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High positive predictive value of 22q11.2 microdeletion screening by prenatal cell-free DNA testing that incorporates fetal fraction amplification

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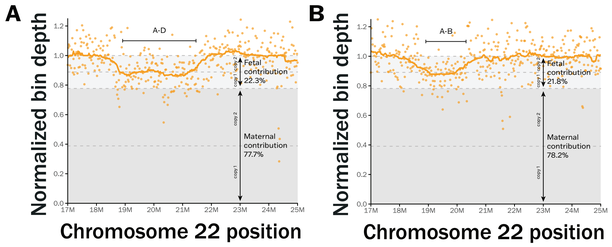
Background

- 22q11.2 deletion syndrome occurs in approximately 1 in 2,000 to 1 in 6,000 births.[1-8]
- Prenatal cell-free DNA screening (pcfDNA) can detect fetuses affected by deletions as small as 2.5 Mb.
- Fetal fraction amplification (FFA), which has been shown to increase fetal fraction (FF) by 2.3x, may further enhance pcfDNA detection of these deletions.[9]
- Positive predictive values (PPV) of pcfDNA screening for 22q11.2 microdeletion have been reported between approximately 20%-98%.[10-15]
- Here, we sought to describe the impact of FFA on the PPV of 22q11.2 microdeletion screening using a whole-genome sequencing (WGS)-based pcfDNA platform.

Study Design and Methods

- We retrospectively analyzed data from patients who underwent WGS-based pcfDNA screening with FFA (Prequel™, Myriad Genetics, Inc.) between 8/20-10/22.
- For screen-positive patients, pregnancy outcome data were requested via a routine HIPAA-compliant process.
- All samples with diagnostic confirmation were used to calculate PPV, defined as: true positives/(true positives + false positives).
- Confidence interval (CI) was estimated using the two-sided Exact Binomial Test.
- Figure 1 shows processed WGS data for two samples called positive for 22q11.2 microdeletion: A. A-D deletion; B. A-B deletion.

Figure 1. Exemplary Samples



Processed WGS data for samples with an "A-D" CNV and an "A-B" CNV of the 22q11.2 microdeletion. The A-D sample (A) has a FF of 22.3%; because one of its two chromosomes has a microdeletion, the drop in signal intensity is roughly 11.2% (FF/2). The A-B sample (B) has a FF of 21.8%; because one of its two chromosomes has a microdeletion, the drop in signal intensity is roughly 10.9% (FF/2). To accommodate the range of clinically characterized breakpoints associated with 22q11.2DS, the analysis algorithm evaluates microdeletion configurations that range in size and location in the 22q11.2 region. Deletions are called positive if the difference from baseline for any configuration exceeds a significance threshold.

References:

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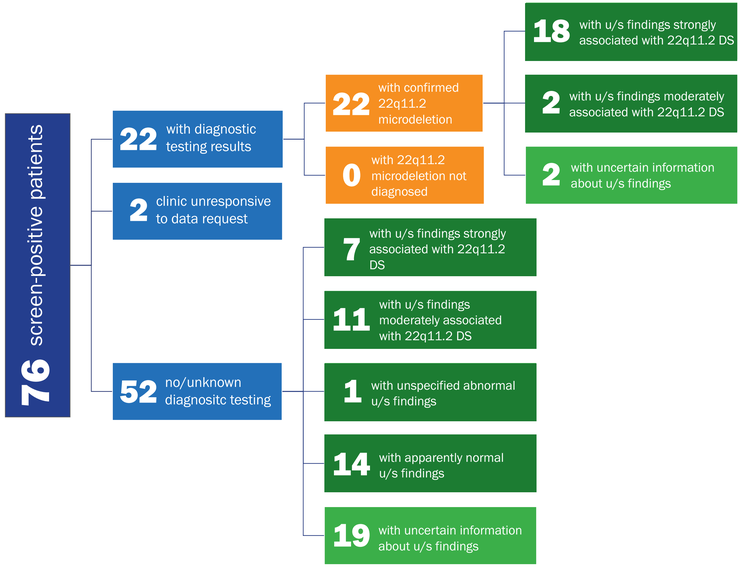
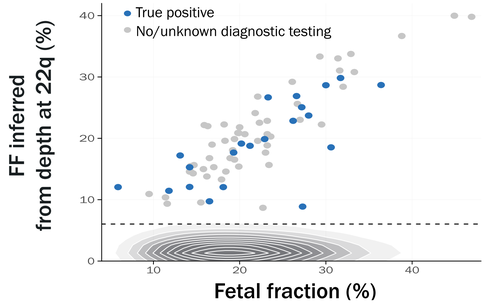
Results

Figure 2. Screen-Positive Patients included in this Study



- 76 patients screened positive for 22q11.2 microdeletion, comprised of 69 (90.8%) A-D, 5 (6.6%) A-B, and 2 (2.6%) A-C deletions.
- 22 screen-positive patients underwent molecular diagnostic testing; all 22 were confirmed as true positives (PPV=100%; 95% CI 84.6%-100%). 20/22 had ultrasound findings strongly or moderately associated with 22q11.2 microdeletion (Figure 2).
- 52 patients had no/unknown diagnostic testing; 33 had ultrasound information. Of those 33, 18 were strongly or moderately associated with 22q11.2. deletion syndrome (e.g. cardiac defects, polyhydramnios, skeletal defects, intrauterine growth restriction) (Figure 2).

Figure 3. Fetal Fraction for each Screen-Positive Sample



Plotted by the fetal fraction (FF) inferred from the observed decrease in depth in the 22q11.2 region, an indication of the strength of the deletion signal for each sample. Decreases in depth are proportional to FF, such that larger decreases in depth occur for pregnancies with higher FF. Each screen-positive sample is represented by a dot; blue dots are true-positive samples and gray dots are samples with no or unknown diagnostic testing. The 22q11.2 deletion signal strength in screen-positive patients substantially exceeded that observed for screen-negative samples (represented by the gray density cloud). The dashed line shows the 99th percentile signal from screen-negatives.

- The average FF was 23% in true positive samples and 22.5% in samples with no/unknown diagnostic testing (p=0.575), and in both true positive samples and those with no/unknown diagnostic testing, the 22q11.2 deletion signal was consistent with the FF of each sample, suggesting FF-based performance was not different between the two groups (Figure 3).

Conclusion

- A pcfDNA screen that incorporates FF amplification has a 22q11.2 microdeletion PPV that is among the highest reported and comparable to that of the common trisomies.