Functional characterization of the 12p12.1 renal cancer-susceptibility locus implicates BHLHE41

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Résumé en anglais	Genome-wide association studies have identified multiple renal cell carcinoma (RCC) susceptibility loci. Here, we use regional imputation and bioinformatics analysis of the 12p12.1 locus to identify the single-nucleotide polymorphism (SNP) rs7132434 as a potential functional variant. Luciferase assays demonstrate allele-specific regulatory activity and, together with data from electromobility shift assays, suggest allele-specific differences at rs7132434 for AP-1 transcription factor binding. In an analysis of The Cancer Genome Atlas data, SNPs highly correlated with rs7132434 show allele-specific differences in BHLHE41 expression (trend P value=6.3 × 10(-7)). Cells overexpressing BHLHE41 produce larger mouse xenograft tumours, while RNA-seq analysis reveals that constitutively increased BHLHE41 induces expression of IL-11. We conclude that the RCC risk allele at 12p12.1 maps to rs7132434, a functional variant in an enhancer that upregulates BHLHE41 expression which, in turn, induces IL-11, a member of the IL-6 cytokine family
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