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# Soluble amyloid precursor protein $\beta$ as blood-based biomarker of Alzheimer's disease

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The aim of this study was to explore concentrations differences of soluble amyloid precursor protein (sAPP)  $\alpha$  and  $\beta$  in blood plasma in patients with probable Alzheimer's disease (AD) and cognitively healthy age-matched control subjects, as well as patients with behavioural variant frontotemporal dementia (bvFTD). Concentrations of sAPP $\alpha$  and  $\beta$  were measured using enzyme-linked immunosorbent assay technology in 80 patients with probable AD, 37 age-matched control subjects and 14 patients with bvFTD. Concentration differences were explored using parametric tests. Significantly decreased plasma concentrations in the AD group compared with both the control group and the bvFTD group were detected for sAPP $\beta$  (P = 0.03for both group comparisons), but not for sAPP $\alpha$ . The study provides a further piece of evidence in support of sAPP $\beta$  as a promising new biomarker of AD, which may potentially improve the diagnostic accuracy of existing markers and also enable a less invasive diagnostic workup. Further research is required to establish normal ranges and to replicate the results in independent cohorts including larger numbers of participants covering a wider spectrum of cognitive impairment. *Translational Psychiatry* (2013) **3**, e227; doi:10.1038/tp.2013.11; published online 19 February 2013

## Introduction

The soluble amyloid precursor proteins (sAPP)  $\alpha$  and  $\beta$ , which are the products of physiological and amyloidogenic cleavage of APP, respectively, are related to central upstream pathophysiological events in Alzheimer's disease (AD).<sup>1</sup> Concentration changes in cerebrospinal fluid (CSF) have been repeatedly observed in AD, and the diagnostic utility of the markers is supported by a growing number of publications.<sup>2,3</sup> The present study explored whether AD is also associated with concentration changes of sAPP  $\alpha$  and  $\beta$  in the blood plasma. Significantly decreased plasma sAPP $\beta$  concentrations were found in patients with probable AD compared with age-matched control subjects and patients with a non-Amyloid- $\beta$  (A $\beta$ ) type of dementia, suggesting a potential role as diagnostic marker.

The clinical diagnosis of AD is traditionally based on evidence of a progressive memory-predominant type of dementia, and the exclusion of alternative causes. This simple set of criteria is neither sensitive for early clinical changes nor is it specific for AD. Indicators of the AD pathophysiological process rather than of its clinical manifestations are therefore urgently needed, especially in view of upcoming disease-modifying strategies. Established biomarkers such as the CSF proteins A $\beta_{1-42}$ , total-Tau and phosphorylated Tau<sub>181</sub><sup>4</sup> and structural and functional imaging techniques such as [18F]-fluorodeoxy-glucose positron emission tomography<sup>5</sup> show reasonable but not perfect accuracy in distinguishing probable AD from physiological aging and other neurodegenerative disorders. However, the need for

invasive manoeuvres such as a lumbar puncture or the necessity of cost- and technology intensive equipment such as cyclotrons and imaging facilities severely limit population-based screening programs and serial assessments of an individual patient. Less invasive procedures for biomarker ascertainment are therefore highly desirable, but no such biomarker is available at present; so far, most research in this area focussed on A $\beta_{1-42}$  in blood, with studies showing mixed results.<sup>6</sup> Our previous research indicates that sAPP  $\alpha$  and  $\beta$  in CSF are promising novel biomarkers of AD.<sup>2,3</sup> The present study aimed to explore their diagnostic potential in plasma.

#### Materials and methods and results

Eighty patients with probable AD (age, years: mean 73.86, s.d. 7.75; 51 men, 29 women; Mini-Mental-State Examination (MMSE) score: mean 19.54, s.d. 6.05) according to the National Institute of Neurological and Communicative Disorders and Stroke/AD and Related Disorders Association criteria, 14 patients with behavioural variant frontotemporal dementia (bvFTD) according to revised consensus criteria<sup>7</sup> (age, years: mean 61.37, s.d. 8.89; 7 men, 7 womer; MMSE score: mean 22.53, s.d.: 3.35) and 37 healthy age-matched control subjects with no subjective memory complaints and normal test results on the MMSE (age, years: mean 67.32, s.d. 9.21; 26 men, 11 womer; MMSE score: mean 29.22, s.d.: 0.98) were recruited for the study at the Department of Psychiatry and Psychotherapy of Technische Universität München. The study was conducted in accordance with the

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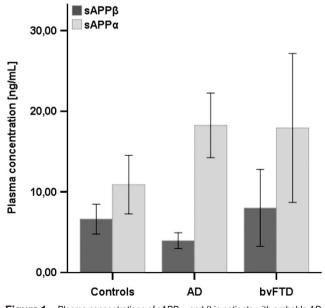
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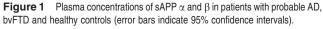
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1975 Declaration of Helsinki and all study participants gave written informed consent. Plasma samples were collected as part of the clinical assessment and immediately stored in aliquots at - 80 °C until further analyses. Plasma concentrations of sAPP  $\alpha$  and  $\beta$  were measured in duplicate with commercial enzyme-linked immunosorbent assays (IBL, Gunma, Japan; detection range for both assays 0.78-50 ng ml<sup>-1</sup>).<sup>2</sup> One-way analysis for variance with posthoc Scheffé-test for normally distributed data (as indicated by the Kolmogorov-Smirnov test) were used to explore differences in plasma protein levels between patients with probable AD on the one hand and healthy control subjects and patients with bvFTD on the other. The analysis showed significantly decreased sAPP<sup>B</sup> plasma concentrations in the AD group compared with both the healthy control group and the bvFTD group (AD: mean 3.94 ng ml<sup>-1</sup>, s.d. 4.36, range  $0.78-22.32 \text{ ng ml}^{-1}$ ; bvFTD: mean  $8.01 \text{ ng ml}^{-1}$ , s.d. 8.26 ng ml<sup>-1</sup>, range 0.78–28.77 ng ml<sup>-1</sup>; controls: mean 5.73 ng ml<sup>-1</sup>, s.d. 0.94, range 0.78–24.03 ng ml<sup>-1</sup>; P = 0.03for both group comparisons; N = 131; Figure 1), whereas the difference did not attain statistical significance for sAPPa due to a higher variability of the measured concentrations (AD: mean 18.24 ng ml<sup>-1</sup>, s.d. 17.90, range 0.78-86.24 ng ml<sup>-1</sup>; bvFTD: mean 17.93 ng ml<sup>-1</sup>, s.d. 15.99 ng ml<sup>-1</sup>, range 2.64– 56.25 ng ml<sup>-1</sup>; controls: mean 9.37 ng ml<sup>-1</sup>, s.d. 1.60, range 0.78-49.93 ng ml<sup>-1</sup>; P = 0.08 for AD vs controls and 0.38 for AD vs bvFTD, N = 131; Figure 1). The plasma biomarker concentrations were not associated with age and gender in either of the diagnostic groups. There was no correlation between the respective protein concentrations in plasma and in CSF (N = 47; results not shown).

## Discussion

To the best of our knowledge, this is the first report on blood sAPP levels in AD. Our results clearly support sAPP $\beta$  in





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plasma as a novel, minimally invasive diagnostic marker of AD; this is an important finding in the light of urgently needed biomarkers to be used for large-scale screening purposes requiring easy and repeatable ascertainment. sAPPß levels were decreased in our study compared with healthy aging and a non-A $\beta$  type of dementia, which is in line with a reduced concentration of sAPPB in AD brain cortex.<sup>8</sup> Even though increased concentrations of full-length APP protein in blood platelets and APP mRNA levels in blood mononuclear cells have been reported in AD.<sup>9,10</sup> peripheral changes of APP cleavage products may be more closely related to cerebral changes due to AD than to a pathological response in the periphery. That is reduced sAPP levels possibly mirror decreased cortical APP expression in AD, which limits APP clearance across the bloodbrain-barrier and/or decreased processing of APP into sAPP in blood.

Limitations of our study include the recruitment of participants at a specialized centre, the lack of histopathological verification of the clinical diagnoses, and the modest number of study participants. To conclude, our study provides a further piece of evidence in support of sAPP $\beta$  as a promising new biomarker of AD, which may potentially improve the diagnostic accuracy of existing markers and also enable a less invasive diagnostic workup. The central message of our study is that sAPP $\beta$  may serve as a blood-based marker of AD with far-reaching practical implications for patient management. Further research is required to establish normal ranges and to replicate our intriguing results in independent cohorts including larger numbers of participants covering a wider spectrum of cognitive impairment.

#### **Conflict of interest**

The authors declare no conflict of interest.

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