

Uncovering the true prevalence of Huntington's disease

Legislation exists to ensure that research into drug development for rare diseases is encouraged. But how sure can we be that a rare disease is, in fact, rare, and what happens when the real prevalence is found to be higher, or lower, than official estimates suggest? Laura Spinney reports.



On June 30, 2010, an All Party Parliamentary Group on Huntington's disease will be launched in the UK. The group's first task will be to investigate the true prevalence of Huntington's disease, because a discrepancy exists between the prevalence estimate that the UK government has been working with and that suggested by the number of people seeking advice from the UK-based Huntington's Disease Association.

"The figure that is generally reported is seven symptomatic people per 100 000", says Michael Rawlins, chairman of the National Institute for Health and Clinical Excellence for England and Wales. "The Huntington's Disease Association has 6376 [symptomatic people] on its books in England, which works out at 12.4 per 100 000." In other words, if these figures accurately reflect the UK situation, the prevalence of Huntington's disease has been underestimated by 80%. Because the figures from the Huntington's Disease Association are themselves almost certainly an underestimate, Rawlins says it is reasonable to suggest that Huntington's disease might be twice as prevalent in the UK as it was previously thought to be.

The prevalence figures from the Huntington's Disease Association have yet to be validated, and Rawlins—along with Sarah Tabrizi of University College London's Institute of Neurology, London, UK, who leads a research programme on Huntington's disease, and Stephen Evans, an epidemiologist at the London School of Hygiene and Tropical Medicine—is now designing a study to do just that. Their research will involve combing general practice databases for diagnoses of Huntington's

disease, validating those diagnoses, and then working out the prevalence of Huntington's disease in the UK. Rawlins is confident that they will have a revised prevalence estimate by the end of 2010. However, measuring prevalence is not easy, he warns, particularly for a disease that has been so stigmatised.

"To understand the problems in getting at the true prevalence you have to understand the shadows people are walking out of."

Huntington's disease is a fatal, genetic neurodegenerative disorder that causes involuntary movements, emotional disturbance, and progressive cognitive loss over 10–20 years. Every child of an affected parent has a 50% chance of inheriting the disease gene, and carriers of the gene will definitely develop the disease although, in most cases, not until the third or fourth decade of life. By then, many patients have already had children, and so these children have to witness the decline that awaits one in two of them.

There are several reasons why Huntington's disease prevalence might have been underestimated. Although the course of the disease is fairly characteristic and therefore misdiagnosis is relatively rare, it does happen, particularly in less common cases in which psychiatric symptoms precede the movement disorder. The introduction of a genetic test in the early 1990s reduced the risk of misdiagnosis; however, many people with a family history of Huntington's disease prefer not to know if they are carriers, and those who have been diagnosed may hide their diagnosis

for as long as they can. In addition, in the UK, doctors are not legally required to enter the cause of death on a death certificate, and so not all deaths from Huntington's disease are recorded.

Nancy Wexler, a geneticist and neuropsychologist at Columbia University in New York, USA, who led the team that located the gene that causes Huntington's disease, is delighted that the prevalence of Huntington's disease will finally be investigated properly. If the prevalence has been underestimated in the UK, she says, it has probably been underestimated elsewhere. In fact, she says, the prevalence usually quoted for the USA—ten symptomatic individuals per 100 000—might be even more of an underestimate than in the UK because Americans have an added incentive to hide their at-risk status owing to insurance companies' practice of refusing health coverage to people with pre-existing conditions.

Although last March, US President Barack Obama signed a law prohibiting insurance companies from denying coverage to children with such conditions, and the protection will be extended to adults in 2014, Huntington's disease remains stigmatised. Wexler—whose mother died of the disease—believes this is in part because of the history of compulsory sterilisation of Huntington's disease carriers in the USA, which was first proposed around 1910 by US eugenicist Charles Davenport, and which continued into the second half of the 20th century. "To understand the problems in getting at the true prevalence", says Wexler, "you have to understand the shadows people are walking out of."

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For the Huntington's Disease Association see <http://www.hda.org.uk/>



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For more on how Huntington's disease affects the brain see *Lancet Neurol* 2009; 8: 791-801

Cath Stanley, who runs the Huntington's Disease Association's care services for England and Wales, says there is likely to be a feedback effect if the higher prevalence figures are confirmed: knowing their condition is more common than they thought might encourage more patients to come forward. Armed with the new figures, the charity plans to campaign for more National Health Service (NHS) resources to be allocated to Huntington's disease, on the principle that the NHS guarantees equality of treatment to all, and patients with Huntington's disease are being underserved because of the underestimated prevalence. The quality of care that is currently on offer is patchy, says Stanley: "If you have a specialist, multidisciplinary Huntington's disease clinic in your area, you probably get very good medical care", she says. "If you don't, that might not be the case."

The revised prevalence figures will be important for several reasons. First, if the prevalence of a disease as relatively easy to diagnose as Huntington's disease has been underestimated, then the prevalence of disorders for which there is no genetic test and for which diagnosis is less clear-cut, such as Alzheimer's disease and Parkinson's disease, might have been

underestimated too. Second, because Huntington's disease often does not manifest until middle age, the number of patients who have symptoms at any given time is just the tip of the iceberg. Carriers who have yet to develop symptoms are not included in the prevalence figures, yet there are more of them: "The rule of thumb is that the number of presymptomatic people in a population is roughly twice the number of symptomatic", says Rawlins.

The presymptomatic population will expand dramatically if the increased prevalence figures are confirmed. In the early stages of Huntington's disease, before the disease manifests, whole-brain volume is significantly reduced and there are differences in regional grey and white matter. Therefore, one goal of pharmaceutical companies is to develop neuroprotective treatments that carriers could take presymptomatically to prevent damage to the brain from ever reaching the threshold at which symptoms emerge.

The CHDI Foundation, a US-based, not-for-profit research organisation, plans to launch clinical trials for two potential treatments for Huntington's disease within the next 2 years. "If they're effective for manifest Huntington's disease, we'll wind the window back and see how effective they are in premanifest populations", says Simon Noble, the foundation's director of communications. He would also like to see research designed to quantify the number of presymptomatic patients.

The USA was the first country to introduce legislation to induce pharmaceutical companies to develop orphan drugs—that is, drugs for rare diseases, such as Huntington's disease—with the 1983 US Orphan Drugs Act. The European Union followed suit in 2000. The incentives these laws put in place included simplified licensing procedures for candidate drugs and extended patent

protection. However, the prevalence threshold for defining a rare disease varies widely, from 11 cases per 100 000 in Australia, to 75 per 100 000 in the USA.

If the UK prevalence figures suggested by the Huntington's Disease Association also applied to Australia, which is by no means a given since Huntington's disease prevalence varies geographically, then Huntington's disease would stop being classed as a rare disease in Australia. According to Christopher McCabe, a health economist at Sheffield University in the UK, this reclassification wouldn't necessarily affect a pharmaceutical company's decision to invest in research on Huntington's disease, because most companies plan globally and Huntington's disease is likely to remain rare in most parts of the world. But it might influence where companies decided to launch any newly licensed treatments: "They'll launch first in the places where they have orphan drug status, because it's easier", he says. This happened in the case of interferon beta for multiple sclerosis, for example, which was marketed first in the USA, where it was considered an orphan drug, and only later in Europe, where it was not.

In the European Union, a rare disease is defined as one that is life-threatening or chronically debilitating, with a prevalence of 50 or fewer cases per 100 000. Therefore, even if the revised prevalence of Huntington's disease in the UK is twice as high as that with which the UK government is currently working, the disease will continue to be defined as rare. Patients could now begin to see a difference, however, as the new All Party Parliamentary Group strives to ensure that they have access to the health care and political representation that is due to them.

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