Comparison of pan-ethnic and ethnic-based carrier screening panels for individuals of Ashkenazi Jewish descent

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I. Introduction

The intent of carrier screening is to identify individuals at risk for a child with a genetic disease. ACMG guidelines currently recommend that individuals of Ashkenazi Jewish descent be screened for carrier status for nine diseases1. A joint statement from ACMG, ACOG, NSGC, SMFM, and the Perinatal Quality Foundation acknowledges benefits of screening for more than nine diseases (expanded carrier screening)2. Here we analyze detection rates for Ashkenazi Jewish individuals screened by panels with different numbers of diseases, to assess the benefit of disease panels targeted to the Ashkenazi Jewish population.

II. Materials and Methods

Array-based hybridization and allele-specific primer extension with a custom illumina infinium™ array (60v1.1) were used to detect 434 mutations in 87 genes that cause 87 diseases or a subset of 147 mutations in 18 genes that cause 18 diseases. Mutations were confirmed by Sangersequencing. The 87-gene panel was intended for pan-ethnic carrier screening (pan-ethnic panel), Table 1, and the 18-gene panel was intended for Ashkenazi Jewish carrier screening (AJ panel).

The study sample comprised individuals self-identified as Ashkenazi Jewish and their indication for testing was carrier screening with no personal or family history of a genetic disorder. A total of 1150 individuals were tested in the pan-ethnic panel and 1248 individuals were tested in the AJ panel.

To compare pan-ethnic and AJ-based panels, positive findings for the AJ individuals tested in the pan-ethnic panel were re-analyzed with the 18 genes in the AJ panel and with the 9 genes recommended by ACMG. Similarly, positive findings for the AJ individuals tested in the AJ panel were re-analyzed with the 9 genes recommended by ACMG.

II. Results and Discussion

Table 2. Comparison of positive results for Ashkenazi Jewish individuals tested in the pan-ethnic and AJ panels.

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of genes assessed</th>
<th>Number of individuals tested</th>
<th>Number of individuals positive:</th>
<th>Total number</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-ethnic panel</td>
<td>87</td>
<td>1150</td>
<td>344</td>
<td>72</td>
<td>13</td>
</tr>
<tr>
<td>AJ panel</td>
<td>18</td>
<td>1248</td>
<td>259</td>
<td>53</td>
<td>5</td>
</tr>
</tbody>
</table>

DISCUSSION: In the pan-ethnic panel 431/1150 (37.5%) AJ individuals were carriers of at least one disease. If these individuals were tested in the AJ panel, the detection rate would be 280/1150 (24.3%). If these individuals were tested for the nine ACMG recommended diseases, the detection rate would be 207/1150 (18.0%). The validity of this extrapolation is demonstrated by the equivalent findings that the detection rate is 25.5% for AJ individuals tested with the AJ panel and 18.9% for the ACMG recommended diseases.

IV. Conclusions

- A pan-ethnic expanded carrier screening panel of 87 genes increased the carrier detection rate in Ashkenazi Jewish individuals by approximately 50%, compared with a panel of 18 genes considered to be relevant to the Ashkenazi Jewish population.
- The detection rate would have increased by approximately 100% if the pan-ethnic panel were compared to just the ACMG recommended genes in this data set.
- These data show that a pan-ethnic panel is more effective than targeted AJ panels in carrier detection among individuals of Ashkenazi Jewish descent.

V. References


DISCUSSION: The pan-ethnic panel identified carriers for 38 diseases among Ashkenazi Jews; however, carrier status for only 17 of these diseases could be assessed using the AJ panel. Therefore, 21 “non-AJ” diseases accounted for the difference in carrier rates between the pan-ethnic and AJ panels (Table 3).