Examining the phenotypes of MGB Biobank participants with the V142I *TTR* variant using a genotype first approach

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Background

- The Mass General Brigham Biobank (MGBB) identified V142I *TTR* variants associated with hereditary transthyretin amyloidosis (ATTRm) and is offering clinical confirmation
- TTR is not currently on the ACMG v3.0 secondary findings list
- The V142I variant is common in populations with African and Latinx ancestry and is associated with symptom onset in the seventh or eighth decade of life
- To better understand the penetrance of the V142I variant, we performed chart reviews for related clinical symptoms

Methods

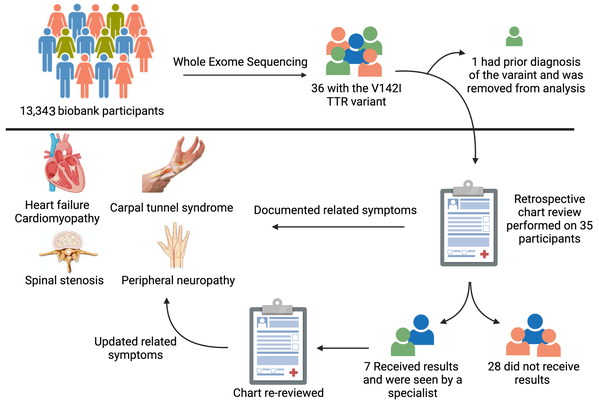

Figure 1. Chart review selection and review process

- Chart reviews were performed on those without a previous documentation of the V142I variant or a clinical diagnosis of ATTRm using methods adopted from Soper et al

Demographics of MGBB and V142I Positive Individuals

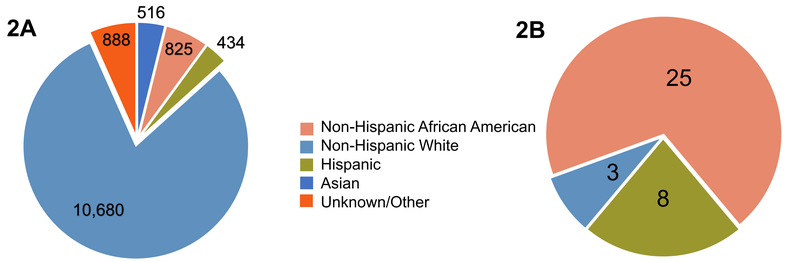

Figure 2. Race/Ethnicity of MGBB participants with whole exome sequencing **A)** Biobank participants with whole exome sequencing **B)** Biobank participants with the V142I variant

- Of the 36 participants with the V142I variant
  - Age at time of chart review was 43y (range: 23-80)
  - 66% (n=23) are female

Results

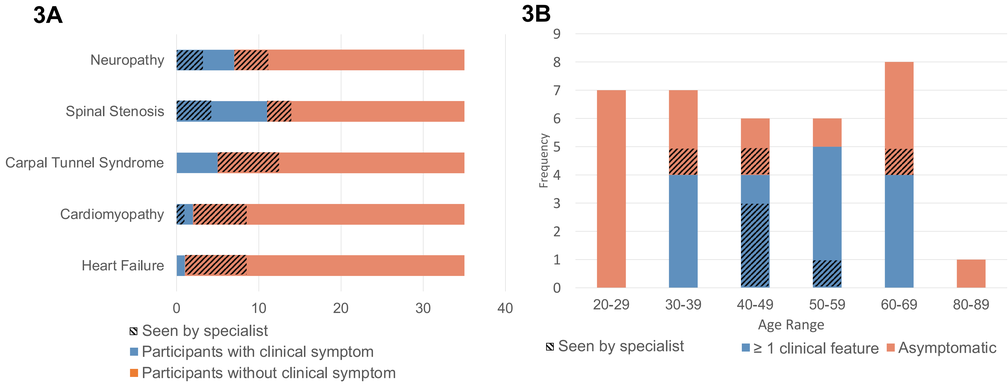

Figure 3. Related clinical symptoms identified in the 35 participants within the MGBB cohort. **A)** Frequency of clinical symptoms identified **B**) Presence of related clinical symptoms by age group

Discussion

- Early symptoms of ATTRm are common and may not lead to a clinical diagnosis
- Symptom age of onset may be earlier when using data from a genotype first approach
- Exclusion of TTR from recommended screening panels may widen existing healthcare disparities in the diagnosis and treatment of genetic disease

Limitations

- Only a portion of participants were seen by a specialist and had a targeted review of systems
- The variant has not yet been CLIA confirmed in 28 participants
- Some features are common or may be sequalae of other common comorbidities and it is difficult to determine if presentation is due to amyloid accumulation or other underlying medical issues

Future directions

- Consider inclusion of TTR on ACMG secondary findings list and other recommended population screening lists
- Document the experience of patients receiving unanticipated *TTR* results and obtain data from pyrophosphate scans and immunoglobulin results
- Perform PheWAS studies of the V142I *TTR* in the MGB Biobank

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