

Title: Deciphering the Genetic Mechanism of Sex Differences in Multiple Myeloma

Authors: Opakunle PhD, Huang PhD, Shan PharmD, Stranger PhD, Huang PhD

Multiple myeloma (MM) is a genetically complex cancer with sex differences in incidence and mortality, with males having a 1.5-fold increased risk for both incidence and mortality compared to females. We aimed to identify the genetic mechanisms underlying these sex differences to guide the development of sex-specific therapeutic interventions. We hypothesized that sex-differentiated genetic effects contribute to sex disparities in MM incidence and mortality. Using genome-wide association studies (GWAS) from the UK Biobank and All of Us, along with transcriptomic and expression quantitative trait loci (eQTL) analyses from MMRF CoMMpass, we identified sex-differentiated genetic regulatory mechanisms influencing MM risk and disease outcomes. We revealed sex-biased genetic effects genome-wide and within immune-related gene regions associated with MM. These genetic sex differences were reflected in sex-specific eQTLs and sex-biased gene expression. Through integrative analyses, we pinpointed putative sex-specific genetic drivers of MM and their transcriptional consequences. Notably, we identified NSD2, which is frequently overexpressed in MM due to the t(4;14) translocation, as a key regulator of malignant plasma cell proliferation, survival, and drug resistance, contributing to sex disparities in MM. Our Cox proportional hazards (CoxPH) analysis showed that NSD2 overexpression was associated with an HR > 1 ( $p = 0.002$ ), indicating poorer survival in males compared to females. Furthermore, using 75 validated sex-biased genes, we confirmed distinct immune and oncogenic pathways enriched in males and females. Taken together, our results highlight sex-differentiated genetic regulatory mechanisms as key contributors to MM risk, as well as sex differences in pathways and survival outcomes, providing insights for precision medicine and targeted therapies.