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## Review

# Glial fibrillary acidic protein is a body fluid biomarker for glial pathology in human disease

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## ABSTRACT

This review on the role of glial fibrillary acidic protein (GFAP) as a biomarker for astroglial pathology in neurological diseases provides background to protein synthesis, assembly, function and degeneration. Qualitative and quantitative analytical techniques for the investigation of human tissue and biological fluid samples are discussed including partial lack of parallelism and multiplexing capabilities. Pathological implications are reviewed in view of immunocytochemical, cell-culture and genetic findings. Particular emphasis is given to neurodegeneration related to autoimmune astrocytopathies and to genetic gain of function mutations. The current literature on body fluid levels of GFAP in human disease is summarised and illustrated by disease specific meta-analyses. In addition to the role of GFAP as a diagnostic biomarker for chronic disease, there are important data on the prognostic value for acute conditions. The published evidence permits to classify the dominant GFAP signatures in biological fluids. This classification may serve as a template for supporting diagnostic criteria of autoimmune astrocytopathies, monitoring disease progression in toxic gain of function mutations, clinical treatment trials (secondary outcome and toxicity biomarker) and provide prognostic information in neurocritical care if used within well defined time-frames.

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## 1. Introduction

The discovery of glial fibrillary acidic protein (GFAP) by Lawrence F. Eng in 1969 published in this Journal represented the first step to unravel the chemical properties of those fibres giving rise to the distinctive intra-cytoplasmic features of astrocytes (Eng et al., 1970, 1971). The GFAP protein equips astrocytes with a nematic liquid crystal hydrogel, able of rapid fibre reorganisation. Like other cellular fibres, GFAP is classified by fibre diameter (8–12 nm) as *intermediate* between the smaller microfilaments (7 nm) and the larger microtubules ( $\approx 25$  nm) (Fuchs and Cleveland, 1998). Expression of GFAP in the human brain occurs pre-dominantly in astrocytes and is about 10 times higher compared to rodent astrocytes (Lundgaard et al., 2014). It is the highly cell-type specificity and stability which qualifies this class III intermediate filament (IF) as a biomarker for human disease.

This review on GFAP as a protein biomarker (1) discusses protein synthesis and assembly; (2) introduces quantitative and qualitative analytical methods; (3) explains the clinico-pathological relationships underlying the biomarker hypothesis; and (4) reviews the evidence to use GFAP biomarker signatures as supportive diagnostic criteria, monitoring disease progression and improving prognostic accuracy.

## 2. GFAP structure and function

GFAP is a relatively non-soluble acidic cytoskeletal protein. It is the principal IF of the human astrocyte. First, viewed with

the electron microscope, GFAP appears as bundled fibres of 8–12 nm diameter in the astrocytes. With the availability of specific antibodies, GFAP can be visualised using routine immunohistochemistry. The specificity of GFAP for astrocytes is such that GFAP has become one of the most useful proteins for identifying astrocytes in the brain (Bignami et al., 1972). There is heterogeneity in astrocytes. Expression of GFAP is higher in white matter compared to grey matter astrocytes (Lundgaard et al., 2014). In the retina GFAP is specific for Müller cells and astrocytes (Goel and Dhingra, 2012).

### 2.1. Genetics

The human GFAP gene was cloned in 1989 and is mapped to chromosome 17q21.1-q25 (about 10 kb DNA) (Reeves et al., 1989; BongcamRudloff et al., 1991). The gene consists of 8 introns and 9 exons, with 4 alternative exons and 2 alternative introns (3 kb, mRNA). Alternative splicing leads to 6 GFAP isoforms (Middeldorp and Hol, 2011) (Fig. 1). Of these  $\alpha$ -GFAP is most abundant in the human CNS (Middeldorp and Hol, 2011). The calculated protein length in aminoacids is 432 for  $\alpha$ -GFAP,  $\geq 321$  for  $\beta$ -GFAP, 431 for  $\gamma/\epsilon$ -GFAP, 438 for  $\kappa$ -GFAP, 374 for  $\Delta 135$ -GFAP,  $\leq 366$  for  $\Delta 164$ -GFAP and  $\leq 347$  for  $\Delta$ exon6-GFAP. The complex regulatory mechanisms governing alternative splicing of the GFAP gene have not yet been fully unravelled (Blechingberg et al., 2007). It is not yet clear if all of these get translated into protein, but there is good evidence for  $\alpha$ -GFAP,  $\beta$ -GFAP and  $\Delta$ -GFAP.

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