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

Margaret M Parker1, Scott M Damrauer2, Daniel J Rader2, Simina Ticau1, David Erbe1, Gregory Hinkle1, and Saul Nioli1

1Aynalem Pharmaceuticals, Cambridge, MA, USA; 2University of Pennsylvania, Philadelphia, PA, USA

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. heart, nerves, liver, and pancreas), which results in functional impairment across multiple organs

• Afflicts ~50,000 people worldwide; median survival of 4.7 years following diagnosis, with a reduced survival of 3.4 years for patients presenting with cardiomyopathy

• Non-specific heterogeneous presentation, 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

• V122I (Val122Ile; p.V142I; rs76992529) variant is the most common pathogenic hATTR amyloidosis to aid in earlier diagnosis and treatment

Methods

Study Population

• The UK Biobank is a prospective cohort study with genetic, physical, and health data on ~500,000 individuals recruited from 2006–2010 across 21 ethnicities

• Recruitment occurred between 2006 and 2010; study follow-up is ongoing

• ID01 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 platform

Statistical Analysis

• A phenotype-wise association study (PHEWAS) of V122I genotype with all ID01 diagnosis codes was performed including all codes with at least 10 diagnoses within the black population of the UK (n=239 ID01 codes)

Results

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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Non-Carriers (GC)</th>
<th>Carriers (GA or AA)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age, years</td>
<td>51.8 (9.1)</td>
<td>52.5 (8.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Male, %</td>
<td>42.7</td>
<td>45.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean (SD) BMI, kg/m²</td>
<td>28.8 (5.6)</td>
<td>28.7 (5.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>29.6</td>
<td>31.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.2</td>
<td>14.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>27.8</td>
<td>27.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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

Phenotypes

- Polyneuropathy (ID02)

Results Concluded

• There was nominally significant evidence that carriers of V122I were at increased risk of other sign/symptoms of TTR amyloidosis, including carpal tunnel syndrome (OR=2.1; 95% CI: 0.9, 4.6; p=0.05)

• No association of V122I with cardiomyopathy (OR=1.6; 95% CI: 1.2, 2.4; p=0.006)

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

- Healthcare providers should have a clinical suspicion for all of the multisystem manifestations of hATTR amyloidosis, including both polyneuropathy and cardiomyopathy, regardless of genotype when diagnosing and monitoring patients with hATTR amyloidosis to aid in earlier diagnosis and treatment

References:


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

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>Primary Cause of Death</th>
<th>Secondary Cause of Death</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>Intracranial hemorrhage</td>
<td>NA</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>56</td>
<td>Cerebrovascular disease</td>
<td>Unspecified</td>
<td>Dementia</td>
</tr>
<tr>
<td>58</td>
<td>Malignant neoplasm of bronchi or lung, unspecified</td>
<td>NA</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>61</td>
<td>Cerebrovascular disease</td>
<td>Unspecified</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>64</td>
<td>Malignant neoplasm of kidney, except renal pelvis</td>
<td>NA</td>
<td>Metastatic renal cancer</td>
</tr>
<tr>
<td>65</td>
<td>Intracranial hemorrhage</td>
<td>Unspecified</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>66</td>
<td>Malignant neoplasm of kidney, except renal pelvis</td>
<td>NA</td>
<td>Metastatic renal cancer</td>
</tr>
<tr>
<td>73</td>
<td>Breast cancer</td>
<td>Unspecified</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>74</td>
<td>Breast cancer</td>
<td>Unspecified</td>
<td>Malignant neoplasm of prostate</td>
</tr>
</tbody>
</table>

Figure 1. PHEWAS Analysis of V122I Genotype across 1,229 ID01 Diagnosis Codes in the Black Subpopulation in the UK Biobank

Figure 2. Descriptive Analysis of ID01 Diagnosis Codes and Operation Codes of 3 Homozygous Carriers of V122I in the UK Biobank