The V122I Mutation in Hereditary Transthyretin-Mediated Amyloidosis Is Significantly Associated with Polyneuropathy

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Introduction

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

- Rare, progressively debilitating, and fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
- Affects ~50,000 people worldwide[4]; median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy[6–9]
- Non-specific heterogeneous clinical presentation[5,10]; historically, patients identified by their predominant phenotype (polyneuropathy or cardiomyopathy), however, recent data have emerged indicating that the majority of patients develop a mixed phenotype of both polyneuropathy and cardiomyopathy[11–14]
  - V122I (Val122Ile; p.V142I; rs76992529) variant is the most common pathogenic *TTR* mutation in the US, with African Americans having ~4% prevalence of the mutation[15]; historically has been predominantly associated with cardiomyopathy[15]; however, recent evidence of polyneuropathy has been described[16,17]

Objective

- To characterize the association of the V122I genotype and International Classification of Diseases,10th revision (ICD10) diagnosis codes in the UK Biobank black subpopulation with replication in the Penn Medicine Biobank

Methods

Study Population

- The UK Biobank is a prospective cohort study with genetic, physical, and health data on ~500,000 individuals recruited between ages 40 and 69 years across the UK[16,17]
- Recruitment occurred between 2006 and 2010; study follow-up is ongoing
- ICD10 diagnosis codes were collected through patient linkage to the National Health Service and any inpatient diagnosis was captured during study follow-up
- The Penn Medicine Biobank enrolls patients from throughout the University of Pennsylvania Health System
- Participants consent to allow the linkage of biospecimens to longitudinal electronic health record data

V122I Genotyping

- V122I was directly genotyped on the Affymetrix UK Biobank Axiom® array
- No subjects were missing genotype at this location and the mutation was in Hardy–Weinberg equilibrium ($p=7.2\times10^{-5}$)

Statistical Analysis

- A phenome-wide association study (PHEWAS) of V122I genotype with all ICD10 diagnosis codes was performed including all codes with at least 10 diagnoses within the black subpopulation of the UK Biobank (n=1,229 ICD10 codes)

Methods

- PHEWAS analysis was performed in PLINK (v2.0) using logistic regression controlling for age, sex, and genetic ancestry via 10 principal components
- A Bonferroni-corrected p-value of 4.4×10^{-5} was considered statistically significant
- Descriptive analysis of the V122I homozygotes (n=3) and deaths (n=6) among the V122I UK Biobank participants was performed

Replication Analysis

- Significant results from the PHEWAS analysis were replicated in the Penn Medicine Biobank, using 5,737 black participants (n=190 V122I carriers)

Results

Baseline Characteristics

- In the UK Biobank, 387 subjects were carriers of the *TTR* V122I mutation (384 heterozygotes, 3 homozygotes) and were primarily of African or Caribbean descent
- Among the 6,063 unrelated black participants of the UK Biobank used for PHEWAS analysis, 243 were carriers of the *TTR* V122I mutation (allele frequency=2.0%)
- V122I carriers were similar to non-carriers on all relevant confounders (**Table 1**)
- Among the V122I carriers, 1 was diagnosed with amyloidosis (ICD10 of E85)

Table 1. Baseline Characteristics of the Black Subpopulation in the UK Biobank by V122I Genotype

	Non-Carriers (GG) (n=5,820)	Carriers (GA or AA) (n=243)	P-Value
Mean (SD) age, years	51.9 (8.1)	52.6 (8.2)	0.2
Male, %	42.7	46.5	0.3
Mean (SD) BMI, kg/m^2	29.6 (5.4)	29.7 (5.1)	0.8
Hypertension, %	29.6	31.9	0.3
Diabetes, %	11.2	14.4	0.2
Smoking, %	27.8	27.2	1.0

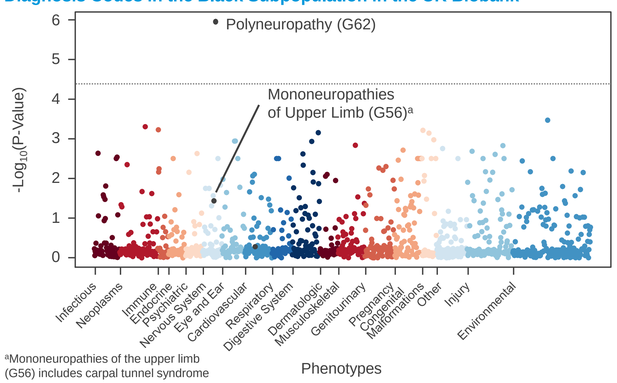
GG, V122I non-carrier; GA, V122I heterozygous carrier; AA, V122I homozygous carrier
SD, standard deviation; BMI, body mass index

Phenome-Wide Association Study (Figure 1)

- Using logistic regression controlling for age, sex, and genetic ancestry, polyneuropathy (ICD10 diagnosis G62) was significantly associated with the V122I genotype (odds ratio [OR]=11.2; 95% confidence interval [CI]: 3.7, 26.6; $p=1.1\times10^{-6}$)
  - Of note, none of the V122I carriers diagnosed with polyneuropathy in the UK Biobank (n=6) were diagnosed with diabetic polyneuropathy
- The significant association of V122I with polyneuropathy was further replicated in the Penn Medicine Biobank (OR=1.6; 95% CI: 1.2, 2.4; p=0.006)

Results Continued

Figure 1. PHEWAS Analysis of V122I Genotype across 1,229 ICD10 Diagnosis Codes in the Black Subpopulation in the UK Biobank



[a]Mononeuropathies of the upper limb (G56) includes carpal tunnel syndrome

- There was nominally significant evidence that carriers of V122I were at increased risk of other signs/symptoms of hATTR amyloidosis, including carpal tunnel syndrome (OR=2.0; p=0.02) and urinary retention (OR=2.1; p=0.05)
- There was no association of V122I with cardiomyopathy (OR=1.6; 95% CI: 0.4, 6.4; p=0.48)

Homozygous V122I Carriers

- Among the 3 homozygous carriers of V122I in the UK Biobank, 2 showed neuropathic signs/symptoms of hATTR amyloidosis (**Figure 2**)
- No homozygous V122I carriers were diagnosed with amyloidosis or cardiomyopathy

Deaths among V122I Carriers

- A total of 6 V122I carriers died during study follow-up, including 1 participant whose death was attributed to congestive heart failure and cardiac amyloid (**Table 2**)

Figure 2. Descriptive Analysis of ICD10 Diagnosis Codes and Operation Codes of 3 Homozygous Carriers of V122I in the UK Biobank

Homozygote #1
Male, Age 54

M77.47 Metatarsalgia-Ankle/Foot
M70.22 Olecranon Bursitis-Upper Arm
M25.57 Pain in Joint (Ankle and Foot)
R31 Unspecified Hematuria
N32.0 Bladder–Neck Obstruction
G62.9 Polyneuropathy, Unspecified
Z72.0 Tobacco Use
R93.6 Abnormal Findings on Diagnostic Imaging of Limbs
I10 Essential (Primary) Hypertension
R39.1 Other Difficulties with Micturition
R33 Retention of Urine
N40 Hyperplasia of Prostate
W15.9 Unspecified Division of Bone of Foot
W09.1 Excision of Lesion of Bone NEC
W08.5 Partial Excision of Bone NEC
M65.3 Endoscopic Resection of Prostate NEC
M47.9 Unspecified Urethral Catheterization of Bladder
M45.9 Unspecified Diagnostic Endoscopic Examination of Bladder
A55.9 Unspecified Diagnostic Spinal Puncture

Homozygote #2
Male, Age 69

R33 Retention of Urine
C61 Malignant Neoplasm of Prostate
K22.2 Esophageal Obstruction
G56.0 Carpal Tunnel Syndrome
R33 Retention of Urine
N39.0 Urinary Tract Infection, Site Not Specified
B96.2 *Escherichia Coli* (*E. Coli*) as the Cause of Diseases Classified to Other Chapters
X99.8 No Procedure Performed
G45.9 Unspecified Diagnostic Fiberoptic Endoscopic Examination of Upper Gastrointestinal Tract
G44.3 Fiberoptic Endoscopic Dilation of Upper Gastrointestinal Tract NEC
A65.1 Carpal Tunnel Release

Homozygote #3
Female, Age 69

H26.9 Cataract, Unspecified
H25.9 Senile Cataract, Unspecified
D25.9 Leiomyoma of Uterus, Unspecified
Z86.7 Personal History of Diseases of the Circulatory System
I10 Essential (Primary) Hypertension
C75.1 Insertion of Prosthetic Replacement for Lens NEC
U21.2 Computed Tomography NEC

NEC, not elsewhere classified

Table 2. Deaths among the V122I Carriers in the UK Biobank

Age at Death	Primary Cause of Death	Secondary Cause of Death	Description of Death
54	I619 intracerebral hemorrhage, unspecified	NA	Intracerebral hemorrhage
74	C349 malignant neoplasm of bronchus or lung, unspecified	Dementia	Lung cancer dementia
50	C809 malignant neoplasm, unspecified	Malignant neoplasm, primary site unknown	NA
77	G309 Alzheimer's disease, unspecified	Bronchopneumonia, malignant neoplasm of prostate	NA
61	C64 malignant neoplasm of kidney, except renal pelvis	NA	Metastatic renal cancer
73	E854 organ-limited amyloidosis	Congestive heart failure, chronic renal failure	Congestive heart failure, cardiac amyloid, chronic kidney disease

NA, no data available

Conclusions

- Carriers of the V122I mutation, historically associated with a predominantly cardiac phenotype, have a significantly increased risk of a clinical diagnosis of polyneuropathy which further supports that patients with hATTR amyloidosis have a mixed phenotype
- There was no association of the V122I mutation with diagnosis of cardiomyopathy; this is potentially because the carriers at the time of this analysis were of a younger age compared with the age that hATTR amyloidosis-related cardiomyopathy typically presents
- Healthcare providers should have a clinical suspicion for all of the multisystem manifestations of hATTR amyloidosis, including both cardiomyopathy and polyneuropathy, regardless of genotype when diagnosing and monitoring patients with hATTR amyloidosis to aid in earlier diagnosis and treatment

Abbreviations: AA, V122I homozygous carrier; BMI, body mass index; CI, confidence interval; GA, V122I heterozygous carrier; GG, V122I non-carrier; hATTR, hereditary transthyretin-mediated; ICD10, International Classification of Diseases, 10th revision; NA, no data available; NEC, not elsewhere classified; OR, odds ratio; PHEWAS, phenome-wide association study; SD, standard deviation; TTR, transthyretin.

Acknowledgments: Editorial assistance was provided by Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals. **Funding:** This study was sponsored by Alnylam Pharmaceuticals.

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