Talk #1. Transancestral mapping and genetic load in systemic lupus erythematosus

Thursday
May 31, 2018
9:00am to 10:00am
The Hospital for Sick Children
Daniels Hollywood Theatre
Room 1246, First Floor, Black Wing
555 University Avenue, Toronto, ON

Abstract:
Systemic lupus erythematosus (SLE) is an autoimmune disease with marked gender and ethnic disparities. We report a large transancestral association study of SLE using Immunochip genotype data from 27,574 individuals of European (EA), African (AA) and Hispanic Amerindian (HA) ancestry. We identify 58 distinct non-HLA regions in EA, 9 in AA and 16 in HA (~50% of these regions have multiple independent associations); these include 24 novel SLE regions (P<5x10^-8), refined association signals in established regions, extended associations to additional ancestries, and a disentangled complex HLA multigenic effect. The risk allele count (genetic load) exhibits an accelerating pattern of SLE risk, leading us to posit a cumulative hit hypothesis for autoimmune disease. Comparing results across the three ancestries identifies both ancestry-dependent and ancestry-independent contributions to SLE risk. The majority of the SLE-risk alleles show increased European ancestry, suggesting increased likelihood of EA origins. Our results are consistent with the unique and complex histories of the populations sampled, and collectively help clarify the genetic architecture and ethnic disparities in SLE.

Talk #2. Predictive ability of SLE genetic risk factors varies across ethnicities

Friday
June 1, 2018
12:00pm to 1:00pm
Mount Sinai Hospital
Main Auditorium, 18th Floor
600 University Avenue, Toronto, ON

Abstract:
Systemic lupus erythematosus (SLE) exhibits marked ethnic disparities. The SLE Immunochip Consortium’s transancestral association study of SLE (27,574 individuals of European (EA), African (AA) and Hispanic Amerindian (HA) ancestry) raised the number of common risk variants to >100 (Langefeld 2017). Previously, we proposed the cumulative hit hypothesis, where the cumulative effect of individual risk loci is greater than if each locus acted independently. Here, we explore the joint contribution of SLE-susceptibility loci, how it varies by ethnicity, and whether there are distinct genetic risk profiles. Specifically, penalized regression (i.e., Lasso regression) and support vector machines identified EA risk SNPs that maximally predict SLE status in EA. We then applied these predictions to an independent set of EA, AA and HA. The odds ratio comparing lowest versus highest 10% of risk allele count was ~30, ~6, and ~3 for EA, HA and AA, respectively, showing EA risk loci were not highly predictive of SLE risk in HA and AA. Lasso regression identified 51 risk alleles that maximally predicted SLE in EA, and a factor analysis identified seven uncorrelated risk profiles (one driven by HLA alleles and six by non-HLA loci). Using predicted probabilities from the lasso in EA, the area under the ROC curve was 0.75 for EA, 0.72 for HA, and 0.60 for AA. Thus, EA SLE risk loci are highly predictive in EA, modestly predictive in HA, and weakly predictive in AA. We posit that the genetic architecture of SLE in AA is meaningfully different from EA and HA, merit increased study, and will require ethnicity-informed treatment strategies.