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POSTER ABSTRACTS

603.LYMPHOID ONCOGENESIS: BASIC

Whole-Genome Sequencing Identifies Structural Variation As a Key Driver of Disease Relapse and Aggressive Clinical Behavior in Multiple Myeloma

Marc Braunstein, MDPhD[1], *Patrick Blaney, MS*[2,3], *Gareth J. Morgan, MD, PhD*[2]

[1] Perlmutter Cancer Center, Multiple Myeloma Research Program, NYU Grossman Long Island School of Medicine, NYU Langone Health, Great Neck, NY
[2] Perlmutter Cancer Center, Multiple Myeloma Research Program, NYU Grossman School of Medicine, NYU Langone Health, New York, NY
[3] Applied Bioinformatics Laboratories, NYU Grossman School of Medicine, NYU Langone Health, New York, NY

INTRODUCTION: Many key genomic events leading to relapse in multiple myeloma (MM) occur outside of coding regions and can only be identified using whole-genome sequencing (WGS). Studies of MM progression examining single nucleotide variants (SNVs) and insertions/deletions (InDels) have identified a distinct pattern of mutations associated with resistance, however these do not fully account for drivers of progression. Studies of relapsed patients provide hints about the molecular mechanisms driving progression based on identification of homozygous loss of tumor suppressor genes, aberrant copy-number variants (CNVs), and rare examples of complex structural variants (SV). We have analyzed a set of presentation and relapsed MM samples, including paired data, derived from WGS of plasma cells and focused on SVs as key drivers of progression.
METHODS: WGS was performed on 338 MM patient samples using CD138-sorted plasma cells, among which 237 samples were paired including 101 patients (30%) at presentation and at relapse, 35 of whom had more than one sample at relapse. A bioinformatics pipeline employing a consensus mechanism for determining the final set of somatic events was used based on Mutect2, Strelka2, and VarScan2 for SNVs; Mutect2, Strelka2, VarScan2, and SvABA for InDels; Battenberg and FACETS for CNVs; Manta, SvABA, DELLY2, and IgCaller for SVs. Additionally, an admixture workflow was used to estimate each individual's ancestral lineage using continentally-distinct references, comprising 23 regional populations within 5 super-populations from the 1000 Genomes Project (https://github.com/pblaney/mgp1000). Complex rearranged genomes were reconstructed using the graph-based R package *JaBbA* (https://github.com/mskilab-org/JaBbA). Additionally, the python package *Pairtree* (https://github.com/morrislab/pairtree) was used to describe the evolutionary history of acquired mutations in these patients.
RESULTS: Themedian age of the cases studied was 67, and 42% were female. Racial admixture correlated with self-identification, including 74% of European ancestry with the remainder being predominantly of African ancestry. High-risk cytogenetic features were found in 10% and 13% at diagnosis and relapse, respectively. As expected, the tumor mutational burden of the relapse cases was higher than that at presentation. The patterns of SNV mutational drivers were similar at relapse in comparison to presentation with again evidence for a role of biallelic tumor suppressor gene inactivation as being a key mechanism. We also found that the number of SVs increased at relapse. Complex SVs including templated insertions, chromoplexy, and chromothripsis were detected and occurred exclusively at relapse in some cases as well as earlier in the natural history in others, suggesting they can occur as both early and late driver events. Characterizing complex SVs, further we identified them at lower levels in cases at presentation compared to relapse, consistent with these being at a higher clonal fraction and providing further evidence for their role as driver events. We did not see the emergence of additional rearrangements at relapse in either the templated insertions or chromoplexy events, suggesting that these occur at a single timepoint and remain structurally stable overtime.
CONCLUSIONS: Complex SVs provide a novel mechanism driving relapse in MM which can deregulate multiple genes simultaneously providing new potential markers of aggressive disease behavior and disease evolution.

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