Contribution of Large Genomic Deletions to Recessive Mendelian Disease Carrier Burden within a Healthy Population

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Introduction: Intragenic deletions

- Copy number variants (CNVs) have been overlooked in published case studies, diagnostic testing, & carrier screening for multiple hereditary disorders:
  - Require specialized protocols to detect with high accuracy
  - Contribution may be considered negligible
- Full contribution to carrier rates remains to be determined for some genetic diseases and ethnic populations
  - Available literature: average 3.6%, median 0%, across 169 recessive Mendelian diseases examined
- **Goal:** Examine population CNV carrier rates among an ethnically diverse cohort of individuals across a range of serious and clinically actionable Mendelian diseases
Methods

346,182 patients: routine Expanded Carrier Screening

NGS: 176 Mendelian recessive disorders

Variant calling: incl. CNVs (leveraging NGS read-depth values)

ACMG-based classification

Contribution of CNV dels & dup‡

Results from 169* genes were interrogated

* 7 genes excluded due to specialized assay design or because loss-of-function was not a disease mechanism
‡ CNV duplications for CFTR & DMD
Results: Self-reported ethnicity among 346,182 patients
Widespread contribution of CNVs to population carrier burden

Pathogenic CNVs detected in 91% of genes (153/169)

CNV contribution to carrier rate

- Estimate (literature)
- ECS cohort
CNV contribution exceeded 5% for 37 genes

% Contribution of CNVs to Carriers by Gene/Disease

% Carriers of CNVs
0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

Overall no. of disease carriers
0 500 1000 1500 2000 2500

Contiguous gene deletion
17% of pathogenic CNVs are completely novel

<table>
<thead>
<tr>
<th>CNV Classification</th>
<th>Published Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely Pathogenic <strong>without</strong> case support</td>
<td>-</td>
</tr>
<tr>
<td>Likely Pathogenic <strong>with</strong> case support</td>
<td>![Icon]</td>
</tr>
<tr>
<td>Known Pathogenic</td>
<td>![Icon]</td>
</tr>
</tbody>
</table>

- Finnish
- Native American
- Ashkenazi
- Jewish
- Hispanic
- Colombian
- Native American
- Southern Indigenous
- Middle Eastern
- Southeast Asian
- South Asian
- East Asian

75.2% of cases are known pathogenic, 17.0% are likely pathogenic **without** case support, and 7.7% are likely pathogenic **with** case support.
Landscape of CNV contribution: 169 diseases
Recurrent CNVs: Multiethnic

Example: **GALC 30 kb del**
- Krabbe disease
- frame N/A (involves last coding exon)
- **31%** disease alleles for total cohort
- seen in **89%** of ethnicities
- Luzi *et al.* 1995, Tappino *et al.* 2010:
  - reported as frequent in Caucasians
## Recurrent CNVs: Multiethnic

<table>
<thead>
<tr>
<th>CNV</th>
<th>Pop freq</th>
<th>% ethnicities</th>
<th>% all carriers</th>
<th>Frame</th>
<th>Published evidence (PMIDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GALC Exon 11-17 del</strong></td>
<td>0.14%</td>
<td>86%</td>
<td>31%</td>
<td>N/A (last coding exon)</td>
<td>‘30kb deletion’ reported as frequent in Caucasians. Nonrecurrent appearance (8634707, 20886637)</td>
</tr>
<tr>
<td><strong>CLN3 Exon 8-9 del</strong></td>
<td>0.19%</td>
<td>71%</td>
<td>82%</td>
<td>OUT-OF-FRAME</td>
<td>‘1 kb deletion’ reported as a founder mutation in a common European ancestor (22545070)</td>
</tr>
<tr>
<td><strong>CTNS 57 kb deletion</strong></td>
<td>0.16%</td>
<td>71%</td>
<td>58%</td>
<td>N/A (1st coding exon)</td>
<td>57 kb deletion reported as a Caucasian founder mutation, but reported in some non-European populations (10417278, 30949462)</td>
</tr>
<tr>
<td><strong>HEXB Exon 1-5 del</strong></td>
<td>0.04%</td>
<td>71%</td>
<td>16%</td>
<td>N/A (1st coding exon)</td>
<td>Recombination between two Alu sequences. Suggested French or French-Canadian founder origin (2147027)</td>
</tr>
<tr>
<td><strong>HBB Exon 1-3 del</strong></td>
<td>0.05%</td>
<td>71%</td>
<td>2%</td>
<td>WHOLE GENE</td>
<td>Deletions of varying size have been reported in a large number of ethnicities (23637309)</td>
</tr>
<tr>
<td><strong>GJB2-D13S1830 del</strong></td>
<td>0.04%</td>
<td>71%</td>
<td>2%</td>
<td>PROMOTER</td>
<td>Founder effect in Ashkenazi Jews and a suggested common founder for countries in Western Europe (14571368)</td>
</tr>
</tbody>
</table>
## Recurrent CNVs: Known ethnicity-specific

<table>
<thead>
<tr>
<th>CNV</th>
<th>Ethnicity-specific</th>
<th>Sub-pop freq</th>
<th>% all carriers</th>
<th>Frame</th>
<th>Significance (p-value)</th>
<th>Published evidence (PMIDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEB Exon 55 del</strong></td>
<td>Ashkenazi Jewish</td>
<td>7.4E-03</td>
<td>75%</td>
<td>IN-FRAME</td>
<td>2.56E-65</td>
<td>Ashkenazi Jewish founder (15221447, 19232495)</td>
</tr>
<tr>
<td><strong>GALT Exon 1-11 del</strong></td>
<td>Ashkenazi Jewish</td>
<td>5.6E-03</td>
<td>76%</td>
<td>WHOLE GENE (bipartite structure)</td>
<td>1.91E-57</td>
<td>Ashkenazi Jewish founder (11286505, 17079880)</td>
</tr>
<tr>
<td><strong>MCOLN1 Exon 1-7 del</strong></td>
<td>Ashkenazi Jewish</td>
<td>2.3E-03</td>
<td>26%</td>
<td>N/A (1st coding exon)</td>
<td>4.01E-21</td>
<td>Ashkenazi Jewish founder (10973263, 11551108)</td>
</tr>
<tr>
<td><strong>ERCC8 Exon 4 del</strong></td>
<td>East Asian</td>
<td>4.7E-04</td>
<td>30%</td>
<td>OUT-OF-FRAME</td>
<td>2.53E-04</td>
<td>East Asian founder rearrangement involving IVS4 (28333167, 29057985)</td>
</tr>
</tbody>
</table>
Recurrent CNVs: Novel ethnicity-specific

**CAPN3 Exon 1-24 del**
- Calpainopathy
- whole gene del
- observed 22 times in *Hispanic* patients
- 15% disease alleles for this ethnicity
- **Reported in different ethnicity:**
  - Jaka *et al.* 2014: 2 Spanish families - authors suggest as possible founder in south of Spain
Recurrent CNVs: Novel ethnicity-specific

\textit{ATP7B} Exon 2 del

- Wilson disease
- out-of-frame
- observed 16 times in \textbf{African or African-American} patients
- 11\% disease alleles for this ethnicity
- \textbf{Reported in different ethnicity:}
  - Hua \textit{et al.} 2016, Chen \textit{et al.} 2019: 4 Chinese cases
Recurrent CNVs: Novel ethnicity-specific

**MAN2B1 Exon 7-16 del**
- Alpha-mannosidosis
- In-frame (37% protein)
- Observed 9 times in **African or African-American** patients
- 16% disease alleles for this ethnicity
- Not found in the literature:
  - Cases with encompassed deletions only
Recurrent CNVs: Novel ethnicity-specific

**BCKDHB Exon 4-6 del**
- Maple syrup urine disease type Ib
- in-frame (34% protein)
- observed 6 times in East Asian patients
- 33% disease alleles for this ethnicity
- **Reported in different ethnicity:**
  - Abiri *et al.* 2019: 1 Iranian case
Conclusions

• Contribution of CNVs to population carrier burden is widespread for serious and clinically actionable Mendelian diseases.

• Recurrent CNVs make a previously unappreciated and clinically relevant contribution to ethnicity-specific disease allele frequency.

• Highlights the need to incorporate CNV calling in testing paradigms to maximize detection rates across the broad spectrum of patients and healthy adult individuals.
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