Disclosure Slide

Financial Disclosure for:
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Objective
- Over 100 distinct missense variants in the TTR gene are known to cause hereditary transthyretin-mediated (hATTR) amyloidosis, a progressively debilitating, life-threatening disease.
- To characterize missense TTR variants in a cohort of 302,330 subjects with available whole exome sequence and to test their association with hATTR amyloidosis.

Methods
- We identified missense TTR variants from 302,330 UK Biobank (UKBB) whole exome sequences
- Variants were classified as pathogenic, benign, conflicting interpretation, uncertain significance, or novel, based on CLINVAR, with “novel” indicating the variant had not been previously assessed for pathogenicity
- For common (MAF >1%) missense TTR variants, we ran a single-variant phenome-wide association study (PHEWAS) testing the association of genotype with available phenotypes, including serum biomarkers, ICD10 codes, and quantitative traits
- For rare variants (MAF < 1%), we aggregated variants across TTR and tested their association with available phenotypes using SKAT-o
- All statistical models were controlled for age, sex and genetic ancestry via principal components and Bonferroni-corrected p-values of $3.68 \times 10^{-5}$ were considered statistically significant

Results
- We identified 71 missense TTR variants, including 9 known pathogenic variants (carried by 270 subjects), 19 variants of uncertain or conflicting interpretation (carried by 483 subjects), and 40 novel variants (carried by 84 subjects)
- 3 of 270 subjects with a known pathogenic variant had a diagnosis of amyloidosis (ICD10 code: ‘E85’)

Common variant PHEWAS
- We found one common missense variant in TTR: rs1800458; Gly6Ser.
- Phenome-wide association analysis of the common Gly6Ser (rs1800458) variant (MAF = 8%, n= 42,728 carriers) revealed no significant associations, supporting the CLINVAR designation of ‘benign’

Rare variant PHEWAS
- SKAT-o analysis aggregating TTR variants of uncertain significance (conflicting, uncertain, or novel by CLINVAR designation) revealed no significant associations with the 1,359 phenotypes tested

Glu89Lys variant of TTR protein found in amyloidosis patient
- One carrier of a rare missense TTR variant that is not in CLINVAR (Chr18:Pos31595244:G:A,p.Glu89Lys) was diagnosed with amyloidosis at 57.9 years of age with other common hATTR manifestations:
  - although very rare (n carrier UKBB = 1), this amino acid change has been previously described in 4 case reports:
    - Glu89Lys variants in patients strongly present with early-onset cardiomyopathy (avg 51.5 yo ± 6.4), progressing with mild-to-moderate polyneuropathy
    - No case reports indicate hATTR as the cause – familial amyloid polyneuropathy and wild type amyloidosis noted
- A CLINVAR pathogenic variant exists at same position (Chr18:Pos31595244:G:C,p.Glu89Gln; rs121918082)

Conclusions
- Characterization of missense TTR variants in 302,330 UKBB whole exome sequences revealed support for the ‘benign’ designation of the Gly6Ser variant and support for the pathogenicity of the Glu89Lys variant

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