The Transthyretin Stabilizing Mutation (T119M) Is Not Associated with Extended Lifespan or Protection Against Vascular Diseases: Analysis of the UK Biobank Cohort

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Introduction

Transthyretin (TTR) and Its Role in Transthyretin-Mediated (ATTR) Amyloidosis

- TTR is a heptatically produced homotetrameric protein; its major function is as a transthyretin of vitamin A and it also has a minor role in the transport of thyroxine [1–3].
- Destabilization of TTR and misfolding into amyloid fibrils can lead to the formation of insoluble deposits in multiple tissues, which can result in two types of progressive ATTR amyloidosis [4–8].
  - Wild-type transthyretin-meditated (wtATTR) amyloidosis: non-hereditary, caused by accumulation of wild-type TTR amyloid fibrils; predominantly manifests as cardiac symptoms but other systems can be involved [9–13].
  - Hereditary transthyretin-meditated (hATTR) amyloidosis: inherited, caused by accumulation of both mutant and wt TTR amyloid fibrils; multisystem disease that can include sensory and motor, autonomic, and cardiac symptoms [14–17].

TTR Thr119Met (T119M) Mutation

- Pathogenic mutations that lead to hATTR amyloidosis destabilize tetrameric TTR leading to dissociation, the rate-limiting step in amyloid fibril formation [15–17].
- TTR Thr119Met mutation encodes a thermodynamically and kinetically stabilized TTR protein that increases the stability of the TTR tetramers composed of wt or mutant TTR [14–16].
- Acts by slowing the dissociation of the TTR tetramer, a mechanism that established the therapeutic rationale for the development of small-molecule TTR tetramer stabilizers [18].

In a Danish cohort of 68,602 participants, the presence of the T119M mutation was associated with extended lifespan and lower risk of cerebrovascular disease.

Objectives

- To investigate the potential effect of the TTR T119M mutation on vascular disease and mortality in the UK Biobank cohort, and assess whether improved clinical outcomes previously reported for cerebrovascular disease could be replicated.

Methods

Study Population

- This analysis includes 337,148 unrelated, white participants from the UK Biobank, a population-based prospective cohort study that recruited ~500,000 participants aged 40–69 years in the UK between 2006 and 2010 [22].

T119M Genotyping

- T119M (rs2892981) was imputed with high accuracy (info score >0.9) from genotyping with the Affymetrix UK Biobank Axon® array.

Data Analysis

- Logistic regression and Cox proportional hazard analysis were used to assess the association between T119M genotype and diagnosis according to International Classification of Diseases (ICD) revision of:
  - Vascular disease (I20–I25, I60–I69, or G45)
  - Cardiovascular disease (I20–I25)
  - Cerebrovascular disease (I60–I69 or G45)
  - Ischemic cerebrovascular disease (I64–I69 and G45)
  - Hemorrhagic stroke (I60–I63)
  - Mortality (obtained from linkage to the National Death Registers)

- All statistical models were controlled for age, sex, smoking status, body mass index (BMI), and genetic ancestry via principal component analysis.

- Age at death or first vascular diagnosis between T119M carriers and non-carriers in time to reaching a diagnosis using a test

- For participants who had a vascular diagnosis and subsequently died, the number of years they survived post diagnosis compared using a test

Results

Baseline Characteristics

- Allele frequency of T119M within the unrelated, white population from the UK Biobank (337,148) was 0.4% (2,499 heterozygotes and 3 homozygotes).
- Table 1 shows the baseline characteristics of the 337,148 participants included in this study.

Table 1. Baseline Characteristics of UK Biobank Study Population by T119M Genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-Carriers (CC)</th>
<th>Carriers (CT or TT)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>56.9 (9.3)</td>
<td>56.7 (8.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Male, %</td>
<td>46.3</td>
<td>47.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean (SD) triglycerides, mmol/L</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Mean (SD) LDL, mmol/L</td>
<td>3.6 (0.9)</td>
<td>3.5 (0.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean (SD) HDL, mmol/L</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m²</td>
<td>27.4 (4.8)</td>
<td>27.4 (4.7)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Association of TTR Thr119Met Gene with Death and Vascular Disease (Figure 1)

- Logistic regression analysis that controlled for age, sex, smoking status, BMI, and genetic ancestry found no significant association between T119M genotype and all-cause mortality, cardiovascular disease, cerebrovascular disease, ischemic cerebrovascular disease, or hemorrhagic stroke.

Association of Vascular Disease as a Function of a T119M Genotype Using Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carriers (CT or TT)</th>
<th>Non-Carriers (CC)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiovascular disease diagnosis, years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ischemic cerebrovascular disease</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Conclusion

- In a large, prospective cohort study of 337,148 participants from the UK Biobank, carriers of the TTR T119M mutation were not found to be protected against vascular disease, cardiovascular disease, cerebrovascular disease, or death.
- The odds ratios and hazard ratios were >1 (p>0.05) for all analyses, indicating no protective effect of the T119M mutation.
- No significant difference was seen between T119M carriers and non-carriers in their time to reaching a diagnosis of vascular disease (including cardiovascular disease and cerebrovascular disease).
- These findings suggest that stabilization of the TTR tetramer via stabilization of TTR tetramer via T119M mutation does not confer protection against vascular disease or death in a general population setting.
- Further research is needed to understand the importance of TTR stabilization in ATTR amyloidosis pathogenesis due to the recent advances in therapeutic strategies and the growing interest in the potential earlier intervention in identified carriers of pathogenic TTR mutations.