Associations of bone mineral density-related genes and marathon performance in elite European Caucasian marathon runners.

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Bone mineral density (BMD) is a multi-factorial phenotype determined by factors such as physical activity, diet and a sizeable genetic component. Athletic populations tend to possess higher BMD than non-athletes due to a larger volume of exercise completed. Despite this, some endurance runners can possess low BMD and/or suffer stress fractures, which can have negative impacts on their health and performance. Therefore, we hypothesised that elite endurance runners would possess a genotype associated with enhanced BMD and a reduced risk of injury, resulting in less training interruption and greater potential success. The study compared the genotype and allele frequencies of 5 genetic variants associated with BMD (*LRP5* rs3736228, *TNFRSF11B* rs4355801, *VDR* rs2228570, *WNT16* rs3801387, *AXIN1* rs9921222) in elite (men < 2 h 30 min, n = 110; women < 3 h 00 min, n = 98) and sub-elite (men 2 h 30 min – 2 h 45 min, n = 181; women 3 h 00 min – 3 h 15 min, n = 67) marathon runners with those of a non-athlete control population (n = 474). We also investigated whether marathon personal best time was associated with a more "advantageous" BMD genotype. Congruent with our hypothesis, the "risk" T allele for the *AXIN1* rs9921222 polymorphism was 5% more frequent in the control group than in sub-elites ($P = 0.030$, $\chi^2 = 4.69$) but no further differences were observed for this variant ($P \geq 0.083$, $\chi^2 \leq 4.98$). *WNT16* rs3801387 genotype frequency differed between athletes and controls ($P = 0.002$, $\chi^2 = 12.02$) and elites vs controls ($P = 0.008$, $\chi^2 = 9.72$), as did allele frequency. However, contrary to our hypothesis, it was the "risk" A allele that was ~5% more frequent in athletes than controls. Similarly, when combining data from all 5 variants, the athletes had a lower Total Genotype Score than controls (53.6 vs 65.7; $P \leq 0.001$), again suggesting greater genetic susceptibility to bone injury in athletes. Personal best times were not associated with genotype in any comparison. These results suggest that high-level endurance runners do not benefit from genetic resistance to bone injury and a resulting ability to sustain large training volumes, contradicting our hypothesis. High-level endurance runners appear to be at a higher risk of bone injury from a genetic perspective, for as yet unexplained reasons, although large inter-individual differences in genetic risk exist.