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Genome-Wide Analysis Identifies Locus Associated with Parathyroid Hormone Levels

Authors : Antonela Matana, Dubravka Brdar, Vesela Torlak, Marijana Popovic, Ivana Gunjaca, Ozren Polasek, Vesna Boraska Perica, Maja Barbalic, Ante Punda, Caroline Hayward, Tatijana Zemunik

Abstract : Parathyroid hormone (PTH) plays a critical role in the regulation of bone mineral metabolism and calcium homeostasis. Higher PTH levels are associated with heart failure, hypertension, coronary artery disease, cardiovascular mortality and poorer bone health. A twin study estimated that 60% of the variation in PTH concentrations is genetically determined. Only one GWAS of PTH concentration has been reported to date. Identified loci explained 4.5% of the variance in circulating PTH, suggesting that additional genetic variants remain undiscovered. Therefore, the aim of this study was to identify novel genetic variants associated with PTH levels in a general population. We have performed a GWAS meta-analysis on 2596 individuals originating from three Croatian cohorts: City of Split and the Islands of Korčula and Vis, within a large-scale project of "10,001 Dalmatians". A total of 7 411 206 variants, imputed using the 1000 Genomes reference panel, with minor allele frequency ≥ 1% and Rsq ≥ 0.5 were analyzed for the association. GWAS within each data set was performed under an additive model, controlling for age, gender and relatedness. Meta-analysis was conducted using the inverse-variance fixed-effects method. Furthermore, to identify sex-specific effects, we have conducted GWAS meta-analyses analyzing males and females separately. In addition, we have performed biological pathway analysis. Four SNPs, representing one locus, reached genome-wide significance. The most significant SNP was rs11099476 on chromosome 4 (P=1.15x10-8), which explained 1.14 % of the variance in PTH. The SNP is located near the protein-coding gene RASGEF1B. Additionally, we detected suggestive association with SNPs, rs77178854 located on chromosome 2 in the DPP10 gene (P=2.46x10-7) and rs481121 located on chromosome 1 (P=3.58x10-7) near the GRIK1 gene. One of the top hits detected in the main meta-analysis, intron variant rs77178854 located within DPP10 gene, reached genome-wide significance in females (P=2.21x10-9). No single locus was identified in the meta-analysis in males. Fifteen biological pathways were functionally enriched at a P<0.01, including muscle contraction, ion homeostasis and cardiac conduction as the most significant pathways. RASGEF1B is the guanine nucleotide exchange factor, known to be associated with height, bone density, and hip. DPP10 encodes a membrane protein that is a member of the serine proteases family, which binds specific voltage-gated potassium channels and alters their expression and biophysical properties. In conclusion, we identified 2 novel loci associated with PTH levels in a general population, providing us with further insights into the genetics of this complex trait.

Keywords : general population, genome-wide association analysis, parathyroid hormone, single nucleotide polymorphisms.
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