Journal of Orthopaedic Surgery and Research

RESEARCH

Open Access

Focusing on spinal stenosis: emerging discoveries concerning Alendronate-induced risks and genetic drug targets

Nan Yang[1†], Jingkai Di[2†], Xiang Han[1], Wei Zhang[1], Xinliang Cui[1] and Haoyu Feng[1*]

Abstract

Background Spinal stenosis is a common disease in clinical practice, and drug use is one of its potential predisposing factors. Alendronate, a widely used clinical drug for osteoporosis treatment, has the potential to trigger spinal stenosis. Based on the real world, this study aims to deeply investigate the association between spinal stenosis and alendronate, and to explore novel drug targets against spinal stenosis at the genetic level.

Methods Alendronate patient data from the FDA Adverse Event Reporting System (FAERS) from Q1 2004 to Q4 2024 were included in the study, and four pharmacovigilance analytic methods and Bonferroni corrected P-values were applied to the baseline data, and subgroups of data were analyzed. Complementarily, Weibull distribution were applied to further parse the data. Meanwhile, in order to explore therapeutic targets against spinal stenosis, Mendelian randomization analyses were carried out based on eQTLGen consortium data as well as genome-wide association study (GWAS) data from two large independent cohorts. Subsequently, the medicinal value of the identified drug targets was verified by drug prediction and molecular docking techniques.

Results Pharmacovigilance analysis showed a strong positive signal between alendronate and spinal stenosis, especially in females and older patients. Fourteen significant drug targets were identified. Their medicinal value was verified by drug prediction and molecular docking, obtaining four protein-drug docking model structures.

Conclusions This study reveals an alendronate-spinal stenosis association, offering insights for clinical prevention. It also identifies new genetic drug targets, opening new treatment pathways for spinal stenosis.

Trial registration Not applicable.

Keywords Spinal stenosis, Alendronate, Pharmacovigilance analysis, Mendelian randomization, Drug targets

Introduction

Spinal stenosis is a spinal degenerative disease in which the anatomical narrowing of the spinal canal cavity compresses neural structures, thereby leading to corresponding clinical symptoms [1]. As a common condition, it can be categorized into cervical, thoracic, and lumbar spinal stenosis depending on the location. Of these, lumbar spinal stenosis is the most common and is estimated to affect approximately 103 million people worldwide [2]. The causes of spinal stenosis are diverse and complex, and can be categorized as congenital or acquired [3].

†Nan Yang and Jingkai Di contributed equally to this work and share first authorship.

*Correspondence:
Haoyu Feng
fenghaoyuspine@126.com
[1] Department of Orthopedics, The Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences Tongji Shanxi Hospital, Shanxi, China
[2] Department of Orthopedics, Second Hospital of Shanxi Medical University, Taiyuan, China

Specifically, congenital spinal stenosis is often caused by genetic factors that result in a narrower-than-normal diameter of the spinal canal during embryonic development, whereas acquired spinal stenosis is more common and is mainly caused by degenerative changes in the spine [4]. This narrowed spinal canal reduces the effective cushioning space around the nerve tissues and impairs local blood circulation, often causing abnormal nerve conduction function and producing symptoms such as pain, numbness, limb weakness, and intermittent claudication, which impose a heavy burden on patients and society.

Alendronate, as an aminodiphosphonate bone metabolism regulator, which specifically adsorbs to hydroxyapatite on the bone surface, inhibits osteoclast activity, and reduces bone resorption, thus effectively enhancing bone density [5]. It has been used in the clinic mainly for the treatment of postmenopausal osteoporosis in women, and is the first-line commonly used drug for anti-osteoporosis treatment [6]. However, as the use of this drug has become more popular, there have been concerns about its safety [7, 8]. Notably, despite the extensive and in-depth research on the adverse events of alendronate, it has not yet been reported for spinal stenosis. Given the serious impact of spinal stenosis on patients' quality of life and health, it is important to explore whether there is a potential risk of alendronate triggering this condition. The aim of this study is to explore the possible association between spinal stenosis and alendronate through in-depth mining and analysis of the FAERS database, in order to provide a more comprehensive reference for clinical drug safety.

In addition to the potential link between Alendronate and the induction of spinal stenosis described above, the results of another large-scale pharmacovigilance study suggest that immune checkpoint inhibitors also trigger such adverse events, which undoubtedly increases the incidence of the disease in the clinic and poses an even greater challenge to existing therapeutic strategies [2, 9]. To effectively address this dilemma, the introduction of genetics into drug development, based on gene-supported therapies that are becoming increasingly sophisticated in clinical trials, may be one of the most effective strategies to address this issue [10–12]. Genome-wide association studies (GWAS) have been effective in identifying single nucleotide polymorphisms (SNPs) associated with diseases. However, its limitations are also evident in its inability to identify disease-causing genes in a stable and consistent manner, thus making it difficult to directly contribute to drug development efforts. Notably, proteins encoded by druggable genes can serve as key targets for drug action [13, 14]. In addition, SNPs such as expression quantitative trait loci (eQTLs), which are associated with changes in gene expression, may be comparable to long-term exposure to drugs that target the encoded proteins [13, 15]. Based on data from large-scale genome-wide association studies of two independent cohorts, a Mendelian randomization (MR) approach combining cis-eQTL and spinal stenosis risk association data was introduced in this study to identify novel therapeutic targets for spinal stenosis. In addition, gene enrichment analysis and protein interaction network construction were used to reveal the functional characteristics and biological relevance of potential therapeutic targets. Complementarily, Phenome-Wide Association Study (PheWAS) analysis was applied by us to explore the associations between potential therapeutic targets and other features, providing valuable insights into their versatility and potential impact mechanisms for further research and development of relevant therapeutic strategies. Finally, we will validate the pharmacological activity of potential spinal stenosis drug targets through drug prediction and molecular docking studies to provide valuable guidance for the development of more effective and targeted therapeutic approaches.

Methods

Pharmacovigilance data analysis

Data from the open-source FDA Adverse Event Reporting System (FAERS) from Q1 2004 to Q4 2024 were included in this study and subjected to pharmacovigilance studies (Fig. 1). Ratio Reporting Ratio (ROR), Proportion Reporting Ratio (PRR), Information Component (IC), and Empirical Bayesian Geometric Mean (EBGM) analyses were used as methods for signal detection for data mining. To comprehensively identify potential drug safety risks, we classified reports as positive adverse event cases only if they met the criteria of all four methods simultaneously and yielded positive signal values. The corresponding formulae are detailed in Table S1. Given the advantages of the ROR method in spontaneous reporting databases, we present only the ROR values in the main text of the article [16]. The signal intensity values of the other three methods can be found in Table S2. In order to avoid Type I errors due to multiple comparisons, Bonferroni's method was applied to correct the calculated P-values, aiming to improve the accuracy and reliability of the study results. Supplementarily, the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 and MeSH subject headings were used for generic and trade name lookups of alendronate to ensure drug name completeness. Finally, we will focus on mining the baseline data and subgroup data. For gender stratification, participants will be divided into male and female groups. Regarding age stratification, the younger group is defined as participants with an age younger than 60

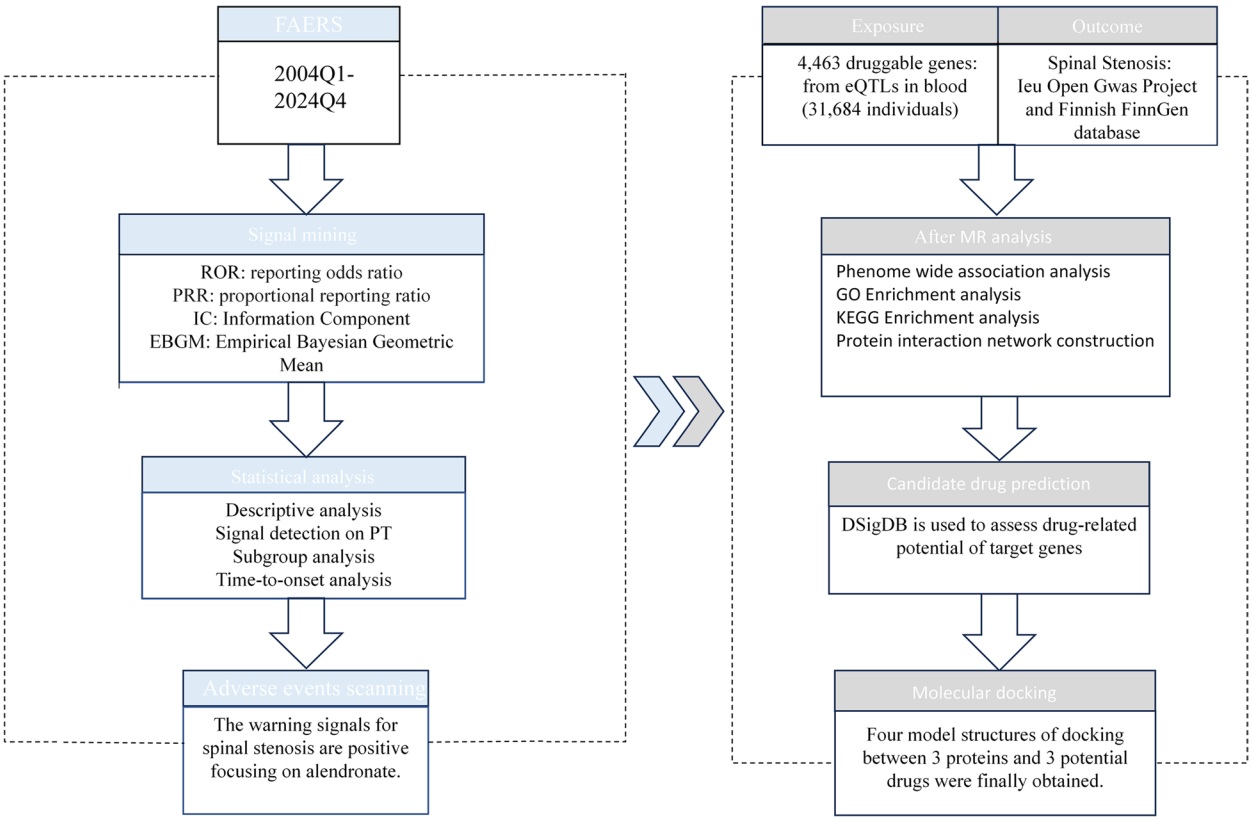

Fig. 1 Flow chart showing the analysis process of the study

years, while the older group encompasses those with an age of 60 years and above. And we will use the Weibull distribution analysis approach to dynamically resolve the evolutionary trajectory of adverse event rates. R 4.4.2 and its integrated development environment, Rstudio, were also used in our study.

Identification and analysis of potential drug targets

Mendelian randomisation analysis

Exposure data is eQTLs data from the eQTLGen consortium (https://eqtlgen.org/) [17]. It was designed to be combined with data from a variety of existing genome-wide association studies to identify druggable proteins, and 4,463 druggable genes were proposed [14]. The discovery cohort for spinal stenosis was derived from the genome-wide association study (GWAS) data of the Open GWAS project. In this study, 1,910 spinal stenosis cases and 359,284 controls from Europe were included, which were used as the discovery cohort for outcome data. To ensure consistency with the exposure data, the GWAS data from the FinnGen database was selected. This dataset was a sample from the European national system, containing 20,807 spinal stenosis cases and 294,770 controls.

The primary method of analysis for MR was random effects inverse variance weighted Inverse variance weighted (IVW), and the secondary methods of analysis were MR Egger, Weighted median, Weighted mode, and Simple mode, and the genetic instrumental variables met the three major assumptions of Mendelian randomization in this process [18]. In terms of samples, the training and validation sets were dominated by individuals of European ancestry aiming to reduce the potential bias of population stratification. For variable selection, weak instrumental variables with F-statistics less than 10 were excluded, and linked single nucleotide polymorphisms (SNPs) with chain disequilibrium coefficients $r^2 < 0.001$ and within a range of 10,000 kilobase pairs were removed. In the discovery cohort, a P value below 5×10^{-8} was defined as significant. Significant genes that passed quality control were repeatedly validated in the FinnGen cohort, and associations with a P value below 0.05 were considered significant. For genes containing more than two instrumental variables, MR-Egger intercept test ($p < 0.05$ decision) was performed to detect horizontal pleiotropy. Heterogeneity was also tested by calculating Cochran's Q value using IVW and MR-Egger method, and $P > 0.05$ indicated that there was no

heterogeneity between groups. In addition, the utilization of funnel plots was also used to assess inter-SNP heterogeneity, whose asymmetry would serve as an indicator of horizontal pleiotropy. MR analysis was carried out in this study using the R package TwoSampleMR 0.6.8.

Phenome-wide association analysis

To further assess the horizontal pleiotropy of potential drug targets and possible side effects, we conducted a phenome-wide association study on the PheWAS portal (https://azphewas.com/) [19]. The probability of false positives was strictly controlled by setting the significance threshold to 2×10^{-9} with reference to the default settings of the AstraZeneca PheWAS portal. During data screening, no relevant valid information was obtained when DYNLT5, TRIM73, BAZ2B-AS1, PDLIM1P4, and LINC00638 were queried. Based on the principles of research rigor and data availability, the above items for which no data were available were excluded to ensure that the subsequent analysis was based on reliable and complete data.

Enrichment analysis

To investigate the functional characterization and biological relevance of prospective therapeutic target genes, we performed GO and KEGG enrichment studies using R package clusterProfiler 4.14.4. Among them, GO enrichment analysis is usually used to demonstrate the interactions between genes and terms, which include three terms: biological process (BP), molecular function (MF), and cellular component (CC). KEGG enrichment analysis, on the other hand, can elucidate the relationship between genes and functional pathways, which in turn provides metabolic pathway information [20]. Additionally, the gene expression data utilized for the enrichment analysis in this article is of a general nature for homo sapiens (human) rather than tissue-specific.

Protein interaction network construction

By evaluating and analyzing protein–protein interaction (PPI) networks, one can better understand how one protein interacts with another. In this study, PPI networks were constructed using the STRING (https://cn.string-db.org/) database with a confidence score of 0.15 as the minimum interaction score required, and all other parameters were left at the default level [21]. The PPI results were further visualized by Cytoscape (v3.10.0) visualization [22]. Supplementarily, GeneMANIA (https://genemania.org/) was also used for PPI analysis [23].

Candidate drug prediction

Evaluation of protein-drug interactions is essential to understand whether a target gene can be used as an actual drug target. In this study, we will use the Drug Signatures Database (DSigDB, URL: http://dsigdb.tanlab.org/DSigDBv1.0/) to accomplish this task [24]. Specifically, DSigDB is a sizable database of 22,527 gene sets, 17,389 different compounds, involving 19,531 genes, which associates drugs and other chemicals with their target genes. We upload the identified target genes into DSigDB, which in turn predicts drug candidates to evaluate the pharmacological activity of these target genes.

Molecular docking

In order to gain a deeper understanding of the action of drug candidates on target genes and the drug-forming properties of the target genes, the present study further carried out molecular docking studies at the atomic level to assess the binding energy and interaction modes between the drug candidates and their targets. Molecular docking simulations can help us to analyze the binding affinity and interaction mode between ligands and drug targets. By identifying ligands with high binding affinity and good interaction modes, we can prioritize drug targets for further experimental validation and optimize the design of potential drug candidates. The drug structure data were obtained from the PubChem Compound Database (https://pubchem.ncbi.nlm.nih.gov/), and the protein structure data were downloaded from the Protein Data Bank (http://www.rcsb.org/). Supplementarily, AutoDockTools 1.5.7 software was used by us [25, 26].

Results

Pharmacovigilance data analysis

Between the first quarter of 2004 and the fourth quarter of 2024, 31,446 adverse event reports for alendronate were recorded in the FAERS database (Table 1). Of these, 466 were for spinal stenosis, with positive signals for both lumbar and cervical stenosis being monitored. Specifically, lumbar spinal stenosis had the highest number of adverse events and the highest value of positive signals (ROR = 30.48, 95% CI = 27.37–33.94, $P < 0.001$, $n = 388$), while cervical spinal stenosis had a lower number of occurrences and relatively lower positive signals (ROR = 9.51, 95% CI = 7.57–11.94, $P < 0.001$. $n = 78$).

Further, we performed a subgroup stratification analysis (Fig. 2). The gender subgroups showed that the number of cases of spinal stenosis occurrence was higher in the female group compared to the male group. And when analyzing signal intensity, the female and male groups' signal intensities were largely alike. But, upon exact calculation and careful comparison, the ROR estimate for the female group showed a marginally stronger relative tendency. When focusing on the age subgroups, the number of spinal stenosis occurrences was higher in the older group than in the younger group and the

Table 1 The clinical distribution characteristics of adverse events reported for alendronate

Characteristic	Alendronate (N, %)
Number of patients experiencing adverse reactions	31,446(100.0%)
Gender	
Female	25,475 (81.0%)
Male	2637 (8.4%)
Missing	3334 (10.6%)
Age (year)	
< 18	66 (0.2%)
18–64.9	6213 (19.8%)
65–85	8994 (28.6%)
> 85	1009 (3.2%)
Missing	15,164 (48.2%)
Weight(kg)	
< 50	919 (2.9%)
50–100	8029 (25.5%)
> 100	295 (0.9%)
Missing	22,203 (70.6%)
Reporter's type of occupation	
Consumer	11,539 (36.7%)
Health Professional	1392 (4.4%)
Lawyer	2333 (7.4%)
Physician	7949 (25.3%)
Other health-professional	4660 (14.8%)
Pharmacist	1231 (3.9%)
Registered Nurse	5 (0.0%)
Missing	2337 (7.4%)

N number of adverse events reported

pharmacovigilance signal for cervical spinal stenosis was higher. Interestingly, the analysis of lumbar spinal stenosis in the age subgroups showed a higher signal for adverse events in the younger group than in the older group. Complementarily, in the assessment of the time to onset of events for spinal stenosis after treatment with alendronate, the mean time to onset of induction for lumbar spinal stenosis was approximately 654.58 days, with a median time to induction of approximately 356 days. In contrast, the mean induction time for cervical stenosis was approximately 478.64 days, and the median induction time was approximately 355.5 days (Fig. 3). The results of Weibull distribution showed that lumbar spinal stenosis events induced by the administration of alendronate showed an early failure type curve model, while cervical spinal stenosis showed a random failure type curve model (Table 2).

Identification and analysis of potential drug targets

Mendelian randomisation analysis

As shown in Fig. 4, in the discovery cohort cohort extracted from Ieu Open Gwas Project, the expression of 241 genes was causally associated with the risk of spinal stenosis. Whereas, in the discovery cohort phase, this study used GWAS data from FinnGen database, and finally the genetically predicted expression of 19 genes was determined to be causally associated with the risk of spinal stenosis (Fig. 5).

Phenome-wide association analysis

To further assess whether the identified 19 potential drug target genes would have beneficial or deleterious effects on other traits and whether there was potential pleiotropy not detected by the Mendelian randomized Egger intercept test, the present study was conducted at the gene level using the database from the AstraZeneca PhenomeWide Association Study (PheWAS) portal.The PheWAS results showed that none of the 14 drug target genes were significantly associated with other traits at the gene level, except for the DYNLT5, TRIM73, BAZ2B-AS1, PDLIM1P4, and LINC00638 genes, which were not monitored, suggesting that the potential side effects of

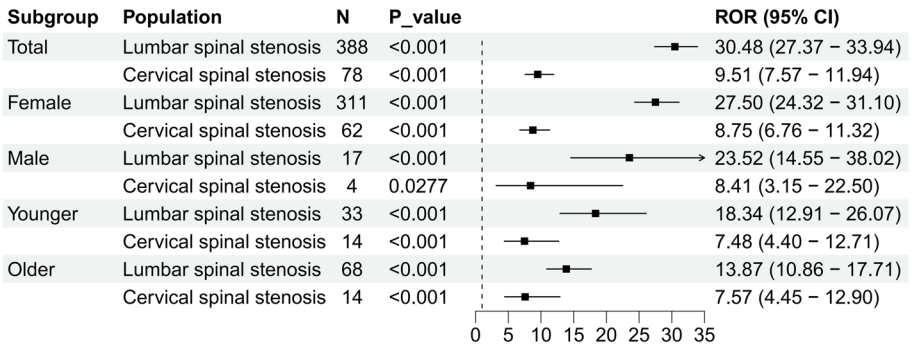

Fig. 2 Forest plot showing the reporting odds ratio and corresponding 95% confidence intervals for signal detection of alendronate at the preferred term level. The younger group consisted of those individuals with an age of less than 60 years, while the older group encompassed participants with an age of 60 years or greater. The dashed line in the graphical representation of ROR values is labeled as OR = 1, serving as a reference line for comparison of the odds ratios

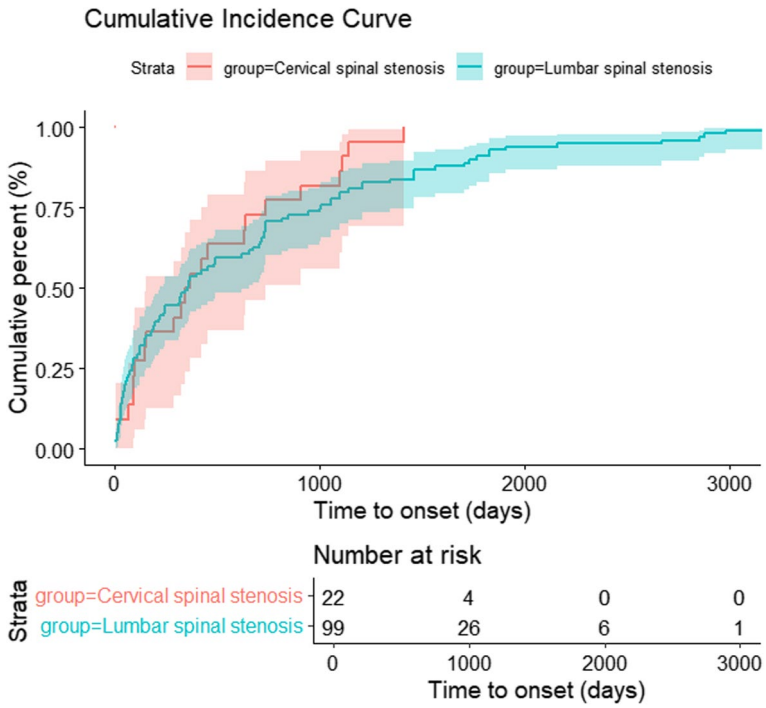

Fig. 3 Cumulative distribution curve of alendronate by time-to-onset

Table 2 Weibull parameter test for spinal stenosis associated with alendronate

PTs	Shape parameter (95% CI)	Scale parameter (95% CI)	Type
Lumbar spinal stenosis	0.76 (0.64–0.88)	561.96 (409.27–714.64)	Early failure
Cervical spinal stenosis	0.98 (0.64–1.31)	474.14 (261.68–686.60)	Random failure

PT preferred terms, *CI* confidence interval, *95% CI* two-sided for Shape parameter and Scale parameter

the drugs that acted on these 14 targets, as well as the low likelihood that horizontal pleiotropy exists in these genes.

Enrichment analysis

As shown in Fig. 6, in the BP category of GO enrichment analysis, significant pathways were mostly associated with natural killer cells. In the CC category, drug target genes were similarly enriched for components related to the inflammatory response, such as the immunological synapseimmunological synapse. Moreover, in the case of MF, these genes are involved in functions closely related to the inflammatory response (certain channel regulatory activities, transporter regulatory activities). As shown in Fig. 7, the top three pathways derived from KEGG enrichment analysis are autophagy-animal and cAMP signaling pathway, where autophagy clears pathogens and regulates immune cells (Figure S2). And cAMP signaling pathway also affects immune cell function and inflammation development.

Protein interaction network construction

These 14 drug target genes were uploaded to the STRING database to construct the network, and the generated files were imported into Cytoscape software for visualization. Figure 8 shows the interactions between 11 of these more closely related drug targets and other proteins. For the PPI network constructed using GeneMANIA, in addition to these 14 drug targets, the network also incorporated another 20 genes with possible interactions. Among them, VEGFA (vascular endothelial growth factor A) and KNG1 (kininogen 1), among others, were strongly correlated with inflammatory responses, which is consistent with the fact that spinal stenosis is closely associated with inflammatory responses.

Candidate drugs prioritized based on gene set enrichment using DSigDB

The DSigDB database was used in this study to prioritized candidate compounds based on gene expression

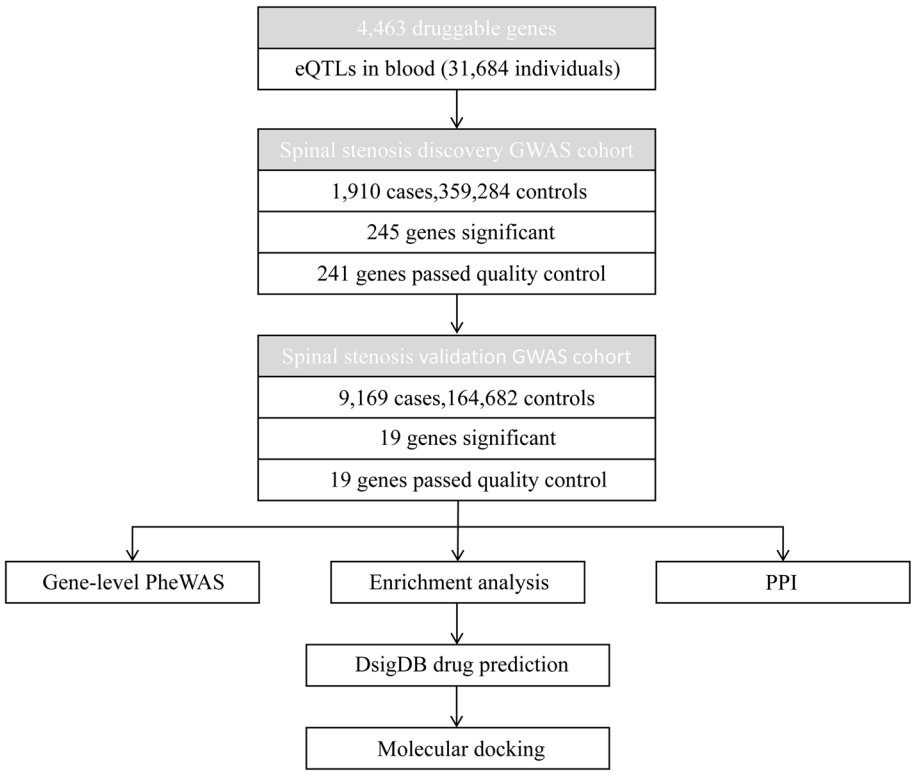

Fig. 4 Overview of the identification and analysis of potential drug targets

signature enrichment. The top ten potential chemical compounds were listed based on corrected p-values using the Benjamini–Hochberg method which is the default method for adjusting p-values in DSigDB (Table 3). The results showed that Zardaverine (Zardaverine HL60 UP) and METHAMPHETAMINE (METHAMPHETAMINE, CTD No. 00006286) were the two most significant drugs, which were associated with the PDE4D gene, MCTP2 gene and DRD4 gene.

Molecular docking

We molecularly docked the top 5 important drugs with the proteins encoded by the corresponding target genes. Among them, METHAMPHETAMINE with toxicity, trichostatin A with stimulant properties and unidentified Prestwick-983 drugs were excluded from our molecular docking cohort. Complementarily, zaprinast, the only drug in the top 10 that is widely used in the clinic, was included in the molecular docking cohort to provide a reference that is closely related to the actual clinical context and to make the results more translationally valuable. Four model structures for the docking of three proteins and three drugs were finally obtained (Table 4 and Fig. 9). Among them, PDE4D and Zardaverine exhibited the lowest binding energy (−6.24 kcal/mol), which indicates that their binding is extremely stable.

Discussion

Potentially induced spinal stenosis with alendronate

Alendronate provides a critical line of defense in the management of osteoporosis globally, and as nitrogen-containing bisphosphonates, it is the most widely prescribed medication for the treatment of bone diseases, with nearly 200 million prescriptions written annually [27]. Based on this high global utilization, the number of potentially induced adverse events is increasing yearly, among which spinal stenosis is emphasized in our study [28]. This section addresses the investigation and analysis of alendronate with the aim of more fully elucidating the potential association of this class of drugs with spinal stenosis during clinical use.

Our results suggest an association between alendronate administration and spinal stenosis in the population. Specifically, there was a strong positive pharmacovigilance signal between alendronate and both lumbar spinal stenosis and cervical spinal stenosis adverse events overall. Spinal stenosis is regarded as a multifactorial disease and is accompanied by a variety of predisposing factors that synergize with it during its development [1]. Among these, the unique effects of alendronate on bone conversion may be an important contributor to this adverse event. Specifically, alendronate potently inhibits bone resorption by inhibiting

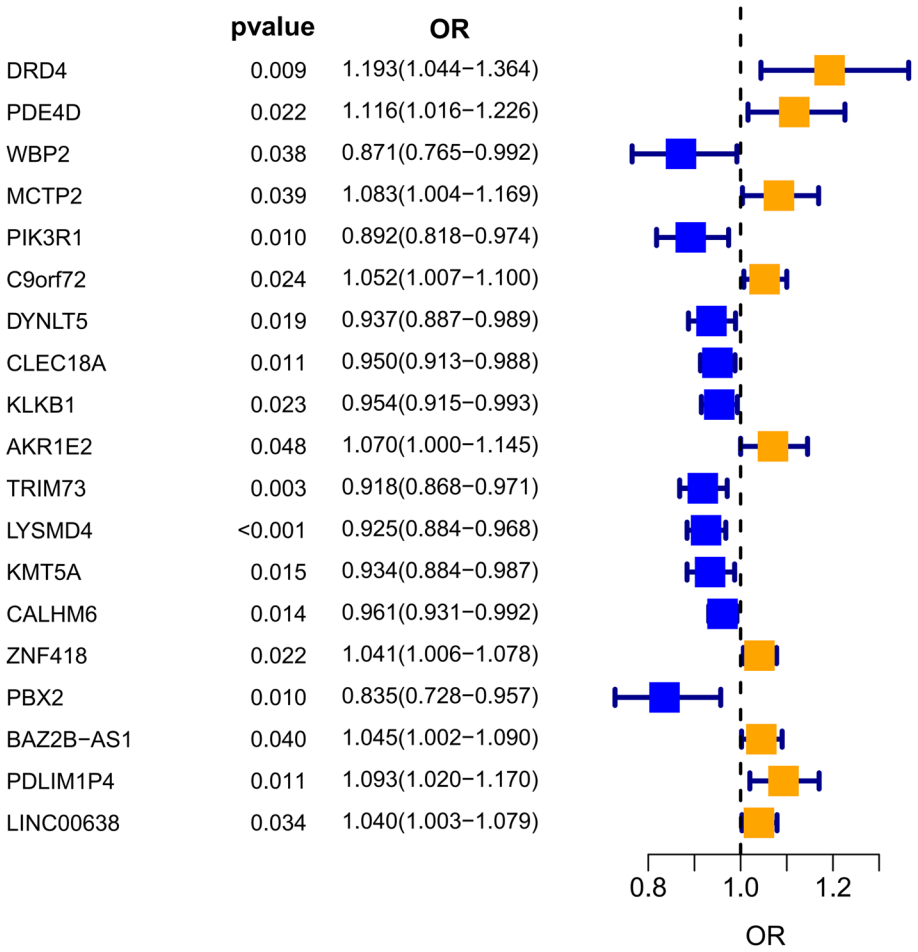

Fig. 5 Forest plots displaying the findings from the validation phase for 19 significant genes

osteoclast activity, which can significantly reduce the rate of bone conversion, which in turn may make the imbalance in the bone reconstruction process more pronounced [29]. In addition, this drug will significantly reduce chondrocyte apoptosis, especially when parathyroid hormone is administered first followed by alendronate, which will significantly increase bone volume [30]. It is also important to note that alendronate may inhibit the expression or activity of angiogenesis-related factors such as vascular endothelial growth factor, thereby altering angiogenesis within the bone tissue, which in turn contributes to the development of osteophytes and spinal stenosis [31]. Complementarily, based on the high bone affinity properties of alendronate, its distribution in bone tissue will accumulate accumulation, which in turn increases the risk of inducing spinal stenosis [32].

The results of the gender subgroup suggest that the positive signal tends to show a higher intensity in the female population compared to male patients. This is corroborated by a recent study in which alendronate alone resulted in a significant increase in cartilage thickness in female individuals, whereas it did not result in an increase in cartilage thickness in male individuals [30]. However, when focusing on age subgroups, the number of spinal stenoses occurring was higher in the older group than in the younger group and the pharmacovigilance signal was higher for cervical spinal stenosis. Interestingly, the analysis of lumbar spinal stenosis showed a higher signal of adverse events obtained from monitoring in the younger age group than in the older. A research indicates that, compared with the elderly population, the young population bears some unique burdens on their lumbar spines, which may potentially

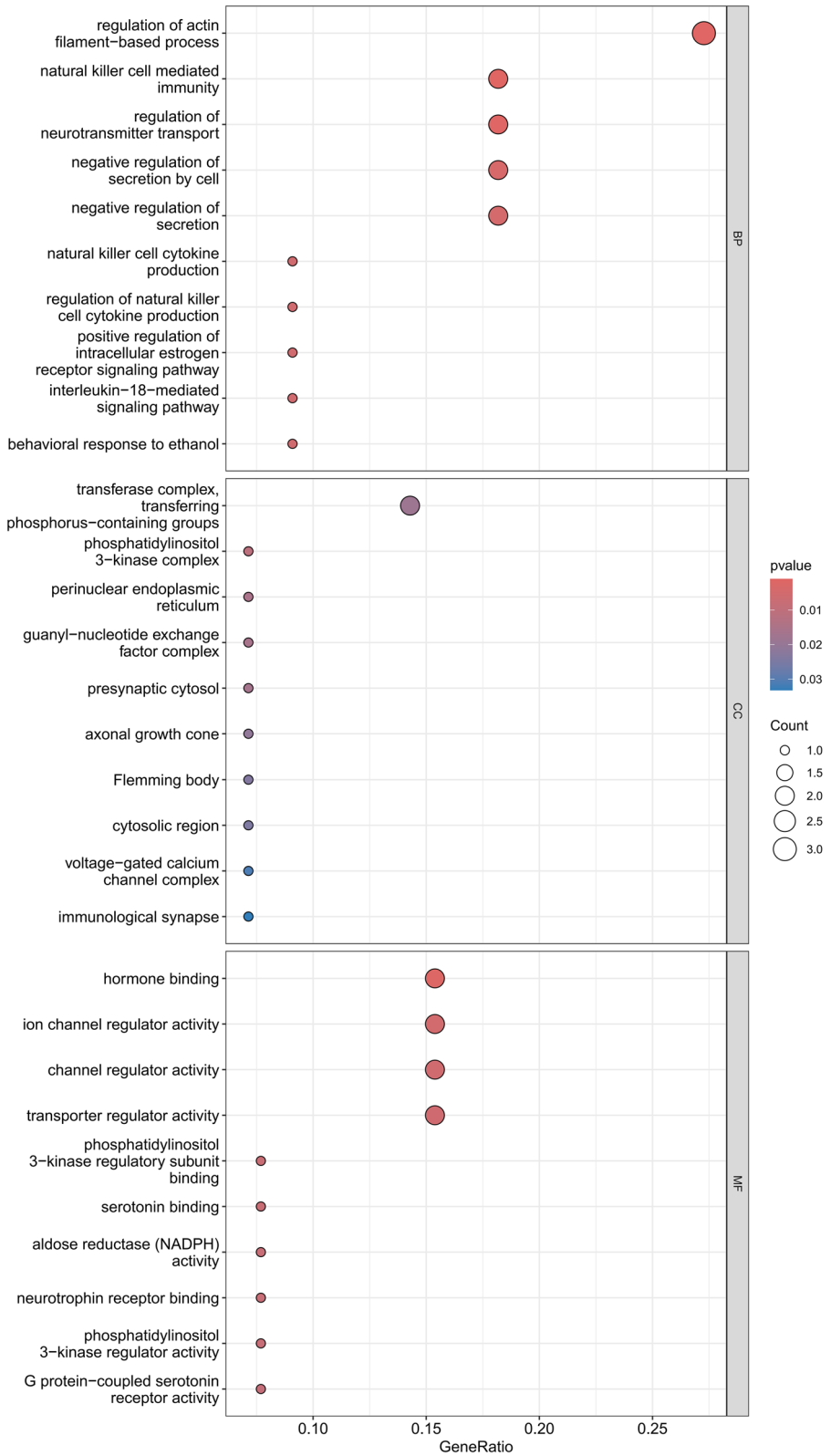

Fig. 6 GO enrichment results for three terms

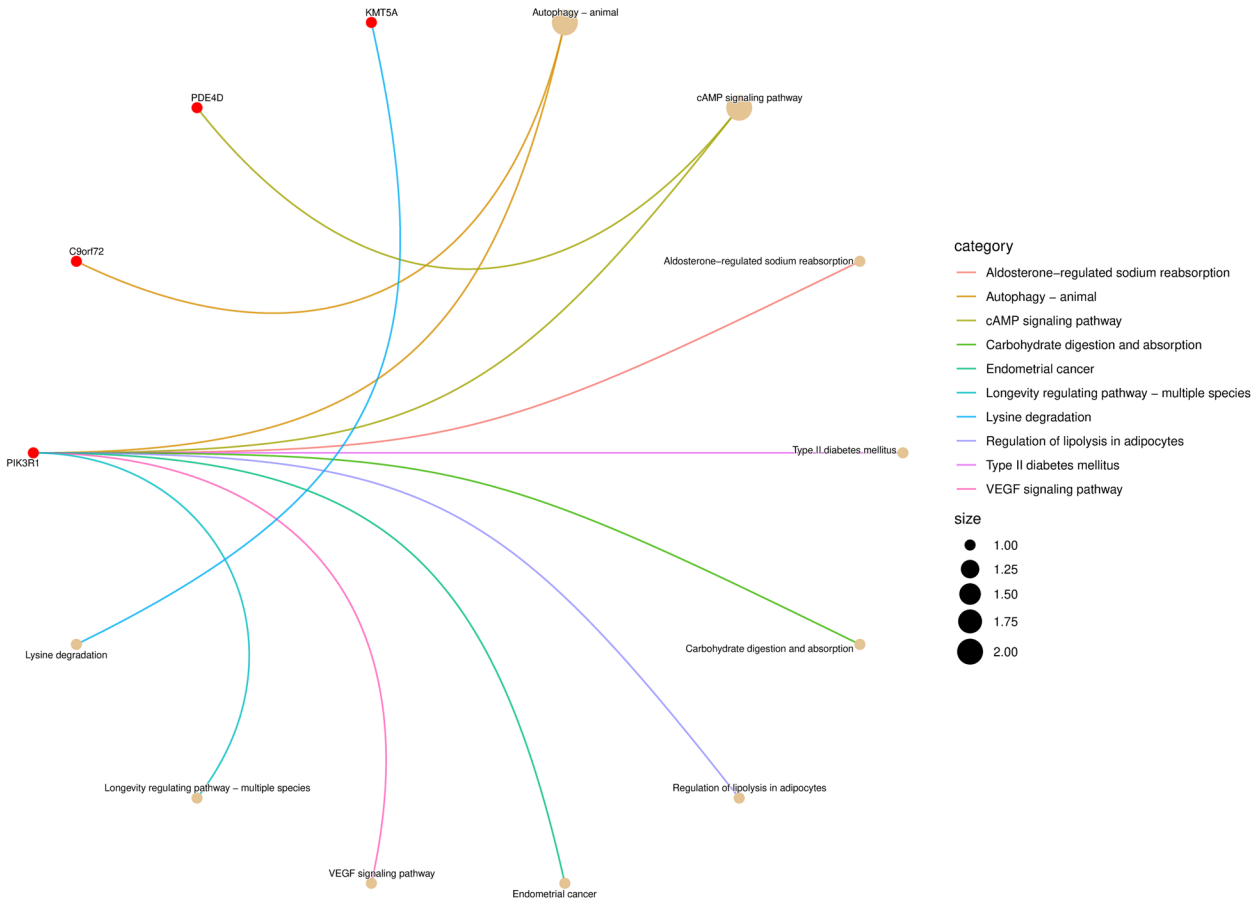

Fig. 7 KEGG enrichment results

lead to lumbar spinal stenosis. For example, young individuals are more likely to develop adverse living habits derived from their learning and living environments. These habits include sedentary behavior, using ill-fitting desks and chairs, taking naps in a prone position, and carrying heavy school bags. Additionally, inappropriate exercise patterns, such as intense, last-minute training for physical fitness tests like the high-school entrance examination physical test, further exacerbate this burden [33, 34]. The Weibull Shape Parameter (WSP) test demonstrated that lumbar spinal stenosis exhibits an early failure-type profile, with a gradual decrease in the incidence of adverse events due to it over time. In contrast, cervical spinal stenosis has a randomized failure type characteristic, and its corresponding adverse event rate is changing over time. This suggests that in actual clinical practice, despite the potential risk of spinal stenosis associated with the use of alendronate, the safety of long-term use can be ensured to a certain extent with early prevention for patients who have to use this type of drug for a long period of time.

Genetics-based discovery of potential drug targets for spinal stenosis

Based on Mendelian randomization method, this study mined the prospective therapeutic target genes and comprehensively analyzed the functional properties and biological relevance of the target genes through GO and KEGG enrichment analysis. Meanwhile, the evaluation and analysis of PPI network elucidated the interaction mechanism between proteins, and 14 drug targets related to spinal stenosis were successfully identified. In addition, DSigDB database and molecular docking technology were used in our study. Finally, we obtained four model structures of three proteins docked with three drugs, which further confirmed the pharmacological value of these target genes and provided a solid theoretical foundation for subsequent drug development against spinal stenosis. Among the four model targets, PDE4D (phosphodiesterase 4D) is a key enzyme in the regulation of intracellular cyclic adenosine monophosphate (cAMP) metabolism, which is involved in the regulation of inflammatory response, cell proliferation and extracellular matrix

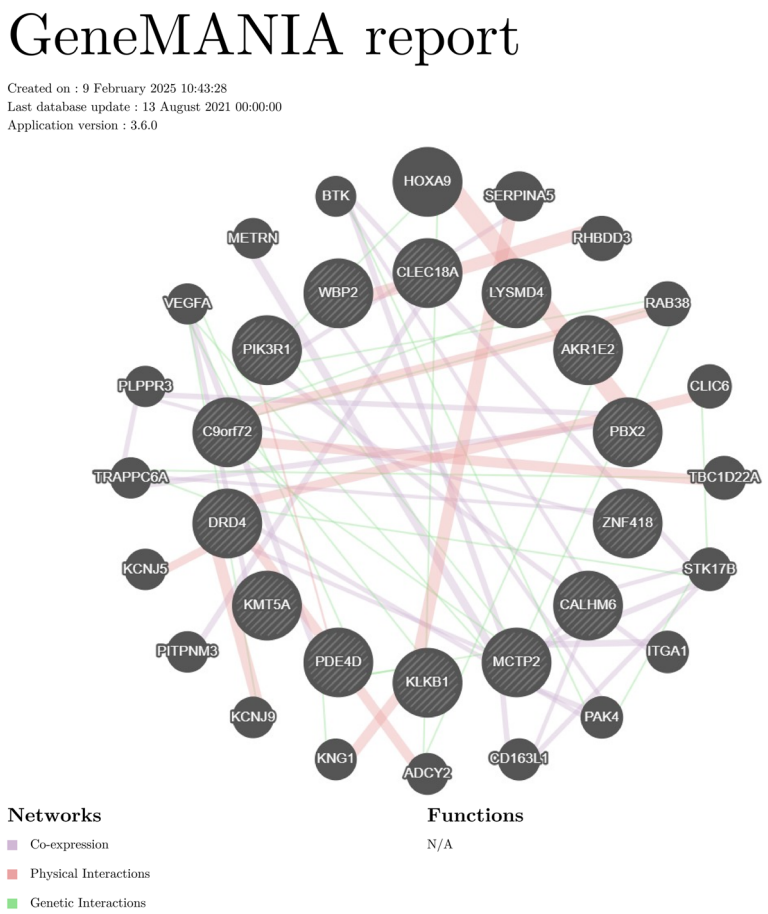

Fig. 8 PPI network built with GeneMANIA

Table 3 Candidate drug predicted using DSigDB

Drug names	*P*-value	Adjusted *P*-value	Genes
Zardaverine HL60 UP	0.002	0.127	PDE4D;MCTP2
METHAMPHETAMINE CTD 00006286	0.002	0.127	PDE4D;DRD4
Trichostatin A CTD 00000660	0.006	0.127	PDE4D;PIK3R1;MCTP2;C9ORF72;KLKB1;CLEC18A;DRD4
Prestwick-983 HL60 UP	0.008	0.127	PDE4D;MCTP2
BP 897 TTD 00002536	0.008	0.127	DRD4
L-745870 TTD 00008863	0.008	0.127	DRD4
DIHYDREXIDINE TTD 00007580	0.008	0.127	DRD4
S-(+)-Rolipram TTD 00010743	0.008	0.127	PDE4D
ISOCLOZAPINE TTD 00008679	0.009	0.127	DRD4
Zaprinast TTD 00011899	0.009	0.127	PDE4D

metabolism through the degradation of cAMP [35]. Studies have shown that modulation of PDE4D levels can rejuvenate senescent nucleus pulposus cells, which in turn attenuates the progression of vertebral degeneration [36]. In contrast, MCTP2 (Multi-C2 structural domain transmembrane protein 2) is a transmembrane protein involved in calcium homeostasis regulation and intercellular signaling, which is able to deregulate apoptosis by regulating cell

Table 4 Docking results of available proteins with small molecules

Target	PDB ID	Drug	PubChem CID	Binding energy (kcal/mol)
PDE4D	8 K4 C	Zardaverine	5723	6.24
MCTP2	2EP6	Zardaverine	5723	5.65
DRD4	5 WIU	BP 897	3,038,495	5.47
PDE4D	8 K4 C	Zaprinast	135,399,235	5.23

The lower the Binding Energy, the better the binding effect and the higher the affinity

proliferation and migration, and thus deregulate apoptosis in response to negative stimuli [37, 38]. Finally, DRD4 (dopamine receptor D4), an important member of the dopaminergic system, affects pain perception, motor function, and inflammatory response mainly by modulating neurotransmitter signaling [39]. Its activation will lead to a decrease in cAMP, which in turn inhibits the activation of the PKA/p38 signaling pathway and ultimately suppresses the inflammatory response in certain macrophages [40]. Complementarily, it has been shown that the dopamine receptor D4 (DRD4) locus may be a candidate locus for reduced bone density [41].

Strengths and limitations

This study has several significant strengths. First, disproportionality analysis was applied to monitor potential predisposing medications for spinal stenosis, which helps healthcare professionals and patients to have a more comprehensive and in-depth understanding of the potential risks of this class of medications. Meanwhile, through in-depth study of baseline data, subgroup data and triggering time, this study provides new ideas and directions for the dosing pattern of alendronate. As for drug development, this study repeatedly validated the results of Mendelian randomization analyses in two large cohorts, which greatly reduced the possibility of false-positive results. In addition, enrichment analysis elucidated the functional properties of these genes, and we obtained the regulatory relationships between these drug target genes by protein–protein interaction (PPI) analysis. The final drug prediction and the high binding activity shown by molecular docking indicate that these genes have a strong potential as drug targets.

Inevitably, there are some limitations to our study. First, the FAERS database, as a database with spontaneous reporting characteristics, tends to have an inherent selectivity bias based on the skill proficiency and autonomy tendency of the informants. In addition, pharmacovigilance analyses do not quantify risk and cannot infer exact causality. In addition, there are some limitations of mining studies for potential drugs that need to be considered. Mendelian randomization provides valuable insights for probing causality; however, it assumes that drug exposures are low-dose and that there is a linear relationship between exposure and outcome, which may not fully reproduce real-world clinical trial situations, where the effects of high-dose drugs are often evaluated over short periods of time. Despite rigorous efforts to minimize bias, Mendelian randomization analyses remain susceptible to unmeasured factors or genetic pleiotropy, which may affect study results. Another limitation stems from the issue of the diversity of the study cohort, i.e., the generalizability of this study is limited by the fact that it primarily included individuals of European ancestry. Extrapolation of the findings to individuals of other ethnicities would require further research and validation to ensure broader applicability of the results. Complementarily, enrichment analysis, which relies on predefined sets of genes or pathways, also has inherent limitations and may not cover all possible biological mechanisms or interactions. Finally, the accuracy of molecular docking analysis relies heavily on the quality of the protein structure and ligand. Although this approach can identify potential drug targets, it does not guarantee the validity of these targets in the clinical setting. Subsequent experimental validation and clinical trials must be conducted to confirm the therapeutic potential of the identified targets. It is critical to recognize these limitations and their potential impact on study conclusions. Inclusion of diverse populations, integration of multi-omics data, and exploration of alternative methods of analysis will advance the field.

Conclusion

Based on the mining analysis of real-world data by multiple strategies, we found that there was an association between spinal stenosis and alendronate, and that the gender of the medication-taking population was female, and the age was relatively high as a risk factor that might induce such adverse events. In addition, this study utilized MR analysis to identify potential drug targets for spinal stenosis, and validated the medicinal value of these targets using drug prediction and molecular docking, resulting in four model

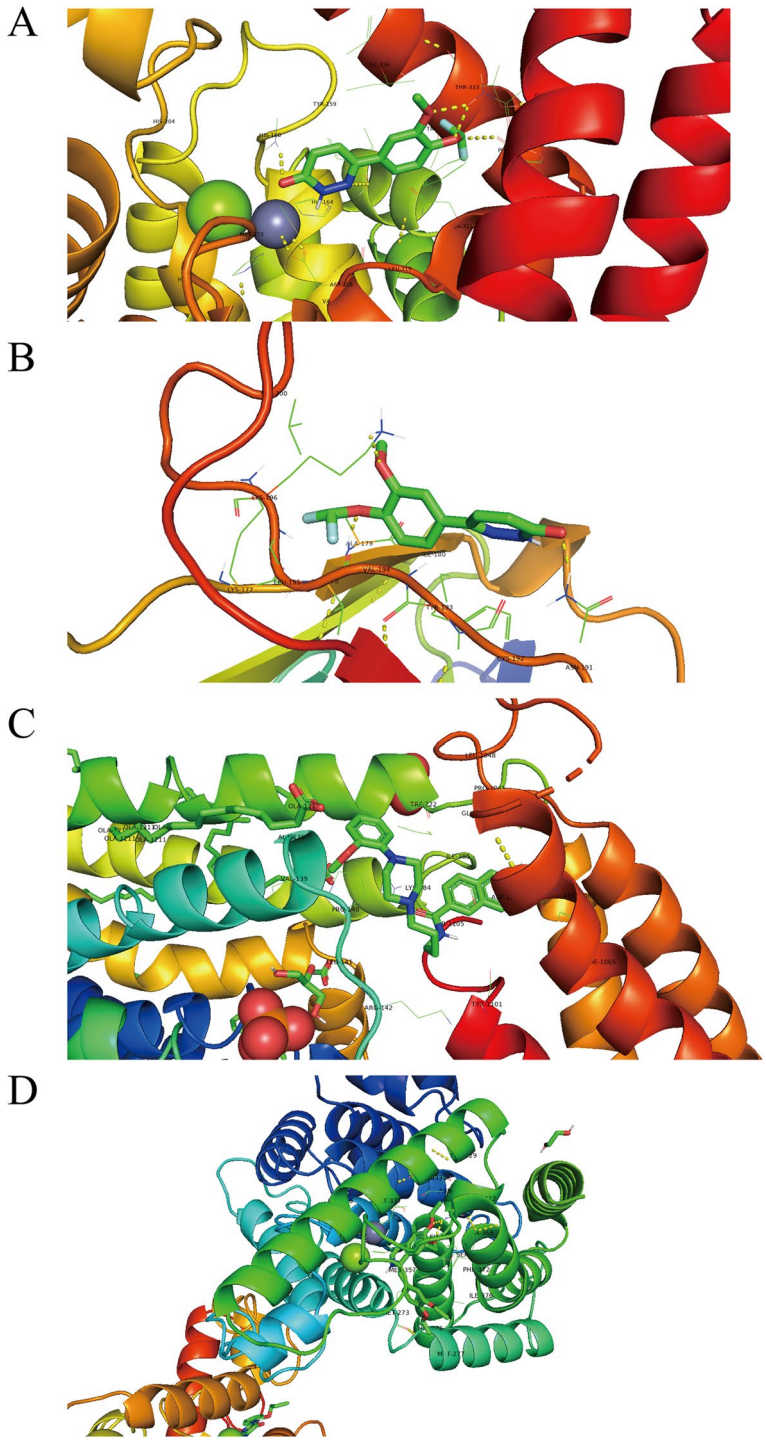

Fig. 9 Docking results of available proteins small molecules. **A** PDE4D docking Zardaverine, **B** MCTP2 docking Zardaverine, **C** DRD4 docking BP 897, **D** PDE4D docking Zaprinast

structures for three proteins and three drug dockings. This study provides a valuable addition to preventive strategies for spinal stenosis as well as promising leads for the treatment of spinal stenosis, which has the potential to reduce drug development costs and advance personalized medicine.

Abbreviations

FAERS	FDA Adverse Event Reporting System
GWAS	Genome-wide association studies
SNPs	Single Nucleotide Polymorphisms
eQTLs	Expression quantitative trait loci
MR	Mendelian Randomization
PheWAS	Phenome-Wide Association Study
ROR	Ratio Reporting Ratio
PRR	Proportion Reporting Ratio
IC	Information Component
EBGM	Empirical Bayesian Geometric Mean
MedDRA	Medical Dictionary for Regulatory Activities
IVW	Inverse variance weighted
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
BP	Biological Process
MF	Molecular Function
CC	Cellular Component
PPI	Protein–Protein Interaction
DSigDB	Drug Signatures Database

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-025-05854-5.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Acknowledgements
We thank the eQTLGen consortium, Ieu Open Gwas Project, the FinnGen team, FAERS database that was provided by the FDA and other researchers and participants for providing publicly available data for this analysis.

Authors' contributions
NY and HYF contributed to conception and design of the study. NY, JKD and XH organized the database. NY, JKD, WZ and XLC performed the statistical analysis. NY wrote the first draft of the manuscript. XH, WZ and XLC wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All authors contributed to manuscript revision, read, and approved the submitted version. Haoyu Feng conceived and designed the study.

Funding
This work was supported by the National Key Research and Development Plan (2022YFC3601900 and 2022YFC3601904).

Data availability
Publicly available datasets were analyzed in this study. These data can be found at the FAERS database (https://www.fda.gov). Besides, the datasets analysed during the current study are available in the in the following repositories: eQTLs data were obtained from eQTLGen Consortium (https://eqtlgen.org/). Spinal Stenosis discovery cohort data was from a previous study and downloaded on ieu open gwas project, with the dataset ID of ukb-d-M13_SPINSTENOSIS (https://gwas.mrcieu.ac.uk). Spinal Stenosis validation cohort data was from FinnGen database, and the version of the data is finngen_R10_M13_SPINSTENOSIS (https://www.finngen.fi/en).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 8 March 2025 Accepted: 24 April 2025
Published online: 04 May 2025

References

1. Kim SL, Lim RD. Spinal stenosis. Dis Mon. 2005;51:6–17.
2. Katz JN, Zimmerman ZE, Mass H, Makhni MC. Diagnosis and Management of Lumbar Spinal Stenosis: A Review. JAMA. 2022;327:1688–99.
3. Byvaltsev VA, Kalinin AA, Hernandez PA, Shepelev VV, Pestryakov YY, Aliyev MA, et al. Molecular and Genetic Mechanisms of Spinal Stenosis Formation: Systematic Review. Int J Mol Sci. 2022;23:13479.
4. Lai M, Cheung P, Cheung J. A systematic review of developmental lumbar spinal stenosis. Eur Spine J. 2020;29:2173–87.
5. Sharpe M, Noble S, Spencer CM. Alendronate: an update of its use in osteoporosis. Drugs. 2001;61:999–1039.
6. Wells GA, Hsieh SC, Peterson J, Zheng C, Kelly SE, Shea B, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev. 2025;1:CD001155.
7. Zhao Z, Ji H, Zhang C, Wang Z, Ren S, Liu C, et al. Mining and analysis of adverse event signals for alendronate based on the real-world data of FDA adverse event reporting system database. Expert Opin Drug Saf. 2025;24(3):297–304.
8. Ji LH, Zhao CL, Wang YQ, Fu ZH. Bisphosphonates-related tendinopathies and ligament disorders: Cases analysis from the US Food and Drug Administration adverse event reporting system. Bone. 2023;177:116919.
9. Liu H, Li Y, Li J, Zhang Q, Wu J, Li X, et al. Musculoskeletal adverse events induced by immune checkpoint inhibitors: a large-scale pharmacovigilance study. Front Pharmacol. 2023;14:1199031.
10. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, et al. The support of human genetic evidence for approved drug indications. Nat Genet. 2015;47:856–60.
11. King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 2019;15: e1008489.
12. Hingorani AD, Kuan V, Finan C, Kruger FA, Gaulton A, Chopade S, et al. Improving the odds of drug development success through human genomics: modelling study. Sci Rep. 2019;9:18911.
13. Schmidt AF, Finan C, Gordillo-Marañón M, Asselbergs FW, Freitag DF, Patel RS, et al. Genetic drug target validation using Mendelian randomisation. Nat Commun. 2020;11:3255.
14. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T, Engmann J, et al. The druggable genome and support for target identification and validation in drug development. Sci Transl Med. 2017;9:eaag1166.
15. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE, et al. Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet. 2016;48:481–7.
16. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13:519–23.
17. Võsa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53:1300–10.
18. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: A review. Res Synth Methods. 2019;10:486–96.
19. Wang Q, Dhindsa RS, Carss K, Harper AR, Nag A, Tachmazidou I, et al. Rare variant contribution to human disease in 281,104 UK Biobank exomes. Nature. 2021;597:527–32.
20. Chen L, Zhang YH, Wang S, Zhang Y, Huang T, Cai YD. Prediction and analysis of essential genes using the enrichments of gene ontology and KEGG pathways. PLoS ONE. 2017;12: e0184129.
21. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein-protein association networks and

functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51:D638–46.
22. Otasek D, Morris JH, Bouças J, Pico AR, Demchak B. Cytoscape Automation: empowering workflow-based network analysis. Genome Biol. 2019;20:185.
23. Warde-Farley D, Donaldson SL, Comes O, Zuberi K, Badrawi R, Chao P, et al. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function. Nucleic Acids Res. 2010;38:W214–20.
24. Yoo M, Shin J, Kim J, Ryall KA, Lee K, Lee S, et al. DSigDB: drug signatures database for gene set analysis. Bioinformatics. 2015;31:3069–71.
25. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res. 2021;49:D1388–95.
26. Morris GM, Huey R, Olson AJ. Using AutoDock for ligand-receptor docking. Curr Protoc Bioinforma. 2008;Chapter 8:Unit 8.14.
27. Surface LE, Burrow DT, Li J, Park J, Kumar S, Lyu C, et al. ATRAID regulates the action of nitrogen-containing bisphosphonates on bone. Sci Transl Med. 2020;12:eaav9166.
28. Chartrand NA, Lau CK, Parsons MT, Handlon JJ, Ronquillo YC, Hoopes PC, et al. Ocular Side Effects of Bisphosphonates: A Review of Literature. J Ocul Pharmacol Ther. 2023;39:3–16.
29. Al Lawati H, Al Busaidi S, Al Rawahi T, Al Lawati A, Kifah A, Das S. Alendronate for Effective Treatment of Male Osteoporosis: An Insight. Curr Pharm Des. 2025;31:26–36.
30. Chen PJ, Wang K, Mehta S, O'Brien MH, Dealy CN, Dutra EH, et al. Anabolic Response of Intermittent Parathyroid Hormone and Alendronate on the Osteochondral Tissue of TMJ. Cartilage. 2022;13:171–83.
31. Mongerard-Coulanges M, Migianu-Griffoni E, Lecouvey M, Jolles B. Impact of alendronate and VEGF-antisense combined treatment on highly VEGF-expressing A431 cells. Biochem Pharmacol. 2009;77:1580–5.
32. Liu G, Li B, Li J, Dong J, Baulin V, Feng Y, et al. EGTA-Derived Carbon Dots with Bone-Targeting Ability: Target-Oriented Synthesis and Calcium Affinity. ACS Appl Mater Interfaces. 2023;15:40163–77.
33. Balagué F, Troussier B, Salminen JJ. Non-specific low back pain in children and adolescents: risk factors. Eur Spine J. 1999;8:429–38.
34. Zanlorenci S, Gonçalves L, de Lima TR, Silva D. Individual and Combined Association between Unhealthy Lifestyle Behaviors and Body Weight Dissatisfaction in a Sample of Adolescents from Southern Brazil. Children (Basel). 2023;10:821.
35. Lusardi M, Rapetti F, Spallarossa A, Brullo C. PDE4D: A Multipurpose Pharmacological Target. Int J Mol Sci. 2024;25:8052.
36. Sun Y, Zhang W, Li X. Induced pluripotent stem cell-derived mesenchymal stem cells deliver exogenous miR-105-5p via small extracellular vesicles to rejuvenate senescent nucleus pulposus cells and attenuate intervertebral disc degeneration. Stem Cell Res Ther. 2021;12:286.
37. Shin OH, Han W, Wang Y, Südhof TC. Evolutionarily conserved multiple C2 domain proteins with two transmembrane regions (MCTPs) and unusual Ca2+ binding properties. J Biol Chem. 2005;280:1641–51.
38. Zhang X, Qin H, Ma Q, Zhang J, Tian H, Meng Y. CircST6GAL1 knockdown alleviates pulmonary arterial hypertension by regulating miR-509-5p/multiple C2 and transmembrane domain containing 2 axis. Clin Respir J. 2024;18: e13771.
39. Ferré S, Belcher AM, Bonaventura J, Quiroz C, Sánchez-Soto M, Casadó-Anguera V, et al. Functional and pharmacological role of the dopamine D(4) receptor and its polymorphic variants. Front Endocrinol (Lausanne). 2022;13:1014678.
40. Liu Q, Zhang R, Zhang X, Liu J, Wu H, Li Y, et al. Dopamine improves chemotherapeutic efficacy for pancreatic cancer by regulating macrophage-derived inflammations. Cancer Immunol Immunother. 2021;70:2165–77.
41. Yamada Y, Ando F, Niino N, Shimokata H. Association of a polymorphism of the dopamine receptor D4 gene with bone mineral density in Japanese men. J Hum Genet. 2003;48:629–33.

Publisher's Note