Employing blood-based gene expression signature to discriminate patients with Alzheimer’s and Parkinson disease.

Anders Lönneborg1, Torbjørn Lindahl2, Solve Sæbe2, Ken Bardsen1, Nina Hagen1, Marianne Jensen1, Pradeep Sharma1, Marion Hirt4, Praveen Sharma1

1DiaGenic ASA, Østensjøveien 15 B, N-665 Oslo, Norway, 2University of Life Sciences, 1432 Ås, Norway, 3IMGM Laboratories, Lochhauser Str. 29, D-82152 Martinsried, Germany.

Introduction

Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the two most common neurodegenerative disorders. Their incidence and prevalence increases with age and it is estimated that about 7% of the population over the age of 67 years suffer from AD, and approx. 1% of the population over the age of 65 years suffer from PD. In case of AD, it has been suggested that the direct-care cost for the 28.8 million sufferers worldwide is staggering 156 billion $ annually.

AD is characterized by a progressive loss of intellectual function. An autopsy examination of an AD patient’s brain reveals gross cerebral atrophy, signifying loss of neurons and the presence of large numbers of extracellular neuritic plaques and intracellular neurofibrillary tangles, predominantly in the frontal and temporal lobes, including the hippocampus. Whereas, PD is caused by degeneration of dopamine-producing cells in the substantia nigra located in the midbrain and is characterized by rigidity, bradykinesia, postural instability, and tremor. While, AD is the most common form of dementia, PD can also affect cognitive processes. Realistic estimates suggest that at least 50% of people with PD have some mild cognitive impairment and as many as 20-40% may have more severe symptoms or dementia.

However, a critical unmet need for clinicians is the availability of an accurate, convenient and objective test for their diagnosis, especially during the early stages of disease development. The potential use of blood-based gene expression profiling in diagnosis of brain disorders has been contemplated and described [1-4]. We recently presented results of a pilot study using macroarrays suggesting that a blood-based gene expression based test can potentially be developed for AD [Sharma et al. (2005)]. Abstract number: 162960. Twelfth Congress of the International Psychogeriatric association, Stockholm, Sweden. We have now performed a large-scale study using ABI microarrays to confirm our previous findings. The detailed results of this study will be presented at the ICAD meeting in Madrid (15-20 July, 2006). Here, we present result of our investigation whether a blood- based gene expression test can be used to discriminate patients with AD and PD.

Materials and methods

Whole blood was collected from 208 individuals in PAX tubes at different hospitals and institutions in Norway. These included 94 patients diagnosed with AD (based on the ICD-10 criteria for dementia syndrome), 73 age- matched controls (mean age, 78.5 yrs; with MMSE score >= 28), 21 control samples from young individuals (mean age, 27 yrs.) to rule out any possibility of AD and 20 patients diagnosed with PD (mean age, 66.2 yrs.), a neurodegenerative disorder with overlapping clinical profile.

Total RNA was extracted from blood samples and gene expression analysis conducted using ABI high-density arrays (Applied Biosystems Human Genome Survey Microarray v2.0) containing 32,878 oligonucleotide probes. The generated expression data were normalized to take account of the differences in the probe intensities resulting from conditions such as hybridization and labelling steps. Partial Least Square Regression (PLSR) was used for model building and a Jackknifing approach based on a double CV routine (Figure 1) was used to identify relevant genes for developing disease-specific expression signatures.

Results and Discussion

Alzheimer- specific gene expression signature was developed by analysing the expression data of AD samples, age-matched controls and samples from young controls. The data pertaining to PD samples were kept out during signature development, and instead used to investigate the specificity of the identified signature in predicting the class of another neurodegenerative disorder. Figure 2 shows that the developed signature correctly classified 19/20 PD samples as non-Alzheimer.

To further validate the above finding, we also developed expression signature for PD by analysing the expression data of PD samples, age-matched controls and samples from young controls and predicted the class of AD samples. The PD- specific expression signature correctly classified most AD samples as non-Parkinson.

Since, AD and PD have different underlying pathologies but overlapping clinical profile as many PD patients also develop dementia, our results indicates that blood based gene expression signatures can be efficiently employed to discriminate brain disorders with overlapping clinical profile.

Conclusions

• Alzheimer specific gene expression signatures in blood cells can be efficiently employed to discriminate AD and PD patients.

• A specific gene expression signature can also be developed for PD.

References


Competing interests

All authors from DiaGenic have competing interests. Authors from other institution have no competing interest.

Development and validation of gene expression signature

Figure 1