

A Genomewide Linkage Scan in a Family with a Highly Penetrant Form of Osteoporosis

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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 seventeen 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. The pedigree is shown in Figure 1 with numbered individuals being those genotyped.

This study was approved by the Research Ethics Committee of the Faculty of Medicine and Surgery, University of Malta.

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

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%.

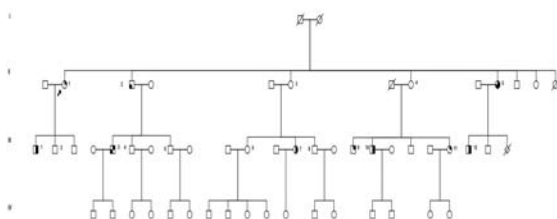


Fig 1. Family Pedigree: Phenotypic features as indicated: Black shading of right upper quadrant-low LS BMD; Shading right half – low LS and FN BMD; Shading of left lower quadrant – individual with fracture.

*LS – Lumbar Spine; FN – Femoral Neck

Results

Suggestive linkage was observed to marker D5S807 where a non-parametric LOD score (NPL) of 4.86 ($p=0.0156$) was obtained. A LOD score of 2.09 was reached for the dominant mode of inheritance with 90% penetrance and phenocopy rate of 1% (Figure 2).

This chromosomal region is being further investigated by increasing the number of markers at this interval.

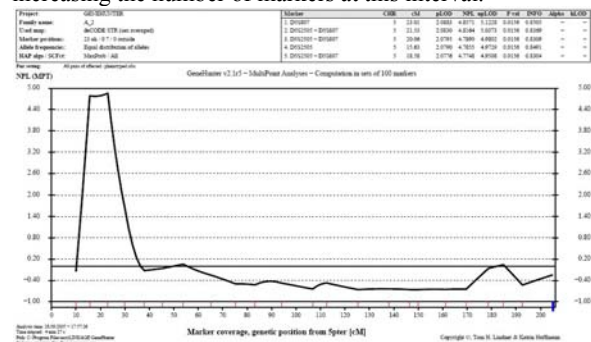


Fig 2. NPL Plot of Chromosome 5

An NPL of 5.75 and a LOD score of 1.21 ($p=0.0156$) for the dominant model was observed to region 11p13 while region 15q15 gave an NPL of 3.65 and LOD of 1.01 ($p=0.0172$) for a recessive mode of inheritance with 30% penetrance for the homozygous mutant.

Four additional markers were analysed at locus 11p13 where an NPL of 4.42 and LOD 1.62 ($p=0.0095$) were observed to marker D11S1392.

Discussion

These results suggest that a number of genes might be involved in the onset of this familial form of osteoporosis.

This study did not confirm loci that were previously linked with BMD such as 1p36, 11q12-13 and 20p12 where genes such as the TNFR2, LRP5 and BMP2 are known to be found [3 – 5].

Our results suggest that a number of genes might be involved in the onset of this familial form of osteoporosis. Such genes found in regions indicated by linkage will be further investigated by direct sequencing to identify any mutations that might be present.

Reference

- [1] Cardon, et al. (2000) Evidence for a major gene for bone mineral density in idiopathic osteoporotic families. *JBMR* **15**, 1132 – 1137.
- [2] Huang et al. (2003) Searching for osteoporosis genes in the post-genome era, progress and challenges. *OI* **14**, 701 – 715.
- [3] Devoto et al. (2001) Variance component linkage analysis indicates a QTL for femoral neck bone mineral density on chromosome 1p36. *Hum Mol Genet* **10**, 2447 – 2452.
- [4] Koller et al. (1998) Linkage of a QTL contributing to normal variation in bone mineral density to chromosome 11q12-13. *JBMR* **13**, 1903 – 1908.
- [5] Stykarsdottir et al. (2003) Linkage of osteoporosis to chromosome 20p12 and association to BMP2. *PLoS Biol* **1**, 1 – 10.