HUNTINGTON'S DISEASE

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SUMMARY

Huntington's disease (HD) is a late-onset degenerative disorder of the central nervous system, caused by a dominantly inherited mutation in a gene on chromosome 4p. The identification of the trinucleotide repeat mutation responsible for this disorder has been an important step towards understanding the molecular pathology of HD, but in the meantime has also made it possible to offer predictive testing and prenatal diagnosis to individuals at high genetic risk. Predictive testing offers obvious benefits for those who receive a favourable result, but also runs the risk of significant psychological and social problems for the families involved. Uptake of testing to date has been limited. Prenatal testing where the pregnancy is at 25% risk carries the same disadvantages as adult predictive testing, because an unfavourable result would also establish that the at-risk parent is a gene carrier; prenatal exclusion testing offers an alternative method of detecting and terminating at-risk pregnancies without revealing the genetic status of the at-risk parent.

KEY WORDS: Huntington's disease; genetic testing; prenatal diagnosis

INTRODUCTION

Huntington's disease (HD) is a chronic, degenerative disorder of the central nervous system which is inherited as an autosomal dominant trait. The characteristic clinical features were first described by George Huntington in 1872 (Huntington, 1872) and include motor, cognitive and behavioural abnormalities; onset occurs most commonly between the ages of 30 and 50 years, and the disease follows a progressive course with a mean interval from diagnosis to death of 17 years (Quarrell and Harper, 1991). Motor abnormalities usually start with involuntary choreiform movements (hence the earlier name of Huntington's chorea), which increase in severity for the first few years but eventually fade away again to be replaced by bradykinesia and hypokinesia or rigidity, which is the real cause of the motor disability in this disorder. Increasingly, the patient develops dysarthria, dysphagia and impairment of balance, gait and coordination. The underlying hypokinetic state gradually comes to dominate the clinical picture so that by the later stages the patient may be completely bedbound or confined to a wheelchair. Although HD is usually thought of as a neurological disorder, the motor symptoms are often preceded by behavioural abnormalities including depression, anxiety, irritability and changes of personality (Folstein et al., 1983a,b) which in many cases cause much more disability than the neurological problems. Suicide is substantially more common than in the general population, especially during the early stages (Schoenfeld et al., 1984; Farrer, 1986). As the disease progresses patients invariably develop a form of dementia with poor concentration, difficulty in switching attention between different tasks, inefficient use of memory, impairment of executive functions and marked slowing of mental activity.

GENETICS

The disorder is inherited as an autosomal dominant trait with complete penetrance. Children of affected individuals have a 50:50 risk of developing the disorder in their turn. HD is unusual among human genetic disorders in that it
clinically from heterozygotes (Wexler et al., 1987; Myers et al., 1989). This finding suggests that the mutation responsible confers a gain of function in some way, rather than disrupting the action of the normal gene. Although penetrance is complete if the individual carrying the mutation lives long enough, the age at onset can vary from early childhood—about 4% of heterozygotes have an onset before the age of 20 (Walker et al., 1981)—to the late 70s or beyond. The resulting uncertainty causes great problems for the offspring of affected individuals, who have to cope with the possibility that they are carrying the HD gene and the difficulty this creates for making decisions about career, marriage and reproductive options (Wexler, 1979). For every individual affected with HD at any given time, there are approximately another 10 at high genetic risk (50% or 25%) who cannot be sure that they have escaped the disease until long after their own families are complete.

There is no cure for HD at present, and no known treatment capable of delaying the onset of the disorder. However, the outlook for affected families has improved greatly during the last 15 years with the advent of modern molecular genetic techniques. The discovery of genetic markers linked to the disease on the short arm of chromosome 4 (Gusella et al., 1983) and subsequent identification of the mutation which causes the disease (Huntington's Disease Collaborative Research Group, 1993) have opened up the possibility of new treatments based on a clear understanding of the molecular pathology of the disorder. The mutation responsible for the disease has turned out to be a (CAG), trinucleotide repeat sequence close to the 5' end of the gene, which is expanded and unstable on affected chromosomes. Most unaffected individuals in the general population have alleles with 11–31 copies of the (CAG) repeat, while affected individuals usually have in excess of 38 repeats (Huntingdon's Disease Collaborative Research Group, 1993; Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993). The situation is not completely clear for the intermediate range between 32 and 38 repeats; recent research suggests there may well be a small region of overlap between the normal and abnormal ranges, with at least one affected case reported to have 36 repeats but several individuals who remain clinically unaffected at an advanced age with up to 39 repeats (Rubinsztein et al., 1966). This mutational mechanism has recently been identified as the basis for a number of inherited disorders including Myotonic Dystrophy, Fragile X Mental Retardation, Spino-Bulbar Muscular Atrophy (SBMA), Dentato-Rubral Pallido-Luysian Atrophy (DRPLA), Spino-Cerebellar Atrophy types I and III (SCA-I and SCA-III) and most recently, Friedreich's Ataxia. Although these disorders are caused by various trinucleotide repeat mutations at different chromosomal locations, those caused by (CAG) repeats are all neurodegenerative diseases with a similar range of normal and abnormal allele sizes, and they are all characterised by onset in middle age followed by a progressive course (Table I).

The disorders caused by unstable (CAG)\textsubscript{n} mutations also resemble one another in that most demonstrate the phenomenon of anticipation (earlier age at onset or increasing clinical severity in successive generations) when the gene is transmitted by the father, but not when it is transmitted by the mother. Age at onset of HD in the offspring is quite strongly correlated with age at onset in the affected parent (Farrer et al., 1984; Myers et al., 1985) but it has been known for many years that juvenile-onset cases are almost always associated with paternal transmission of the gene (Merritt et al., 1969; Stevens, 1976; Newcombe et al., 1981) and that paternal transmission is associated with a slightly earlier onset in the child than in the father across the whole range of ages at onset (Myers et al., 1983; Farrer and Conneally 1985; Ridley et al., 1988). The explanation for this has become clear with the discovery that age at onset is correlated with the number of (CAG) repeats, larger expansions being associated with earlier onset (Huntington's Disease Collaborative Research Group, 1993) although it is clear that other factors must also be involved as repeat number only explains about 50% of the variance in age at onset and even less in older patients (Andrew et al., 1993). When the gene is transmitted by the mother, and in most cases where transmission is from an affected father, the child inherits a gene with approximately the same number of repeats and has a similar age at onset; however, in about a third of cases with paternal transmission the offspring inherits a larger number of repeats than in the affected parent and has an earlier onset (Table II). This may be a matter of particular concern to males at risk for HD, who run a small but not insignificant risk of passing on the disorder to their children in its juvenile-onset form.
Table I—Disorders caused by trinucleotide repeat mutations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Repeat</th>
<th>Normal range</th>
<th>Full mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR1 (Fragile X)</td>
<td>CGG</td>
<td>5–52</td>
<td>230–&gt;1000</td>
</tr>
<tr>
<td>SBMA</td>
<td>CAG</td>
<td>11–33</td>
<td>40–62</td>
</tr>
<tr>
<td>HD</td>
<td>CAG</td>
<td>10–39</td>
<td>36–100</td>
</tr>
<tr>
<td>DRPLA</td>
<td>CAG</td>
<td>7–23</td>
<td>49–75</td>
</tr>
<tr>
<td>SCA I</td>
<td>CAG</td>
<td>6–44</td>
<td>40–82</td>
</tr>
<tr>
<td>SCA III (Machado-Joseph)</td>
<td>CAG</td>
<td>13–40</td>
<td>68–79</td>
</tr>
<tr>
<td>DM</td>
<td>CTG</td>
<td>5–37</td>
<td>100–4000</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>GAA</td>
<td>7–22</td>
<td>200–&gt;900</td>
</tr>
</tbody>
</table>

Table II—Anticipation with paternal transmission in Huntington’s disease: number of CAG repeats in fathers transmitting the disorder and their affected offspring

<table>
<thead>
<tr>
<th>Number of CAG repeats (father)</th>
<th>Number of CAG repeats (child)</th>
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<tbody>
<tr>
<td>48</td>
<td>45</td>
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<td>44</td>
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<td>42</td>
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<td>43</td>
<td>51</td>
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PREDICTIVE TESTING

The practical goal of research into the molecular genetics of HD is to develop new approaches to treatment of the disorder, and work is in progress to elucidate the molecular mechanisms by which the mutation produces the characteristic pathology of HD. In the meantime, the discovery of the gene has also created the possibility of predictive testing both for at-risk individuals who have not yet developed symptoms, and for prenatal testing to determine whether an at-risk fetus is a carrier of the HD mutation. Initially this was done using RFLP markers known to be linked to the disease locus, but this has now been replaced by a direct test measuring the number of repeats at the HD locus which allows quicker, cheaper and more accurate prediction of carrier status.

Predictive testing offers the prospect of freedom from the psychological burdens associated with being at risk, if the individual is shown not to be a carrier of the disease mutation. It also means that all the descendants of someone receiving a favourable test result will no longer be at risk. Unfortunately, this has to be balanced against the potential psychological problems facing those who receive an unfavourable result. These individuals will know that they are inevitably going to develop the family illness if they live long enough, and it may be very difficult to maintain a positive attitude and avoid despair in these circumstances (Wexler et al., 1985). It has been argued that even those who prove to carry the gene will benefit from the resolution of uncertainty and may be able to use the information to plan their future lives more effectively (Bates, 1981; Thomas, 1982). However, molecular genetic testing does not allow useful prediction of the likely age at onset (Craufurd and Dodge, 1993) and the test may therefore replace concern about whether the individual will develop HD with the equally difficult question of when this will occur. Wexler et al. (1985) also pointed out that predictive testing may have unforeseen effects on other family members, and that even those receiving favourable results may experience feelings of guilt about being more fortunate than their siblings—the so-called 'survivor syndrome'. In addition to these psychological problems, concern has been expressed about practical problems such as the possibility of discrimination by insurance companies or potential employers (Craufurd and Harris, 1986; Berg and Fletcher, 1986).

In spite of these potential problems, several studies carried out just before the introduction of predictive testing reported that between 56%–80%
of at-risk individuals would choose to have a predictive test if this were available (Stem and Eldridge, 1975; Barette and Marsden, 1979; Teltscher and Polgar, 1981; Tyler and Harper, 1983; Kessler, 1987). In practice, the uptake of predictive testing has been much more limited and suggests a considerable degree of caution among the at-risk population about the potential psychological problems involved. A study of 110 previously counselled at-risk individuals in regular contact with the Manchester Genetic Family Register service, who were contacted and offered the test, found that only 8 (7.3%) had actually gone ahead while 9 were still undecided, giving a maximum possible uptake of 15.5% (Craufurd et al., 1989). Analysis of uptake figures for the UK as a whole shows that almost two thirds of those who do proceed with testing are female (Tyler et al., 1992); this sex difference may well reflect concern about passing on the gene to future generations of the family and the generally greater role of women in the process of making reproductive decisions (Bloch et al., 1989), although it may also be due to different methods of coping used by men and women.

The data available to date suggest that most people cope surprisingly well after adverse predictive test results (Bloch et al., 1992; Wiggins et al., 1992; Tibben et al., 1993; Codori and Brandt, 1994) although many of these authors have drawn attention to the difficulties sometimes experienced by partners of predictive test patients and even by those receiving favourable results (Huggins et al., 1992). Even so, the decision about whether to have a predictive test is clearly a difficult one and a consensus has emerged about the need for adequate counselling and support to be offered both before and after such tests are carried out. Ethical guidelines have been published by a joint committee of the International Huntington Association and the World Federation of Neurology Research Group on Huntington's chorea (International Huntington Association, 1994) and there is a detailed protocol which is used by all centres offering predictive testing in the United Kingdom (Craufurd and Tyler, 1992). It is recommended that predictive testing should only be offered in specialist genetic counselling units knowledgeable about the issues involved, that care should be taken to ensure the decision is solely the choice of the individual concerned (without pressure from third parties, family or otherwise) and that testing should not be available to children under the age of majority of the country concerned. Testing should only take place in the context of a suitable protocol for pre- and post-test counselling and support, which in the UK protocol involves a minimum of two pre-test sessions separated by an interval of a few weeks, so that the person has an opportunity to reflect on the issues involved. Those in stable long-term relationships are advised to involve their spouse/partner in the decision making process, and everyone requesting testing is encouraged to select a companion to accompany him or her throughout all stages of the testing process. Results should be given as soon as reasonably possible after completion of the test, but laboratories are advised not to disclose the outcome to the clinician involved until very close to the time when the result is due to be given to the patient; this avoids problems if the patient has second thoughts and contacts the clinician requesting further counselling.

**PRENATAL TESTING**

One of the more common reasons mentioned by those requesting predictive tests is that the result will help to make reproductive decisions. In a study of 63 individuals receiving predictive test results in The Netherlands, this was cited as a major reason by 60% of subjects (Tibben et al., 1993). While some at-risk individuals may seek predictive testing with the intention of limiting their families, or refraining from having children altogether if they prove to be carriers of the HD mutation, there are many others who would decide to go ahead and have a family if it were possible to be sure that the children do not inherit the abnormal gene. Prenatal testing, either by linkage or direct mutation testing, provides a way to achieve this. In Tibben's study (Tibben et al., 1993) there were 17 carriers who had not previously regarded their families as complete, of whom 5 had decided to refrain from having more children when interviewed six months after receiving the unfavourable result, while 12 still wished to enlarge their families of whom 7 were definitely considering prenatal testing with selective termination of pregnancy in the event of an affected fetus.

Prenatal testing differs little from adult presymptomatic testing when one of the parents is
affected or has been given an unfavourable predictive test result, and the advent of direct mutation testing has greatly simplified the process of prenatal diagnosis. Fetal DNA can be obtained by chorionic villus biopsy (CVB), and the test can be carried out directly without the need to culture cells, allowing the result to be obtained within the first trimester. However, it is fairly uncommon for couples to embark on a pregnancy after one of them has been diagnosed with HD, perhaps because there are concerns not only about the risk of passing on the gene to another generation, but also about the ability of the affected individual to function adequately as a parent until the child is old enough for this to be no longer necessary. Prenatal testing is more frequently requested by couples where one partner is at 50% risk, but may perhaps prefer not to know whether he or she is a carrier of the HD mutation. In this situation a test which demonstrated that the fetus carries an expanded HD allele would simultaneously reveal that the at-risk parent is also a carrier. This creates a number of problems. One option would be for the at-risk parent to undergo predictive testing first, but if preparation for this were not already under way before the pregnancy it would be impossible to adhere to the ethical guidelines and allow an adequate interval for reflection within the time available; furthermore, the relatively low uptake of predictive testing among the at-risk population means that most parents in this situation would ideally prefer not to be tested themselves.

An alternative solution for prospective parents who would prefer not to be tested themselves but feel strongly that they could not risk passing the disease on to yet another generation is prenatal exclusion testing (Hayden et al., 1987; Quarrell et al., 1987), where linked genetic markers are used to determine whether the HD allele passed to the fetus by the at-risk parent originated with the affected or the unaffected grandparent. If the fetus has inherited the relevant markers from the affected grandparent it shares the same 50:50 risk as the intervening parent and the pregnancy is terminated, whereas the haplotype from the unaffected grandparent leaves the fetus at very low risk and the parents can be reassured. The advantage of prenatal exclusion testing is that it does not provide any additional information about the carrier status of the at-risk parent, although many couples have difficulty grasping this point (Tyler et al., 1990; Adam et al., 1993). The disadvantage is that an unfavourable result leaves the fetus at 50% risk, and the couple are faced with the prospect of terminating a wanted pregnancy in the knowledge that this may eventually prove to have been unnecessary. The ethical justification for selective abortion in these circumstances is controversial (Post, 1992) and although it is clearly a matter for personal choice, the uncertainty of the result and the possibility that science may devise an effective cure for HD before the child is old enough to be affected makes the decision a very difficult one for many couples. Some have chosen to undergo a stepwise procedure (Fahy, 1989) involving a preliminary exclusion test, with subsequent definitive testing for themselves and the fetus only if the exclusion result is unfavourable; this approach removes the risk of terminating an unaffected pregnancy, but has the drawback that an unfavourable result leaves the at-risk parent having to cope with the loss of a wanted pregnancy at the same time as coming to terms with his/her own unfavourable predictive test result for which neither partner has been adequately prepared. Although this is clearly an unsatisfactory situation, it may be more acceptable to some at-risk individuals than terminating a possibly unaffected pregnancy, and does at least offer a better chance of a favourable result than going straight to predictive testing because there is a 25% probability that the fetus will be affected while their own risk is 50%. Essentially the same result can nowadays be achieved more simply by testing the fetus directly for the HD mutation, although this does not provide the useful pause for reflection offered by the 'exclusion-definitive' approach.

Another ethical problem associated with prenatal testing arises when at-risk parents request prenatal diagnosis and subsequently change their minds about the decision to terminate the pregnancy. Even with exclusion testing, a fetus which has inherited linked markers from the affected grandparent will share with the at-risk parent a 50% risk of HD; if the pregnancy were allowed to continue and the at-risk parent subsequently developed symptoms, it would immediately be apparent that (in the absence of recombination) the child must also be a carrier of HD. Not to terminate the pregnancy after an unfavourable prenatal test result creates a situation where the child potentially will have to grow up with the knowledge that he or she will one day develop HD, and deprives the child of any
personal say in this decision. While some parents may believe they are entitled to this information about their child, nothing can be done at present to modify or delay the onset of the disease and there is a widespread consensus among clinical geneticists that testing children for late-onset genetic diseases in these circumstances is unethical (Clinical Genetics Society, 1994). It is therefore inappropriate to carry out prenatal testing if the at-risk couple do not intend to terminate the pregnancy in the event of an unfavourable result (Quarrell et al., 1987) although there have been reports of couples who start out with this intention and have a last-minute change of mind (Tolmie et al., 1995).

It is also important for couples contemplating prenatal testing to consider the implications for any pre-existing children, who will have to know in due course that they are at risk for HD, while any siblings born after prenatal testing are not. There is a risk that this will create problems with family relationships later on. A very similar problem applies to subsequent pregnancies; having once terminated a pregnancy because of an unfavourable prenatal test, it may be very difficult to adopt a different strategy later on and embark on a pregnancy without testing. It is possible that a couple may find the psychological cost of terminating a much-wanted pregnancy too high to be able to face the prospect of going through it all again after another unsuccessful test, but at the same time feel constrained by a sense of obligation to the lost child that makes it impossible to simply take the risk without testing.

The development of a rapid, direct PCR test for the HD mutation has greatly simplified the process of prenatal diagnosis from the laboratory perspective, because it is no longer necessary to analyse DNA samples from the parents and grandparents of the fetus to be tested. The problem of identifying an informative marker for linkage testing can sometimes be quite time-consuming and involve a considerable amount of work, often carried out under pressure, in order to allow a first-trimester termination of pregnancy in the event of an unfavourable result. In circumstances where couples have decided to have exclusion testing by linkage analysis, it is always preferable to obtain DNA from the prospective parents and grandparents in advance so that informative markers can be identified before prenatal testing is carried out. Linkage analysis is less precise than direct mutation testing because of the need to allow for genetic recombination between the marker and the HD locus. It is also more difficult to detect inconsistent haplotypes due to laboratory or clerical errors (or non-paternity) when analysing marker data from small family groups (King et al., 1993). However, in the case of exclusion testing it is not possible to avoid the potential for this type of error by typing larger numbers of relatives without the risk of obtaining information which would be fully predictive for the at-risk parent (Millan et al., 1989). In spite of all the advantages of the new direct test there is still a strong case for retaining the option of exclusion testing for those who do not want to know their own carrier status (Rubinsztein et al., 1994) and direct testing is not without its own technical problems, notably the difficulty interpreting the significance of intermediate alleles and the theoretical possibility of misleading results due to mitotic instability of the CAG repeat copy number. Reassuringly, a recent study by Benitez et al. (1995) of two fetuses aborted after prenatal diagnosis showed the same number of repeats in many different fetal tissues as well as the sample taken at CVB; the authors suggest that previous reports of somatic instability in tissues from affected patients may be a secondary consequence of neuronal degeneration and gliosis.

As with predictive testing, early surveys suggested a high level of demand for prenatal testing among the at-risk population. When linkage markers for the HD gene were first identified, three studies of at-risk people in the USA indicated that between 42% and 66% of those surveyed would consider making use of prenatal testing, although in each case rather fewer said they would terminate in the event of a high-risk pregnancy (Kessler et al., 1987; Markel et al., 1987; Meissen and Berchek, 1987). On the other hand, a very similar study carried out at exactly the same time in New England found that only 12% of respondents thought they were likely to use prenatal testing (Mastromauro et al., 1987) and a study looking at the attitudes of young women in Belgium found that although 50% of those surveyed found prenatal testing for late-onset disease acceptable, only 28% of the group would be prepared to terminate a pregnancy in these circumstances (Decruyenaere et al., 1993). Among subjects actually requesting presymptomatic testing in North West England (Craufurd, 1989) 81% of those regarding their families as incomplete said they would consider...
prenatal testing in pregnancy, but only 65% would consider termination of pregnancy and this fell to 35% when the risk to the fetus was 50% (the outcome of an unfavourable exclusion test). In the Canadian predictive test programme, attitudes were very similar with 29% who would consider prenatal testing with a view to selective termination of pregnancy (Bloch et al., 1989). However, the partners of predictive test patients appear to be more in favour, with 75% stating that prenatal testing should be available (Evers-Kiebooms et al., 1990), while a survey of 308 clinicians in the UK concerning knowledge and attitudes to prenatal testing for HD and other serious genetic disorders, found that 95% thought it was always or often appropriate to offer the test (Firth and Lindenbaum, 1992).

In practice, the uptake of prenatal testing has been even less than these figures would suggest. In the first five years of the predictive test programme in Canada (Adam et al., 1993), there were 47 pregnancies, of whom 14 (30%) requested prenatal testing while 24 (51%) did not and 9 (19%) had no need because they had already received a favourable predictive test result; 7 subsequently decided not to go ahead, leaving an overall uptake rate for prenatal testing of 7/38 (18%). The most frequently cited reason for not having a prenatal test was the hope that a cure would be found in time for their children to benefit from this. World-wide, a recent international survey identified a total of less than 250 prenatal tests performed between 1986 and the end of 1994 whereas the number of predictive tests during the same period amount to several thousand (Evers-Kiebooms, 1995).

CONCLUSION

The recent major advances in understanding the molecular basis of Huntington's disease have created a climate of considerable optimism about the development of new approaches to treatment in the foreseeable future. The same advances have also provided at-risk individuals with a range of choices such as predictive and prenatal testing which potentially give them much more control over the way the disorder affects their lives and those of their families; however, these choices also bring new responsibilities and ethical problems which can be very difficult to resolve. Prenatal testing in particular has the potential to impose severe strains and tensions on relationships, especially where it is the male at risk while the female partner is the one who may have to go through the trauma of an unwanted termination of pregnancy. There are no simple solutions to these problems which can be applied to everyone, and it is the art (and duty) of the genetic counsellor to guide our patients through these difficult waters and help them find their own course in the full knowledge of the dangers that lie ahead.

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