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ORIGINAL ARTICLE

Unveiling the role of ubiquitin-specific protease family in osteoporosis: A focus on *USP17L2* and *USP19*

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Abstract

Background: The ubiquitin-proteasome system is vital for regulating protein stability and function, influencing numerous cellular processes, including bone homeostasis. **Aim:** This study aims to uncover the role of the ubiquitin-specific protease (USP) family in osteoporosis. **Methods:** The osteoporosis expression microarray profile was analyzed to identify differentially expressed genes (DEGs). DEGs related to ubiquitins were isolated, followed by the analysis of biological pathways and gene ontology for these genes. The interactions between differentially expressed ubiquitins (DE-Ubs) and their targets were examined using the UbiBrowser database. Ultimately, a network of interactions between DE-Ubs and their targets in the context of osteoporosis was constructed. The diagnostic potential of the DE-Ubs was evaluated using receiver operating characteristic (ROC) analysis. Additionally, antisense oligonucleotide design and validation were performed using various bioinformatics tools, including Sfold, IDT OligoAnalyzer, RNAfold, RNAhybrid, and HNADOCK. **Results:** Among the 1,082 DEGs, *USP19* and *USP17L2* were recognized as statistically significant due to their involvement in the mitogen-activated protein kinase and Ras signaling pathways. The diagnostic potential of *USP19* as a biomarker was confirmed through ROC analysis, demonstrating its high predictive accuracy in osteoporosis. Among the designed antisense oligonucleotides for *USP19*, the sequence TGTCACGCCAGATAAAACTA

showed the most favorable predicted properties according to the ΔG values and structural stability. **Conclusion:** This study provides insights into the USP family genes associated with osteoporosis and identifies potential therapeutic targets for further investigation. **Relevance for patients:** This study identifies *USP19* as a promising biomarker for early osteoporosis detection.

Keywords: *USP19; USP17L2;* Antisense oligonucleotides; Osteoporosis; Protein–protein interaction

1. Introduction

Osteoporosis is a significant health problem for societies and is called the "silent disease" of the century.[1] The disease is common among postmenopausal women, with one in three women over 50 at risk of experiencing osteoporotic fractures. It is largely asymptomatic until a fracture occurs because of reduced bone density and increased fracture risk.[2,3] The stabilization of bone structure and function relies on various cellular and molecular interactions, including ubiquitination and deubiquitination in bone homeostasis.[4,5] Ubiquitination is described as a crucial post-translational process where a small protein called ubiquitin is covalently attached to specific target proteins.[6] Ubiquitination results in the degradation or alteration of the target protein's function. In contrast, deubiquitination can counteract these effects, reinstating the stability and function of the target protein.[7] The ubiquitin process has a high level of specificity for its substrate.[8–10] The Ubiquitin-specific protease (USP) family comprises almost 60 members, making it the largest of the five families of deubiquitinases (DUBs). These families are categorized based on the structure of their catalytic domains.[11,12] The USP family is essential in cellular protein degradation and turnover and may contribute to maintaining bone homeostasis. USPs emerge as crucial regulators, offering new insights into the molecular mechanisms of osteoporosis and potential therapeutic targets. USPs oppose protein ubiquitination by hydrolyzing ubiquitin linkages, thereby controlling the function or abundance of targeted proteins and influencing physiological or pathological processes.[13] The diagnostic potential of USP suggests that they could serve as biomarkers for early detection of osteoporosis, facilitating timely and effective intervention.[4,14] Targeting deubiquitinating enzymes could modulate the ubiquitin-proteasome pathway to promote osteogenesis over resorption, presenting a promising approach for osteoporosis treatment. USPs are involved in key signaling pathways, including mitogen-activated protein kinase (MAPK) and Ras, which influence osteoblast and osteoclast activity in bone formation and resorption. Data from human expression profiles can be utilized to investigate the molecular basis of osteoporosis. The results could illuminate the pathogenesis of osteoporosis and potentially guide therapeutic strategies.[15,16] Despite increasing evidence that USPs shape osteoblast and osteoclast differentiation and thereby influence bone homeostasis, the specific USP members most relevant to human osteoporosis remain incompletely prioritized in a systematic, data-driven manner. In particular, studies that integrate human expression profiling with pathway and network context to identify USP candidates remain limited.[17] This study aims to investigate the role of USPs, particularly *USP19* and *USP17L2*, in osteoporosis by analyzing gene expression data from the Gene Expression Omnibus (GEO) dataset in osteoporotic versus normal bone, focusing on differentially expressed ubiquitin (DE-Ub) genes. These findings were further validated through pathway enrichment analyses.

2. Materials and methods

2.1. Data collection and gene expression analysis

The human expression profile related to osteoporosis was obtained from the National Center for Biotechnology Information (NCBI)-GEO (https://www.ncbi.nlm.nih.gov/gds) and is based on research conducted by Xie *et al.*[18] The human expression profile for osteoporosis has accession number GSE230665 (GPL10332). The samples were taken from the femur bone tissue of 15 postmenopausal women (three healthy controls and 12 patients with osteoporosis). Differentially expressed genes (DEGs) were identified using the limma package in Bioconductor (3.66.0, Bioconductor Project, USA) as those showing significant differences between healthy and osteoporosis samples. Genes were considered differentially expressed using $|\log_2 FC| > 0.5$ and adjusted $p < 0.05$ criteria.[19] These thresholds were selected to balance detection of biologically relevant expression changes with control of false positives in this sample size.

2.2. Identification of differentially expressed ubiquitins

A list of human Ub genes was obtained from the UbiBrowser 2.0 (http://ubibrowser.bio-it.cn/ubibrowser_v3/home/index/), a comprehensive database of experimentally validated ubiquitin–protein interactions.[20,21] The DEGs identified through expression analysis, along with the ubiquitin (Ub) genes collected, were compared using Venny (2.1, National Center for Biotechnology, Spain). Ultimately, we identified the DE-Ub genes in this study.

2.3. Gene ontology and pathway enrichment analyses

The ToppGene tool (Cincinnati Children's Hospital Medical Center, USA) was employed to identify enriched biological pathways and gene ontology (GO) associated with the final target.[22] A false discovery rate cutoff of 0.05, based on the Benjamini–Hochberg procedure, was deemed significant. To visualize the GO and pathway enrichment Analysis results, the GOPlot package in R software (1.0.2, R Foundation for Statistical Computing, Austria) was utilized to assess the Reactome pathway and biological process enrichment for the final target in this study.[23]

2.4. Validation of genes: receiver operating characteristic analysis

The diagnostic value of DE-Ub gene expression in individuals with osteoporosis, compared to healthy individuals, was evaluated using receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) was calculated to compare the diagnostic potential of the candidate genes. ROC analysis was performed at a significance level of 0.05 (p-value < 0.05), and the results were considered statistically significant within a 95% confidence interval. This statistical analysis was conducted using GraphPad Prism software (version 9.1.0, GraphPad Software, Inc., USA).

2.5. Protein–protein interaction network construction

The proteins interacting with DE-Ub were searched in the UbiBrowser database. We downloaded all the targets of ubiquitin-specific peptidase 19 (USP19) and ubiquitin-specific peptidase 17-like family member 2 (USP17L2) from the UbiBrowser database. Subsequently, we compared these targets to the significant genes identified in the current study using Venny. As a result, we identified targets for the two ubiquitins, USP19 and USP17L2, involved in osteoporosis. Accordingly, the interaction network between ubiquitin and its targets was visualized using Cytoscape (3.10.2, Cytoscape Consortium, USA).

2.6. *USP19* antisense oligonucleotides design

The mRNA sequence of the *USP19* gene (NM_001400288.1) was accessed from the NCBI database.[24] The sequence was entered into the Sfold web server to design candidate antisense oligonucleotides (ASOs). Information was recorded in the Soligo part of the Sfold server.[25] Candidate antisense oligonucleotides were generated using the server. The designed ASOs were evaluated using the IDT OligoAnalyzer (Integrated DNA Technologies, USA) to check their structural stability.[26] The RNAfold web server (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) was used to analyze the structure of the target mRNA.[27] The RNAhybrid server was used to determine the minimum free-energy hybridization between the target mRNA and the ASOs.[28] The best ASOs were selected based on several factors, including hairpin ΔG, oligo binding energy, minimum free energy hybridization, GC content, absence of GGGG motif. The docking score of the best ASO with its binding site was examined using the HNADOCK server (v2.4, Utrecht University, Netherlands).[29] The similarity of the best ASO sequence with other human genome sequences was compared using the online Ensembl tool to ensure specificity.[30]

3. Results

3.1. Identification of differentially expressed ubiquitin genes

One expression profiling by array dataset (GSE230665) was used in this study. We identified 1,082 DEGs (511 up-regulated and 571 down-regulated) by comparing the osteoporosis groups (n = 12) to the control group (n = 3) using the limma package (Supplementary File 1). We obtained 112 Ub genes from the UbiBrowser database and literature review (Supplementary File 2). To identify DE-Ubs, we compared all DEGs with the collected ubiquitinated proteins using the online tool Venny. Finally, this study assigned two DE-Ub genes, including *USP19* and *USP17L2* (Table 1).

3.2. GO and pathway enrichment analysis

In the Reactome pathway analysis, ubiquitin-specific processing proteases, deubiquitination, post-translational protein modification, metabolism of proteins, Ras processing, and MAPK family signaling cascades were more significant (Figure 1A). Besides, protein K48-linked deubiquitination, protein deubiquitination, protein modification by small protein removal, negative regulation of proteolysis, and ubiquitin-dependent protein catabolic process were significant in the GO category (Figure 1B).

3.3. Receiver operating characteristic analysis

The ROC analysis evaluated the accuracy of the selected DE-Ub in predicting diagnostic status. The expression level of *USP19* showed significant diagnostic value, as indicated by its AUC, while *USP17L2* was not significant (Figure 2).

3.4. Protein–protein interaction network of USP19 and USP17L2

The protein–protein interactions of USP19 and USP17L2 were retrieved from the UbiBrowser database. The identified interacting partners for USP19 and USP17L2 were mouse double minute 2 homolog (MDM2), POU class 4 homeobox 1 (POU4F1), synovial apoptosis inhibitor 1 (SYVN1), HECT, UBA, and WWE domain containing E3 ubiquitin protein ligase 1 (HUWE1), protocadherin 8, aryl hydrocarbon receptor nuclear translocator, retinoblastoma 1, WW domain-containing oxidoreductase, homeodomain-interacting protein kinase 2, and myogenic factor 6, as shown in Figure 3.

3.5. *USP19* antisense oligonucleotide design

The results of the analyses performed on the servers mentioned in Section 2.6 for designing and selecting the best ASOs are shown in Table 2.

In Table 2, the first to the sixth column are related to the Sfold server, including the position of target sequences, target sequences, designed antisense oligonucleotide sequence, the percentage of GC content in ASOs (with range from 40 to 60% is acceptable; an amount out of this range will affect the structural stability of ASOs and prevent their proper functioning), average probability of unpaired binding site nucleotides (with probability equal to or greater than 0.5 is acceptable), ASOs binding energy (smaller values are preferable; values below −8 kcal/mol are more suitable). The seventh column is related to the RNAhybrid server, which provides the minimum free energy of hybridization between mRNA and ASO; the eighth column is related to the IDT Oligoanalyzer server, which provides the hairpin G in ASO structures. Generally, a 3' end hairpin with a ΔG of −2 kcal/mol and an internal hairpin with a ΔG of −3 kcal/mol is tolerated. The ninth column is related to the RNAfold server, which shows the centroid secondary structure of the target mRNA binding sites for ASOs as dot-bracket notation, where dots indicate unpaired bases and brackets indicate paired bases. It should also be noted that the lowest free energy of the predicted centroid secondary structure of mRNA was −1,928.12 kcal/mol. Furthermore, the investigations conducted using the Ensembl server showed that the designed ASO does not interact significantly with other mRNAs in the server's database. Docking interaction score of the best candidate ASO with its binding site on USP19, calculated using HNADOCK server, was −335.80 kcal/mol (Figure 4).

4. Discussion

Several USP protein family members have been shown to be crucial for maintaining the balance between bone formation and resorption, as well as for preventing bone diseases.[17,20] The post-translational modifications mediated by the ubiquitin and deubiquitin system have a significant impact on protein metabolism and degradation, which are crucial for the balance between bone formation and bone resorption.[15,31] In recent years, the use of DUBs, particularly the USP family, as new targets for disease treatment has gradually attracted attention.[32] An integrated analysis of microarray studies found altered gene expression profiles in the peripheral blood mononuclear cells of individuals with osteoporosis, identifying several genes, including *IFT52*, *GATA6*, *TRIM25*, and *USP19*. While a direct link to osteoporosis has not been documented, they have been connected to the development of bone and skeletal muscle.[33] In this work, the microarray data analysis on bone samples revealed that *USP19* and *USP17L2* are differentially expressed between osteoporotic and normal bone samples. The subsequent enrichment analysis showed these USPs are associated with the MAPK and Ras signaling pathways. As the results of the ΔG values of the hairpin in the structure of ASOs, the three sequences AAGGGGTAGCCAATGTTCTC, TGTCACGCCAGATAAAACTA, and GACATCTTGAGCCGCTTGGT were prioritized because, in addition to meeting the selection criteria across multiple metrics, they showed predicted hairpin ΔG values close to the tolerated threshold (approximately −3 kcal/mol). Among these three selected sequences, the TGTCACGCCAGATAAAACTA sequence has the best conditions in this respect, especially, the self-dimer ΔG value of this sequence (−3.61 kcal/mol), which was obtained from the IDT Oligoanalyzer server, was close to −3 kcal/mol. These ASOs have structural stability suitable for protection against enzymatic degradation, and this structural stability lies within the range that opens when the ASO is adjacent to the mRNA binding site, without hindering the interaction of the ASO with mRNA.[34] Therefore, these three introduced sequences can be selected for experimental investigations and final confirmation. While these *in silico*-designed ASOs demonstrate favorable predicted binding affinity, specificity, and accessibility in our models, their therapeutic potential remains exploratory at this stage and awaits rigorous experimental validation, including *in vitro* binding assays, cellular uptake studies, and in vivo efficacy and safety evaluations.

Nevertheless, the successful implementation of such

Table 1. List of differentially expressed genes and AUC scoring of the ROC plots

Gene	Official full name	Expression condition	Log_2FC	Adjusted *p*-value	ROC AUC	ROC *p*-value
USP19	Ubiquitin-specific peptidase 19	Upregulated	2.132036	0.003338	1.000	0.0094
USP17L2	Ubiquitin-specific peptidase 17-like family member 2	Downregulated	−0.78549	0.041328	0.8333	0.0833

Abbreviations: AUC: Area under the receiver operating characteristic curve; FC: Fold change; ROC: Receiver operating characteristic.

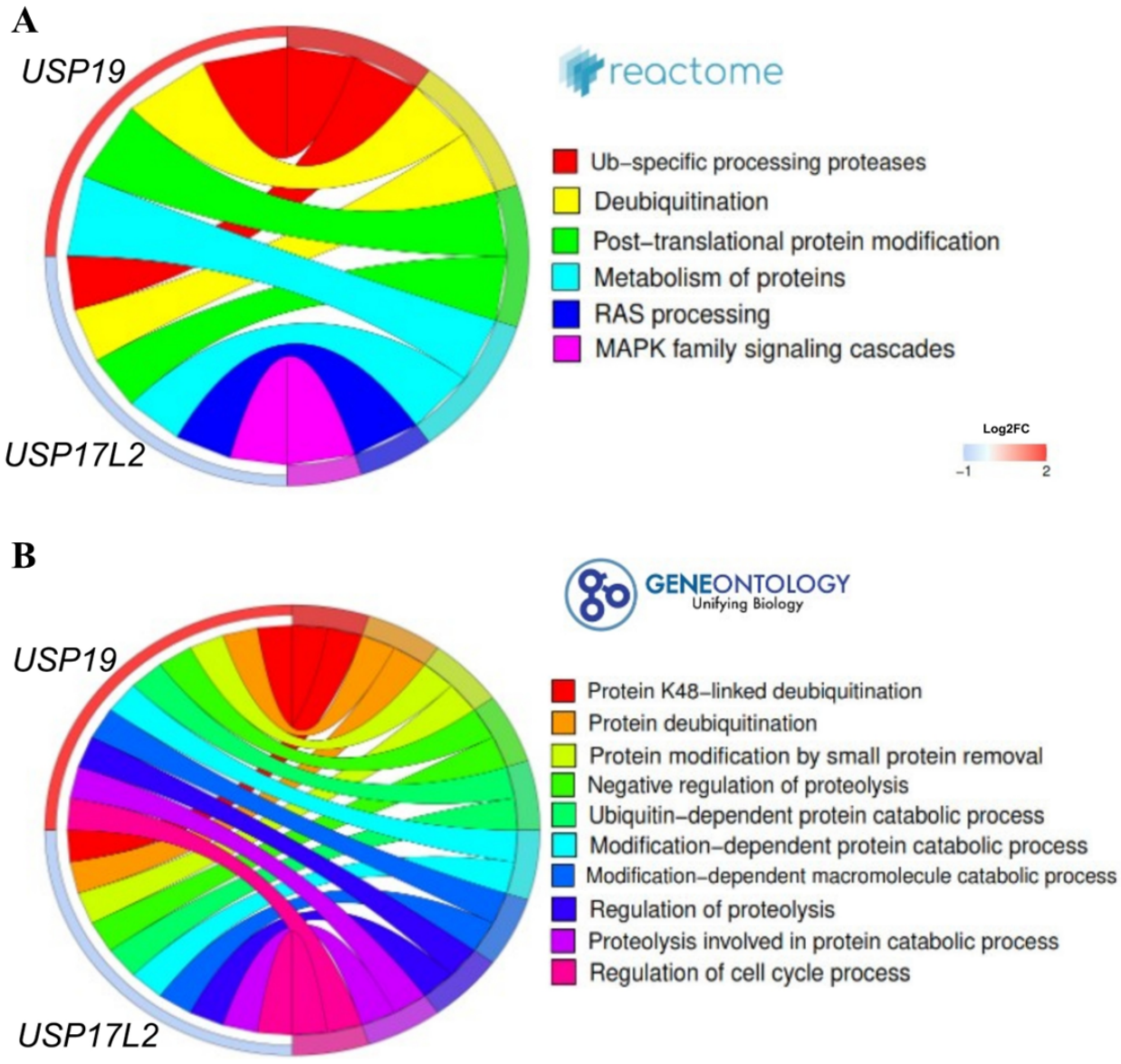

Figure 1. Functional enrichment analysis of *USP19* and *USP17L2*-associated processes. (A) Reactome pathway analysis showing associations with deubiquitination, post-translational protein modification, protein metabolism, Ras processing, and mitogen-activated protein kinase (MAPK) signaling cascades (color-coded sectors). (B) Gene ontology analysis highlighting terms related to the biological process (color-coded sectors). The color scale represents log_2FC of associated genes, ranging from downregulation (blue) to upregulation (red).

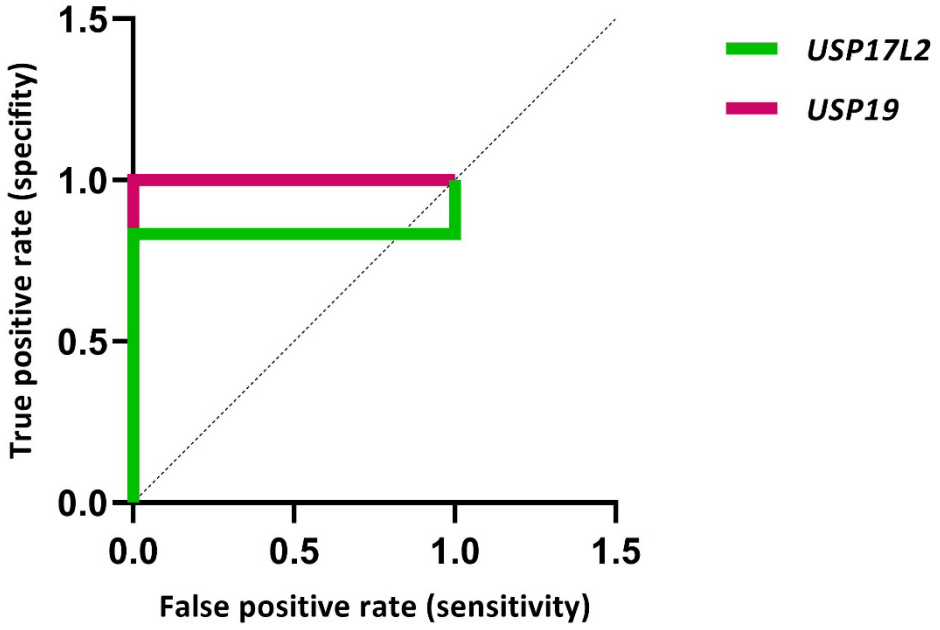

Figure 2. Receiver operating characteristic (ROC) curves for *USP19* and *USP17L2*. The plot compares the discriminatory performance of *USP19* (magenta) and *USP17L2* (green) in distinguishing patients with osteoporosis vs healthy controls. The dashed diagonal line represents random classification (area under the ROC curve [AUC] = 0.5). Higher AUC indicates better overall performance. *USP19* achieved AUC > 0.8 in this dataset.

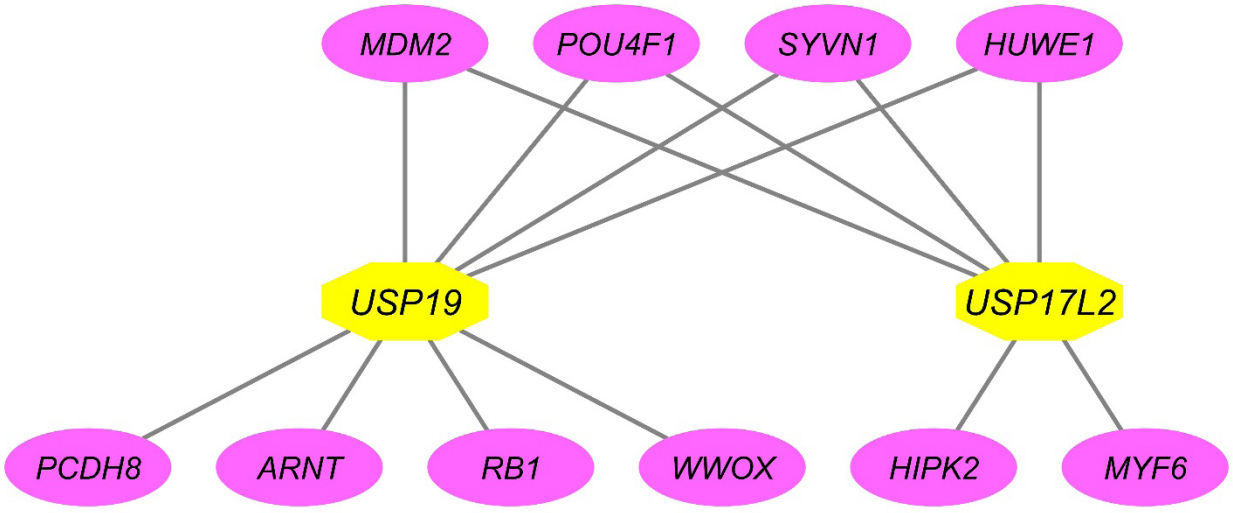

Figure 3. Protein-protein interaction network of *USP19* and *USP17L2*. The network illustrates shared (top) and individual (bottom) interacting partners for *USP19* and *USP17L2*.

Table 2. The design and information of *USP19* ASOs

Start_end	Target sequence (5' to 3')	ASO (5' to 3')	GC content (%)	Average unpaired probability for target site nucleotides	Oligo binding energy (kcal/mol)	MFE hybridization (kcal/mol)	Hairpin ΔG (kcal/mol)	Base pairing of the target sequence[a]
478_497	ACCAAGCGGCUCAAGAUGUC	GACATCTTGAGCCGCTTGGT	55.00	0.646	−10.2	−44.5	−3.26	the....))))).....
479_498	CCAAGCGGCUCAAGAUGUCU	AGACATCTTGAGCCGCTTGG	55.00	0.624	−8.8	−44	−1.01	...)))))..........(
547_566	GACACCACUAGUAAGAAGAA	TTCTTCTTACTAGTGGTGTC	40.00	0.65	−8.7	−38	−2.53	(((.................(
548_567	ACACCACUAGUAAGAAGAAG	CTTCTTCTTACTAGTGGTGT	40.00	0.651	−8.7	−37.7	−2.53	((.................((
2143_2162	AUGGAGCAUGUAACCCCAAA	TTTGGGGTTACATGCTCCAT	45.00	0.639	−13.7	−41.2	−9.32	....(((((((........(
2155_2174	ACCCCAAAGCCAGAGACACA	TGTGTCTCTGGCTTTGGGGT	55.00	0.724	−15.9	−45.3	−4.19	.......(((((.....
2156_2175	CCCCAAAGCCAGAGACACAC	GTGTGTCTCTGGCTTTGGGG	60.00	0.714	−15.6	−45.8	−3.48	......(((((.....)
2286_2305	CUUCACUGGCCUUGUCAAUU	AATTGACAAGGCCAGTGAAG	45.00	0.646	−6.7	−38.9	−1.78	....))))).....
2287_2306	UUCACUGGCCUUGUCAAUUU	AAATTGACAAGGCCAGTGAA	40.00	0.662	−6.3	−38.2	−1.78	...))))).....)
2600_2619	UGCACGAGGACCUGAAUCGC	GCGATTCAGGTCCTCGTGCA	60.00	0.639	−15.4	−46.5	−4.68	.....((((((...)
2601_2620	GCACGAGGACCUGAAUCGCA	TGCGATTCAGGTCCTCGTGC	60.00	0.659	−15.7	−45.3	−4.75	.....((((((...))
2780_2799	CCAAGGUCUCCAUCACUUUU	AAAAGTGATGGAGACCTTGG	45.00	0.659	−8.4	−39.7	−0.78	)).((((.....)
2781_2800	CAAGGUCUCCAUCACUUUUG	CAAAAGTGATGGAGACCTTG	45.00	0.658	−8.4	−39	−1.41	).((((.....))
3307_3326	GAGAACAUUGGCUACCCCUU	AAGGGGTAGCCAATGTTCTC	50.00	0.638	−11.4	−41.5	−2.85	....))))))).....
3308_3327	AGAACAUUGGCUACCCCUUC	GAAGGGGTAGCCAATGTTCT	50.00	0.643	−11.6	−42.6	−3.69	...))))))).....
3401_3420	CUGUGAGUGUAUUCCAGCCA	TGGCTGGAATACACTCACAG	50.00	0.638	−10.0	−42.1	−3.83	.)))))..... (

(*Cont'd...*)

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Table 2.(*Continued*)

Start_end	Target sequence (5' to 3')	ASO (5' to 3')	GC content (%)	Average unpaired probability for target site nucleotides	Oligo binding energy (kcal/mol)	MFE hybridization (kcal/mol)	Hairpin ΔG (kcal/mol)	Base pairing of the target sequence[a]
4139_4158	GUAGUUUUAUCUGGCGUGAC	GTCACGCCAGATAAAACTAC	45.00	0.698	−9.8	−39.5	−2.51	.....
4140_4159	UAGUUUUAUCUGGCGUGACA	TGTCACGCCAGATAAAACTA	40.00	0.693	−9.5	−38.4	−2.95	.....
4141_4160	AGUUUUAUCUGGCGUGACAA	TTGTCACGCCAGATAAAACT	40.00	0.697	−9.8	−38	−4.07	.....
5020_5039	UAAAACCAGACUAUUCAGGC	GCCTGAATAGTCTGGTTTTA	40.00	0.654	−9.0	−38.1	−5.63	.....))))

Notes: [a]The base-paired nucleotide on the left side "(" or right side ")" of a stem, with "." Indicating the unpaired nucleotides.
Abbreviations: ASO: Antisense oligonucleotide; MFE: Minimum free energy.

computationally optimized ASOs could hold significant promise for precision medicine applications. Earlier research has indicated that various signaling pathways are important in the pathogenesis of osteoporosis. Ras signaling is known to be crucial for the proliferation of immature osteoprogenitor cells, thereby increasing the number of osteoblastic descendants.[35] Signaling mediated by MAPKs, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, and p38, is acknowledged as vital for the proper differentiation and activation of osteoclasts.[36] Emerging evidence also supports the notion that the osteogenic differentiation of skeletal progenitors is a crucial factor in overall bone formation and bone mass. Numerous studies have highlighted the significance of the ERK MAPK pathway in facilitating the early commitment and differentiation of skeletal progenitors into the osteoblast lineage, as well as promoting skeletal mineralization.[37]

Although the correlation between *USP19* and *USP17L2* in osteoporosis has not been previously reported, several other USP family members have been shown to play roles in bone homeostasis and the pathogenesis of osteoporosis. *USP7* regulates osteogenesis by deubiquitinating high-mobility group homeobox 1, facilitating the differentiation of *CD14*$^{+}$ peripheral blood mononuclear cells into osteoclasts. Inhibition of *USP7* significantly reduces bone loss in osteoporosis *in vivo*. Evidence has highlighted the critical role of *USP7* in regulating bone remodeling. For instance, *USP7* influences osteogenic differentiation by binding to and deubiquitinating axis inhibition protein, a major inhibitor of the Wnt signaling pathway and part of the β-catenin complex. *USP7* expression was notably elevated in osteoporotic osteoclasts and rose during the differentiation of osteoclasts from peripheral blood monocytes *in vitro*.[31] Additionally, other members of the USP family, such as *USP1* and *USP6*, have also been associated with bone homeostasis.[11] DUB USP1 is crucial for bone formation.[38] *USP34* has been recognized as a novel regulator of osteogenesis. Conditional knockout of *Usp34* results in reduced bone mass in mice, diminished bone morphogenic protein 2 responses, and compromised bone regeneration. Mechanistically, *USP34* stabilizes both Smad1 and Runt-related transcription factor 2, and the depletion of Smurf1 restores the osteogenic potential of *Usp34*-deficient mesenchymal stem cells *in vitro*.[3] All of these studies showed the important role of USP family members in regulating bone modeling. Importantly, genes encoding proteins that interact with USP19 and USP17L2 are among the DEGs. Interestingly, four of them—MDM2, POU4F1, SYVN1, and HUWE1—are common interactors for both USP19 and USP17L2. According to the literature, MDM2 plays a crucial role as a proto-oncogene in bone

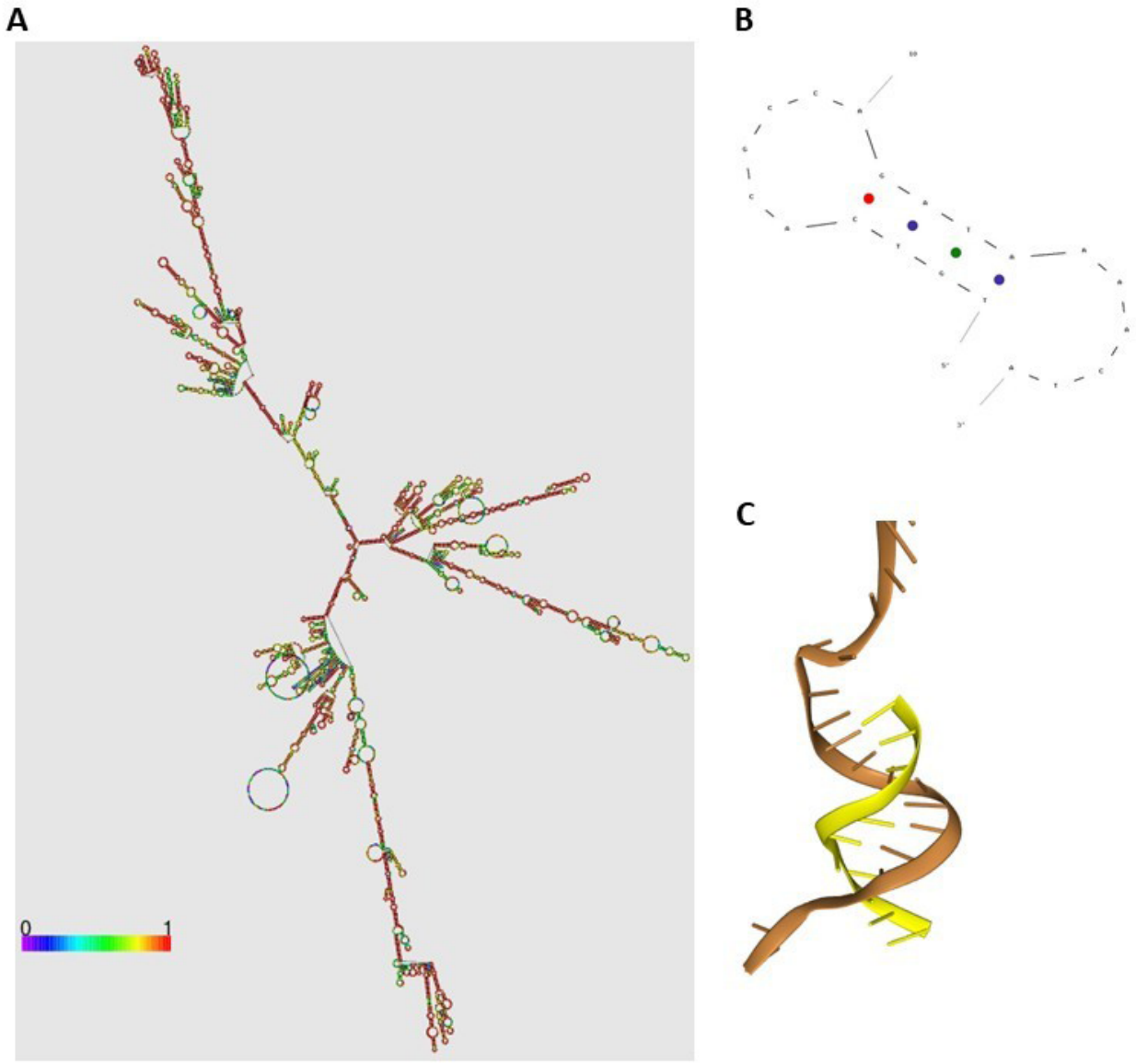

Figure 4. Antisense oligonucleotide (ASO)–mRNA interaction. (A) The secondary structure of the mRNA of the *USP19* gene (the areas with blue color: the probability of single-stranded mRNA is higher, and the areas with red color: the probability of double-stranded mRNA is higher). (B) Best selected ASO. (C) Interaction of the best ASO with its binding site on the *USP19* estimated using HNADOCK server (docking score = −335.80 kcal/mol).

formation. Consequently, reduced MDM2 levels could be linked to human bone disorders. Additionally, increasing MDM2 expression may be an effective strategy to mitigate age-related osteoporosis.[39]

The current study is best interpreted as hypothesis-generating, because all conclusions are derived from computational analyses and have not yet been supported by experimental validation at either the transcript or protein level. Moreover, our inferences are based on a single public dataset with a limited number of control samples, which can reduce statistical power and may lead to optimistic estimates in classification analyses. The *USP19* ASOs proposed in this study should be viewed as proof-of-concept candidates rather than therapeutic-ready agents, given that their activity, specificity, and tolerability have not yet been experimentally evaluated. In clinical development, ASO performance is strongly shaped by chemistry (backbone and sugar modifications), tissue exposure, pharmacokinetics, and the delivery strategy. Systemic delivery to non-hepatic tissues remains a major challenge for oligonucleotide therapeutics, making it essential to pair sequence design with practical considerations, including

off-target profiling, immunostimulatory risk assessment, and strategies to improve distribution to skeletal compartments.[40,41] Future studies should therefore: (i) validate *USP19* and *USP17L2* expression in independent cohorts using orthogonal assays, (ii) investigate the impact of abnormal *USP19* expression on osteoporosis-related phenotypes, e.g., on MAPK/Ras-related signals, in relevant osteoblast/osteoclast *in vitro* and *in vivo* models, and (iii) evaluate candidate ASOs for their ability to modulate *USP19* expression.

5. Conclusion

In conclusion, these findings suggest that the USP family of proteins may play an essential role in maintaining bone homeostasis and the pathogenesis of osteoporosis. Understanding how USPs may influence bone metabolism could help identify therapeutic targets for osteoporosis. However, the specific roles of individual USP members and their translational relevance remain incompletely defined. Continued research in this field could lead to the development of new and more effective therapies for osteoporosis.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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