About you

My name is Mark Hamilton, and I'm a research fellow with a background in clinical genetics at the University of Glasgow. My research work involves exploring how an inherited condition, called myotonic dystrophy type 1, affects the brain to cause problems such as cognitive difficulties and excessive sleepiness. In 2018, in the final year of my PhD, I was fortunate to be awarded £425 from the David Fleming-Brown Postgraduate Travel Scholarship to support a collaborative visit to Iowa City, USA.

Why did you apply for the Travel Scholarship?

Myotonic dystrophy type 1 (DM1) is a highly variable, complex, inherited condition. In addition to muscle weakness, affected people may develop cataracts, problems with the electrical system of the heart, gastrointestinal symptoms, and hormonal changes. DM1 also affects the brain, which can result in cognitive problems, fatigue, excessive sleepiness and difficulties with social interaction. These symptoms may have a profound impact on affected people's quality of life.

DM1 is caused by the expansion of a repeated sequence of DNA. Generally speaking, larger expansions are associated with more severe symptoms. The DNA repeat is inclined to increase in size as it is passed down through generations of a family, and so severity of the condition can be widely variable even in a single family. The team led by Prof Darren Monckton at the University of Glasgow has a long history of world-leading research towards understanding how the size of the DNA expansion a person inherits, and how this changes over an individual's lifetime, influences the severity of their symptoms.

Working with Prof Monckton's group, my own project aims to think about ways to measure brain involvement in DM1. This is particularly relevant in the context of clinical trials for potential treatments, where it is crucial to determine whether a drug is having a meaningful effect on the disease. We are also interested in how the structural brain changes, which can be seen on MRI scans, lead to symptoms such as excessive sleepiness and cognitive difficulties.

To meet these aims, 40 people with the adult-onset form of myotonic dystrophy were recruited from the West of Scotland population. All have completed questionnaires about their symptoms, undergone a cognitive assessment, and had genetic analysis of their DNA repeat. The majority have also had MRI scans of brain and overnight sleep studies. Twenty control participants, who do not have myotonic dystrophy, underwent MRI scans and cognitive assessment.

Our preliminary analysis of the MRI scans gave some highly encouraging results, identifying changes in brain regions with very plausible links to key symptoms observed in people affected by DM1.

To explore our observations further, we approached the team led by Prof Peggy Nopoulos at the University of Iowa, USA, with whom our group have an existing collaborative relationship. Prof Nopoulos and her colleagues have a strong history of using sophisticated MRI processing techniques to gain important insights into progression neurological conditions, most notably in Huntington disease. The Iowa group have also recently recruited a cohort of patients with DM1, comparable in size to our own, to undergo MRI. We therefore hoped our teams could work together, to share our own expertise in the genetics of DM1, and to benefit from

the Iowa group's extensive experience and expertise in MRI brain analysis. A major challenge to research in rare conditions, such as DM1, is that often only a relatively small number of participants can be recruited in a single city. By combining our results, the final analysis contained almost 80 people with DM1 – a much larger sample than any DM1 MRI study previously reported in the scientific literature.

Details of the visit

I travelled to Iowa City (via Newark, Chicago and Cedar Rapids airports) on the 19th May 2018, for a one week visit. Dr Ellen van der Plas, a senior researcher with Prof Nopoulos' team, met me at the airport and took me to the lovely rental accommodation that the team had kindly arranged for my stay.

The Iowa Old Capitol Building, with University mascot Herkey the Hawk in the foreground

A packed itinerary was planned for the week. This included a detailed seminar on MRI processing led by the Iowa imaging team, in which I learned a huge amount about the core principles of research using MRI. Specific processes that were covered included preparation of scans for analysis, and adjusting for differences that may arise due to different MRI scanners being used (for example, in order to combine the Glasgow and Iowa images). We also covered joint label fusion – a novel method for accurately measuring the volume of specific structures in the brain in an automated way – and a method for measuring the thickness of grey matter.

Later that week, I was given the opportunity to present my own findings to the group. I detailed our observations in the Glasgow participants to date. I was also able to more thoroughly outline the key genetic findings of the Monckton research group, and our thoughts about how genetic variation might influence brain changes in DM1.

Prof Monckton was able to join me in Iowa for part of the visit. During this time, the Iowa group arranged an all-day seminar on the theme of DM1 research, including excellent talks on DM1 genetics, muscle MRI analysis, physiotherapy and microscope studies of brain. This led to fruitful discussion of future directions for our research together, which continued through dinner.

Towards the end of the visit, I was able to spend some time undertaking statistical analysis of the study results with Ellen, and developing a plan to prepare our results for submission to a scientific journal. I was delighted that the results appeared to describe, in unprecedented detail, the landscape of structural brain changes occurring in DM1. In particular, the results highlight regions in which volume loss was most strongly driven by the size of the DNA repeat. Some of the structures identified play a role in cognitive processing, motivation and in maintaining wakefulness – hence the represent strong candidates to act as MRI markers for clinically important symptoms.

On my final evening in Iowa, the team treated me to a fantastic all-American evening watching the local baseball team, the Kernels, play in Cedar Rapids (pictured). Hot dogs and ice cream sandwiches were in plentiful supply.

Mark Hamilton (right) with Dr Ellen van der Plas (left), Prof Peggy Nopoulos (centre), and Ellen's daughter Riley, watching the Kernels play baseball.

Impact of the Travel Scholarship

The collaborative visit facilitated by the travel award was invaluable in strengthening our relationship with the team in Iowa, and enabling us to gain the very best from our joint imaging analysis. As a clinical researcher, I am conscious and grateful for the time and efforts made by study participants to provide us with MRI scans and other data. It is therefore important that this data should be used to its fullest potential to benefit the research community, and the expertise gained by working with the Iowa team was critical in achieving this aim. While technology can facilitate collaborative working from overseas, there can be no substitute for

discussions in person, and my time in Iowa was highly effective in sharing ideas and making strides in driving our joint research forward.

Work undertaken during the trip has led directly to the preparation of a manuscript, with Ellen and myself as first authors, which will be submitted for publication in the near future. It is likely several further papers will arise from our collaboration. The discussions which took place during the visit also set the scene for future collaborations with the Monckton group, whose genetic interests are highly relevant to the Iowa group's work on both Huntington disease and DM1. Having access to samples from clinically well-characterised cohorts is a positive step for the Monckton group, as this allows further exploration of how genetic observations made in the laboratory relate to symptoms experienced by patients.

From a personal perspective, the trip was an unforgettable and inspiring experience. It was a pleasure to make firm friends with Ellen and her husband Tim, who were excellent hosts. Furthermore, the teaching provided by the Iowa imaging scientists greatly broadened my horizons with respect to research imaging analysis, and contributed many insights that I hope to apply to future clinical research work. I am extremely grateful to Prof Nopoulos for enthusiastically supporting our collaboration, and would like to thank again the travel award committee for their support of this trip.