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Identifying Gene Variants That Are Pathogenic In Osteoporosis Using An Omics Data And Bioinformatics Approach

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ABSTRACT

Introduction. The biological cause of osteoporosis, a metabolic bone disease, is osteoclastic bone resorption that is not offset by osteoblastic bone synthesis. Fractures become more likely as a result of the bones being brittle and weak. Common genetic variants that indicate hereditary susceptibility factors to osteoporosis in the general population, as well as mutations affecting specific genes that cause uncommon monogenic causes of osteoporosis, are the two main types of osteoporosis. Bone defects can now be caused by numerous additional genes. In this study, we aimed to identify variants of this pathogen across continents using genome-based and bioinformatics methodologies. **Methods.** We integrated osteoporosis-associated variants into this study using various bioinformatics-based techniques by using GWAS data from the National Human Genome Research Institute (NHGRI). **Results.** We found that the variant rs3742909 is likely to cause osteoporosis. SMOC1 gene expression in whole blood tissue also appears to be affected by this variant. We found that this genomic variant requires additional research to validate functional and clinical studies in patients with osteoporosis. **Conclusions.** We suggest that better understanding of disease susceptibility, including osteoporosis, can be achieved through the merging of genome-based databases and bioinformatics. Our goal is to validate the findings of this study both in vitro and in vivo during the preclinical stage.

1. Introduction

Osteoporosis is a metabolic bone disease that, at the cellular level, is caused by osteoclastic bone resorption that is not compensated by osteoblastic bone formation.[1] This causes the bones to become weak and brittle, thereby increasing the risk of fractures.[2] Osteoporosis is characterized by a decrease in bone mass and breakdown.[3,4] According to the internationally agreed definition, people with BMD ≤ − 2.5 have a smaller standard deviation than the average of the healthy young population suffering from osteoporosis.[1] In the last century, the average life expectancy of society has increased due to increased safety, life expectancy , and adherence to health principles. As a result, the elderly population has increased significantly.[5] According to WHO, the elderly population will reach 12 billion by 2025.[6] Aging is associated with chronic disease, disability, and cognitive decline. Hypertension, sleep disorders, malnutrition, obesity, and osteoporosis as well as an increased risk of falls are other problems associated with aging. Therefore, the costs of treatment and social support are increasing day by day. Osteoporosis is the most common metabolic disease, especially in the elderly. Osteoporosis and osteoporotic fractures directly and indirectly have a major impact on the global economy. The annual cost of osteoporosis to the US healthcare system is at least $5–10 billion. Osteoporosis increases the risk of bone fractures. Fractures can cause decreased quality of life, hospitalization, disability and increased mortality.[5,7] Osteoporotic fractures, especially vertebral fractures, can be associated with chronic, debilitating pain. One in five patients with a hip fracture dies within one year. Fractures make daily activities difficult. Only one-third of patients with

fractures return to their previous level of function, and one-third of these patients require nursing home admission.[5] In addition to fractures, osteoporosis can increase hospitalization rates due to associated secondary complications. There are more than 8.9 million osteoporotic fractures worldwide. In other words, an osteoporotic fracture occurs every three seconds.[5,8]

Osteoporosis consists of mutations affecting single genes responsible for rare monogenic causes of osteoporosis, and common genetic variants that represent genetic susceptibility factors to osteoporosis in the broader population.[9,10] Many other genes are now known to cause bone disorders similar to OI. Osteogenesis Imperfecta (OI) is primarily caused by mutations in the COL1A1 and COL1A2 genes, which affect type I collagen production. However, several other genes can also lead to bone disorders with symptoms similar to OI.[11,12] Some of them interfere with type I collagen function, such as cartilage-associated protein (*CRTAP*), while others may act by interfering with bone mineralization, as proposed for Plastin3 (*PLS3*).[2] There is also great interest in the discovery of mutations that impair osteoblast differentiation and function, as these may also prove useful therapeutic targets for osteoporosis in the wider population.[13] These include genes involved in WNT signaling, which have an important role in bone homeostasis, such as *WNT1* , and WNT inhibitor frizzled-related protein 4 (*SFRP4*); mutations in these two genes are involved in rare cases of monogenic osteoporosis.[2] However, not many studies have explored pathogenic gene variations. There is evidence that several single nucleotide polymorphisms (SNPs) are associated with the pathogenesis of osteoporosis through GWAS.[14,15] A single genetic susceptibility has not yet been discovered that causes osteoporosis. Instead, the disease is caused by a complex interaction of different variants, which serve as genetic biomarkers.[9] Identifying genomic variants is essential to understand human genome structure and disease biology. Identification of the most important pathogenic variants causing osteoporosis via missense mutations by using genome databases and bioinformatics techniques is still very limited.

The aim of this study was to discover genetic variations associated with the pathogenesis of osteoporosis in different populations. It is hoped that this study will provide a comprehensive picture of prospective biomarkers. These candidates can be used to further investigate the complex pathogenesis of osteoporosis associated with genetic profiles. This will support current goals in drug discovery and development for osteoporosis.

2. Methods

We integrated osteoporosis-associated variants into this study using various bioinformatics-based techniques. GWAS data from the National Human Genome Research Institute (NHGRI) was used to conduct this study. The GWAS database is a research method that examines the relationship between genetic variation (polymorphism) and phenotype. In the context of osteoporosis, GWAS can help identify genetic variants associated with osteoporosis risk. The term "osteoporosis" was downloaded on March 16, 2024. The result was 65 osteoporosis-associated gene variations. We then focused on missense variants because of their potential to alter proteins. This resulted in 1 gene being implicated which was then evaluated using the GTEx Portal to understand gene expression across tissues. This data was obtained on March 30, 2024. The GTEx Portal is a tool used to identify genetic variation and gene regulation across various human tissue types. The GTEx Portal is used to assist in the interpretation of the GWAS catalog for study. GTEx provides Cis-Expression Quantitative Trait Loci (eQTLs) data across multiple tissues associated with various diseases(18,19).[16,17] The GTEx portal provides open access to data including gene expression, QTLs, and histology images. eQTLs are loci that explain a small portion of the genetic variance of some expression in a tissue.[18,19]

A summary of the methodology used to screen osteoporosis variants is illustrated in the various steps of the bioinformatics pathway (Figure 1). Similar methods were also used to differentiate genomic variants in SLE.[20] In addition, the same approach was used to identify pathogenic gene variants associated with coronavirus and chickenpox diseases.[21–24]

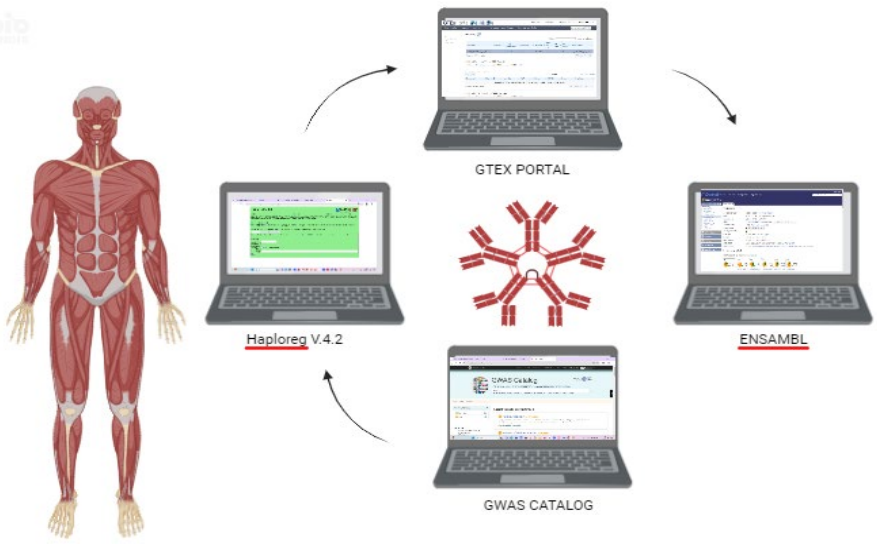

Figure 1. Bioinformatics pipeline scheme for identifying osteoporosis susceptibility genes across continents, GWAS: genome-wide association studies, SNPs: single nucleotide polymorphisms

3. Results

The GWAS catalog is a powerful molecular method by screening thousands of DNA to determine loci associated with a particular disease phenotype. The search results from the GWAS catalog are Single Nucleotide Polymorphism (SNP) corresponding to polymorphic alleles in the human genome that are marked as genetic markers for use in predicting a disease disorder.[23] In GWAS, the statistical significance threshold of the P value is very important in controlling the number of false positive associations.[22,25,26] The GWAS significance value is with a p value of $\leq 10^{-8}$.[24] In bioinformatics research, very small p-values such as $p < 10^{-8}$ are used to indicate very high levels of significance. This is important because such research often involves analyzing large amounts of data and many statistical tests simultaneously, which increases the likelihood of false positives. By using smaller p-values, researchers can more effectively control the type I error rate (false positives) and ensure that statistically significant results have real biological relevance. Very small p-values have also become standard in many areas of bioinformatics research to ensure that reported results are truly significant and not the result of chance. SNPs associated with Osteoporosis were extracted from the GWAS catalog database. We identified 36 SNPs associated with HSCR that passed the inclusion criteria (Table 1). Then, the SNP data was filtered based on missense variants and a p value $<10^{-8}$. One SNP obtained was associated with osteoporosis (Table 2).

Table 1. Variants associated with osteoporosis with criteria and p-value $<10^{-8}$

Gene	SNPs	Variant	P-Value
WNT16	rs3779381	intron_variant	5,00E-15
MEPE - HSP90AB3P	rs33983260	intergenic_variant	7,00E-12
NICN1 - RNA5SP130	rs34240317	intergenic_variant	9,00E-12
SP7 - SP1	rs144680237	intergenic_variant	2,00E-11
TNFRSF11B - RNU6-12P	rs2062375	intergenic_variant	3,00E-11
DDN	rs3741619	intergenic_variant	4,00E-11
LINC01700 - LINC02940	rs11088458	intergenic_variant	5,00E-10
LRP5	rs56154705	intron_variant	9,00E-10
HLA-DRB9 - HLA-DRB5	rs2071805	intron_variant	9,00E-10

Gene	SNPs	Variant	P-Value
GNG12-AS1, WLS	rs2566755	intron_variant	1,00E-09
ALDH7A1	rs13182402	intron_variant	2,00E-09
LRP5	rs880610	intron_variant	2,00E-09
STK39	rs578031265	intron_variant	2,00E-09
RSPO3	rs9482772	intron_variant	2,00E-09
MIMT1 - RPL7AP69	rs73056959	intergenic_variant	4,00E-09
CCDC170	rs4869744	intron_variant	4,00E-09
CSRNP3 - GALNT3	rs10204976	intergenic_variant	8,00E-09
SOX6	rs112725769	intron_variant	8,00E-09
RPS27P4 - MRPS31P1	rs389264	intergenic_variant	9,00E-09
HNRNPKP2 - UBBP1	rs6430612	intergenic_variant	9,00E-09
PPIAP34 - ZBTB40	rs34414754	intergenic_variant	1,00E-08
FTCDNL1	rs7605378	3_prime_UTR_variant	2,00E-08
SFRP4 - STARD3NL	rs397932743	intergenic_variant	2,00E-08
CDC42SE1	rs2864700	intron_variant	2,00E-08
WNT16 - FAM3C	rs10242100	intergenic_variant	3,00E-08
THORLNC - LINC01956	rs115242848	intergenic_variant	3,00E-08
MUC22 - HCG22	rs9262558	intergenic_variant	3,00E-08
AXIN1	rs10794639	intron_variant	3,00E-08
MECOM	rs784288	intron_variant	4,00E-08
SEM1	rs4448201	intron_variant	4,00E-08
SVIL	rs12775980	intron_variant	4,00E-08
KRT18P57, RAP1A	rs494453	intron_variant	4,00E-08
MXRA8 - AURKAIP1	rs12408050	intron_variant	4,00E-08
HOXC6, HOXC4	rs7308105	3_prime_UTR_variant	5,00E-08
LINC02554 - CPMER	rs139959245	intron_variant	5,00E-08
SMOC1	rs3742909	missense_variant	5,00E-08

Table 2. Variant associated with osteoporosis with missense variant criteria and p value <10^{-8}

Gene	SNPs	Variant	P-Value
SMOC1	rs3742909	missense_variant	5.00E-08

Using the GTEX portal database, we then evaluated the tissue expression of one SNP associated with Osteoporosis. This procedure is intended to verify that the SNP is closely related to gene expression. Our study proposes that SNPs, including rs3742909, are SNPs of the SMOC1 gene that are missense variants. where missense variants are genes that have the potential to cause and can affect Osteoporosis tissue expression.

To assess the expression of related genes, the authors conducted a study aimed at identifying genes in human tissues, in our study we used the GTEx portal database. This database concentrates on eQTL expression in various human tissues. eQTL analysis can display gene expression data and show differences in gene expression caused by naturally occurring genetic variations in tissues. Interestingly, the GTEX portal database found one gene symbol related to osteoporosis, namely *SMOC1* (Table 1). We used the GTEx portal database because we know that the functional role of these variants impacts protein expression. eQTLs associated with osteoporosis expression were identified using the GTEx portal database of 65 different gene variants, indicating gene expression in various body tissues. But only one gene influences *SMOC1 expression* (Figure 2).

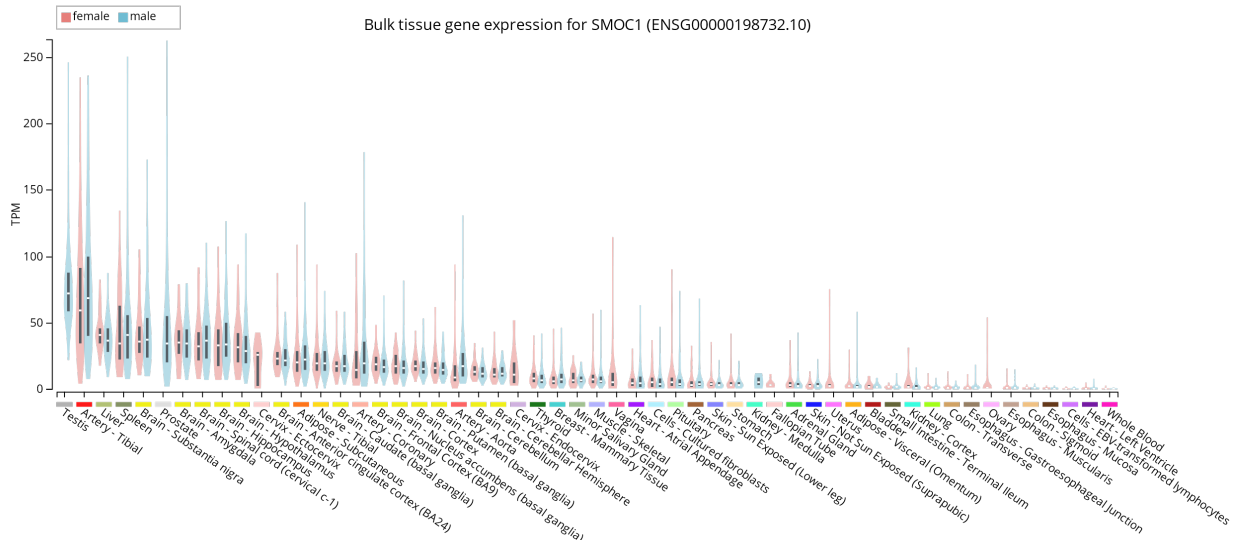

Figure 2. Gene expression network for *SMOC1* according to the GTEx Portal database

The allele frequencies of selected variants in populations that differ the genetic basis of the allele frequencies of one *SMOC1 gene* as well as their expression and function are still unknown. Therefore, we determined the allele frequencies of human populations on different continents after discovering differences in Osteoporosis expression. Allele frequencies in African, American, Asian and European populations are shown in Table 2. Figure 6 shows the variation in allele frequencies across populations, obtained from the Haploreg database version 4.1, which can be accessed at https://pubs.broadinstitute.org/mammals/haploreg/haploreg (accessed 30 March 2024). These variations were obtained from the Ensembl Genome Browser database: .http://www.ensembl.org/Homo_sapiens/Variation. The frequency of the A allele at rs3742909, which is associated with *SMOC1* expression , is highest in Asia, namely around 40%, America 32% and Europe around 26%, while the lowest allele frequency is in African countries around 2%. Our current findings suggest that these susceptibility genes and associated genetic variants may play an important role in the development of osteoporosis based on host genetics with clinical implications.

Table 3. Allele frequencies for each variant associated with Osteoporosis

Gen	SNPs	chr	References	Alternate	1000 Genomes Phase 1 Frequencies				Sequence constraints		dbSNP functional annotation
					AFR	AMR	ASN	EUR	by GERP	by SiPhy	
SMOC1	rs3742909	chr14	G	A	0.02	0.31	0.4	0.26	Yes	Yes	Missense

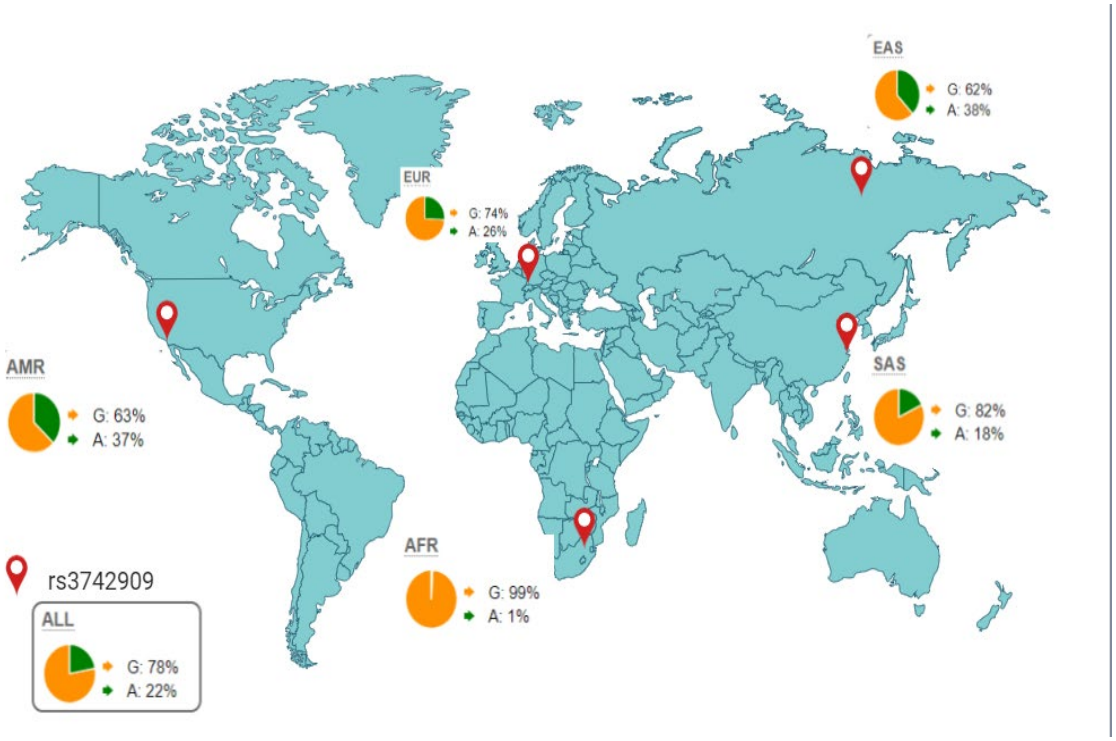

Figure 3. Frequency distribution of the variant allele (rs3742909) affecting *SMOC1* between populations on different continents. This image was created with BioRender.com under agreement number "CX24TS7TWB"

4. Discussion

Osteoporosis is the most common bone disease and is closely related to the risk of fracture, so it is a major public health problem.[27] This disease is more often found in elderly women and is influenced by various factors. Osteoporosis is also known as a disease that is not felt ("silent disease") because the incidence of decreased bone mass can occur for years without any signs (symptoms).[28,29] In this study, we examined the effect of *SMOC1* on the expression of osteoporosis tissue. *SMOC1*, or "SPARC related modular calcium binding 1," is a protein involved in many biological processes, including the regulation of cell growth and differentiation. In the context of osteoporosis, research shows that inflammation plays an important role in the regulation of osteoblasts and osteoclasts, which contribute to bone remodeling processes this can be influenced by various molecules, including *SMOC1,* which can influence gene expression in bone tissue and potentially influence the development of osteoporosis.[30] Osteoporosis is a condition characterized by decreased bone mass and increased bone fragility, which increases the risk of fracture. known as "inflamm-ageing," and the interaction between the immune system and bones, especially in the elderly. The molecular mechanisms involving *SMOC1* in osteoporosis involve several important biological pathways. *SMOC1* plays a role in regulating osteoblast cell differentiation, which is important for bone formation. Following are some key points regarding the molecular mechanism *of SMOC1* regulation of osteoblastogenesis.[30,31] SMOC1 can influence the differentiation and function of osteoblasts, cells responsible for the subsequent synthesis of new bone matrix Interaction with Runx2, SMOC1 is regulated by the transcription factor Runx2, which is a key regulator of the expression of genes related to bone formation and Ossification, *SMOC1* plays a role in the process ossification, both intramembranous and endochondral, which is important for the formation and maintenance of healthy bone structure.[32] The expected clinical implications in the future are the development of atherosclerosis disease therapy based on pharmacogenomics and bioinformatics. Where the bioinformatics approach helps in finding genes that have the potential for mutations to cause osteoporosis and then mapping the gene by looking at SNP expression in various human body tissues. Bioinformatics can also see what drugs can affect

the *SMOC1* gene and the effects of osteoporosis disease therapy. This is certainly interesting for health workers, doctors, pharmacists, and other health experts in developing genomic-based treatments for a disease in the clinical field of health.

In our study, we highlighted that the rs3742909 variant may affect *SMOC1* expression. Based on our study, Genotype A in the rs3742909 variant is higher in the testicular area. The A allele at rs3742909 is most common in Asia, namely around 40%, America 32% and Europe around 26%, while the lowest allele frequency is in African countries around 2%. Thus, it can be assumed that the Asian population is higher compared to Europeans, Americans and Africans with increased *SMOC1 expression* which can contribute to an increased risk of developing osteoporosis. However, we believe that a meta-analysis-based approach is critical to sharpen our predictions as more comprehensive data on genetic variants associated with osteoporosis become available. In addition, further research is needed to validate our findings using functional studies. This validation aims to confirm whether this variant has an important role and can be a variant that can be followed up clinically for osteoporosis, so that in the future it can become a reference material in the treatment and therapy of osteoporosis.

5. Conclusion

The focus of our research is on *SMOC1* expression-revealing genetic variants that affect osteoporosis. In both individuals and populations, these genes affect the risk of osteoporosis. A *SMOC1* expression was seen in the rs3742909 variation. Predicting the vulnerability to osteoporosis illness across different continents requires careful consideration of allele frequencies. In the future, research endeavors will validate the significance of these variations and their clinical efficaciousness in the diagnosis and treatment of individuals with osteoporosis.

6. Acknowledgements

None

7. References

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