Genetic Effects on Gene Expression and Survival in Patients with Multiple Myeloma

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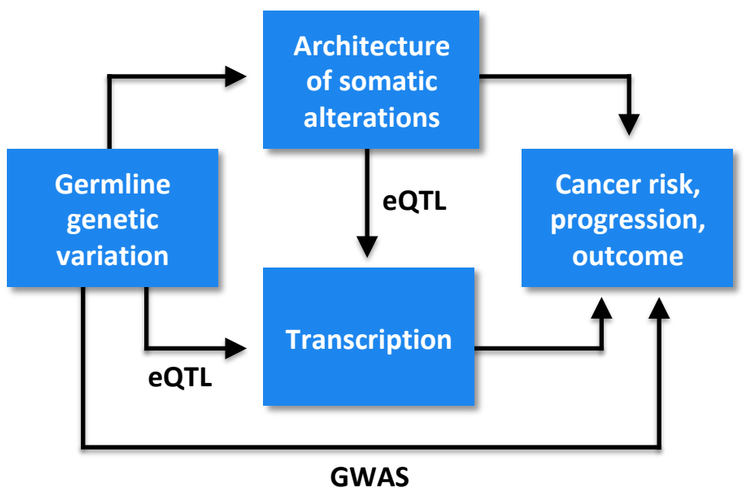
Background

- Multiple Myeloma (MM) is the 2nd most common hematological malignancy, accounting for 2.1% of all cancer deaths[1]. MM remains incurable and nearly all patients experience relapse.
- MM exhibits a disparity in occurrence and mortality between the sexes and ethnicities, men and African Americans being in at a higher risk than women or those of European ancestry[2,3].
- Genome Wide Association Studies have identified germline variants associated with MM risk[4]. Many GWAS loci are located on regulatory regions, and are likely to affect disease risk by altering transcription.

MMRF CoMMpass Project

- The Multiple Myeloma Research Foundation's CoMMpass project is a longitudinal study aiming to understand how the patients' genetic makeup affects their disease progression and response to treatment.
- This work has discovered somatic alterations associated with MM progression and patient survival, as well as a novel classification of MM into 12 distinct subtypes based on gene expression.

Hypothesis and Approach



Data Analysis

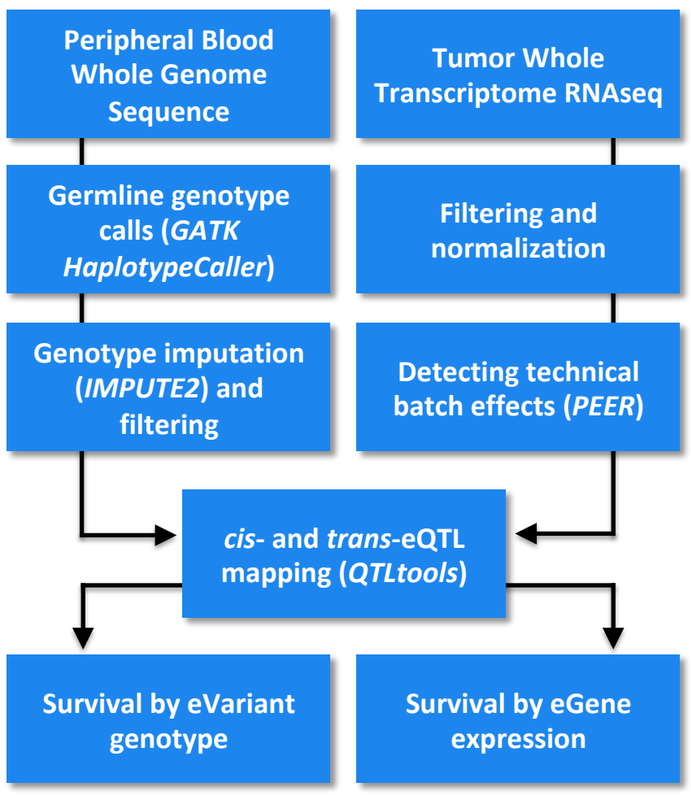


Figure 1. Computational analysis pipeline. Baseline Whole Genome and Whole Transcriptome data from 607 (363 male, 244 female, 401 European, 82 African American) patients and survival data from 521 patients (317 M, 204 F, 401 EUR, 82 AFR) were included in the initial analyses.

Results and Conclusions

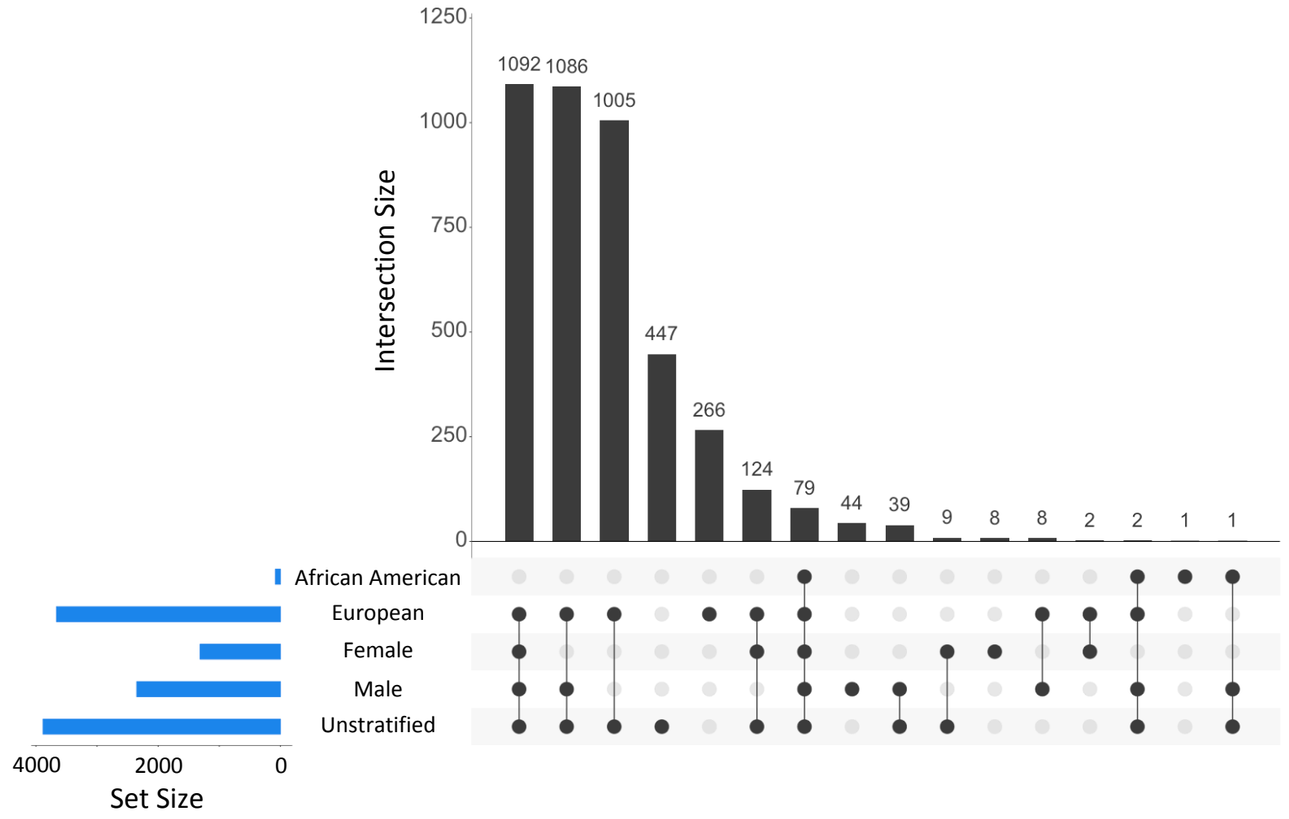


Figure 2 (left). Stratified analyses detect differential regulatory effects between the sexes and ethnicities. These effects may contribute to the observed biases in MM occurrence and mortality. Overlap of genes under germline regulatory control in the joint analysis of all data and in sex- and population-specific analyses. Number of eGenes in each group (blue bars), intersections with at least one gene (dot matrix), number of eGenes in each intersection (black bars).

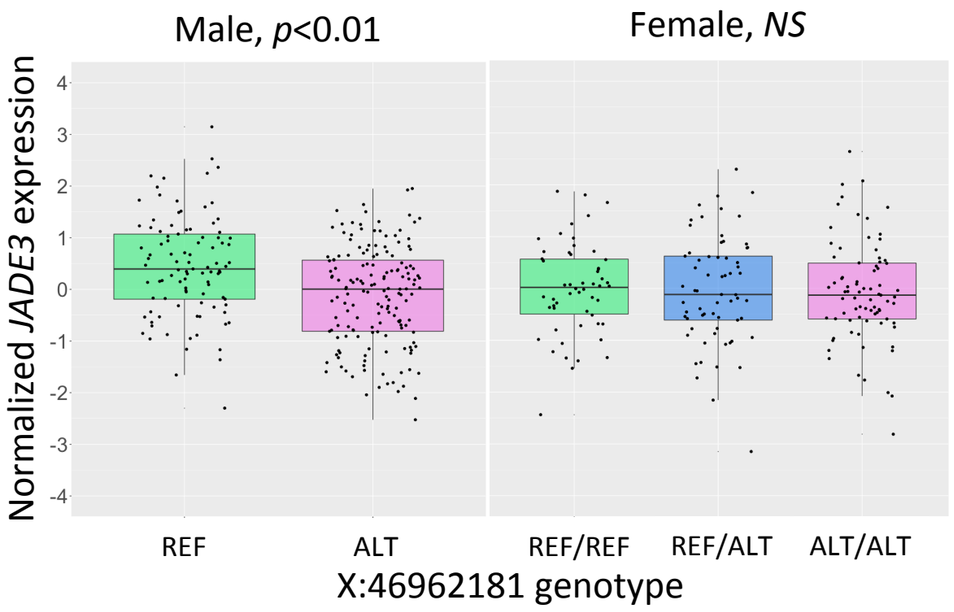
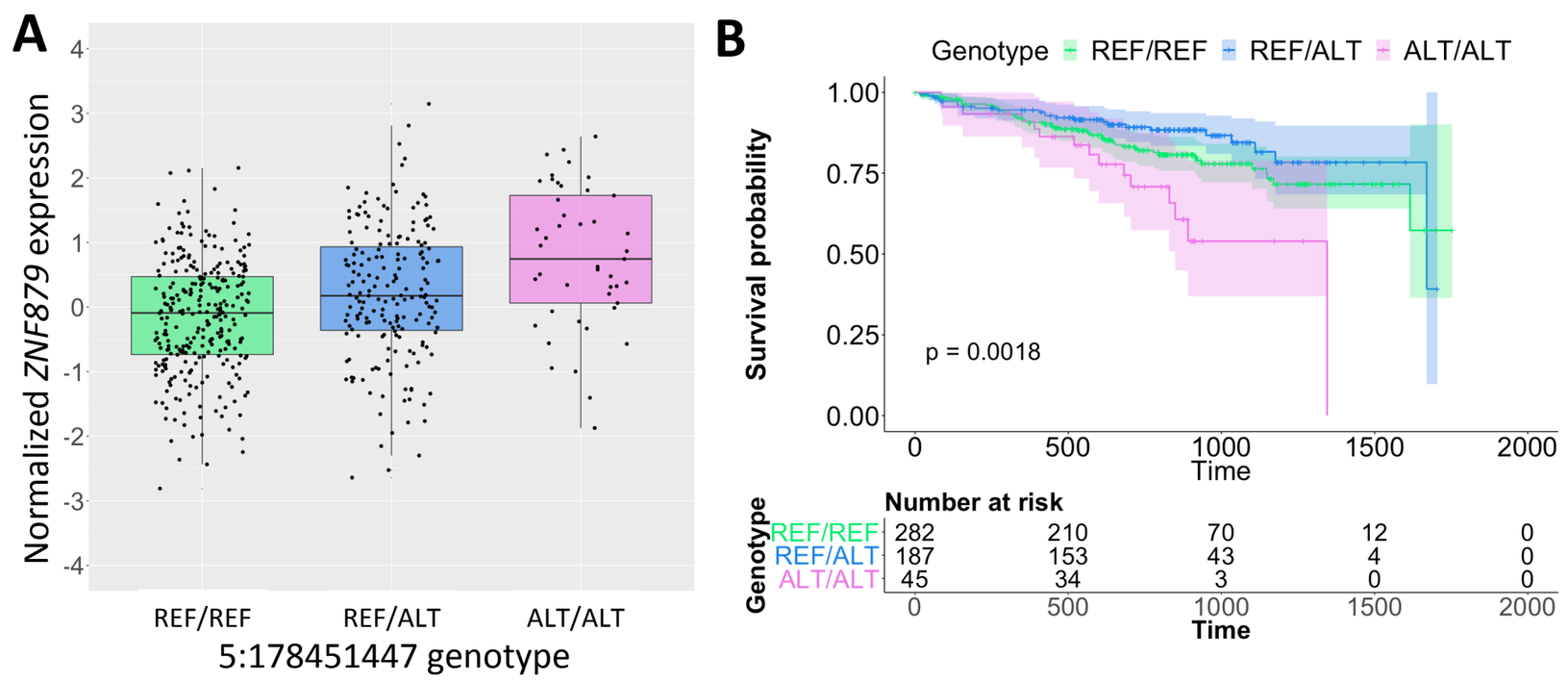


Figure 3 (left). An example of a male-specific eQTL. X-linked allele alters target gene expression in male, but not in female or in joint analysis of both sexes. Sex-specific regulatory effects may contribute to the widely observed male-bias in cancer occurrence.

Figure 4 (below). Germline variants modulate gene expression and survival in MM. An example of a germline regulatory variant associated with survival. Sex-shared intronic germline variant alters **(A)** *ZNF879* expression and **(B)** overall survival in the CoMMpass cohort. This is the first discovery of eQTLs altering survival in MM.



Ongoing Work and Future Prospects

- Co-localization analyses of regulatory variants and MM GWAS loci to uncover regulatory mechanisms underlying MM risk loci.
- Integrating germline, somatic and transcriptome data: germline effects on somatic alterations and somatic eQTL mapping.
- ATAC-seq assays for chromatin accessibility in MM cell lines to reliably annotate regulatory regions.
- *In vitro* validation of regulatory variants utilizing MM cell lines and CRISPRi-CRISPRa assays.

Literature

1 NCI SEER 18 2011-2015, **2** Mohamed et al. 2007 Am J Hematol, **3** Landgren & Weiss 2009 Leukemia, **4** Mitchell et al. 2016 Nat Commun

Acknowledgements

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