Gene-sex interaction in Alzheimer's disease

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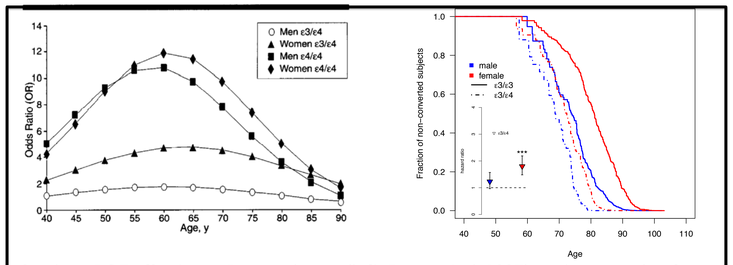
Introduction

Alzheimer's disease (AD) is an increasingly prevalent, ultimately fatal neurodegenerative disorder for which there are no disease-modifying treatments. The E4 allele of the Apolipoprotein E gene (APOE4) is a potent genetic risk factor for sporadic and late-onset familial AD. A critical, and commonly overlooked, feature of the APOE4 link to AD is that several case-control studies suggest it is far more pronounced in women than in men. Shortly after the identification of APOE as a risk factor for AD, a study found an interaction between sex and APOE: women in their sixties with one APOE4 allele had a 4-fold increased risk whereas male APOE4 heterozygotes did not bump their risk much.



Sex-by-APOE effect on AD prevalence (left; Farrer et al. 1997) and progression from healthy aging to mild cognitive impairment (right; Altmann et al. 2014).

In this study, we screened genome-wide association studies (GWAS) for (i) further genes with a gene-by-sex interaction on AD risk and (ii) genes with an APOE-by-gene-by-sex interaction on AD risk.

Methods

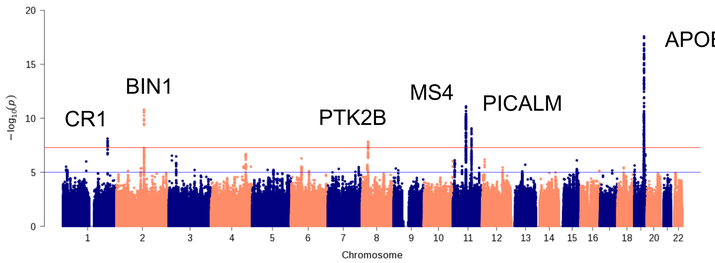
Data. Data from 15 case-control genome-wide association studies with a total of 21,940 subjects (AD: 11,449, healthy control: 10,491). The studies used different genotyping chips to measure single nucleotide polymorphisms (SNPs). Prior to the analysis a common set of about 7.1 mio SNPs was imputed.

Statistical model. For each study we applied logistic regression models to compute the association strength for
(i) SNP main effect
(ii) SNP-by-sex interaction effect
(iii) SNP-by-sex-by-APOE interaction effect.
In the models we corrected for the age, population structure, APOE, and SNP main effect (models ii and iii only).

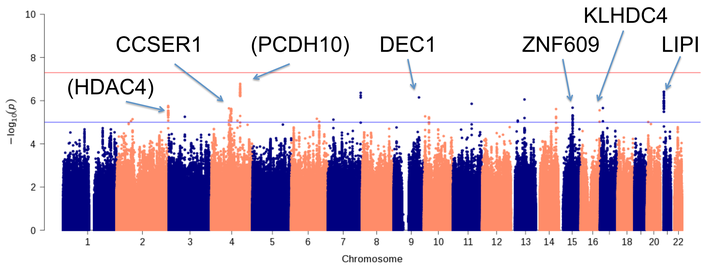
Meta analysis. Each study was analyzed separately. And the joint p-value was computed using the inverse variance weighted method implemented in METAL.

Results (I)

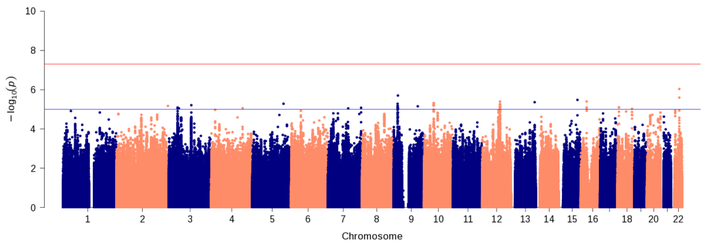
(i) SNP main effect. By looking at the SNP main effect we could confirm a number of reported AD risk genes. The manhattan plot below shows the association strength with AD risk for all 7 mio SNPs. The horizontal line marks the level of genome-wide significance.



(ii) SNP-by-sex interaction effect. No SNP showed a genome-wide significant interaction with sex. Some loci, however, yielded suggestive effect sizes. *HDAC4* and *PCDH10* are the most interesting regarding neurodegenerative disorders. For both, however, SNPs were located far outside the coding region.

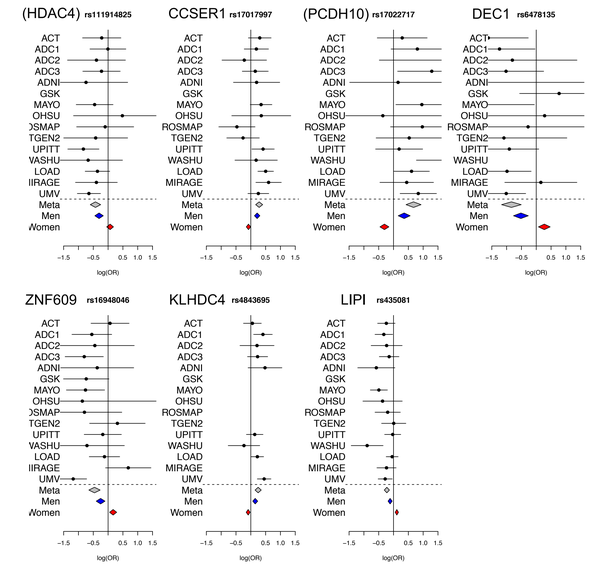


(iii) SNP-by-sex-by-APOE interaction effect. P-values for the 3-way interaction effect were in general much lower. Only very few SNPs pass the threshold for "suggestive" association (blue line). This is most likely due to the reduced power for detecting 3-way interactions.



Results (II)

SNPs with suggestive sex-dependent effect on AD.



Conclusions

Our analysis confirmed the main effects of previously identified AD genes. However, no SNP passed the level of genome-wide significance ($P=5x10^{-8}$) for the SNP-by-sex interaction or for the SNP-by-sex-by-APOE interaction.
Although we did not identify new genes with a SNP-by-sex interaction, some genes are suggestive. Further, we are currently using the established APOE-by-sex interaction to define a group of healthy older APOE4 carriers and are searching their whole genome sequence for protective variants.

Funding

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References

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Farrer et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA (1997) vol. 278 (16) pp. 1349-56

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