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 in the early detection of Alzheimer’s disease (AD) [1-2]. The test is based on measuring the expression of selected genes in blood defined as the AD specific gene signature. ADtect® comprises a low density array of 96 selected genes on a low density format. The performance of the 96 gene array together is calculated with an algorithm resulting in a positive or negative test score indicating the presence or absence of AD. In two independent multicenter studies including 204 subjects in total the test is able to discriminate AD subjects from cognitively healthy controls with a 72% overall agreement with clinical diagnosis [2]. The test shows a similar and consistent performance in both studies [2]. Although the 96 gene expression signature was selected based on predictive value in the algorithm and not on a presumed association with AD pathology, we have previously shown that more than 30 genes are encoding proteins with a biological function associated with AD brain or neuronal function [2]. We now present a further analysis showing the close connection with known pathways in AD biology for many of the encoded by the genes included in ADtect®.

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 AD. The development of the convenient blood based test ADtect® have given clinicians a new tool to aid the diagnosis of the disease. As the 96 genes included in the test was selected based on their predictive value and not on knowledge of the biology associated with the disease it was of interest to see what connections the encoded proteins might have with known pathways associated with AD biology.

Methods
The analysis is based on a comparison between the list of known genes included in the ADtect® test with the KEGG pathway of AD [3] complemented with a limited search in available literature. The Cytoscape software version 2.6.3 [4] and the Pathway Commons web service client [5] was used to link the encoded proteins with different pathways. Pathways analyzed include biochemical reactions, complex assembly, transport and catalysis events, and physical interactions involving proteins, DNA, RNA, small molecules and complexes.

Results
The KEGG pathway of AD cover proteins that genetically and/or biologically has been connected with the disease [2-3, 5-6, 8]. There are 29 genes described here of which we have previously described 16 [2] while 13 have not previously been linked to AD biology. In total we have now found that at least 44 of the 96 genes included in ADtect® can be associated with known AD pathways. Of the 29 genes analyzed to date all but six are either directly included in a biological pathway or associated with a gene product in a biological pathway connected with the disease. This is especially interesting when considering that the genes included in the test based on their predictive value when expressed in blood and not on knowledge of their biological function.

Discussion
We have previously shown that 32 of the genes included in ADtect® are associated with genetics or biology of AD [2]. (Figure 1) and three of these genes (PS2, TARDBP, TC12) are also included in the list. Several are also associated with oxidative stress, mitochondrial function, inflammation, calcium regulation, neuronal or brain function (Figure 2). These findings encouraged us to conduct more extensive association studies to see if other connections to AD might be found. In this context we have analyzed if proteins encoded by the ADtect® genes are connected to known biological pathways associated with the disease. Although not yet completed we have found that several of these proteins are indeed connected to known biology of Alzheimer’s disease pathways.

It is noteworthy that so many of the analyzed genes from the ADtect® test encode proteins that are connected to known AD pathways. Of the 29 genes analyzed to date all but six are either directly included in a biological pathway or associated with a gene product in a biological pathway connected with the disease. This is especially interesting when considering that the genes included in the test based on their predictive value when expressed in blood and not on knowledge of their biological function.

Conclusions
+ The ADtect® test include at least 44 genes that encode proteins closely connected to known AD biology.
+ The systemic response of AD detected in peripheral blood contains information connected to known biology of the disease.

References