

TCF3/E2A (19P13.3) IS A NOVEL HODGKIN LYMPHOMA SUSCEPTIBILITY LOCUS; A META-GWAS STUDY FROM THE INTERLYMPH HODGKIN LYMPHOMA CONSORTIUM

Van den Berg A1, Cozen W*, Li D*, Timofeeva M*, Diepstra A*, Hazelet D*, Delahaye-Sourdeix M*, Edlund CK*, Rostgaard K, Van Den Berg DJ, Glaser SL, Robison LL, Mack TM, Ghesquieres H, Salle G, Bhatia S, Strong LC, Hwang AE, Nieters A, Smedby K, de Sanjose S, Cortessis VK, Lightfoot T, Roman E, Becker N, Foretova L, Benavente Y, Maynadie M, Visser L, Veenstra RN, Staines A, Cocco PL, Boffetta P, Kiemeny L, Lake A, Montgomery D, Slager SL, Cerhan JR, Gallagher A, Taylor GM, Brennan P, Conti DV&, Coetzee GA&, Onel K&, Jarrett RF&, Hjalgrim H&, McKay JD&.

**Co-first authors, &Co-Last authors. Presented on behalf of the Hodgkin lymphoma working group of the InterLymph consortium. 1Department of Pathology and Medical Biology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands*

Hodgkin lymphoma (HL) is known to have a strong genetic susceptibility component, with a highly increased risk in co-twins of patients. Currently reported GWAS's identified several HLA and non-HLA risk loci. In order to identify additional variants associated with HL, we performed a meta-analysis of three HL GWAS studies followed by a validation study. 1,810 cases and 7,879 controls, all of European descent, were included in the meta analysis. Promising variants were tested in an independent set of 1,163 cases and 2,580 controls. We noted strong associations in HLA, with 564 genetic variants presenting with $P < 10^{-4}$, and in non-HLA loci, *i.e.* REL, PVT1 and GATA3, consistent with previous publications. In addition, we identified a novel variant at 19p13.3 that was associated with risk of HL (rs1860661; odds ratio [OR]= 0.81, 95% confidence interval [95% CI]= 0.76-0.86, $P_{\text{combined}} = 3.5 \times 10^{-10}$). This SNP is located in intron 2 of the TCF3/E2A gene, a key regulator of B-cell lineage commitment. In silico analysis indicates that rs1860661 is located in a genomic region with an open chromatin structure, active histone marks and a ZBTB7A/LRF transcription factor binding motif. The protective minor G allele maps to a ZBTB7A binding motif, which is disrupted by the major A allele. Two additional variants highly correlated with rs1860661, rs10413888 ($r^2=0.90$) and rs8103453 ($r^2=0.89$), are within an E2F1 and another ZBTB7A/LRF binding motif, respectively. Analysis of TCF3 expression levels in LCL cell lines of 31 genotyped individuals revealed a trend towards lower levels of expression for AA individuals, intermediate levels for AG individuals and the highest levels for GG individuals. This supports a direct functional and protective effect of the rs1860661 SNP by enhancing binding of ZBTB7A and as a result increasing TCF3/E2A expression levels. Thus, this meta-analysis identified a novel association with TCF3/E2A and supports previously reported susceptibility associations with SNPs in other HLA and non-HLA genes. Because the allele predicted to have enhanced TCF3/E2A expression is protective for HL, we suggest that TCF3/E2A functions as a tumor suppressor gene for HL, probably via promotion and/or maintenance of the B-cell phenotype.