Employing blood-based gene expression signature to detect Parkinson disease

Anders Lönneborg¹, Torbjørn Lindahl², Ken Bårdsen³, Nina Hagen³, Marianne Jensen³, Pradeep Sharma⁴, Marion Hirt⁴, Dag Aarsland⁵
Praveen Sharma⁴

¹DiaGenic ASA, Grenseveien 92, N-663 Oslo, Norway, ²IMGM Laboratories, Lochthamer Str. 29, D-82152 Martinsried, Germany, ³Stavanger University Hospital, 4011 Stavanger

Introduction

Parkinson’s disease (PD) is a chronic, progressive, neurodegenerative disorder, affecting approximately 1.5% to 2.0% of the population older than age 60. It is caused by idiopathic degeneration of dopamine-producing cells in the substantia nigra, located in the midbrain, and is characterized by symptoms like rigidity, bradykinesia, postural instability, and tremor.

Clinically, PD is diagnosed primarily by its symptoms. The asymmetrical and unilateral onset of resting tremor is the single best clinical clue for PD. However, PD may also present with other symptoms, and other diseases may also present with parkinsonism. A robust response to levodopa is also considered a strong evidence of true Lewy Body PD. There is a growing literature on the usefulness of imaging techniques, such as computerized tomography (CT), magnetic resonance imaging (MRI), visualising the dopamine transporter system in the basal ganglia using SPECT, or positron-emission tomographic (PET), in distinguishing PD from disorders with related symptoms. However, a critical unmet need for clinicians is the availability of an accurate, convenient and objective laboratory test for PD 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 [1,3-5]. We recently presented results of a large study showing that the potential use of blood-based gene expression profiling in diagnosis of brain disorders has been contemplated and described [1,3-5]. Since in the model developed for PD detection, the number of controls (98) far exceeded the number of PD samples (27) we also checked the accuracy when both PD and non-PD classes were balanced. This was done by randomly picking 27 controls from the 98 control data set (20,000 iterations) and determining the accuracy in iteration (Figure 3). The average accuracy, sensitivity and specificity observed were 86.2%, 88.4% and 84.0% respectively.

Materials and methods

Whole blood was collected in PAX tubes at different hospitals and institutions in Norway. These included 27 patients diagnosed with clinically diagnosed PD and responsive to levodopa (mean age, 66.2 yrs.), 98 controls with no reported brain disorder, and 125 patients diagnosed with AD (based on the ICD-10 criteria for dementia syndrome), another neurodegenerative disorder that may exhibit 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 pre-processed and analyzed using Partial Least Square Regression (PLSR). A PLSR model was built relating the expression variables to a dummy coded (-1/1) health status response variable. A Double Cross-Validation (DCV) routine was used for proper validation of the PLSR models were built and significant variables identified for each N-1 segments using Jackknifing approach. The identified variables in each case were then used to predict the class of each segment one unique sample was kept out from the data. Cross-validated PLSR models were built and significant variables identified for each N-1 segments using Jackknifing approach. The identified variables in each case were then used to predict the class of each segment one unique sample was kept out from the data.

Results and Discussion

Parkinson-specific gene expression signature was developed by analyzing the expression data of 27 PD samples and 98 controls with no reported brain disorder. We identified 502 variables as significant using Jackknifing approach. The DCV routine gave an accuracy, sensitivity and specificity observed were 86.2%, 88.4% and 84.0% respectively.

We further investigated the ability of a model developed for PD detection using the 502 significant variables in discriminating AD, Parkinson-specific gene expression signatures in blood cells can be efficiently employed to discriminate AD and PD patients but these preliminary results need to be complemented with new studies to validate the model further.

Conclusions

- A blood-based gene expression signature can be developed for PD.
- The developed signature can accurately discriminate between PD and AD.

References


Competing interests

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