

Clinical Experience of an Alpha Thalassemia Carrier Screening Assay with an Increased Detection Rate Due to Novel Variant Calling

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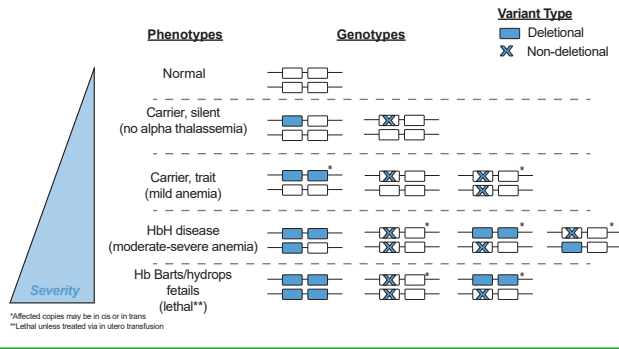
All authors were employed by Myriad Genetics, Inc. at the time of this study

INTRODUCTION

- Carrier screening for alpha thalassemia, a prevalent genetic disease up to 200x more common than cystic fibrosis in certain ethnic populations, is recommended for all women who are pregnant or planning a pregnancy.¹
- Disease severity varies from mild anemia to in utero fetal demise (Figure 1). Most alpha thalassemia carrier screening assays detect only common copy number variants (CNVs) and the Hb Constant Spring variant.²
- To increase our detection rate, particularly across ethnicities to meet the needs of a diverse population, we expanded our assay to include novel variant calling of single nucleotide variants and insertions/deletions.
- Here we present the clinical experience of our improved assay.

Figure 1. Disease severity as a function of the number of functional *HBA* copies.

Severity depends on the specific type and/or combination of mutations that renders the *HBA* copies non-functional. Detection of non-deletional variants is important for understanding risk of developing Hb Barts.



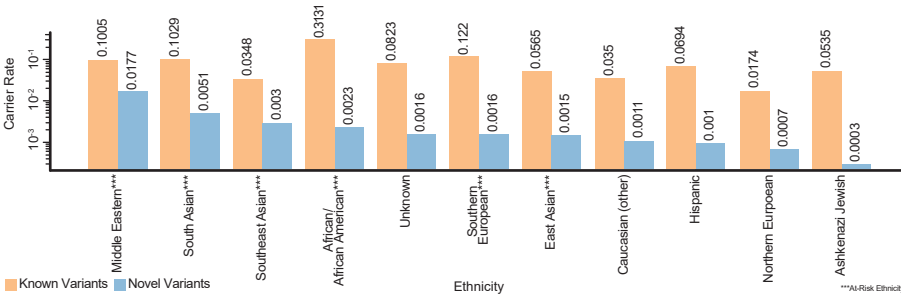
METHODS

- We collected data from 114,818 patients that received the Foresight Carrier Screen over a nine-month period.
- We compared the percentage of patients that would have been identified as alpha thalassemia carriers before and after the addition of novel variant calling.
- Variants were classified according to case, functional and structural data, consistent with ACMG/AMP variant interpretation guidelines.³

RESULTS

Figure 2. Carrier rate by ethnicity.

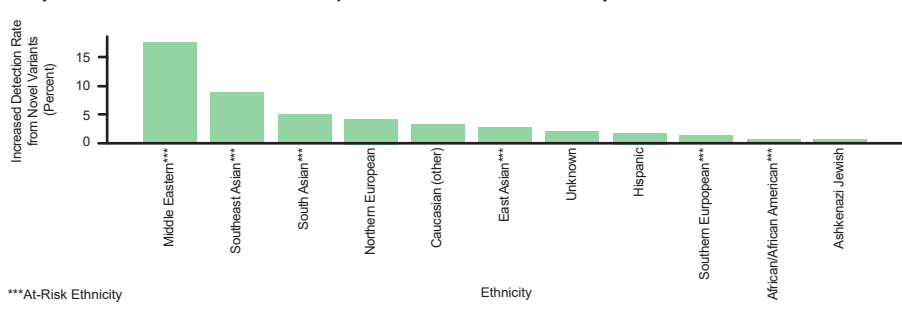
Known variants are CNVs and the Constant Spring SNV detected by most alpha thalassemia carrier screens. Novel variants are all other SNVs and indels. Only ethnicities with ≥ 1000 samples shown. Data sorted by novel variant frequency.



Detection rate improvement due to novel variants was highest in ethnicities that are frequently alpha thalassemia carriers. For example, ~10% of Middle Eastern patients were carriers of a CNV or Hb Constant Spring while ~1.7% were carriers of a novel variant (Figure 2). Thus, novel variant calling increased carrier detection in the Middle Eastern population by ~17% (Figure 3). Other ethnicities with the highest increases in detection rate include Southeast Asian (9%) and South Asian (5%). Interestingly, the “at risk” ethnicities have the highest novel variant carrier rates of all ethnicities (***) in Figure 2).

Figure 3. Increase in Alpha Thalassemia carrier rate from addition of novel variant detection in *HBA1* and *HBA2*.

Only ethnicities with ≥ 1000 samples shown. Data sorted by increased detection rate.



In our cohort, we detected one novel variant, c.95+2_95+6del5 (Figure 4), more often than Hb Constant Spring, a well-characterized pathogenic variant. The c.95+2_95+6del5 variant is common in Mediterranean populations and leads to reduced α -globin expression.³ This variant produces a more severe phenotype than the corresponding deletion of the same gene.^{4,5} Clinically-relevant phenotypes are seen in subjects with only two inactivated α -globin copies while deletional Hb H disease is only seen in subjects with 3 inactivated α -globin copies.⁶

CONCLUSIONS

- Our results demonstrate novel variant calling for alpha thalassemia increases carrier detection rate.
- Despite the clinical importance of identifying novel variants, the inclusion of novel variant calling is not a routine part of all carrier screening and should be considered by healthcare providers.

REFERENCES

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Figure 4. Frequency of reportable variants observed twice or more in the 114,818 patient cohort.

