Dokumenttyp: journal article

Autor(en) des Beitrags:
Painter, Jodie N, JN; O’Mara, Tracy A, TA; Batra, Jyotsna, J; Cheng, Timothy, T; Lose, Felicity A, FA; Dennis, Joe, J; Michailidou, Kyriaki, K; Tyrer, Jonathan P, JP; Ahmed, Shahana, S; Ferguson, Kaltin, K; Healey, Catherine S, CS; Kaufmann, Susanne, S; Hillman, Kristine M, KM; Walpole, Carina, C; Moya, Leire, L; Pollock, Pamela, P; Jones, Angela, A; Howarth, Kimberley, K; Martin, Lynn, L; Gorman, Maggie, M; Hodgson, Shirley, S; National Study of Endometrial Cancer Genetics Group (NSECG); CHIBCHA Consortium; De Polanco, Ma Magdalena Echeverry, MM; Sans, Monica, M; Carracedo, Angel, A; Castellvi-Bel, Sergi, S; Rojas-Martinez, Augusto, A; Santos, Erika, E; Teixeira, Manuel R, MR; Carvajal-Carmona, Luis, L; Shi, Xiao-Ou, XO; Long, Jirong, J; Zheng, Wei, W; Xiang, Yong-Bing, YB; The Australian National Endometrial Cancer Study Group (ANECS); Montgomery, Grant W, GW; Webb, Penelope M, PM; Scott, Rodney J, RJ; McEvoy, Mark, M; Attia, John, J; Holliday, Elizabeth, E; Martin, Nicholas G, NG; Nyholt, Dale R, DR; Henders, Anjali K, AK; Fasching, Peter A, PA; Hein, Alexander, A; Beckmann, Matthias W, MW; Renner, Stefan P, SP; Dörk, Thilo, T; Hillemanns, Peter, P; Dürst, Matthias, M; Runnebaum, Ingo, I; Lambrechts, Diether, D; Coenegrachts, Lieve, L; Schrauwen, Stefanie, S; Amant, Frederic, F; Winterhoff, Boris, B; Dowdy, Sean C, SC; Goode, Ellen L, EL; Teoman, Attila, A; Salvesen, Helga B, HB; Trovik, Jone, J; Njolstad, Tormund S, TS; Werner, Henrica M J, HM; Ashton, Katie, K; Proietto, Tony, T; Otton, Geoffrey, G; Tzortzatos, Gerasimos, G; Mints, Miriam, M; Tham, Emma, E; RENDOCAS; Hall, Per, P; Czene, Kamila, K; Liu, Jianjun, J; Li, Jingmei, J; Hopper, John L, JL;
Fine-mapping of the HNF1B multicancer locus identifies candidate variants that mediate endometrial cancer risk.

Common variants in the hepatocyte nuclear factor 1 homeobox B (HNF1B) gene are associated with the risk of Type II diabetes and multiple cancers. Evidence to date indicates that cancer risk may be mediated via genetic or epigenetic effects on HNF1B gene expression. We previously found single-nucleotide polymorphisms (SNPs) at the HNF1B locus to be associated with endometrial cancer, and now report extensive fine-mapping and in silico and laboratory analyses of this locus. Analysis of 1184 genotyped and imputed SNPs in 6608 Caucasian cases and 37 925 controls, and 895 Asian cases and 1968 controls, revealed the best signal of association for SNP rs11263763 (P = 8.4 × 10(-14), odds ratio = 0.86, 95% confidence interval = 0.82-0.89), located within HNF1B intron 1. Haplotype analysis and conditional analyses provide no evidence of further independent endometrial cancer risk variants at this locus. SNP rs11263763 genotype was associated with HNF1B mRNA expression but not with HNF1B methylation in endometrial tumor samples from The Cancer Genome Atlas. Genetic analyses prioritized rs11263763 and four other SNPs in high-to-moderate linkage disequilibrium as the most likely causal SNPs. Three of these SNPs map to the extended HNF1B promoter based on chromatin marks extending from the minimal promoter region. Reporter assays demonstrated that this extended region reduces activity in combination with the minimal HNF1B promoter, and that the minor alleles of rs11263763 or rs8064454 are associated with decreased HNF1B promoter activity. Our findings provide evidence for a single signal associated with endometrial cancer risk at the HNF1B locus, and that risk is likely mediated via altered HNF1B gene expression.