Lay Summary

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Delineating the neuropathophysiological mechanisms underpinning severe drug-resistant epilepsy in Alpers' syndrome

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Background and aims:
Alpers' syndrome is a rare mitochondrial disease caused by changes in a gene known as *POLG1* which results in very severe childhood epilepsy with rapid neurological decline and premature death. Since the causes of this epilepsy are poorly understood, it has not been possible to develop effective treatments. This project will identify the problems that occur in the brain of individuals with Alpers' syndrome so that we can develop new treatments or repurpose existing drugs.
In Alpers' syndrome a genetic change affects the function of mitochondria, the parts of the cell that supply energy. As brain cells require high levels of energy, changes to mitochondria have a major impact on their function, altering electrical brain activity and causing frequent seizures.
Using post-mortem brain tissue from individuals with Alpers' syndrome, we have identified changes in specialised brain cells which control electrical brain activity and could contribute to seizures in Alpers' syndrome.

The study:
We shall use post-mortem brain tissue from individuals with Alpers' syndrome to further understand what changes occur to the brain. **To do this, we will compare Alpers' syndrome brains to 'healthy' control brains and brains from individuals with Dravet syndrome (a rare childhood epilepsy with similar features to Alpers' syndrome). This is important as it will help identify shared epilepsy changes with Dravet syndrome, and those which are specific to Alpers' syndrome.** This work will also help discover new effective drug targets, which can be tested in model systems.

Project outcome and impact:
Our project will help to understand what causes epilepsy in Alpers' syndrome and Dravet syndrome and will inform how seizures could be managed which would improve the quality of life for patients. The project will have reach beyond these two epilepsy syndromes, particularly in relation to the drug targets identified, which could be used to investigate and treat many epilepsies and mitochondrial diseases.

- **Abbreviations:** *POLG* (gene – DNA polymerase gamma)