Rett Syndrome's Next Top Model

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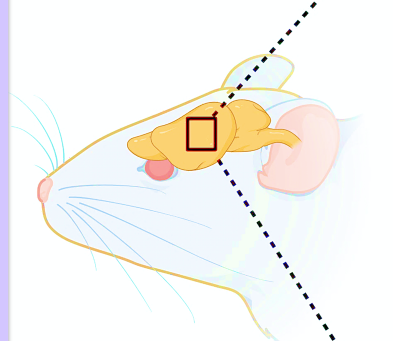
Rett syndrome (RTT)

RTT is a **rare neurodevelopmental disorder** caused by mutations in the methyl-CpG binding protein 2 (*MECP2*) gene, affecting 1:10,000 girls.

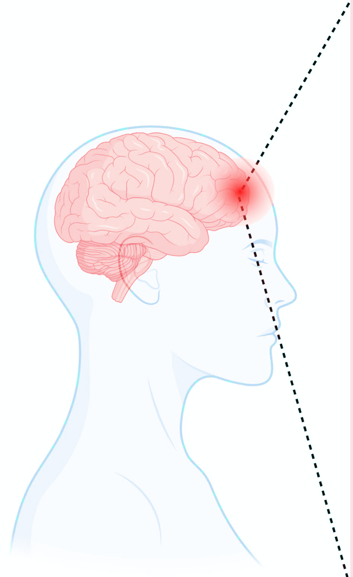
MECP2 is highly expressed in **neurons**, demonstrating its essential role in **normal brain development.**



Problem

Although murine models have advanced our understanding of the disease, anatomical and biochemical differences between humans and rodents make **translational studies challenging.**

To develop a cure, we need to bridge these gaps in our knowledge.



Novel approach

Induced pluripotent stem cells (iPSCs) open a new avenue for disease modelling.

Using this approach, we can create **patient-derived neurons** to build a translatable human model, enabling a better understanding of the underlying disease pathophysiology.

Hypothesis

Patient-derived iPSCs can be used to create an *in vitro* model for Rett syndrome

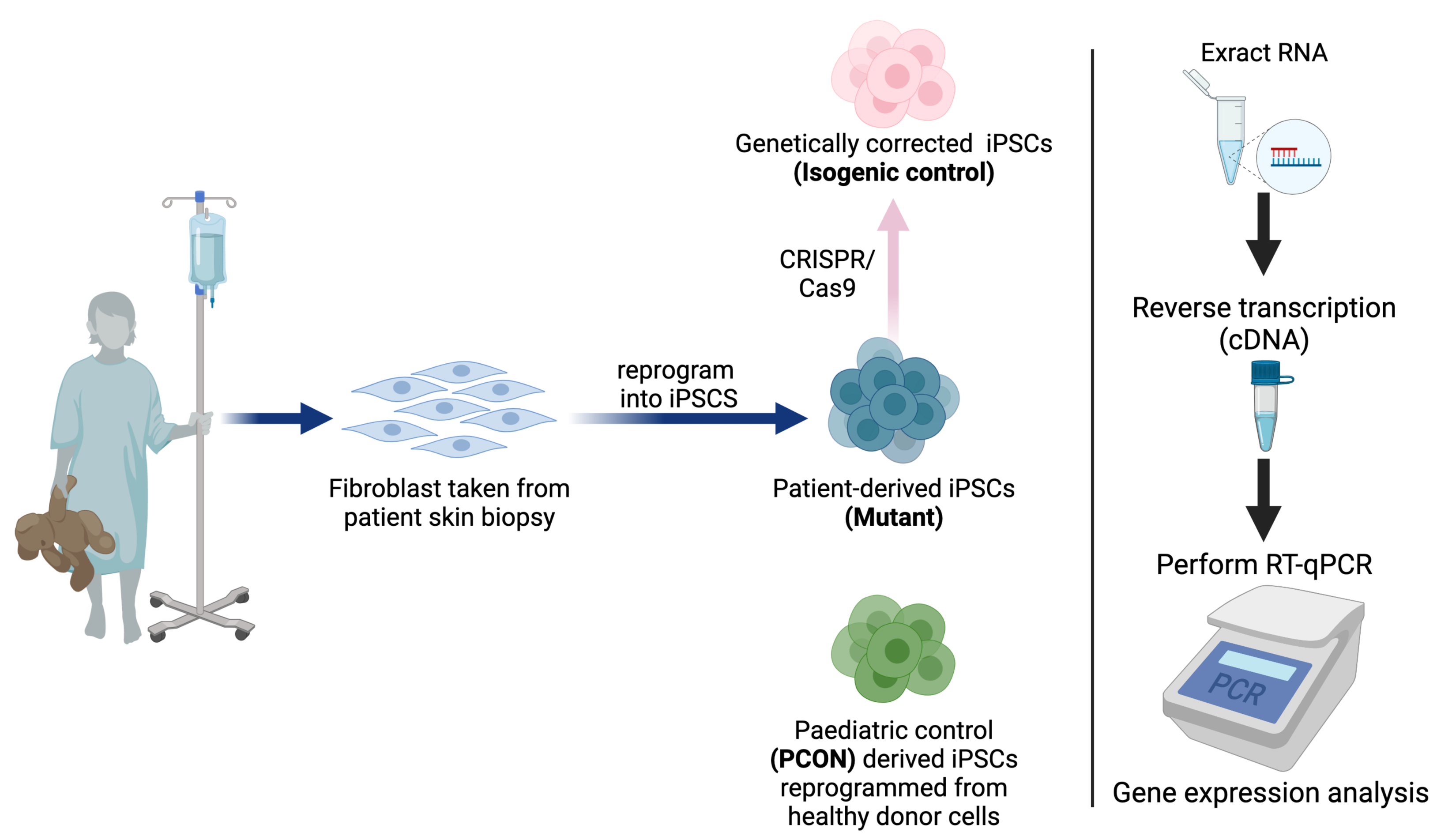
Research approach

Results

Aim 1

Characterise patient-derived iPSCs

Using male RTT patient and control lines to characterise iPSCs



Patient-derived iPSCs and controls express transcriptional factors confirming pluripotency

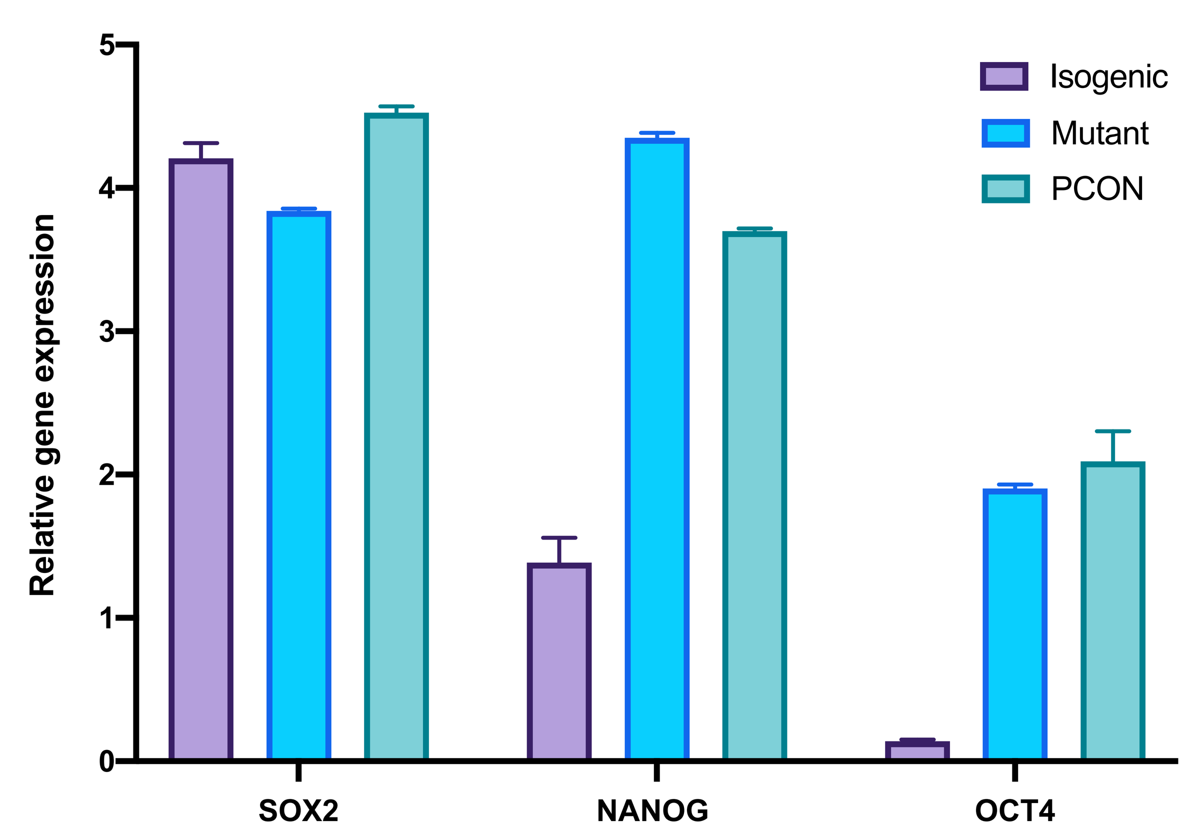
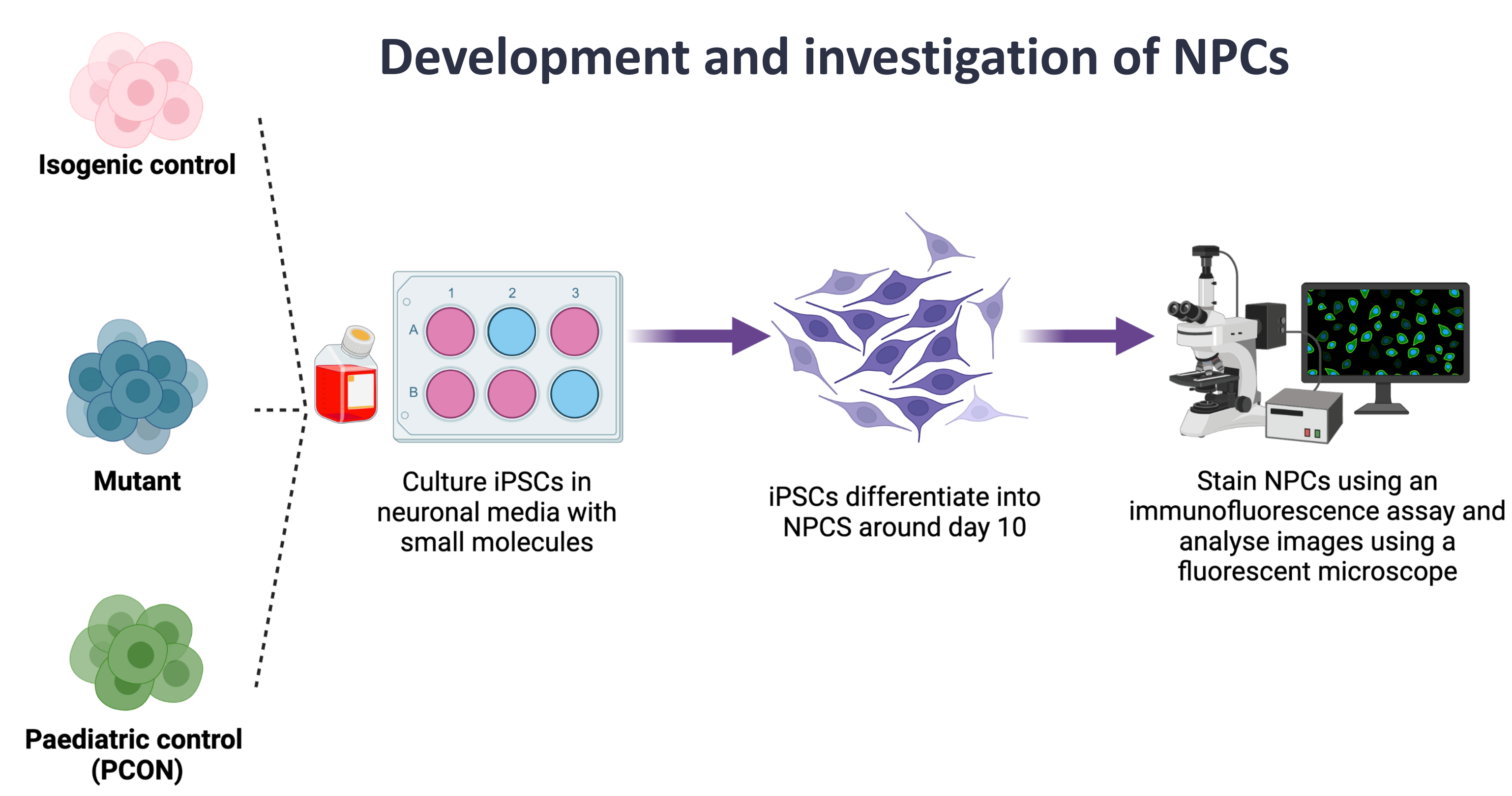


Figure 1. Pluripotent markers (SOX2, NANOG, OCT4) relative expression to GAPDH across all 3 cell lines. ($P < 0.0001$; ± SEM)

Aim 2

Differentiate and characterise patient iPSC derived neural progenitor cells (NPCs)

Development and investigation of NPCs



NPCs positively express neuronal markers

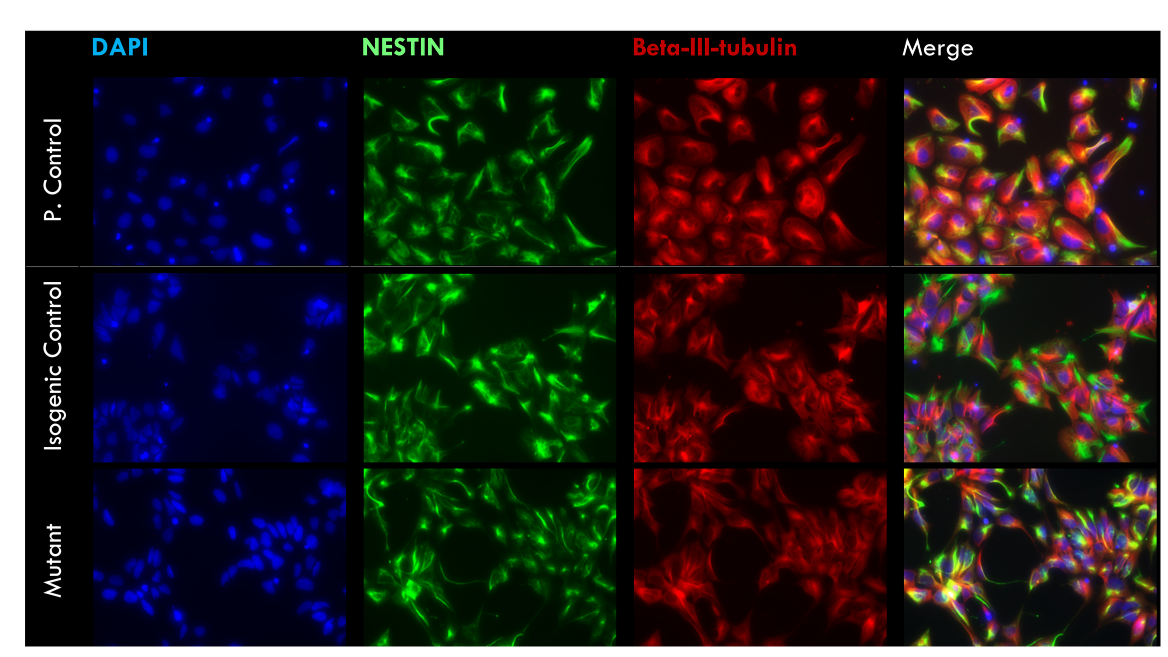
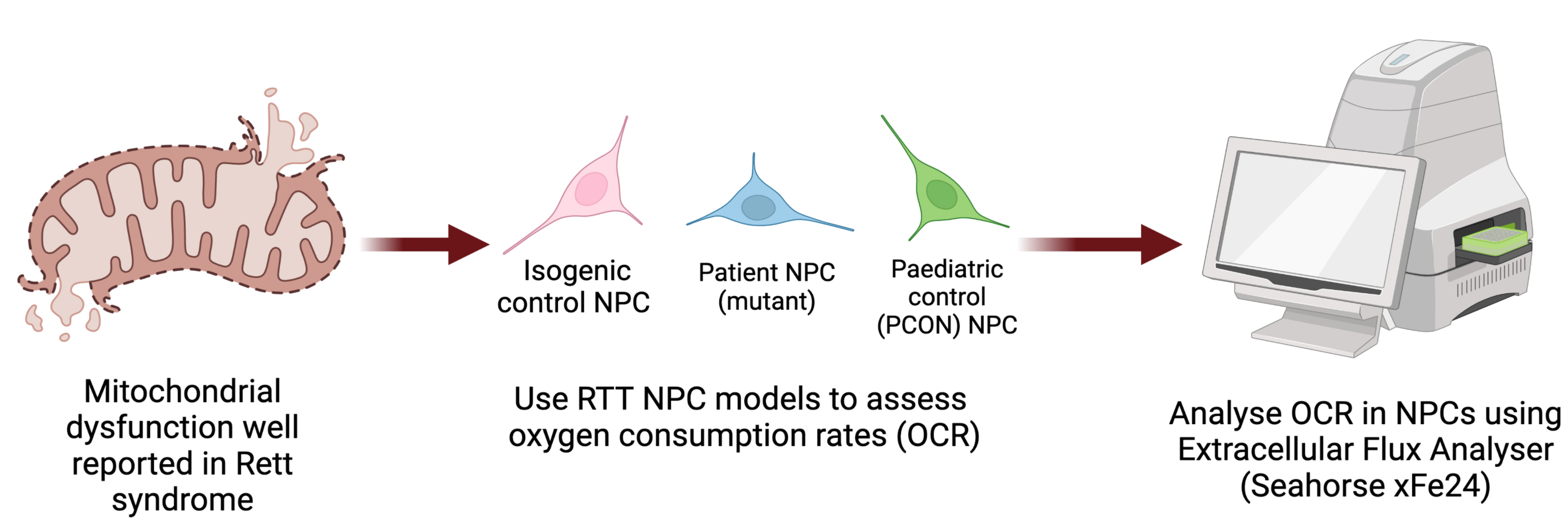


Figure 2. IFA used to detect NPC marker (NESTIN) and neuronal marker (B-III-tubulin) to characterise for NPCs in all cell lines.

Aim 3

Model validation

Assessing model's ability to recapitulate RTT phenotype



Mutant NPCs result in a significantly lower oxygen consumption rate (OCR) than the controls

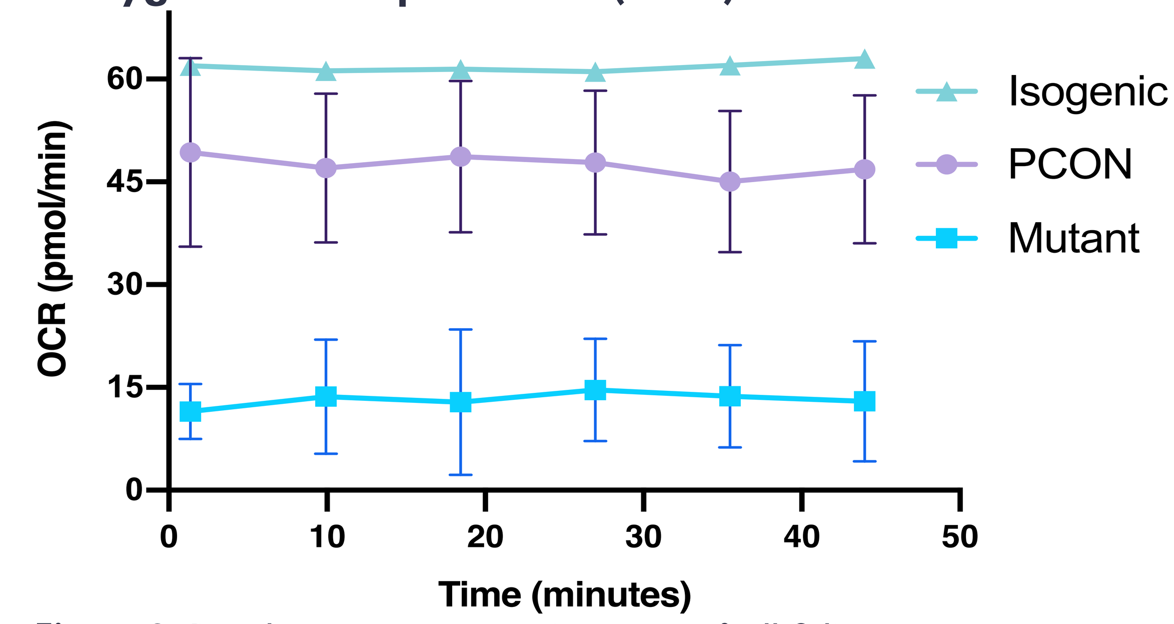


Figure 3. Basal oxygen consumption rates of all 3 lines ($P < 0.0001$; ± SEM)

Conclusions & future directions

- Patient-derived **iPSCs characterised** for pluripotency
- **NPCs positive for neuronal markers**
- Patient-derived NPCs have lower OCR demonstrating mitochondrial dysfunction, which **validates our model**
- **Future directions:** to characterise female patient lines and further investigate mitochondrial function

Significance of study

- **No curative therapies** to date, and treatment is purely symptomatic
- Pre-clinical animal trials have been successful but are not clinically translatable, suggesting a **gap in translational studies**
- The rationale to develop a useful translatable human model for RTT will allow us to understand the disease pathophysiology, and **aid in the development of novel therapies**

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