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Myelodysplastic Syndromes

SEX-BASED DIFFERENTIAL DNA METHYLATION SIGNATURES IN MYELODYSPLASTIC NEOPLASMS

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Introduction: Disparities in MDS incidence, mutational landscape, and treatment outcomes based on sex are increasingly evident in Myelodysplastic Neoplasms (MDS). However, underlying epigenetic mechanisms remain elusive. We previously performed an in-depth analysis on sex-based disparities in lower-risk (LR)-MDS, showing significant differences in mutational burden and landscape, including mutations in epigenetic regulator genes e.g. *TET2* (enriched in males) and *DNMT3A* (enriched in females), with a trend of reduced response to erythropoietin stimulating agents (ESAs) in the latter. We hypothesized that the epigenomic landscape in MDS not only is influenced by prevalence of specific somatic mutations; but might also be sex-specific and could partially explain previously observed clinical differences.

Methods: We performed genome-wide DNA methylation profiling using Illumina EPIC v2.0 arrays on bone marrow mononuclear cells (BMNCs) from 141 LR-MDS patients (according to IPSS-R). Raw IDAT files were processed with SeSaMe in R. Quality control excluded 44.950 probes with detection $p > 0.05$ in >10% of samples, samples with >10% failed probes, and SNP/sex-chromosome probes. Sex-stratified differential methylation analysis identified autosomal DMRs using limma and DMRcate ($\lambda = 1000$, $C = 2$, FDR < 0.05). DMRs were annotated to genomic features and classified as hyper- or hypomethylated in females. Epigenetic age acceleration (EAA) was calculated using Horvath, Hannum, PhenoAge, GrimAge (v1/v2), and principal component (PC)-based clocks to assess sex-specific biological aging.

Results: Sex-stratified differential methylation analysis of 141 LR-MDS cases (46 females, 95 males) identified 751 significantly differentially methylated CpGs (FDR<0.05), which associated into 117 DMRs. Of these DMRs, 84 (72%) were hypermethylated and 33 (28%) were hypomethylated in females compared to males. 47.9% of DMRs localized to promoter regions and 36.8% in intergenic regions. Hypermethylated DMRs were concentrated in promoters (60.7%), while hypomethylated DMRs were predominantly intergenic (66.7%). Regarding CpG island context, 35% of non-open sea DMRs localized near CpG islands, with the remaining distributed across shores and shelves. EAA analysis revealed significant differences in biological aging across multiple clocks. Males demonstrated significantly higher GrimAge EAA ($p<0.01$), shorter DNAm telomere length ($p<0.01$), and a trend towards accelerated pace-of-aging with DunedinPACE ($p<0.05$) compared to females. PC clocks confirmed these findings, with PCGrimAge ($p<0.001$), PCHannum ($p<0.05$), showing significantly increased EAA in males, while PCDNAmTL was consistently lower ($p<0.01$). Sex-stratified DMRs enriched in regulatory regions combined with differential epigenetic aging patterns indicates sex differences both for regional methylation at functionally relevant sites; as well as global epigenetic aging in LR-MDS, potentially underlying observed sex-based clinical disparities.