APOE Genotype by Gender Interaction Revealed in CSF Biomarkers and Clinical Conversion Rates in the ADNI database

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Introduction

The influence of the APOE genotype on the risk of developing AD is well characterized. However, the fact that APOE4-carrying women are at higher risk of developing AD than their male counterparts is not as well known. Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database we studied the interaction between APOE genotype and gender in two domains: (i) CSF biomarker levels and (ii) conversion rates from healthy control to either MCI or AD.

Methods

Data. All data originate from the ADNI database and subjects were either APOE3 homozygotes (APOE3/3) or APOE3/4 heterozygotes.

CSF Biomarker. CSF biomarker levels for Aβ, Tau, phosphorylated Tau (Ptau), and Tau/Aβ-ratio were studied separately in healthy controls (N=182) and MCI patients (N=372). The APOE-by-gender interaction was examined using an ANCOVA adjusting for APOE, gender, age, years of education, and ADNI study phase.

		HC			MCI		
		Abeta	Tau	Ptau	Abeta	Tau	Ptau
Male	E3/E3	72	71	72	127	125	127
	E3/E4	24	23	24	92	90	92
Female	E3/E3	66	65	65	80	79	80
	E3/E4	20	20	20	73	73	73

Conversion Risk. For studying conversion rates we analyzed 285 healthy controls who had at least 12 months of follow-up at time of analysis. During the observation period 44 subjects converted to MCI or AD. In addition we analyzed data obtained from 521 MCI patients; of those 172 converted to AD during the observation period. Conversion rates were modeled using a left-truncated, right-censored Cox proportional hazards model with APOE, gender, and APOE-by-gender interaction as covariates. The analysis is stratified by education and MMSE at baseline.

		E3/E3	# Conv.	E3/E4	# Conv.
HC	Male	109	20	38	6
	Female	95	11	43	7
MCI	Male	167	44	140	62
	Female	118	26	94	40

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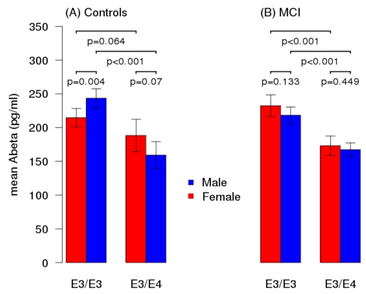
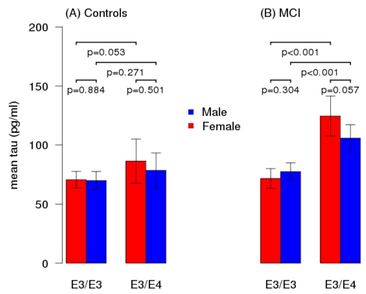
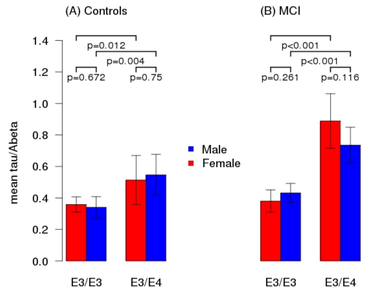
Results (I)



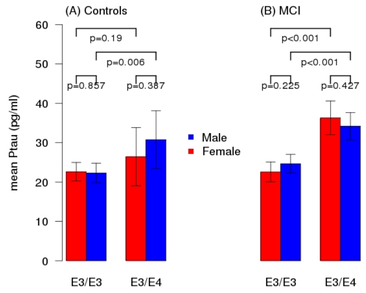
CSF Aβ. The ANCOVA revealed a **significant** interaction between APOE4 carrier status and gender for **HC** (p=0.019) **but not for MCI** patients (p=0.58).



CSF Tau. The ANCOVA revealed a **significant** interaction between APOE4 carrier status and gender for **MCI** (p=0.014) **but not for HC** (p=0.39).

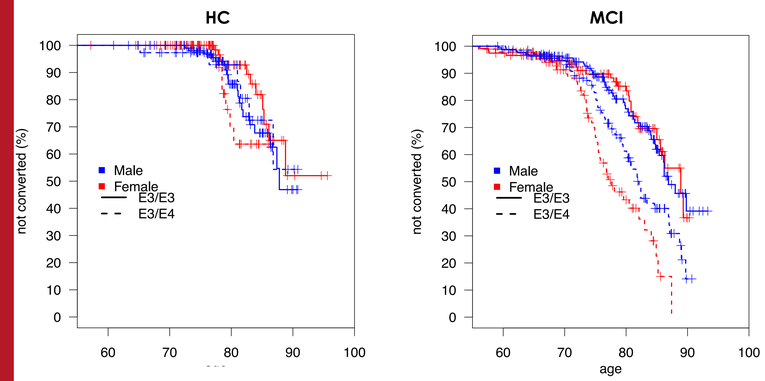


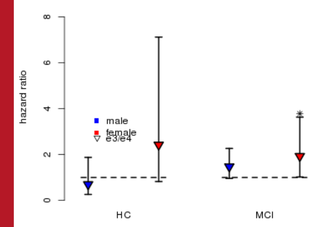
CSF Tau/Aβ ratio. The ANCOVA revealed a **significant** interaction between APOE4 carrier status and gender for **MCI** (p=0.043) **but not for HC** (p=0.9).



CSF phosphorylated Tau. The ANCOVA revealed **no significant** interaction between APOE4 carrier status and gender (p>0.34).

Results (II)





Conversion Risk. The term for the APOE4-by-gender interaction in the Cox model is neither significant for HC (p=0.1054) nor for MCI (0.2424). However, when genders are analyzed separately, the risk conferred by the APOE4 genotype is more pronounced in women than in men. In fact, the APOE4 carrier status is significant in females with MCI (p=0.042) but not in males with MCI (p=0.076).

Conclusions

Although sample sizes are limited, Aβ levels in controls suggest increased vulnerability in APOE4-carrying men, and tau levels in MCI patients suggest increased vulnerability in APOE4-carrying women. In the most relevant outcome, clinical conversion, the APOE4 effect is more potent in women. These results support a pathogenic model in which the APOE4 allele lowers beta-amyloid levels in both genders but has additional downstream effects in women.

In order to validate the CSF findings, **larger sample sizes** are required, e.g., the healthy female E3/E4 group comprises only 20 individuals. The low number of samples may be a reason for discrepancy to earlier studies, e.g. [1]. This holds true especially for the survival analysis, e.g., there are only 6 converters in the healthy male E3/E4 group.

References

1. J Damoiseaux et al. (2012) "Gender modulates the APOE4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels" J Neurosci 32: 8254-8262.