A TOMM40 polymorphism, a variable length intronic poly T repeat (rs10524523), has been shown to influence age of Alzheimer’s disease (AD) onset (Roses et al., 2009). In this study, we tested the hypothesis that subjects homozygous for TOMM40 short poly T sequences <21 (SPT) would show better performance on measures of learning and memory than those who were homozygous for longer poly T sequences ≥21 (LPT) in middle-aged subjects enrolled in WRAP.

METHODS

The study population includes 613 middle-aged asymptomatic persons enrolled in the Wisconsin Registry for Alzheimer’s Prevention (WRAP) who had been genotyped for APOE and TOMM40 (Sager et al., 2005).

Study groups were defined by TOMM40 genotyping based on the length of the poly T sequences regardless of APOE genotype.

A total of 128 were homozygous for SPT sequences <21 (low risk) and 219 were homozygous for LPT sequences ≥21 (high risk).

• Serial position profiles and total learning on the Rey Auditory Verbal Learning Test (AVLT) were compared between groups controlling for age, gender and education (La Rue et al., 2008).

• There were no significant age, gender or verbal IQ differences that were significant in the serial position curve with significantly poorer recall from the primacy region on the AVLT (p=.001) (see Table 3). There were no significant differences in the serial position curve with significantly poorer recall from the primacy region on the AVLT (p=.001) (see Table 3).

• Nineteen percent of the SPT group had an APOE ε4 compared with 56% of the LPT group. The LPT group was also more likely to have a parental history of AD (see Table 2).

• When APOE genotype (ε4 carrier vs. non-carrier) was added to the model, TOMM40 remained significant on both measures (Figure 2 shows AVLT total results).

RESULTS

There were significant differences in the serial position curve with significantly poorer recall from the primacy region on the AVLT (p=.001) (see Table 3). There were no significant differences in the serial position curve with significantly poorer recall from the primacy region on the AVLT (p=.001) (see Table 3). Longer TOMM40 poly T sequence length was associated with differences in memory and learning that are seen in early AD. These changes were seen in middle-aged asymptomatic persons, suggesting that TOMM40 genotyping may prove useful in stratifying persons at different levels of AD risk in studies of pre-symptomatic AD. The role that TOMM40 plays in AD pathogenesis and its relationship to APOE genotype as a genetic risk factor for AD remains to be determined. Additional analyses are planned as TOMM40 genotyping becomes available for the complete WRAP sample.

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Table 3: Neurocognitive differences by TOMM40 genotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SS (n=128)</th>
<th>Homozygous ≥20 (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Primacy</td>
<td>77 (1.17)</td>
<td>72 (0.87)</td>
</tr>
<tr>
<td>% MTL Recall (ave of 5 trials)</td>
<td>56.2 (0.67)</td>
<td>58.3 (0.61)</td>
</tr>
</tbody>
</table>

*Values are demographically adjusted mean scores (standard error) *p = .001; **p < .001; ***p = .006