Title of the project: Sequence-Based Association Study Using Biological Features

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Principal Investigator: O. Libiger

Co-investigators: M. Červinka

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Summary of 2009 results

Title of the presentation: DNA Sequence-based Analysis Via Regression Modeling that Leverages Genomic Annotations.

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Recent whole genome association studies (GWAS) yielded unequivocal statistical associations between a number of common single nucleotide polymorphisms (SNPs) and a variety of diseases. However, each of these SNPs only accounts for a very small proportion of the incidence of the associated disease. Possible explanations are that structural variants or rare single nucleotide variants not captured by the variation assayed in the GWAS are important genetic determinants of complex diseases. It could also be the case that many loci contribute to the manifestation of a disease either in isolation or through epistatic interactions. We devised a novel approach to assessing associations between groups of variants and disease based on high-dimensional regularized regression models. Our approach can accommodate the analysis of the full range of genomic variations identified by DNA sequencing assays, and addresses locus heterogeneity and interaction effects by leveraging genomic annotations for collections of variations. We have assessed the utility of the method through analytical and simulation studies and showcase its application in a number of empirical studies including studies of complete mtDNA sequences obtained on individuals with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as well as two genes sequenced in their entirety for a study of obesity.

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