Employing Blood-Based Gene Expression Signature to Detect Alzheimer’s Disease

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Diagnostic methods today

- Cognitive impairment (MMSE, Clock Test, OLT)
- Functional decline & changed behavior
- Interview with relative
- Structural imaging (MR, CT)
- Functional imaging (PET, SPECT)
- Neurophysiological changes (EEG, qEEG)
- CSF markers (Tau, β-Amyloid)
- ApoEε4
Why peripheral blood?

The ideal clinical sample

- Circulates in all parts of the body
- A highly dynamic tissue
- Allows repeated measurements
- The most readily accessible source of RNA
- Easily integrated into a clinical lab setting
- Used in several gene expression studies
Can a diagnostic test based on a gene expression signature in peripheral blood be developed for the diagnosis of Alzheimer’s disease?
**Experimental design**

- **125 AD**
- **94 Age Matched**
- **28 Young**
- **27 Parkinson**
- **56 Technical**

**Training Set**
- 250 samples (94 AD)

**Test Set**
- 80 samples (31 AD)

Peripheral blood collected in PAXgene tubes

Total RNA from whole blood

Applied Biosystems Whole Genome Microarray

AD according to ICD-10
Mean age 77.0
Mean MMSE 24.0

Age matched
Mean age 78.9
MMSE at least 28.0
Results: Training set

A Leave-One-Out Cross Validated model is able to predict AD with

Specificity: 88%
Sensitivity: 85%
Accuracy: 87% (±5%)

Positive likelihood ratio: 7.3
Results: Training set

ROC Curve

AUC: 0.93
The number of samples in the training set is large enough to generate a reliable gene expression model.

A test set validated model is able to predict AD with

**Specificity:** 91%

**Sensitivity:** 84%

**Accuracy:** 87% (±8%)

**Positive likelihood ratio:** 8.9
Can distinguish between different Neurodegenerative diseases

• 24 out of 27 Parkinson classified as Non-Alzheimer’s disease
Results: Test set

ROC Curve

AUC: 0.93
Results

Biological processes significantly over-represented among the predictive genes (p < 0.05)
Results

Initial validation on TaqMan®:

- confirms results from Whole Genome Microarrays
- confirms RT-PCR based TaqMan® Low Density Array as a potential diagnostic platform.

Accuracy: 85% (±9%)
YES,

A highly accurate blood-based diagnostic method for the diagnosis of Alzheimer’s disease can be developed!
Conclusions

- Large enough number of samples used to build the model
- Test set validated
- High Sensitivity (84%)
- High Specificity (91%)
- High Accuracy (87%)
- High Likelihood ratio (8.9)
- High AUC (0.93)
- Selective for AD
- High accuracy on initial validation on TaqMan®
Next steps

• Validation of remaining informative gene probes on TaqMan®
• Evaluation of other low density gene expression platforms
• Clinical trials of prototype design