How basic science is advancing our understanding of PWS

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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
- 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

![Diagram showing the process of iPSCs differentiation](image)

- **Day 0:** iPSCs
- **Day 6:** Neural induction
- **Day 12:** Arcuate specification and Differentiation & maturation

- **Neural induction:** 1 μM LDN, 2 μM A83-01
- **Arcuate specification:** 10 μM IWR-1-endc, 1 μM SAG
- **Differentiation & maturation:** Mouse hypothalamus astrocyte conditioned medium: 20 ng/ml BDNF, 20 ng/ml GDNF

**Different hypothalamic neuron-types**

![Images showing differentiation stages](image)
Loss of hierarchical imprinting regulation at the Prader–Willi/Angelman syndrome locus in human iPSCs


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


Animal models - Mouse
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
Core endophenotypes
- Increased neonatal mortality
- Growth deficiency
- Increased ghrelin
- Hyperphagia
- Learning deficits

Psychiatric endophenotypes
- Abnormal sensory-motor gating
- Decreased attention
- Decreased behavioural inhibition

“Deletion” PWS mouse model

“Vulnerable” PWS mouse model
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

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

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

Combining human and animal research

• 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

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

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