

**Presenting Author Name**

Karmen Britton

**Phonetic spelling of your (full) name**

KAR-men BRIT-uhn

**Presenting Author Category**

PhD Student

**Supervisor Name**

Dr. Paul Marcogliese

**Research Category**

Basic Science

**Abstract Title**

Characterization of *Irf2bpl* Knock-in Mice: Relevance to Rare Disease and Juvenile Parkinsonism

## Authors

| Name                 | Role              | Profession          |
|----------------------|-------------------|---------------------|
| Karmen Britton       | Presenting Author | PhD Student         |
| Dr. Paul Marcogliese | Co Author         | Assistant Professor |
| Danielle Pascual     | Co Author         | PhD Student         |

**Background**

IRF2BPL (Interferon Regulatory Factor 2 Binding Protein Like) is a single-exon gene in which de novo pathogenic variants cause NEDAMSS (neurodevelopmental disorder with abnormal movements, loss of speech, and seizures). NEDAMSS is a severe neurodevelopmental disorder characterized by developmental regression, epilepsy, and movement abnormalities. Approximately half of affected individuals, particularly those with onset later in adolescence, develop dystonia and parkinsonism. Post-mortem analysis has shown nigrostriatal dopaminergic degeneration, the same vulnerable neurons selectively lost in Parkinson's disease. IRF2BPL function remains poorly understood.

**Objective**

Characterize the functional and neuroanatomical consequences of the *Irf2bpl* p.Y153X knock-in (KI) mouse model representing a variant observed in multiple NEDAMSS patients. We will determine its potential relevance to NEDAMSS-associated neurological dysfunction and parkinsonism.

**Methods**

We generated a novel *Irf2bpl* KI mouse carrying the p.Y153X truncating variant. Mice are undergoing behavioural phenotyping at 3 and 12 months to assess activity, including motor function and anxiety-related behaviours. Neuroanatomical characterization includes immunohistochemical assessment of *Irf2bpl* expression and evaluation of substantia nigra dopaminergic neurons using tyrosine hydroxylase (TH) staining, along with assessment of striatal dopamine transporter and TH levels.

## **Results**

Preliminary characterization demonstrates that *Irf2bpl* KI/KI mice are born at reduced Mendelian ratios and exhibit reduced body mass compared with wild-type and heterozygous littermates, suggesting an essential role for *Irf2bpl* in mammalian development and viability. Open-field studies indicate a trend toward female mice spending more time in the centre relative to the perimeter, suggesting altered anxiety-related behaviour. Immunohistochemical analysis confirmed *Irf2bpl* expression in the primary motor and primary somatosensory cortices.

## **Conclusion**

This study establishes a novel mammalian model of an IRF2BPL pathogenic variant. Preliminary findings support a role for IRF2BPL in mammalian development, behaviour, and brain function. Ongoing characterization will determine whether *Irf2bpl* pathogenic variants produce progressive motor dysfunction and nigrostriatal degeneration, providing a foundation for understanding NEDAMSS and parkinsonism and for future therapeutic development.