

YOU CAN'T TURN YOUR BACK

Ed Wild discusses the latest breakthrough in Huntington's disease and explains why he will always remain dedicated to the field.

Have you ever felt so proud of your research you've wanted to put it on a T-shirt? Ed Wild has – and he and his colleagues wore the T-shirts to presentations. He says: “It did create some slightly awkward situations. I found myself pointing to my chest saying ‘these are the main take-home points’.”

Ed is a neurologist who specialises in Huntington's Disease (HD), an inherited neurodegenerative disorder that affects mental abilities, mood and physical coordination, and which can devastate

whole families. *The Biomedical Scientist* spoke to him, just after the publication in *The Lancet Neurology* of what he calls a very important development in understanding the disease.

The significant finding was the discovery that the blood of HD patients contains heightened levels of the protein neurofilament light (NFL). The amount of NFL rises as the condition worsens. And it can be mapped almost perfectly on to the number of ‘CAG’ repetitions a patient has in their huntingtin gene (HD patients have more than 35, those without HD generally have around 17).

“Essentially the question was, could your baseline NFL level predict how your HD would subsequently progress?” Ed says. “We found that NFL predicted brain atrophy and clinical progression, even after adjustment for age and CAG repeat length. So NFL is a speedometer where a single measurement gives you an almost instant readout for how quickly someone's HD is progressing.”

The long view

To understand how Ed and his team got to this point we need to go back to 1993, when the cause of HD, a mutation of the huntingtin gene, was discovered.

“I think the advantage we have in HD is that, unlike almost every other relatively prevalent neurodegenerative disease, HD is monogenic. So everyone with the disease has the same basic mutation. Everyone with that mutation gets HD,” Ed says. “After the discovery of the huntingtin mutation, the hope was that it would rapidly lead to treatment. In fact, it's taken us about 23 years, but we are now giving drugs that essentially silence or aim to lower the expression of the mutant gene. So the whole field has been focusing on drug development to treat the known cause of HD.”

The difficulty is that while carriers of the huntingtin mutation have a 100% chance of getting symptoms, it hasn't been possible to predict when they will appear. “For 40 or 50 years you might look

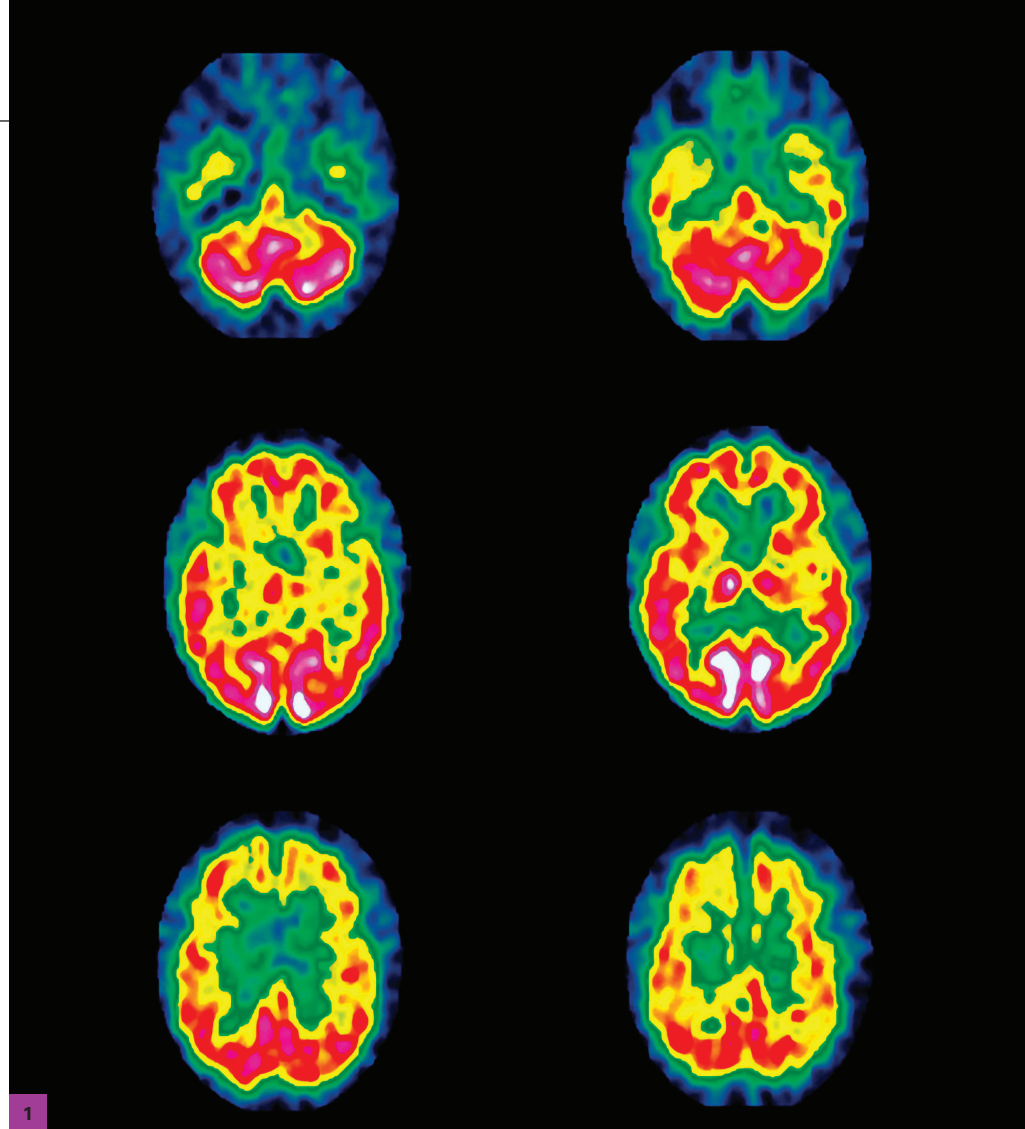
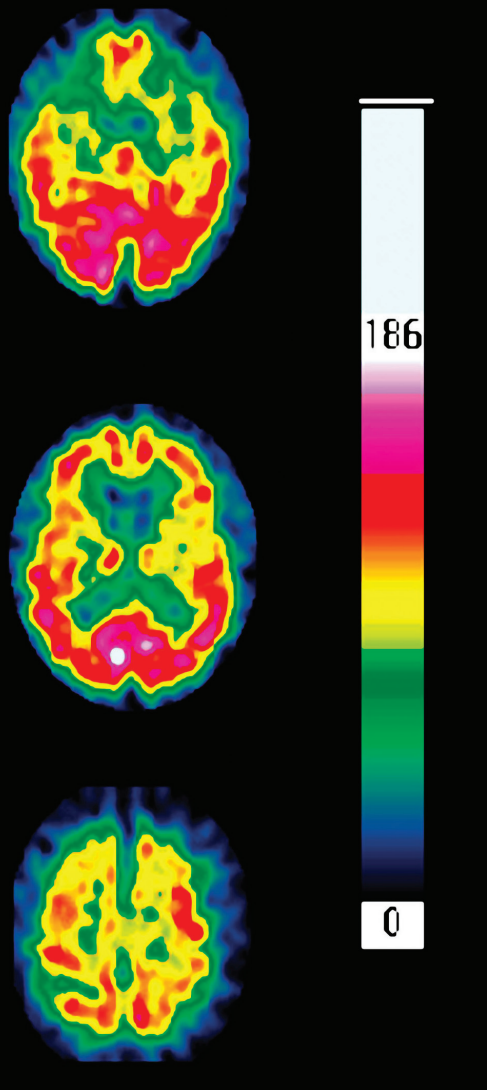


Fig 01: Coloured single photon emission computed tomography (SPECT) scans of axial sections through the brain of a patient with Huntington's disease



ALL ABOUT ED

- ✓ Studied medicine at Christ's College, Cambridge
- ✓ Is an MRC Clinician Scientist at UCL Institute of Neurology and Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery
- ✓ Has authored six book chapters and more than 50 peer-reviewed publications
- ✓ Has undergone three lumbar punctures to act as a control in his research. Some HD drugs are administered in this way, so it also helps him to reassure patients
- ✓ Is a fervent science communicator: he co-founded hdbuzz.net, a plain-English HD research news site.



completely normal on the outside and on brain scans," Ed says. "So even if we had a perfect drug, if we gave it to someone, five years later we would have no way of knowing whether it had worked. This is where the promise of biomarkers came up, and why NFL work is so important."

In 2007, in an exemplary act of forward-thinking, Ed's long-time mentor Sarah Tabrizi, a neurologist at UCL, led a study called Track HD which included more than 360 HD patients. "We collected plasma blood samples. We had no idea what they would be used for, except that some day we might need good quality plasma," Ed says. "Nearly a decade later, we ran this neurofilament test on the plasma, not really having any expectation that we would see anything striking. And the results knocked our socks off – there were highly significant NFL increases in all the HD groups compared to controls."

Next steps

So now the NFL biomarker has been discovered, what's next for Ed and his colleagues? "We have to find out how to make it useful," he says. "There are ongoing and planned clinical trials. As a matter of urgency, we need to figure out whether neurofilament changes if you give a drug that's working."

He points out that there are still unanswered questions. "Our study only went up to the mid-stage of HD but we need to know what happens later on in the disease. We also need much bigger cohorts of very young patients who are very far from onset, so we can study in more detail the factors that predict progression. Plus, what I'd really like to do is translate this into animal models. So lots of work to do."

A vocation

Like many passionate scientists, Ed is clearly hooked on his work. He first encountered HD when searching for a topic for his PhD in 2005. After an chat with Sarah Tabrizi, he

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went along at her suggestion to an HD clinic. "I found the idea quite depressing because HD is incurable and it decimates whole families. It's an incredibly challenging disease for anyone, including doctors and carers, to cope with. But one HD clinic as an observer was all it took to completely convert me," Ed says.

"The determination in the hearts of these family members not to let the disease get the better of them, even when things were going terribly badly and their whole family was at risk, was incredible. And once you're in HD research, it's very difficult to leave. I've been in the field long enough now to see people who were completely well when I first met them start to develop symptoms and really that's not something you can turn your back on. You think we didn't quite get there to save that person, but maybe we can do something to make life different for his kids, for his younger brother. It's really that which motivates me." **BMS**