A plasma microRNA signature for early detection of paediatric cerebellar atrophy caused by PMM2-CDG

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Abstract

Cerebellar atrophy (CA) is caused by the loss of neurons in the cerebellum. miRNAs play a pivotal role in the development of the brain and are associated with multiple brain and cerebellar diseases. In this study, we used plasma miRNAs and NGS to obtain the whole miRNome of CA patients and controls. With this information, we constructed a model using machine learning (ML) algorithms to distinguish between CA patients and controls.

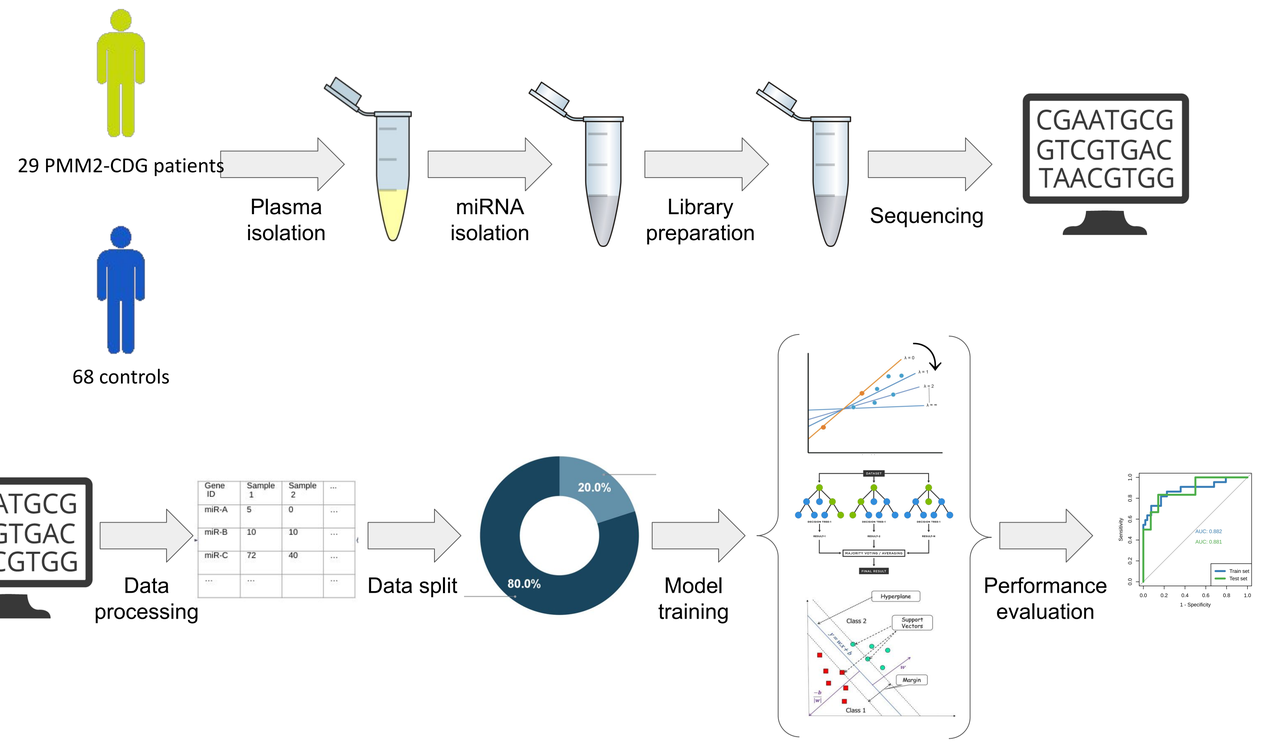
Introduction

Paediatric cerebellar atrophies (CA) are disorders that cause an irreversible loss of the cerebellar tissue. They are diagnosed in children, mostly when the symptoms have appeared and the damage is irreversible. Thus, a non-invasive early diagnosis method for paediatric CA is needed.

During the last few years, there has been a rising interest in miRNAs as non-invasive biomarkers, due to their important role as regulators of gene expression in many complex diseases and their remarkable stability in plasma. Although CA currently has no cure, different strategies of treatment are under development, and the early diagnosis of this aetiology has the potential to improve the quality of life of the patients and facilitate familiar genetic counselling.

The goal of this study is to find a minimally invasive plasma-based miRNA signature to differentiate PMM2-CDG patients (a specific subset of CA patients) from controls.

Materials and methods



Results

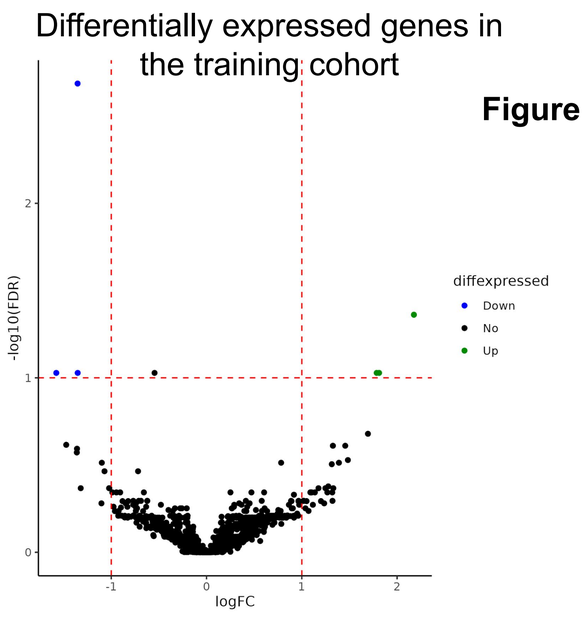


Figure 1

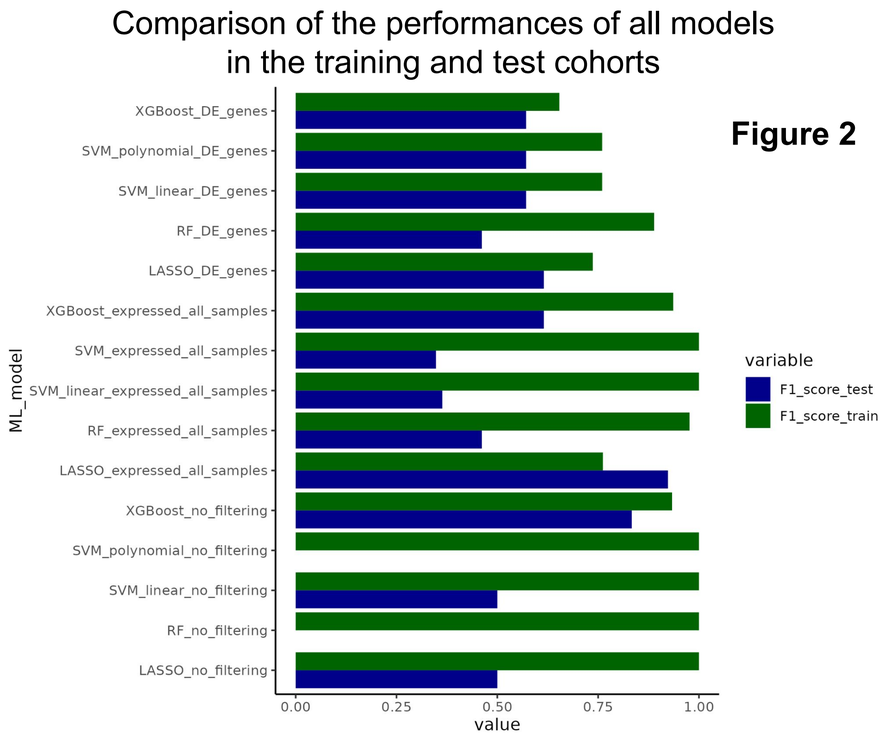


Figure 2

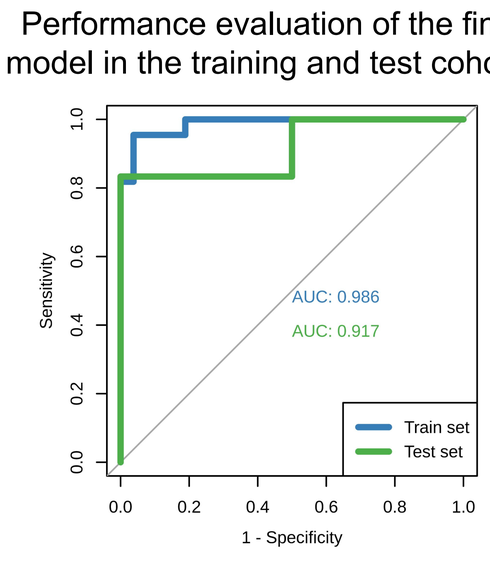


Figure 3

We found 6 differentially expressed (DE) genes in the between controls and PMM2-CDG samples in the training cohort (Figure 1). Using 3 different filtering methods and 5 different ML algorithms, we obtained multiple models with different accuracies (Figure 2). The best model obtained an AUC of 0.986 on the training set and an AUC 0f 0.917 in the test set (Figure 3).

Conclusions and next steps

This is the first study proposing the detection of plasma miRNAs as a non-invasive method for the early detection of PMM2-CDG. Our approach paves the way to a non-invasive diagnosis for children with presymptomatic cerebellar atrophy while highlighting the relevance of miRNA biomarkers for the diagnosis of PMM2-CDG.

The next steps for this project will be:

- Test the specificity of the signature against other brain diseases.
- Test if this signature can be used to monitor the disease treatment.
- Apply the same methodology with other types of CA, to create a general signature for the early detection of CA.