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ORIGINAL ARTICLE

Investigating the potential impact of ELF3-associated SNPs on chondrocyte inflammation

Beren Karaosmanoğlu[1]
ORCID: 0000-0001-5564-4813

Büşra Aydın[2]
ORCID: 0000-0003-3922-8953

Gözde İmren[1,2]
ORCID: 0000-0002-2556-0421

Erdal Sağ[3]
ORCID: 0000-0002-6542-2656

Ekim Z. Taşkıran[1,2]
ORCID: 0000-0001-6040-6625

[1] Department of Medical Genetics, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

[2] Department of Medical and Surgical Research, Institute of Health Sciences, Hacettepe University, Ankara, Türkiye

[3] Department of Pediatric Rheumatology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

Corresponding Author: Beren Karaosmanoğlu
E-mail: berenkaraosmanoglu@gmail.com

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ABSTRACT

Objective: Chondrocyte inflammation is a critical factor in degenerative joint diseases, such as osteoarthritis (OA), significantly impairing quality of life through chronic pain and limited mobility. Genetic predisposition is recognized as a critical factor in the progression of chondrocyte inflammation and OA, with particular focus on the role of genetic variants in the expression and regulation of inflammatory mediators. This study aimed to obtain information about the potential roles of a few genes containing ELF3-associated SNPs in the pathogenesis of chondrocyte inflammation.

Materials and Methods: GVAT Database was used to select top candidate SNPs associated with ELF3, a cardinal transcription factor in chondrocyte inflammation. Inflammation was induced by IL-1β treatment in differentiated chondrocytes to analyze gene expression patterns. Transcriptome analysis was done by RNA sequencing.

Results: The most important SNPs that could potentially affect the binding affinity of ELF3 transcription factor were analyzed. As a result of the analysis, 52% of ELF3-associated SNPs were found in protein-coding regions, 40% in gene-free intergenic regions, and 8% in non-coding RNA sequences. Some of these SNPs are located in regulatory regions (enhancers). A significant increase in expression levels in the ELF3 gene was detected after IL-1β administration, indicating that IL-1β promotes the activity of this transcription factor. mRNA expressions of TLN2, BABAM2, PEPD, and NUDT5 were also increased after IL-1β stimulation.

Conclusion: The presence of ELF3-associated SNPs in the enhancer sequences of TLN2 and BABAM2 genes, in addition to the increased expression of these two genes upon IL-1β stimulation, suggested that TLN2 and BABAM2 genes may be associated with the severity of chondrocyte inflammation and OA.

Keywords: osteoarthritis, ELF3, TLN2, chondrocyte inflammation, IL-1β.

INTRODUCTION

Osteoarthritis (OA) is one of the most common types of arthritis, affecting millions of people worldwide and significantly reducing quality of life [1]. Typically characterized by joint pain, swelling and reduced mobility, the condition develops as a result of a combination of genetic predisposition, environmental factors and lifestyle [2, 3]. The pathogenesis of OA is characterized by cartilage destruction and degenerative changes in joint structures, the understanding of which is critical in the development of treatment modalities for this disease. Genetic predisposition plays a significant role in the inflammatory processes involved in the progression of OA. While environmental factors and lifestyle have an impact on the development of the disease, genetic predisposition can be decisive in factors such as disease severity, rate of progression and response to treatment.

The ELF3 (E74 Like ETS Transcription Factor 3) gene is a member of the ETS (E26 transformation-specific) transcription factor family and is commonly expressed in epithelial cells [4]. This gene helps regulate critical biological processes such as cell growth, differentiation and renewal [5, 6]. ELF3 binds to various target genes that modulate intracellular signaling pathways and regulate gene expression [7, 8]. It plays an important role in the modulation of inflammation and immune response, and can influence the course of disease by regulating the expression of various cytokines and inflammatory mediators [9]. Both in vitro and in vivo settings, ELF3 was shown to be important specifically in chronic arthritis in different studies [9, 10]. Therefore, a more detailed understanding of the molecular mechanisms of ELF3 may open new avenues for the development of therapeutic strategies for various rheumatologic diseases. Furthermore, studying the effects of genetic variants of ELF3 on the disease process may be critical in the development of more personalized therapies for these diseases.

ELF3, a pivotal regulator of inflammatory and immune responses, emerges as a candidate of interest due to its role in epithelial cell function and potential influence on chondrocyte behavior. The potential role of ELF3-associated Single Nucleotide Polymorphisms (SNPs) in chondrocyte inflammation has not been thoroughly investigated. Exploring these variants could offer new perspectives and aid in developing targeted therapeutic strategies. This highlights the need for continued research on how these SNPs might modulate disease processes through transcriptional regulation. This gap in knowledge presents a critical barrier to the development of targeted therapeutic strategies and underscores the need for research focused on genetic variants that could modulate disease processes through transcriptional regulation. Our study leverages in-silico methods coupled with cellular models to dissect the relationship between ELF3-associated SNPs and chondrocyte inflammation. The existing literature has provided important insights into the complex pathogenesis of OA and the role of genetic factors in the disease process. However, the potential effects of SNPs linked to specific transcription factors such as ELF3 on disease mechanisms are still poorly understood. GVATdb (Genetic Variants Allelic Transcription Factor Binding Database) was used to select top candidate SNPs associated with ELF3. SNPs that alter the binding sites of ELF3 may affect the expression of related genes and consequently influence the severity of chondrocyte inflammation. This study aimed to obtain information about the potential roles of a few genes containing ELF3-associated SNPs in the pathogenesis of chondrocyte inflammation.

MATERIALS AND METHODS

Bioinformatic Analysis

ELF3 associated SNPs were identified using the GVATdb, which contains the results of SNP-SELEX (Single Nucleotide Polymorphism Evaluation by Exponential Enrichment with Systematic Evolution of Ligands by Exponential Enrichment), ultra-high-throughput multiprotein-DNA binding experiments to assess the binding affinity of 270 human transcription factors to selected variants which provides comprehensive information on genomic locations, allelic frequencies and their potential impact on gene expression [11]. The top 25 SNPs were selected according to the lowest p-values indicating significant associations. Detailed data on the specific locations and allelic frequencies of these SNPs were meticulously

compiled in a tabular format to understand their distribution within the structure of the gene and their potential importance.

In order to determine the allele frequencies for selected ELF3-associated SNPs, the most reliable frequency data was obtained from the Genome Aggregation Database (gnomAD), which has a large collection of exome and genome sequencing data. This data repository facilitated the acquisition of Minor Allele Frequencies (MAFs) for most of the SNPs and ensured the robustness of the frequency estimates. However, some SNPs did not have MAF data in gnomAD, which required searching alternative databases. For these cases, the search was expanded as to include other reputable genomic databases, maintaining the integrity of our dataset (1000Genomes data). Genomic position information of SNPs was added to the table according to GRCh38. University of California, Santa Cruz (UCSC) Genome Browser was used in order to identify the SNP locations, in terms of regulatory regions, within the human genome [12]. None of the SNPs detected contained ClinVar entries. Therefore, no information was available in terms of pathogenicity. The JASPAR database was used to examine transcription factor binding sites.

Cell Culture

Human Bone Marrow Mesenchymal Stem Cells (MSCs) were obtained from ATCC (No: PCS-500-012, Lot:63208778), cultured in DMEM-LG supplemented with 10%FBS, 1% L-glutamine and 1% Penicillin-Streptomycin in standard culture conditions (37°C with 5% CO_2). Passage 3 cells were used for further experiments. Chondrogenesis differentiation was induced with Stem Pro Chondrogenesis Differentiation Kit (Cat. No: A1007101, Thermo Fisher Scientific) for 21 days, according to the manufacturer's instructions. In order to trigger inflammation, on the 10th day of differentiation, cells were treated with 1 ng/ml IL-1β.

RNA-Sequencing and Data Analysis

Total RNA was isolated with TRIzol (Roche), according to the manufacturer's instructions, and quality control was measured spectrophotometrically (NanoDrop One, Thermo Fisher Scientific). RNA-Seq library was prepared from equal amounts of each RNA by Lexogen SENSE mRNA-Seq Library Prep Kit (Lexogen GmbH) and run was performed on Ion Proton Semiconductor Sequencing Platform (Thermo Fisher Scientific). The raw data were analyzed with the Transcript Per Million (TPM) method by RaNA-Seq software [13]. TPM values were calculated after read numbers mapped to each gene. Differential expression analysis was performed with DESeqR package. Genes with an adjusted p value lower than 0.05 were assigned as differentially expressed. The expression values were visualized with GraphPad Prism (v8.0) (www.graphpad.com/scientific-software/prism/).

RESULTS

Analysis of ELF3-Associated SNPs and Their Implications for Gene Regulation

The most significant SNPs that potentially affect the binding affinity of the ELF3 transcription factor were selected for further analysis in this study (Table 1). The distribution of single nucleotide polymorphisms (SNPs) associated with the ELF3 gene examined in this study is summarized in Figure 1. While 52% (n=13) of ELF3-associated SNPs were found in protein-coding regions, 40% (n=10) were localized in intergenic regions (regions containing no genes) and 8% (n=2) in non-coding

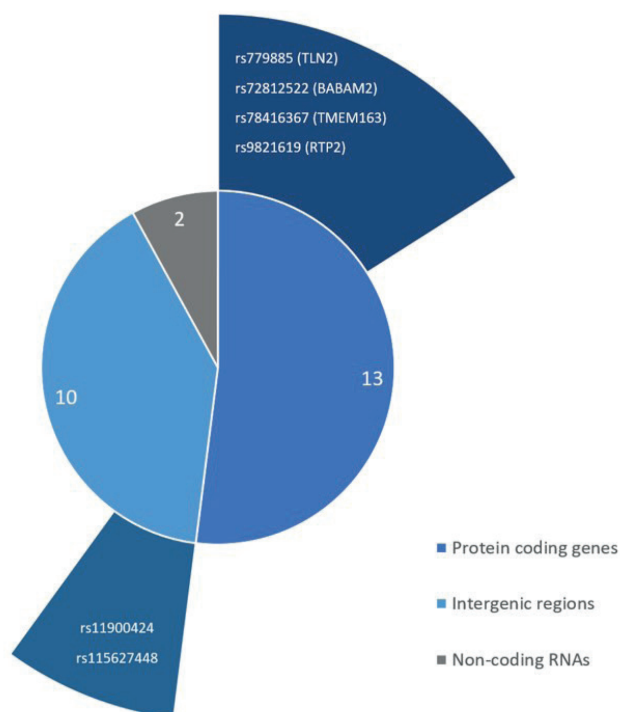

Figure 1. Graph for SNP numbers that associated with ELF3. Protein coding genes, Intergenic regions and non-coding RNA targets are given. Critical SNPs within the regulatory regions in each group are shown in the outer ring. rs: reference SNP number

Table 1. All SNPs associated with ELF3, analyzed with GVAT database, that could be significant importance for rheumatologic diseases and their details. rs ID: reference SNP number, ref: reference base, alt: alternative base.

rs ID	Genomic region (GRCh38)	ref	alt	p-value	Global MAF (GnomAD)	Gene	Regulatory region
rs4745991	chr10:69523734	C	T	0	C=0.449334	TSPAN15 (intronic)	None
rs562897	chr10:78770483	G	A	0	A=0.400848	Intergenic	None
rs10404460	chr19:33469490	T	C	0	C=0.145462	PEPD (intronic)	None
rs73279624	chr20:44449217	G	A	0	A=0.021152	LINC01430 (intronic)	None
rs13318430	chr3:11908851	T	C	0	C=0.242005	Intergenic	None
rs62262911	chr3:123805176	G	A	0	A=0.038679	MYLK (intronic)	None
rs7068603	chr10:79012784	C	T	0.00002	T=0.193161*	ZMIZ1-AS1 (intronic)	None
rs11900424	chr2:5849827	G	C	0.00002	C=0.216115*	Intergenic	EH38E1969349 distal enhancer-like signature
rs7017487	chr8:94910524	C	T	0.00002	C=0.395885	NDUFAF6 (intronic)	None
rs115627448	chr9:21674924	T	C	0.00002	C=0.027165	Intergenic	EH38E2687073 distal enhancer-like signature
rs779885	chr15:62470173	C	T	0.00003	C=0.394861	TLN2 (intronic)	EH38E1768118 distal enhancer-like signature
rs28549270	chr15:62528241	G	C	0.00003	C=0.015287	TLN2 (intronic)	None
rs72812522	chr2:27966013	T	C	0.00003	C=0.028585	BABAM2 (intronic)	EH38E1983168 distal enhancer-like signature
rs9471049	chr6:39293745	T	C	0.00003	C=0.012014	Intergenic	None
rs10977092	chr9:8432445	T	G	0.00005	G=0.279858	PTPRD (intronic)	None
rs10842946	chr12:27592997	T	A	0.00008	A=0.269119	PPFIBP1 (intronic)	None
rs78416367	chr2:134468413	T	C	0.00008	C=0.031631	TMEM163 (intronic)	EH38E2034674 distal enhancer-like signature
rs3758379	chr10:12194774	G	A	0.0001	A=0.092262	NUDT5 (intronic)	None
rs9821619	chr3:187703248	G	A	0.00012	A=0.389633	RTP2 (intronic)	EH38E2266715 proximal enhancer-like signature
rs10121752	chr9:81472715	C	T	0.00012	T=0.036575	Intergenic	None
rs16921782	chr9:4670573	C	T	0.00013	T=0.460724	Intergenic	None
rs7641618	chr3:186537260	A	G	0.00017	G=0.049333	Intergenic	None
rs617523	chr2:160748153	C	T	0.00021	T=0.024147	Intergenic	None
rs116004702	chr11:93042150	T	G	0.00025	G=0.015590	Intergenic	None
rs6749329	chr2:134716795	T	C	0.00031	C=0.207290	TMEM163 (intronic)	None

* The MAF scores for these SNPs are presented from the 1000Genomes data.

RNA sequences. Among the 25 SNPs, 6 were located in regulatory sequences (enhancers); 4 of them are located in protein coding genes (rs779885, rs72812522, rs78416367, and rs9821619), other 2 are in intergenic regions (rs11900424 and rs115627448) (Figure 1).

Considering the possibility that SNPs located in the introns of protein-coding genes may lead to alterations in the expression of these genes, this group was first analyzed. There were two SNPs associated with both TLN2 (rs779885 and rs28549270) and TMEM163 (rs78416367 and rs6749329). Moreover, rs779885 was localized in a regulatory region within the TLN2 gene. This region, referred to as 'EH38E1768118 distal enhancer-like signature' in the UCSC, was predicted to regulate the expression of the TLN2 gene. A similar situation was also observed for rs78416367 in the TMEM163 gene. This genomic region had an 'EH38E2034674 distal enhancer-like signature' according to the UCSC database. Two different SNPs in the introns of RTP2 (rs9821619) and BABAM2 (rs72812522) were also located within the regulatory sequences (Table). Among the 10 SNPs located in intergenic regions, only 2 were in regulatory sequences (rs11900424 and rs115627448). The two SNPs were within the intronic sequences of two different non-

coding RNAs (LINC01430 and ZMIZ1-AS1) and were not associated with regulatory regions.

Impact of IL-1β Stimulation on Gene Expression

The transcriptomic dataset in which IL-1β treated chondrocytes was used to determine whether the candidate genes (containing ELF3-associated SNPs) were associated with the chondrocyte inflammation. The results of transcriptomic analysis revealed the effects of IL-1β on gene expression compared to the control group. Significant increases in ELF3 expression was observed after IL-1β administration compared to the control group. This, in line with the literature, suggests that ELF3 plays an increasing role in inflammatory processes and that IL-1β promotes the transcriptional activity of this transcription factor [14]. In addition to ELF3, the demonstration of increased expression of MMP13 is also an important finding for the accuracy of the established inflammatory cell model. Similarly, TLN2, BABAM2, PEPD and NUDT5 genes have also increased mRNA expression after IL-1β stimulation (Figure 2). There was no change in expression in the MYLK gene, while there was a decrease in expression in the PPFIBP1 gene, and no expression of other protein-coding genes and non-coding RNAs was detected in chondrocytes.

DISCUSSION

This study highlights the significant role of ELF3 and its associated SNPs in chondrocyte inflammation and OA pathogenesis through in-silico analysis and expression assays. In particular, SNPs in regulatory sequences may be important for ELF3's activity as a transcription factor and its regulatory functions on target genes. Our findings suggest that these SNPs may affect ELF3 activity on these target genes and consequently the course of OA. These effects were also seen in animal studies as well, where ELF3 knockout mice had attenuated cartilage loss proving its pro-catabolic role in cartilage degradation and re-modelling [10, 15]. Studying the effects of ELF3 gene and its associated SNPs on OA is considered as an important step in this field.

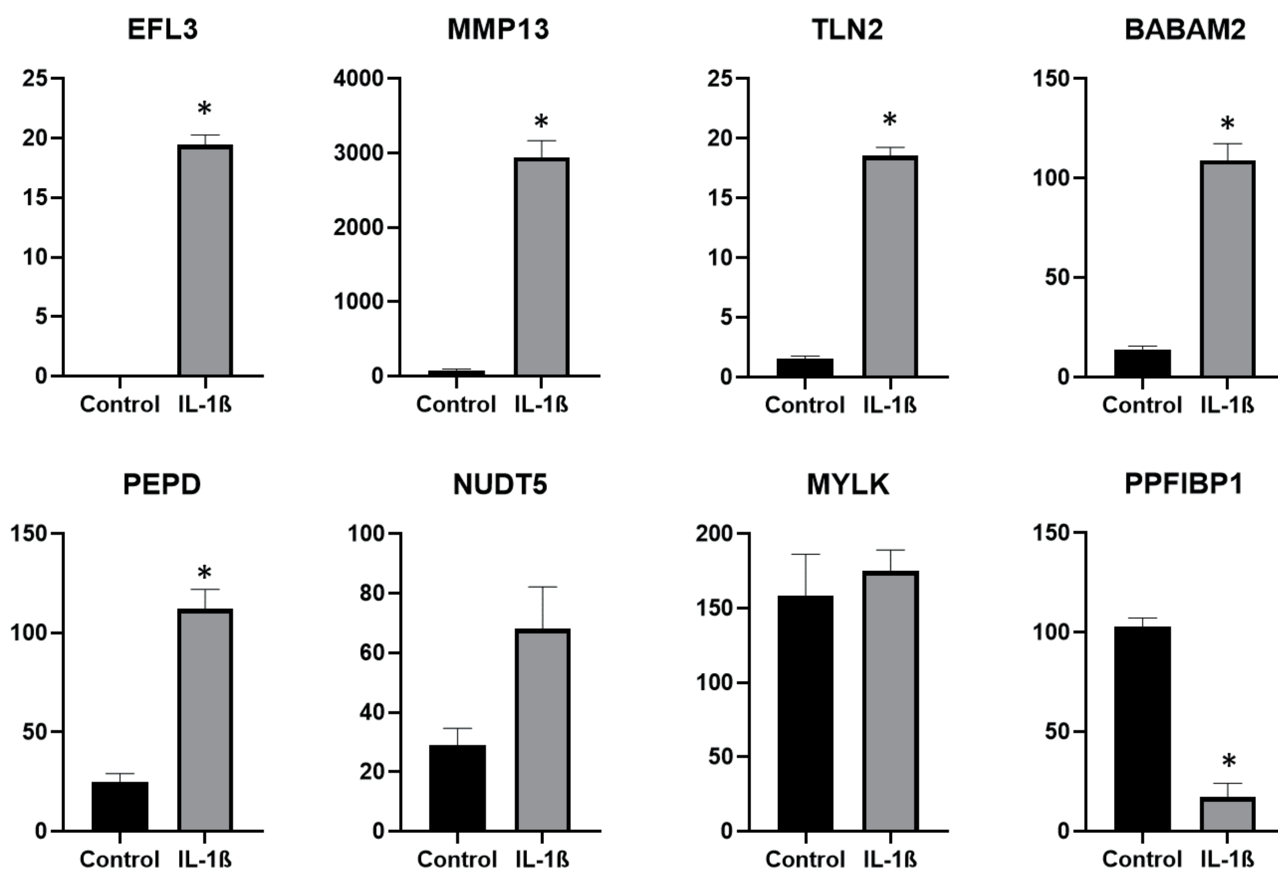

Figure 2. mRNA expression levels of the genes in IL-1β Treated Chondrocytes. The y-axis represents the expression levels measured in Transcripts Per Million (TPM). Based on TPM values, significant increases were observed in the expression of ELF3, TLN2, BABAM2 and PEPD genes after IL-1β treatment (*: $p < 0.05$). While no significant change was observed in MYLK and NUDT5 genes, a significant decrease was observed in PPFIBP1 gene

With this aim, this study was designed, and the results revealed an important link between ELF3-associated SNPs and the genomic background of OA. These findings underscore the need to explore specific SNPs and their regulatory roles in gene expression.

Among the SNPs analyzed in this study, rs779885 (TLN2), rs72812522 (BABAM2), rs78416367 (TMEM163), and rs9821619 (RTP2) SNPs, which are located in protein coding regions and regulatory regions, draw attention. In our opinion, the candidate genes containing ELF3-associated SNPs whose expression is increased in the chondrocyte inflammation model are of critical importance. The increased expression of TLN2 and BABAM2 in the chondrocyte inflammation model, which is noteworthy due to SNPs in their enhancer regions, suggests that these genes may be related to the pathogenesis and severity of OA (Figure 3). These SNPs may have important roles in regulating gene expression and cellular functions. Figure 3 illustrates the binding motifs of ELF3 and the locations of critical SNPs within the TLN2 and BABAM2 genes, highlighting the potential regulatory impact of these SNPs on ELF3 binding.

In addition to TLN2 and BABAM2, the 'EH38E2034674 distal enhancer-like signature' region where rs78416367 is located in the TMEM163 gene indicates a regulatory effect on the transcriptional activity of the gene. The rs11900424 and rs115627448 SNPs in intergenic regions are localized within regulatory sequences and may play a role in regulating gene expression and modulating inflammatory responses. The presence of these specific SNPs strengthens the hypothesis that they may modulate the functionality of ELF3 in processes such as cellular adhesion, signal transduction and inflammation, and thereby serve as critical factors in the pathogenesis of OA.

Given the importance of SNPs in regulatory regions, those located in enhancer sequences can affect ELF3 activity significantly. The 'enhancer-like signature' findings in the UCSC database indicate that the SNPs analyzed are located in enhancer

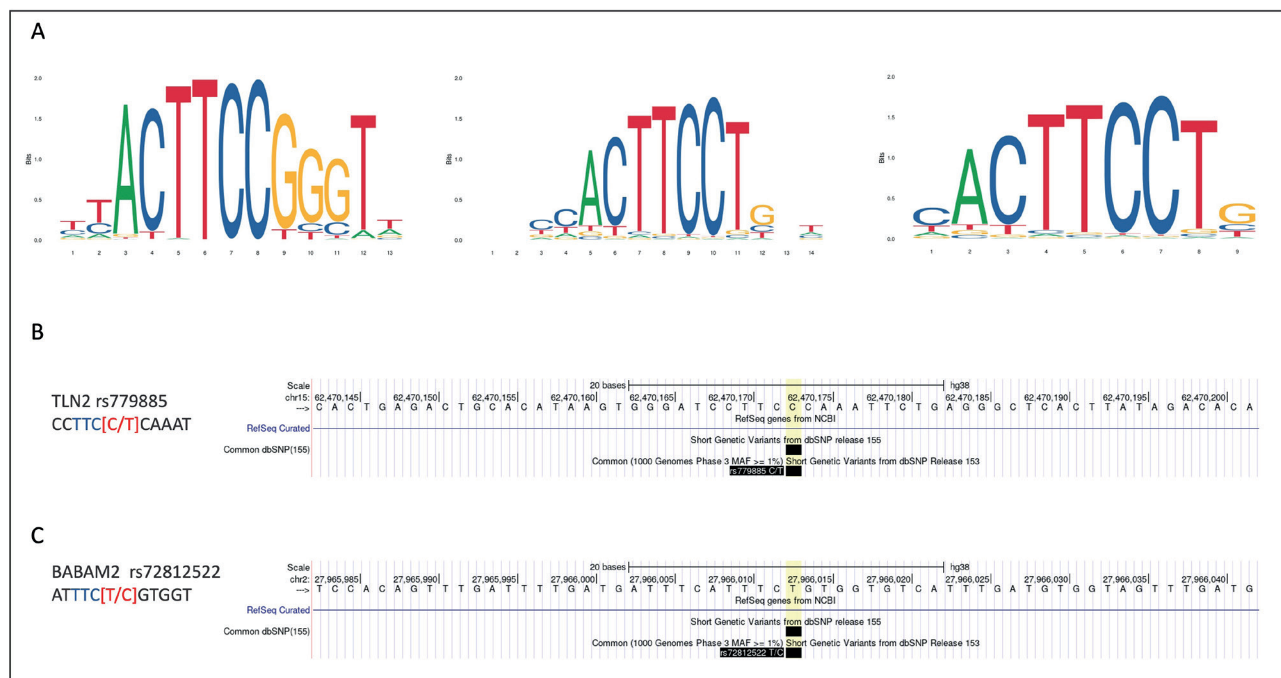

Figure 3. ELF3 Binding Motifs and SNPs Locations. A. Position weight matrix of ELF3 binding site motifs. The sequence logos represent the binding motifs of ELF3, illustrating the probability of each nucleotide at specific positions within the binding site. These motifs were obtained from the JASPAR database, highlighting the critical nucleotides that are essential for ELF3 binding. The height of each letter corresponds to the frequency of the nucleotide at that position, with higher letters indicating a higher likelihood of being involved in ELF3 binding. B. The sequence surrounding the SNP rs779885 within the TLN2 gene. The sequence is shown with the critical bases of the ELF3 binding motif highlighted in blue (TTC) and the alternative alleles (C/T) at the SNP location are indicated in red. This SNP falls within the TTCC core motif of ELF3. C. The sequence surrounding the SNP rs72812522 within the BABAM2 gene. Similar to TLN2, the sequence is shown with the essential bases of the ELF3 binding motif highlighted in blue (TTC) and the alternative alleles (T/C) at the SNP location are indicated in red. This SNP falls within the TTCC core motif of ELF3

regions that contribute to genetic regulation. These regions can function as binding sites of transcription factors and play critical roles in the remote regulation of gene expression. In particular, concerning the activity of a transcription factor such as ELF3, which plays central roles in inflammation and immune response, the presence of these enhancer-like sequences may indicate a potential influence in the modulation of the expression of target genes and thus, cellular responses. Therefore, we hypothesized that the SNPs identified in this study and thought to be associated with ELF3 are important regulatory factors in the pathogenesis of rheumatologic diseases.

Potential interactions between ELF3 and TLN2 genes in the pathogenesis of OA may contribute to a better understanding of these diseases and the development of new therapeutic approaches. Functional studies are required to elucidate the effects of intronic SNPs such as rs779885 and rs28549270 on transcriptional or post-transcriptional mechanisms mediated by ELF3. These studies can determine what role these SNPs play in ELF3-responsive gene expression. In this context, the discovery of the role played by SNPs in the TLN2 gene in OA thought to be associated with ELF3 will deepen the understanding of genetic mechanisms and novel targetable molecular pathways. Given the roles of Talin-2 in cellular adhesion and signal transduction, these SNPs may be involved in the modulation of pathways regulated by ELF3. When the role of ELF3's contribution in the inflammatory response and immune response is considered, this may indirectly influence the effects of SNPs in the TLN2 gene on cell-matrix interactions and migration of immune cells. Impairments in the function of TLN2 may contribute to cartilage degradation and OA development by weakening the interactions of chondrocytes with the matrix. In addition, TLN2 gene is also draw attention as an OA related SNP in a GWAS study [16]. TMEM163, a member of the Zinc Efflux Transporter Family, may also be associated with the severity of the inflammatory response, suggesting that SNPs in this gene may play a role in OA. TSPAN15, which has an ELF3-related rs4745991 SNP in its intronic region, is the subunit of the ADAM10 complex and is directly associated with inflammation. Given the capacity of ELF3 to regulate the expression of this gene, it is conceivable that this SNP could affect gene expression levels and could have indirect effects on cellular adhesion and peptide processing mechanisms. Another SNP (rs7017487), located in mitochondrial complex I assembly factor NDUFAF6, also related to ELF3 binding activity. The correlation of this SNP with ELF3 activity may elucidate the complex interplay between genetic predisposition and the emergence of OA. Alterations in mitochondrial function may affect cellular metabolism and influence the chronic inflammation characteristic of these diseases [17].

While some genes such as BABAM2, PTPRD, PPFIBP1, NUDT5, and RTP1 currently have no known relationship with OA, their critical cellular roles warrant further investigation. However, BABAM2 and NUDT5 have roles in DNA damage and repair [18, 19], PTPRD and PPFIBP1 are involved in cancer development [20, 21]. According to our current knowledge, although these genes are not directly associated with OA, should kept in mind due to their critical roles in critical cellular processes. The role of BABAM2 in DNA damage response and repair is crucial in maintaining the genomic stability of chondrocytes. Dysfunctions in DNA repair mechanisms may contribute to OA's pathogenesis by accelerating cartilage tissue's degradation, leading to cellular senescence and apoptosis in chondrocytes. These functions of BABAM2 may become more prominent especially when cartilage tissue is under mechanical stress.

Each of the SNPs may alter the effects of ELF3 on gene expression, which in turn may affect cellular pathways associated with the pathogenesis of OA. Understanding these pathways and genetic interactions could help discover potential targets for the treatment of OA. Furthermore, these SNPs may allow for a better understanding of the genetic networks regulated by ELF3 and more detailed exploration of the molecular mechanisms of OA.

It is also important to note the limitations of the study. Although the GVAT database provides a large SNP data, the functional consequences of these SNPs on ELF3 activity and subsequent gene regulation should be experimentally validated. In addition, the impact of environmental factors on gene expression was beyond the scope of this study and warrants further investigation in the future. By addressing these gaps, future research can further our understanding of ELF3-mediated pathways and their therapeutic potential.

In conclusion, our findings expand the understanding the ELF3's role in OA and set the stage for future research to explore the therapeutic potential of targeting ELF3-mediated pathways. Such research could ultimately lead to novel treatments that more effectively address the genetic underpinnings of these complex conditions. The findings of the study suggest that the interaction between ELF3 and specific SNPs may be helpful in predicting disease course and response to treatment to facilitate more personalized treatment plans based on individual genetic background.

Author contribution

Study conception and design: BK, ES, and EZT; data collection: BK, BA, GI, and EZT; analysis and interpretation of results: BK, GI, ES, and EZT; draft manuscript preparation: BK and EZT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This study did not require ethical approval as it exclusively utilized publicly available data and commercially purchased cell lines.

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Conflict of interest

The authors declare that there is no conflict of interest.

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