Alzheimer’s disease biology of a 96 gene expression assay developed to aid in the diagnosis of the 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 measure the expression of selected genes in blood and is defined as an AD-specific gene expression signature. ADtect® comprises a low density array of 96 selected gene assays and a diagnostic algorithm is used to provide a positive or negative test prediction indicating the presence or absence of AD. In a multicenter study of 412 subjects the test was able to discriminate AD subjects from healthy controls with a 72 % overall agreement with clinical diagnosis, an imperfect “gold standard”(L2). The test performance was confirmed in two independent validation studies both showing a similar and consistent good performance.

In the present review it was found that 64 of 84 genes in ADtect® encode proteins with a biological function associated with AD or AD related biological processes. The identity of the 12 remaining genes of the 96 included in the test could not be found in available databases.

Introduction
Early and accurate detection of AD is critical for implementing active management strategies which may delay the onset of the more debilitating symptoms of the disease. A convenient blood test to help detect AD can be a valuable addition to the clinician’s diagnostic tool box. Several independent studies have indicated that a blood based test could be used for diagnostic profiling in neurodegenerative diseases(4-10). Gene expression is able to detect subtle changes and have the potential to detect even minimal alterations in biology associated with a disease like AD and studies have demonstrated a significant degree of co-variability in gene expression between brain tissue and peripheral blood cells(11,12). Liew et al(12) indicate that about 80% of the genes expressed in brain tissue are also expressed in blood cells and that at least some of the genes are regulated in a similar way in the two tissues. This opens an alternative approach using gene expression in a blood sample to find useful biomarkers for the early detection of AD. Some gene expression studies for detection of AD in blood have been described(13,14) but they were all performed on relatively small sample sizes and no models for AD prediction were developed.

With the blood test ADtect® it is now for the first time possible to examine if there are similarities in the set of genes known to be associated with AD in brain tissue and in the genes found to be informative for AD in blood.

Methods
The networks and pathway analyses were generated through the use of IPA (Ingenuity Systems, www.ingenuity.com). IPA has also been used to make a comparison between the list of known genes included in the ADtect® test and the KEGG pathway of AD(15).

Results and Discussion
AD is associated with profound biochemical and pathologic alterations in the brain, including aberrant amyloid precursor protein (APP), amyloid-β (Ab) protein metabolism, tau protein phosphorylation, cell cycle control, inflammation, cellular Ca²⁺ signaling, and lipid dysregulation. AD is assumed to result from the progressive loss of synaptic function and neurologic degeneration. We find that among the genes included in the ADtect® test there are genes associated with essentially all biochemical alterations that has been related to AD (Box 1).

As can be seen in Box 1 there are ADtect® genes are involved in or associated with all biological and pathologic processes that has been associated with AD. There are between 12 and 35 ADtect® genes involved in or associated with any of the listed biological processes including Apal-processing, Apoptosis, Calcium signaling, Cell Cycle Control, Inflammation, Mitochondrial Function, Neurodegeneration, Tau Processing and Oxidative Stress. Several of the proteins encoded by the ADtect® genes are associated with several of the AD associated biological processes.

Based on available published data, essential genes and biochemical pathways have been assembled in The KEGG pathway for Alzheimer’s disease (Box 2). ADtect® genes associated with these pathways have been depicted (red symbols and frame). Four ADtect® genes are also directly included in the KEGG Alzheimer’s disease pathways (BRIC®, GAPDH, TNF, UBE4B).

Concluding remarks
AD is multifactorial and heterogeneous disorder in both its clinical and histopathological appearance and it is unlikely that a single biomarker will be able to detect AD with required sensitivity and specificity. A test that includes a broader set of biomarkers will cover a broader range of processes of the disease. The 96 genes included in ADtect® cover several biological and pathologic processes involved in AD. We now show that 64 of the 84 known genes included in ADtect® (76 % of the ADtect® predictive gene assay) encode proteins directly involved in or closely associated to known AD biology and pathology. Since these genes were selected on their informative value to classify AD and not based on known function in relation to AD it is interesting that the majority of the selected genes actually encode proteins associated with the disease.

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. The results also support previous studies suggesting that blood can be used as a surrogate tissue in CNS research(4,8-11). 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 AD pathology previously not recognized.

A blood based test, ADtect®, developed to aid AD detection.
64 of 84 ADtect® genes associated to known AD pathology.

References:

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