The Biological Significance of a 96 Gene Expression Assay Developed to Aid the Diagnosis of Alzheimer’s disease

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Summary

A new blood test, ADtect®, has been developed to aid early detection of Alzheimer’s Disease (AD). The test is based on measuring the expression of selected genes in blood and defined as an AD-specific gene signature. ADtect® comprises a low-density array of 96 selected gene assays. Expression in blood cells is measured in test samples and an already developed diagnostic algorithm is used to provide a positive or negative test score value indicating the presence or absence of AD. In a multicenter study of 412 subjects the test was able to discriminate AD subjects from cognitively healthy controls with a 72% overall agreement with the clinical diagnosis, an imperfect ‘gold standard’. The test performance was confirmed in two independent validation studies and shows a similar and consistent good performance.

Methods

The networks and pathway analyses were generated through the use of IPA (Ingenuity Systems, www.ingenuity.com). IPA has also been applied in a multicenter study of 412 subjects that include the list of known genes included in the ADtect® test and the KEGG pathway of AD. AD is associated with profound biochemical and pathologic alterations in the brain, including aberrant amyloid precursor protein (APP) metabolism, tau protein phosphorylation, cell cycle control, inflammation, calcium dysregulation, lipid dysregulation, and synaptic dysfunction. AD is assumed to result from the progressive loss of synaptic function and neurologic degeneration. As shown in Box 1 we find that among the genes included in the ADtect® test there are genes associated with essentially all biochemical alterations that have been related with AD.

Results and Discussion

AD is associated with profound biochemical and pathologic alterations in the brain, including aberrant amyloid precursor protein (APP) metabolism, tau protein phosphorylation, cell cycle control, inflammation, calcium dysregulation, lipid dysregulation, and synaptic dysfunction. AD is assumed to result from the progressive loss of synaptic function and neurologic degeneration. As shown in Box 1 we find that among the genes included in the ADtect® test there are genes associated with essentially all biochemical alterations that have been related with AD.

All of the 15 genes listed under AD-associated proteins in Box 2 were also included in the ADtect® test. The ADtect® test has been performed in several clinical settings and commercial laboratories and the results are consistent with other studies (see Table 1).

Concluding remarks

AD is multifactorial and heterogeneous in both its clinical and histopathological appearances and it is unlikely that a single biomarker will be able to detect AD. However, some of the genes included in ADtect® do cover several biological and pathologic processes involved in AD. We now show that 60 of the 94 known genes included in ADtect® (71% of the ADtect predictive gene assays) encode proteins directly involved in or closely associated to known AD biology and pathology.

Concluding remarks

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The results suggest that many of the biological processes associated with AD not only is localized to brain tissue but can also be detected in blood and maybe other tissues as well. It would be of interest to explore if also some of the ADtect® genes where no links to AD have been found actually have some connection to the biology or pathology of the disease. The exploration of these genes may aid the discovery of novel aspects of the AD pathology previously not recognized.

✓ A blood based test, ADtect®, has been developed to aid the detection of Alzheimer’s Disease.

✓ 60 of the 84 known genes included in ADtect® encode proteins directly involved in or closely associated to known AD biology and pathology.

References