

Directionality of gains of allele-specific DNA methylation at germline risk loci for multiple myeloma

Panteha Behboodi¹, Carolina Alberca Doto¹, Andy Madrid¹, Angelica Castano¹, Martha Salas¹, Mariam Tariq¹, Andrew Cummins¹, Amber Zhou¹, Rohan Sarkar², Reilly Kobbe¹, James Di Palma-Grisi¹, Jens Hillengass³, Michael Slade⁴, Samir Parekh⁵, Alessandro Lagana⁵, Noa Biran¹, Kar Chow¹, David Siegel¹, Rena Feinman¹, Lara Sucheston-Campbell⁶, Benjamin Tycko¹

Author affiliations: ¹Hackensack Meridian Health- Center for Discovery and Innovation, Nutley, NJ, United States, ²Cornell University, Ithaca, NY, United States, ³Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States, ⁴Washington University School of Medicine Campus, Saint Louis, MO, United States, ⁵Icahn School of Medicine at Mount Sinai, New York, NY, United States, ⁶Karmanos Cancer Institute, Detroit, MI

To assess the frequency and directionality of allele-specific DNA methylation (ASM) gains at germline multiple myeloma (MM) risk loci, we performed Nanopore-SEQ in 28 primary MM cases, paired PBMCs from 23 cases, and peripheral blood B cells from six individuals. A custom pipeline visualized ASM and associated SNP genotypes in genome-browser tracks. MM showed markedly increased ASM differentially methylated regions (ASM-DMRs), with a median of 101,621 per case (range, 7,939–332,542), compared with 815 in PBMCs (477–6,224) and 1,229 in normal B cells (537–3,185). ASM-DMRs were compact (median length, 283 bp), supporting their value for localizing functional post-GWAS SNPs. Nearly all published MM GWAS loci harbored strong ASM-DMRs within 10-kb windows centered on lead SNPs in at least one MM case, and 28 DMRs directly overlapped lead SNPs. Directionality analysis identified two patterns. At *DNAH11* (Chr7, rs4487645) and *CBX7* (Chr22, rs877529), compact ASM-DMRs showed concordant directionality across informative MM cases using a single index SNP, without haplotype stratification (Type I concordance). In contrast, at *JARID2/JARID2-DT* (Chr6) and the chromosome 3 *TERC-ACRT3-MYNN-LRRC34* cluster, concordance emerged only after stratification by local haplotypes (Type II concordance). Although analysis remains ongoing, we have not encountered risk loci showing random ASM-gain directionality among MM cases sharing an identical haplotype. Thus, ASM gains are pervasive in MM and frequently occur at germline risk loci. Their directionality can clarify the relative functional importance of individual SNPs versus local haplotypes in controlling epigenetic states at these loci in MM cells.