14-3-3 protein

14-3-3 proteins were originally discovered as a family of proteins that are highly expressed in the brain. Through interactions with a multitude of binding partners, 14-3-3 proteins impact many aspects of brain function including neural signaling, neuronal development, and neuroprotection.

Reincke et al. performed exome sequencing of 10 corticotroph adenomas. They found somatic mutations in the USP8 deubiquitinase gene in 4 of 10 adenomas. The mutations clustered in the 14-3-3 protein binding motif and enhanced the proteolysis cleavage and catalytic activity of USP8. Cleavage of USP8 led to increased deubiqutination of the EGF receptor, impairing its downregulation and sustaining EGF signaling. USP8 mutants enhanced promoter activity of the gene encoding proopiomelanocortin. In summary, our data show that dominant mutations in USP8 cause Cushing's disease via activation of EGF receptor signaling [1)].

There is no practical and reliable premortem test for Creutzfeldt-Jakob disease and the related transmissible spongiform encephalopathies. Two proteins designated 130 and 131, which have been detected in low concentrations in cerebrospinal fluid from patients with Creutzfeldt-Jakob disease, appear to be sensitive and specific markers for the disease. Attempts to identify these proteins, however, have been unsuccessful. Hsich et al. detected proteins 130 and 131 in the normal human brains, partially sequenced their amino acids and found that they matched the brain protein known as 14-3-3. They then developed a simple, rapid immunoassay for this protein and tested it in cerebrospinal fluid samples from 71 humans and 30 animals with spongiform encephalopathies and in control samples from 186 humans and 94 animals.

The immunoassay detected the 14-3-3 protein in cerebrospinal fluid from 68 of the 71 patients with Creutzfeldt-Jakob disease (96 percent, 95 percent confidence interval, 92 to 99 percent). Among 94 patients with other dementias, the specificity was 96 percent. If one excludes the three patients with dementia who had strokes within one month before testing, the specificity was 99 percent. The test was positive in 12 of 24 patients with viral encephalitis. In animals, the sensitivity of the assay was 87 percent and the specificity was 99 percent.

In patients with dementia, a positive immunoassay for the 14-3-3 brain protein in cerebrospinal fluid strongly supports a diagnosis of Creutzfeldt-Jakob disease. This finding, however, does not support the use of the test in patients without clinically evident dementia [2)]

1)
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2)
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