

Genetics Working Group Summary

InterLymph Annual Meeting

April 15-16, 2010, Bethesda, MD

Genetic studies

Candidate genes

As a follow-up to a recent pooled genetic study of immunity-related genes published in the *American Journal of Epidemiology*, the Genetics Working Group met at the 2011 meeting to discuss the analysis of the 80 candidate SNPs nominated by InterLymph members that were genotyped by three large Interlymph study groups (Epilymph, Canada and the Mayo Clinic) for validation. It was agreed that to keep in line with a timely and current report, Dr. Skibola's group would conduct the pooled analysis of the data and that a manuscript of the findings would be prepared in the coming months. The pooled analysis of the data is currently underway. Further independent validations will be considered, but given the current environment and the urgency of completing and publishing a "candidate gene study" in the world of GWAS, it was agreed that a quick turnaround was in the best interest of InterLymph members.

Genome-wide association studies (GWAS)

Dr. Skibola presented findings from her group's GWAS that included validation genotyping by all InterLymph member studies but one. Through these studies, a new susceptibility locus in the major histocompatibility complex (MHC) was identified for follicular lymphoma (FL). This is the second independent genetic risk locus for FL that Dr. Skibola's group identified in the MHC, highlighting the important role of the MHC region in susceptibility to FL. These findings will be published online in *Nature Genetics* on July 18th.

Briefly, Dr. Skibola's group carried out a GWAS with validation involving InterLymph member studies in a sample of 1,465 FL cases and 6,958 controls of European descent. The researchers found two SNPs, rs10484561 and rs7755224, were associated with two-fold increased risks of developing FL (combined p -values= 1.12×10^{-29} , 2.00×10^{-19}). Tag SNP genotyping suggested that MHC Class 2 extended haplotypes may be involved in the pathogenesis of FL. Samples from two other subtypes of NHL (diffuse large B-cell lymphoma [DLBCL] and chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]), were also part of the GWAS. Researchers found that the same SNPs did not significantly influence the risk of developing these DLBCL and CLL/SLL. Dr. Skibola's study suggested that the influence of genetic variation in the MHC region in DLBCL or CLL/SLL was not as significant as for FL, and that the genetic basis for these NHL subtypes may be vastly disparate.

Gene-environment studies

Genetic data from the original 12 SNPs genotyped within InterLymph has been sent to the InterLymph Data Coordinating Committee. These data are being crossed with environmental variables such as sunlight, BMI, reproductive factors, history of atopy, transfusions, hepatitis C infection, and other factors. Genetic data from the 80 SNPs currently being genotyped by InterLymph investigators will also be available for future GXE analyses.

GWAS initiative

Nat Rothman is leading an InterLymph GWAS effort to identify global and subtype specific genetic susceptibility loci for NHL. Representatives from member studies met to discuss the project including future studies that could be followed up post-GWAS. Groups that have already conducted genome scans (UCSF/UCB, SCALE and the Mayo) will send NCI their datasets to be included in the pooled analyses.