When to consider: ExomeNext + mtDNA sequencing

Mitochondrial disease refers to any illness resulting from deficiency of the electron transport chain, fatty acid oxidation, Krebs cycle, or pyruvate dehydrogenase complex resulting from mutations in one or more mitochondrial or nuclear-encoded proteins. Sequencing of the mitochondrial genome (mtDNA) specifically interrogates mutations in the maternally-inherited mtDNA.

In an effort to continue to provide responsible, cost-effective, and rapid genetic testing, Ambry Genetics retrospectively analyzed all of our previous ExomeNext results, including mtDNA sequencing and analysis of known mtDNA mutations, to determine the positive yield of mtDNA mutations.

Among thousands of cases performed over the course of 5 years, only 0.1% were found to be positive for a mtDNA mutation. Of important note, a mitochondrial disorder was included as part of the differential diagnosis in each of the patients with identified mtDNA mutations. This suggests that a mitochondrial condition is unlikely to be diagnosed via whole exome sequencing, unless the patient’s clinical features specifically suggest a mitochondrial disorder. These features, although highly variable, generally feature multi-organ or multi-systemic involvement.

MtDNA positive case examples

<table>
<thead>
<tr>
<th>Overall Results</th>
<th>Differential Diagnosis</th>
<th>Gene</th>
<th>Nucleotide Change</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely Positive</td>
<td>Respiratory chain defect</td>
<td>MT-ATP6</td>
<td>m.8969G&gt;A</td>
<td>de novo</td>
</tr>
<tr>
<td>Positive</td>
<td>Mitochondrial/FA oxidation disorder</td>
<td>MT-TL1</td>
<td>m.3243A&gt;G</td>
<td>inherited</td>
</tr>
<tr>
<td>Positive</td>
<td>Mitochondrial disorder (Leigh’s disease, MELAS), organic acidurias, primary dystonias, juvenile Huntington disease, likely AD due to mother and maternal uncle similarly affected.</td>
<td>MT-ND6</td>
<td>m.14459G&gt;A</td>
<td>undetermined</td>
</tr>
<tr>
<td>Positive</td>
<td>MTTK gene A3243G mutation</td>
<td>MT-TL1</td>
<td>m.3243A&gt;G</td>
<td>likely maternal</td>
</tr>
<tr>
<td>Positive</td>
<td>Mitochondrial disorder</td>
<td>MT-NDS</td>
<td>m.13513G&gt;A</td>
<td>inherited</td>
</tr>
</tbody>
</table>

Today, due to the low yield of positive mtDNA findings, mtDNA sequencing is now available as an add-on to standard ExomeNext testing. If a mitochondrial disorder is suspected, ExomeNext-Proband/Trio plus mtDNA is indicated.

ExomeNext-Proband

- Whole exome sequencing of the Proband only.

ExomeNext-Proband plus mtDNA

- Whole exome sequencing PLUS mtDNA analysis of the Proband only.
- Indicated for patients with a complex differential diagnosis including a suspected mitochondrial disorder.

ExomeNext-Trio

- Whole exome sequencing of the Trio. This test provides increased diagnostic yield over Proband only options.
- Indicated when a Trio is available for testing.

ExomeNext-Trio plus mtDNA

- Whole exome sequencing PLUS mtDNA analysis of a Trio. This test provides increased diagnostic yield over Proband only options.
- Indicated for patients with a complex differential including a suspected mitochondrial disorder and a Trio is available.