Quick guide

Huntington's disease

Also known as ... Huntington's chorea. The disease was named after a young physician, George Huntington, who in 1872 described the spasmodic and uncoordinated limb movement (chorea) afflicting a handful of families of English descent living in a region of Long Island, New York. He had first encountered these patients when he was just 8 years old, accompanying his father and grandfather on medical rounds. For more than a century, the disease has also erroneously been referred to as 'Huntingdon's disease'.

What are the symptoms? The disease is characterized by involuntary movements, severe emotional disturbance and cognitive decline. It usually strikes in mid-adulthood and progresses inexorably until death occurs ten to twenty years later. The disease, which affects about 1 in 10,000 people, is a dominantly inherited trait.

Most famous case ... Woody Guthrie, the father of American folk music, who died of Huntington's disease in 1967, at the age of 55. His son Arlo, 50, still shows no signs of the disease and says "I'm living on free time."

Most likely to be mentioned by ... Nancy Wexler, a remarkable woman whose mother died of the disease and left Nancy and her sister with a 50:50 chance of developing it. Wexler collected hundreds of blood samples from the isolated inhabitants of Lake Maracaibo in Venezuela — who included scores of people affected with Huntington's disease — in the hope they would somehow provide the key to understanding it. As President of the Hereditary Disease Foundation (www.hdfoundation.org), Wexler raises millions of dollars for research.

Has the gene been mapped? With the realization in the early 1980s that inherited disease genes could be mapped in large families, Wexler's Venezuelan samples became a precious commodity. In 1983, James Gusella started linkage studies with a random collection of polymorphic markers on different chromosomes. Incredibly, one of the first dozen tested, called G8, from chromosome 4, tracked with the disease gene.

A short step to isolating the gene, then? No. For the next decade, research teams struggled to narrow the gap between G8 and the Huntington's disease gene and to resolve confusing data that prevented them from pinpointing its precise location.

Who found the gene? A consortium of almost 60 researchers, including Gusella and Wexler, from six teams working in Boston, London, Cardiff, Michigan and California finally identified the disease gene in 1993. The lab name for the gene was 'IT15', for 'interesting transcript 15'; the protein was subsequently dubbed 'huntingtin'.

What causes the disease? In common with genes involved in a number of neurodegenerative diseases, the Huntington's disease gene contains a triplet repeat sequence (CAG) that encodes a run of glutamine residues in the corresponding protein. Healthy people have about 35 CAG repeats in this gene but expansions above this limit, sometimes to more than 100, are invariably associated with the disease. In general, the longer the repeat, the earlier the age of onset.

What is known about huntingtin? Not much, other than that it is a large protein (about 350 kDa), widely expressed and essential for mouse embryonic development. The recent identification of proteins that interact with huntingtin specifically and in a glutamine-dependent manner should shed some light on this. What is clear is that the increased run of glutamines causes the mutant huntingtin protein to form aggregates in and around the nucleus in certain neurons. The pathological significance of this is borne out by similar observations in other triplet repeat diseases, including spinocerebellar ataxia.

Is any of the research looking promising? The transgenic mouse models that have recently been developed should begin to pay dividends. On the clinical front, there is a trial under way in the US of two drugs, Remacemide and Coenzyme Q10, which may be able to slow the pace of nerve damage. Inhibitors of transglutaminases and apoptosis could also prove effective therapeutics down the line.

Meanwhile, what hope is there if you carry the mutant gene? Nancy Wexler summarized the profound ethical dilemmas facing people who learn they carry the gene for a fatal disease with no immediate prospect for a cure in the words of Tiresias, who warned Oedipus: "It is but sorrow to be wise when wisdom profits not."

Where can I find out more?

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