What is the link between glaucoma and mitochondrial function: a deep dive

Joanna Hodgkinson,
Head of Research

We're delighted to announce that the recipient of the 2024 Glaucoma UK/UKEGS grant is Dr Bledi Petriti. In our August 2024 edition of Insight, we discussed his previous project looking at mitochondrial function in normal tension glaucoma, which was published in the prestigious journal Nature Medicine. Bledi's new research project builds on that, investigating some genetics which may be stopping mitochondria from working. We awarded him just under £50,000 for his project "Mitochondrial metabolism in glaucoma: Effects of the Optineurin E50K mutation and the reversal of dysfunction through pharmacological intervention." Joanna Hodgkinson, our Head of Research, spoke to him to find out more.

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▲ Image courtesy of Bledi Petriti

Can you explain briefly what your project is about?

We previously found a relationship between how quickly someone's glaucoma develops and how well their mitochondria work. People with faster-progressing glaucoma had less effective mitochondria, especially those with normal tension glaucoma (NTG).

Mitochondria are described as the powerhouse of the cell. The cells within the optic nerve are very active, so they need their mitochondria to work efficiently. In healthy cells, mitochondria come to the end of their natural life, break down, and new ones are made. This is called mitophagy.

We have found some families with a variant in a gene affecting their mitochondria. Many of these individuals also develop NTG at a young age, around 40 years old. In affected individuals, mitophagy isn't happening properly. The mitochondria are fragmented,

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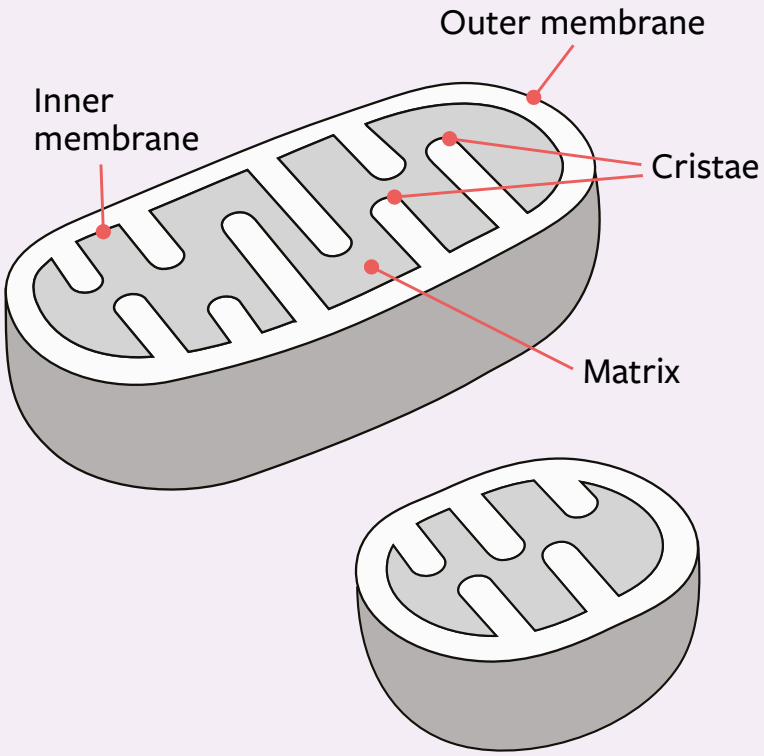

◀ **Simplified diagram showing healthy mitochondria (top) compared with how mitochondria look in those with the E50K mutation (bottom)**

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smaller, and aren't working well. They produce substances which damage the cell, and they don't communicate well with each other. The nerve cells stop working properly, can't send signals to the brain, and ultimately die, resulting in glaucoma.

This study involves exploring the effect of this impaired mitophagy on glaucoma. Other research has shown a link between impaired mitophagy and diseases such as Alzheimer's and Parkinson's, which also relate to nerve cells not working properly. We've identified a drug, used to treat conditions such as Parkinson's, that improves the appearance of the mitochondria so they look more typical and elongated (less fragmented). The first part of our project is to see whether the drug improves the mitochondrial function or just their appearance.

We've also found another family with the same gene variant, so we want to see if the two families have mitochondria which look similar. We also want to look at the mitochondria of the younger members of the families who haven't (yet) developed glaucoma. This might give us insight into how glaucoma develops and what comes first: the mitochondrial dysfunction or the glaucoma.

What difference are you hoping it might make to our members and glaucoma patients?

This might enable us to use existing drugs to treat glaucoma in new ways. These drugs already exist for other conditions affecting nerves, so we know they're safe and effective. If we're successful, it might pave the way for treatments that restore mitochondrial function. These could be used in two ways for people with the genes impairing mitochondria: slowing down progression in people already diagnosed with glaucoma and possibly stopping it from developing in younger people.

We will need further research to see whether the results are applicable to the wider population affected by glaucoma. Glaucoma is complex, with many genes involved, so it's unlikely that everyone could benefit. But this type of treatment could help people we identify with glaucoma and mitochondrial dysfunction, in addition to the current pressure-lowering drugs.

When might we expect to see some of your results?

We are writing up the initial research, looking at the mitochondrial changes in the first family. This new project will take nine months, so hopefully, we can publish our results in early 2026. I'm currently doing a Fellowship at Yale University in America, and the lab I'm working at conducts experiments into mitochondria. I'm going to utilise the expertise here, even though the families we're investigating are treated at Moorfields.

What would be next steps for the research if all goes well?

If we see positive results in these families,

the next step would be to try giving the drugs to more people with glaucoma, to see whether they can slow the disease down. There are many similar drugs we can investigate that might improve mitochondrial function.

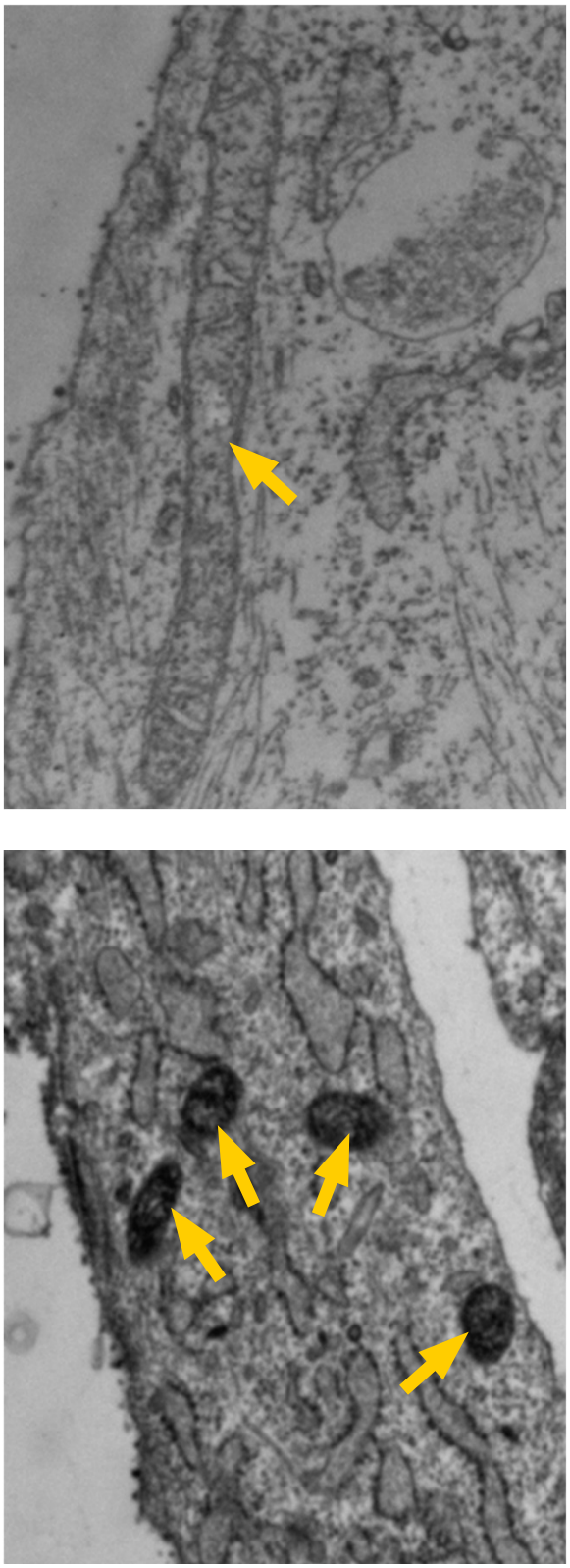
We also hope to follow up with the younger members of the family to see whether they develop glaucoma and whether there are patterns we can identify in how their mitochondria function over time.

Can you tell us how you came into glaucoma research and a bit about yourself?

I'm an optometrist. Glaucoma has always fascinated me because it's a condition where you can closely monitor changes in the optic nerve, eye pressure, and visual field. With some diseases, such as Parkinson's, it can be challenging to track progression. With glaucoma, you can clearly see if interventions are helping. That ability to track outcomes and really help patients drew me into this field. However, I wanted to go beyond clinical practice and make a broader impact, so I transitioned into research.

In 2016, I was working in clinics at Moorfields Eye Hospital when I approached Professor David Garway-Heath. I was eager to learn from him because of his reputation as a leading glaucoma researcher, and I asked if I could collaborate on some of his projects. That's how our research on mitochondria in glaucoma began—an area that was relatively unexplored at the time, but incredibly exciting.

I'm from Albania and moved to the UK in 2002 to pursue my A-Levels. I initially wanted to be an architect, but my father, who's a civil engineer, had other ideas—he used to joke that architects get all the glory while engineers do the hard work! So, I decided to explore healthcare, and eventually found my passion in research. It turned out to be the right path for me, and I feel I've found my niche.



▲ **Mitochondria in those with the E50K mutation (bottom) compared to healthy mitochondria from a control subject**

Electron microscope images courtesy of Bledi Petriti