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 CLINICAL PRACTICE IN MEDICAL GENETICS
 

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## Predictive testing for Huntington's disease: after the gene

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### Abstract

**The discovery of a mutation responsible for Huntington's disease (HD) offers the possibility of accurate predictive testing, as well as hope for treatment or prevention of this disease. We urge caution in the use of this new test as considerable ethical and counselling problems still exist, and new issues have arisen. The current guidelines for predictive testing should still apply, since it remains vital that subjects and their families have time to come to terms with the diagnosis of HD, and the implications of testing. Mutation analysis may allow the diagnosis of HD in isolated cases, or reverse a test result produced using linkage. Problems will arise as those at 25% risk may now receive a result despite the lack of support of their parent at 50% risk who may not wish to have their own status defined. In addition, couples who seek the exclusion test in pregnancy may find it difficult to investigate the pregnancy without producing information on themselves. Different centres should cooperate in maintaining the confidentiality of family members, ensuring that adequate counselling is given before results are produced which may affect the wider family.**

*(J Med Genet* 1993;30:1036-8)

The gene responsible for Huntington's disease (HD) has been isolated<sup>1</sup> after a search which has taken 10 years.<sup>2</sup> This finding offers new hope for treatment or prevention for the families affected by this neurodegenerative disorder, but we urge caution in its application in clinical practice.

Presymptomatic predictive testing using linked DNA markers has been available since 1987.<sup>3,4</sup> Family studies have been necessary to establish segregation of genetic markers within the disease locus in any family. This has meant that for some subjects, testing has not been possible, as not enough relatives are available or wish to cooperate, and some families are genetically uninformative. In addition, there has always been the possibility of error because of recombination between the gene and the linked genetic markers.

These technical problems will now be greatly reduced. Once the laboratory tech-

niques are established for clinical use it will be possible, using their blood sample, to tell an at risk subject whether or not he or she carries the mutation responsible for this disease. The procedure will be much faster, especially since the polymerase chain reaction will be the technique of choice for defining the polymorphic trinucleotide repeat which is expanded and unstable on HD chromosomes.<sup>1</sup> It remains desirable to analyse DNA from an affected relative and confirm that this mutation is the cause of HD in the family. Misdiagnosis of HD does occur, and it is not yet entirely clear that HD is genetically homogeneous at a mutational level. Thus identification of the HD mutation will have wide diagnostic and predictive applications. Some problems of predictive testing, however, especially those related to ethical and counselling issues, have not gone away. The purpose of this article is to discuss these areas of potential difficulty.

### Predictive testing programmes

International guidelines for presymptomatic predictive testing were prepared by the members of the World Federation of Neurology Research Group on Huntington's Chorea in 1989 in conjunction with many lay HD organisations from all over the world.<sup>5</sup> In 1992, the United Kingdom Huntington's Disease Prediction Consortium published its recommendations for predictive testing.<sup>6</sup> Most centres in the UK use protocols which conform to the standards set by the UK Consortium, and the guidelines are considered as minimum requirements for any centre planning to offer such tests. Specialists in other fields, such as cancer genetics and psychiatric genetics, are looking to the experience of these centres to plan the testing of those at risk of inherited cancers and Alzheimer's disease.

The need for a careful, structured period of reflection before making a decision to undergo predictive testing is recognised by all in this field. Understanding the procedure and its limitations is an important component of the test. Because of the previous need for family studies, and the time that this inevitably takes, it has been possible to allow a sufficient interval for any person to reconsider their decision to take the test, and to assess the impact on his or her family of any result produced. It is clear

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Received 12 August 1993.  
Accepted 8 September 1993.

that individual testing for a mutation will remove the natural barrier to hasty decision making which was created by family studies. It is important that the test programmes continue to offer time for reflection before receiving a result, with at least two counselling sessions with a clinical geneticist or another specialist with appropriate training.

There are continuing concerns about the ethics of predictive testing, since there is still no cure for this disease, and the benefits of testing are unproven. The effects of test results on subjects and their families is the subject of intensive study by several centres from the UK Prediction Consortium and others from around the world.

Those centres who presently offer the predictive test have cooperated in the past to produce the most accurate information for family members scattered between the various centres. This cooperation must now be structured so that revised results are not produced inadvertently for family members from other areas. The status of a parent may be clarified or revised, or a different risk may be given to someone who received a predictive test result as a result of linkage analysis, but where subsequent analysis of the gene changes that result. The extent of the information available to the family should be considered, and counselling offered to all those who may be affected by any new result.

#### **Research samples**

Many laboratories in the UK have samples stored from earlier family studies and 'for future research' which could now produce important information about, for example, late onset cases, previously unsuspected cases, and cases wrongly diagnosed.<sup>7</sup> The counselling of their families is crucial. When critical persons are now dead, family members should be approached about the power of the information which could be produced for them. All results should be treated in confidence, and results from samples taken for research purposes ought not to be given to the patients or their families. New samples should, ideally, be obtained for the purpose of producing a result for a person (unless the key subject has died), consent should be given, and counselling provided about the implications of any result.

#### **Exclusion testing in pregnancy**

When applied to pregnancies, the exclusion test has provided people who do not wish to know their risk status with the opportunity to have children with a negligible risk of developing HD. For those with uninformative family structures for predictive testing, the option of evaluating the status of the fetus was valuable. Those who have terminated an 'at risk' fetus after these tests may now find that they do not have the mutant gene after all. These patients will need sensitive counselling which takes these factors into account before they receive predictive test results.

The dilemma now is whether or not the new

test should be applied to those who do not wish to have predictive testing themselves, but only want to ensure that they have children who are not at risk. An alternative is to continue exclusion testing using linked markers and to abort the fetus who is at 50% risk, knowing that it would be possible to produce an accurate result and save the 50% of fetuses who are in fact unaffected. Each couple seeking exclusion testing must be fully informed of the information which can be made available. The International Huntington's Association suggests that centres should still offer exclusion testing using linkage analysis to couples who seek it, although there are clinicians who would not support this view.

#### **Those at 25% risk**

There are many for whom the predictive test has not been possible because an at risk parent would not undergo testing themselves. There is now no need for this intervening generation to give their blood sample, and therefore the prospect arises of people finding out their high risk status because their son or daughter has been shown to have the mutation. These people may be ill-prepared for such news. Great care should be taken with such families and every effort made to ensure that the intervening generation receives adequate information and counselling before their offspring receive a test result.

#### **Diagnosis**

The diagnosis of Huntington's disease is not always straightforward, particularly if there is no family history. Geneticists and neurologists can now be expected to verify the diagnosis in suspected or doubtful cases of HD by mutation detection. The ability to use a single blood test to make the diagnosis will dramatically change the investigation and management of someone believed to be affected by Huntington's disease. It is important that the resulting information is handled with care. For some families the diagnosis of an inherited disease will be unexpected and devastating. Genetic counselling must be offered to family members.

There are those with a family history of the disease, and suspicious signs, who may refuse investigation. They have that right, but their offspring have the right to make decisions about their own future and seek testing themselves. The diagnosis may be thrust upon some subjects despite their reluctance to be investigated.

With such investigative power it is reasonable to suppose that general practitioners, neurologists, psychiatrists, and other clinicians will routinely take blood from appropriate patients so that it can be tested for the HD mutation. If the patient is able to give informed consent for such an investigation then it should be obtained before testing is performed. Counselling must be provided for those family members of the new cases by

centres recognised as having experience of Huntington's disease. Care must be taken to protect asymptomatic subjects from casual prediction of their status. There is also a risk that subjects at risk with symptoms such as depression will be subjected to a 'diagnostic' test which is in fact predictive.

Who should request and coordinate these tests? In this era of the free market, it is entirely likely that laboratories in the United Kingdom independent of the National Health Service may offer DNA analysis of the HD gene. It is possible that insurance companies and potential employers may wish to make screening for HD part of their medical examination, with or without the permission of the person concerned. It is vital that the standards for predictive testing set by geneticists in the

UK are maintained now that the gene has been defined.

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