Genomics and Genetics of Immunoglobulin in the Rat

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Traits reflect interaction between genetic and environmental variation. Immunoglobulin genes encode antibodies forming a host defense mechanism capable of adapting to a limitless range of environmental inputs. Genetic variation in antibody formation arising both in the immunoglobulin genes and in the genes involved in regulating antibody production are central to the formation of pathogenic antibodies in autoimmune disease. Here we report annotation of the GRCr8 immunoglobulin locus and its validation and extension by alignment to the genome assembly of heavy chain transcripts obtained using PacBio Iso-Seq methods. Comparison of the structure of this locus between GRCr8 and other high quality inbred rat genome assemblies reveals remarkable variation. In the SHR-A3 strain the locus is ~4Mb in length, while in SHR-B2 the locus has expanded to ~8Mb. Comparison of the two loci reveals a complex pattern of expansion by duplication and genomic loss from this locus. We wish to understand the genetic effects arising from such variation. However, this task is made challenging by the fact that antibodies exist to adapt to varying environmental inputs which make discerning genetic from environmental effects on antibody gene expression challenging. In order to isolate purely genetic effects arising from the SHR-A3 and SHR-B2 loci we have constructed a congenic line in which the genetic background is SHR-A3, but in which one parental haplotype at the heavy chain locus is SHR-A3 and the other is SHR-B2. Such individuals will have a single environmental input that acts on antibody formation which allow purely genetic differences arising from the two immunoglobulin haplotypes to be observed. Trans-acting effects will be limited to those produced in the SHR-A3 genetic background. We illustrate how genetic variation in coding sequences of the heavy chain genes allow us to assess heritable effects on antibody formation using a gene expression approach.