How basic science is advancing our understanding of PWS

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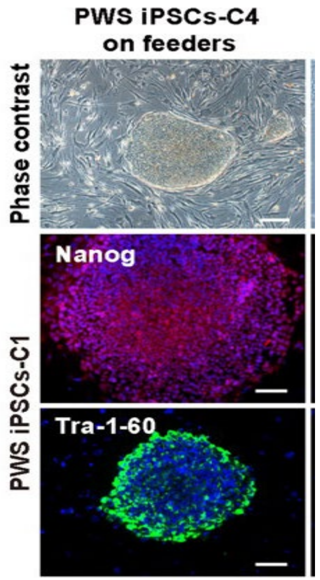
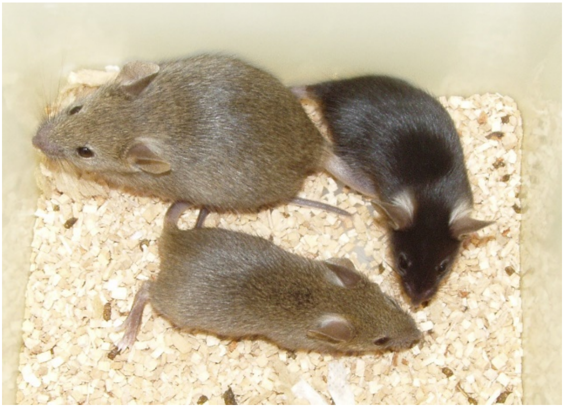
Prifysgol Caerdydd

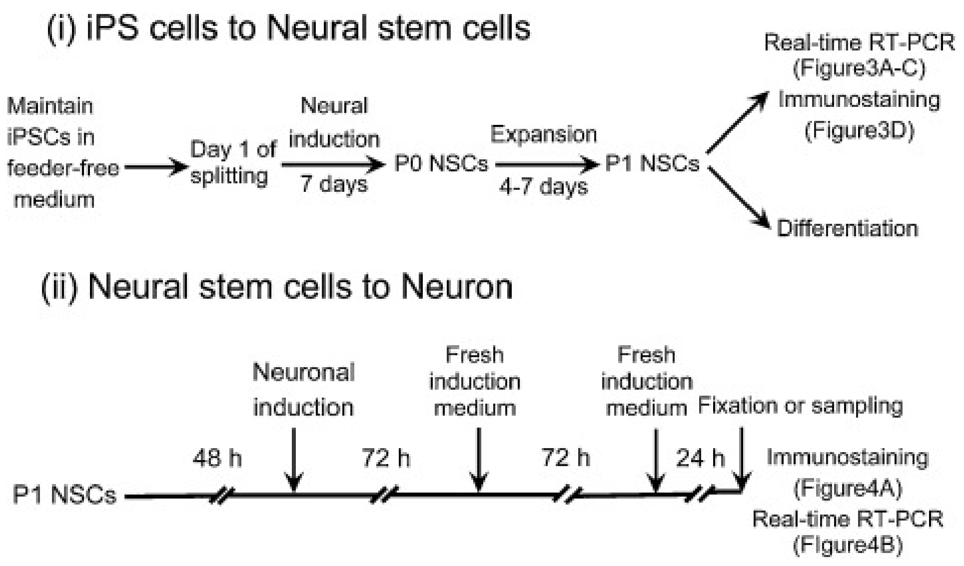
Cell models – iPSC & organoids

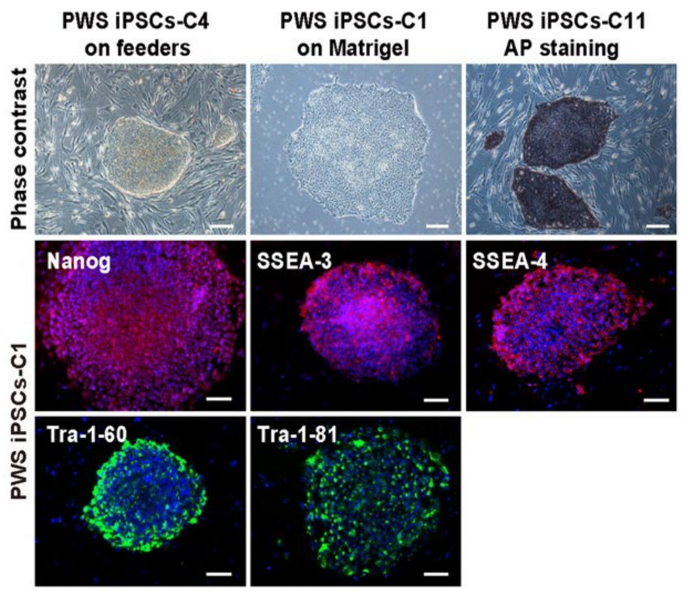
Animal models - mouse





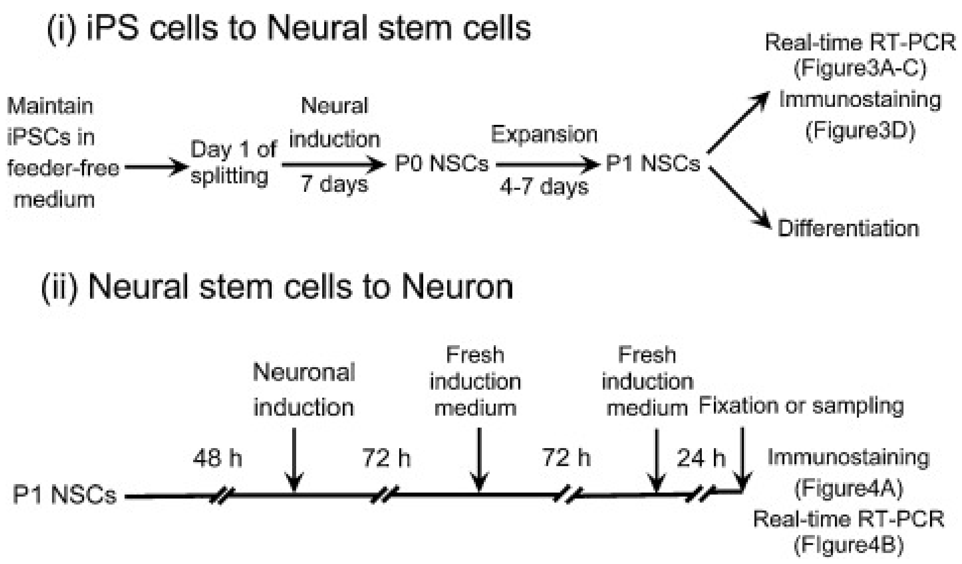
Induced pluripotent stem cells - iPSCs

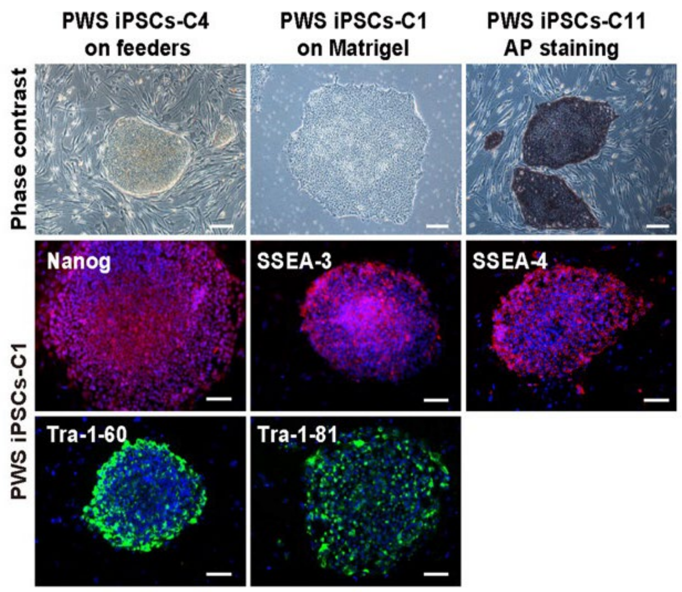


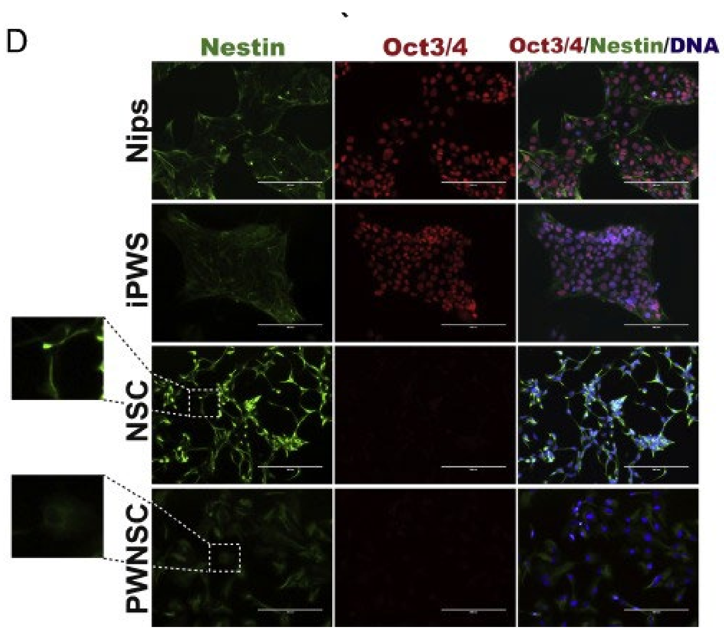


- Cells from skin, dental pulp or hair samples
- Made into iPSCs in the lab

Induced pluripotent stem cells - iPSCs





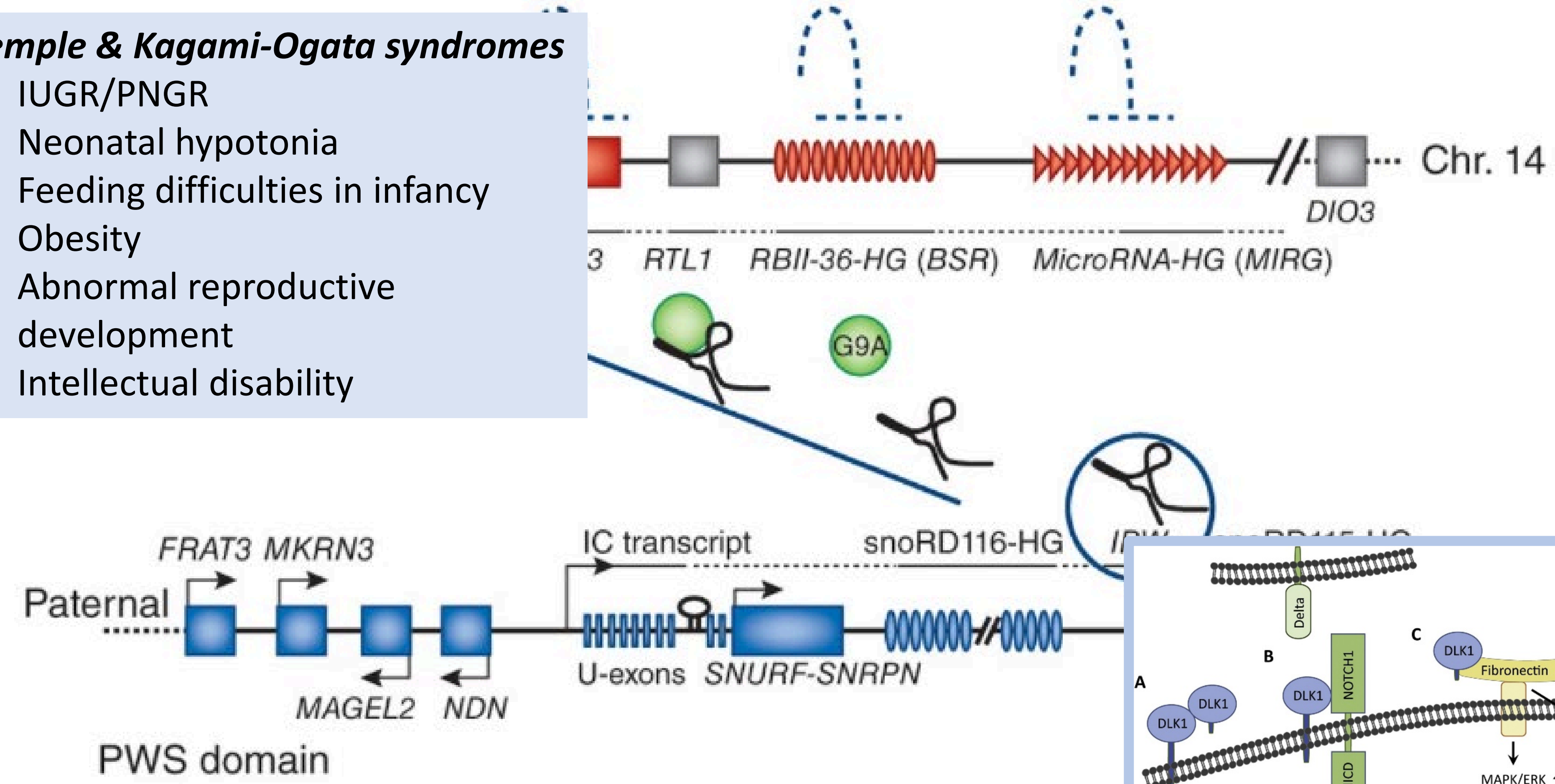


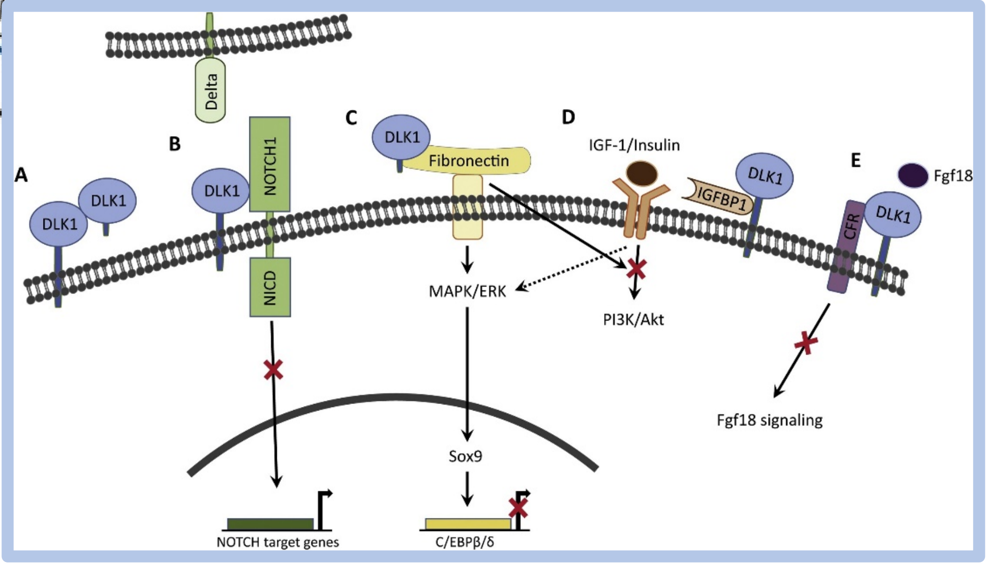
- Cells from skin, dental pulp or hair samples
- Made into iPSCs in the lab
- Can be transformed into a variety of cell types including **neurons**

Induced pluripotent stem cells - iPSCs

Temple & Kagami-Ogata syndromes

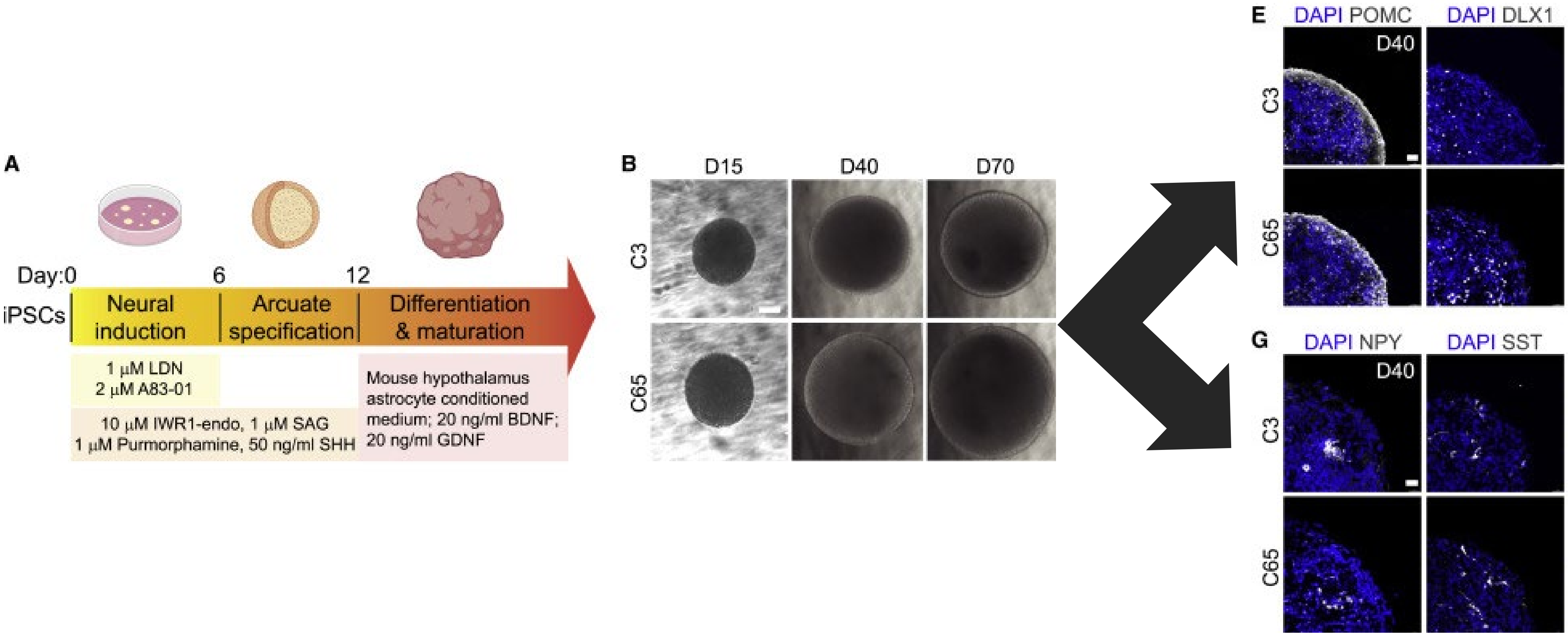
- IUGR/PNGR
- Neonatal hypotonia
- Feeding difficulties in infancy
- Obesity
- Abnormal reproductive development
- Intellectual disability





Induced pluripotent stem cells - iPSCs

Organoids *- Can begin to explore neuron function in a network*

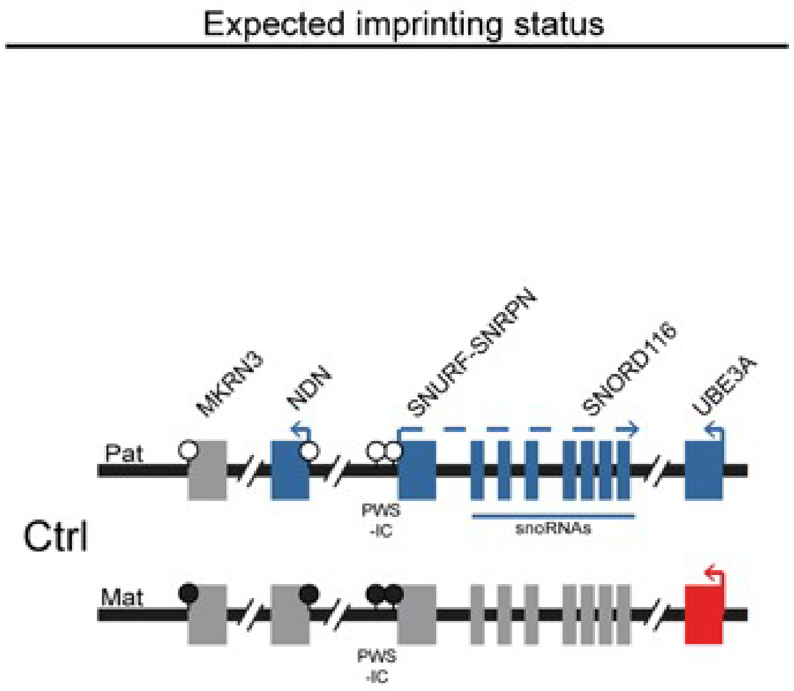


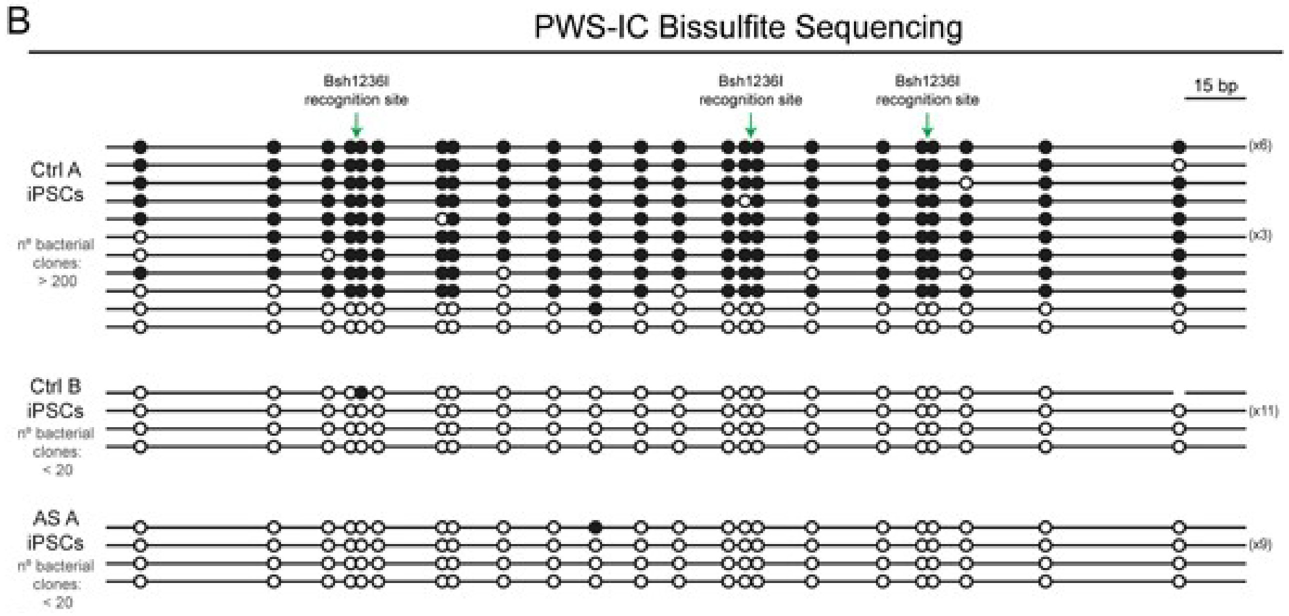
Different
hypothalamic
neuron-types

Loss of hierarchical imprinting regulation at the Prader–Willi/Angelman syndrome locus in human iPSCs

Duarte Pólvora-Brandão, Mariana Joaquim, Inês Godinho, Domenico Aprile, Ana Rita Álvaro, Isabel Onofre, Ana Cláudia Raposo, Luís Pereira de Almeida, Sofia T Duarte, Simão T da Rocha

Human Molecular Genetics, Volume 27, Issue 23, 1 December 2018, Pages 3999–4011,
https://doi.org/10.1093/hmg/ddy274





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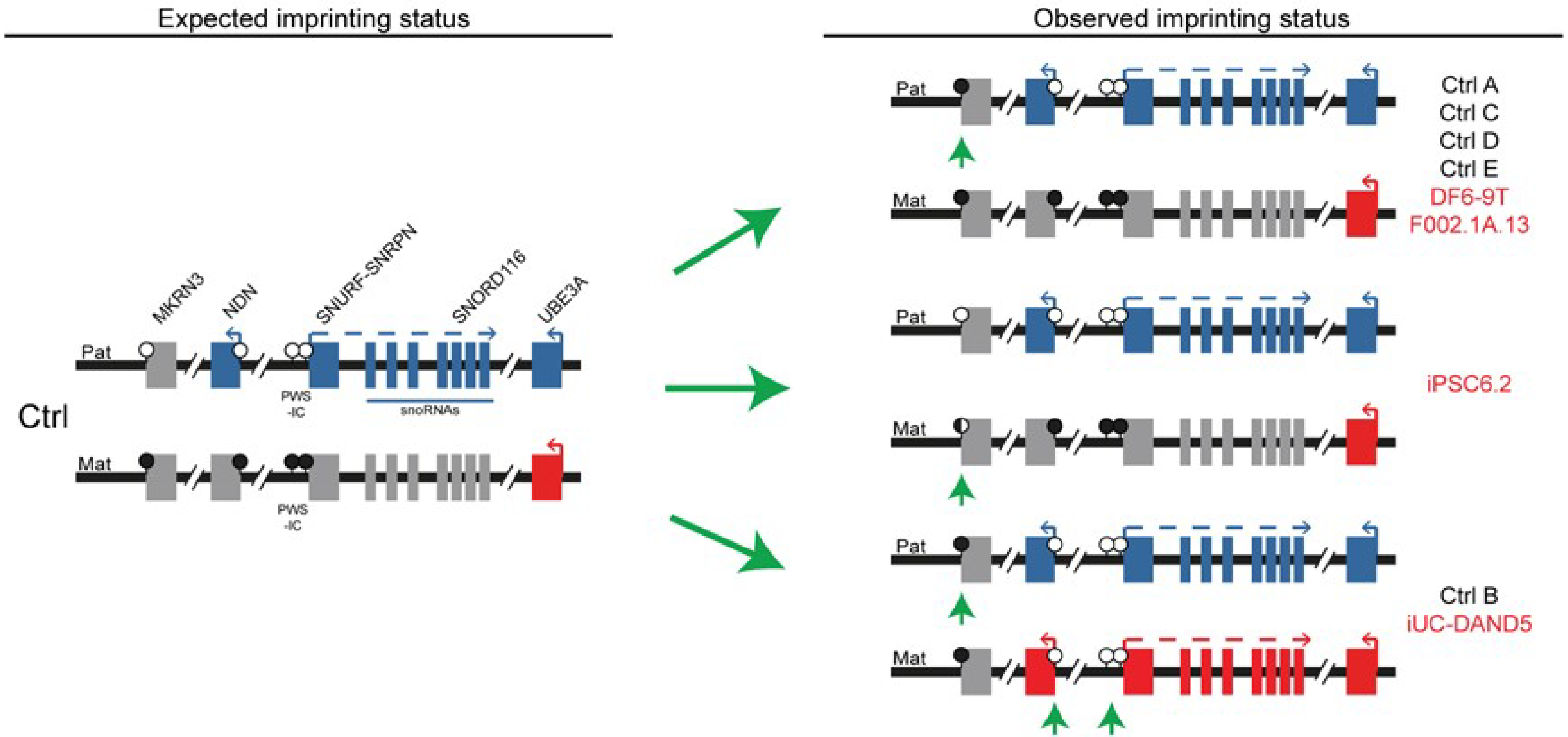
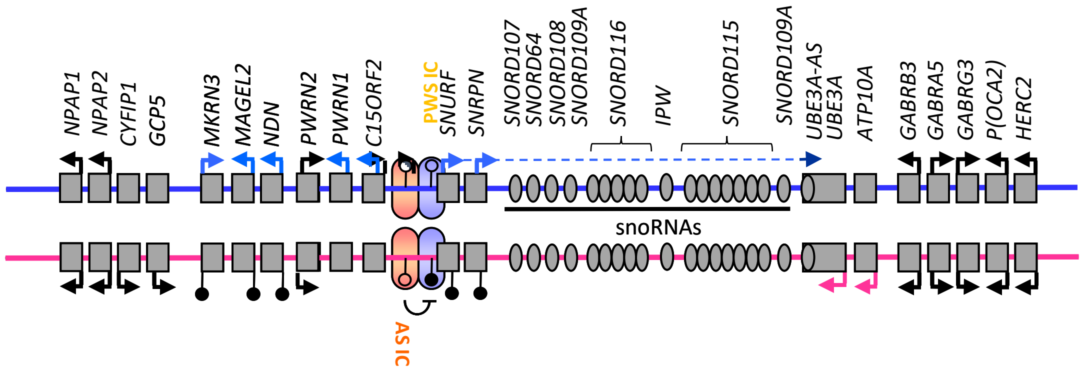
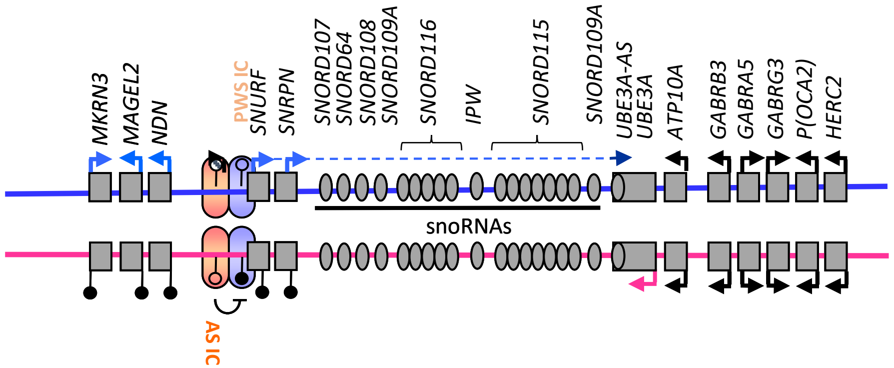
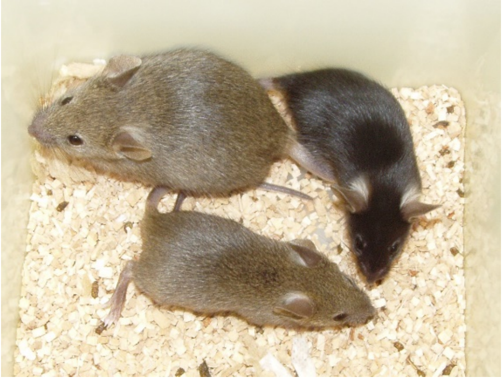


Animal models - *Mouse*







15q imprinting cluster and psychosis - PWS

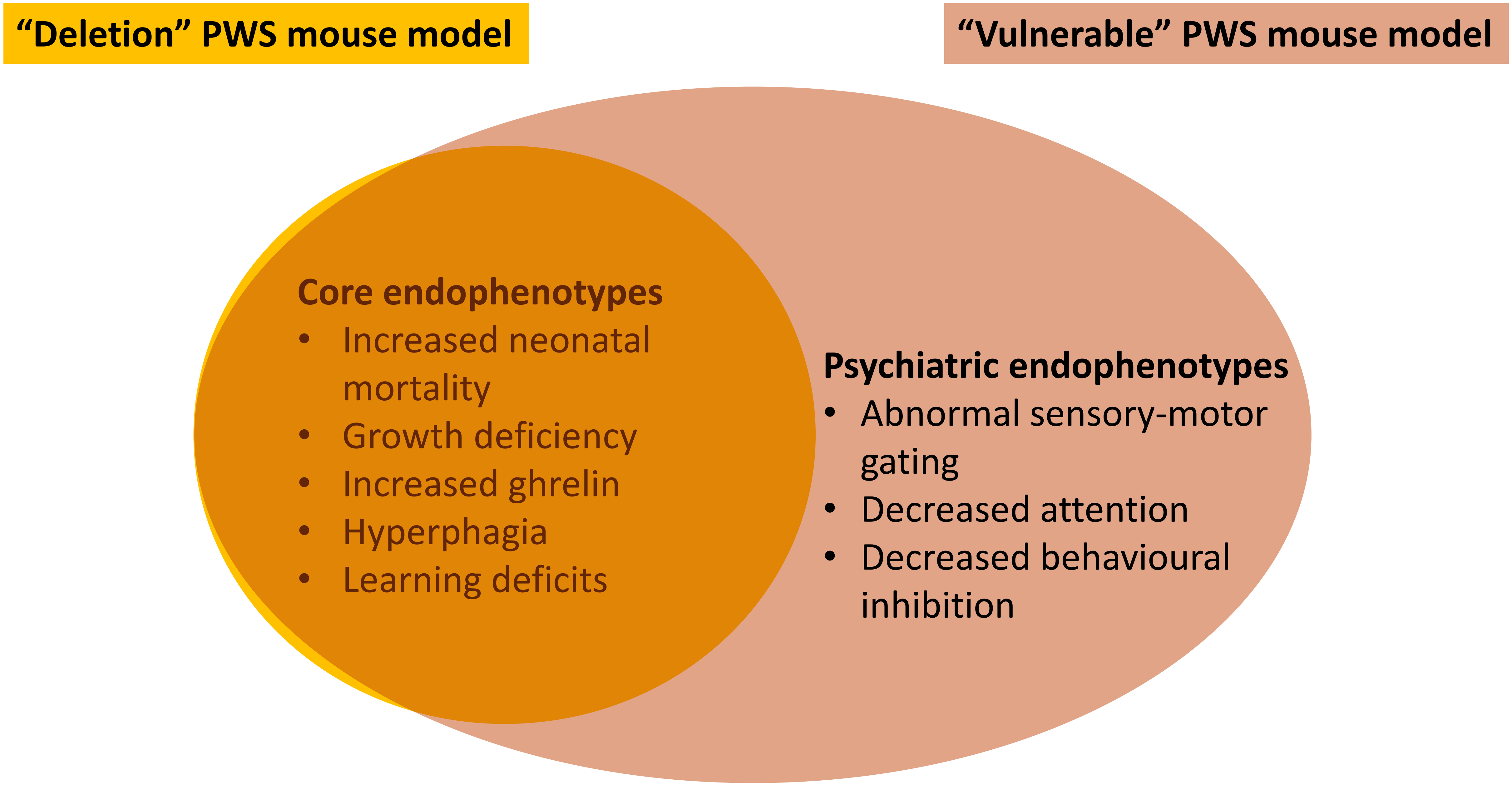
Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by (epi)genetic mutations affecting the imprinted gene cluster on chromosome 15q11-q13

Core diagnostic characteristics

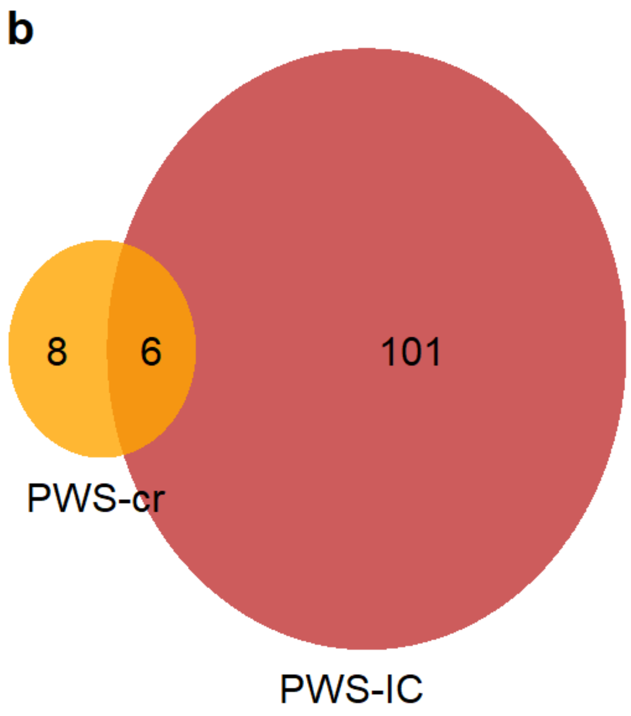
- Genetic mutations affecting chromosome 15q11-q13
- Infantile hypotonia and failure to suckle
- Endocrine problems
- Age 2-6 individuals develop hyperphagia

Behavioural and Psychiatric problems

- Obsessive compulsive disorder
- Negative affect and psychotic illness → **More prevalent in certain PWS genotypes**


“Deletion” PWS mouse model
“Vulnerable” PWS mouse model
Core endophenotypes
• Increased neonatal mortality
• Growth deficiency
• Increased ghrelin
• Hyperphagia
• Learning deficits
Psychiatric endophenotypes
• Abnormal sensory-motor gating
• Decreased attention
• Decreased behavioural inhibition

Are there brain gene expression changes that reflect the behavioral differences?



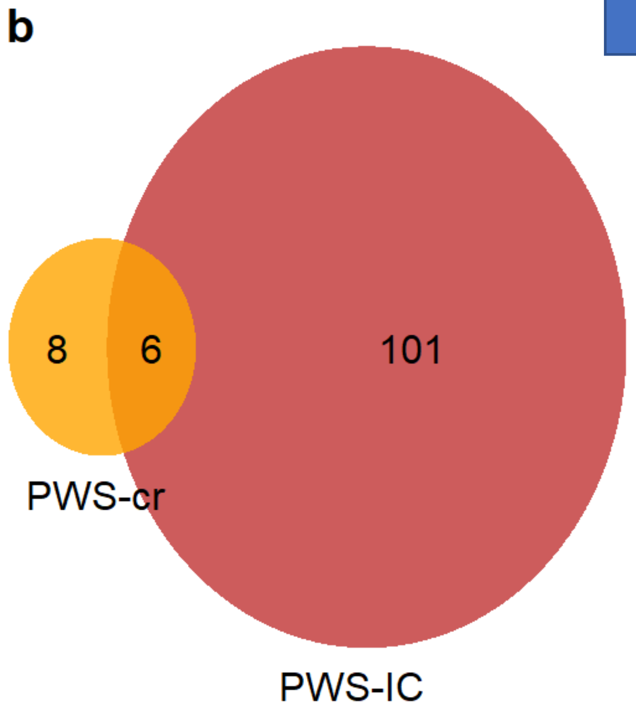
Common brain gene expression differences between **deletion PWS mouse model** and **vulnerable PWS mouse model**

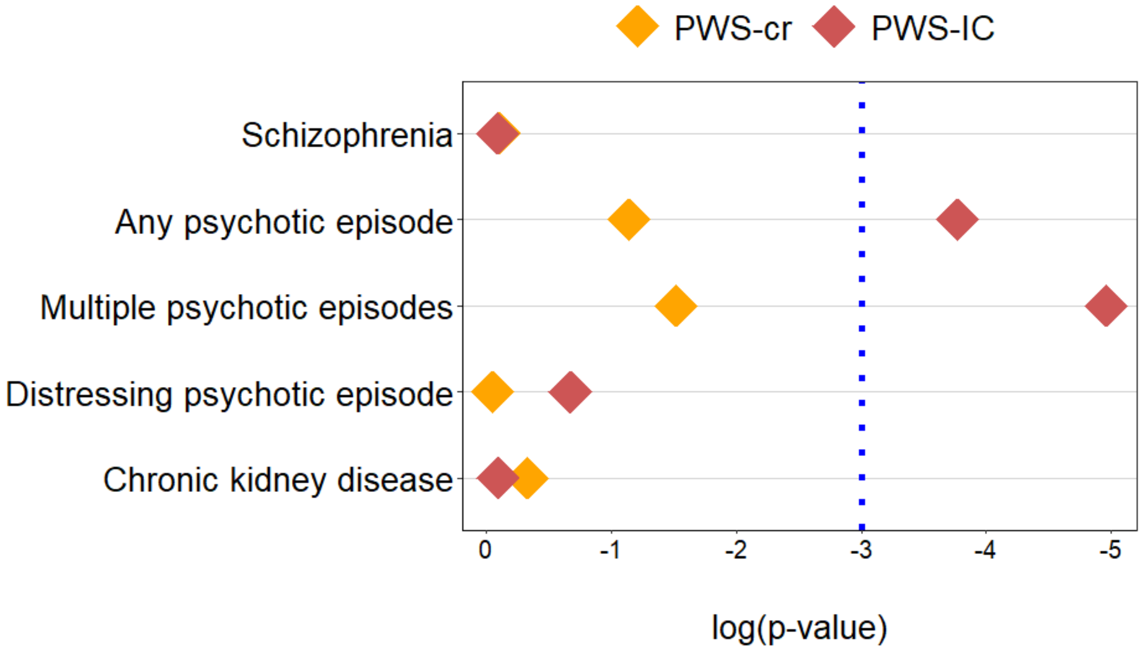
Large number of unique brain gene expression changes in **vulnerable PWS mouse model**

Zahova, S.K., Humby, T., Davies, J.R. *et al.* Comparison of mouse models reveals a molecular distinction between psychotic illness in PWS and schizophrenia. *Transl Psychiatry* **11,** 433 (2021).

Enrichment of human genetic variants associated with disease in gene & isoform expression changes

- Provides biological basis for clinical observation
- Suggests treatments for schizophrenia may not be appropriate for PWS





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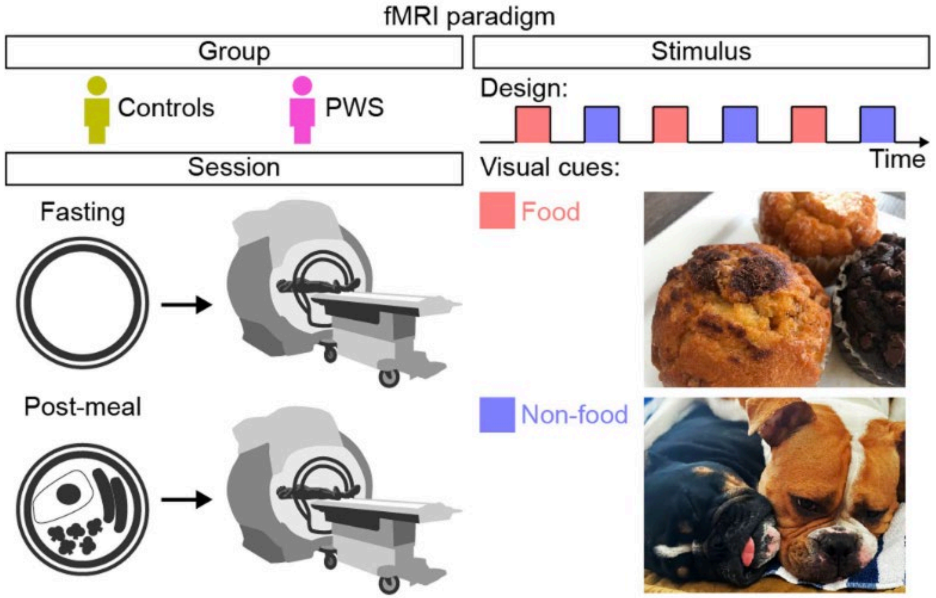
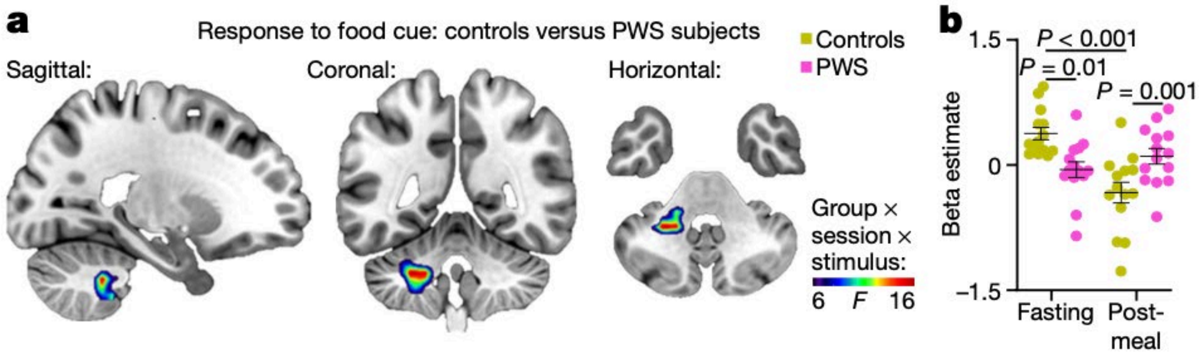
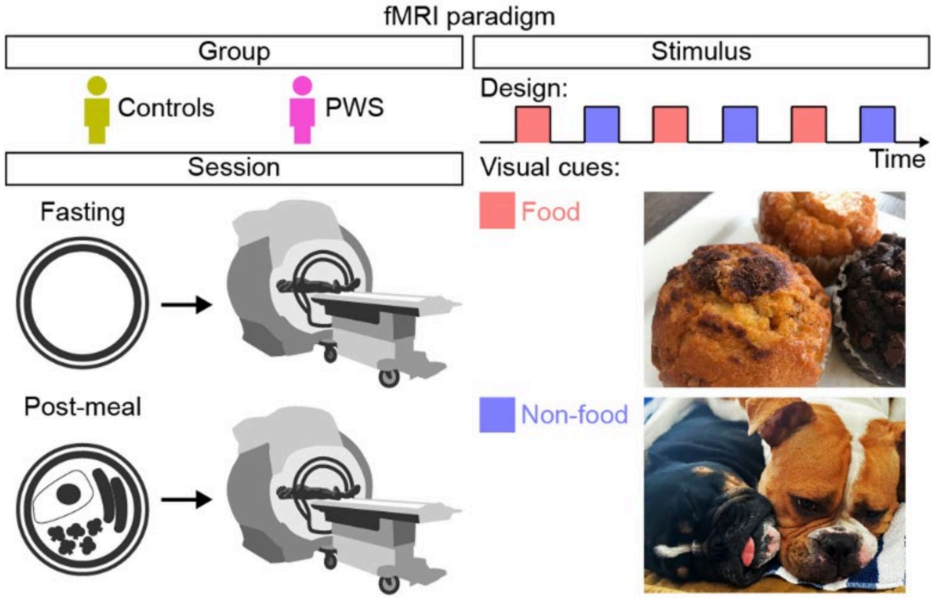


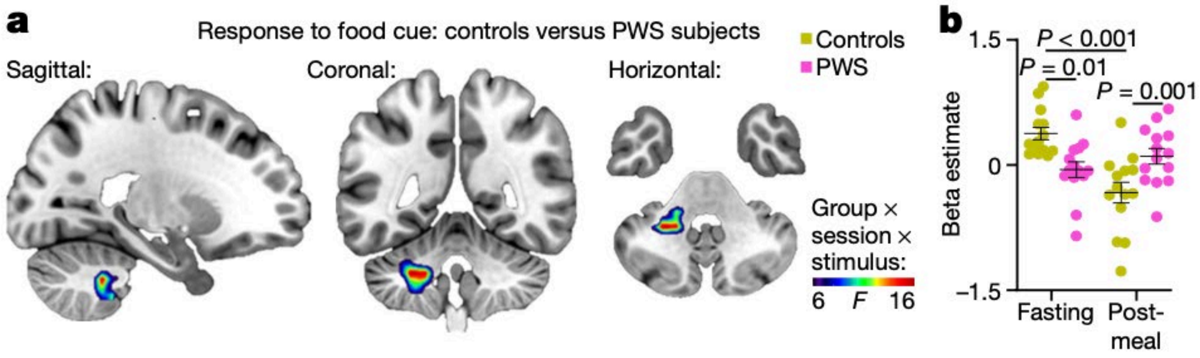


- Identified novel food related neurons in cerebellum

Combining human and animal research

Low, A.Y.T., Goldstein, N., Gaunt, J.R. *et al.* Reverse-translational identification of a cerebellar satiation network. *Nature* (2021).





- Identified novel food related neurons in cerebellum
- Identified equivalent in mouse

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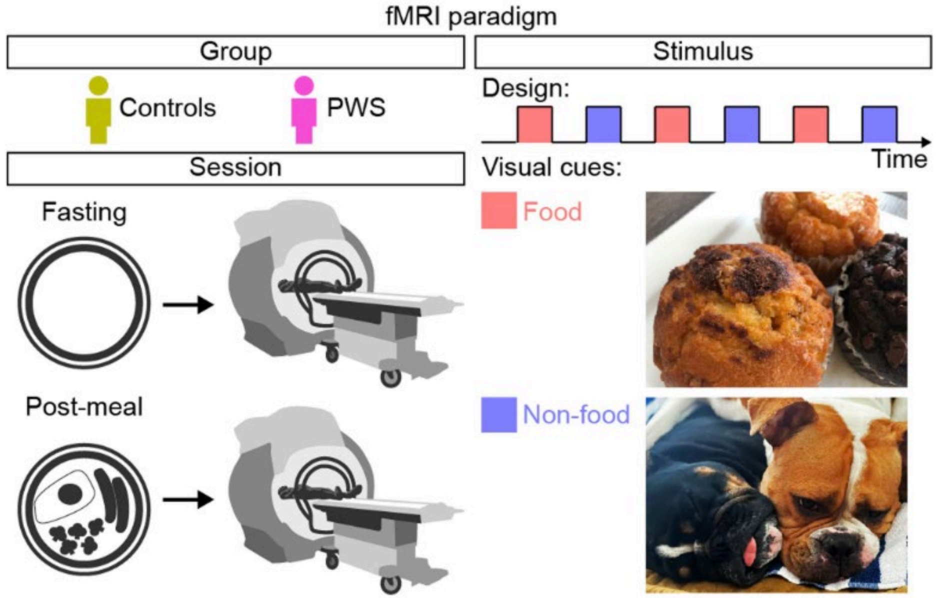
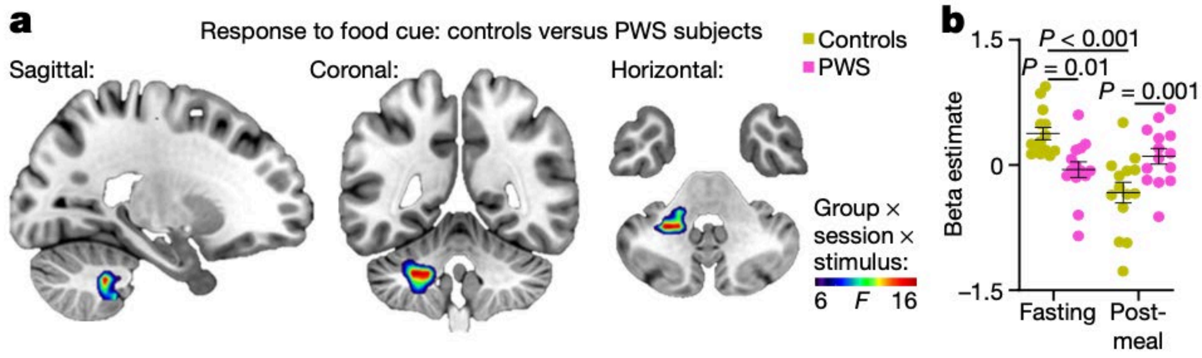
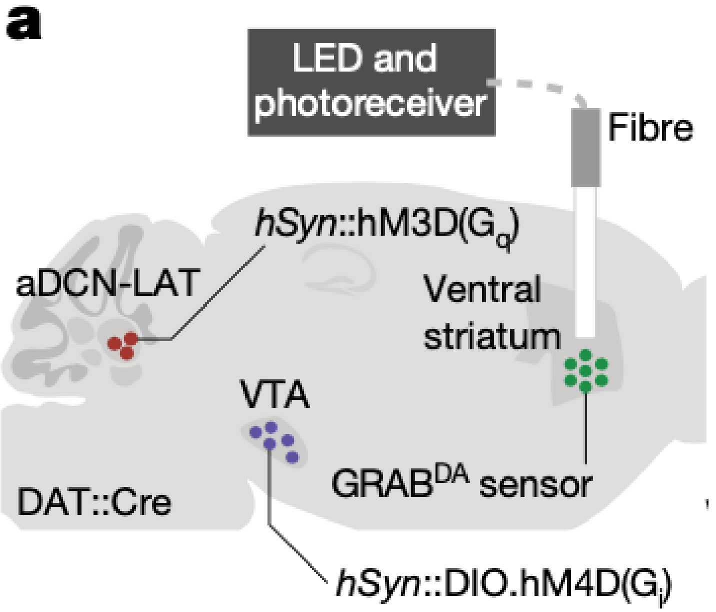




- Identified novel food related neurons in cerebellum
- Identified equivalent in mouse
- Using optogenetic techniques dissected links to known food-related neural circuitry



Combining human and animal research

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Relevant papers

Hum Mol Genetics 18(12):2140
Eur J Neuroscience 31(1):156
Behav Neuroscience 126(3):488
Hum Mol Genetics 28(18):3013
Transl Psychiatry 11(1):433

Simona Zahova, Dinko Relkovic, Christine Doe, Jennifer Davies, Joanne Morgan, Trevor Humby

BBSRC bioscience for the future
Foundation for Prader-Willi Research
Research Councils UK
GSK GlaxoSmithKline
MRC Medical Research Council
The Health Foundation