A potential new warning system for glaucoma progression

Joanna Hodgkinson, Head of Research,
in conversation with **Dr Bledi Petriti**

We are delighted that research we funded has resulted in a paper being published in one of the most prestigious journals, called Nature Medicine. The research was carried out by Professor David (Ted) Garway-Heath and Dr Bledi Petriti at the Institute of Ophthalmology at University College London. The project, titled "Identifying the genetic basis for heritable Normal Tension Glaucoma, with a focus on mitochondrial function", received £40,000 through the 2017 UKEGS award. Our Head of Research, Joanna Hodgkinson, spoke to Bledi to find out more about the project and why it's so exciting.

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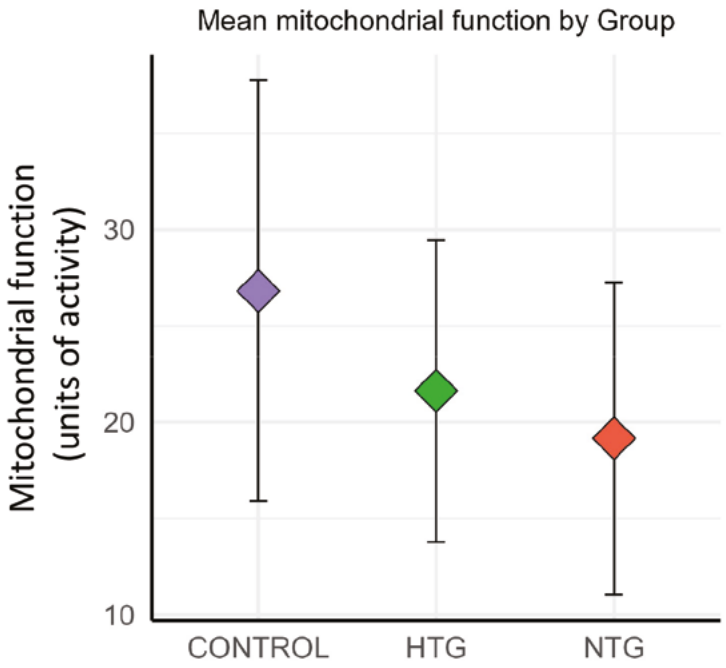
What was the aim of the project?

Glaucoma is a leading cause of irreversible blindness worldwide, and we normally manage it by reducing eye pressure. However, this approach doesn't prevent all cases of vision loss, which means other factors must be involved. We set out in 2017 to try to understand what might be causing vision loss even when eye pressure is under control and within the normal range.

Our research focuses on the role of mitochondria, the packets within cells which generate energy. The optic nerve head, where the nerve leaves the back of the eye and goes to the brain, is believed to be the site of initial damage in glaucoma. It needs a lot of energy, and so is densely packed with mitochondria. We wanted to investigate whether there was a link between how well the mitochondria functioned and whether someone's glaucoma got worse.

As mitochondria are in nearly all the cells in our body, we wanted to explore whether a simple blood test could be used to analyse the mitochondria, potentially identifying



patients at higher risk of vision loss. If poor mitochondrial function is shown to be a cause of glaucoma, we hoped that a new treatment could be identified which helps the mitochondria work better and give us an alternative to the current options which control eye pressure. Understanding mitochondrial health could be a key factor in better managing glaucoma and preventing vision loss.

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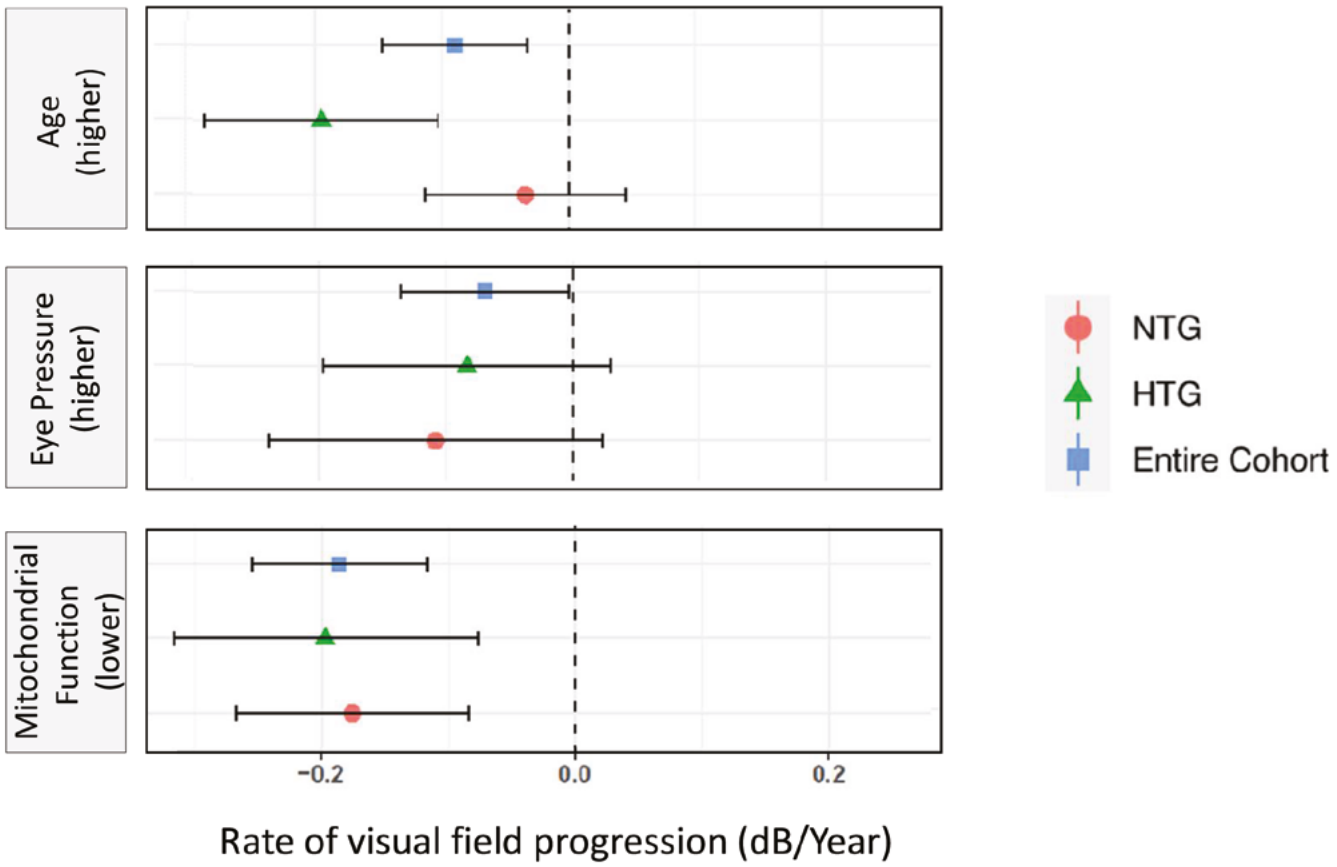
What have you found out so far?

We recruited three groups of people: some with normal tension glaucoma (NTG), some with high tension glaucoma (HTG) and some who had no glaucoma at all (called controls). We collected a small blood sample from their arm (similar to the one done through a routine blood test). Our main findings showed that people with glaucoma had reduced mitochondrial function compared to controls. We found that people with NTG had the lowest mitochondrial function followed by those with HTG.

We also looked at the visual field tests of people with glaucoma, to see how quickly they were losing vision and compared this to their mitochondrial function. We found that study participants with the lowest mitochondrial function lost vision fastest. We already knew that age and eye pressure were significant risk factors for



glaucoma sight loss. This study shows that mitochondrial function is another important risk factor. If someone's mitochondrial function is one unit lower, that increases their risk of losing vision as much as having an eye pressure 2-7 mmHg higher or being 21 years older.

We also looked at another measure of mitochondrial function: levels of nicotinamide adenine dinucleotide (NAD). NAD is a helper molecule which the mitochondria use to generate energy. We found that people with glaucoma in our study had lower levels of NAD compared to people without glaucoma. The lower the NAD levels, the lower the mitochondrial function. We hope we can increase NAD levels by giving someone vitamin B3, which makes this an especially exciting finding.

Read more about research into the possible benefits of vitamin B3 on page 55

Why is this project important or useful to people with glaucoma?

We've identified that mitochondrial function and NAD levels are "biomarkers" which can help us predict how quickly someone with glaucoma might lose vision. A biomarker is like a biological "fingerprint" that helps doctors understand what's happening inside your body. It can be a substance in your blood or other body fluids that indicates how well your organs are working or if you have a disease. We hope the findings of the study will be useful in three ways:

1. Improving our understanding of glaucoma and what causes it. The more we understand it, the more likely we are to be able to find a cure in the future.
2. These biomarkers give us a new way of identifying people at greatest risk of vision loss. This could be clinically very important, as we will know who needs more regular appointments and who is at lower risk so doesn't need to be seen as often.
3. We might be able to develop new treatments which target mitochondria. We know that just lowering someone's eye pressure doesn't fix everything. If we can boost mitochondrial function, we might be able to slow down or prevent vision loss in people with glaucoma. It gives us another option for treatments, even if we still also rely on traditional pressure-lowering ones.

What are the next steps for the research?

We are currently running a multicentre clinical trial giving patients vitamin B3, which the body uses to make NAD. We hope that by restoring NAD levels we can slow down glaucoma progression. We also want to study the biomarkers for mitochondrial function in more people. We want to make the blood test simpler and easier to do in a clinic setting – at the moment it's quite laborious. Hopefully we'll be able to establish quick blood tests to help us identify people at greatest risk of losing vision. And if we're successful we might be able to use the biomarkers to find another supplement which people can take. This could improve mitochondrial function and slow down vision loss due to glaucoma. It's really exciting to think of the different directions this research could take.