Using machine learning to predict prognosis and treatment response following silent MRI activity in multiple sclerosis

Personalised treatment is needed to reduce long-term disability in multiple sclerosis (MS), while limiting the risks of treatment. MS is one of the most common causes of disability in young adults. Many MS treatments can reduce the development of disability, but the strongest treatments can have more serious side effects. I aim to solve three common problems to improve MS management.

Firstly, even when someone with MS is on a treatment and has no new symptoms, MRI scans often show new "silent lesions". This indicates that the disease is still active. We do not know the long-term prognosis following silent lesions, or whether changing to stronger treatments improves outcomes. I aim to solve this problem by analysing the largest international database of people with MS.

The second problem is that lesions are often missed when doctors report MRI scans. Recent studies have shown that artificial intelligence (AI) can detect most of these missed MS lesions. However, since these lesions are harder to detect, they may also be less important. I will analyse whether this is the case. This will be crucial if we are to use AI to help report MRI scans in MS clinics.

Finally, the severity of MS varies widely between affected people. We are currently unable to accurately predict which people could benefit most from early use of the strongest treatments. To address this, I will use existing clinical and MRI data from thousands of people with MS to train cutting-edge AI tools. This will be the first step towards developing a software tool to assist with personalised treatment decisions in MS clinics.

Cyrus Daruwalla
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Discovering intergenerational genes in Huntington’s Disease

Huntington’s disease (HD) is a genetic movement disorder with dementia and psychiatric symptoms. This research is a sperm study aiming to better understand HD inheritance to improve genetic counselling of HD gene carriers. HD therapies under development may reach clinical trial stage within the next 5 years. This study will help determine whether sperm are affected by these drugs and therefore has important implications for drug development.

DNA is made up of four molecules: A(adenine), T(thymine), C(cytosine) and G(guanine) and contains ‘repeat regions’; repetitive combinations of these molecules. The huntingtin (HTT) gene is a repeat region with repeated CAG units. Normally there are up to 26 CAGs in HTT but those carrying the HD mutation have 36 or more.

Over 50 neurological human diseases exist, called repeat expansion disorders (REDS), are caused by abnormal repeat numbers in different DNA regions.

We know in HD, and many REDs, that when the mutation is inherited the gene length may change in sperm and sometimes children inherit a different sized gene compared to their parent. Expansions can lead to the child developing disease symptoms earlier than their parent, termed ‘genetic anticipation’. Although genetic anticipation is widely recognised, the reason it happens in some families and not others is unclear.

This project involves donation of blood and semen from men with HD for genetic analysis of repeat region changes in sperm and to identify potential causative genetic factors. This will improve understanding of HTT mutation inheritance risk and may reveal biological pathways for further investigation which may be applicable to other REDs.

Sangeeth Rajagopal
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Investigating the consequences of HnRNPM mislocalisation in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) results in degeneration and death of motor nerve cells (motor neurons, MNs) which control walking, speaking, swallowing and breathing. It is fatal and untreatable. To develop treatments, we must understand precisely what causes MN degeneration.

Important proteins which bind and regulate RNA messages are dysfunctional in MNs in ALS. I have discovered that another protein in this class, called HnRNPM, is abnormally ‘mislocalized’ from nucleus to cytoplasm in MNs in ALS. This is especially interesting since HnRNPM binds a specific abnormal RNA message in ALS and could be a new target for treatments.

To study ALS, we transform skin cells from ALS patients and healthy volunteers into stem cells then into MNs in the lab, and compare these. I hypothesise a loss of HnRNPM’s normal functions due to its mislocalisation in ALS. To model this, I will deplete HnRNPM in healthy MNs, then look for typical MN features of ALS, and for differences in RNA messages due to loss of HnRNPM’s functions. I will also examine all interactions of HnRNPM with RNA messages in healthy and in ALS MNs. I will assess whether increasing HnRNPM levels can resolve features of ALS.

This work will help us understand the contribution of HnRNPM to MN degeneration, and whether manipulating HnRNPM could treat ALS. If HnRNPM manipulation shows promise as an ALS treatment, development could progress to animal studies and subsequently clinical trials. From initial studies to approval of a treatment for patients could take approximately 10-15 years.

Stephanie Taylor
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