	2.73E-10	11
	GO:0044270	cellular nitrogen compound catabolic process	2.73E-10	11
	GO:0006417	regulation of translation	2.73E-10	11
	GO:0019439	aromatic compound catabolic process	2.73E-10	11
	GO:1901361	organic cyclic compound catabolic process	4.27E-10	11
	GO:0072523	purine-containing compound catabolic process	1.71E-07	5
	GO:0110154	RNA decapping	1.99E-07	4
	GO:0006413	translational initiation	2.30E-07	6
	GO:0008334	histone mRNA metabolic process	2.52E-07	4
	GO:0000339	RNA cap binding	2.26E-30	12
MF	GO:0000340	RNA 7-methylguanosine cap binding	3.65E-17	7
	GO:0140098	catalytic activity, acting on RNA	2.89E-06	7
	GO:0045182	translation regulator activity	3.14E-05	6
	GO:0008173	RNA methyltransferase activity	2.15E-07	5
	GO:0090079	translation regulator activity, nucleic acid binding	2.10E-06	5
	GO:0008168	methyltransferase activity	2.71E-05	5
	GO:0016741	transferase activity, transferring one-carbon groups	2.82E-05	5
	GO:0003743	translation initiation factor activity	2.89E-06	4

Huo Z., et al., Fortune J Rheumatol 2024
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	GO:0008135	translation factor activity, RNA binding	1.62E-05	4
CC	GO:0005845	mRNA cap binding complex	8.91E-14	6
	GO:0034518	RNA cap binding complex	8.91E-14	6
	GO:0036464	cytoplasmic ribonucleoprotein granule	4.61E-06	6
	GO:0035770	ribonucleoprotein granule	5.83E-06	6
	GO:0000932	P-body	1.64E-06	5
	GO:0016281	eukaryotic translation initiation factor 4F complex	3.48E-06	3
	GO:0034708	methyltransferase complex	< 0.01	3
	GO:0031209	SCAR complex	< 0.001	2
	GO:0016442	RISC complex	< 0.01	2
	GO:0031332	RNAi effector complex	< 0.01	2
KRGG	hsa03015	mRNA surveillance pathway	9.71E-05	4
	hsa03018	RNA degradation	< 0.001	3
	hsa03013	Nucleocytoplasmic transport	< 0.01	3

BP, biological process; CC, cellular component; MF, molecular function; KEGG, Kyoto Encyclopedia of Genes and Genomes

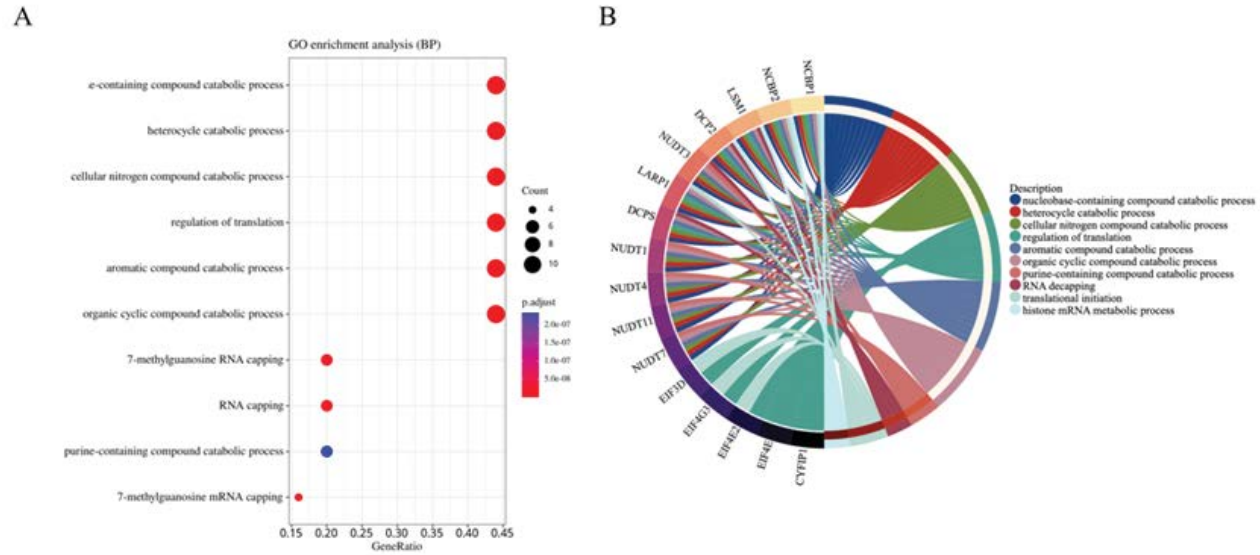

Figure 2: GO terms of the 25m7G RNA methylation regulators from aspects of BP. A, B Bubble Chart and Circle Graph of GO terms of the regulators from aspect of BP

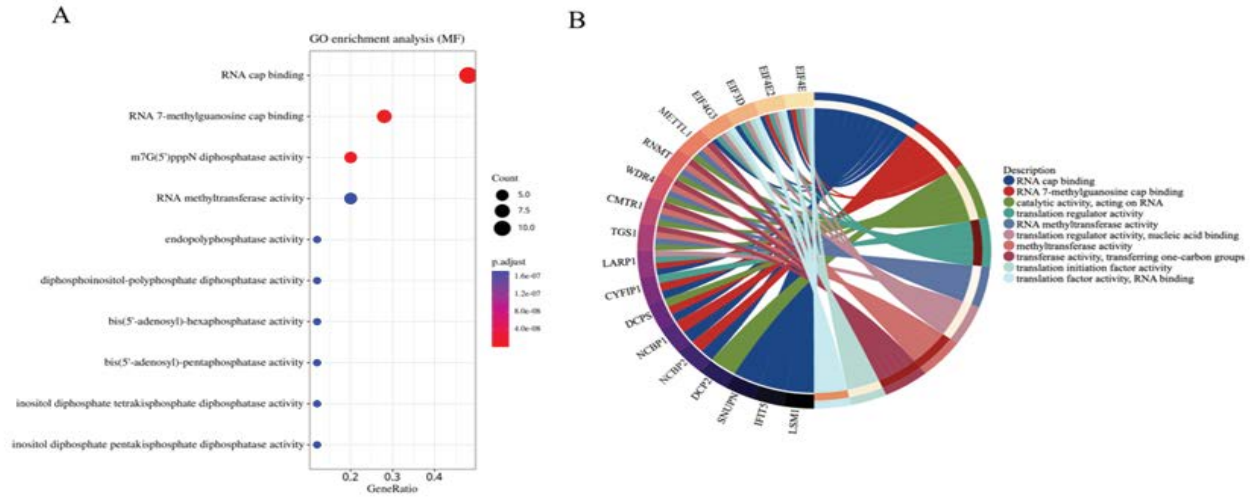

Figure 3: GO terms of the 25m7G RNA methylation regulators from aspects of MF. A, B Bubble Chart and Circle Graph of GO terms of the regulators from aspect of MF

Huo Z., et al., Fortune J Rheumatol 2024
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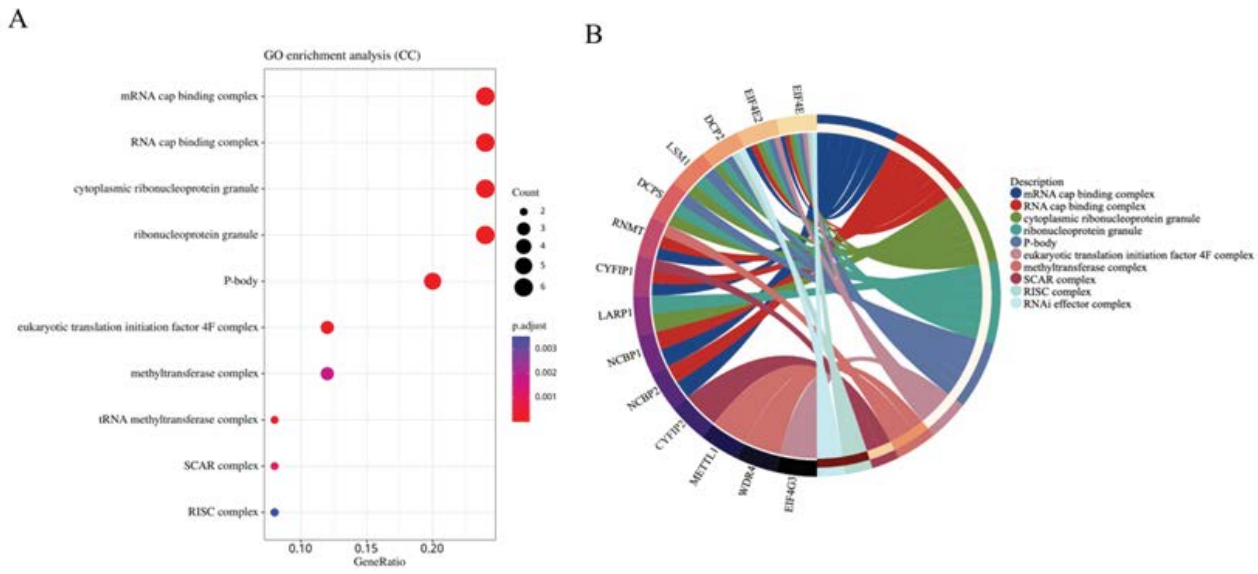

Figure 4: GO terms of the 25m7G RNA methylation regulators from aspects of CC. A, B Bubble Chart and Circle Graph of GO terms of the regulators from aspect of CC

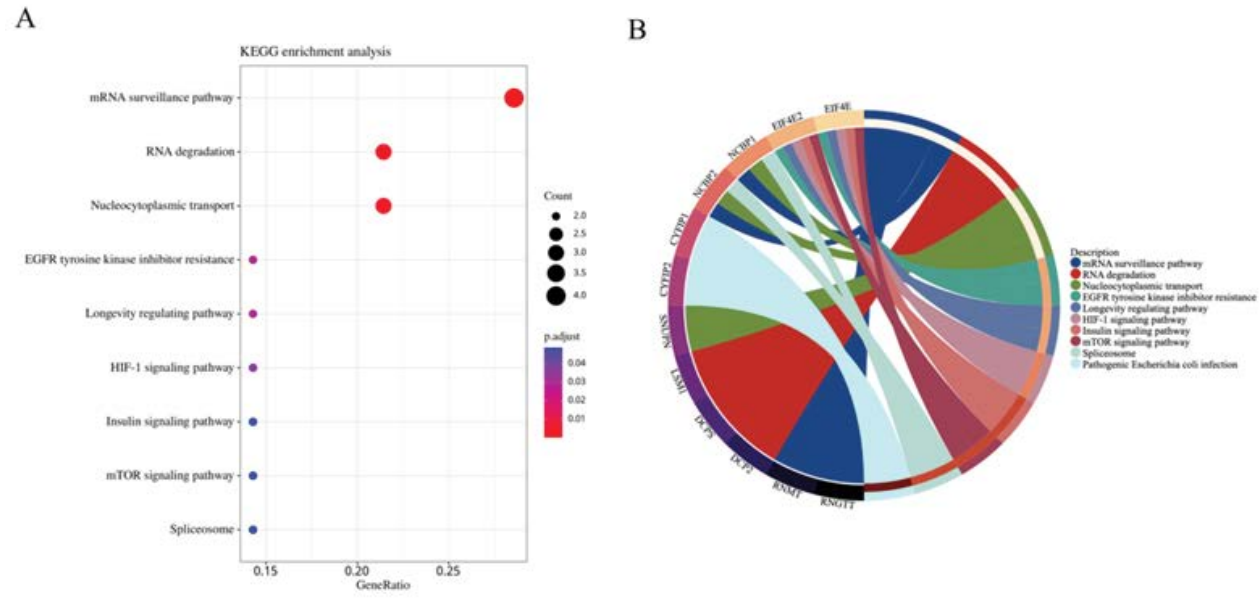

Figure 5: GO terms of the 25m7G RNA methylation regulators from aspects of KEGG pathways. A, B Bubble Chart and Circle Graph of GO terms of the regulators from aspect of KEGG pathways

The relationship between m7G RNA methylation regulators and OA

To elucidate the changes in m7G RNA methylation regulators associated with OA, we performed an expression differentiation analysis of m7G RNA methylation regulators. We extracted 6 DEGs of m7G RNA methylation regulators from the gene expression matrix of OA patients and normal patients (Figure 6A). The expression of the 6 DEGs between the groups were visualized using the violin plot (Figure 6B). Six of the 25 genes were identified as differentially expressed between normal and OA patients (Table 2). Quantitative analysis showed that SNUPN ($P < 0.05$) 、NUDT11 ($P < 0.05$), and NUDT1 ($P < 0.05$) were expressed at high levels in patients with OA. Conversely, NUDT4 ($P < 0.05$) 、IFIT5 ($P < 0.05$) and RNMT ($P < 0.05$) were expressed at low levels in OA. The distribution of DEGs between OA patients and normal controls was then visualized by a heatmap (Figure 6C). The expression of 6 m7G RNA methylation regulators showed related.

Table 2: The relative expression of m7G RNA methylation-related genes

Genes	logFC	*P* Value
CMTR1	-0.0813032	0.622
CYFIP1	0.2002844	0.266
CYFIP2	0.3131376	0.396
DCP2	0.2105	0.297
DCPS	0.1994243	0.228
EIF3D	0.0836587	0.509
EIF4E	-0.1752564	0.553
EIF4E2	0.3041538	0.0632
EIF4G3	0.0232268	0.914
IFIT5	-0.365105	0.0452*
LARP1	-0.3833775	0.0787
LSM1	0.29774	0.0851
METTL1	-0.2378296	0.168
NCBP1	-0.2129643	0.306
NCBP2	-0.0837419	0.655
NUDT1	1.2384947	0.04*
NUDT11	0.9948905	0.0164*
NUDT3	0.0393284	0.884
NUDT4	-1.4161426	0.0283*
NUDT7	-0.2247438	0.387
RNGTT	0.2399528	0.236
RNMT	-0.3588973	0.0473*
SNUPN	0.5227087	0.0123*
TGS1	0.030794	0.911
WDR4	-0.3316364	0.175

*, P < 0.05

Diagnostic value of m7G RNA methylation regulators in OA

To explore the relationship between m7G RNA methylation-related genes and early prognosis of OA, we first found 6 valuable genes by logistic univariate analysis. The results show that SNUPN ($P < 0.05$), NUDT11 ($P < 0.1$), IFIT5 ($P < 0.1$), RNMT ($P < 0.1$), EIF4E2 ($P < 0.1$), and LSM1 ($P < 0.1$) were meaningful. After dividing these 6 genes with the DGEs, the results show that two of the genes were significant, namely SNUPN and NUDT11 (Figure 7A). We used ROC and AUC to analyze and evaluate the genetic diagnostic efficacy of gene pairs to distinguish OA and normal patients. The results indicated that SNUPN and NUDT11 genes were associated with OA and can be used as valuable biomarkers. Specifically, the AUC for SNUPN was 0.900 (95% confidence interval, 0.766 ~ 1.000, $P < 0.05$) and the AUC for NUDT11 was 0.800 (95% confidence interval, 0.605-0.995, $P < 0.05$), suggesting that two differential genes had diagnostic value in OA (Figure 7B).

Discussion

OA is a progressive joint disease found worldwide and is considered a degenerative inflammatory disease of articular cartilage, with inflammatory mediators released from the synovium, bone, and cartilage [34]. Synovitis exists in OA, which is also a feature of advanced OA [35]. Recently, many studies have reported that synovitis occured through the formation of an inflammatory pannus, leading to bone and cartilage damage and increased pain [13, 14, 36]. As important post-transcriptional regulators, RNA modification is involved in the biological processes of eukaryotes and plays important regulatory roles in a variety of diseases [37]. m7G modification is a kind of epigenetic modification, which is necessary for RNA biosynthesis and function. This is largely due to the protein factors that specifically bind to the cap structure, namely the cap-binding complex in the nucleus and the eIF4E in the cytoplasm [30]. There are few

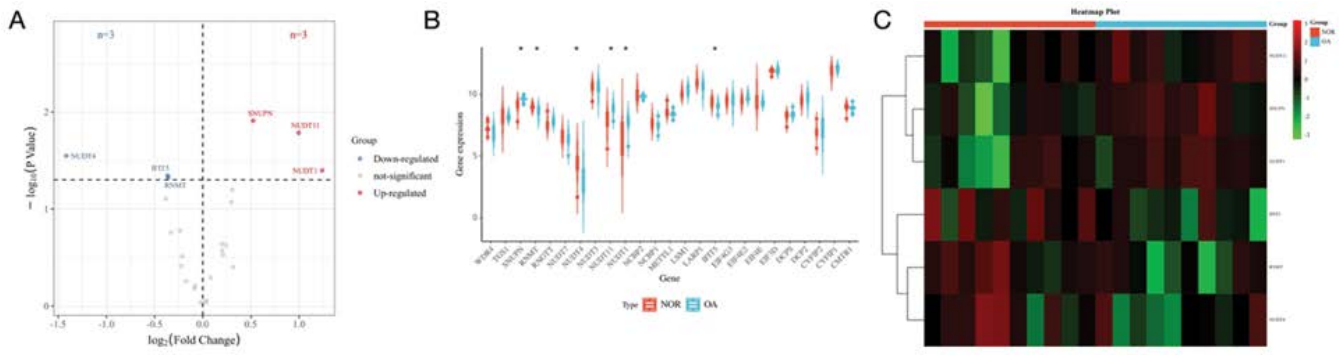

Figure 6: Differentially-expressed m7G methylation regulators between OA and normal patients. A Volcano map showing differences in m7G methylation regulators expression between normal and OA patients. B Boxplot showing differences in the expression of m7G methylation regulators in OA and normal patients. C Heatmap showing differences between 6 m7G methylation regulators expression between normal and OA patients. *, P < 0.05; NOR, normal; OA, Osteoarthritis

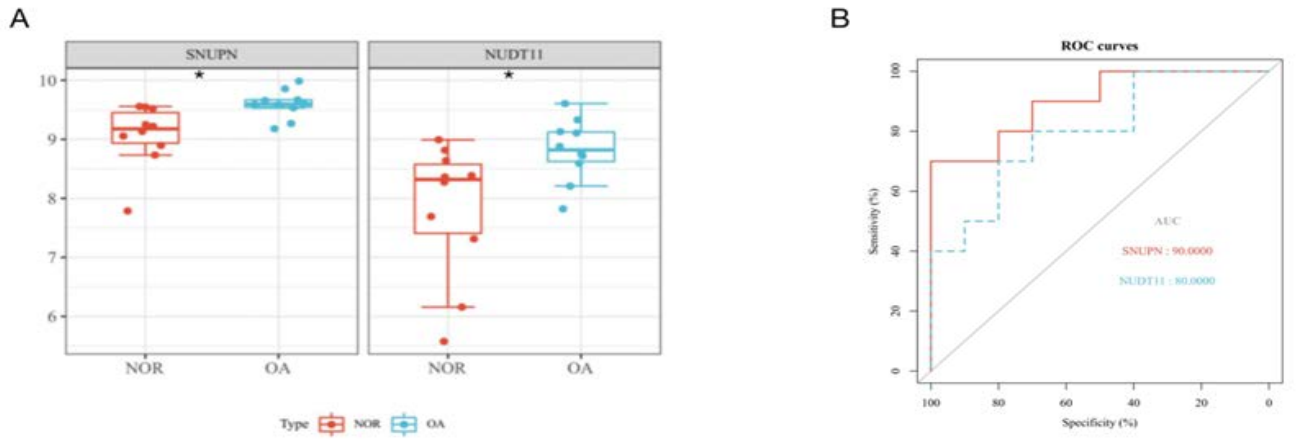

Figure 7: Diagnostic value of m7G RNA methylation regulators in OA. A Boxplot demonstrating the gene (SNUPN 、 NUDT11) expression of m7G methylation regulators. B ROC curves of m7G methylation regulators for OA diagnosis. *, P < 0.05; ROC, receiver operating characteristic; NOR, normal; OA, Osteoarthritis

studies on the relationship between m7G RNA methylation and OA. Therefore, we sought to open up a new prospect for the clinical prognosis of OA. In this research, we selected the GSE55457 dataset from the GEO database to perform a detailed bioinformatics analysis of the data, which provided effective insights into the early diagnosis of OA. We first constructed a PPI network for 25 genes associated with m7G RNA methylation regulators, revealing a close interaction relationship of these 25 regulators. This suggests that the role of these genes in osteoarthritis is synergistic rather than isolated. GO and KEGG enrichment analysis were then performed to investigate their associated biological functions. The results showed that these genes are mainly involved in RNA metabolism, RNA cap binding and, the formation of RNA cap binding complex. And m7G RNA methylation-related genes are enriched in mRNA surveillance pathway, RNA degradation, and nucleocytoplasmic transport. Interestingly, in the GO enrichment analysis, the cell component (CC) and molecular function (MF) mostly showed that these 25 genes were mostly related to the RNA cap. The RNA cap is synthesized on the first transcribed nucleotide, protecting the RNA from nucleases and recruiting protein complexes involved in RNA processing and translation initiation [38, 39]. The regulation of RNA cap formation has a powerful effect on gene regulation, and the core of mRNA processing is the addition of a methyl 7 guanosine (shown at left) "cap" to its 5 ′ end of the mRNA [40]. This also proves that m7G plays an important role in the development of the disease. We observed differential expression of some m7G RNA methylation regulators between healthy and OA patients and found three up-regulated genes and three down-regulated genes (SNUPN, NUDT11, NUDT 1, NUDT 4, IFIT 5, and RNMT). These results suggested that m7G RNA methylation regulators, especially SNUPN, NUDT11, and NUDT 1, may be involved in the development and development of OA. Furthermore, we observed a correlation between the expression levels of the m7G regulators. In predictive analysis, the expression levels of SNUPN and NUDT11 were closely related with the early diagnosis of OA. This should provide new settings for further understanding of OA that can contribute to the development of its diagnosis and treatment.

SNUPN belongs to the snurportin family and acts as U snRNP specific nuclear import adaptors involved in the trimethylguanosine cap-dependent nuclear import of U snRNP. Related pathways include translocation of intron-containing pre-mRNA and SLBP-independent mature mRNA. Chen [13] studied four genes, including SNUPN and other regulators associated with m7G, as novel biomarkers of OA to predict the occurrence of OA. Assessing m7G methylation patterns in OA individuals will help enhance our perception of immune infiltration characteristics and guide more effective immunotherapeutic strategies. Hao [30] constructed an m7G-related scoring model using four key genes, including SNUPN, which could significantly distinguish OA patients and correlate them with different states of the immune microenvironment to diagnose OA patients. SNUPN is also associated with chronic lymphocytic leukemia, cancer, etc. SNUPN is also associated with chronic lymphocytic leukemia, cancer and so on. The binding of XPO1 to various proteins is mediated by the recognition of leucine-rich nuclear export signals at the N-terminus of SNUPN. Overexpression or dysfunction of XPO1 has been reported in different cancers [30, 41]. Previous studies on SNUPN have mainly focused on cancer and further studies are needed to understand the role of SNUPN in OA. Our study found that SNUPN can be used as a more accurate predictor of OA, which was important for the accurate prediction of future OA.

NUDT11 belongs to the Nudix hydrolase family. It may play a role in signal transduction. NUDT11 takes Ap6A and Ap5A as the preferred substrates, which can catalyze the hydrolysis of oligo-nucleoside phosphate. The GO pathway associated with NUDT11 includes the catabolic processes of adenosine and the synthesis of pyrophosphate in cytoplasm. Studies showed that NUDT11 as a key gene in m7G predicts the prognosis of patients with bladder cancer and was associated with immunotherapy and response to chemotherapy [42]. And NUDT11 is associated with ovarian cancer, prostate cancer and other cancers [43, 44]. However, previous studies have not paid attention to and discussed the relationship between NUDT11 and OA, and have not noticed the role of NUDT11 in OA, which may become a potential topic for future research. Compared with normal patients, NUDT1, NUDT4, IFIT5 and RNMT were differentially expressed in OA patients. NUDT1 can play a key role in T cell differentiation in patients with head and neck squamous cell carcinoma by changing the m7G modification pattern[45]. It also plays a role in gliomas, lymphomas, and renal clear cell carcinoma. Overexpression of NUDT4 promotes the proliferation of tumor cells and NUDT4 is an independent risk factor for lung adenocarcinoma. The m7G modified protein NUDT4 may be a new biomarker to promote the progress of lung cancer [46]. NUDT4 also plays an important role in diagnosing heart failure and determining the prognosis of gastric cancer. IFIT5 can induce epithelial transformation of bladder cancer and promote cell migration and invasion [47]. IFIT5 is a novel oncogene in bladder cancer. Yin [48] constructed a random forest model for diagnostic OA based on RNMT and RBM in cartilage tissue, providing a promising clinical tool and a possible entry point for clarification of molecular mechanisms. As an RNA cap methyltransferase, RNMT plays a key role in many steps of RNA metabolism.

Up to now, OA is often diagnosed by X-ray and clinical symptoms in clinical practice, which is a relatively accurate method [49-51]. However, with the development of OA, the joint pain caused by OA and its influence on patients' daily life and sports ability are becoming more and more serious. Therefore, early and timely diagnosis of OA is urgent and necessary. However, some limitations still resided in this study. First, this study was retrospective in nature, and therefore, it was imperative to conduct prospective studies with larger sample sizes and diverse methodologies in order to authenticate the findings of the present study. Second, the data source was obtained from a public database, and input errors could not be assessed. Third, it was worth mentioning that this study did not encompass any clinical information. Finally, prior to the clinical application of the study's findings, it was essential to conduct in-vivo and ex-invivo experiments, which should include investigations on human samples as well as animals. It should also be noted that these biomarkers of synovium still lack OA specific diagnostic value, and whether they are triggers for early OA remains to be further investigated.

Conclusion

Our study demonstrated for the first time that SNUPN and NUDT11 played a key role in OA. As biomarkers for accurate prognosis and the formulation of treatment strategies of OA in the future, it also provided new insights into the pathogenesis of OA. However, the clinical effects of these biomarkers on OA need further study.

Abbreviations

OA, Osteoarthritis; m6A, N6-methyladenosine; m7G, N7-methylguanosine; Ψ, pseudouridine; m1A, N1methyladenosine; Nm, ribose methylations; m5C, 5methylcytidine; ac4C, N4-acetylcytidine; lncRNA, long non-coding RNA; mRNA, messenger RNA; ROC, Receiver operating characteristic; AUC, Area under the curve; GEO, Gene Expression Omnibus; GSEA, Gene Set Enrichment Analysis; BP, Biological process; CC, cellular component; MF, molecular function; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, Protein–protein interaction; FC, Fold change; DEG, Differentially expressed gene.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Third Hospital of Hebei Medical University and followed the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all patients to authorize the publication of their data.

Availability of data and materials

The datasets presented in this study can be found in online repositories (GEO data repository, https://www.ncbi.nlm.nih.gov/geo/, accession number GSE55457). Further inquiries can be directed to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZH and KH are co-first authors. ZH, YN, and FW contributed to the conception and design of the research. Material preparation, data collection, and analysis were

performed by ZH and XW. The first draft of the manuscript was written by ZH and KH. ZH and CF prepared all the Figurers and the table. All authors commented on previous versions of the manuscript. And all authors read and approved the final manuscript.

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