Tracing prion-induced neurotoxicity

Through its transcriptional signature

Protein misfolding neurodegenerative diseases are invariably fatal conditions that include Alzheimer's disease and Parkinson's disease. These conditions are caused by the accumulation of disease-specific misfolded protein in the brain of affected individuals.
These misfolded proteins were introduced into fruitfly larvae to study their effects on gene transcription.
The data has been reviewed and visualized to uncover the transcriptional siganture of these diseases.

Figure 2

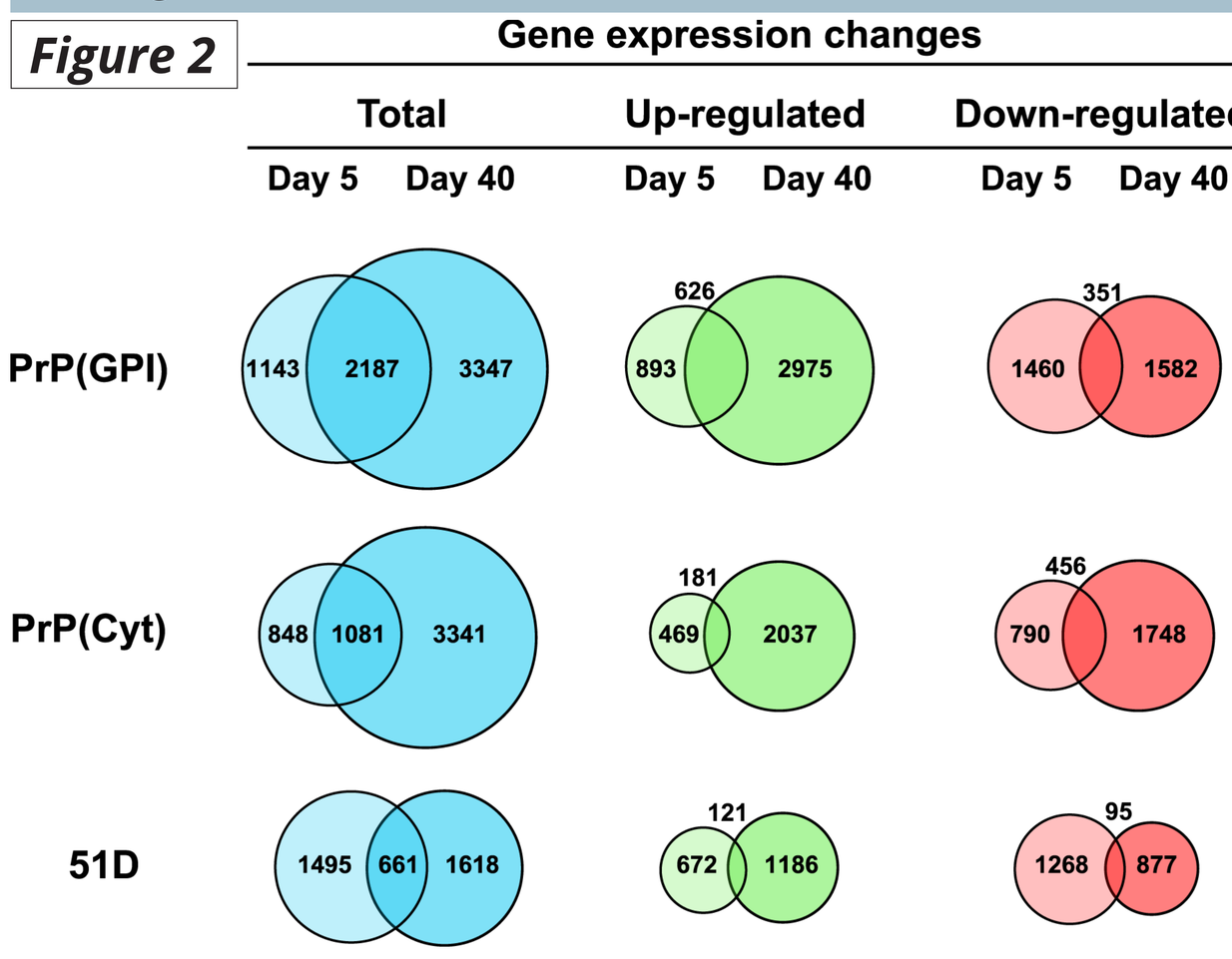


Figure 2: Venn diagram representation of the number of prion-specific differentially expressed genes in Drosophila at 5 and 40 days post hatching following exposure to scrapie-infected sheep brain homogenate at the larval stage.

- **DESeq2**
- **pheatmap**
- **ggplot2**
- **PoiClaClu**
- **BiocParallel**

Figure 1

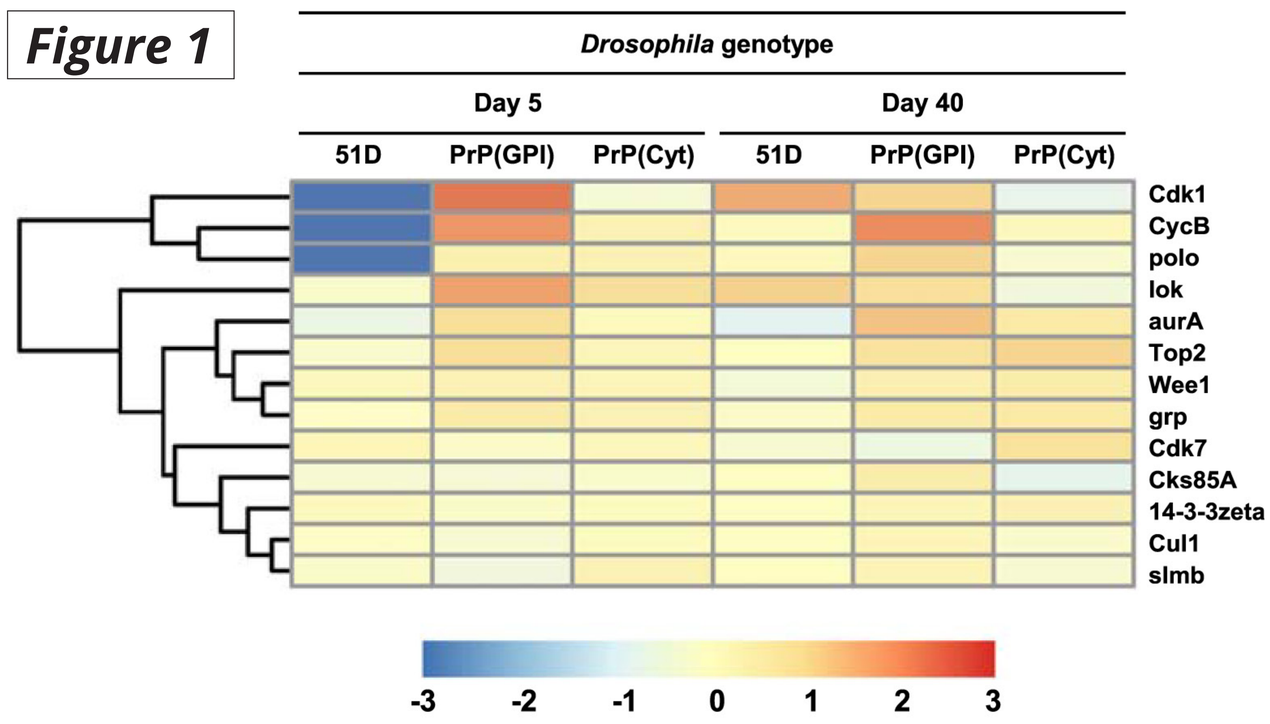


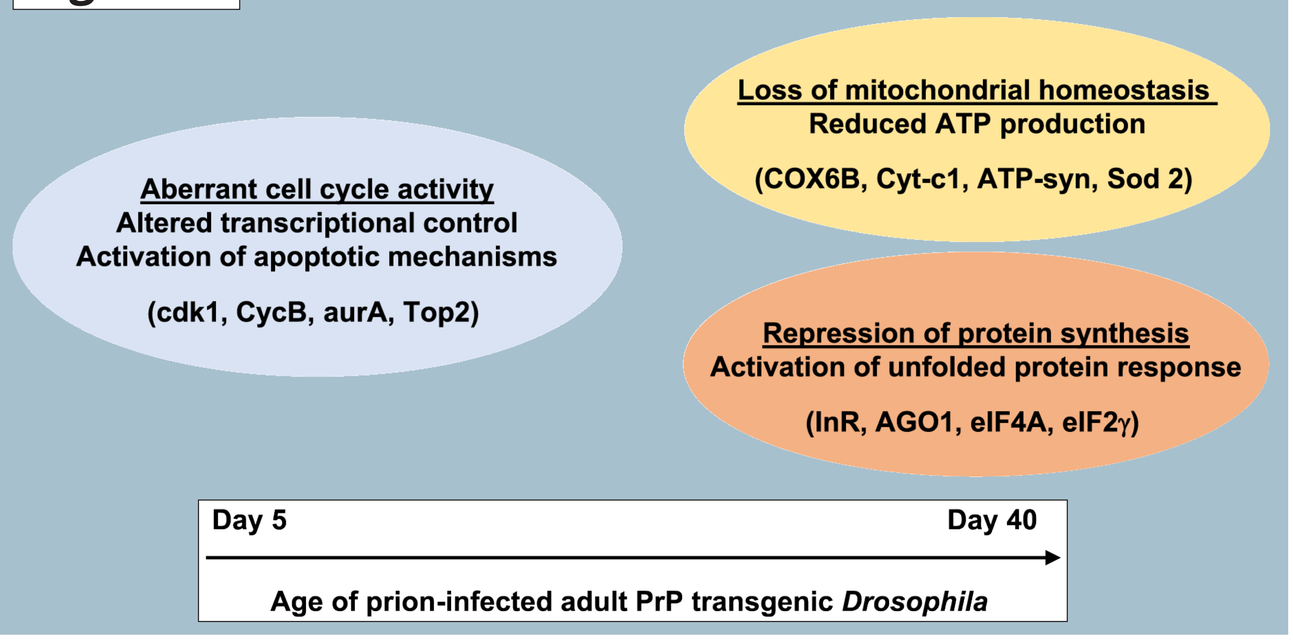
Figure 1: Heatmap showing the effect of prion-infection on cell cycle:G2/M DNA damage checkpoint regulation pathway gene expression in Drosophila. Colour indicates the log2-fold difference between prion-exposed and control-treated Drosophila gene expression.

The quality of sequence reads was examined using FastQC while Multiple Genome alignment was used to rule out contamination from other DNA sources throughout the experimental procedures. A total of 17.5 ± 1.3 million reads per sample was acquired for the study presented here. A total of 83.4% of sequence reads were successfully mapped onto the Drosophila melanogaster reference genome released from the Berkeley Drosophila Genome Project using TopHat. Raw gene-level abundance was determined through the use of Htseq-count. Trimmed mean of M values normalisation and differential gene expression analysis was performed using EdgeR and Limma. Firstly, Fisher's exact test was used to calculate a P-value that determined whether the probability of association between the genes in the Drosophila data set and the proposed pathway could be attributed to chance alone. Secondly, the ratio of the number of genes from the Drosophila data set that map to the pathway divided by the total number of molecules that map to the pathway or toxicity function was calculated. The statistical computing package P-heatmap was used for visualisation of differentially expressed genes in each genotype of prion-exposed Drosophila. The changes visualised for each specific gene in the heat map presentations refer to the log2-fold change between expression in scrapie-exposed versus prion-free sheep brain homogenate-exposed Drosophila.

Results

We cannot yet differentiate whether the proposed loss of mitochondrial homeostasis, which will invariably be accompanied by a reduction in ATP production, is the stimulus for repression of protein synthesis, or whether loss of protein synthesis drives loss of normal mitochondrial status. We are now in a position to test these possibilities through our use of Drosophila, a genetically well defined tractable experimental host amenable to silencing and overexpression of specific genes, to probe the role of mitochondrial dysfunction in prion-induced neurotoxicity, a cellular function increasingly implicated in protein misfolding-induced neurodegeneration.

Figure 3



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