The Prevalence of Sickle Cell Phenotype and its Association with Clinical Outcomes in persons of African descent with Solid Malignancies

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Background

- Sickle cell disease (SCD) is the most common inherited blood disorder in the United States and is caused by a mutation of β-globin (*HBB* MT).
- The risk of developing solid malignancies in this population remains controversial.
- We report the prevalence of *HBB* mutations across a cohort of solid tumors and clinical outcomes between *HBB*-Wild type (WT) v Mutant (MT) tumors.

Methods

- Non-small cell lung cancer (NSCLC, N = 3307), breast (BC, N = 1960), colorectal (CRC, N = 2161), prostate (N = 899), and gynecologic cancers (N = 2,805) in persons of African descent were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (whole exome) and RNA (whole transcriptome). Tumor types that had the top 8 highest absolute number of *HBB*-Mt cases were included.
- Her2/Neu (+: ≥3+ and >10%) and HR (ER or PR+: ≥1+ and ≥1%) expression was tested by immunohistochemistry.
- Tumors were assessed for single nucleotide variations (SNVs) and insertions/deletions (indels) in *HBB* associated with a sickle cell phenotype.
- Mutation prevalence for all other genes was calculated for pathogenic SNVs/indels. Differentially regulated pathways were assessed by gene set enrichment analysis (GSEA).
- Fisher's Exact/χ^2 tests were applied with p-values adjusted for multiple comparisons ($p < .05$).
- Real-world overall survival (OS) and ethnicity data was obtained from insurance claims and log-rank estimates were calculated for molecularly defined subpopulations.

Results

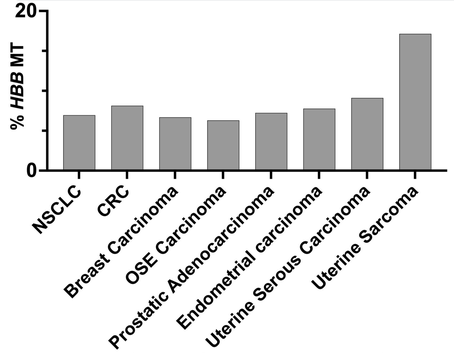

Table 1: Demographic information

	NSCLC HBB WT	NSCLC HBB MT	Statistic	q-value
Count (N)	3077	230		
Median Age [range] (N)	67 [24 - >89]	66.5 [36 - >88]	Mann-Whitney U	0.50
Female	48.8%	54.8%	chi-square	0.40
	CRC HBB WT	**CRC HBB MT**	**Statistic**	**q-value**
Count (N)	1985	176		
Median Age [range] (N)	64 [17- >89]	62 [19 - >89]	Mann-Whitney U	0.85
Female	51.5%	49.4%	chi-square	0.85
	BC HBB WT	**BC HBB MT**	**Statistic**	**q-value**
Count (N)	1829	131		
Median Age [range]	61 [23 - >89]	61 [27 - >89]	Mann-Whitney U	0.29

Figure 1: Prevalence of *HBB* WT in the indicated tumor types (tumors shown had the highest absolute number of HBB MT cases in the Caris database). OSE: Ovarian surface epithelial.

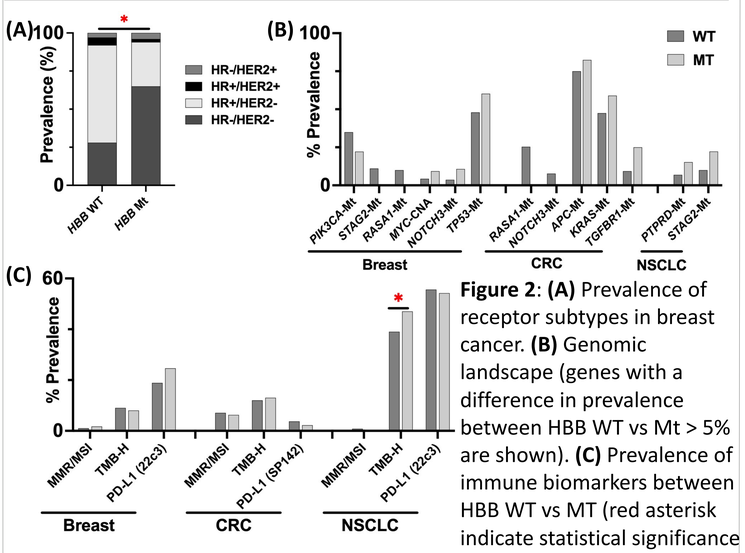

Figure 2: **(A)** Prevalence of receptor subtypes in breast cancer. **(B)** Genomic landscape (genes with a difference in prevalence between HBB WT vs Mt > 5% are shown). **(C)** Prevalence of immune biomarkers between HBB WT vs MT (red asterisk indicate statistical significance $p < 0.05$).

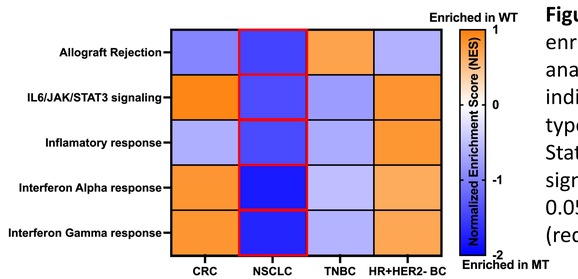

Figure 3: Gene set enrichment analysis for the indicated tumor types. Statistical significance: p < 0.05, FDR < 0.2 (red outline).

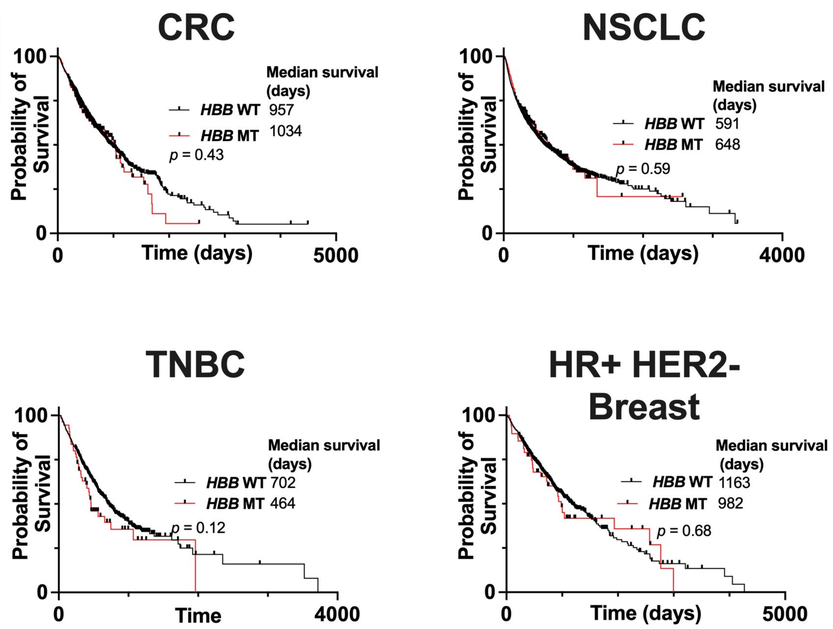

Figure 4: No significant difference in overall survival (collection to last contact) was observed between *HBB* WT vs MT for CRC, NSCLC, TNBC nor HR+/HER2- breast cancer.

Study Highlights

- No significant differences in the genomic landscape nor in OS of *HBB*-MT vs -WT NSCLC, CRC or BC were observed.
- NSCLC *HBB*-Mt was enriched with inflammatory response genes.

Conclusions

- Future work should focus on the potential role *HBB*-Mt plays in NSCLC.

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