

# How mutations in the DJ-1 gene cause nerve cell death



## Project information

Lead researcher	Dr Gyorgy Szabadkai
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## Project background

A small number of people – probably less than 5% - have an inherited form of Parkinson's. But by examining the genes involved, we can get vital clues as to what is going on within a nerve cell when it starts to die. We know that the DJ-1 gene is one of those involved in certain inherited forms of Parkinson's. While we think that the gene works within the nerve cells to protect them from certain types of damage, we don't understand how mutations in this gene may upset how it works and how this could affect the nerve cells.

- **Mutations in the DJ-1 gene** are present in some people with an inherited form of Parkinson's. So understanding what the gene does will provide vital information about the causes of Parkinson's and why specific types of nerve cells are affected.
- **Although the precise function of DJ-1 is unknown**, it is thought to be important in protecting the brain from oxidative stress. This is a biochemical process that leads to the build up of toxic chemicals known as free radicals inside cells. Cells are normally

able to dispose of the free radicals, but this is not the case in specific nerve cells in Parkinson's. These toxins damage the cells, making them sick and eventually causing them to die. One reason for this is that the cells do not have enough energy to work properly to dispose of the toxins.

- **Mitochondria are like tiny power stations inside cells.** Nerve cells need lots of energy, for example to communicate with each other or to make important chemicals such as dopamine. So properly functioning mitochondria are vital for healthy nerve cells.

## What the researchers are doing

The purpose of this study is to investigate in detail what DJ-1 does within the nerve cell and how mutations influence how it works. By changing the amount of the protein that is contained within the nerve cell, or changing it to the mutated form, they will obtain information about its role. This can then be used to give us a much better understanding about what causes cells to die.

## Progress so far

- Dr Szabadkai has developed experimental models with which to look at the role of DJ-1 in the cell. This involves the use of cells with different amounts of normal or mutant DJ-1
- Cells with a decrease in the levels of DJ-1 are less efficient in producing energy because their mitochondria aren't working correctly. The same is seen in cells which have a mutant form of the protein. This highlights the vital role that DJ-1 plays in keeping the cells alive and working normally and how mutations can compromise this.
- Cells with a decrease in levels of DJ-1 or which have the mutant form are less well able to deal with treatment with toxins such as free radicals.

## What is the next stage?

The researchers have so far shown that DJ-1 is responsible for maintaining the cell's energy levels at the right level and that this is vital for keeping the cell in a healthy state. The

next stage of the study is to look at this in more detail to ask how (and why) this happens so that we can build up a better picture of the key elements that a nerve cell requires to remain healthy.

### How the research will help people with Parkinson's

Although the number of people who develop Parkinson's due to mutations in the DJ-1 gene is small, understanding what the gene does and how this is affected by mutations may point to some vital clues about the condition. Finding out why these changes in the gene cause cells to die will help us to understand better what happens within a nerve cell when it starts to die. The results may also uncover new mechanisms by which drugs could halt or even reverse the progression of Parkinson's.

### Publications by the research team

1. Duchen MR, Szabadkai G (2010). Roles of mitochondria in human disease. *Essays Biochem.*;47:115-37.
2. Vicencio JM, Lavandero S, Szabadkai G (2010).  $Ca^{2+}$ , autophagy and protein degradation: thrown off balance in neurodegenerative disease. *Cell Calcium.*;47(2):112-21.

### For more information, please talk to the Research Team

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