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Biomarkers for Alzheimer's disease and the *APOE* polymorphism

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten

I. Olsson B, **Lautner R**, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K and Zetterberg H.
CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis.
Lancet Neurology. 2016; **15**(7): p. 673–684.

II. Andreasson U, **Lautner R**, Schott JM, Mattsson N, Hansson O, Herukka SK, Helisalmi S, Ewers M, Hampel H, Wallin A, Minthon L, Hardy J, Blennow K and Zetterberg H.
CSF biomarkers for Alzheimer's pathology and the effect size of APOE ε4.
Molecular Psychiatry. 2014; **19**(2): p. 148–149.

III. **Lautner R**, Palmqvist S, Mattsson N, Andreasson U, Wallin A, Pålsson E, Jakobsson J, Herukka SK, Owenius, R, Olsson B, Hampel H, Rujescu D, Ewers M, Landén M, Minthon L, Blennow K, Zetterberg H, Hansson O and the Alzheimer's Disease Neuroimaging Initiative.
Apolipoprotein E genotype and the diagnostic accuracy of cerebrospinal fluid biomarkers for Alzheimer disease.
JAMA Psychiatry. 2014; **71**(10): p. 1183–1191.

IV. **Lautner R**, Insel PS, Skillbäck T, Olsson B, Landén M, Frisoni GB, Herukka SK, Hampel H, Wallin A, Minthon L, Hansson O, Blennow K, Mattsson N and Zetterberg H.
Preclinical effects of APOE ε4 on cerebrospinal fluid Aβ42 concentrations.
Alzheimer's Research & Therapy. 2017; **9**(1): p. 87.

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Biomarkers for Alzheimer's disease and the *APOE* polymorphism

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Abstract

Alzheimer's disease (AD) is the most common form of dementia and cerebrospinal fluid (CSF) biomarkers reflecting the core pathology of AD are now widely used for diagnosis making, in particular β-amyloid$_{1-42}$ (Aβ42) reflecting amyloid plaque pathology, phosphorylated tau (P-tau) reflecting neurofibrillary tangle pathology and total tau (T-tau) reflecting general neurodegeneration. In addition, blood-based biomarkers for AD are in the pipeline with recent studies showing promising diagnostic potential. The most important genetic risk factor for sporadic AD is the ε4 allele of the apolipoprotein E (*APOE*) polymorphism, increasing risk for AD diagnosis in a dose-dependent manner as well as lowering the age of onset.

We conducted a comprehensive meta-analysis of the AD biomarker literature from 1984 to 2014, which could confirm the robust diagnostic performance of the above-mentioned established CSF biomarker triad for AD, and also revealed possible new biomarker candidates in both CSF and blood that could contribute to the diagnostic work-up of the disease as well as serve as tools for monitoring new disease-modifying treatments. In a large multicentre study, we confirmed the strong association between the *APOE* ε4 genotype and AD and showed that the ε4 allele also affects concentrations of CSF Aβ42 in a dose-dependent manner. However, the *APOE* polymorphism does not blur the diagnostic accuracy of the established AD biomarkers and CSF Aβ42 was shown to reflect cerebral amyloid pathology irrespective of the *APOE* genotype. In another multicentre cohort consisting of solely cognitively healthy subjects, we showed that the dose-dependent effect of *APOE* ε4 on CSF Aβ42 was absent in younger subjects and CSF Aβ42 concentrations started to drop around age 50 and even earlier in ε4-carriers, pinpointing the earliest disturbances in amyloid homeostasis, long before cognitive impairment becomes apparent.

Taken together, the results from this thesis underline the usefulness of AD biomarkers as well as their robust diagnostic performance irrespective of the most prominent genetic risk factor. In addition, since biomarkers (in particular CSF Aβ42) can reflect pathological changes already in the preclinical stage of the disease, they could become valuable in future AD prevention, once disease-modifying therapies become available.

Keywords: Alzheimer's disease, biomarkers, *APOE*, cerebrospinal fluid, β-amyloid

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