John B. Waldron
L4
LSU Health Sciences Center, New Orleans, LA

Dr. Diptasri Mandal:
LSUHSC Department of Genetics

“Identification of copy number variants in hereditary lung cancer families”

Lung cancer is the most common cause of cancer mortality and the third most common cancer by incidence in the United States. While environmental factors (e.g. tobacco smoke) play an important role in its development, lung cancer risk also exhibits a high degree of heritability. Linkage analyses and genome-wide association studies have identified multiple loci associated with increased lung cancer risk; however, much of the heritability has yet to be explained by these loci. Structural mutations, including a gain or loss of DNA (copy number variants or CNVs), contribute to phenotypic diversity through dosage and/or cis-regulatory effects. CNVs are important sources of phenotypic variation and likely contribute a larger fraction of genomic variation among individuals than SNPs. Unbiased CNV mapping is only possible with the use of high-depth, short-read sequencing and remains much more complicated and prone to false positives than SNP detection. As a result, the contribution of CNVs to genetic variation is not as well understood as the impact of SNPs. As the tools necessary for CNV detection have improved, both somatic and germline CNVs have been shown to play an important role in disease, especially cancer. Although CNVs have been shown to be common and often benign, they account for a significant proportion of pathogenic variants. Little has been done to understand the role of germline CNVs in the biological pathways of hereditary lung cancer. The goal of the current project is to utilize the whole exome sequencing (WES) data in identifying the CNVs in the hereditary lung cancer (HLC) families (≥3 LC/family) recruited by the Genetic Epidemiology of Lung Cancer Consortium (GELCC). This work uses germline WES data from 203 individuals (60 with a lung cancer diagnosis) from 25 HLC families. We limited our investigation to CNVs called by two independent tools using read depth to infer copy number changes and genomic breakpoints: GATK 4 (https://gatk.broadinstitute.org) and XHMM (https://atgu.mgh.harvard.edu/xhmm/). Those CNVs that segregate with disease, are consistent with Mendelian expectations, and appear to be uncommon in the general population, are subjected to bioinformatic annotation to detect the most probable causal variants in each family. The enrichment of rare variants in oncogenically associated genes that co-segregate with lung cancer provides specific mutations for future work and improves our understanding of the inheritance and pathogenesis of lung cancer.