Principal Component Analysis (PCA) Based Data Fusion Approach for a Mouse Model of CLN6 Batten Disease

Timo Bragg1, Tuula Huhtala1, Jukka Puolivirta1, Jon Brudvig2, Tyler Johnson2, Derek Tam2, Jussi Rytkönen1, Jill Weiner2, Antti Nurmi1, Kimmo Lehtimäki1

1Charles River Discovery Services, Kuopio, Finland, 2Sanford Research, Sioux Falls, SD, USA

1 INTRODUCTION

We have characterized the progressive phenotype in the Cln6nclf model for Batten disease from 3 to 12 months of age with a multimodal approach, combining advanced technologies such as kinematic gait analysis (KGA), MR based imaging techniques (T1, DTI, spectroscopy [1H-MRS]), and metabolic profiling (FDG-PET). This approach is essential for the study design and original data.

Our data reveal the distinctly progressive nature of the genetic model both at functional (behavioral) and pathological level, where the majority of readouts suggest clear connections between structure and function. However, individual phenotypic models and the time course of their development do capture quantitative connections between the various pathologies. Therefore, we used a PCA-based approach to look at all measured variables together aiming to identify which readouts are connected in a consistent manner, and further, which combination of readouts best captures the imaging techniques (T2, DTI), spectroscopy (1H-MRS), and metabolic profiling (FDG PET) with a multimodal approach, combining advanced technologies such as kinematic gait analysis (KGA), MR based imaging techniques (T1, DTI, spectroscopy [1H-MRS]), and metabolic profiling (FDG-PET).

We have characterized the progressive phenotype in the Cln6nclf model for Batten disease from 3 to 12 months of age with a multimodal approach, combining advanced technologies such as kinematic gait analysis (KGA), MR based imaging techniques (T1, DTI, spectroscopy [1H-MRS]), and metabolic profiling (FDG-PET).

2 STUDY DESIGN AT A GLANCE

- Phase 1 Principal components
- Phase 2 PCA, using phase 1 PC scores
- Two-Way Mixed ANOVA

3 DATA REDUCTION AND FUSION

4 PRINCIPAL COMPONENTS OF THE MODALITIES

5 PHASE 1 PC SCORES

6 CONTRASTIVE PCS

7 FINAL RESULTS

8 MAIN FINDINGS

- Core set of strongly correlated phenotypes which best describe the progressive nature of the Cln6nclf was identified as cPC1, composed of:
  - Decrease in structural brain volume (MRI PC1), associated with decrease in gait performance (KGA PC1), metabolic changes (FDG PC3), overall demyelination (DTI PC1) as well as local changes in diffusions (DTI PC2).

9 CONCLUSIONS

- Cln6nclf mice show progressive and profound changes in brain anatomy, brain metabolism, and gait.

- Using cPCA, we captured the most consistent changes across these multiple modalities to produce a non-invasive score of disease progression.

- This approach can be utilized in any multi-modal preclinical models and can lead to biomarker tools that are reliable, non-invasive, and already at use in the clinic.

Acknowledgements — this work was supported by the National Institutes of Health (R01NS082243); JB, TJ, DT and JW