Alnylam Act®: Heterogeneous Disease Manifestations of Hereditary Transthyretin-Mediated Amyloidosis

Ruthvik Malladi[1], Rebecca Truty[2], Tom Winder[2], Quinn Dinh[1], Maria Melanson[1], and Sonalee Agarwal[1]

[1]Alnylam Pharmaceuticals, Cambridge, MA, USA; [2]Invitae San Francisco, CA, USA

Introduction

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in the multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
- Non-specific heterogeneous clinical presentation[5,6] that is often misdiagnosed[6]; majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[7–10]
- Early and accurate diagnosis is needed due to the aggressive natural progression of disease and to enable initiation of appropriate treatment[6,11–13]

Alnylam Act®: Sponsored Genetic Testing Program

- To facilitate earlier diagnosis, Alnylam Pharmaceuticals partnered with Invitae and InformedDNA to offer Alnylam Act®, a sponsored, third-party genetic testing and counseling program offered at no-charge to individuals who may carry gene mutations known to be associated with hATTR amyloidosis (Figure 1)
- Alnylam Act® was created in 2014 to reduce barriers to genetic testing and help individuals and their healthcare providers make informed decisions about their health
  - Expanded in 2016 to provide third-party genetic counseling via telephone for individuals and families at risk for hATTR amyloidosis
- Genetic testing service available in the United States (US) and Canada and is performed by Invitae; genetic counseling available only in the US through InformedDNA
- Alnylam receives certain de-identified patient information from Invitae

Figure 1. Alnylam Act® 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

Objective

- To describe the frequency of signs and symptoms observed in individuals with hATTR amyloidosis identified through Alnylam Act®

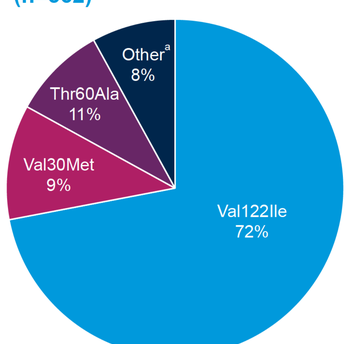
Methods

- Individuals included were age ≥18 years with a suspected diagnosis, or a confirmed family history of hATTR amyloidosis
- Patients' phenotypic information was captured through the eligibility criteria in the form of a symptom checklist on the test requisition form
- One of three testing options offered through Alnylam Act® (**Figure 1**): next-generation sequencing with the Transthyretin Amyloidosis Test, Comprehensive Neuropathies Panel, or the Cardiomyopathy Comprehensive Panel
- Descriptive analysis performed to establish the frequency of signs/symptoms reported in Alnylam Act® across various genotypes

Results

- From April 2017 to February 2019, 562 individuals tested through Alnylam Act® were found to have pathogenic *TTR* mutations
- Most common *TTR* mutations identified were Val122Ile (n=407; 72%), Thr60Ala (n=60; 11%), and Val30Met (n=50; 9%) (**Figure 2**)
  - Other mutations were identified in 45 individuals (8%): Ala97Ser, Leu58His, Phe64Leu, Ser77Tyr, and Thr49Ser

Figure 2. Distribution of *TTR* Mutations Identified through Alnylam Act® (n=562)

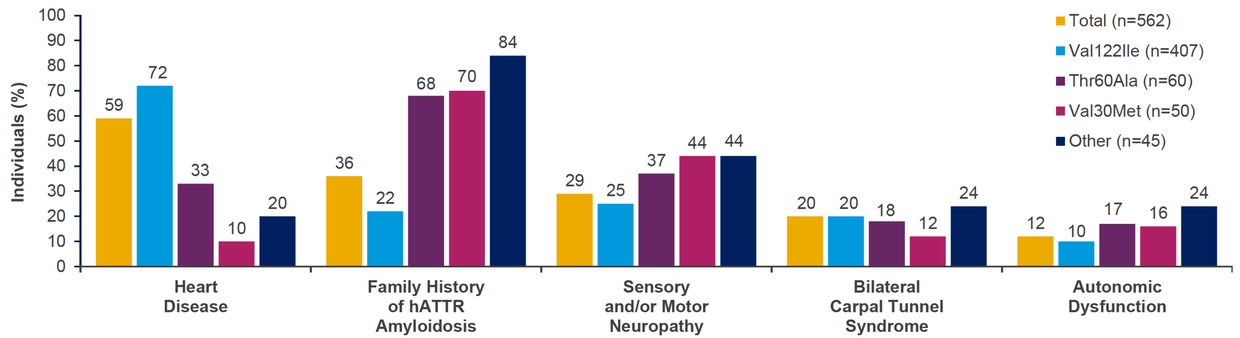


[a]Other genotypes: Ala97Ser, Leu58His, Phe64Leu, Ser77Tyr, and Thr49Ser

Results

- Overall, 204 individuals (36%) presented with a family history of hATTR amyloidosis and/or the following signs and symptoms: heart disease (n=329; 59%), sensory and/or motor neuropathy (n=164; 29%), bilateral carpal tunnel syndrome (n=110; 20%), and autonomic dysfunction (n=70; 12%) (**Figure 3**)
- Heart disease occurred more frequently in individuals with the Val122Ile mutation (72%) compared with individuals harboring other mutations (10–33%); however, evidence of polyneuropathy was also seen in these patients (sensory and/or motor neuropathy: 25%, autonomic dysfunction: 10%)
  - Bilateral carpal tunnel syndrome was also seen in 20% of Val122Ile patients
  - The multisystem signs and symptoms were evident across all mutations, even in patients with mutations that have been considered predominantly cardiac phenotype (Val122Ile)

Figure 3. Proportion of Individuals by *TTR* Mutation with a Family History or Signs and Symptoms of hATTR Amyloidosis from Alnylam Act®



Conclusions

- Data from the Alnylam Act® program highlights the heterogeneity of manifestations in hATTR amyloidosis; individuals presented with multiple overlapping signs and symptoms, including but not limited to neuropathy, cardiac manifestations, and autonomic dysfunction, irrespective of their underlying genotype
  - Individuals with the most common mutations reported multisystem signs and symptoms, including both cardiac and neuropathic manifestations
  - Sponsored genetic testing has the potential to further delineate the genotypic and phenotypic picture of hATTR amyloidosis, and inform the healthcare community on the prevalence, distribution, and clinical presentation of this rapidly progressive and fatal disease
- The Alnylam Act® program participants include asymptomatic individuals (carriers reporting only family history of hATTR amyloidosis); therefore, frequency of manifestations may be skewed
- These data highlight the importance of incorporating a multidisciplinary approach to diagnosis and management
- When assessing individuals who present with multisystem disease manifestations, a high clinical suspicion of hATTR amyloidosis is required for expediting accurate disease diagnosis

Abbreviations: hATTR, hereditary transthyretin-mediated; TTR, transthyretin.
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