Original Article

Population-based studies of genetic variants of FRZB with osteoarthritis at three joint sites: a comprehensive meta-analysis

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Abstract: To address the ambiguities raised by inconsistent results among molecular genetic studies between the rs288326 (R200W) and rs7775 (R324G) variants of the FRZB gene and osteoarthritis (OA), we synthesized standardized data on hip, knee, and hand OA according to a common meta-analysis protocol. There were nine independent case-control studies that were candidates for performing an association analysis of the SNPs rs288326 and rs7775 in the FRZB locus of patients with OA at three joint sites. For SNP rs288326, the case and control sample sizes were 3,803 and 5,972 for hip OA, 2,305 and 2,514 for knee OA, and 2,761 and 1,463 for hand OA, respectively, and for SNP rs7775, the case and control sample sizes were 3,849 and 8,843 for hip OA, 2,315 and 2,506 for knee OA, and 2,796 and 1,456 for hand OA, respectively. Using a fixed-effect model, the summary effect for the T-allele of rs288326 was statistically significant in females with knee OA between patients and controls (Subtotal OR=1.24, 95% CI=1.01-1.53, Z=2.02, P=0.04), and an association trend was revealed for this SNP in females with hip OA (Subtotal OR=1.12, 95% CI=0.99-1.28, Z=1.75, P=0.08). In summary, our study supports the hypothesis that FRZB may play a small but important role in the pathogenesis of OA in females, at least in females with hip OA or knee OA. Further gender-based studies are needed to elucidate the actual role of FRZB in the physiology of human bone and cartilage and in the pathogenesis of skeletal disorders.

Keywords: Osteoarthritis, FRZB, SNP, gender, meta-analysis

Introduction

Osteoarthritis (OA) is a common complex disorder affecting ~5% of the population mostly above 45 years of age [1]. OA can result in joint pain and disability, and its development and progression are associated with both genetic and environmental risk factors, including age, gender, ethnicity, behavioral influences, obesity, and occupation [2]. From the results of epidemiological studies in twins, sibling pairs, and families, genetic components of OA have an estimated heritability of 60% for the hip, 40% for the knee, and 65% for the hand [3, 4].

Though a genome-wide linkage analysis and association study, Loughlin et al. initially identified the single-nucleotide polymorphism (SNP) rs7775 (a R324G substitution) in the frizzled-related protein (FRZB) gene associated with hip OA in females [3]. FRZB is located at chromosomal position 2q32.1, spans ~33.5 kb, consists of six exons, and encodes a secreted glycoprotein that inhibits signalling for the wingless-type (Wnt) ligands through Frizzled receptor [5, 6].

The Wnt/β-catenin signalling pathway has been implicated in the pathogenesis of OA, and this pathway is of key importance during skeletal patterning in embryogenesis, and is also involved in the homeostasis of bone and cartilage in adults [7-11]. Accumulated results from human studies have demonstrated a link between the rs288326 (R200W) and rs7775 and OA [5, 7, 12-14]. However, not every study has replicated these findings [6, 15-18], and two recent meta-analyses failed to demon-
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...strate a consistent link between FRZB variants and OA [14, 16]. Since then, multiple studies on the relationship of OA and FRZB have been published [7, 17]. Therefore, to address the ambiguities raised by inconsistent results among molecular genetic studies, additional studies and more reliable estimates of OA with FRZB are warranted [19, 20].

In the current study, we synthesized standardized data on hip, knee, and hand OA according to a common meta-analysis protocol, and performed a comprehensive meta-analysis of individual-level data on the relationship of the rs288326 and rs7775 SNPs within the FRZB locus with OA at three different joint sites.

Methods

Identification of eligible studies and data extraction

A search for studies that examined associations between FRZB polymorphisms and OA was performed. The literature was searched using the PubMed (http://www.ncbi.nlm.nih.gov), SCOPUS (http://www.scopus.com), and EMBASE (http://www.elsevier.com/solutions/embase) databases to identify available studies in which FRZB polymorphisms were analyzed in OA patients. Combinations of keywords, such as “frizzled-related protein”, “FRZB”, “polymorphism”, “osteoarthritis”, and “OA”, were entered as medical subject heading (MeSH) components and as text words. References in identified studies were also investigated to identify additional studies not indexed by the above-mentioned databases [21]. A study was included in the present meta-analysis if the following criteria were met: (1) the study was published by October 2015; (2) the study was published in a peer-reviewed English journal; (3) the study presented original data on allele and/or genotype frequencies in both case and control samples; (4) the study was independent of other studies, i.e., studies that included and/or re-analyzed a previously published data set were not regarded as independent, and in such cases, only the first published data set was included in the meta-analysis; and (5) the study contained sufficient data to calculate an effect size [20, 22]. The exclusion criteria were as follows: (1) studies in which family members were studied, such as by a transmission disequilibrium test, because their analyses were based on linkage considerations; (2) studies that presented non-original data, such as reviews, editorials, opinion papers, or letters to the editor; and (3) studies that used non-human subjects or specimens. The following information was extracted from each included study: (1) the first author; (2) the journal; (3) the year of publication; (4) the study design; (5) the ethnicity of the subjects; (6) the sample size; (7) the phenotype information; and (8) the allele and/or genotype distribution of subjects with and without OA [23].

Quality control

For genetic association studies with conflicting results on the same genetic variants, the quality of the study design should be controlled by appropriate criteria to limit the risk of introducing bias into the meta-analysis. Therefore, three phenotypes of OA, i.e., hip OA, knee OA and hand OA, were addressed separately. Population-based studies were also subdivided into females and males.

Evaluation of statistical associations

Allele and/or genotype distribution data were entered into tables. If genotypic data were available, the Hardy-Weinberg equilibrium (HWE) was assessed separately for the control group of each study. Deviation from HWE was considered nominally statistically significant if P<0.05. The allele frequencies in these studies were analyzed using the Epi_Info program (http://www.cdc.gov/epiinfo), and P<0.05 was used as the criterion for statistical significance. Before the pooling procedure, Cochran’s Chi-squared-based Q-statistic, which is considered significant at P<0.10, was performed to assess the heterogeneity within the group of odds ratios (ORs) [1, 14]. The natural logarithm of the OR estimates were determined using random-effects models or fixed-effects models. Random-effects models yield wider confidence intervals (CIs) when heterogeneity exists; otherwise, random and fixed effects coincide [22]. The significance of the pooled OR was determined by a Z test. A sensitivity analysis, which determines the influence of individual studies on the pooled OR, was performed by sequentially removing each study and recalculating the pooled OR and 95% CI. Furthermore, an ancillary procedure for funnel plot asymmetry was also used to qualitatively assess evidence of publication bias. The above-described statistical analyses were performed using the soft-
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Table 1. Characteristics of the included case-control studies between rs288326 of FRZB and OA

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country</th>
<th>Assessment of cases</th>
<th>HWE</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
<th>Mixed</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
<th>Female</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
<th>Male</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip OA</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Loughlin et al, 2004</td>
<td>UK</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>145/814</td>
<td>189/1132</td>
<td>0.588</td>
<td>86/494</td>
<td>91/612</td>
<td>0.331</td>
<td>59/320</td>
<td>98/520</td>
<td>0.903</td>
<td>90/573</td>
<td>109/591</td>
<td>0.804</td>
<td></td>
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</tr>
<tr>
<td>Min et al, 2005</td>
<td>Netherlands</td>
<td>K/L grade ≥2</td>
<td>&gt;0.05</td>
<td>37/259</td>
<td>237/1597</td>
<td>0.840</td>
<td>26/126</td>
<td>66/410</td>
<td>0.326</td>
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</tr>
<tr>
<td>Lories et al, 2006</td>
<td>Belgium</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>71/543</td>
<td>89/499</td>
<td>0.068</td>
<td>37/335</td>
<td>26/204</td>
<td>0.597</td>
<td>34/208</td>
<td>63/295</td>
<td>0.247</td>
<td>24/180</td>
<td>30/209</td>
<td>0.562</td>
<td></td>
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</tr>
<tr>
<td>Lane et al, 2006</td>
<td>USA*</td>
<td>JSN grade ≥3</td>
<td>&gt;0.05</td>
<td>157/981</td>
<td>307/2327</td>
<td>0.066</td>
<td>10/82</td>
<td>177/1373</td>
<td>0.872</td>
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<tr>
<td>Rodriguez-Lopez et al, 2007</td>
<td>Spain</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>317/3135</td>
<td>194/2144</td>
<td>0.244</td>
<td>116/786</td>
<td>151/1051</td>
<td>0.839</td>
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<td></td>
</tr>
<tr>
<td>Kerkhof et al, 2008</td>
<td>UK</td>
<td>K/L grade ≥2</td>
<td>NA</td>
<td>88/630</td>
<td>99/805</td>
<td>0.414</td>
<td>17/89</td>
<td>63/295</td>
<td>0.709</td>
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</tr>
<tr>
<td>Evangelou et al, 2009</td>
<td>Iceland</td>
<td>NDI</td>
<td>&gt;0.05</td>
<td>155/1051</td>
<td>135/1063</td>
<td>0.233</td>
<td>79/531</td>
<td>57/541</td>
<td>0.060</td>
<td>76/520</td>
<td>78/522</td>
<td>0.898</td>
<td>50/372</td>
<td>59/381</td>
<td>0.302</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker-LePain et al, 2012</td>
<td>USA*</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>201/1943</td>
<td>194/2144</td>
<td>0.204</td>
<td>50/372</td>
<td>26/204</td>
<td>0.836</td>
<td>5/49</td>
<td>63/295</td>
<td>0.124</td>
<td>45/454</td>
<td>194/2144</td>
<td>0.351</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K/L=Kellgren/Lawrence; JSN=Joint Space Narrowing; NDI=no detailed information; ACR=American College of Rheumatology; NA=Not applicable. *Caucasian descent.
Table 2. Characteristics of the included case-control studies between rs7775 of FRZB and OA

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country</th>
<th>Assessment of cases</th>
<th>HWE</th>
<th>Allele (G/C)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mixed</td>
<td>Female</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>P-value</td>
<td>Cases</td>
</tr>
<tr>
<td>Hip OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loughlin et al, 2004</td>
<td>UK</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>89/918</td>
<td>111/1288</td>
<td>0.428</td>
<td>68/530</td>
</tr>
<tr>
<td>Min et al, 2005</td>
<td>Netherlands</td>
<td>K/L grade ≥2</td>
<td>&gt;0.05</td>
<td>22/272</td>
<td>144/1760</td>
<td>0.961</td>
<td>15/137</td>
</tr>
<tr>
<td>Lories et al, 2006</td>
<td>Belgium</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>75/529</td>
<td>64/514</td>
<td>0.473</td>
<td>52/316</td>
</tr>
<tr>
<td>Lane et al, 2006</td>
<td>USA</td>
<td>JSN grade ≥3</td>
<td>&gt;0.05</td>
<td>318/3190</td>
<td>202/2136</td>
<td>0.576</td>
<td>81/821</td>
</tr>
<tr>
<td>Rodriguez-Lopez et al, 2007</td>
<td>Spain</td>
<td>Knee replacement</td>
<td>&gt;0.05</td>
<td>62/486</td>
<td>64/514</td>
<td>0.898</td>
<td>49/395</td>
</tr>
<tr>
<td>Kerkhof et al, 2008</td>
<td>UK</td>
<td>K/L grade ≥2</td>
<td>NA</td>
<td>49/655</td>
<td>75/827</td>
<td>0.313</td>
<td>48/548</td>
</tr>
<tr>
<td>Evangelou et al, 2009</td>
<td>Iceland</td>
<td>NDI</td>
<td>&gt;0.05</td>
<td>56/418</td>
<td>64/514</td>
<td>0.707</td>
<td>51/369</td>
</tr>
<tr>
<td>Baker-LePain et al, 2012</td>
<td>USA</td>
<td>Hip replacement</td>
<td>&gt;0.05</td>
<td>442/4676</td>
<td>202/2132</td>
<td>0.979</td>
<td>51/369</td>
</tr>
<tr>
<td>Knee OA</td>
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</tr>
<tr>
<td>Rodriguez-Lopez et al, 2007</td>
<td>Spain</td>
<td>Knee replacement</td>
<td>&gt;0.05</td>
<td>105/1101</td>
<td>91/1107</td>
<td>0.320</td>
<td>57/553</td>
</tr>
<tr>
<td>Valdes et al, 2007</td>
<td>UK</td>
<td>NDI</td>
<td>&gt;0.05</td>
<td>200/1972</td>
<td>202/2132</td>
<td>0.515</td>
<td>51/369</td>
</tr>
<tr>
<td>Kerkhof et al, 2008</td>
<td>UK</td>
<td>K/L grade ≥2</td>
<td>NA</td>
<td>49/655</td>
<td>75/827</td>
<td>0.313</td>
<td>48/548</td>
</tr>
<tr>
<td>Evangelou et al, 2009</td>
<td>Iceland</td>
<td>NDI</td>
<td>&gt;0.05</td>
<td>56/418</td>
<td>64/514</td>
<td>0.707</td>
<td>51/369</td>
</tr>
<tr>
<td>Hand OA</td>
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</tr>
<tr>
<td>Rodriguez-Lopez et al, 2007</td>
<td>Spain</td>
<td>ACR</td>
<td>&gt;0.05</td>
<td>442/4676</td>
<td>202/2132</td>
<td>0.979</td>
<td>51/369</td>
</tr>
<tr>
<td>Evangelou et al, 2009</td>
<td>Iceland</td>
<td>NDI</td>
<td>&gt;0.05</td>
<td>442/4676</td>
<td>202/2132</td>
<td>0.979</td>
<td>51/369</td>
</tr>
</tbody>
</table>

K/L=Kellgren/Lawrence; JSN=Joint Space Narrowing; NDI=no detailed information; ACR=American College of Rheumatology; NA=Not applicable. *Caucasian descent. Significant P values (<0.05) are in boldface.
Results

Available studies

26 references were identified by the combined search. After discarding reviews and studies that were not written in English, 23 references remained. Furthermore, 14 references were excluded, because they did not clearly meet the criteria, or were not association studies of SNPs. This resulted in nine independent case-control studies that were candidates for use in an association analysis of SNPs rs288326 and rs7775 in the FRZB locus with OA at three joint sites [3, 5-7, 12-16]. Among these available studies, only three studies showed genotypic data and had an applicable HWE test for their samples [6, 7, 12]. For these studies, two SNPs were in HWE (P>0.05) in both the case and control samples (data not shown). Moreover, an analysis of genetic models was not performed because of limited genotyping data.

In the end, for SNP rs288326, the case and control sample sizes were 3,803 and 5,972 for hip OA, 2,305 and 2,514 for knee OA, and 2,761 and 1,463 for hand OA, respectively. For SNP rs7775, the case and control sample sizes were 3,849 and 8,843 for hip OA, 2,315 and 2,506 for knee OA, and 2,796 and 1,456 for hand OA, respectively. All of the subjects were of Caucasian descent (Tables 1 and 2).

SNP rs288326 and OA

Hip OA. No significant evidence of between-study heterogeneity was found among the group of allele-wise ORs in the combined samples (P=0.37), in females (P=0.78), and in males (P=0.40). Using a fixed-effect model, a trend of association was revealed between the patients and controls for the T-allele of rs288326 in females (Subtotal OR=1.12, 95% CI=0.99-1.28).
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### Table 1. Meta-analysis of the association studies between SNP rs288326 of FRZB and knee OA. Data are displayed from studies from all gender groups Combined (1.2.1), Female (1.2.2), and Male (1.2.3).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cases</th>
<th>Total</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
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<tr>
<td>1.2.1 Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evangelou(Iceland) 2009</td>
<td>201</td>
<td>2144</td>
<td>38.5%</td>
<td>1.14 [0.93, 1.41]</td>
</tr>
<tr>
<td>Kenholt(UK) 2008</td>
<td>89</td>
<td>718</td>
<td>17.6%</td>
<td>1.14 [0.84, 1.54]</td>
</tr>
<tr>
<td>Rodriguez.(Spain) 2007</td>
<td>76</td>
<td>542</td>
<td>16.8%</td>
<td>0.91 [0.66, 1.27]</td>
</tr>
<tr>
<td>Valdes(UK) 2007</td>
<td>155</td>
<td>1206</td>
<td>27.0%</td>
<td>1.16 [0.91, 1.48]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1764</td>
<td>1732</td>
<td>100.0%</td>
<td>1.11 [0.97, 1.26]</td>
</tr>
<tr>
<td>Total events</td>
<td>520</td>
<td>517</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.55, df = 3 (P = 0.67), P = 0%</td>
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<tr>
<td>Test for overall effect: Z = 1.56 (P = 0.12)</td>
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</tbody>
</table>

### Figure 1. Meta-analysis of the association studies between SNP rs288326 of FRZB and knee OA. Data are displayed from studies from all gender groups Combined (1.2.1), Female (1.2.2), and Male (1.2.3).

1.28, Z=1.75, P=0.08). However, no significant difference was identified in the combined samples (Subtotal OR=1.07, 95% CI=0.97-1.17, Z=1.32, P=0.19) and in males (Subtotal OR=0.89, 95% CI=0.68-1.18, Z=0.81, P=0.42) (Figure 1).

Knee OA. The fixed-effects model was utilized in the meta-analysis because no heterogeneity was observed in the three analysis groups (P=0.67, P=0.66, and P=0.80, respectively). The summary effect for SNP rs288326 was statistically significant in females (Subtotal OR=1.24, 95% CI=1.01-1.53, Z=2.02, P=0.04), but not in the combined samples (Subtotal OR=1.11, 95% CI=0.97-1.26, Z=1.56, P=0.12) and in males (Subtotal OR=0.96, 95% CI=0.71-1.28, Z=0.30, P=0.76) (Figure 2).

Hand OA. The result of the homogeneity test in the meta-analysis showed significant heterogeneity (X²=3.73, df=1, P=0.05), and no significant difference was found between patients and controls with the random-effects model (Subtotal OR=0.92, 95% CI=0.63-1.35, Z=0.42, P=0.68) (Supplementary Figure 1A).

SNP rs7775 and OA

Hip OA. No significant heterogeneity was detected in the combined samples (P=0.86), in females (P=0.23), and in males (P=0.29). Using a fixed-effect model, a non-statistically significant summary OR was found in three samples (Combined samples: Subtotal OR=1.05, 95% CI=0.94-1.17, Z=0.91, P=0.36; Females: Subtotal OR=1.10, 95% CI=0.95-1.28, Z=1.32, P=0.19; Males: Subtotal OR=0.72, 95% CI=0.50-1.05, Z=1.71, P=0.09) (Figure 3).

Knee OA. No significant evidence of between-study heterogeneity was found in three samples (P=0.55, P=0.12, and P=0.53, respectively), and no significant association was observed with a fixed-effect model in the combined samples (Subtotal OR=1.04, 95% CI=0.91-1.20, Z=0.59, P=0.55), in females (Subtotal OR=1.04, 95% CI=0.81-1.32, Z=0.29, P=0.77), and in males (Subtotal OR=0.99, 95% CI=0.69-1.40, Z=0.07, P=0.94) (Figure 4).

Hand OA. No significant difference was found (Subtotal OR=1.01, 95% CI=0.86-1.18, Z=0.13, P=0.89) between the patients and controls

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SNP rs7775 and OA

Hip OA. No significant heterogeneity was detected in the combined samples (P=0.86), in females (P=0.23), and in males (P=0.29). Using a fixed-effect model, a non-statistically significant summary OR was found in three samples (Combined samples: Subtotal OR=1.05, 95% CI=0.94-1.17, Z=0.91, P=0.36; Females: Subtotal OR=1.10, 95% CI=0.95-1.28, Z=1.32, P=0.19; Males: Subtotal OR=0.72, 95% CI=0.50-1.05, Z=1.71, P=0.09) (Figure 3).

Knee OA. No significant evidence of between-study heterogeneity was found in three samples (P=0.55, P=0.12, and P=0.53, respectively), and no significant association was observed with a fixed-effect model in the combined samples (Subtotal OR=1.04, 95% CI=0.91-1.20, Z=0.59, P=0.55), in females (Subtotal OR=1.04, 95% CI=0.81-1.32, Z=0.29, P=0.77), and in males (Subtotal OR=0.99, 95% CI=0.69-1.40, Z=0.07, P=0.94) (Figure 4).

Hand OA. No significant difference was found (Subtotal OR=1.01, 95% CI=0.86-1.18, Z=0.13, P=0.89) between the patients and controls

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Figure 2. Meta-analysis of the association studies between SNP rs288326 of FRZB and knee OA. Data are displayed from studies from all gender groups Combined (1.2.1), Female (1.2.2), and Male (1.2.3).
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with the fixed-effects model (Heterogeneity: P=0.72) (Supplementary Figure 1B).

For SNPs rs288326 and rs7775, the sensitivity analysis showed that the removal of any one of the studies did not significantly change the heterogeneity of the population in the above-described three analysis groups, and the P value of Z test was not significantly altered (data not shown). The results of publication bias tests for these SNPs are presented in Supplementary Figures 2 and 3. No significant evidence of publication bias was revealed within the analysis group.

Discussion

We performed a meta-analysis due to the concern that the individual studies may have insufficient power to detect the small effect of the genetic variants of FRZB on OA susceptibility in populations of Caucasian descent [1]. In the present study, we investigated the association of the SNPs rs288326 and rs7775 in the FRZB locus with OA at three joint sites using gender-diverse independent samples detailed in nine published references from six countries across two continents.

For SNP rs288326, the P value in females was 0.08, indicating a potential association with hip OA. A further investigation revealed that the P value of this SNP for the association tests was significant (0.04), which provides evidence for an association with knee OA in females. However, we failed to find an association between SNP rs288326 and hand OA in females. For SNP rs7775, no associated signal was detected between this SNP and OA at three joint sites in females, in males, or in the combined populations (P>0.05). To the best of our knowledge, these results are similar to those obtained in a meta-analysis previously performed by Evangelou et al. [14]. A comparison of our results with those reported by Evangelou et al. revealed that two SNPs were analysed in both studies.
Of these, neither the analysis performed by Evangelou et al. nor our analysis found an association between SNP rs7775 and OA. Interestingly, SNP rs288326 showed a significant association in female subjects with hip OA in the study conducted by Evangelou et al. (P=0.007), and a trend of association in our female samples with hip OA. In addition, this SNP showed a potential association in female subjects with knee OA in the study conducted by Evangelou et al. (P=0.06) and a significant difference in our female samples with knee OA. The slight difference for SNP rs288326 between the two studies may be due to the different sample sizes obtained based on the different inclusion criteria used [14].

Based on the above-described analysis, sex appears to play a small but important role in the pathogenesis of OA, at least in hip OA and/or knee OA. In fact, epidemiological observations provide evidence for an association between oestrogen deprivation and OA development, as demonstrated by the finding that the age-related increases in the incidence and prevalence of hip, knee, and hand OA were greater in males than in females prior to 50 years of age, but subsequently greater in females at older age [1, 25]. Spector et al. found that hysterectomy was significantly more prevalent among cases with OA than among controls [26, 27]. In a study of OA, hormone replacement therapy (HRT) was associated with trends toward lower prevalences of symptomatic hip and knee OA [28]. A longitudinal study in the Chingford population found that HRT offers significant protection against radiological knee OA compared with a control group [29]. Therefore, oestrogen deprivation at menopause may be associated with increases in the frequency of OA, and HRT due to menopause appears to decrease the incidence and progression of hip and knee OA [25].

The importance of Wnt/β-catenin signalling in bone and cartilage homeostasis was recently highlighted by the observation that animals deficient in Frzb (also called secreted Frizzled-related protein 3, SFRP3) [7, 30], present alterations in hip shape and articular cartilage properties. FRZB consists of two protein domains, a cysteine-rich domain responsible for Wnt/β-catenin interactions, and a netrin domain identified as a unique C-terminal basic domain in laminin-related modular proteins called netrins [30, 31]. The netrin domain is homologous to
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the N-terminal domain of tissue inhibitors of metalloproteinases, and the interactions between FRZB and matrix metalloproteinase 2 and 3 (MMP-2, MMP-3) have been demonstrated [30, 32]. Cytosolic β-catenin protein is the principal mediator of Wnt/β-catenin signalling [33]. In the activation of Wnt/β-catenin signals, β-catenin is dephosphorylated and accumulates in the cytoplasm, which leads to the subsequent translocation of the protein into the cell nucleus. Nuclear β-catenin interacts with DNA bound T-cell factor/lymphoid enhancer factor (TCF/LEF) proteins and thereby induces the expression of Wnt-target genes [34]. The upregulation of Wnt/β-catenin signalling may be deleterious for the joint cartilage because it induces the release of metalloproteases that promote cartilage catabolism and degradation. Wnt/β-catenin signals also have a stimulatory effect on bone formation [9]. Serine/threonine protein kinase GSK3β is a key negative regulator of β-catenin in the Wnt/β-catenin signalling pathway because it phosphorylates and promotes the degradation of β-catenin in quiescent cells [35]. Interestingly, 17β-estradiol (E2) can induce the phosphorylation of Akt at serine 473 and subsequently activate the phosphorylation of GSK-3β at serine 9, leading to the inhibition of GSK-3β activity, and the activation of Wnt/β-catenin signalling [36].

In summary, our study supports the hypothesis that FRZB may play a small but important role in the pathogenesis of OA in females, at least in females with hip OA or knee OA. Together, the results suggest that the function of FRZB (Wnt signals) may influence bone anabolism in females with OA, and that oestrogen receptor signalling may be an important regulator of bone mass and bone cell differentiation. However, the underlying mechanisms of FRZB in females with OA are not fully understood. Therefore, further gender-based studies are needed to elucidate the actual role of FRZB in the physiology of human bone and cartilage and in the pathogenesis of skeletal disorders.

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Disclosure of conflict of interest

None.

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References


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Supplementary Figure 1. Meta-analysis of the association studies between two SNPs of FRZB and hand OA. A: rs288326; B: rs7775.

Supplementary Figure 2. Funnel plot of the studies of rs288326 of FRZB and OA at three joint sites. A: Hip OA; B: Knee OA; C: Hand OA.
Supplementary Figure 3. Funnel plot of the studies of rs7775 of FRZB and OA at three joint sites. A: Hip OA; B: Knee OA; C: Hand OA.