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Before the mutation causing Huntington disease was identified, predictive testing of 25% at-risk persons with a 50% at-risk parent who did not wish to know his/her genetic status, was only possible by exclusion testing. The exclusion test, using linked markers, ensures the parent’s wish not to know because the parent’s risk is not changed. When mutation analysis became available in 1993, new testing options for 25% at-risk persons emerged: viz., the exclusion-definitive test and direct mutation analysis. These new tests not only disclose the risk of the test candidate, but may also change the risk of the at-risk parent and siblings. The testing options for 25% at-risk test applicants and their consequences are discussed and the testing procedures and results of testing 64 25% at-risk persons in the period 1987 to 1997 are described. Relatives received unsought information in 56% of the test procedures before and 34% after the mutation was identified. A decision tree and guidelines for predictive testing of 25% at-risk test applicants are proposed. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88: 662–668, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: predictive testing; Huntington disease; 25% at-risk individuals

INTRODUCTION

Huntington disease (HD) is an autosomal dominant, progressive neuropsychiatric disorder, usually presenting in adult life. Because the mean age at onset is 40 years with a range of 5 to 70 years, at-risk individuals may remain at risk for a long period of their life. The main clinical symptoms are chorea, dementia, and changes in personality, mood, and behaviour. The disease is incurable and leads to death usually within 17 years after onset, with a range of 2 to 45 years [Roos et al., 1993; Harper, 1996].

In 1983 the HD gene was localised on the short arm of chromosome 4 [Gusella et al., 1983] and in 1993 the gene was identified [Huntington's Disease Collaborative Research Group, 1993]. Before 1993 predictive testing of 25% at-risk persons with a 50% at-risk parent who did not wish to know his/her genetic status was only possible by exclusion testing using linked markers (Fig. 2). Blood sampling, informed consent, co-operation of the parent(s) and grandparent(s), and a three-generation pedigree were needed. In only half of the cases, when the risk could be excluded, a definitive result was obtained for the 25% at-risk person, which did not change the risks for the other family members.

After the gene was identified, any individual, even a 25% at-risk person, could apply for a direct mutation test. Blood sampling, co-operation, consent, or even acknowledgement of the at-risk parent is technically no longer needed and a definitive result is always obtained. Consequently the test result may well change the risk of the at-risk parent and siblings [Simpson et al., 1993]. Therefore, a serious conflict of interest between the 25% at-risk person and the 50% at-risk parent may arise. Whose right should have priority: the right of the adult child to know, or the right of the parent not to know? The International Huntington Association and World Federation of Neurology Research Group on Huntington’s Chorea [1994] have declared in their recommendations about the guidelines for the molecular genetics predictive test in HD that extreme care should be exercised in situations where the test might provide information about another person who has not requested the test. The 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.

The aim of this study was to evaluate predictive testing of individuals with a 25% risk for HD. The different
test procedures available for 25% at-risk applicants in different clinical situations are discussed. The test procedures performed in the period 1987 to 1997, both before and after mutation testing was available, the results obtained, and the problems encountered will be described. A decision tree and guidelines for predictive testing of 25% at-risk persons are proposed.

PATIENTS AND METHODS

Patients

In 1987, predictive testing for HD was introduced in The Netherlands within a structured testing procedure, which was centralised until 1994, in the Department of Clinical Genetics in Leiden. The applicants described in this study are those counselled in Leiden for the period October 1987 until September 1997. The general inclusion criteria for predictive testing are that the person be at risk for HD, and that major psychiatric illness and/or clinical signs of HD are absent. Patients have to be over 18 years old and well informed about the test and related consequences. Furthermore, testing should not provide unsought information for others and should not be performed on request of third parties [International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea, 1990, 1994]. The following five clinical situations of 25% at-risk applicants can be discerned: applicants whose 50% at-risk parent (1) wishes to be tested first, (2) does not wish to know but co-operates in testing, (3) declines to co-operate in testing, (4) is unavailable, or (5) died without symptoms of HD.

Methods

The testing protocol includes at least two pre-test and one post-test counselling sessions, according to the international published guidelines [International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea, 1990, 1994]. Motivation for predictive testing and communication possibilities between 25% at-risk applicant and 50% at-risk parent are explored and clarified to find the optimal test applicable to the test applicant's personal situation. The clinical geneticist discusses the fact that the 25% risk, based on half of the healthy parent's prior risk, will be less, depending on the age of the healthy at-risk parent and of the 25% at-risk test applicant. For every applicant we calculate the actual risk using second-degree risk curves [Harper and Newcombe, 1992]. The actual risk might influence the decision to be tested and/or the choice of the test procedure. After pedigree analysis, the possible options and consequences of predictive testing for the applicant and the family members are discussed in a non-directive way. The test candidate is encouraged to discuss the test with at-risk relatives. We invite the test candidate to be accompanied by at-risk relatives, to inform and to involve them in the counselling sessions or to be counselled separately as wished. Psychological support is offered in the decision-making process.

The following test procedures can be offered in the five different clinical situations (Fig. 1):

1. Testing the 50% at-risk parent first. If a 50% at-risk parent is informed about the wish of the 25% at-risk test applicant to know his/her genetic status, the former may prefer to or feel obliged to be tested first. In half of the cases, when the at-risk parent is found not to be a carrier, predictive testing of the 25% at-risk person is no longer necessary. Although it is possible to test them simultaneously, the parent receives the result before the 25% at-risk person does. The test result of a 50% at-risk parent changes the prior risk of his/her children from 25% to 50% or 0%. These children, excluding the 25% at-risk child who wants to know his/her genetic status, who did not ask for the test, might therefore receive unsought (and undesired) information.

2. Testing when the 50% at-risk parent does not wish to know but co-operates in testing.
   a. Exclusion test. Blood sampling, informed consent, co-operation of the parent(s) and grandparent(s), and a three-generation pedigree structure are necessary to perform linkage analysis and to discern whether the 25% at-risk person inherited the 50% risk allele or not (Fig. 2). The test result will never disclose or change the risk of the parent and siblings. In half of the cases, the risk will be reduced to almost 0% or excluded and only then can a definitive result be obtained. In the other half, the risk of the 25% at-risk person will change from 25 to 50%; i.e., the same risk as the at-risk parent, which thereby leaves the 25% at-risk person still with uncertainty for that moment. Because the genetic and health status of the 25% at-risk person and 50% at-risk parent are allied this uncertainty may however change: firstly, if the at-risk parent becomes symptomatic the 25% at-risk person, who received a 50% risk by the exclusion test, knows...
then that he/she is a carrier or secondly, if the at-risk parent later decides to be tested him or herself, the risk of the 25% at-risk person, who received a 50% risk by the exclusion test, is changed simultaneously, which may be undesired at that moment, or if, thirdly, inadvertently the risk of the at-risk parent is altered if other family members are genotyped [Benjamin et al., 1994]; therefore the results of genotyping other family members were kept strictly apart from the results of the exclusion test. The reliability of the exclusion test is dependent upon the informativeness of the available markers, which varies usually between 98 and 99%.

3. Testing if the 50% at-risk parent declines to co-operate in testing or is unavailable. Direct mutation analysis is available even if the parent either declines to be tested, is unavailable, or if the risk cannot be excluded by exclusion testing. In direct mutation analysis, no informed consent or blood sampling of the parent(s) and grandparent(s) are needed. Although the at-risk parent is technically not needed to perform this test, the at-risk parent can be involved in the testing procedure. In 25% of the cases, the mutation will be detected in a 25% at-risk test candidate and simultaneously the carrier status of the parent will be established, changing the risk of siblings from 25 to 50%. This information may be unsought and undesired. This test is relatively easy and fast, has the highest reliability (>99%), can be applied in every pedigree structure, and always provides a result for the 25% at-risk person.

5. Testing when the at-risk parent is deceased. If the 50% at-risk parent has died without any symptoms of HD, stored DNA of the deceased at-risk parent or the 25% at-risk test candidate can be tested. In these situations, testing, initiated by a 25% at-risk person, may result in unsought information for siblings, who did not ask for testing, because their risk may change from 25% to 50% or 0%.

Several aspects of the exclusion test, the exclusion-definitive test, and the mutation test, like the ethical dilemma of the risk of disclosure of the genetic status of parents and siblings, the risk of no test result for the test candidate, reliability of the test, and logistical limitations are schematically given in Table I. The exclusion-definitive test is only possible in a three-generation pedigree and the exclusion test is the only

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<thead>
<tr>
<th>TABLE I. Comparison of Exclusion Test, Exclusion-Definitive Test, and Mutation Test</th>
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<tr>
<td>Test options for 25% at-risk test applicants</td>
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<td>Informed consent and blood needed of parent(s) or grandparent(s)</td>
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<td>Applicable to every pedigree</td>
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<td>Reliability test result (%)</td>
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<td>Risk of no test result for 25% at-risk person (%)</td>
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<td>Risk of disclosure genetic status 50% at-risk person (%)</td>
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<td>Risk of disclosure/change status/risk sibling (%)</td>
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Fig. 2. Exclusion test: III:1, at 25% risk, inherits the grandpaternal (B) 50% risk allele and III:2, at 25% risk, inherits the grandmaternal (C) 0% risk allele from II:3, the 50% at-risk parent who does not wish to know her status. Exclusion-definitive test: If after exclusion testing in III:1, the mutation is tested and found, the at-risk sib, III:1, and at-risk parent, II:3, will be carriers and the risk of the other sibling not tested, III:3, changes from 25 to 50%. If the mutation is not found they all will be non-carriers.
test in which the risk of relatives does not change. There is, however, a 50% risk the test candidate does not receive a definitive result. The mutation test is possible in every situation and always provides a result and compared to the exclusion-definitive test causes only half the risk of disclosure of the status of relatives.

In the pre-test sessions the procedure of disclosing the test result of the 25% at-risk test applicant and possibly of at-risk relatives should be discussed and well prepared, because the genetic status of the 50% at-risk parent might be disclosed and the status or the risk of the sibling(s) might be altered. If the test candidate is accompanied by at-risk relatives, we offer each of them the possibility of receiving their test result in a separate room as a result of testing their 25% at-risk relative individually. Afterwards they can meet if they wish. After the test result is disclosed follow up, according to the guidelines, is offered to the test candidate as well to family members if they so wish.

The statistical significance of differences between several groups in this study was assessed by means of the chi-squared test, Poisson regression test, Fisher's exact test, and Student's t-test. Difference between groups was regarded as significant when \( P < 0.05 \). Data were analysed using the Statistical Package for Social Sciences (SPSS).

RESULTS

In the period from October 1987 until September 1997, 721 individuals at risk for HD applied for predictive testing in our department. Most of the applicants (n = 657) had a prior risk of 50%, 64 (9%) had a prior risk of 25%. Test applicants with 25% prior risk have significantly less children (30%), compared with those with a 50% prior risk (49%) (\( P = 0.005, \chi^2 = 8.00, df = 1 \)). Mean age (35 years), sex (m/f (%)) = 42/58, and number of applicants tested (79%) were comparable between applicants with prior risks of 50 and 25%.

The mean actual risk of the 25% at-risk test applicants, using second-degree risk curves [Harper and Newcombe, 1992] was 11% (range 0.7–22.8%), which was significantly lower (\( P < 0.0001, t = 20.04, df = 63 \)) than the prior risk of 25%, explained by the relative high mean age of the at-risk parents (56 years).

From 1993, the number of 25% at-risk test applicants increased (Fig. 3). After 1994 the number of applicants in Leiden decreased because of the decentralisation of the counselling of HD. From 1995 the total number of 25% at-risk applicants in The Netherlands decreased, as did the the total number of all applicants for HD (data not shown).

The testing procedures performed both before and after the mutation test was available are given in Table II. Twenty-four individuals applied for the test before (1987–1993) and 41 after the mutation test was available (1993–1997). Therefore the mean number of individuals rose significantly from 3.7/year to 9.0/year (\( P < 0.001, \chi^2 = 12.51, df = 1 \)). One of the test candidates was seen both before and after 1993, because of new testing options; therefore, 65 test procedures were performed for 64 candidates.

The distribution of the different test procedures performed has changed since the mutation was first identified. Before the mutation was identified, testing the parent first and after 1993 the mutation test are the test procedures of choice. Before the mutation test was available, the incidence of the at-risk parent who underwent predictive testing first was twice as frequent as after (\( P = 0.04, \chi^2 = 4.46, df = 1 \)), as was exclusion testing (\( P = 0.24, \chi^2 = 1.38, df = 1 \)). The exclusion test has never been a test procedure of choice in our series, although it is the only testing procedure in which the risk of family members will not change. Many applicants have a pedigree structure that makes linkage-based testing impossible, because either family members are deceased, or simply unavailable and when the risk is not excluded, the at-risk person is left in uncertainty.

Before the mutation test was available, there were 8 of 24 (33%) test candidates for whom it was not possible to perform predictive testing, either because the at-risk parent refused to co-operate (5/8) or because the at-risk parent had died and no other family members were available for linkage analysis (3/8). Although it is now possible to test every 25% at-risk test candidate, 6 of 41 (15%) decided not to be tested (two because of a pregnancy, four undecided or respecting their parent’s wish not to know).

For six applicants the clinical situation in the family changed during the counselling procedure, by change of mind of the parent: clinical situation 3 became 1 or 2 and clinical situation 1 became 3. If the 25% at-risk applicant discussed the fact that he/she wanted to know his/her genetic status with the at-risk parent the at-risk parent was usually more co-operative than was presumed. One of the at-risk parents thought he was needed for predictive testing of the 25% at-risk adult child. Once he had heard that he was technically not needed for mutation testing he decided not to be tested himself but agreed that his child be tested. Nine of the 51 (18%) 25% at-risk persons who were tested appeared to be gene carriers and in one, the risk became 50% (Table II).
Because the at-risk parent becomes a test applicant himself or herself in clinical situation 1 the at-risk parent usually accompanied the 25% at-risk applicant in half of the cases at the first and in half of the cases at the second pre-test counselling session. Most of the tests of parent and child were performed simultaneously (12/16). The parent always received the result before the child and usually they met afterwards.

In clinical situation 2 there is a direct contact in a pre-test session with about half of the at-risk parents who co-operate but do not want to know their own genetic status. In the three exclusion-definitive tests performed, only one parent was involved in the predictive testing procedure and the other parent of two siblings, both applying for predictive testing, was not. Both of these parents agreed to be tested, but stated they did not want to know the test result. The 25% at-risk person whose parent was involved in counselling received a decreased risk and informed the parent about the test result. The parent was angry that the test result was disclosed to him and could not believe that his risk was also decreased. The sibling was very happy receiving simultaneously this result. The parent of the two siblings, both of whom had received an increased risk, was informed of the unfavourable test result, but received the result without any comment. Since then the family have not communicated with each other about HD as far as we know from our follow up of the 25% at-risk test candidates. Another child of this parent had earlier received an exclusion of the risk by exclusion test.

Only one-third of the at-risk parents in clinical situation 3 who decline to be tested themselves are seen for counselling; the others are informed usually before the test result is disclosed. Reasons for opting for the mutation test were, according to the 25% at-risk test applicants and some of the at-risk parents who were involved in counselling in our series, the at-risk parents were too frightened and declined to be tested (15/16). Almost all at-risk parents agreed that the 25% at-risk person should be tested themselves. In other cases (2/16), the parents were over 70 years old and were not informed about the test or involved in counselling because the 25% at-risk persons wanted to protect the at-risk parent. In all cases family members were informed about the test result by the 25% at-risk person and none of them showed much reaction, especially not a happy reaction in case of a favourable test result, which was difficult to endure and understand for the 25% at-risk person, but can be explained by the fear for their own genetic status.

None of the parents were unavailable (clinical situation 4). The majority of the sibships were informed about the test and its result by the 25% at-risk person in all clinical situations. There were no significant differences between involvement of the parent or siblings in counselling in a specific clinical situation before and after the mutation was identified. The mean number of counselling sessions was 4 (range 1–13), not significantly different in the five clinical situations or before and after the mutation was identified.

Three parents (3/35, 9%) and 21 sibships (21/45, 46%) acquired unsought information, either a change in prior risk or being a carrier or not, as a result of predictive testing of 25% at-risk relatives (Table II). Two sibships and one other applicant opted for an exclusion-definitive test (clinical situation 2b), which explains why only two parents and two sibships received unsought information. In one case, a DNA sample of one of the at-risk parents who had died without symptoms (clinical situation 5) had been stored. On testing, this parent appeared to be a carrier, while the 25% at-risk person who applied for predictive testing was not. This result changed the risk of the siblings of this person from 25% to 50%. This sibship, together with sibships of the two test applicants with an at-risk parent who died without symptoms, but who appeared to be carriers, and the sibship of the test applicant with an at-risk parent who died without symptoms and who appeared not to be a carrier, comprise the four sibships who received unsought information as a result of predictive testing after the parent died. In total, 21 of 51 test procedures (41%), 9 of 16 (56%) before and 12 of 35 (34%) after the mutation test became available, were performed before and after the mutation test became available (P = 0.14; \( \chi^2 = 2.19; df = 1 \)), resulted in unsought information for parents and/or siblings. Before the mutation test was available no parents (0/12) and after 3 of 23 (13%) parents received unsought information (P = 0.19; \( \chi^2 = 1.71; df = 0.19 \)) because of performance of the mutation or the exclusion-definitive test. The number of sibships receiving unsought information decreased after the mutation was identified from (9/15) 60% to (12/30) 40% (P = 0.20; \( \chi^2 = 1.61; df = 1 \)).

### TABLE II. Uptake of Predictive Test Procedures for HD by 25% At-Risk Test Applicants Before and After Mutation Detection, Results and Unsought Information for Family Members After Predictive Testing of 25% At-Risk Test Applicants (1987–1997)

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<td>0/12</td>
<td>3/23</td>
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*See text.

bNot possible.
because in almost half of the cases a mutation test was performed with a favourable outcome. The mutation test caused significantly less unsought information than the exclusion-definitive test for parents as well for sibships (8% versus 100%; Fisher’s exact test, P = 0.033).

None of the parents or sibships were seen for follow up, although it was offered in each clinical situation, before as well as after the mutation was identified. According to our follow up of all 25% at-risk test candidates, 1 year or more after disclosure of the test result, no family distress, feelings of guilt in the test candidate, litigation proceedings, or other consequences of the conflict of interests, according to the test candidate, were reported.

**DISCUSSION**

In our series, a relatively small number of test applicants appeared to be at 25% risk (9%), which is comparable with the results of the European Community Collaborative Study (11%) [European Community Huntington’s Disease Collaborative Study Group, 1993]. For one-third of the test applicants it was not possible to perform predictive testing before the mutation was available, either because relatives were dead or unavailable or declined to be tested. Those for whom it was not possible to be tested could now be tested. More testing options became available after mutation detection and the number of 25% at-risk test applicants did rise significantly (Table II, Fig. 3).

Unsought information for other family members as a result of predictive testing is one of the exclusion criteria described in the guidelines [International Huntington Association and World Federation of Neurology Research Group on Huntington’s Chorea, 1990, 1994]. When the exclusion-definitive and mutation test are compared (Table I), the mutation test provides the least unsought information for relatives. This is also shown in our series. Unsought information for other family members as a result of testing a 25% at-risk applicant was found in our series not only after either mutation testing or exclusion-definitive testing but also after predictive testing when the parent was tested first or had died (Table II). The problem of unsought information was even more frequent before (56%) than after (34%) mutation testing was available. Parents and sibships received unsought information due to mutation or exclusion-definitive testing. Sibships received also unsought information because of testing the parent or because of testing after the parent had died. The reduction of unsought information for sibships can be explained by the fact that almost half of the test procedures were mutation tests with a favourable outcome.

Although a relatively large number of relatives received unsought information, no problems due to unsought information were reported, according to our follow up. This may be due firstly to the fact that we did not follow up the parents and siblings. The test applicant might underestimate the negative reactions of their relatives or the relatives may have hidden their feelings from the test applicant. Secondly, that we had a relatively short follow-up period after the test result, and thirdly, most of the tests (15 of 17 mutation tests and one of three exclusion-definitive tests) resulted in a favourable test result, although a favourable test outcome might also cause problems.

We agree with the lay organisations that the right of the 25% at-risk person to know has priority over the right of the parent not to know [International Huntington Association and World Federation of Neurology Research Group on Huntington’s Chorea, 1994]. The right to know is highly appreciated in our individualistic Western society. This is reflected in the conclusion of the majority of the representatives of the lay organisations, in which the interest of the individual to know has priority. This is in contrast to Japan, where no (individual) informed consent can be given, but only family consent. To take the test or not is usually an individual enterprise of the person at risk and is usually not a family enterprise [Dudok de Wit et al., 1997]. For a 25% at-risk test applicant, wishing to take the test, testing might well however, become a family enterprise, because it may result in a situation in which not only an at-risk person is tested, but possibly simultaneously also the at-risk parent and siblings, who may not wish to know their genetic status, may be unprepared for the test result, and with whom the counsellor is not able to communicate directly if this is not permitted by the 25% at-risk test applicant.

The mutation test provides an opportunity for autonomy in the decision-making process of the test candidate. This autonomy is however considered to be relative, because the risk of other at-risk family members may change by mutation detection. Individuals in the situation of a 25% at-risk person do not take these decisions on their own and only for their own well being. They make these decisions influenced by the interest of their partner, their (future) children, parents, and siblings. They weigh their interests and do not on purpose harm their at-risk relatives. They feel responsible that unsought information is penetrating the family, fear that the family is unable to cope, and that one may have to pay too heavy a price for one’s own personal choices. In the complex situation of a 25% at-risk person who wants to know with a parent who does not want to know it is perhaps impossible not to harm. We think that the test applicant as well as the counsellor do have the duty and the responsibility to limit the damage. The communication possibilities between the at-risk parent and test candidate should be explored and the test candidate should be well informed about the testing options and consequences for himself or herself as well as the family members. Information and counselling are offered to at-risk relatives, not directly, but by the 25% at-risk test applicant. We do however not “make every effort to ensure that the intervening generation receives adequate information and counselling before their offspring receives a test result” [Simpson et al., 1993]. Only if the 25% at-risk person initiates a contact of the at-risk parent and our department and the at-risk parent gives consent, is the at-risk parent directly informed and counselled. Although solutions are looked for and the parent is treated with respect for his/her decisions, we do not “decide what
The test would be performed in order to protect the parents’ right not to know” [European Community Huntington’s Disease Collaborative Study Group, 1993]. The 25% at-risk test applicant must find a balance between involvement of the parent and autonomy in the decision-making process. Genetic counselling and psychological support are offered in the complex decision-making process to find a test option best suited to his/her personal situation. A decision tree (Fig. 1) and guidelines for predictive testing of 25% at-risk test applicants are proposed (Table III).

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