Research Summary

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My primary research interests are in population, evolutionary, and statistical genetics, with a particular emphasis on the study of immune-related genes. The objectives of my research are to improve our understanding of the global distribution of polymorphism in immune-related genes, the selective and demographic forces that have shaped these distributions, and the implications of these complex genetic systems for anthropological, disease association, and transplantation studies.

The genes in the human leukocyte antigen (HLA) region, located within the human major histocompatibility complex on chromosome 6, are highly polymorphic (over 400 alleles for some genes), control several functions in the immune response, and influence susceptibility to over 200 diseases. The killer-cell immunoglobulin-like receptor (KIR) genes, located on chromosome 19, encode both activating and inhibitory receptors, which are expressed on natural killer (NK) cells and a subset of T cells, and regulate NK cell activity. Certain HLA alleles serve as ligands for NK cells, a key component of the innate immune system. That is, the KIR receptors recognize particular motifs of HLA molecules and the presence/absence of the HLA ligand for a particular KIR determines whether or not it is functional. The extreme variability at HLA and KIR loci is thought to provide protection against a wide variety of pathogens. Specific polymorphisms at these loci have been associated with susceptibility to, and protection from, various auto-immune and infectious diseases, as well as certain cancers. Several functional and population studies have indicated that the extensive variation at these genes is due to natural selection.

A major focus of my research is the study of single- and multi-locus variation at both the allele and amino acid levels in population and patient groups, using non-HLA data to place HLA results in the context of whole genome-level variation and aid in the detection of non-HLA genes involved in disease. Through the PyPop software project I have developed tools to test whether the effect of selection can be attributed to specific amino acid sites or combinations of sites, in order to determine the functional level (serological, molecular, amino acid) at which selection is acting in different populations.

A key challenge in the interpretation of genetic polymorphism data is that natural selection and demographic history can have similar effects on frequency distributions, making it difficult to differentiate between the effects of these processes. I have addressed this issue at both the design and analysis stages in previous studies (Meyer, Single et al., 2006; Single, Martin et al., 2007) by developing resampling and other empirical methods to allow comparisons of results obtained for HLA/KIR to those for non-HLA/KIR data sets, which presumably have not been shaped by the same selective processes as the HLA/KIR loci and therefore serve as genomic controls, offering information on the demographic history of the populations. We are now using the database and analysis tools that we have developed to search for candidate genes to type in disease cohorts that may interact epistatically with HLA and/or KIR based on the population-level findings.

A secondary line of research is in the area of medical biostatistics focusing on outcomes in cancer research. In this capacity I collaborate with oncologists at UVM on studies that address utilization and practice patterns, outcomes, and quality measures. I have remained active in this research because of the opportunity to contribute at all levels to these important studies: database and study design, research hypotheses, analyses, and writing.

Increasing our knowledge of population level polymorphism and linkage disequilibrium (the non-random association of allelic variants at two or more genes) patterns in the HLA and KIR regions is critical to the study of evolutionary patterns, identification of selection events, evaluation of HLA/KIR associations with disease, research on vaccine design (e.g., HIV), and understanding the mechanisms by which disease-predisposing genes can become relatively common in a population. Knowledge of HLA and KIR variation in different ethnic groups is also vitally important in hematopoietic stem cell transplantation. Elucidating the patterns of association between and among the unlinked KIR and HLA loci using population-based approaches is an important consideration for these loci, which have multiple homologues that share functional activity, because it can aid in identifying the actual disease locus among several candidates.