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

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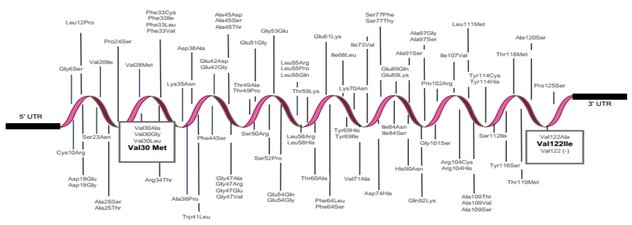
Background and Rationale

Hereditary ATTR (hATTR) Amyloidosis

- Inherited, rapidly 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[1-5]
  - Affecting approximately 50,000 people worldwide[6,7] with a median survival of 4.7 years following diagnosis and a reduced survival of 3.4 years for patients presenting with cardiomyopathy[8-10]
  - More than 120 different pathologic TTR mutations have been identified (Fig. 1)[11]
- Multisystem disease with heterogeneous clinical presentation; includes sensory, motor, autonomic, and cardiac symptoms[1,12,13]
  - Some individuals present predominantly with polyneuropathy symptoms (formerly known as FAP), while others present with cardiomyopathy symptoms (formerly known as FAC); yet many patients experience a mixed phenotype
  - hATTR amyloidosis is an autosomal dominant condition. Clinical manifestations (e.g., disease penetrance and rate of progression) may be influenced by TTR genotype, which can vary by geographical region[13]
- 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

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



Third-Party Genetic Testing

- Via the Alnylam Act™ program, Alnylam Pharmaceuticals sponsors a no-charge third-party genetic testing and counseling program for individuals who may carry gene mutations known to be associated with hATTR amyloidosis
- Alnylam Act program was created (2014) to potentially reduce barriers to genetic testing to help people and their healthcare providers (HCP) make informed decisions about their health and was later expanded (2016) to include optional third-party genetic counseling via telephone for individuals and families at risk for hATTR amyloidosis
- Benefits of genetic testing and counseling include the ability to identify risk of disease, shorten the time to diagnosis, tailor care, enable clinical trial enrollment, and connect individuals with support services
- The program started with a single TTR gene test and was expanded (2017) to include comprehensive neuropathy and cardiomyopathy panels to test for conditions with clinical presentations that overlap with hATTR amyloidosis (Fig. 2); program also began to collect HCP reported signs and symptoms with each test requisition form
- Genetic testing service is available in the United States and Canada and is performed by Invitae through next generation sequencing with deletion/duplication testing.

Objective

- To evaluate the usage of third-party genetic testing service in individuals who may carry gene mutations known to be associated with hATTR amyloidosis since the implementation of the expanded neuropathy and cardiomyopathy panels in April 2017

Methods

- The number of registered HCP accounts, number of individuals tested, variants found, and symptoms reported in the test requisition form are reported to the sponsor every other week. These reports contain no patient identifiers

Figure 2: Testing Options

Transthyretin Amyloidosis Test
Single-gene testing for TTR gene, which is associated with hATTR amyloidosis

Comprehensive Neuropathies Panel
Testing for ~70 genes that cause dominant, recessive, and X-linked hereditary neuropathies, including hATTR amyloidosis

Cardiomyopathy Comprehensive Panel
Testing for ~50 genes associated with inherited cardiomyopathy conditions, including hATTR amyloidosis

Results

- As of March 2018, ~4,600 individuals were tested via Alnylam Act resulting in ~350 individuals with TTR mutations. Starting in April 2017, Alnylam Act provided options for comprehensive neuropathy and cardiomyopathy panels and collect 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)
  - 493 (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 3: Test Results for Hereditary Neuropathies or Cardiomyopathies

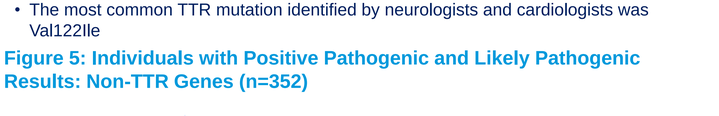


Figure 4: Usage of Alnylam Act Genetic Testing by State in the United States

- Alnylam Act has been used by HCPs in 45 states in the United States
- States with the highest usage of Alnylam Act are Kansas, Pennsylvania, Maryland, and New York

Table 1: Percent Positive hATTR Amyloidosis Results by Specialty

Specialty	HCPs	Total Tests	TTR Positive Results	TTR Percent Positive
Cardiology	72	301	60	19.9%
Neurology	222	2201	31	1.4%
Other	114	425	50	11.7%
Total	**408**	**2927**	**141**	**4.8%**

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

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)

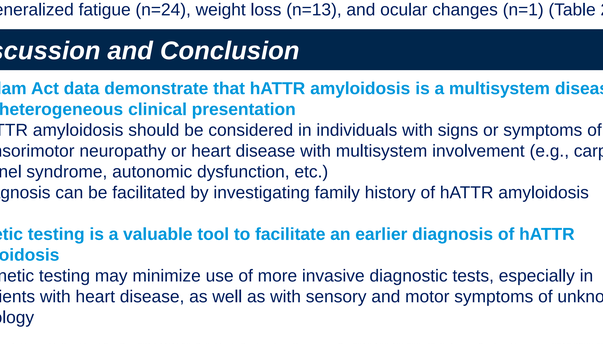


Table 2: Frequency of hATTR Amyloidosis Signs and Symptoms Reported by Mutation

Symptom	Total (n=141)	Val122Ile (n=88)	Val30Met (n=14)	Thr60Ala (n=23)	Other (n=16)
Family history of hATTR amyloidosis	47%	32%	57%	78%	52%
Sensory and motor	29%	25%	43%	22%	35%
Autonomic dysfunction	15%	10%	14%	17%	26%
Heart disease	41%	58%	0%	13%	17%
Carpal tunnel syndrome	21%	23%	7%	9%	30%
Generalized fatigue	17%	18%	21%	9%	13%
Unintentional weight loss	9%	5%	21%	13%	13%
Ocular changes	1%	0	7%	0%	4%

- hATTR amyloidosis signs and symptoms were reported with 141 positive TTR results and included: family history of hATTR amyloidosis (n=66), sensory and motor (n=41), autonomic dysfunction (n=21), heart disease (n=58), 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

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- Jordanna Mora and Angela M Partisano: employed by Alnylam Pharmaceuticals
- Daniel Anderson and Rebecca Truty: employed by Invitae Corporation
- Ruthvik Malladi: Post-PharmD Fellow at Alnylam Pharmaceuticals; employed by Northeastern University
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