Copy number variant calling on a 176 disease expanded carrier screening panel including DMD

**Introduction**

Expanded carrier screening (ECS) identifies couples whose future children are at increased risk of Mendelian conditions and may be performed using either targeted genotyping (TSG) or next-generation sequencing (NGS). Historically, ECS panels have focused on deleterious SNPs and indels but have been performed with limited or no copy number variant (CNV) calling. Using the Modeled Fetal Disease Risk—an approach to evaluate the performance of hypothetical ECS panels—we also evaluate the impact of deletion CNVs on two ECS panels with 94 conditions and 176 conditions, respectively.

**Methods**

Previously, carrier frequency and carrier couple frequency have been used to quantify the sensitivity of ECS panels. However, to serve this purpose more effectively, we developed an expanded ECS panel with 176 conditions and panel-wide deletion calling. Using the Modeled Fetal Disease Risk—here we evaluate the performance of hypothetical ECS panels. We also evaluate the impact of deletion CNVs on two ECS panels with 94 conditions and 176 conditions, respectively.

**Lessons from Hypothetical Panels**

To assess the sensitivity of various ECS approaches, we compared the modeled fetal disease risk captured by hypothetical panels containing up to 176 “Severe” and “Profound” conditions. We first considered an NGS panel that excludes several “special case” diseases (e.g., fragile X syndrome, α-thalassemia, and spinal muscular atrophy) that are technically challenging to probe. We then considered the effect of adding special cases and panel-wide (i.e., non-founder) CNV calling. We finally considered “best-possible” TG panels with a fixed number of optimally-selected variants, both with and without the special cases.

**Conclusions**

Modeled fetal disease risk allows systematic comparison of ECS panels and identifies non-founder CNVs as a potential avenue for improving sensitivity. We therefore developed an expanded ECS panel with 174 conditions and panel-wide deletion calling. On this new panel, panel-wide deletion calling is expected to identify more than twice as many variants as deletion calling that is limited to six founder variants.

**High-Prevalence Genes Dominate Disease Risk**

A common question is how to best improve the sensitivity of an ECS panel. While adding more genes always increases the assessed disease risk, typically the most prevalent diseases contribute over half of the disease risk. Thus, improving ECS panels will likely require both increasing detection rate for existing diseases (such as six-panel-wide CNV calling) and adding additional conditions.

**Panel-wide CNV Calling on a 176 Disease Panel**

Based on the previous observations, we developed an expanded ECS panel with 176 diseases and panel-wide deletion calling. Here we report CNV deletion statistics for the autosomal genes on this panel. Although the genes with the most observed deletions include known founder mutations, 62% of deletions are located outside of the six genes for which we previously called deletions (CGA, CTG, GALC, HOX, MCOLN1, and N4HD), highlighting the importance of not restricting CNV analysis to a handful of founder variants.

**Disclosure**

All authors are current or former employees of Counsyl, Inc.

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**References**