Utility of Genetic Testing for Diagnosing hATTR Patients: Results from a European and Middle East Genetic Testing Programme

Akash Singh[1], Marie Théaudin[2], Berthold Streubel[3], David Kasper[4], Karen Frascello[5], Antoine Bondue[6]

[1]Global Diagnostics, Alnylam UK Ltd, Maidenhead, UK; [2]Department of Neurology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [3]Medical Genetics, Medical University of Vienna, Vienna, Austria; [4]Diagnostics and Research, ARCHIMEDlife, Vienna, Austria; [5]Global Diagnostics, Alnylam Pharmaceuticals, Cambridge, MA; [6]Department of Cardiology, Hôpital universitaire de Bruxelles, Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium

Conclusions

- The genetic testing programme achieved a 3.5% diagnostic yield, identifying 18 unique pathogenic/likely pathogenic *TTR* gene variants, with 95 patients reaching a genetic diagnosis
- The results underscore the importance of genetic testing for early identification of hereditary transthyretin amyloidosis (hATTR), especially in patients with cardiac and neuropathy symptoms
- Genetic testing has the potential to improve outcomes in patients with hATTR by facilitating early diagnosis

Introduction

hATTR

- hATTR is an underdiagnosed and fatal disease characterised by the build-up of toxic transthyretin (TTR) amyloid fibrils in various organs, leading to progressive dysfunction of tissues and organs and resulting in various clinical presentations, including neuropathy and cardiomyopathy amongst other manifestations[1–3]
- hATTR is an autosomal dominant genetic disease, with variable penetrance, caused by variants in the *TTR* gene[1]
- Non-specific symptoms and rarity of the disease can lead to diagnostic delays of several years[4,5]
- Early diagnosis is critical for early treatment intervention that may increase survival and/or prevent irreversible deterioration of physical function and quality of life[6,7]

Objective

- To determine the diagnostic yield and efficacy of a single gene sequencing combined with patient eligibility criteria for hATTR from a European and Middle East genetic testing programme (GeneAct™)

Methods

- GeneAct™ is an Alnylam Pharmaceuticals-sponsored, no-charge genetic testing service in Europe and the Middle East, utilising Sanger sequencing-based single gene testing
- Blood samples for genetic analysis were collected on CE-certified dried blood spot cards
- Testing was conducted using a Sanger sequencing-based single-gene test (ARCHIMEDlife) and included analysis of the entire *TTR* gene (exons 1–4) and flanking intronic regions (+/- 20 base pairs) for single nucleotide variants and small deletions/insertions
- Potentially pathogenic variants were compared with known variants in the PubMed, HGMD®, ClinVar, and MASTERMIND databases
- Patient eligibility criteria were ≥18 years of age with a family history of hATTR or suspicion of hATTR based on ≥1 of the following findings: sensory neuropathy, motor neuropathy, autonomic dysfunction, heart disease, bilateral carpal tunnel syndrome, lumbar spinal stenosis, renal abnormalities, ocular changes, chronic inflammatory demyelinating polyneuropathy – atypical, motor neuron disease – atypical, gait disorders, unexplained weight loss, and positive imaging/biopsy
- Diagnostic yield was defined as one pathogenic or likely pathogenic variant in the *TTR* gene

Results

TTR Positivity

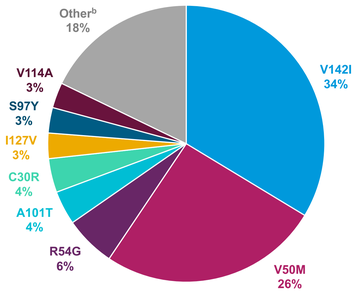
- A total of 2713 samples were analysed from January 2022–May 2024, from 22 countries in Europe and the Middle East (**Figure 1**)

Results

Figure 1. Countries Included in the GeneAct hATTR Genetic Testing Programme

- Genetic diagnosis was established in 95 participants with pathogenic or likely pathogenic variants resulting in a 3.5% diagnostic yield
- Overall, 18 unique pathogenic or likely pathogenic *TTR* gene variants were identified, with the most common variants being V142I and V50M, found in 34 (33.7%) and 26 (25.7%) participants, respectively (**Figure 2**)

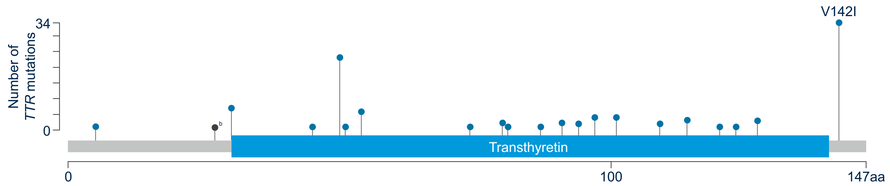
Figure 2. Variants Identified in the *TTR* Gene (n=101[a])



[a]Includes 5 variants of unknown significance that were identified in 6 symptomatic participants, but which were excluded from the calculation of diagnostic yield.
[b]Other includes D94H, T80A, and V91A (all n=2) and A45S, R123H, R5H, E109Q, E109K, E27*, E74Q, E81G, G87V, H51N, S120T, and S97F (all n=1).
*Indicates a stop codon. Percentages may not add up to 100 due to rounding.

- Identified variants occurred throughout the *TTR* gene (**Figure 3**), with the largest number of unique variants detected in exon 3
- An additional six symptomatic participants had *TTR* variants of unknown significance (these were excluded from the diagnostic yield calculation)

Figure 3. Distribution of Variants Within the *TTR* gene (n=101[a])



[a]Includes 5 variants of unknown significance that were identified in 6 symptomatic participants, but which were excluded from the calculation of diagnostic yield.
[b]The black colour represents a stop codon in the variant.

Baseline Characteristics

- Mean (SD) age at testing for all participants (n=2713) was 65.0 (15.9) years, and 1730 (63.8%) participants were male
- In participants who had *TTR* gene variants (n=101[a]):
  - The mean (SD) age was 57.2 (18.2) years, and 57 (56.4%) participants were male; median age at testing decreased over the duration of the analysis period, dropping from 73.0 years in the first half of 2022 to 58.0 years in the first half of 2024 (**Figure 4**)
  - A family history of hATTR was reported in 61 (60.4%) participants, three of whom were confirmed by their physician as being asymptomatic

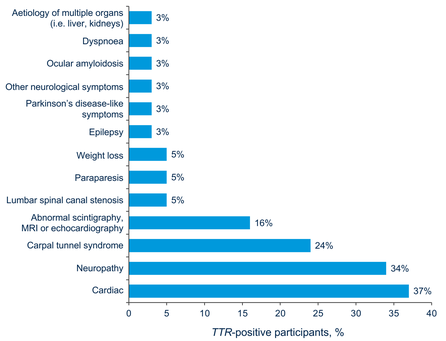
Figure 4. Median Age of Participants with Variants in the *TTR* Gene at Genetic Testing (n=101[a])

[a]Includes 5 variants of unknown significance that were identified in 6 symptomatic participants, but which were excluded from the calculation of diagnostic yield.

Presenting Signs and Symptoms

- The most commonly reported clinical manifestations among participants testing *TTR*-positive were cardiac (36.8%) and neuropathy (34.2%) signs or symptoms, followed by carpal tunnel syndrome (23.7%) (**Figure 5**)

Figure 5. Presenting Signs or Symptoms in Participants with Variants in the *TTR* Gene (n=38[a])



[a]Data available for 38 of 101 participants with variants in the *TTR* gene. Multiple symptoms may be reported by same patient.

Thank you to the patients and their physicians for their participation in the study.

Acknowledgements: Medical writing assistance was provided by Clare McCleverty, PhD, as contracted by Adelphi Communications Ltd, UK, and Rachael Powis, PhD of Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice guidelines.

Funding: This study was funded by Alnylam Pharmaceuticals.

Presented at: Heart Failure 2025, 17–20 May, 2025, Belgrade, Serbia.

Disclosures: A.S. and **K.F.** are employees of, and own shares in, Alnylam Pharmaceuticals. **M.T.** reports honoraria received to her institution for advisory boards, travel grants, and supportive grants from Alnylam, AstraZeneca, and Sobi. **B.S.** reports no competing interests. **D.K.** is an employee of ARCHIMEDLife. **A.B.** has acted as a consultant for Alnylam Pharmaceuticals, Amicus Therapeutics, Bayer, Bristol Myers Squibb, Pfizer, and Sanofi-Genzyme; and received research funding from Fonds De La Recherche Scientifique – FNRS, Fonds Erasme pour la Recherche Scientifique, and Fonds pour la Chirurgie Cardiaque.

References: 1. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 2. Ruberg et al. *JAMA* 2024;331:778–791; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–172; 4. Vera-Llonch et al. *Orphanet J Rare Dis* 2021;16:1–115; 5. Rozenbaum et al. *Cardiol Ther* 2021;10:141–159; 6. Kittleson et al. *J Am Coll Cardiol* 2023;81:1076–1126; 7. Ando et al. *Amyloid* 2022;29:143–155.

Footnote: [a]Includes 5 variants of unknown significance that were identified in 6 symptomatic participants, but which were excluded from the calculation of diagnostic yield.

Abbreviations: 1H, first half of the year; 2H, second half of the year; aa, amino acids; hATTR, hereditary transthyretin amyloidosis; HCP, healthcare professional; MRI, magnetic resonance imaging; SD, standard deviation; TTR, transthyretin.

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.