LETTER TO THE EDITOR

A founder heterozygous mutation in methyl-CpG binding domain protein 4 (MBD4) prevalent among Israeli Christian Arabs predisposes to increased mutagenesis

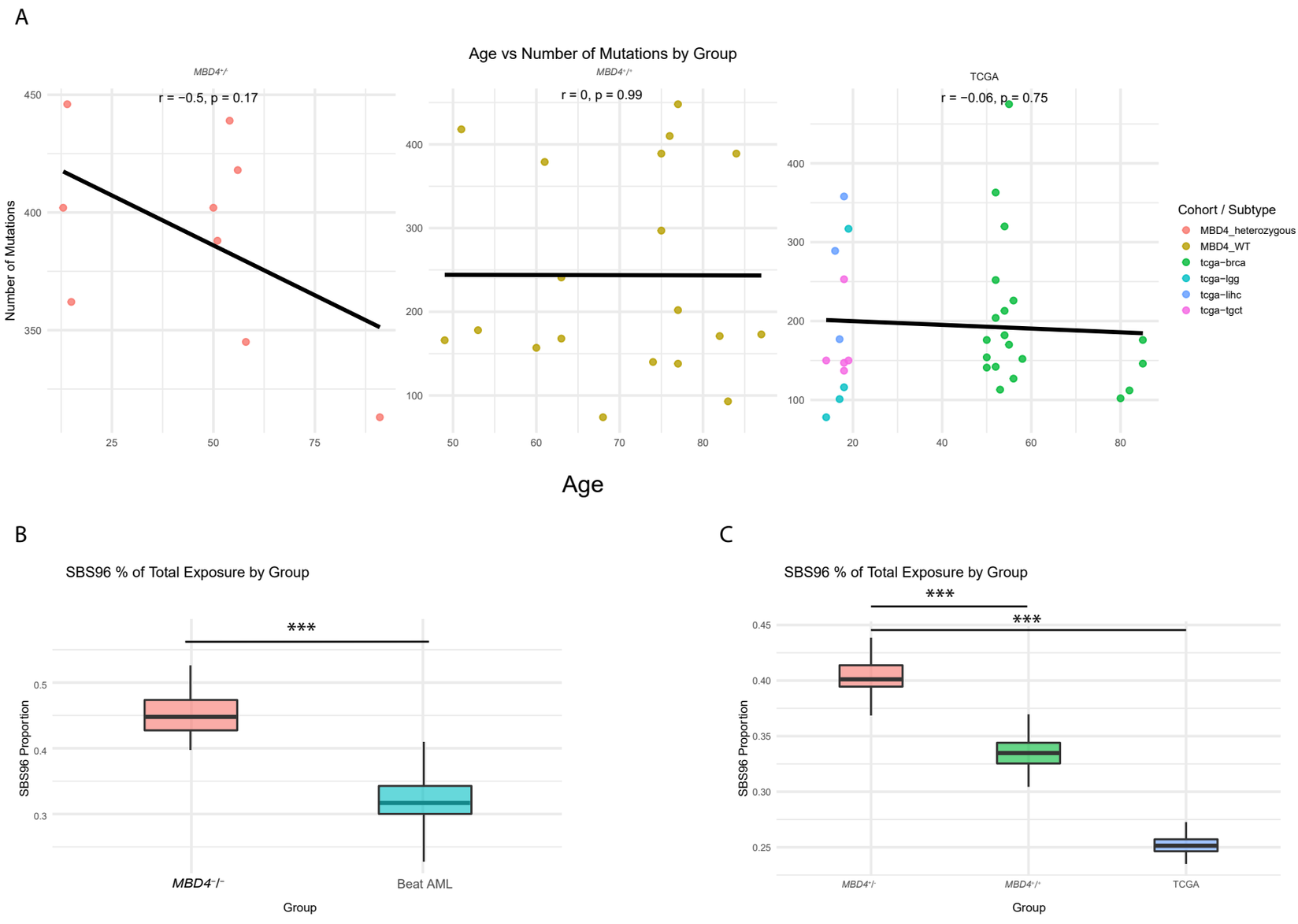
Authors

Gal Dadi,[1] Sara Rosen,[1] Hadas Naor,[1] Elias Hellou,[2,3] Noa Chapal-Ilani,[1] Tal Bacharach,[1] Nathali Kaushansky[1] and Liran I. Shlush[1]

[1]Weizmann Institute of Science, Rehovot, Israel; [2]Mayo Clinic Rochester, Rochester, MN, USA and [3]Nazareth Hospital EMMS, Nazareth, Israel
Correspondence:
G. DADI - galdadi@gmail.com

https://doi.org/10.3324/haematol.2025.287690

Received: February 26, 2025.
Accepted: August 22, 2025.
Early view: September 4, 2025.



Supplementary Figure 1. Somatic mutations, age correlations, and CpG-biased mutational signatures in *MBD4*-deficient individuals. (A) Correlation between age and total number of somatic mutations in peripheral blood in three cohorts: *MBD4* c.612_615del heterozygous carriers (left), in-house $MBD4^{+/+}$ controls (middle), and TCGA blood-derived normals (right). No significant correlation was observed (*MBD4* c.612_615del heterozygous carriers: Pearson r = –0.5, p = 0.17; $MBD4^{+/+}$: r = 0, p = 0.99; TCGA: r = –0.06, p = 0.75), suggesting age alone does not account for the increased mutation burden in *MBD4* c.612_615del heterozygous carriers. Each point represents one donor; TCGA samples are color-coded by tumor type. (B) SBS96 mutational signature contribution in leukemic samples from the *MBD4* biallelic c.612_615del patient compared to 11 AML samples from the Beat AML cohort (***p < 0.001, Wilcoxon rank-sum test). (C) SBS96 signature proportion in MBD4 c.612_615del heterozygous carriers (n = 9), in-house $MBD4^{+/+}$ healthy donors (n = 19), and TCGA blood-derived normal samples (n = 36) from peripheral blood, showing significantly increased SBS96 contribution in *MBD4* c.612_615del heterozygous carriers compared to both controls (***p < 0.001, Wilcoxon rank-sum test). Abbreviations: AML – Acute myeloid leukemia; SBS, Single Base Substitution; TCGA- The Cancer Genome Atlas; WT- wild type.