The association of novel polymorphisms with Stress Fracture Injury in Elite Athletes: Further insight into the SFEA cohort.

Abstract

Objective: To determine, in conjunction with a wider investigation, whether 11 genetic variants in the vicinity vitamin D, collagen and Wnt signalling pathways were associated with stress fracture injury in the Stress Fracture Elite Athlete (SFEA) cohort.

Design: Genotype-phenotype association study.

Method: Self-reported stress fracture history and demographic data were recorded in 518 elite athletes, 449 male and 69 female (mean age 24.2±5.5 y) from the SFEA cohort. Elite athletes were assigned to two groups based on history stress fracture injury. Data were analysed for the whole cohort and sub-stratified in male only and multiple stress fracture cases. Genotype was determined using a proprietary fluorescence-based competitive allele-specific polymerase chain reaction assay.

Results: SOST SNP rs1877632 and VDR SNPs rs10735810 and rs731236 were associated with stress fracture (p<0.05). In the whole cohort, rs1877632 heterozygotes and homozygotes of the rare allele combined made up 59% of stress fracture sufferers in comparison to 46% in the non-stress fracture group (p=0.05). In the multiple stress fracture cohort, homozygotes of the rare allele of rs10735810 and rs731236 showed an association with stress fracture when compared to those homozygotes for the common allele combined with heterozygotes (p=0.03; p=0.01). No significant associations were shown in the other SNPs analysed (p>0.05).

Conclusions: These data suggest an important role for SOST SNP rs1877632 and VDR SNPs rs10735810 and rs731236 in the pathophysiology of stress fracture. This might be due to the
role of the SNPs in the regulation of bone remodelling and adaptation to mechanical loading, with potential implications for the prevention and treatment of stress fracture.

Keywords
Bone; Genetics; bone remodelling; SOST; Wnt Signalling.

Introduction
Stress fracture injuries are caused by mechanical loading that is applied in a rhythmic, repeated, sub-threshold manner (1), although the exact pathophysiology is not fully understood (2). The high volume, intensity and type of training that is required to be successful in elite sport makes athletes in body weight loaded sports particularly susceptible to sustaining this type of injury (3).

Stress fracture injuries account for 0.7%-20% of all athletic sports injuries (Bennell et al., 1997; Fredericson et al., 2006), cause significant discomfort, result in a prolonged loss of training time (Ranson et al., 2010) and can have a significant detrimental financial effect on the athlete and/or the club/organisation. The pathophysiology of stress fracture is complex (4) including, but not limited to risk factors such as: the female athlete triad (Barrack et al 2014), unaccustomed or excessive exercise (5), nutritional deficiencies (6), previous stress fracture (Tenforde et al., 2013) and abnormal bone mineral density (BMD) (7). To further compound the complexly related to the cause of injury, an individual’s genotype has also been associated with an increased susceptibility to stress fracture injury (8;9).

Initial analysis of genetic associations with stress fracture prevalence in the SFEA cohort has shown that single-nucleotide polymorphisms (SNPs) located in the vicinity of components of the RANK/RANKL/OPG signalling pathway, and the P2X7 receptor are associated with stress fracture injuries in elite athletes and military recruits (10;11). Other SNPs, which are thought
to control other bone regulatory pathways, in the vicinity of \textit{VDR} (12), \textit{GC} (13), \textit{COLIA1} (14) and \textit{Wnt} (15) have been associated with bone phenotypes, but any association with stress fracture in athletes is yet to be shown. SNPs in the vicinity of genes in the \textit{Wnt} signalling pathway, such as \textit{SOST}, are particularly strong candidates to be associated with stress fracture injury in an athletic population, due to their suggested role in the regulation of bone formation, and mechanotransduction (16). While \textit{VDR} SNPs have been shown to regulate of vitamin status, protein-protein interactions and mediate cell transcriptional factors (17).

Therefore, the aim of the present study was determine whether 11 SNPs in the vicinity vitamin D, collagen and \textit{Wnt} signalling pathways were associated with stress fracture injury in the Stress Fracture Elite Athlete (SFEA) cohort.

\textbf{Method}

A sample of 518 male (n=449) and female (n=69) elite athletes (table 1) were recruited to form the Stress Fracture in Elite Athletes (SFEA) cohort. Professional athletes were classified as elite due to their full time participation in sport; nonprofessional athletes were classified as elite if they regularly competed at international or national level. Each participant completed a statement of informed consent and a health status questionnaire, which was followed by an athletic status questionnaire detailing age and playing position if applicable. Participants with stress fracture injuries confirmed by medical imaging (\textit{e.g.}, magnetic resonance imaging or computed tomography), were classified as cases, while those who had never experienced a stress fracture injury, or reported symptoms of stress fracture, were classified as controls. Athletes that reported to have suffered a stress fracture injury without imaging confirmation and those who had experienced symptoms of stress fracture injury were withdrawn from the analysis (n=17). Participating elite athletes competed in various sports including, football (n = 218), cricket (n = 156), track and field (n = 67, running events n = 62), rowing (n = 13),
boxing (n = 2), tennis (n = 12), hockey (n = 26) and gymnastics (n = 7), with each sport having both stress fracture Cases and non-stress fracture Control participants. Elite athletes were mainly white Caucasian (83.2% in the stress fracture Cases and 79.9% in the non-stress fracture Controls). Ethical approval was granted by the Nottingham Trent University Ethical Review Committee, and each participant provided written informed consent prior to their involvement in the study.

**Sub-classifications**

Athletes were recruited from a range of sports (football, cricket, track and field, field hockey, gymnastics, rowing and boxing) and ranged from elite national class to Olympic medallists. Males, and individuals with multiple stress fractures were analysed in separate sub-classifications due to the size of the cohort (males n=449) and the greater genetic component that may be present in cases of multiple stress fracture injury.

**Procedures**

**Genotyping**

Saliva samples were collected, and genomic DNA was extracted with Norgen saliva collection and extraction kits (Norgen Biotek Corp., Saliva DNA Collection Kit, Thorold, Canada). All procedures were conducted in accordance with manufacturers guidelines.

SNPs were selected on the basis of their association with BMD and fragility fracture (12, 13, 14, 15, 17, 20, 23, 26, 28) and samples were genotyped by LGC genomics (Herts, UK), who were blinded to the clinical status (case or control) of the genotyped individuals, using proprietary fluorescence-based competitive allele-specific polymerase chain reaction assay.
**Statistical analysis**

Statistical analyses were performed using statistical package SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Student’s t test was used for analysis of descriptive variables. Pearson’s chi-squared ($\chi^2$) test was used to assess associations in genotype frequencies and to assess the observed frequency of each genotype with what would be expected in accordance with Hardy-Weinberg equilibrium. The Benjamini and Hochberg false discovery rate test was applied in order to account for multiple comparisons. Acceptable level of significance was classified as $p<0.05$.

**Results**

All SNPs were in accordance with Hardy Weinberg equilibrium (HWE; Supplementary table 1.) and none of the SNPs are in linkage equilibrium.

Stress fracture injury were recorded in 125 of the athletes that participated (Breakdown of stress fracture injuries by sport: Football n = 34, Cricket n = 42, running events n =27, Hockey n = 4, Rowing n = 5, Tennis n = 6, Boxing n = 1, gymnastics n = 4, field events n = 2).

Of the 11 SNPs investigated, three were significantly associated with stress fracture injury in one or more of the classifications (Table 2). Significant associations ($p<0.05$) with stress fracture injury were shown with $SOST$ and $VDR$ alleles. No differences were seen in the other SNPs investigated ($p>0.05$).

**Wnt Signalling**
SOST SNP rs1877632 heterozygotes were associated with stress fracture risk in the whole cohort, and cases of multiple stress fracture, when compared to homozygotes of the common allele (p<0.05; Table 3). Associations were also shown when heterozygotes were combined with homozygotes of the rare allele and compared to homozygotes of the common allele in the same classification (p<0.05). The frequency of the rare allele was greater in stress fracture sufferers in the whole cohort and cases of multiple stress fracture in comparison to non-stress fracture Control groups (p<0.05). No associations were shown when stress fracture occurrence was assessed with either LRP5 SNP rs3736228 or Wnt16 SNP rs3801387 genotypes (p>0.05).

Vitamin D SNPs

An association between VDR SNP rs10735810 and increased occurrence of multiple stress fracture injury was shown in homozygotes of the rare f allele, when compared to homozygotes of the common allele combined with heterozygotes (p<0.05; Table 3). Stress fracture occurrence was associated with the frequency of the rare allele in cases of multiple stress fracture and in male athletes (p<0.05). Those with at least one copy of the rare allele of rs731236 had a greater stress fracture occurrence in cases of multiple stress fractures (p<0.05). No significant associations were shown between VDR SNPs rs1544410 and rs79752321, GC SNPs rs7041 and rs4588, CTR SNP rs1801197 and COL1A1 SNP rs1800012 and stress fracture occurrence (p>0.05).

After correcting for multiple comparisons, using the Benjamini and Hochberg false discovery rate test, none of the associations above remained significant.
Discussion

The present study shows that three novel SNPs, in close proximity to SOST and VDR genes, were associated with stress fracture injury in elite athletes. The sclerostin encoding SOST SNP rs1877632, suggested to have a role in the functioning of the Wnt signalling pathway (15), was associated with stress fracture injury in elite athletes, and in cases of multiple stress fracture. The Wnt signalling pathway is a predominant regulator of bone metabolism, having a role in the mediation of the differentiation and longevity of osteoblasts, thus positively affecting bone formation (18). The purported role of VDR SNPs in the mediation of vitamin D status (17) and transcription activation characteristics of the VDR protein (19) may be causative factors in the aetiology of stress fracture injury.

The current study’s finding, shows for the first time that SOST SNP rs1877632 is associated with stress fracture injury and is in accordance with previous research showing associations between SOST SNPs and bone phenotypes including, sclerosteosis (20) and BMD at the lumbar spine (15) and femoral neck (17). That said, the A allele was associated with increased stress fracture risk in the present study, whereas previous research (15) has shown that A allele homozygotes were associated with increased BMD at the lumbar spine in a large cohort of elderly male participants. Dissimilarity in phenotypic and lifestyle characteristics of elite athletes and elderly males make it difficult to directly compare the findings; moreover a reduction in bone formation as a result of ageing has recently been suggested to be due to insufficient Wnt activity in response to mechanical loading (20), thus explaining a potential mechanistic reason for these contrasting associations. The mechanisms underlying the increased stress fracture risk in those with the variant A allele are not known, although allelic variation in SOST SNPs has been associated with serum sclerostin levels (21) and SOST null
mice have increased bone formation compared to their wild-type counterparts (23). It is possible that the rare allele of rs1877632 down regulates sclerostin expression, and, as sclerostin inhibits Wnt signalling (24), this could result in an increased susceptibility to stress fracture injury due to a reduction in bone formation.

The elite athletes in the present study were all competing in weight bearing sports, such participation been associated with high levels of sclerostin (25). The reason for the greater sclerostin concentrations in the athlete population could be due to the increased number of sclerostin expressing osteocytes located within an athletes’ bone mineral compared to a non-athletes (26). Currently, the effect of repeated mechanical loading has on SOST expression has been equivocal, but somewhat paradoxically, it has been shown that osteocyte SOST expression is down regulated during exercise (27). This suggests that there may be a mechanostransductive element of sclerostin mediation, and changes in levels of sclerostin act through a negative feedback loop to limit ‘excessive’ increases in bone formation as the result of high volume loading (26). Therefore, the habitual high volume and high magnitude mechanical loading that elite athletes encounter may result in transient increases in sclerostin concentrations (25) which, combined with the SNP rs1877632 genotype, may be the reason for the increase in stress fracture susceptibility.

VDR SNPs rs731236 and rs10735810 were significantly associated with stress fracture injury in the whole cohort, in males, and in cases of multiple stress fracture. The present data in elite athletes showing the variant allele of rs10735810 to be associated with stress fracture injury is in line with previous research in military personnel (9). The confirmation of this SNPs role in stress fracture injury in a separate population that experience different exercise demands,
may underline its important role in bone homeostasis and suggests the need for further investigation into the role of this SNPs in the repair and maintenance of bone tissue.

The variant allele of rs731236 was associated with stress fracture injury in cases of multiple stress fractures. Previous studies have shown the rare allele of rs731236 to be associated with decreased bone phenotypes consisting mainly of trabecular bone (12). Despite showing some agreement with previous research, the role of the VDR gene in bone homeostasis and stress fracture prevalence is contentious due to seemingly divergent findings. The absence of any VDR SNPs consistently associated with bone phenotypes in GWAS studies suggest the VDR SNPs could be a proxy for other functional SNPs, and/or the associations are restricted to certain populations (28). Also, the majority of the candidate gene studies focusing on VDR can be characterised by relatively small cohorts, which is particularly the case in those investigating the association with stress fracture prevalence (n=64, 9; n=192, 8), increasing the likelihood of false positives. Although the mechanisms by which VDR SNPs influence stress fracture risk remain unclear, the binding of the VDR to 1,25(OH)\(_2\)D induces absorption of calcium and phosphate for bone mineralisation and homeostatic metabolism (27). Mutations in VDR cause vitamin D-resistant rickets, characterised by increased risk of fracture and genu varum (Kristjansson et al., 1993), due to insufficient absorption of calcium and phosphate by the intestine rather than a direct influence on 1,25(OH)\(_3\)D\(_3\) concentrations (Ralston and de Crombrugghe, 2006). McClung and Karl (2010) suggest that allelic variation in polymorphisms within the VDR gene can increase the concentration of 1,25(OH)\(_2\)D, which may facilitate bone health and therefore reduce the risk of bone injury. VDR null mice have low bone mass characterised by hypocalcaemia, as well as elevated 1,25(OH)\(_2\)D\(_3\) levels, while VDR activity has been shown to influence RANKL expression (29), thus offering possible mechanistic explanations for the associations shown.
The number of SNPs showing an association with stress fracture injury in the SFEA cohort (10;11) and in previous research (8;9) highlights the likely complexity of stress fracture aetiology. Alterations in bone remodelling, and mechanotransductive responses to mechanical loading are two plausible explanations for the associations. GWAS have shown two main biological pathways to be related to bone mineral density and fragility fracture (28); the RANK/RANKL/OPG signalling pathway and the Wnt-signalling pathway. The majority of SNPs associated with stress fracture prevalence in the present study are either directly related to or have a downstream influence on these pathways, adding substantiation to their role as major regulatory pathways in bone health.

Although the SFEA cohort is the largest to be studied for genetic associations with stress fracture prevalence to date, it is not without its limitations. Whilst heterogeneity in ethnicity, sport type, training loads/stresses and environmental factors (e.g., nutrition/energy availability) are acknowledged as variable factors in the present study, these factors are currently unavoidable given the low number of elite athletes available to participate in such studies and the difficulty in recruiting participants due to perceived disruption of training schedules. Investigations into large numbers of single sport athletes is recommended to confirm our findings, however divergent playing styles and positions with sports make this a challenging undertaking. After correcting for multiple comparisons none of the findings remained significant. However, the SNPs were not randomly selected, and were selected based on existing evidence of a bone phenotypic association with known mechanisms supporting their potential role in stress fracture injury. The conservative nature and problems with conducting multiple comparison testing (30) increase the chances of a type two error.
occurring. We are confident that a type II error is unlikely to have occurred in the present study as the direction of the effect is consistent with previously published data related to bone phenotypes. If the findings were to have occurred by chance, effects in different directions would be expected. Further studies are needed to establish the underpinning mechanisms that explain how SNPs are associated with stress fracture injury as it is not clear how allelic variations influence bone adaptations and subsequently escalate stress fracture risk.

In conclusion, SNPs in the vicinity of VDR and the Wnt signalling pathways are associated with increased stress fracture prevalence in elite athletes. These data suggest an important role for SNPs in stress fracture susceptibility, possibility through the regulation of bone adaptation to mechanical loading.

Practical implications

- Elite athletes with particular genetic variances may have an increased susceptibility to stress fracture injury.
- Knowledge related to the SOST and VDR pathways and there implications for bone health may be of use to sport and exercise practitioners in the multifaceted management, treatment and prevention of stress fracture injury.
- The findings suggest that genetic regulators of bone adaptation to mechanical loading are key to stress fracture injury pathophysiology. This should be considered when managing an athlete’s training load.

Acknowledgments

The authors would like to thank all participants that took part in the study.

References


Table 1. Athlete characteristics for stress fracture and non-stress fracture groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stress fracture (n=125)</th>
<th>Non-stress fracture (n=376)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.7±7.5</td>
<td>24.4±5.4</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Other Mean ± SD</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age at stress fracture (y)</td>
<td>19.9±3.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.82±0.10</td>
<td>1.81±0.08</td>
<td>0.45</td>
</tr>
<tr>
<td>Body Mass(kg)</td>
<td>77.3±14.5</td>
<td>77.8±10.5</td>
<td>0.72</td>
</tr>
<tr>
<td>BMI</td>
<td>23.2±2.7</td>
<td>23.7±2.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Age at elite (y)</td>
<td>18.2±4.2</td>
<td>17±2.2</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Current Training (h/wk)</td>
<td>20±11.3</td>
<td>18.2±10.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Current alcohol consumption (units/wk)</td>
<td>5.2±6.9</td>
<td>4.1±6.1</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* was used to denote significance.
Table 2. Association of SNPs with stress fracture injury in elite athletes for the whole cohort, males and multiple stress fractures. (Gene) = closest gene; (p) = p value; (Homo) = homozygote for the variant allele; (Combined with Heterozygote) = homozygote for the variant allele combine with heterozygote; (AF) = allele frequency.

<table>
<thead>
<tr>
<th>RS Number</th>
<th>Location</th>
<th>Gene</th>
<th>Whole cohort (n = 518). P values</th>
<th>Males (n = 449). P values</th>
<th>Multiple Stress Fractures (n= 49). P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homo AF</td>
<td>Homo AF</td>
<td>Homo AF</td>
</tr>
<tr>
<td>rs1544410</td>
<td>12q13.11</td>
<td>VDR</td>
<td>0.46 0.44</td>
<td>0.27 0.39</td>
<td>0.61 0.84</td>
</tr>
<tr>
<td>rs731236</td>
<td>12q13.11</td>
<td>VDR</td>
<td>0.50 0.61</td>
<td>0.36 0.45</td>
<td>0.61 0.84</td>
</tr>
<tr>
<td>rs7975232</td>
<td>12q13.11</td>
<td>VDR</td>
<td>0.62 0.92</td>
<td>0.54 0.92</td>
<td>0.28 0.64</td>
</tr>
<tr>
<td>rs10735810</td>
<td>12q13.11</td>
<td>VDR</td>
<td>0.17 0.35</td>
<td>0.20 0.39</td>
<td>0.62 0.21</td>
</tr>
<tr>
<td>rs7041</td>
<td>4q12-q13</td>
<td>GC</td>
<td>0.50 0.84</td>
<td>0.99 0.71</td>
<td>0.84 0.74</td>
</tr>
<tr>
<td>rs4588</td>
<td>4q12-q14</td>
<td>GC</td>
<td>0.31 0.65</td>
<td>0.22 0.65</td>
<td>0.09 0.88</td>
</tr>
<tr>
<td>rs1801197</td>
<td>7q21.3</td>
<td>CTR</td>
<td>0.72 0.57</td>
<td>0.74 0.57</td>
<td>0.53 0.99</td>
</tr>
<tr>
<td>rs1800012</td>
<td>17q21.33</td>
<td>COL1A1</td>
<td>0.38 0.57</td>
<td>0.93 0.67</td>
<td>0.96 0.81</td>
</tr>
<tr>
<td>rs3801387</td>
<td>7q31.31</td>
<td>WNT16</td>
<td>0.30 0.30</td>
<td>0.45 0.30</td>
<td>0.29 0.62</td>
</tr>
<tr>
<td>rs1877632</td>
<td>17q11.2</td>
<td>SOST</td>
<td>0.05* 0.28</td>
<td>0.02* 0.28</td>
<td>0.12 0.11</td>
</tr>
<tr>
<td>rs3736228</td>
<td>11q13.4</td>
<td>LRP5</td>
<td>0.46 0.73</td>
<td>0.27 0.73</td>
<td>0.44 0.75</td>
</tr>
</tbody>
</table>

* depicts significant differences (p<0.05).
Table 3. Distribution of genotypes between stress fracture and non-stress fracture participants for SNPs showing significant associations in the whole cohort, males only or multiple stress fracture.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Whole cohort</th>
<th>Male</th>
<th>Multiple stress fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stress fracture N</td>
<td>Non-stress fracture N</td>
<td>Stress fracture N</td>
</tr>
<tr>
<td>VDR rs10735810</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>49</td>
<td>169</td>
<td>F</td>
</tr>
<tr>
<td>Ff</td>
<td>50</td>
<td>145</td>
<td>f</td>
</tr>
<tr>
<td>ff</td>
<td>20</td>
<td>38</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>352</td>
<td></td>
</tr>
<tr>
<td>VDR rs731236</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tt</td>
<td>13</td>
<td>46</td>
<td>t</td>
</tr>
<tr>
<td>Tt</td>
<td>61</td>
<td>168</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>40</td>
<td>142</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>356</td>
<td></td>
</tr>
<tr>
<td>SOST rs1877632</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>50</td>
<td>191</td>
<td>C</td>
</tr>
<tr>
<td>TC</td>
<td>59</td>
<td>131</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>13</td>
<td>38</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>VDR rs10735810</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>42</td>
<td>150</td>
<td>F</td>
</tr>
<tr>
<td>Ff</td>
<td>36</td>
<td>129</td>
<td>f</td>
</tr>
<tr>
<td>ff</td>
<td>15</td>
<td>33</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>312</td>
<td></td>
</tr>
<tr>
<td>VDR rs731236</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tt</td>
<td>9</td>
<td>43</td>
<td>t</td>
</tr>
<tr>
<td>Tt</td>
<td>48</td>
<td>149</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>32</td>
<td>126</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>318</td>
<td></td>
</tr>
<tr>
<td>SOST rs1877632</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>43</td>
<td>172</td>
<td>C</td>
</tr>
<tr>
<td>TC</td>
<td>42</td>
<td>114</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>11</td>
<td>33</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>319</td>
<td></td>
</tr>
<tr>
<td>VDR rs10735810</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>14</td>
<td>169</td>
<td>F</td>
</tr>
<tr>
<td>Ff</td>
<td>21</td>
<td>145</td>
<td>f</td>
</tr>
<tr>
<td>ff</td>
<td>12</td>
<td>38</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>352</td>
<td></td>
</tr>
<tr>
<td>VDR rs731236</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tt</td>
<td>3</td>
<td>46</td>
<td>t</td>
</tr>
<tr>
<td>Tt</td>
<td>31</td>
<td>168</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>9</td>
<td>142</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>356</td>
<td>0.01*</td>
</tr>
<tr>
<td>SOST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1877632</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>15</td>
<td>175</td>
<td>C</td>
</tr>
<tr>
<td>TC</td>
<td>28</td>
<td>143</td>
<td>T</td>
</tr>
<tr>
<td>TT</td>
<td>6</td>
<td>43</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>361</td>
<td></td>
</tr>
</tbody>
</table>

* depicts significant differences (p<0.05). Values have not been adjusted for multiple comparisons.