TOMM40 VARIABLE LENGTH POLYMORPHISM IS ASSOCIATED WITH MEMORY FUNCTION IN ASYMPTOMATIC MIDDLE-AGED PERSONS

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BACKGROUND

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).

La Rue A, et al. (2008). *Effect of parental family history of Alzheimer's disease on serial position profiles.* Alzheimers Dement, 4(4):285-290.

Roses AD, et al. (2009). *A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease.* Pharmacogenomics J.

Sager MA, Hermann BP, La Rue A (2005). *Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention.* J Geriatr Psychiatry Neurol, 18(4):245-249.

ACKNOWLEDGEMENTS

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TABLES & FIGURES

FIGURE 1. THEORETICAL TOMM40 AD RISK PROFILE

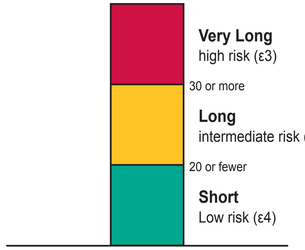

TABLE 1. APOE/TOMM40 DISTRIBUTIONS IN WRAP

TOMM40 Genotype	2,2 (n=3)	2,3 (n=55)	2,4 (n=13)	3,3 (n=313)	3,4 (n=205)	4,4 (n=25)
SS	0%	36%	0%	27%	12%	0%
SL	0%	0%	47%	1%	41%	0%
SVL	67%	35%	0%	46%	3%	0%
LL	0%	0%	0%	0%	3%	100%
LVL	0%	6%	54%	3%	31%	0%
VLVL	33%	24%	0%	22%	9%	0%
Total	100%	100%	100%	100%	100%	100%

N = 613 non-Hispanic caucasians with complete AVLT data; neurological disorders excluded.

FIGURE 2. MEMORY SCORES FOR TOMM40 AND APOE GROUPS

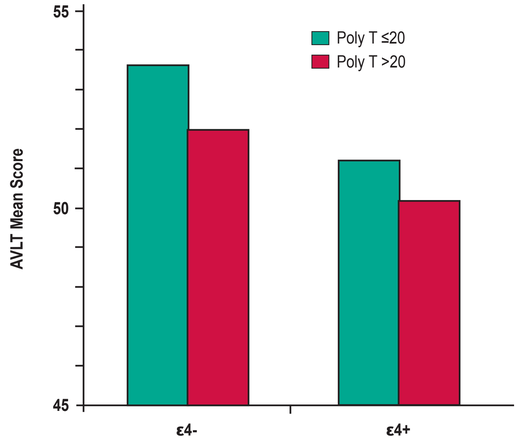

TABLE 2. CHARACTERISTICS OF SS AND HOMOZYGOUS POLY T >20 GROUPS

Characteristic	SS (n=128)	Homozygous >20 (n=219)
Age	54	54
% Female	69	69
Verbal IQ	111	111
% APOE ε4	19	56*
% Family History of AD	57	77*

*p < .001

TABLE 3. NEUROCOGNITIVE DIFFERENCES BY TOMM40 GENOTYPE

Cognitive Measure	SS (n=128)	Homozygous >20 (n=219)
% Primacy	77 (1.15)	72 (.88)*
AVLT Total (sum of 5 trials)	53.2 (.67)	50.9 (.51)**

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

RESULTS

- The mean age of the study population was 54 years and 69% were female.
- There were no significant age, gender or verbal IQ differences between SPT and LPT groups (see **Table 2**).
- The two TOMM40 groups differed significantly in total words learned on the AVLT (p=.006) with the LPT TOMM40 group remembering fewer words.
- 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**).
- Nineteen percent of the SPT group had an APOE ε4 compared with 19% and 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).

CONCLUSIONS

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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