Review Article

Pharmacogenomics of osteonecrosis of the jaw

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ABSTRACT

Osteonecrosis of the jaw (ONJ) is a rare but serious drug induced adverse event, mainly associated with the use of antiresorptive medications, such as intravenous (IV) bisphosphonates (BPs) in cancer patients. In this review, we evaluated all the pharmacogenomic association studies for ONJ published up to December 2018. To date, two SNPs (\textit{CYP2C8} rs1934951 and \textit{RBMS3} rs17024608) were identified to be associated with ONJ by two genome-wide association studies (GWAS). However, all six subsequent candidate gene studies failed to replicate these results. In addition, six discovery candidate gene studies tried to identify the genetic markers in several genes associated with bone remodeling, bone mineral density, or osteoporosis. After evaluating the results of these 6 studies, none of the SNPs was significantly associated with ONJ. Recently, two whole-exome sequencing (WES) analysis (including one from our group) were performed to identify variants associated with ONJ. So far, only our study successfully replicated discovery result indicating \textit{SIRT1} SNP rs7896005 to be associated with ONJ. However, this SNP also did not reach genome-wide significance. The major limitations of these studies include lack of replication phases and limited sample sizes. Even though some studies had larger sample sizes, they recruited healthy individuals as controls, not subjects treated with BPs. We conclude that a GWAS with a larger sample size followed by replication phase will be needed to fully investigate the pharmacogenomic markers of ONJ.

1. Introduction

Pharmacogenomics, or the genetic/genomic determinants of drug response and adverse effects, is a tool that has been useful in individualizing medication therapy in order to improve drug efficacy and minimize adverse effects \cite{1,2}. Osteonecrosis of the jaw (ONJ) is a rare but severe drug induced adverse event, which is defined as the exposure of jaw bone (mandible, maxilla, or both) with slow healing for > 8 weeks, or even no healing \cite{3}. ONJ was first reported in 2003 among cancer patients treated with high doses of intravenous (IV) bisphosphonates (BPs) (pamidronate and zoledronate) \cite{4}. Hence, the term “Bisphosphonates Related Osteonecrosis of the Jaw” (BRONJ) was initially used by the American Association of Oral and Maxillofacial Surgeons (AAOMS) to describe this drug induced complication. In 2009, the term BRONJ was replaced with “Antiresorptive Related Osteonecrosis of the Jaw” (ARONJ) because another class of antiresorative agents, receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, denosumab (Prolia\textsuperscript{®}, Xgeva\textsuperscript{®}) was found to be associated with ONJ \cite{5}. Later in 2014, the term “Medication Related Osteonecrosis of the Jaw” (MRONJ) was introduced in light of the fact that antiangiogenic therapies were also linked to this complication \cite{6}. For simplicity, we will use the term ‘ONJ’ in this review.
2. Potential mechanisms of ONJ

Although many risk factors of ONJ have been identified, the mechanisms of ONJ is still not clear. Based on the different potential mechanisms of ONJ development, three main hypotheses have been proposed [6]. The first hypothesis involves bone remodeling inhibition i.e. disruption of bone formation and bone resorption induced by osteoclasts and osteoclasts, respectively. Both BPs and RANKL inhibitor (denosumab) are antiresorptive agents which interfere with the bone resorption process. The second hypothesis is angiogenesis inhibition which results in bone nerosis secondary to prevention of the formation of new blood vessels in the bone. Bevacizumab, an angiogenesis inhibitor, has been reported to be associated with ONJ [7]. The third hypothesis is inflammation and infection. Studies showed that most ONJ patients had record of tooth extraction (~50%) [8–10]. Lots of bacteria live in human mouth with gum disease and they likely induce inflammation/infection after tooth extraction and lead to ONJ.

Even though increasing numbers of medication classes have been reported to be associated with ONJ, antiresorptive agents still show the highest risk for ONJ. Studies have shown that the average incidence of ONJ was around 1.8% and 1.3% for denosumab and BPs, respectively, but the difference was not significant [11,12]. The risk of ONJ in cancer patients treated with IV BPs is ~10 times higher than that in osteoporosis patients based on the higher doses or more frequent administration in cancer patients. The incidence rates of ONJ range from 0.8% to 18% depends on oral or IV route of administration [12–14]. For this review, we will focus on ONJ related to BPs since all the pharmacogenomic association studies for the ONJ phenotype were for BPs-related ONJ.

BPs, as stable analogue of pyrophosphate, contain two phosphonate groups with a central carbon. The chemical structure also contains one short side chain (R1) and one long side chain (R2), which determine the chemical properties of BPs. The BP structure creates high affinity for hydroxyapatite binding sites on the bone surface [15]. BPs are incorporated into osteoclasts cells when the bone mineral is resorbed by osteoclasts through bone remodeling [16–18]. After embedding into the osteoclasts, BPs induce osteoclast apoptosis that leads to inhibition of bone resorption. Based on the difference in the structure of the R2 side chain, BPs are divided into two classes: nitrogen containing BPs and non-nitrogen containing BPs. These two classes of BPs inhibit osteoclasts differentiation and induce osteoclast apoptosis [19–21] through different mechanisms. Nitrogen containing BPs, such as zoledronate and pamidronate, inhibit bone resorption by binding and inhibiting farnesyl pyrophosphate synthase (FPPS) in the HMGA-CoA reductase pathway also known as mevalonate pathway [15,22]. This results in the disruption of osteoclasts cytomembrane ruffles that lead to osteoclasts apoptosis. On the other hand, non-nitrogen containing BPs, such as etidronate and clodronate are metabolized in the cells to compounds that replace the pyrophosphate moiety from ATP to form a non-functional molecule. The accumulation of non-functional molecules (toxic analog of ATP) leads to inhibition of protein synthesis through competition with ATP in mitochondria [23], which then induces apoptosis in osteoclasts. Based on the effect on osteoclasts, BPs are used as anti-resorptive agents for treatment and prevention of osteoporosis. Studies have shown that BPs significantly decrease the risk of fractures and increase bone mass density (BMD) in osteoporosis patients [12,24–26]. Given their non-proliferative action, BPs are important and effective medications for preventing bone loss in cancer patients [15,21,27] especially used for patients with multiple myeloma (MM) and other cancers which metastasize to the bone, to prevent skeletal related events (SREs) [28].

Metastasis is one of the main properties of cancer cell [29]. Most cancers with metastases have high morbidity and mortality. Bone is the third common site for the metastasis that is observed in MM and many other solid cancers, such as breast, lung, and prostate cancers [30]. Previous studies have shown that cancer cells from breast and prostate are most likely to migrate to bone during late-stage of these diseases [31,32]. Based on the data from National Cancer Institute, almost 50% of the breast and prostate cancer patients die due to bone metastases. Bone metastasis occurring commonly in breast and prostate cancer results in the increase of osteoclasts cell growth and differentiation [33,34]. The increasing osteoclastic activity leads to SREs, such as bone pathological fractures and severe bone pain, which decreases the quality of life of cancer patients.

The incidences of ONJ reported by European Association for Cranio-Maxillo-Facial Surgery (EACMFS) and AAOMS are higher than those reported in Japan [6,35,36]. MM shows a higher incidence in African-American individuals, but ONJ cases in MM patients mostly occur in those of European ancestry. Based on these, genetic factors likely contribute to the development of ONJ. So far, multiple studies that have been performed to assess the genetic determinants for ONJ [37–50]. This review evaluated all articles identifying genetic factors for ONJ and recapitulated the current evidence on pharmacogenomics of ONJ.

3. Search strategy

Online literature searches were performed using PubMed databases to retrieve the published studies. The search strategy was based on the combination of the following separate terms: “genetic ONJ”, “pharmacogenetics ONJ”, “pharmacogenomics ONJ”, “polymorphisms ONJ”, “SNPs ONJ”, “GWAS ONJ”, “genome ONJ”, “exome ONJ” or “genome wide ONJ”. These terms were searched again replacing “ONJ” with “osteonecrosis of the jaw”.

4. Eligibility criteria

Literature was reviewed by two authors (GY, YC) independently. Studies matching the following items were included: (1) Articles focusing on investigating the risk of ONJ; (2) Case control ONJ studies or clinical studies comprising of baseline data; (3) Studies that included genetic or SNPs analysis. Exclusion criteria were: (1) reviews or letters about ONJ; (2) Studies that included ONJ but not genes or SNPs research.

Based on the eligibility criteria, fifteen publications were included in the review consisting of two genome-wide association study (GWAS) [37,38], two whole exome sequencing analyses [39,40], and eleven candidate gene studies [41–48,50–52] (Fig. 1).

5. Discovery candidate gene studies on ONJ

A total of six discovery candidate gene studies were published between 2010 and 2018 [43,46,47,50–52] (Table 1). These studies investigated the effects of variants in several genes, which had been selected based on a potential role in BPs metabolism and/or ONJ pathogenesis (e.g. bone turnover). Most of these studies genotyped only a small number of variants and had small cohorts and are therefore susceptible to limitations such as inadequate power. None of the single-nucleotide polymorphisms (SNPs) tested in these studies reached significance level after accounting for multiple comparisons.

The study by Di Martino et al [43] used Affymetrix DMT™ plus platform [53], which genotyped a total of 1936 SNPs in 225 drug target genes, to identify 8 SNPs with p-value < 0.05 located in 4 different genes that are associated with development of ONJ (Table 1). This case-control study comprised of 19 MM patient samples including 9 cases suffering from ONJ induced by zoledronate and the other 10 MM patients were controls, who did not develop ONJ after treatment with zoledronate. However, although this study genotyped total 1936 SNPs which makes the Bonferroni corrected alpha as 2.5×10⁻⁶, none of 8 SNPs reached this alpha level. The top SNP rs1152003 was located on PPARG (peroxisome proliferator-activated receptor gamma) gene with the strongest p-value of 0.0064. PPARG is a compelling candidate gene that is associated with bone remodeling [54–57], and is involved in
Genes have shown that gene, which encodes a key enzyme of the mevalonate pathway. Studies showed that the aromatase SNP, rs10046, was significantly associated with ONJ (corrected p-value = 0.0097 (OR: 11.2; 95% confidence interval (CI): 1.8–69.9). For this study, the combined genotype of OPG, COL1A1, RANK, MMP2, and OPN was significantly associated with ONJ development (p-value = 0.0097 (OR: 11.2; 95% confidence interval (CI): 1.8–69.9).

Several clinical studies and animal studies have demonstrated that inflammation/infection is associated with ONJ development [69–72]. Major histocompatibility complex (MHC) class II molecules are important in immune responses, and one study has shown that mice with MHC class II deficiency were more susceptible to infection [73]. The study of Stockmann et al [47] conducted so far the largest discovery candidate gene study to investigate the effect of the SNPs of MHC class II on ONJ development. Total 204 MM or malignant cancer participants treated with BPs were recruited, including 12 ONJ cases and 66 non-ONJ controls) [51]. This study showed FDPS intronic region SNP, rs2297480, was significantly associated with ONJ with a p-value of 0.03.

Katz et al [46] investigated 10 SNPs in 7 candidate genes (CYP2C8, COL1A1, RANK, OPN, MMP2, OPG and TNF) in total 78 MM patients treated with zoledronate and/or pamidronate, including 12 ONJ cases and 66 non-ONJ controls. All 7 genes were selected because they were associated with bone remodeling, BMD, or osteoporosis. Upon analysis, none of these SNPs were associated with ONJ (all p-values > 0.05). However, this study constructed genotype scores for 5 candidate gene (OPG, COL1A1, RANK, MMP2, and OPN) to study the potential combined effect of all five SNPs located in these genes. Genotype score is a method to estimate multiple SNPs or genes effects on complex diseases [67,68]. For this study, the combined genotype of OPG, COL1A1, RANK, MMP2, and OPN was significantly associated with ONJ development with p-value = 0.0097 (OR: 11.2; 95% confidence interval (CI): 1.8–69.9).

6. Genome-wide association studies (GWAS) on ONJ

GWAS is a method for researchers to identify genetic variants associated with risk of disease or drug response to medications. GWAS evaluate the entire genome for genetic polymorphisms and sequence SNPs based on the linkage disequilibrium (LD). As of the time of writing of this review, only two GWASs of ONJ have been published [37,38] (Table 2). The study of Sarasquete et al [37] was the first GWAS on the phenotype of ONJ. This study included 87 MM patients (22 cases and 65 controls) [59–61]. The aim of this study was to test the effect of these 3 SNPs in VEGF gene on ONJ. This study compared ONJ cases with BPs tolerant control or healthy controls, respectively. Upon analysis, none of these three SNPs was associated with ONJ development. However, the haplotype AC determined by two SNPs rs2010963 and rs699947 was significantly associated with ONJ development. Moreover, DRB1*01H (p-value = 0.0003, OR 3, 95% CI 1.7–5.5) were even more significantly associated with ONJ.

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Several clinical studies and animal studies have demonstrated that inflammation/infection is associated with ONJ development [69–72]. Major histocompatibility complex (MHC) class II molecules are important in immune responses, and one study has shown that mice with MHC class II deficiency were more susceptible to infection [73]. The study of Stockmann et al [47] conducted so far the largest discovery candidate gene study to investigate the effect of the SNPs of MHC class II on ONJ development. Total 204 MM or malignant cancer participants treated with BPs were recruited, including 94 ONJ cases and 110 non-ONJ controls. After Bonferroni correction, HLA haplotype DRB1*15–DQB1*06:02 (p-value = 0.032, OR 2.5, 95% CI 1.3–5.0), was significantly associated with ONJ development. Moreover, DRB1*01H and/or DRB1*15H (p-value = 0.0003, OR 3, 95% CI 1.7–5.5) were even more significantly associated with ONJ.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Disease</th>
<th>BPS</th>
<th>Cases/ control (N)</th>
<th>SNPS</th>
<th>Genes</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Martino MT, et al.</td>
<td>Not reported</td>
<td>Multiple myeloma</td>
<td>Zoledronate</td>
<td>9/10</td>
<td>rs1152003, rs10893, rs4725373, rs1049793, rs2461347, rs903247, rs2468110, rs2097917</td>
<td>PPARγ, ABP1, ABP1, CHST11, CHST11, CROT</td>
<td>0.0064</td>
<td>NA</td>
<td>0.0327</td>
</tr>
<tr>
<td>Katz J, et al. (2011)</td>
<td>White American</td>
<td>Multiple myeloma</td>
<td>Pamidronate</td>
<td>12/66</td>
<td>rs1934951, rs1934980, rs1800012, rs1245817, rs243865, rs2073618, rs3192735, rs1730582, rs28357094, rs180629</td>
<td>CYP2C8, CYP2C8, COL1A1, RANK, MMP2, OPG, OPG, OPG, OPN, OPN, TNF</td>
<td>0.033</td>
<td>NA</td>
<td>0.67 (0.13-3.95)</td>
</tr>
<tr>
<td>Marini F, et al. (2011)</td>
<td>Not reported</td>
<td>Multiple myeloma Mammary cancer</td>
<td>Zoledronate</td>
<td>34/34</td>
<td>rs2297480</td>
<td>FDPS</td>
<td>0.117</td>
<td>2.76 (1.09-4.94)</td>
<td>3'-UTR</td>
</tr>
<tr>
<td>Arduino PG, et al. (2011)</td>
<td>Caucasian</td>
<td>Multiple myeloma Breast cancer</td>
<td>Zoledronate</td>
<td>30/155</td>
<td>rs2010963, rs3025039, rs699947</td>
<td>VEGF, VEGF, VEGF</td>
<td>0.117</td>
<td>2.76 (1.09-4.94)</td>
<td>5'-UTR</td>
</tr>
<tr>
<td>La Ferla F, et al. (2012)</td>
<td>White</td>
<td>Multiple myeloma Breast cancer</td>
<td>Zoledronate</td>
<td>30/53</td>
<td>rs2234693, rs9340799, rs10946</td>
<td>ESR1, CYP19A1</td>
<td>&gt; 0.05</td>
<td>NA</td>
<td>2.83 (1.2-4.6)</td>
</tr>
<tr>
<td>Stockmann P, et al. (2012)</td>
<td>White</td>
<td>Malignant cancer</td>
<td>Zoledronate</td>
<td>94/110</td>
<td>rs3135388, rs10988217</td>
<td>HLA-DRBI, HLA-DQBI</td>
<td>0.014</td>
<td>2.3 (1.2-4.6)</td>
<td>Intergenic</td>
</tr>
</tbody>
</table>

BPs: bisphosphonates; OR: odds ratio; 95% CI: confidence interval.
Table 2: Summary of genome-wide association studies for ONJ.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Disease</th>
<th>SNP(s)</th>
<th>Genes</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>Function</th>
<th>Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastritis et al (2008)</td>
<td>European prostate cancer patients</td>
<td>Zoledronate 78 MM</td>
<td>rs1934951</td>
<td>RBMS3</td>
<td>10.2 (3.2–32.1)</td>
<td>4.231*10^{-6}</td>
<td>Intronic</td>
<td>No</td>
</tr>
<tr>
<td>Such et al (2012)</td>
<td>European men</td>
<td>Pamidronate 30/1743</td>
<td>rs17024608</td>
<td>RBMS3</td>
<td>13.88 (4.0–46.7)</td>
<td>1.07 *10^{-6}</td>
<td>Intronic</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Intronic

7. Replication studies

So far, five candidate gene studies have attempted to replicate the results of GWAS of Sarasquete ME, et al [41,42,45,46,48] (Table 3). These studies investigated the effect of CYP2C8 SNP, rs1934951, on the development of ONJ in other independent cohorts. All five studies failed to demonstrate significant association between SNP rs1934951 and ONJ development (p-value < 0.05). English et al [41] failed to replicate the result of first GWAS performed by Sarasquete ME, et al. in prostate cancer patients with p-value > 0.47 (OR = 0.63, 95% CI: 0.165–2.42). Such et al [42] tried to use similar samples and medication conditions as the study by Sarasquete ME, et al to replicate the effect of CYP2C8 SNP rs1934951 on ONJ development, but they also failed to replicate this association.

Another replication candidate gene study focused on VEGF gene was published by Choi H, et al in 2015 [44]. This study genotyped VEGF SNPs rs699947, rs2010963, and rs3025039 in a total of 45 patients (26 cases and 19 controls). The results showed that rs699947 and
associated with ONJ (\(p\) determined by two SNPs rs2010963 and rs699947 was not significantly = 0.04, (rs2010963 were nominally associated with ONJ development
BPs: bisphosphonates; OR: odds ratio; 95% CI: confidence interval.

Table 3
Summary of replication candidate gene studies for ONJ.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Disease</th>
<th>BPS</th>
<th>Cases/controls (N)</th>
<th>SNPs</th>
<th>Genes</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>English BC et al. (2010)</td>
<td>Caucasian American Hispanic Asian European</td>
<td>Prostate cancer</td>
<td>Zoledronate</td>
<td>17/83</td>
<td>rs1934951</td>
<td>CYP2C8</td>
<td>&gt; 0.05</td>
<td>0.63 (0.165–2.42)</td>
<td>Intronic</td>
</tr>
<tr>
<td>Such E, et al. (2011)</td>
<td>White African American Hispanic Other</td>
<td>Multiple myeloma</td>
<td>Zoledronate</td>
<td>42/37</td>
<td>rs1934951</td>
<td>CYP2C8</td>
<td>0.13</td>
<td>NA</td>
<td>Intronic</td>
</tr>
<tr>
<td>Katz J, et al. (2011)</td>
<td>White African American Hispanic Other</td>
<td>Multiple myeloma</td>
<td>Zoledronate Pamidronate</td>
<td>12/66</td>
<td>rs1934951</td>
<td>CYP2C8</td>
<td>0.63</td>
<td>0.68 (0.14–3.22)</td>
<td>Intronic</td>
</tr>
<tr>
<td>Balla B, et al. (2012)</td>
<td>Hungarian</td>
<td>Osteoporosis Multiple myeloma Breast cancer Cervix cancer Prostate cancer Renal cancer</td>
<td>Alendronate Pamidronate Zoledronate Ibandronate Risedronate Clodronate</td>
<td>46/224</td>
<td>rs1934951</td>
<td>CYP2C8</td>
<td>0.015</td>
<td>NA</td>
<td>Intronic</td>
</tr>
<tr>
<td>Kastritis E, et al. (2017)</td>
<td>European</td>
<td>Multiple myeloma</td>
<td>Zoledronate</td>
<td>36/104</td>
<td>rs1152003</td>
<td>PPARG</td>
<td>&lt; 0.05</td>
<td>NA</td>
<td>Intergenic</td>
</tr>
</tbody>
</table>

BPs: bisphosphonates; OR: odds ratio; 95% CI: confidence interval.

rs2010963 were nominally associated with ONJ development (\(p = 0.04, p = 0.03\), respectively). However the haplotype AC determined by two SNPs rs2010963 and rs699947 was not significantly associated with ONJ (\(p = 0.126\)), even though these two SNPs have high LD (\(r^2 = 0.96\)).

There are some potential reasons for the failure of the replication efforts. Firstly, there were differences in the population that was used for replication in the candidate gene studies. The first GWAS by Sarasquete ME, et al was conducted in individuals of Spanish ancestry whereas none of other replication efforts used subjects of Spanish ancestry, even though some studies used European patients. Secondly, the GWAS was conducted in MM patients treated with zoledronate and/or pamidronate. However, only two of the replication studies focused on MM patients. Moreover, subjects in these two studies were treated with zoledronate only.

The discovery candidate gene study for VEGF used patients of European ancestry, but replication effort for this gene was undertaken using patients of Korean ancestry. HaploReg v4.1 [77] shows that the LD (\(r^2\)) for SNP rs699947 and rs2010963 is 0.45 in Europeans, but 0.96 in Asians.

8. Whole-exome sequencing analysis

Whole-exome sequencing (WES) determines the sequence of all protein-coding genes in human genome. This method covers < 2% of human genome, but contain > 85% of known disease-related variants [78]. Based on above mentioned, WES is a cost-effective alternative to whole-genome sequencing.

So far, two WES studies have been published [39,40] (Table 4). Kim et al [40] identified four genes (ARSD, SLC25A5, CCNYL2, and PGTYM) associated with ONJ with the lowest p-value (p-value < 0.05) using WES and Gene set enrichment analysis (GSEA) methods. GSEA is a computational method that investigates genetic variants in a group of genes to elucidate the gene differences between cases and controls. This was the first study that combined WES and GSEA methods to investigate the function of SNPs between ONJ patients and non-ONJ participants.

The WES from our group [39] was the first study that performed both discovery and replication followed by meta-analysis so far. Moreover, our study included not only MM but also other metastatic solid cancers as cases and controls. The meta-analysis identified SIRT1 SNP rs7896005 and HERC4 SNP rs3758392 to be associated with ONJ with the lowest p-value (3.9×10^{-7}) approaching genome-wide significance. The HERC4 SNP rs3758392 had the same p-value as rs7896005 because of high LD (\(r^2 = 0.88\)). These two SNPs were both expression quantitative loci (eQTLs) for SIRT1. SIRT1 was a very compelling candidate gene of bone remodeling. Studies had shown that SIRT1 plays a vital role in bone remodeling by affecting the Wnt signaling pathway [79–82] and RANK/RANKL/OPG pathway [83,84].

9. Conclusion

ONJ is a rare but serious drug induced adverse event, which critically increases discomfort and reduces quality of life in patients. Studies have shown that the risk of ONJ development is higher in patients of European ancestry than other populations [12,14,85]. Investigators believe that genetic factors play an important role in ONJ development. Candidate gene studies have focused on investigating the association between genetic variations within certain genes of interest and ONJ. However, the selection of candidate genes is limited by prior knowledge. WES approach identifies potentially functional genetic variations through sequencing protein-code region of genes in the human genome.
Table 4
Summary of Whole-exome sequencing studies for ONJ.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Disease</th>
<th>BPS</th>
<th>Cases/controls (N)</th>
<th>SNPS</th>
<th>Genes</th>
<th>P-value</th>
<th>OR (95% CI)</th>
<th>Function</th>
<th>Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim JL et al. (2015)</td>
<td>Oriental</td>
<td>Tooth extraction</td>
<td>Alendronate</td>
<td>16/126</td>
<td>Not reported</td>
<td>ARSD</td>
<td>SLC25A5</td>
<td>&lt; 0.05</td>
<td>Not reported</td>
<td>No</td>
</tr>
<tr>
<td>Yang G, et al. (2018)</td>
<td>European ancestry</td>
<td>Multiple myeloma</td>
<td>Zoledronate</td>
<td>39/22</td>
<td>rs7896050</td>
<td>SIRT1</td>
<td>3.9–10^7</td>
<td>0.07 (0.01–0.46)</td>
<td>Intronic</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BPs: bisphosphonates; OR: odds ratio; 95% CI: confidence interval.

However, since it only cover < 3% of human genome, WES may also miss the important genetic markers that are potentially associated with ONJ. Even though GWAS surveys the entire genome, it requires larger sample sizes and replication phase. So far, none of the genetic polymorphisms reported in the ONJ GWAS studies have been replicated, largely due to limited sample size and lack of validation. In summary, after reviewing the ONJ Pharmacogenomics literature, no genetic markers for ONJ have been replicated or functionally validated. We conclude that a GWAS with larger sample size followed by replication and functional validation will be needed to fully investigate the pharmacogenomics of ONJ.

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All authors contributed to the conception, drafting, and critical review of the manuscript and provided final approval.

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Conflict of interest
The authors report no relationships that could be construed as a conflict of interest.

References