The effects of an intronic polymorphism in TOMM40 and APOE genotypes in sporadic inclusion body myositis

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A previous study showed that, in carriers of the apolipoprotein E (APOE) genotype ε3/ε3 or ε3/ε4, the presence of a very long (VL) polyT repeat allele in “translocase of outer mitochondrial membrane 40” (TOMM40) was less frequent in patients with sporadic inclusion body myositis (sIBM) compared with controls and associated with a later age of sIBM symptom onset, suggesting a protective effect of this haplotype. To further investigate the influence of these genetic factors in sIBM, we analyzed a large sIBM cohort of 158 cases as part of an International sIBM Genetics Study. No significant association was found between APOE or TOMM40 genotypes and the risk of developing sIBM. We found that the presence of at least 1 VL polyT repeat allele in TOMM40 was significantly associated with about 4 years later onset of sIBM symptoms. The age of onset was delayed by 5 years when the patients were also carriers of the APOE genotype ε3/ε3. In addition, males were likely to have a later age of onset than females. Therefore, the TOMM40 VL polyT repeat, although not influencing disease susceptibility, has a disease-modifying effect on sIBM, which can be enhanced by the APOE genotype ε3/ε3.

1. Introduction

Sporadic inclusion body myositis (sIBM) is known as the most common acquired myopathy among people 50 years and older (Machado et al., 2014). Given its similarities with Alzheimer’s disease such as the late age of onset and the abnormal accumulation of proteins, the apolipoprotein E (APOE, OMIM#107741) gene has been one of the most popular genes studied in sIBM (Gang et al., 2014), but no association with sIBM disease risk was confirmed.
Table 1

| Variable       | Count | Age of onset (mean ± SD; y) | Regression coefficient | p Value\(^b\) |
|----------------|-------|-----------------------------|------------------------|--------------|
| **Ethnicity**  |       |                             |                        |              |
| Non-Caucasian  | 16    | 56.7 ± 5.7                  | Reference              |              |
| Caucasian      | 141   | 60.0 ± 10.0                 |                        |              |
| Gender         |       |                             |                        |              |
| F              | 52    | 57.9 ± 10.4                 | Reference              | 0.28         |
| M              | 105   | 60.6 ± 9.3                  | 2.7 (–0.5, 5.9)        | 0.095        |
| **APOE**       |       |                             |                        |              |
| ε2/ε4\(^a\)   | 6     | 56.8 ± 5.8                  | Reference              |              |
| ε3/ε3         | 99    | 60.2 ± 9.8                  |                        |              |
| ε2/ε3         | 19    | 56.9 ± 10.0                 | Reference              | 0.23         |
| ε3/ε4 and ε4/ε4| 33    | 60.4 ± 9.7                  | –2.9 (–7.7, 1.9)       | 0.43         |
| **TOMM40 polyT** |     |                             |                        |              |
| No VL carriage| 74    | 58.1 ± 9.7                  | Reference              | 0.027        |
| VL carriage   | 83    | 61.2 ± 9.6                  | 3.7 (0.4, 6.9)         |              |
| **APOE-TOMM40** |      |                             |                        |              |
| ε3/ε3 and polyT| 38    | 57.3 ± 9.9                  | Reference              |              |
| non-VL carriage|       |                             |                        |              |
| ε3/ε3 and polyT| 61    | 62.0 ± 9.4                  | 4.9 (1.1, 8.7)         | 0.013        |
| VL carriage   |       |                             |                        |              |

Key: APOE, apolipoprotein E; CI, confidence interval; F, female; M, male; SD, standard deviation, sIBM, sporadic inclusion body myositis; TOMM40, translocase of outer mitochondrial membrane 40; VL, very long.

\(^a\) Each analysis was adjusted for gender, ethnicity, tissue, and genetic factors, except for the variable under study.

\(^b\) p value < 0.05 was considered statistically significant (marked in bold).
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