Title: IFNGR1 and TNFAIP3 in a Maltese family with a highly penetrant form of Osteoporosis

Abstract

Osteoporosis is a complex metabolic bone disease with a strong genetic component. It is characterised by decreased bone mineral density (BMD), deterioration of the microarchitecture of bone and an increased susceptibility to fractures.

A recent genome-wide linkage study reported an area of suggestive evidence of linkage to a marker at 6q23-24 in a Maltese family with a history of osteoporosis, with all members being affected (Vidal et al., 2007). Following fine mapping by the addition of 5 STR markers, evidence of linkage was still observed to the same marker (D6S1009). The peak multipoint parametric LOD score was of 1.9080 and a non-parametric LOD score (NPL) of 7.064 at D6S1009 under a dominant mode of inheritance with 90% penetrance and a phenocopy rate of 1% by Easylinkage v5.05 using GENEHUNTER v2.1. With the addition of more STRs, the putative susceptibility region was reduced from 18cM (127.cM to 145.75cM) to 7cM (136.31 to 143.59cM). The exons of genes within this region were sequenced to identify the potential gene or genes responsible for the observed area of linkage. Based on knowledge of bone physiology, interferon gamma receptor 1 (IFNGR1; 137.58cM) and tumour necrosis factor alpha-induced factor 3 (TNFAIP3; 138.22cM) were the two genes chosen for sequencing. Both genes are located approximately 1cM away from the indicated marker (138.78cM). The sequencing of two transcripts of IFNGR1 gene revealed a number of sequence variants. Amongst these were three variants (IFNGR1 transcript ENST00000367739) which were observed in all the family members. One of these variants is a known SNP (rs2234711) located in exon 1, whereas the other two variants are located in intron 1. Two other unknown variants (IFNGR1 transcript ENST00000367735), both in exon 7, were isolated in two affected family members. Sequencing of TNFAIP3 (transcript ENST00000237289) did not result in the identification of any variants. Analysis by allele-specific amplification is being performed to determine whether any of these sequence variants are common polymorphisms by establishing the frequency in a population of cord blood samples.