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Huntington's is still holding out

***In situ* expression studies show that the selective pathology of Huntington's disease is not explained by a simple pattern of gene expression in the brain.**

HUNTINGTON'S disease is a disorder to be reckoned with. The causative gene managed to remain hidden for a full ten years of intensive international gene searching after linkage was established, and now the fear that finding it might have been the easy bit seems to be being borne out. As Francis Collins and his colleagues report in this month's *Nature Genetics*[1], the pattern of gene expression does nothing to clarify the intriguing specificity of the disease pathology.

In 1872 George Huntington[2] described an inherited chorea that he, his father and his grandfather had all remarked upon. But the description was not widely read, and it had to wait 20 years before W. Osler once more drew attention to the heritable chorea[3] which is also characterized by progressive intellectual deterioration and severe depression. At this time Osler remarked that he had attempted to investigate the original family described by Huntington, only to be told that the patients could not be seen because of their sensitivity about their condition.

For many years, remarkably little progress was made in describing the condition, although in 1932 the original families with Huntington's disease (HD) were traced back to a pair of English brothers[4] and hence the stability of the disease was established. In the 1950s and 1960s, several groups reported on large studies documenting the huge variation in age of onset (typically between the third to fifth decade, although some patients develop signs in the first decade and others are symptom-free for more than 60 years) and death (usually ten years after onset of symptoms). In the 1970s, some progress was made in explaining these variations when it was noted that the juvenile form, with a very early onset, was significantly more frequent in those who had inherited the defective gene from their father. As this theme continued to develop, the possibility of chromosomal imprinting became clear.

In the 1980s, molecular genetic linkage studies gained ground as the method of choice for identifying wayward genes. After a number of false starts, an anonymous marker (G8, mapped to chromosome 4; ref. 5)was found to be linked to the disease in a massive Venezuelan kindred. (This huge pedigree also provided access to homozygote HD patients who, on the basis that they had a phenotype indistinguishable from heterozygote patients, proved that HD showed complete dominance.)

The first, albeit rudimentary, localization of the HD gene was expected to herald great things. The devastating nature of the disease had become widely understood and mapping the HD gene to chromosome 4 was the first really tangible step towards isolating, understanding and presumably treating or even curing the condition. But despite the close attention of the medical and research communities, progress was slow, with little or no significant advance either in understanding the basic defect, the selective neuronal loss seen in the striatum, or in the treatment of patients. HD continued to prove frustrating and puzzling. New and ever-closer markers were described, and over a period of ten years the gene locus was gradually refined until just the very tip of the long arm of chromosome 4 was in the spotlight. Elaborate and powerful molecular techniques were used to scour the region and candidate genes were picked up and discarded.

In March of this year the breakthrough came when the Huntington's Disease Collaborative Research Group described a large (210-kilobase) gene that included a polymorphic trinucleotide (CAG)*n* repeat which is expanded in HD chromosomes[6]. Early analysis (since confirmed in larger studies) showed that in normal chromosomes the repeat was always 34 units or less, whereas in HD chromosomes it was 42 or more. The excitement of finding the HD gene was all the greater with the discovery of another unstable triplet repeat giving rise to yet another neurological disorder[7].

Unfortunately the ten kilobases of HD transcript (IT15) reveal a sequence unrelated to any previously described, and hence predict a protein of unknown function, making comparisons impossible. Strong *et al.* therefore tried a different tack and postulated that the selective neuronal loss in brains of HD patients might reflect selective expression of IT15. Rat and human brain sections were both tested using RNA *in situ* hybridization with riboprobes directed against the human IT15 transcript or the rat homologue. Looking in sections taken from normal and diseased brains, they found that in both rat (normal) and human (normal and HD) sections the HD gene appears to be expressed in neurons throughout the brain. Although some variation in expression levels was seen, the striatum (the area of severe neuronal loss in HD brains) did not show unusually high expression, and in the human sections there was no difference between the HD and control brain. HD messenger RNA was also found in non-neural tissues (pancreas, colon, liver and sperm), although at slightly reduced levels compared with brain. From a cursory glance at the generalized brain and non-neural expression (and bearing in mind that no HD pathology has been described in extraneural tissues), it is not clear that HD pathology is a function of IT15 expression. These results have been confirmed by a second group[8].

Strong *et al.* point out that as HD appears to act in a truly dominant manner a gain-of-function mutation is a plausible disease mechanism and their results do not support this idea, at least not in any straightforward fashion. They also point out that they only looked at adult brain tissue and a transient overexpression of IT15 could occur, or there may be something about neuronal cells of the striatum that makes them particularly sensitive to IT15. No doubt many other explanations will be suggested, which may demand many years of investigation.

Shortly after the gene linkage was published, Peter Little wrote a *Nature* News & Views article[9] on why the search for the HD gene had been so protracted. He concluded "Isolating the gene is, in truth, only the end of the beginning."

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