

## **MULTIPLE PI LEADERSHIP PLAN**

### **Rationale:**

This TOPMed project represents an inter-institutional effort that leverages existing, strong collaborative relationships among three leaders in the field of structural variant (SV) detection and functional interpretation— Drs. Charles Lee, Mark Gerstein and Li Ding. Each PI brings significant experience in leading and participating in large-scale genome sequencing consortia, which will be enable successful execution of project goals and facilitate integration within the broader NHLBI TOPMed Program. The unique and complementary expertise that each PI brings to the program justifies a multi-PI approach. The scientific success of the proposed project is to provide a platform of pipelines for comprehensive, high-resolution and large-scale SV analysis.

### **Leadership Roles and Responsibilities:**

Dr. Charles Lee is Professor and Scientific Director of The Jackson Laboratory for Genomic Medicine. He is well-recognized for his contributions to the genomics field among the first to define copy number variants as a highly abundant form of natural human genetic variation and as a pioneer in the development of high-resolution methods for identifying human structural genomic variants. He has also been highly successful as leader of the 1000 Genomes Project SV group, in which he oversaw the comprehensive identification of the full repertoire of SV events in 2,500 healthy genomes and defined the methodology for identifying SVs from whole genome sequencing datasets. For this project, he will lead efforts to develop and integrate tools for high-resolution SV discovery and to build a reference database of complex SVs from TOPMed cohort data as more fully described in the Research Strategy as Aim 1. As contact PI, Dr. Lee will be responsible for communications with NHLBI and the TOPMed Program, including the submission of annual progress reports.

Dr. Mark Gerstein is the AL Williams Professor of Biomedical Informatics at Yale University and Co-Director of the Yale Computational Biology Program, and he is a leader in the field of computational genomics. He has designed and developed a wide array of databases and computational tools to mine genomic data in humans, as well as in many other organisms. He has developed quantitative approaches and practical tools for the processing of next-generation sequencing data, including those related to chIP-seq, RNA-seq and the detection of DNA structural variation. He has also served as a computational lead on numerous NIH-funded genomics projects (e.g., ENCODE & 1000 Genomes Project), and is co-leading the International Cancer Genome Consortium's analysis of mutations in regulatory regions group. For this project, Dr. Gerstein will lead efforts to develop tools to examine the functional impact of the identified SVs and to develop a novel pipeline of methodologies for functional annotation of variants and characterization of associated biological processes (described in Aim 2).

Dr. Li Ding is Associate Professor of Medicine at Washington University School of Medicine with recognized research expertise that includes the development of computational tools for analyzing NGS data, with a particular emphasis on variant detection and interpretation. Dr. Ding has led several landmark multi-center studies and produced a number of seminal publications in the field of genomics. Dr. Ding is currently co-leading the ICGC mutation calling group and she also serves as a co-chair for the oncogenic process group for the TCGA PanCanAtlas project. For this project, Dr. Ding will lead efforts to develop the cloud pipeline for genotyping high-impact SVs across a large number of samples in the TOPMed Program as described in Aim 3.

### **Communication:**

The PIs are committed to regular and productive communication between each other and all relevant staff to facilitate the goals and objectives of the project. At the beginning of the project, the PIs will conduct a kickoff joint group meeting at The Jackson Laboratory for Genomic Medicine, to be attended by all key personnel and significant contributors to discuss program objectives, tasks, roles and responsibilities. Thereafter, the PIs will meet by video- or tele-conference on a biweekly basis to discuss research progress, address challenges and find solutions and alternative outcomes as needed. They will share their respective discussions with other key personnel to ensure that everyone is up to date with the latest status of the projects and results.

The PIs will also meet with their respective project staff weekly to evaluate progress and discuss any issues that have arisen in their work. These meetings can often clarify processes, bring to light new data sources, and to identify areas where others need to be consulted or indicate what additional resources are needed to accomplish a particular aspect of the project. Additional one-on-one communications (e.g., between key

personnel, laboratory and administrative personnel) will take place on an *ad hoc* basis by email, phone or videoconference. A group meeting with all PIs and key personnel will be scheduled quarterly at a minimum to discuss project progress as a group. These meetings are also important for maintaining open communication between all key personnel and enable all to work together to discuss any changes in direction of the research projects.

The PIs will seek maximal communication with TOPMed Project Scientists and leaders of the data production, data analysis and coordinating centers of the TOPMed Program. As a collaborative NIH-funded program, the PIs also anticipate interactions with NHLBI scientific program officials. The PIs will attend TOPMed steering committee meetings through regular teleconferences and two annual in-person meetings at the NIH.

**Organization, Governance and Administration:**

All three of the Principal Investigators, Drs. Lee, Ding and Gerstein, participated in the preparation of this proposal, and are in agreement with the scientific and management plans. In particular, each has agreed to accept responsibility for the scientific leadership of the this project. Although Drs. Lee, Gerstein and Ding have synergistic expertise, the scientific direction for each Aim will generally be the domain of the PI with relevant expertise. Any dispute will be addressed first by the PIs. Should there be a scientific conflict, the PI with the most relevant expertise for the question will make the decision. If a resolution cannot be obtained, then the PIs will work with NHLBI program staff responsible for the TOPMed Program to resolve the dispute. All PIs agree to abide by the decisions made in such an instance.

The PIs have an established track record of successful scientific collaboration and will communicate frequently and regularly via email. The research group under the direction of each PI will meet weekly in person, and include, via video or teleconference, other project researchers as appropriate. Through the standing biweekly video- or teleconference meetings, the PIs will collectively oversee and coordinate of the scientific direction of the project and discuss management issues. New and major changes in research direction will be discussed with NHLBI program officials, as appropriate.

The Jackson Laboratory will be the prime grantee, and subaward agreements will be established with the McDonnell Genome Institute at the Washington University in St. Louis and Yale University. All institutions participating in this proposal have signed a Statement of Intent to enter into an inter-institutional agreement to include terms and conditions consistent with the NHLBI TOPMed Program and NIH policies for the U01 Cooperative Agreement mechanism. These include agreeing to accept close coordination and participation of NHLBI Project Scientists, and adhering to NHLBI policies regarding intellectual property, data release and other policies that might be established during the course of the TOPMed Program. The anticipated budget and funding distributions for the project, as delineated in the proposal budget and budget justifications, have been agreed upon by the PIs. The PIs will be responsible for the fiscal management, research compliance and related research administration management at their respective institutions.