Clinical practice in medical genetics

Guidelines for the molecular genetics predictive test in Huntington's disease

Audrey Tyler (UK)*, Ralph Walker (Canada), Loe Went (Holland)*†, Nancy Wexler (USA)*.

The committee is very much indebted to the late Chris De Somviele (Belgium), who has been the driving force in the first years.

Recommendations concerning the use of a predictive test for the detection of Huntington's disease (HD) were drawn up by a committee consisting of representatives of both the International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea.

The establishment of a committee with the specific task of preparing such guidelines was decided at the WFN and IHA conferences in Lille, September 1985. The first recommendations were adopted by both organisations at their respective meetings in Vancouver, Canada, 30 June to 3 July 1989 and published in *J Neurol Sci* 1989;**94**:327–32 and *J Med Genet* 1990;**27**:34–8.

Revision of these Guidelines was necessary in view of the publication of the detection of the gene defect in March 1993.

Members of the committee were or are (in alphabetical order): Jytte Broholm (Denmark)*, Jean-Jacques Cassiman (Belgium)*, David Craufurd (UK)*, Arthur Falek (USA)*, Carys Farmer-Little (France/UK)†, Michael Hayden (Canada)*, Robyn Kapp (Australia)*, Kai Krahnen (Germany)†, Ascuncion Martinez-Descals (Spain)*, Marion Mol (Belgium)*, Ntinos Myrianthopoulos (USA), Henry Petit (France)*†, Kimberly Quaid (USA)*, Chris De Somviele (Belgium)†, Elaine Taylor (Canada),

* Present members.
† Members of the original committee.

Introductory remarks

(1) The present document provides realistic, ethical principles based on current knowledge and techniques in molecular genetics.
(2) We are convinced that the different stages of these recommendations are inextricable parts of a whole. The test should only be offered if all the recommended provisions are available.
(3) These recommendations are set forth by members of the HD family organisations and the biomedical community as guidelines to protect at risk persons; therefore, it is of the utmost importance that the guidelines are at all times available to them so that they can freely make an informed decision.
(4) The guidelines are also intended to assist clinicians, geneticists, and ethical committees as well as lay organisations to resolve difficulties arising from the application of the test. The committee is willing to provide advice on problems related to the interpretation of these guidelines.
(5) In these guidelines the use of the DNA test for diagnostic purposes, for example, in the case of a suspicious or uncertain clinical picture, has not been considered, but it may have a profound (predictive) effect on sibs and other relatives.

Recommendations

1 All persons who may wish to take the test should be given up to date, relevant information in order to make an informed voluntary decision.

2 The decision to take the test is the sole choice of the person concerned. No requests from third parties, be they family or otherwise, shall be considered.

2.1 The test is only available to persons who have reached the age of majority (according to the laws of the respective countries).

Comments

1 The highest standards of counselling should be available in each country. It is recommended that informed consent for the test be documented with the signature of the person to be tested and the professional responsible for the counselling as a standard medical practice.

2 The person must choose freely to be tested and not be coerced by family, friends, (potential) partners, physicians, insurance companies, employers, governments, etc.

2.1 A prenatal test may be an exception to this rule. Testing for the purpose of adoption should not be permitted, since the child to be adopted cannot decide for itself whether it wants to be tested. It seems appropriate and even essential, however, that the child when reaching the age of reason should be informed about its at risk status.

Correspondence to
Dr L Went,
Terweeweg 142,
2341 CX Oegstgeest,
The Netherlands.

2.2	Each participant should be able to take the test independently of his/her financial situation.	2.2 Each national lay organisation should use its influence with government departments, public and private health insurers, etc, to reach this goal.
2.3	Persons should not be discriminated against in any way as a result of genetic testing for Huntington's disease.	
2.4	Extreme care should be exercised when testing would provide information about another person who has not requested the test.	2.4 This will arise when a child(ren) at 25% risk request(s) testing with full knowledge that his/her parent does not want to know his/her status. Every effort should be made by the counsellors and the persons concerned to come to a satisfactory solution of this conflict. A considerable majority of representatives from the lay organisations feel that if no consensus can be reached the right of the adult child to know should have priority over the right of the parent not to know.
2.5	For applicants with evidence of a serious psychiatric condition, it may be advisable that testing should be delayed and support services put into place.	
2.6	Testing for HD should not form part of a routine blood investigation without the specific permission of the subject.	2.6 Such a specific permission should in principle also be required for symptomatic persons.
2.7	Ownership of the test results remains with the person who requested the test. Legal ownership of the stored DNA remains with the person from whom the blood was taken.	2.7 The consent form should address this issue. Local legal opinions may be helpful.
2.8	All laboratories are expected to meet rigorous standards of accuracy. They must work with genetic counsellors and other professionals providing the test service.	2.8 The lay organisations can provide an inestimable service in enquiring about the rigorous standards of the laboratory and can assist persons who want to be or have been tested with their enquiries and concerns.
2.9	The counsellors should be specifically trained in counselling methods and form part of a multidisciplinary team.	2.9 Such a multidisciplinary team should consist, for example, of a geneticist, neurologist, social worker, psychiatrist, and somebody trained in medical ethical questions.
3	The participant should be encouraged to select a companion to accompany him/her throughout all the different stages: the pre-test, the taking of the test, the delivery of the results and the post-test stage.	3 This companion may be the spouse/partner, a friend, a social worker, or any person who has the confidence of the participant. It may not be appropriate that the companion should be another at risk person.
3.1	The counselling unit should plan with the participant a follow up protocol which provides for support during the pre- and post-test stages, whether or not a person chooses a companion.	3.1 Support should be available close to the person's community.
4	Testing and counselling should be given within specialised genetic counselling units knowledgeable about molecular genetic issues in Huntington's disease, preferably within a university department. These centres should work in close collaboration with the lay organisation(s) of the country.	4 Often the test will be conducted at a site different from the counselling centre. If no lay organisation exists in the country, the centre should contact the IHA.
4.1	The laboratory performing the test should not communicate the final results to the counselling team until very close to the time the results are given to the participant.	4.1 The aim is to protect the participant from the possibility of counselling bias at any time (see also comment 5.2.5).
4.2	Under no circumstances shall any member of the counselling team or the technical staff communicate any information concerning the test and its results to third parties without the written permission of the applicant.	4.2 Only in the most exceptional circumstances, for example, prolonged coma, death, etc, may information about the test result, if so requested, be provided to family members.

4.3	Neither the counselling centre nor the test laboratory should establish direct contact with a relative whose DNA may be needed for the purpose of the test without permission of the applicant and of the relative. All precautions should be taken when approaching such a relative.	
5	ESSENTIAL INFORMATION	5 "Essential information" means information which is absolutely vital to the whole test procedure.
5.1	GENERAL INFORMATION	5.1 This information should be both written and oral and be provided by the team responsible for the test service.
5.1.1	On Huntington's disease, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, options for procreation, availability of treatment, etc.	5.1.1 It must be pointed out that at this time neither prevention nor cure is possible.
5.1.2	On the implications of non-paternity (and non-maternity).	5.1.2 Genetic testing may show that the putative parent is not the biological parent; this aspect should be drawn to the attention of the applicant and discussed. With the presently available techniques of in vitro fertilisation etc, even occasional non-maternity may occur.
5.1.3	On lay organisations, including their documentation on HD, their addresses for help and social contacts, etc.	5.1.3 If no lay organisation exists in the country, contacts can be made with the IHA or lay organisation of a neighbouring country.
5.1.4	Psychosocial support and counselling must be available before the test procedure commences.	5.1.4 Lay organisations should be mentioned as an additional source of support and information.
5.2	INFORMATION PERTAINING TO THE TEST	
5.2.1	How the test is done.	
5.2.2	Possible need for DNA from one other affected family member and the possible problems arising from this.	5.2.2 Asking an affected person, who may be unaware of or unwilling to acknowledge his/her symptoms, to contribute a blood sample may be an invasion of privacy.
5.2.3	The limitations of the test (error rate, the possibilities of an uninformative test, etc).	
5.2.4	Although the gene defect has been found, the counsellor must explain that at the present time no useful information can be given about age at onset, on the kind of symptoms, their severity, or the rate of progression.	5.2.4 Much more information will be needed about implications of the number of repeats.
5.2.5	The predictive test indicates whether someone has or has not inherited the gene defect, but it does not make a current clinical diagnosis of HD if the gene is present.	5.2.5 Particular care should be taken with participants who are believed to be showing early symptoms of HD; however, persons with established, unacknowledged symptoms should not automatically be excluded from the test and should receive additional counselling.
5.3	INFORMATION ON CONSEQUENCES	5.3 All consequences have to be discussed, the presence or absence of the gene defect as well as not taking the test.
5.3.1	For the person him/herself.	
5.3.2	For the spouse/partner and children.	5.3.2 If the companion of the participant is not his/her spouse/partner, special consideration should be given to such spouse/partner.
5.3.3	For the affected parent and his/her spouse.	5.3.3 The feelings of this affected parent, who may well become aware of the results, must be taken into account.
5.3.4	For the other members of the participant's family.	5.3.4 Whatever information is obtained, it will influence the feelings of and the relationship with other relatives.

5.3.5 Socioeconomic consequences, including employment, insurance, social security, data security, and other problems which may occur as a consequence of the test result.

5.4 INFORMATION ON ALTERNATIVES THE APPLICANT CAN ADOPT

5.4.1 Not to take the test for the time being.

5.4.2 To deposit DNA for research.

5.4.3 To deposit DNA for possible future use by family and self.

5.4.4 DNA deposited under 5.4.2 above would be made available to the donor's family members at their request after the death of the donor if it is essential to obtain an informative result.

5.4.5 In the case of DNA deposited under 5.4.2 and/or 5.4.3 above, the unit collecting the DNA must provide a written declaration that samples will not be used for purposes other than specified in the said declaration with the exception of the provisions of 5.4.4.

6 IMPORTANT PRELIMINARY INVESTIGATIONS

6.1 It is important to verify that the diagnosis of HD in the person's family is correct.

6.2 Neurological examinations and psychological appraisal are considered important to establish a baseline evaluation of each person. Any other specialised tests are *always* non-compulsory; refusal may not affect participation in the test.

6.2 Refusal to undergo these and other additional examinations will not justify the withholding of the test from applicants.

7 PRENATAL DIAGNOSIS

7.1 It is essential that prenatal testing for the HD mutation should only be performed if the parent has already been tested. For a possible exception see 7.3.

7.1 It is highly desirable that both parents should agree to a prenatal test. If there is a conflict, every effort should be made by the counsellors and the couple to reach an agreement. Exceptional circumstances (for example, rape, incest) may justify deviating from this recommendation.

7.2 The couple requesting prenatal testing must be clearly informed that if they intend to complete the pregnancy if the fetus is a carrier of the gene defect, there is no valid reason for performing the test. Furthermore this situation is contrary to recommendation 2.1.

7.2 Testing a fetus carries with it a small additional risk of miscarriage and, possibly, of congenital abnormality.

7.3 Test centres may still perform an exclusion test for a future pregnancy if a 50% at risk person specifically requests it. For this test the person at risk, partner, parents, and fetus are tested only with adjoining DNA probes.

7.3 The purpose of the exclusion test, which was frequently performed before the gene defect itself had been found, was to permit a 50% at risk person to exclude the possibility of affected children without changing his/her 50% at risk status. This does include the termination of pregnancies of a 50% at risk fetus and continuation of pregnancies of a low risk fetus only.

8 THE TEST AND DELIVERY OF RESULTS

8.1 Excluding exceptional circumstances there should be a minimum interval of one month between the giving of the pre-test information and the decision whether or not to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the applicant's request.

8.2 The result of the predictive test should be delivered as soon as reasonably possible after completion of the test, on a date agreed upon in advance between the centre, the counsellor, and the person.

8.3 The manner in which results will be delivered should be discussed between the counselling team and the person.

8.4 The participant has the right to decide, before the date fixed for the delivery of the results, that these results shall not be given to him/her.

8.5 The results of the test should be given personally by the counsellor to the person and his/her companion. No result should ever be given by telephone or by mail. The counsellor must have sufficient time to discuss any questions with the person.

8.6 All post-test provisions (see section 9) must be available from the moment the test results are given.

9 POST-TEST COUNSELLING

9.1 The frequency and the form of the post-test counselling should be discussed between the team and the participant before the performance of the test, but the participant has the right to modify the planned programme. Although the intensity and frequency will vary from person to person, post-test counselling must at all times be available.

9.2 The counsellor should have contact with the person within the first week after delivery of the results, regardless of the test result.

9.3 If there has been no further contact within one month of the delivery of the test result, the counsellor should initiate the follow up.

9.4 It is essential that post-test counselling is made available regardless of the person's financial situation.

9.5 The lay organisation has an important role to play in the post-test period. The information and support that it can provide should always be offered to the participant, whether or not he/she belongs to that organisation.

8.1 Prenatal testing may be such an exception. Such an interval is necessary to give the person sufficient time to assimilate the pre-test information in order to make an informed decision. During this interval, specialists from the test centre must be available for further consultation.