

Linkage of a Familial Form of Osteoporosis to Chromosome 5q34

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Introduction

Osteoporosis [MIM 166710] is a polygenic disease where multiple gene variants each having a small effect contribute to the individual's increased susceptibility to the disease, although a major gene might also be involved [1]. Family based linkage studies were performed by a number of investigators to try to identify loci that might contain genes responsible for an increased susceptibility to osteoporosis [2]. In this study a whole genome-wide scan was performed in an extended family with a highly penetrant form of osteoporosis

Aims of Study

To determine a locus and identify the gene that might be responsible for this form of osteoporosis.

Methodology

An extended family consisting of nine individuals with a known family history of osteoporosis was recruited. The phenotype was defined by lumbar and femoral z-scores calculated from measurements of bone mineral density by DEXA. Affected status was defined by z-scores of <-1.0 for a mild low BMD phenotype and a severe form with affected individuals being those individuals having a z-score of <-1.5. The pedigree is shown in Figure 1 with numbered individuals being those genotyped.

All participants signed an informed consent and answered a detailed questionnaire concerning medical history and lifestyle habits. This study was approved by the Research Ethics Committee of the Faculty of Medicine and Surgery, University of Malta.

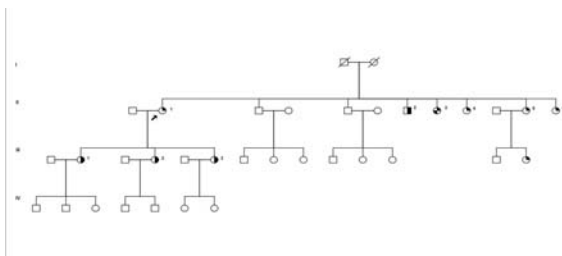


Fig 1. Family Pedigree: Phenotypic features as indicated: Black shading of right upper quadrant-low LS BMD; Shading right half – low LS and FN BMD; Shading of left lower quadrant – individual with fracture.

*LS – Lumbar Spine; FN – Femoral Neck

Methodology cont.

Four hundred STRs spread across the 22 autosomes and x-chromosome with average spacing of 8.63cM and heterozygosity of 0.77 were used for the initial scan.

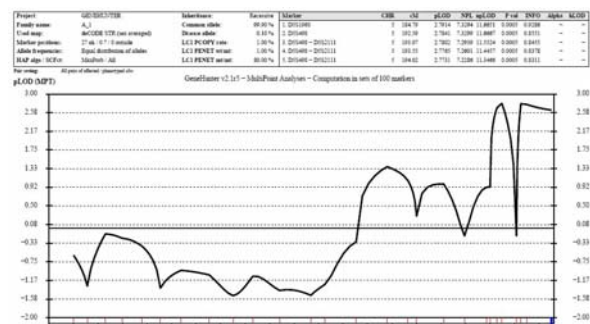
Multipoint parametric and non-parametric linkage analyses were performed by EasyLinkage v4.01 using GENEHUNTER v2.1. Parametric analysis was performed using variable penetrance for dominant and recessive models. Disease allele frequency used was of 0.001 and phenocopy rate of 1%.

Following the initial scan four additional markers were added in the indicated region on chromosome 5.

Results

Following the initial scan evidence of linkage was observed to marker D5S1960 where a non-parametric LOD score (NPL) of 7.17 (p=0.0005) was obtained. A LOD score of 2.78 was reached for the recessive mode of inheritance with 80% penetrance and phenocopy rate of 1%.

Following fine mapping a LOD of 2.79 and NPL of 7.33 (p=0.0005) were observed for the same marker 184.79cM from 5pter, for the recessive model.



Discussion

These results suggest that a major gene might be involved in the onset of this familial form of osteoporosis. In this study, suggestive linkage was observed to other chromosomal loci including 6q22, 9q21, 13q33 and 17q21, suggesting that other gene variants might also be involved. Further investigations of the FGF18 gene found in locus 5q34 are suggested.

Reference

[1] Cardon, et al. (2000) Evidence for a major gene for bone mineral density in idiopathic osteoporotic families. *JBRM* 15, 1132 – 1137.

[2] Huang et al. (2003) Searching for osteoporosis genes in the post-genome era, progress and challenges. *OI* 14, 701 – 715.