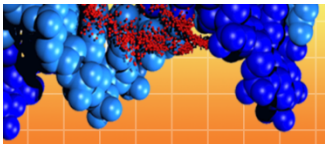

CENTER FOR BIOINFORMATICS & COMPUTATIONAL BIOLOGY

BIOINFORMATICS 2016 SPRING SEMINAR SERIES

Hosted by: Department of Computer and Information Sciences,
Department of Electrical and Computer Engineering &
Center for Bioinformatics and Computational Biology
http://bioinformatics.udel.edu/Seminars/Current

NOTE: Change of Time / Date / Venue

THURSDAY, April 7, 2016

2:00 - 3:15pm

Willard Hall 007

Tying Genome Variation in Regulatory Regions to Neurodegenerative Phenotypes

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ABSTRACT: The use of exome sequencing (genome-wide sequencing enriched to cover exons) to identify disease-causing genomic changes has focused to date on the interpretation of variants within protein coding regions. We have developed computational and statistical methods to use exome data to examine introns, promoters and untranslated regions (UTRs) in the context of disease cohorts compared with general populations including the 1000 Genomes (1000G), Exome Sequencing Project (ESP), and the Exome Aggregation Consortium (ExAC) and control populations in the Alzheimer's Disease Sequencing Project. These methods were applied to 333 patients of European descent and 12 patients of African descent with progressive optic nerve degeneration due to primary open angle glaucoma (POAG), 13 patients of Taiwanese descent with migraine, and 32 patients of mixed descent born with congenital glaucoma. All patients analyzed have first-degree relatives with disease, thus increasing the likelihood of finding genetic explanations for disease. Relationships between sequenced individuals, if any, are known. The genetics of POAG, migraine, and congenital glaucoma are complex; to date, no single causative genomic variant has been established as causing any of these diseases. Our analysis of regulatory regions provides new insights for further functional study through targeted experiments.

In the case of POAG, genome-wide sequencing of exons from protein coding and non-coding genes in 285 patients revealed ~50 associated SNP sites within ~30 genes. Of these, two-thirds were located in introns or untranslated regions (UTR). To rank and prioritize genes and generate hypotheses about molecular mechanisms disrupted by associated variant sites, mRNA and small RNA (microRNA) were sequenced from ocular tissues relevant to the disease. Intronic SNPs were assessed for impact on alternative splice isoforms, and UTR SNPs were assessed for impact on microRNA binding. An additional cohort of associated SNPs appear between genes and in follow-up analysis may implicate enhancers or promoters in disease processes.

Analysis protocols and techniques for integrated data interpretation to construct putative regulatory networks underlying disease will be discussed. The data collection and analysis methods are generally applicable beyond glaucoma to other chronic, progressive diseases associated with aging.