Investigation of Genetic Architecture of Multiple Myeloma by Next Generation Sequencing

Myeloma is a genetically heterogeneous disease and is sub-classified based on the presence of structural variants and genetic mutations. Structural variants/copy number changes are historically identified by traditional methods such as karyotyping and fluorescence in situ hybridization (FISH). Although microarray based genome wide analyses greatly improve the resolution of structural variation, they may be limited by probe density. Consequently, identification of structural variation may be insensitive to specific disrupted gene(s), neglecting the sequence complexity that might underlie these rearrangements. Determination of the specific breakpoints of structural variants at the nucleotide level is required for a better understanding of the genetic causes and to enhance the development of therapeutics for patients.

The emergence of Next-Generation Sequencing (NGS) technology has led to the identification of structural variants in the genome at a higher resolution relative to currently used cytogenetic methods. We analyzed DNA extracted from a set of patients with multiple myeloma, who had Affymetrix® SNP array (~2.7 million probes) (Affymetrix, Inc.) data, by whole exome sequencing (WES) at 100X coverage on the Illumina® HiSeq platform (Illumina, Inc.) to identify the full spectrum of associated genomic aberrations. Sequence data was mapped to the hg19 reference sequence and analyzed by various in-house developed and open source data analytic tools. Additionally, a custom sequence analysis pipeline was written to interrogate chromosomal deletions and translocations in these samples. Our analysis showed that ~43% (6/14) of patients have deletions in chr17p and/or chr13q. We further confirmed structural variants using the Integrative Genomics Viewer (IGV). These data indicate the efficacy of WES for the precise determination of translocation and inversion breakpoints. In addition, we were able to identify single nucleotide variants (SNVs) and insertions/deletions (indels) in these samples. We then used the Ingenuity Variant Analysis (IGV) program to identify clinically actionable variants. These datasets are being further analyzed by various pathway analysis tools to define possible pathogenic mechanisms in multiple myeloma.