The Association of Maternal *HBB* Pathogenic Variant Status and Fetal Fraction in Non-Invasive Prenatal Screening

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INTRODUCTION

- Hemoglobinopathy is associated with an increased risk for several conditions, such as renal medullary cancer, hematuria, renal papillary necrosis, splenic infarctions, and even sudden death.
- In addition, β-globin hemoglobinopathies may include structural hemoglobinopathy. This includes hemoglobin-S, which is associated with sickle-cell disease.
- Women affected with β-globin hemoglobinopathies have been observed to have lower fetal fraction on noninvasive prenatal screening (NIPS), possibly resulting from a higher rate of necrosis of maternal cells and associated increase in maternal cell-free DNA (cfDNA).

OBJECTIVES

To evaluate the clinical implications of NIPS for pregnant women with β-globin hemoglobinopathies, we evaluated fetal fraction and the NIPS "no-call" rate due to low fetal fraction in *HBB* pathogenic variant carriers and non-carriers.

For comparison, we also assessed pregnant women with α-globin hemoglobinopathies.

METHODS

STUDY DESIGN

- We retrospectively analyzed women tested in our laboratory from 2016-2019 who have had both whole-genome sequencing NIPS and carrier screening that included hemoglobinopathies.
- A corrected fetal fraction was determined using multivariable linear regression to adjust for maternal age, gestational age, and BMI.
- NIPS "no-call" rates were calculated using a fetal fraction cut-off of 4%, where all samples with a fetal fraction <4% would be failed.
- Subgroup analyses were performed on the hemoglobin S-carriers and non-hemoglobin-S carriers.

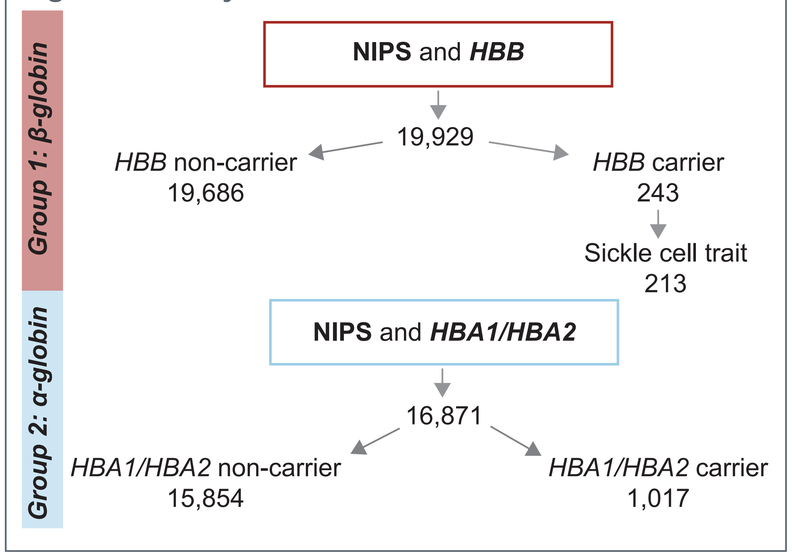
COHORTS

- **Group 1** consisted of all women with NIPS who were carriers of the *HBB* gene hemoglobinopathies (Figure 1). This includes:
  - Structural hemoglobinopathy carriers (S, C, E trait)
  - Quantitative hemoglobinopathy carriers (β-thalassemia minor and trait)
- **Group 2** consisted of women with NIPS who were also carriers for α-globin (*HBA1*/*HBA2*) gene(s) hemoglobinopathies, which included α-thalassemia silent carriers and traits (Figure 1).
- Both groups were compared to women who were not carriers for *HBB* or *HBA1*/*HBA2* hemoglobinpathies.
- All women affected by *HBB* and *HBA1*/*HBA2* hemoglobinopathies were excluded from the study.

Presented at ACMG on March 19, 2020.

RESULTS

Figure 1 . Study Cohort Flow Chart



- The corrected fetal fractions for *HBB* carriers was distinct from non-carriers, with a shift toward lower fetal fraction (Figure 2A).
  - The same was observed for hemoglobin-S carriers (Figure 2A inset).
- If a standard fetal fraction cut-off of 4% had been used during NIPS testing, the no-call rate among *HBB* carriers would have been 1.8-times higher than non-carriers (7.9% versus 4.4%; Figure 2B).
- When *HBA1/HBA2* carriers were assessed, there were no differences in the corrected fetal fraction or the expected no-call rates for carriers and non-carriers (Figure 3).
  - This demonstrates that the impact on fetal fraction is specific to β-globin hemoglobinopathies.

Figure 2. (A) Fetal Fraction Distribution and (B) Expected "No-Call" Rate for HBB Carriers (HbS in inset)

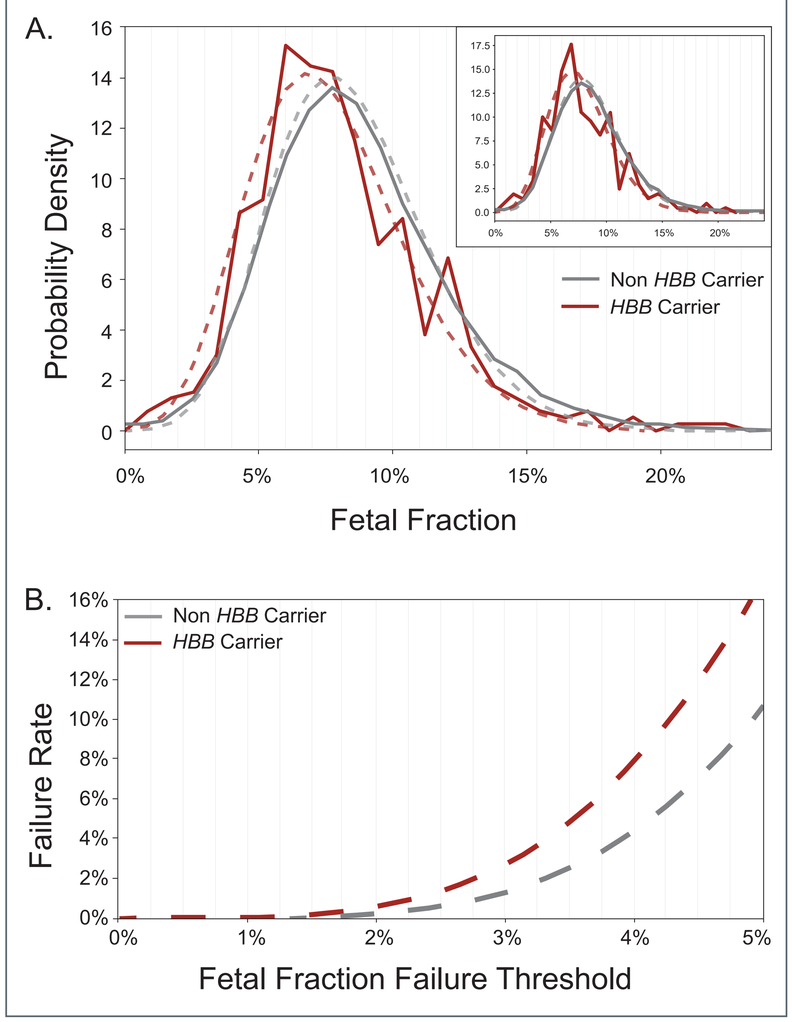
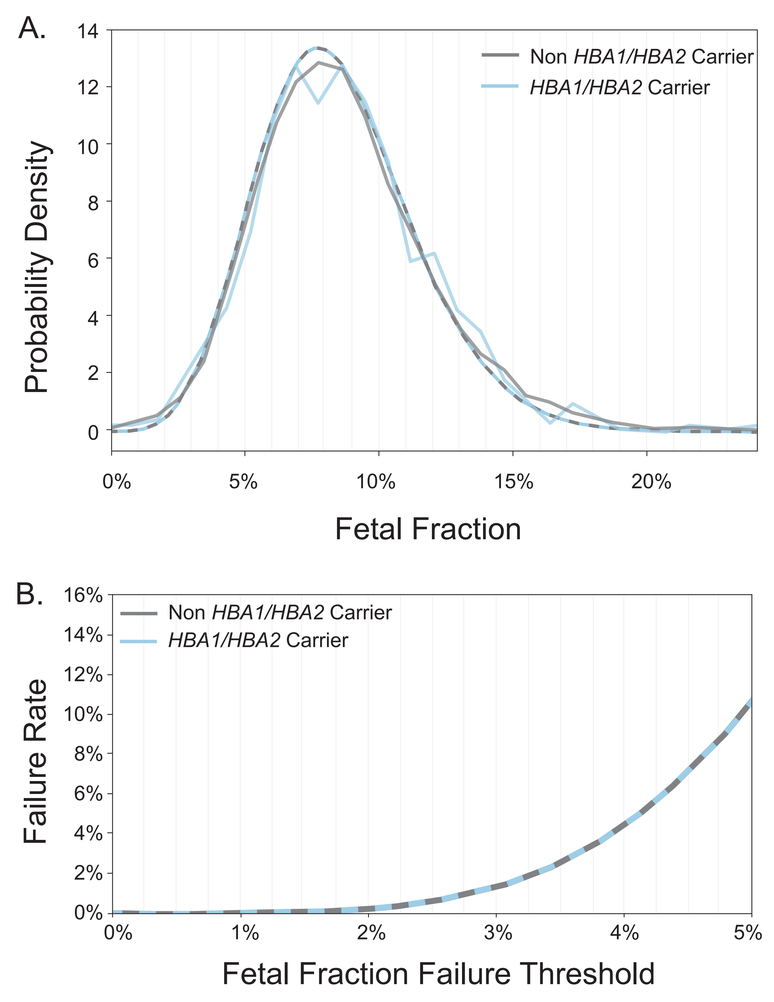


Figure 3. (A) Fetal Fraction Distribution and (B) Expected "No-Call" Rate for HBA1/HBA2 Carriers



CONCLUSIONS

- *HBB* carriers had lower fetal fraction and a higher potential "no-call" rate than non-carriers with a similar effect seen among women with sickle cell trait.
- There were no differences in fetal fraction level between *HBA1*/*HBA2* carriers and non-carriers.
- This is the first study to describe the association of *HBB* gene pathogenic variant carriers and lower fetal fraction level.
- Pretest counseling should be adjusted to indicate the increased potential of no-call results in this population.