Prevalence, cardiac phenotype and outcomes of TTR variants in the UK Biobank Population

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Date of revision: 24/05/2024

Word count: 3,033

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Key Points

Question: What are the prevalence, cardiac phenotypes and outcomes of TTR variants in the UK Biobank Population?

Findings: Approximately 1/1000 UK Biobank (UKB) participants were found to be likely pathogenic/pathogenic vATTR carriers, which is higher than previously reported. Despite clinical codes suggesting low disease penetrance, cardiac expression of these genotypes was evident from the associations with left ventricular mass, conduction disease, incident heart failure and all-cause mortality.

Meaning: Genotype-first screening in the UKB revealed higher prevalence of potential disease-causing TTR variants, emphasizing the need for clinical vigilance in identifying individuals at risk of developing transthyretin amyloidosis and associated poor outcomes.

Abstract

Importance: The population prevalence of transthyretin cardiac amyloidosis caused by pathogenic variation in the *TTR* gene (vATTR) is unknown.

Objective: We sought to estimate population prevalence of disease-causing *TTR* variants and describe associated phenotypes and outcomes.

Design: Whole-exome sequencing data for 470,000 UK Biobank (UKB) participants was analysed. Participants were enrolled from 2006-2010, with 12 years median follow-up (analysis date: 12th March 2024). Sixty-two candidate *TTR* variants were extracted based on rarity (allele frequency ≤0.0001) and/or previously described associations with amyloidosis if more frequent. Adjusted Cox proportional hazards models evaluated the relationship between *TTR* variants and atrial fibrillation, conduction disease, heart failure and all-cause mortality. Associations of *TTR* carrier status with electrocardiogram and cardiovascular magnetic resonance phenotypes were explored. Genotypic and diagnostic concordance was examined using the International Classification of Diseases, Tenth Revision (ICD10).

Setting: Population-based cohort study.

Participants: 470,000 UKB participants with whole-exome sequencing data, those with electrocardiogram (N=28,927), and cardiovascular magnetic resonance data (N=42,453).

Exposure: vATTR carrier status.

Main Outcomes and Measures: vATTR prevalence, cardiovascular imaging and ECG traits, and adverse cardiovascular outcomes (from clinical codes).

Results: A likely pathogenic/pathogenic (LP/P) *TTR* variant was detected in 0.10% of UKB participants (n=473) with Val142Ile the most prevalent (n=367); 97 individuals (0.02%) were carriers of variant of unknown significance (VUS). The overall prevalence of LP/P variants was 0.02% in individuals with European ancestry and 4.3% in individuals with African

ancestry. LP/P variants were associated with higher LV mass and Val142Ile was associated with longer PR interval. LP/P carrier status associated with higher heart failure risk (HR 2.68, 95% CI 1.75 - 4.12, P<0.001) and conduction disease (HR 1.88, 95% CI 1.25-2.83, P =0.003). Higher all-cause mortality risk was observed for non-Val142Ile LP/P variants (HR 1.98, 95% CI 1.06-3.67, P=0.03). Thirteen (3%) individuals with LP/P variants had ICD10 codes compatible with cardiac or neurologic amyloidosis. VUS were not associated with outcomes.

Conclusions and Relevance: Approximately 1/1000 UKB participants were vATTR carriers, exceeding previously reported prevalence. Although clinical codes show a low penetrance, expression of these genotypes was evident from associations with LV mass, conduction disease, incident heart failure and all-cause mortality.

Key words:

Cardiac amyloidosis, cardiovascular remodeling, heart failure, cardiovascular magnetic resonance imaging.

Abbreviations

vATTR, Transthyretin cardiac amyloidosis caused by pathogenic variation in the TTR gene.

TTR, Transthyretin.

UKB, UK Biobank.

LP/P, Likely pathogenic/pathogenic.

VUS, Variant of unknown significance.

ECG, Electrocardiogram.

CMR, Cardiovascular magnetic resonance.

ICD10, International Classification of Diseases, Tenth Revision.

LV, Left ventricular.

GLS, Global longitudinal strain.

AF, Atrial fibrillation.

BMI, Body mass index.

QC, Quality control.

MAF, Minor allele frequency.

WES, Whole exome sequencing.

VEP, Variant Effect Predictor.

Introduction

Transthyretin (TTR) amyloidosis is caused by dissociation of TTR tetramers into oligomers, which then polymerize into amyloid deposits in the heart, peripheral nerves and other tissues. This process can result from pathogenic variations in the *TTR* gene leading to tetramer instability (vATTR) or the accumulation of wild-type TTR (wtATTR) (1). More than 130 amyloidogenic missense TTR variants have been described (2), (3), which are associated with different phenotypes including predominantly neuropathic, cardiac or mixed forms.

Cardiomyopathy caused by vATTR is characterized by progressive heart failure with a mean survival of 2 to 5 years after diagnosis in the absence of treatment (4), (2), (1). Until very recently, management of ATTR consisted only of palliative treatment of symptoms and complications, but therapeutic advancements including TTR stabilisers and oligonucleotides provide new options for disease modification (1) (5). Novel therapies are more effective in an

earlier phase of the disease, providing justification for early identification of affected individuals (6),(7).

vATTR is known to be much more prevalent in individuals of Black African descent and in certain geographic clusters in Portugal, Japan, and Sweden (2). Genetic variants attributable to these clusters include Val50Met variant in northern Portugal, where the prevalence of TTR polyneuropathy is approximately 1 in 538 individuals (2), and Val142Ile which is reported in 3.4% of individuals with Black African ancestry (8). Other examples associated with predominantly cardiac involvement include Leu131Met and Ile88Leu, reported in Denmark and Italy respectively, and Thr80Ala in the UK and Ireland (2). The population prevalence of these variants is unknown (1).

In this study, we sought to determine the prevalence of potential disease-causing *TTR* gene variants in the UK Biobank (UKB) population and to evaluate their relations with cardiac structure and function, electrocardiogram (ECG) parameters and association with cardiovascular events and survival.

Methods

Study cohort

The UKB is a large, prospective, population cohort of 500,000 individuals aged 40-69 years when first enrolled from 2006 to 2010 (9). Each UKB participant has given signed consent and provided information on demographics, lifestyle, medical history along with data on physical measurements and biological samples (10). The imaging assessment which includes cardiovascular magnetic resonance (CMR) of the UKB cohort was initiated in 2015. The

research ethics for the UKB studies was approved by the NHS National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382). This was extended on 18th June 2021 (Ref 21/NW/0157).

The UKB CMR protocol and analysis methodologies have been detailed previously (11),(12, 13). CMR studies were acquired using a wide-bore 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). Segmentation of the left and right ventricular and atrial cavities and left ventricular myocardium were performed by automated machine learning algorithms as published previously (12). LV global longitudinal strain (GLS) was derived by a feature-tracking algorithm implemented in the CVI42 software (Prototype v5.13.7, Circle, Calgary, Canada). Native (non-contrast) myocardial T1 values were estimated with the Shortened Modified Look-Locker Inversion recovery protocol (ShMOLLI, WIP780B) (14).

Digital 12-lead ECGs were acquired at a frequency of 500 Hz for 10 seconds (Cardiosoft v6.51 GE) and stored in XML file format at the imaging visit. The raw ECG signals were processed to extract relevant ECG measurements using GE MUSE v9.0 SP4, Marquette 12 SL. (15) (16)

Genetic sequencing and interpretation

Whole exome sequencing (WES) was performed in the UKB as previously described (17) and the final data release covered over 470,000 participants. We applied a series of variant-level and sample-level quality control (QC) filters which included minor allele count (MAC) < 1, variant-level call rate < 90%, sample-level call rate < 90%, and Hardy-Weinberg

equilibrium test ($P < 1x\ 10^{-15}$). Additionally, we excluded variants that failed the QC filter requiring at least 90% of all genotypes for a given variant (independent of variant allele zygosity) have a read depth of at least 10 (i.e. DP>=10), as recommended by the UK Biobank. Following this step, we annotated *TTR* variants with Ensembl Variant Effect Predictor (VEP) (18) version 108 and extracted a total of 62 candidate *TTR* variants, based on maximum population based minor allele frequency on GnomAD (MAF <=0.0001) or previously known to be pathogenic if above this rarity threshold (e.g. Val142Ile and Val50Met variants) after excluding all benign or likely benign, and synonymous variants. From these variants, 27 were variants of uncertain significance (VUS), 24 likely pathogenic (LP) and 11 pathogenic (P) (**eTable 1**), manually classified according to the American College of Medical Genetic and Genomics (ACMG) criteria (19).

Statistical analyses

Baseline characteristics are presented as mean ± standard deviation (SD) for continuous variables or counts (proportion) for categorical variables, stratified by *TTR* carrier status. Inter-group differences were evaluated by unpaired t-test or Chi-square test. The prevalence and 95% confidence interval (CI), according to Wald method, of *TTR* variants was estimated using R *Prevalence* package (20). We considered genetic ancestry as a population descriptor due to the differential preponderance of certain *TTR* variations according to genetic ancestry. Genetic ancestry was determined from the clustering analysis of genotypic principal components as previously published (13). We explored the associations between *TTR* variant carrier status (and variant sub-groups) compared to *TTR* variant non-carriers for eight CMR derived left ventricular (LV) phenotypes: LV end-diastolic volume indexed to body surface area (BSA) (LVEDVi), LV stroke volume indexed BSA (LVSVi), LV ejection fraction

(LVEF), LV myocardial contraction fraction (LVMCF), LV mass indexed to BSA (LVMi), LV maximum wall thickness (MWT), LV myocardial global longitudinal strain (GLS), LV myocardial non-contrast T1 values (Native T1); and five ECG parameters (PR interval, QRS duration, corrected QT [QTc] interval, QRS axis and total QRS voltage to indexed LV mass ratio [Vol/LVMi]) in subsets of individuals with valid CMR (Nmax=42,342) and ECG data (Nmax=26,635), by multivariable linear regression adjusted for age, sex, body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus and smoking status. LVMCF was calculated as (LVSV/LV myocardial volume) * 100.

Outcome data were obtained from the linked Hospital Episodes Statistics (HES) data and national death registries. The relationships between *TTR* carriers including sub-groups (vs TTR variant non-carriers) and incident adverse outcomes (atrial fibrillation [AF], conduction disease, heart failure [HF] and all-cause mortality) were first examined by Kaplan-Meier survival analysis. We next evaluated the prognostic relationship between *TTR* carrier status and adverse outcomes using Cox proportional hazards models. All association analyses were further stratified by *TTR* variant classes (VUS, Val142Ile which was considered due to its high prevalence, LP/P variants, LP/P variants excluding Val142Ile). Similar to linear regression models, all Cox analyses were adjusted for age, sex, BMI, hypertension, hyperlipidemia, diabetes mellitus and smoking status. In Kaplan-Meier and Cox proportional hazards analyses, participants who died from non-cardiovascular causes were right censored. As a sensitivity analysis, we performed a competing risks analysis for death from other causes according to Fine and Gray subdistribution hazards model (21) adjusted for the same covariates as Cox models. Lastly, we examined the genotypic and diagnostic concordance for amyloidosis and other frequently associated conditions including spinal stenosis, carpal tunnel syndrome and biceps tendon injury, using the linked hospital episode statistics data

according to the International Classification of Diseases, Tenth Revision (ICD10) codes (**eTable 2**). A two-sided P value of <0.05 was considered statistically significant. All statistical analyses were performed in R version 4.1.1.(https://www.R-project.org/). All observational reporting followed EQUATOR guidelines, including the completion of a STROBE (strengthening the reporting of observational studies in epidemiology) checklist (22).

Results

The overall cohort characteristics are presented in **Table 1**. The mean age (±SD) of the study cohort was 57±8 years; 46% were male. A predicted LP/P or established pathogenic *TTR* variant or a VUS was detected in 0.12% of UKB participants (564 out of 469,789 individuals); these were predominantly LP/P variants (in 473 individuals, 0.10% or 1 in 1000 individuals). Individuals carrying *TTR* variants were younger (53 years vs 57 years, P < 0.001) and more likely to be of African genetic ancestry and had a higher prevalence of hypertension and diabetes. Val142Ile accounted for the majority of LP/P variants (367 individuals, representing 77.6% of all participants carrying LP/P variants). Aligning with prior reports of Val142Ile, 313 out of 367 (85.3%) individuals with Val142Ile variants were of African ancestry (**eTable 3**). The overall prevalence of LP/P variants was 0.02% in individuals with European ancestry and 4.3% in individuals with African ancestry. It should be noted that genetic ancestry determined from the genotype data differs from self-designation of ethnicity or race and should be considered as part of a broad continuum instead of an absolute grouping. The majority of clinical, imaging and ECG parameters overlapped between non-carriers and LP/P variant carriers as evident in **eTable 3**. Other well-known prevalent variants included Val50Met in 26, Thr80Ala in 19, Ile88Ala in 13 and

Ser97Tyr in 3 participants. VUS were present in 91 individuals. The prevalence of TTR variant classes is illustrated in **Figure 1**.

Relationship with left ventricular imaging measurements and ECG parameters

Individuals with *TTR* LP/P variants had a higher LVMi (β=4.66g/m^2, 95% confidence interval [CI]: 1.87 to 7.44g/m^2, P = 0.001) and LV maximum wall thickness (β=0.80mm, 95% CI: 0.31 to 1.28mm, P = 0.001) after adjusting for age, sex, BMI and cardiovascular risk factors (**Figure 2A** and **eTable 4**). In subgroup analyses, these associations remained significant for non-Val142Ile LP/P variants. *TTR* status had no influence on LV functional measures (LVEF, LVMCF and GLS) or LV myocardial tissue characteristics (native T1) in the multivariable adjusted analyses. As for the ECG parameters, *TTR* LP/P carriers had a longer PR interval (β=18.34ms, 95% CI:5.41 to 31.27ms, P = 0.005), although this association was mainly driven by Val142Ile carriers (β=24.54ms, 95% CI: 8.42 to 40.66ms, for Val142Ile carriers vs β=7.18ms, 95% CI: -14.45 to 28.81ms, for non- Val142Ile LP/P carriers) (**Figure 2B** and **eTable 5**). No other significant associations between *TTR* status and the remaining ECG traits were identified.

Prognostic associations with adverse outcomes

Over a median (interquartile range) follow-up of 12 (11 to 13) years, 26,040 (5.6%) individuals experienced incident AF, 17,010 (3.6%) developed conduction disease, 10,547 (2.3%) had incident HF, and 32,317 (6.9%) died. In the unadjusted Kaplan-Merier survival analyses, *TTR* LP/P variant carrier status was associated with an increased risk of incident HF (Log-rank P < 0.001, **Figure 3**). No clear separation of survival curves was found for other outcomes except

for the sub-group of non-Val142Ile LP/P variants with conduction disease (Log-rank P = 0.025, **eFigures 1-3)**. After adjusting for age, sex, BMI and cardiovascular risk factors, individuals with *TTR* LP/P variants had a higher risk of developing HF (hazard ratio [HR] = 2.68, 95% CI: 1.75-4.12, P < 0.001) (**Figures 4**). *TTR* LP/P carriers were at a higher risk of developing conduction disease (HR = 1.88, 95% CI: 1.25 – 2.83, P = 0.003). The magnitude of effect-size point estimates were higher for those carrying non-Val142Ile LP/P variants although the confidence intervals overlapped widely (HF HR = 3.52, 95% CI: 1.58 – 7.83, conduction disease HR = 2.97, 95% CI: 1.49 – 5.94, all for non-Val142Ile LP/P variants). Only those carrying non-Val142Ile LP/P variants had a higher incidence of AF (HR = 2.23, 95% CI: 1.16 – 4.29, P = 0.02) and all-cause mortality (HR = 1.98, 95% CI: 1.06 – 3.67, P = 0.031). *TTR* VUS status was not associated with adverse events. Sensitiviy analyses accounting for the competing risk of death produced slightly attenuated hazard ratios but did not change our overall results (**eTable 6**).

Concordance with clinical diagnoses

Approximately three percent (n = 13) of individuals with *TTR* LP/P variants had a diagnostic ICD10 code compatible with amyloidosis (**eTable 7**). *TTR* LP/P variant carriers had 34 times higher prevalence of amyloidosis ascertained from the clinical codes than non-carriers (2.75% vs 0.08%). Among less common LP/P variants, individuals with Thr80Ala had the highest proportion of a known ICD10 clinical diagnosis of amyloidosis (~16%). When other clinical traits related to amyloidosis (e.g. neuropathies, spinal stenosis, carpal tunnel syndrome and biceps tendon injury), were included, the proportions of a diagnostic code compatible with amyloidosis more than doubled.

Discussion

In this study, we established the prevalence of potential and established pathogenic variants in *TTR* in a large general population cohort and evaluated the associations with cardiac imaging and ECG phenotypes as well as clinical amyloid-associated phenotypes and outcomes. With the exception of Val142Ile (23), no prior study has applied a genotype-first approach for this condition. The total prevalence of LP/P variants was around 1/1000 (0.1%), which was mostly driven by Val142Ile with a prevalence of 3.8% in individuals with African ancestry. This is in line with previously published data (2),(8) which also reported an increased risk of HF in individuals carrying this variant (2), including a UK-based study (24) in which this variant was reported as the fourth most common cause (11%) of HF in Afro-Caribbeans. Similarly, a HR of 2.43 for mortality in Val142Ile variant carriers was reported in an US based study in 7,514 individuals of African-descent (25).

Association between TTR variants and a clinical diagnosis of amyloidosis

The overall association of LP/P *TTR* variants with hospital diagnostic codes suggestive of amyloidosis in UKB was low (3%). This might be explained by the age of the UKB population which was between 40-69 years at recruitment (10) and the fact that most *TTR* amyloid variants manifest clinically at older ages. When individual variants were considered, however, Thr80Ala showed a higher prevalence of amyloid-related clinical codes of nearly 16% which is consistent with the previously described earlier age of onset (by ~10 years) for this variant compared with Ile88Leu or Val142Ile (4). In addition, the use of ICD10 codes to identify vATTR might also have reduced sensitivity, although we tried to overcome this limitation by capturing clinical features frequently associated with amyloid deposition such as lumbar spinal

stenosis and carpal tunnel syndrome. Inclusion of these additional traits doubled the number of *TTR* variant carriers with probable amyloidosis, suggesting possible under recognition of the condition in the early stages of disease development.

Cardiac traits associated with TTR variants

The classical features of cardiac amyloidosis are well recognized and include atrial arrhythmia, conduction disease, ventricular hypertrophy and progressive heart failure with preserved or reduced left ventricular ejection fraction, usually without LV dilatation. From the ECG analysis, Val142Ile was associated with a longer PR interval, but a risk of conduction disease based on clinical codes was mostly evident for non-Val142Ile variants. This might be explained by an earlier predisposition to more clinically significant AV conduction disease in non-Val142Ile variants, but this has not been reported in the previous literature. Similarly, earlier expression of disease may explain the association of non-Val142Ile LP/P variants – but not Val142Ile – with LV hypertrophy. (3) Furthermore, other rarer non-Val142Ile variants including Thr80Ala are a cause of a cardiac predominant or mixed phenotype (3) (2) and could explain this observation, although limited sample sizes precluded formal statistical evaluation. Thr80Ala is a well-recognized cause of vATTR amyloidosis in the UK and Ireland (4). Interestingly, at a population level, we did not find any association between *TTR* variants and LV functional parameters (including global longitudinal strain thought to be sensitive to early disease processes) or myocardial tissue characteristics. While these observations could represent true findings, the absence of associations could also be attributable to the smaller available sample sizes and possible larger measurement errors due to the technical complexity in their derivation.

Clinical outcomes in carriers of TTR variants

After adjusting for age, sex, BMI and cardiovascular risk factors, individuals with *TTR* LP/P variants had a higher risk of developing HF and conduction disease but only those carrying non-Val142Ile LP/P variants had a higher incidence of AF and all-cause mortality. Similar to intermediate cardiac imaging phenotypes, the adverse associations between *TTR* LP/P variants and clinical outcomes were mostly driven by non-Val142Ile variants for AF and all-cause mortality. It should be noted that unlike Cox regression models, Kaplan-Meier analyses did not show clear survival differences between *TTR* variant carrier and non-carrier groups for certain outcomes including AF and all-cause mortality. This is likely attributable to multivariable adjustment in Cox models which could have mitigated the influence of confounding factors. Reassuringly, TTR VUS carriers did not have cardiac manifestations or elevated risk of clinical events.

Clinical implications

From the screening perspective, an overall prevalence of 1/1000 individuals with potentially amyloidogenic variants is certainly much higher than the usual estimates of vATTR amyloid, particularly considering the UKB population consists predominantly of participants who have European ancestry with no known clusters of high prevalence for this condition, unlike some other European countries. This indicates that a significant number of individuals are at risk of developing transthyretin amyloidosis, associated with poor outcomes. While the optimal screening strategy is yet to be determined, a greater clinical vigilance for possible vATTR amyloidosis in patients with unexplained LV hypertrophy or associated traits such as spinal stenosis or carpal tunnel syndrome is recommended in light of these findings.

Limitations

While our study provides multiple novel epidemiologic insights into the clinical trajectory of TTR variant carriers using a large population based, deeply phenotyped dataset, some limitations should be recognised. First, UKB participants are predominantly of European descent, which limits the generalisibility of our results in more diverse populations. Second, only a subset of UKB participants had CMR and ECG data, which reduces the sample size and the power to detect differences. Thirdly, the lack of association of Val142Ile variants with all-cause mortality, previously reported but not present here, might reflect a relatively smaller cohort and middle age of the cohort. Fourthly, the number of individuals carrying certain LP/P variations (e.g. Ser97Tyr) and VUS were small resulting in dimished statistical power for some of the sub-group analyses. Lastly, we had limited information on family history and we ascertained the diagnosis of amyloidosis using ICD10 codes from hospital admissions which is likely to have underestimated the true disease prevalence.

Conclusion

By using a genotype-first screening approach to analyse the prevalence of amyloidogenic variants, 1/1000 individuals were found to be the carriers of LP/P TTR variants in the UKB population cohort. This is higher than the available prevalence estimates for vATTR. Despite an apparent low penetrance assessed by clinical codes, cardiac expression of these genotypes can be appreciated by their association with left ventricular hypertrophy, conduction disease, incident heart failure and, for non-Val142Ile LP/P variant carriers, atrial fibrillation and all-cause mortality.

Data Sharing Statement

The individual-level data can be requested from the UK Biobank via the standard access request process (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Additional supporting information (statistical/analytic code) are available upon request.

Acknowledgements

N.A. acknowledges support from Medical Research Council for his Clinician Scientist Fellowship (MR/X020924/1). S.E.P. and S.C. received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825903 (euCanSHare project). ER is supported by the mini-Centre for Doctoral Training (CDT) award through the Faculty of Science and Engineering, Queen Mary University of London, United Kingdom. S.E.P and P.B.M acknowledge support from the National Institute for Health and Care Research (NIHR) Barts Biomedical Research Centre (NIHR203330); a delivery partnership of Barts Health NHS Trust, Queen Mary University of London, St George's University Hospitals NHS Foundation Trust and St George's University of London. S.E.P acknowledges the British Heart Foundation for funding the manual analysis to create a cardiovascular magnetic resonance imaging reference standard for the UK Biobank imaging resource in 5,000 CMR scans (www.bhf.org.uk; PG/14/89/31194). S.E.P acknowledges support from the SmartHeart EPSRC programme grant (www.nihr.ac.uk; EP/P001009/1). LRL was supported by an UKRI MRC UK CARP award (MR/T005181/1).

This study was conducted using the UK Biobank resource under access application 2964. Barts Charity (G-002346) contributed to fees required to access UK Biobank data.

We would like to thank all the participants, staff involved with planning, collection and analysis, including core lab analysis of the CMR imaging data.

We would like to thank Dr Olga Azevedo for expert insight regarding the effect of novel therapies on early phenotype.

The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. N.A. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

S.E.P provides consultancy to Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada. P.M.E has received consultancies and speaker fees from Pfizer. LRL has received speaker fees from Alnylam, Sanofi-Genzyme and BMS, Other authors have no disclosures to make.

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Figure 1. Prevalence of *TTR* gene variants in the UK Biobank

The proportions of Val142Ile vs TTR LP/P excl. Val142Ile are presented as a pie chart in the inset diagram.

CI, confidence interval; TTR, Transthyretin gene; VUS, variant of uncertain significance; LP/P, likely pathogenic/pathogenic

Figure 2. Relationship between *TTR* variants and (A) left ventricular imaging measurements and (B) ECG parameters

LVEDVi, left ventricular end-diastolic volume indexed to body surface area (BSA); LVSVi, left ventricular stroke volume indexed to BSA; LVEF, left ventricular ejection fraction; LVMCF, left ventricular myocardial contraction fraction; LVMi, left ventricular mass indexed to BSA; MWT, left ventricular maximum wall thickness; GLS, global longitudinal strain; Native T1, myocardial non-contrast T1 values; CI, confidence interval; TTR,

Transthyretin gene; VUS, variant of uncertain significance; LP/P, likely pathogenic/pathogenic; ECG, electrocardiogram; Vol/LVMi, total QRS voltage to LVMi ratio

Figure 3. Kaplan-Meier survival curves for heart failure

Individuals with prevalent heart failure were removed from survival analyses.
TTR, Transthyretin gene; VUS, variant of uncertain significance; LP/P, likely pathogenic/pathogenic

Figure 4. Prognostic associations between *TTR* variants and adverse outcomes in Cox models

AF, atrial fibrillation; HF, heart failure; HR, hazard ratio; CI, confidence interval; TTR, Transthyretin gene; VUS, variant of uncertain significance; LP/P, likely pathogenic/pathogenic

Table 1. Cohort characteristics

	Entire cohort	**TTR variant -ve**	**TTR variant +ve**	**P (TTR +ve vs -ve)**
n	469,789	469,225	564	
Age, years	56.5 (8.1)	56.5 (8.1)	53.4 (8.3)	<0.001
Male sex	215163 (45.8)	214921 (45.8)	242 (42.9)	0.181
Female sex	254626 (54.2)	254304 (54.2)	322 (57.1)	
Genetically-inferred ancestry				<0.001
Africans	7533 (1.6)	7208 (1.5)	325 (57.6)	
East Asians	2457 (0.5)	2456 (0.5)	1 (0.2)	
Europeans	444243 (94.6)	444061 (94.6)	182 (32.3)	
Multiple ethnicities*	4934 (1.1)	4886 (1.0)	48 (8.5)	
South Asians	10622 (2.3)	10614 (2.3)	8 (1.4)	

Height, cm	168.5 (9.3)	168.5 (9.3)	167.6 (9.1)	0.023
Weight, kg	78.1 (15.9)	78.1 (15.9)	81.4 (16.0)	<0.001
BMI, kg/m^2	27.4 (4.8)	27.4 (4.8)	29.0 (5.5)	<0.001
BSA, m^2	1.88 (0.21)	1.88 (0.21)	1.90 (0.20)	0.003
SBP, mmHg	137.9 (18.6)	137.9 (18.6)	137.8 (18.9)	0.923
DBP, mmHg	82.3 (10.1)	82.3 (10.1)	83.9 (10.4)	<0.001
HR, bpm	69.4 (11.3)	69.4 (11.3)	70.6 (10.4)	0.015
Smoking status				<0.001
Never	258189 (55.0)	257818 (54.9)	371 (65.8)	
Previous	162212 (34.5)	162087 (34.5)	125 (22.2)	
Current	49388 (10.5)	49320 (10.5)	68 (12.1)	
Hypertension	136386 (29.0)	136183 (29.0)	203 (36.0)	<0.001
Hyperlipidemia	140654 (29.9)	140500 (29.9)	154 (27.3)	0.186
Diabetes mellitus	28178 (6.0)	28109 (6.0)	69 (12.2)	<0.001

BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

*Genetic ancestry not categorised by clusetering into the main population groups according to 1000 Genome Project.