A Tale of Two Hbs: DNA Sequencing and Hemoglobin Electrophoresis

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All authors were employed by Myriad Genetics, Inc. at the time of this study

INTRODUCTION

- Hemoglobinopathies, including α- and β-thalassemias, are the most common inherited disorders worldwide.
- Carrier screening can identify individuals who are at risk of having affected offspring, but to be clinically effective, it must have both high sensitivity and specificity.
- Current ACOG guidelines recommend traditional methods for hemoglobinopathy screening, i.e., a combination of complete blood counts and hemoglobin electrophoresis.
- However, the most common pathogenic hemoglobinopathy variant worldwide, α+ -thalassemia, is not detected by these traditional screening methods.
- Recent work by our group has demonstrated the superior sensitivity of next generation sequencing (NGS) over traditional screening methods for hemoglobinopathy variant detection (>95% detection rate), including the detection of α+ -thalassemia.

In this poster, we present support for the superior specificity of NGS and illustrate the undue burden caused by misidentification of hemoglobin variants through traditional screening methods.

REFERENCES


RESULTS

Table 1. Internal Observations of Hb S Mimics at Myriad Genetics

We compiled all HBA1/2 and HBB variants reported at Myriad to have the same mobility as Hb S seen among 173,118 samples. We removed variants that met ACMG/AMP guidelines for classification as pathogenic or likely pathogenic, and those lacking literature support for Hb S mimicry. Myriad, with the superior specificity of NGS, can mitigate undue clinical burden caused by misidentification of Hb S mimics with the potential for undue emotional, financial, and reproductive burden.

CONCLUSIONS

- The validated sensitivity and specificity of NGS allows for the detection of >99% of HbA1c and HBB variants reported at Myriad.
- Present case and literature support for the misidentification of Hb S mimics due to low specificity of traditional screening methods.
- Low specificity of traditional methods places an undue burden on:
  - Patients, potential for undue personal and reproductive clinical management.
  - Partners and biological relatives of patients, triggering unnecessary follow-up testing.

Using data from individuals screened by Myriad, we demonstrate how NGS-sequencing of HBA1/2 and HBB can mitigate undue clinical burden caused by false positives reported by traditional screening.

This work suggests that adoption of NGS as the primary or sole method for hemoglobinopathy screening is in the best interest of the patient, given the personal and reproductive risks associated with the heterozygous state.

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