Susceptibility to Paget's disease of bone is influenced by a common polymorphic variant of Osteoprotegerin

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ABSTRACT

To clarify the role of the *TNFRSF11B* gene, encoding osteoprotegerin (OPG), in Paget's disease of bone (PDB), we studied *TNFRSF11B* polymorphisms in an association study of 690 UK subjects and in a worldwide familial study of 66 kindreds. We found that the *G1181* allele of *TNFRSF11B*, encoding lysine at codon 3 of OPG, predisposes to both sporadic and familial PDB.

Introduction: Paget's disease of bone (PDB) is a common disorder characterized by focal abnormalities of bone turnover. Genetic factors are important in the pathogenesis of PDB and studies have shown that inactivating mutations of the *TNFRSF11B* gene, encoding Osteoprotegerin (TNFRSF11B) cause the rare syndrome of juvenile Paget's disease. In this study we sought to determine whether polymorphisms of the *TNFRSF11B* gene contribute to the pathogenesis of classical PDB.

Methods: We screened for polymorphisms of the *TNFRSF11B* gene by DNA sequencing of the proximal promoter, coding exons and intron-exon boundaries in 20 PDB patients and 10 controls. Informative single nucleotide polymorphisms (SNPs), including a G1181C SNP, which predicts a lysine-asparagine substitution at codon 3 of the TNFRSF11B signal peptide and haplotypes, were related to the presence of PDB in 312 cases as compared with 378 controls, and to transmission of PDB in 140 affected offspring from 66 kindreds with familial PDB.

Results and Conclusions: The 1181G allele was significantly over-represented in the PDB patients (χ^2 =5.7, df=1, p=0.017, adjusted α=0.024), equivalent to odds ratio for PDB of 1.55 [95%CI: 1.11-2.16]. The distribution of *TNFRSF11B* haplotypes significantly differed in sporadic PDB cases and controls (χ^2 =30.2, df=9, p<0.001), due to over-representation of haplotypes containing the 1181G allele in cases. The family study showed that the most common haplotype containing the 1181G allele was transmitted more frequently than expected to 140 individuals with familial PDB (χ^2 =7.35, df=1, p<0.01), and the transmission disequilibrium was even more pronounced in a subgroup of 78 familial PDB patients who did not carry mutations of the *SQSTM1* gene (χ^2 = 8.44, df=1, p<0.005). We conclude that the G1181 allele of *TNFRSF11B*, encoding lysine at codon 3 of the TNFRSF11B protein, predisposes to the development of sporadic PDB and familial PDB that is not caused by *SQSTM1* mutations.

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