Aberrant gene expression can play a large part in complex disease. **Professor Greg Gibson**'s study at the Center for Integrative Genomics at Georgia Tech uses advanced statistical methodologies and evolutionary comparisons to refine the identity of a small number of sequence variants that are most likely to regulate expression of genes in the immune system. His team then confirms their role in inflammatory autoimmune disease, in part using genome engineering technologies to experimentally confirm their function.

**eQTL mega-analysis – a tool for functional assessment of multi-enhancer gene regulation**

Professor Gibson’s work harnesses the power of expression quantitative trait loci (eQTL), which are regions of the genome containing DNA sequence variants that influence the expression level of one or more genes. eQTL has emerged as an important tool for unravelling the relationship between genetic risk factors and disease or clinical phenotypes. Whereas most sequence variants have no effect on gene expression, there are some that do. A major current focus in the field is to fine-map the functional sites within loci that have been identified by studying genetically different individuals. In order to investigate these further, it is necessary to compare individual genotypes with the level of gene expression observed. Statistical approaches are subsequently used to test whether a particular sequence variant has a marked effect on the expression of a particular gene. This project also incorporates evolutionary insight into the fine mapping, since conservation across species is the best signature of functional importance.

**THE CHANGES IN GENE EXPRESSION THAT CAUSE DISEASE**

Many of the associations between genetics and risk of disease are thought to be the result of regulation of gene expression; that is when, where and at what level the relevant genes are expressed. Particularly in recent years, whole exome sequencing (sequencing all of the protein-coding genes in a genome), has demonstrated that there is a burden of rare variants in individuals with a variety of neurological and developmental conditions. Given that approximately 90% of disease-associated variants can have regulatory functions, it is reasonable to hypothesise that these variants may be ones that cause misregulation in individuals with common chronic diseases or congenital abnormalities.
This resource can be used to understand the genetic mechanisms behind some of our most rare and complicated diseases.