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Clinical Characteristics of Patients With Hereditary Transthyretin Mutations Primarily Associated With Cardiomyopathy and Other Rare Transthyretin Mutations: Insights From a Genetic Testing Programme

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BACKGROUND

- Hereditary transthyretin amyloidosis (hATTR or ATTRv [variant]) is a progressive, fatal disease caused by mutations in the transthyretin gene (*TTR*) that result in deposition of amyloid throughout the body, including the heart[1,2]
- Patients can experience a variety of symptoms and manifestations, including polyneuropathy and cardiomyopathy[1-4]
- The p.V142I and p.T80A mutations typically manifest with a cardiomyopathy phenotype, but patients with these mutations can also experience polyneuropathy and other symptoms/manifestations[3,4]
- Early diagnosis, which is key to optimising patient outcomes, is enabled by genetic testing[2,3]

PURPOSE

- To characterise the clinical profile and symptom burden of patients with hereditary transthyretin mutations traditionally associated with a predominant cardiomyopathy phenotype and rare hereditary transthyretin mutations

METHODS

- We analysed data from patients enrolled in the hATTR Compass programme, which provides confidential genetic testing to patients in the United States (including Puerto Rico) and Canada with possible hATTR with polyneuropathy or with a family history of hATTR
- Next-generation sequencing was performed using a *TTR* single-gene test, a 92-gene panel associated with inherited cardiovascular disease (CardioNext), or an 81-gene panel associated with neuromuscular disorders (NeuropathySelect)
- Descriptive analyses were performed[a]
- Symptoms may have been underreported because of the simplified, voluntary nature of participation and data collection

[a]Akcea is aware of data quality issues due in part to manual capture of initial patient requisition data. Because these account for a very low percentage of the overall data, the overall conclusions are not affected. Akcea and its partner are now using automated capture to improve data quality.

RESULTS

- Cardiology specialists referred 466 patients with a p.V142I mutation, 15 with a p.T80A mutation, and 28 with rare *TTR* mutations to this programme
  - There were 19 different rare *TTR* mutations, each with <5 patients

Figure 1. 74%, 53%, and 54% of the p.V142I, p.T80A, and rare *TTR* mutations cohorts, respectively, were aged 65 years or older

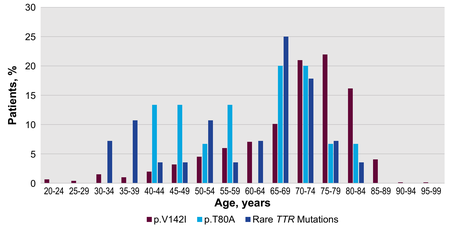
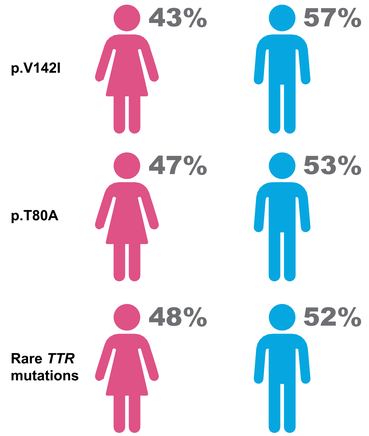
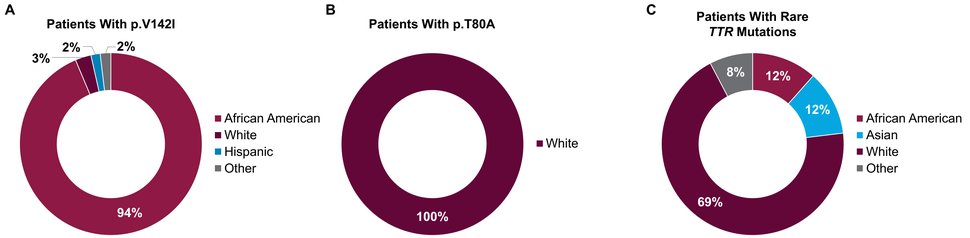


Figure 2. Of patients who reported sex, slightly more were male for all mutations cohorts



463/466 (99%) patients with p.V142I, 15/15 (100%) patients with p.T80A, and 27/28 (96%) patients with rare *TTR* mutations reported sex

Figure 3. Of patients who reported ethnicity, most with (A) p.V142I were African American, whereas all patients with (B) p.T80A and a majority of patients with (C) rare *TTR* mutations were White



426/466 (91%) patients with p.V142I reported ethnicity

13/15 (87%) patients with p.T80A reported ethnicity

26/28 (93%) patients with rare *TTR* mutations reported ethnicity

Figure 4. A minority of patients with (A) p.V142I had a family history of hATTR, whereas a majority of patients with (B) p.T80A and half of patients with (C) rare *TTR* mutations had a family history of hATTR

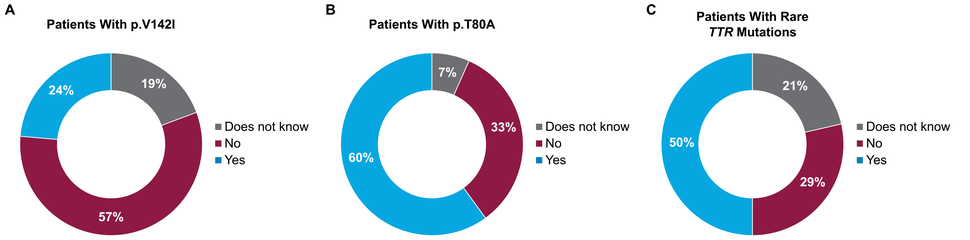
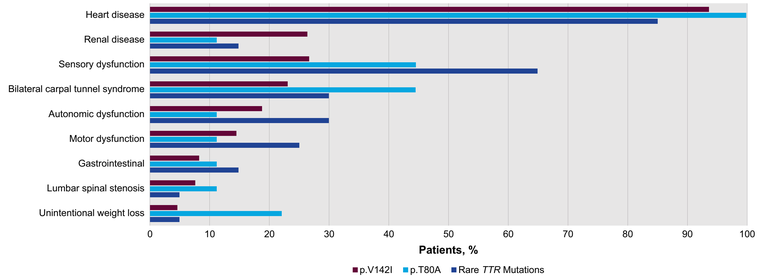


Figure 5. Among patients who reported symptoms/manifestations, many experienced heart disease, bilateral carpal tunnel syndrome, and sensory dysfunction



391/466 (84%) patients with p.V142I, 9/15 (60%) patients with p.T80A, and 20/28 (71%) patients with rare *TTR* mutations reported symptoms/manifestations

CONCLUSIONS

- In this cohort, most patients with a p.V142I mutation were African American, whereas most with a p.T80A mutation and half of those with rare *TTR* mutations were White
- Family history was not commonly reported in those with a p.V142I mutation but was commonly reported in those with p.T80A or rare *TTR* mutations. In the absence of family history, it is more difficult to diagnose patients with this hereditary disease
- Red-flag symptoms such as heart disease, bilateral carpal tunnel syndrome, and sensory dysfunction were fairly common, regardless of the underlying *TTR* mutation
- In patients presenting with a combination of cardiomyopathy, polyneuropathy, bilateral carpal tunnel syndrome, and/or other symptoms, further work-up and genetic testing is recommended
- In order to slow deterioration or maintain patient quality of life, it is critical that clinicians recognize red-flag hATTR symptoms, perform initial diagnostic testing, refer patients for genetic testing, and institute early disease-modifying therapy, as appropriate

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