In a Population Based Association Study
IAPP Gene Variants Are Not Associated With
Bone Phenotypes in Elderly Women

Adam Mitchell1,2, Peter Grabowski2, Kristina Akesson1, Fiona E McGuigan1
1Lund University, Dept of Clinical Sciences Malmö and Skåne University Hospital, Sweden; 2University of Sheffield, Human Nutrition Unit, Department of Oncology and Metabolism, UK; 3Uppsala University, Dept of Surgical Sciences, Uppsala, Sweden

**Introduction**

Osteoporosis is a systemic skeletal disease characterized by reduced bone mineral density (BMD), leading to enhanced bone fragility, and a consequent increase in fracture risk (1). Amylin, also known as Islet Amyloid Polypeptide (IAPP), is co-secreted with insulin from pancreatic B-cells; stimulates bone formation and decreases bone resorption via its action on osteoblasts and osteoclasts (2,3) and also has the ability to reduce body weight (4,5). Osteoporosis is a complex, polygenic disorder (6) and the potential for amylin as a candidate gene is highlighted by the large number of diabetics who suffer from osteopenia (7).

**Patients and Methods**

We investigated the association between 4 single nucleotide polymorphisms (SNPs) in the *IAPP* gene and BMD, quantitative ultrasound (QUS) and fracture risk - taking into account body composition- in 75 year old women prospectively followed for up to 15 years (OPRA cohort; n=1003) (8). The association between *IAPP* genotype and BMD and QUS was analysed using a general liner model analysis of variance (GLM-ANOVA). The association between genotype and incident fractures was estimated using binary logistic regression and the association between genotype and incident fractures over 15 years of follow up was determined using a Cox’s regression model. All analyses were adjusted for the covariates weight and current smoking status. The OPRA study had >80% power to detect relative risks for fracture of at least 1.2.

**Table 1.** Association of *IAPP* SNP rs5484 and incident fracture in the OPRA cohort

<table>
<thead>
<tr>
<th>rs5484</th>
<th>Genotype</th>
<th>Without fracture (%)</th>
<th>With fracture (%)</th>
<th>P value</th>
<th>Odds ratio (OR)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporotic fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>34 (68)</td>
<td>16 (32)</td>
<td>.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>172 (52.6)</td>
<td>155 (47.4)</td>
<td>.06</td>
<td>1.8</td>
<td>.98</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>338 (54.3)</td>
<td>284 (45.7)</td>
<td>.08</td>
<td>1.7</td>
<td>.94</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Any type fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>29 (58)</td>
<td>21 (42)</td>
<td>.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>155 (47.4)</td>
<td>172 (52.6)</td>
<td>.21</td>
<td>1.5</td>
<td>.81</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>311 (50)</td>
<td>311 (50)</td>
<td>.32</td>
<td>1.4</td>
<td>.75</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

Reference category (rare homozygote, TT). P values calculated by binary logistic regression; adjusted for weight and current smoking status. "Any type" fracture sites include hip, vertebra, distal radius, shoulder, pelvis and proximal tibia fractures. "Osteoporotic" fracture sites include hip, vertebra, distal radius, shoulder, and pelvis.

**Results**

No association was found between any *IAPP* SNP and altered phenotypes of BMD, QUS or body composition.

For *IAPP* rs5484, heterozygous (CT) individuals and those homozygous for the major allele (CC) had a 1.8 and 1.7 times risk respectively of osteoporotic fracture compared to those homozygous for the minor allele (TT), however neither were significant (p=0.058 and p=0.080).

An increased risk of fracture was also apparent when measured over a 15 year follow up in those heterozygous (CT) subjects (HR 1.6 (CI: 0.962-2.67), P = 0.07) and homozygous for the major allele (CC) (HR 1.52 (CI: 0.919-2.52), P = 0.10) compared to those homozygous for the minor allele.

**References**


**Fig. 1** Association between *IAPP* SNP rs5484 and incident osteoporotic fracture over a 15 year follow up

**Fig. 2** Total body BMD (TB BMD) & femoral neck BMD (Fn BMD) by SNP rs5484 genotype