Utility of Genetic Testing to Identify Individuals Suspected of Having Hereditary ATTR (hATTR) Amyloidosis

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Background and Rationale

Hereditary ATTR (hATTR) Amyloidosis

- Inherited, rapid, progressive, life-threatening disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR proteins accumulating as amyloid deposits in multiple sites including nerves, heart, and gastrointestinal tract
- Affecting approximately 50,000 people worldwide with a median survival of 4.7 years following diagnosis and a reduced survival of 3.4 years for patients presenting with cardiomyopathy
- More than 120 different pathologic TTR mutations have been identified (Fig. 1)
- Disease penetrance and rate of progression may be influenced by TTR genotype, which can vary by geographical region
- Individuals with hATTR amyloidosis require an early and accurate diagnosis due to rapid natural progression of disease
- hATTR amyloidosis is often misdiagnosed due to its constellation of symptoms, which may overlap with other diseases; multiple specialists are often seen prior to diagnosis
- Since the etiology of hATTR amyloidosis is different from that of other types of polyneuropathy and cardiomyopathy, misdiagnosis could lead to ineffective or possibly detrimental treatment

Results

- As of March 2018, 4,600 individuals were tested via Alnylam Act resulting in ~300 individuals with TTR mutations. Starting in April 2017, Alnylam Act provided options for comprehensive neurology and cardiomyopathy panels and collected HCP reported signs and symptoms. Here we present data between April 2017 and January 2018 (Fig. 1)
- 2,927 samples from individuals over the age of 18 were tested using Alnylam Act between April 2017 and January 2018; total of 408 unique physicians submitted samples during this period (Fig. 3, Table 1)
- 490 (16.8%) positive results for pathogenic or likely pathogenic mutations related to hereditary neuropathies or cardiomyopathies were identified (Fig. 5 and 6)
- 141 (4.8%) positive results for pathogenic or likely pathogenic TTR gene mutations were identified (Fig. 6)

Figure 1: Select Examples of Variants Identified in the TTR Gene

Figure 2: Testing Options

Table 1: Percent Positive hATTR Amyloidosis Results by Specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>HCPs</th>
<th>Total Tests</th>
<th>TTR Positive Results</th>
<th>TTR Percent Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>72</td>
<td>301</td>
<td>60</td>
<td>19.9%</td>
</tr>
<tr>
<td>Neurology</td>
<td>222</td>
<td>2201</td>
<td>31</td>
<td>1.4%</td>
</tr>
<tr>
<td>Other</td>
<td>114</td>
<td>425</td>
<td>50</td>
<td>11.7%</td>
</tr>
<tr>
<td>Total</td>
<td>408</td>
<td>2927</td>
<td>141</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

- The most common TTR mutation identified by neurologists and cardiology was Val122Ile

Figure 3: Test Results for Hereditary Neuropathies or Cardiomyopathies

Table 2: Frequency of hATTR Amyloidosis Signs and Symptoms Reported by Mutation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total (n=408)</th>
<th>Val122Ile (n=199)</th>
<th>Val50Met (n=120)</th>
<th>Thr60Ala (n=76)</th>
<th>Thr60Pro (n=13)</th>
<th>Other (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of hATTR amyloidosis</td>
<td>47%</td>
<td>32%</td>
<td>52%</td>
<td>78%</td>
<td>52%</td>
<td>52%</td>
</tr>
<tr>
<td>Sensory and motor</td>
<td>29%</td>
<td>25%</td>
<td>35%</td>
<td>22%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>15%</td>
<td>10%</td>
<td>14%</td>
<td>17%</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>41%</td>
<td>56%</td>
<td>0%</td>
<td>13%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>21%</td>
<td>23%</td>
<td>7%</td>
<td>9%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Generalized fatigue</td>
<td>17%</td>
<td>18%</td>
<td>21%</td>
<td>9%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>9%</td>
<td>5%</td>
<td>21%</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Ocular changes</td>
<td>1%</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- hATTR amyloidosis signs and symptoms were reported with 141 positive TTR results and included: family history of hATTR amyloidosis (n=86), sensory and motor (n=41), autonomic dysfunction (n=21), heart disease (n=59), carpal tunnel syndrome (n=30), generalized fatigue (n=24), weight loss (n=13), and ocular changes (n=1) (Table 2)

Discussion and Conclusion

Alnylam Act data demonstrate that hATTR amyloidosis is a multisystem disease with heterogeneous clinical presentation
- hATTR amyloidosis should be considered in individuals with signs or symptoms of sensorimotor neuropathy or heart disease with multisystem involvement (e.g., carpal tunnel syndrome, autonomic dysfunction, etc.)
- Diagnosis can be facilitated by investigating family history of hATTR amyloidosis

Genetic testing is a valuable tool to facilitate an earlier diagnosis of hATTR amyloidosis
- Genetic testing may minimize use of more invasive diagnostic tests, especially in patients with heart disease, as well as with sensory and motor symptoms of unknown etiology

References

10. The use of this tool is intended to support healthcare providers in their decisions related to patient care.

Figure 4: Usage of Alnylam Act Genetic Testing by State in the United States

Figure 5: Individuals with Positive Pathogenic and Likely Pathogenic Results: Non-TTR Genes (n=352)

Figure 6: Distribution of TTR Positive Variants Identified through Alnylam Act (n=141)