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Predictive testing for Huntington's disease: ten years' experience in two Italian centres

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Abstract Pre-symptomatic testing for Huntington's disease (HD) has been available as a clinical service in the medical centres of Rome and Genoa since December 1987, initially by DNA-linkage and since mid-1993 by direct mutation analysis. A multidisciplinary approach and a protocol which follows the Ethical Issue Policy Statement on Huntington's Disease Molecular Genetics Predictive Test has been used. In the period under study, 332 subjects requested the test, 288 were enrolled in the protocol and nearly half of these completed it. One hundred and forty-eight people withdrew from the testing procedure for various reasons but most frequently due to a more realistic evaluation of all possible consequences of test results, induced by psychological counselling. Therefore, 140 people completed the test. The overall gene-carrier/non-carrier ratio was 0.46:1. None of the identified gene carriers had catastrophic reactions such as suicide, suicide attempts or major psychiatric disorders. All appear to have had a similar pattern of reactions to an adverse result and none expressed regret for undergoing the test. In conclusion, presymptomatic testing for HD can be considered a safe procedure without adverse consequences when framed in an integrated protocol at qualified genetic centres.

Key words Huntington's disease · Predictive testing · Genetic counselling

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Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder inherited as a truly autosomal dominant trait affecting 1 in 10 000 individuals in most European populations [1, 2]. In Italy, prevalence estimates vary from 1 in 39 000 [3] to 1 in 20 000 [4], with a frequency of subjects at risk of having the disease in the future of 1 in 3000 (Frontali M., unpublished data). The disease is usually characterised by motor disturbances, cognitive loss and psychiatric manifestations with a duration of about 20 years. Age at onset is highly variable and ranges from less than 10 years to over 70 years, with a mean around 40 years. This implies that most heterozygotes unknowingly pass the defective gene on to their offspring, and the children at risk watch their possible future acted out in their parents' suffering.

In 1983, the HD gene was mapped by linkage analysis to chromosome 4p13 by Gusella et al. [5]. This created the possibility of using markers linked to the HD gene for predictive testing. The probability of recombination between the linked markers and the disease gene limited the test reliability to 95%-98%. In addition, due to the necessity of phasing the markers, an adequate family structure and DNA analysis of affected and/or healthy relatives were necessary. It has been estimated that about 40% of persons at-risk for HD do not have a family structure large enough to allow for linkage analysis [6]. Furthermore, uncooperative or inaccessible relatives made this test unfeasible for many others wishing to be tested. Several types of testing procedures were offered to subjects at risk, all based on linkage analysis, namely definitive or exclusion presymptomatic and prenatal testing. Concerns for ethical problems related to HD predictive testing [7, 8], such as severe psychological stress in subjects with an unfavourable result, possible violations of subjects' autonomy in the decision-making process, and inadvertent risk alteration for relatives not wishing to know their genetic condition, led very quickly to restrictions in the circulation of the molecular probes used for marker typing and later to

the elaboration of ethical guidelines to be followed in testing programs [9].

In 1993, the mutation responsible for the disorder was identified as an expansion of a polymorphic trinucleotide repeat (CAG) in the coding sequence of gene IT-15 [10]. The exact number of CAG repeats can be assessed by amplification of the sequence with a set of primers that excludes the adjacent polymorphic CCG repeat, and gel electrophoresis of amplified fragments [11]. The normal allele contains between 10 and 34 triplets, while disease-causing alleles have from 36 to over 100 triplets [12, 13]. Pilot studies performed in the Italian population showed a remarkably similar distribution, with the same discriminating threshold [14, 15]. The ability to assess the number of CAG repeats offered a direct HD presymptomatic test with a high degree of specificity and sensitivity, independent of the family structure and cooperation of relatives of the subjects at risk [12]. The CAG direct mutation assay also provided a molecular diagnosis in patients with HD-like symptoms. While this issue is beyond the scope of the present report, it should be noted that sometimes the distinction between presymptomatic and symptomatic states may be very subtle.

Presymptomatic testing for HD has been available in Genoa at the Medical Genetic Service and in Rome at the CNR (Institute of Experimental Medicine in conjunction with the Institute of Psychology) since 1987 and 1989, respectively. Linked markers were initially used up to 1993, and the direct test, i.e. assessment of CAG repeats, has been used after that date. In both centres, a similar protocol was adopted based on World Federation of Neurology guidelines [9, 16]. The results of ten years' experience in HD presymptomatic testing in both centres are reported here, while prenatal and symptomatic testing will be reported elsewhere.

Protocol

Criteria for inclusion in the protocol were: (1) a suitable family structure (for linkage analysis); (2) age over 18 years; (3) lack of outside pressure for testing; (4) adequate emotional and cognitive functioning; (5) absence of early clinical signs of HD; (6) ability to give informed consent; (7) absence of ethical conflicts with other family members (e.g. test required by the offspring of a 50% at-risk individual not wishing to know his genetic condition).

The testing protocol, designed according to the Ethical Issue Policy Statement on Huntington's Disease Molecular Genetics Predictive Test [9, 16], is reported in the following column. No official announcement of the availability of the test was made, as a policy of restraint was desired. The protocol was conducted by a medical geneticist and a psychologist. A neurologist was also part of the team in Genoa, while in Rome applicants had the clinical examination performed by a neurologist of their choice. The examination was performed using an HD rating scale which was completed by the neurologist and sent back to the team with the scores for each item. The protocol included at least 2 sessions of pre-test counselling, a disclosure session and post-disclosure follow-up interviews. After the first session, the timing and number of the pre-test sessions were left to the applicant.

The protocol structure was aimed at allowing the applicant to: (1) make an autonomous and informed choice; (2) analyse all possible consequences of the test result personally and on familial and social life; and (3) evaluate accurately the ability to cope with an unfavourable result, before actual testing is carried out. Thus, the applicant was given the opportunity to prepare for the possible results before the test was actually performed, favouring the prevention of catastrophic events once the results have been communicated. The pre-test and post-test sessions were conducted on the basis of non-structured interviews, in order to favour the formation of a trusting relationship between the applicant and the counsellors. The use of structured interviews, psychometric tests and questionnaires was avoided to prevent the applicant from feeling required to pass an examination to gain access to the test, which may activate defence mechanisms, e.g. the applicant hiding true feelings. The test result was communicated to the applicant both verbally and in written form during the same session, in order to protect the applicant's privacy. Disclosure of the test result by telephone, often requested by applicants, was always denied. From the start of the protocol, the applicant was invited to share the entire experience of the testing protocol with another person and was asked to be accompanied by that person at least during the disclosure session. Participants were allowed to withdraw from testing whenever they wished, and could be readmitted by starting again with a counselling session.

Testing protocol

Stage 1

- Collection of family history and confirmation of the diagnosis in the family
- Information on the genetics of the disease and assessment of genetic risk
- Information on all possible test procedures (linkage/CAG repeat definitive presymptomatic or prenatal test, presymptomatic or prenatal exclusion test) and on the limits and accuracy of each of them
- Information on the protocol (number of sessions, team, disclosure)
- Collection of applicant's data on life experience with the disease; working, familial and social life; emotional and cognitive functioning; inner motivation for undergoing the test; autonomy in decision-making; expectations of the test results
- Discussion of pros and cons of each test outcome related to the aspects listed above

Neurological examination of the applicant for the assessment of early signs of HD

Team evaluation of fulfilment of inclusion criteria

Stage 2

- Assessment and discussion of coping strategies and defence mechanisms elaborated by the applicant and evaluation of their adequacy in minimising the impact of the test and its result upon the applicant and applicant's family
- Assessment of comprehension of the genetic information received
- Informed consent signature
- Blood sample collection (samples in case of indirect test)

Stage 3

- Disclosure of test results (verbal and written communication)
- Opportunity for the applicant to express feelings about results
- Counselling regarding coping with test results

Early follow-up phone call (one week interval):

- Informal assessment of emotional state

Long-term follow-up (1, 6, 12 and 36 month intervals):

- Exploration of long-term psychological impact on personal and social life

DNA Analysis

After informed consent was given, blood samples were taken from applicants and their relatives. Genomic DNA was extracted according to standard methods. For linkage analysis, several chromosome 4p markers were used, as described elsewhere [17]. Since 1993, the CAG trinucleotide expansion in the IT15 gene has been examined through polymerase chain reaction (PCR) analysis and acrylamide gel electrophoresis, as previously described [14, 15]; PCR products were sized by comparison with cosmid L111F1 and GUS72-2130 [10]. Samples from members of the same family were run on the same gel. The whole CAG typing procedure was carried out on two independently prepared samples by different operators. Whenever possible, analysis was also performed on parents or an affected relative, in order to avoid testing for HD in misdiagnosed families and to have a further control against tube mislabelling. For a short period in 1995, results were obtained both with linkage analysis and CAG analysis.

Results

From December 1987 until November 1996, a total of 332 at-risk subjects entered the HD presymptomatic test protocol (181 at Genoa and 151 at Rome). The average age for all subjects was 33.1 years (range, 18-63 years); 53 % were females and 47% were males, and 49% of subjects were married or had stable relationships.

Of the 332 applicants, 288 individuals were enrolled in the predictive testing program, and 148 concluded the testing procedure; a slight excess of female applicants (54%) was observed. Sixty-three individuals underwent the procedure by linkage analysis, 77 by CAG typing and 5 subjects were tested using both methods. Table 1 reports the distribution of applicants according to the procedure used. The words gene-carrier and non-carrier are used to refer to an increased risk and a decreased risk, respectively. Seven tests are pending and were not considered in the current analysis.

Table 1. Number of tests provided at the Genetic Centres in Genoa and Rome, during the period 1987-1996

	1987-1993 (Linkage analysis)		1994-1996 (CAG typing)[a]		Total	
	n°	%	n°	%	n°	%
Requests	145	100.0	187	100.0	332	100.0
Enrolled	131	90.3	157	83.9	288	86.7
Concluded	63	48.1	77	49.0	140	48.6
Withdrawn	68	51.9	80	51.0	148	51.4

[a] Five subjects who underwent the testing through both linkage analysis and CAG typing are included.

Forty-four applicants were excluded because inclusion criteria were not fulfilled. Reasons for exclusion are reported in Table 2. It should be noted that the reasons for exclusion were always explained to and discussed with the applicants, usually resulting with the subject being in full agreement with the protocol criteria. In 11 cases a delay in

Table 2. Reasons for exclusion

	Genoa	Rome	Total
Non-informative pedigree	2	2	4
HD signs present	3	14	17
Minors	1	4	5
Test requested for third parties	10	1	11
Wrong clinical HD diagnosis	3	1	4
Psychological impairment and/or psychiatric disturbances	3	0	3
Total	22	22	44

the testing procedure was suggested because of a transient condition of psychological or emotional fragility (e.g. ongoing pregnancy, etc.), but none of them requested testing later. They were, therefore, considered subjects withdrawn from testing.

As shown in Table 1, nearly half of the applicants (48.6% of the enrolled subjects) completed the protocol. Table 3 reports the results obtained for the 140 subjects who completed the test. The overall gene-carrier/non-carrier ratio was 0.46:1. However, this ratio is lower for linkage analysis (0.29:1) than for CAG typing (0.57:1). The overall percentage of carriers in the group of subjects who had tests performed was 28.6%, ranging from 17.5% for linkage analysis to 36.4% for CAG typing.

Table 3. Predictive tests performed during the period 1987-1996, according to the method applied

Result	Genoa			Rome		
	Linkage	CAG typing	Total	Linkage	CAG typing	Total
Gene carriers	11	17	28	1	11	12
Non-carriers	29	31	60	9	18	27
Non-informative	12	--	12	1	--	1
Total	52	48	100	11	29	40

One hundred and forty-eight people withdrew from the testing procedure for various reasons. The most frequent reason was a more realistic evaluation of the possible consequences of test results, emerging from psychological counselling. Some subjects withdrew from testing as they began to realise, through the counselling, that their worries and dissatisfaction with life were only in part due to their risk. They therefore decided to reconsider testing later on. In a few cases, subjects withdrew due to lack of family cooperation (refusal to donate blood samples for linkage testing) or to external constraints in proceeding with the test (e.g. spousal disagreement). In both centres, all those who withdrew from testing took their decision before signing the informed consent.

Follow-up

In the post-test period, applicants were followed-up through telephone calls and counselling sessions. Usually a first phone call was made one week after the test disclosure in order to assess the subject's emotional state and to explore initial reactions. A second interview was carried out after one month, in order to provide a more in-depth discussion of emotional reactions and everyday life problems. A long-term assessment of the consequences of the test was scheduled at up to 36 months. Testees were encouraged to visit or call the psychologist outside the scheduled interviews whenever they wished. Subjects living outside the cities where the centres are located usually maintained contact by telephone. During the follow-up interviews, the psychologist encouraged the participants to explore their own emotions and worries about the test result and to cope with them by using strategies devised during the pre-test counselling sessions. Follow-up was considered completed 3 years after the test disclosure (75 subjects) while follow-up is in progress for subjects who received the result less than 3 years ago (65 subjects).

None of the gene carriers had catastrophic reactions, such as suicide, suicide attempts or major psychiatric disorders. All appear to have had a similar pattern of reactions to an adverse result. After a period of depression lasting a few months (2-4), frequently associated with the fear of being already affected, they entered a recovery phase which was based mainly on: (a) the acknowledgement that for the time being they were disease-free and able to get the best out of life before the onset of HD; (b) avoiding long-term programs and fantasies while trying to accelerate the achievement of personal goals; (c) optimism regarding the possibility of new therapies in the future. None has expressed regret for undergoing the test. It is noteworthy that most of our testees kept in touch with the team after the end of the follow-up period. This is due to the level of trust which developed between the testees and the team.

The following short case histories better express more subtle aspects of the reaction to a high risk (gene carrier) result.

Case 1

MG is a 35-year-old male who is married and has no children. He lives abroad and works as a skilled labourer. After the disclosure of his test results, he told the psychologist that he felt ashamed of his gene carrier status and that his self-esteem had decreased. After several interviews with the psychologist, he was able to verbalise his being envious of his 2 sisters, neither of whom was a gene carrier. He mostly felt ashamed of this feeling. He received encouragement from the psychologist in legitimating this reaction as being very human and perfectly understandable, which contributed to his recovery from the depressive status.

Case 2

MT is a 46-year-old female with 3 adult children, one of whom is married. Her motivation for undergoing the test was mainly to provide the children with information on her genetic status in order to know if they were at risk, in which case they could decide to do the test themselves. After the test disclosure she was depressed for about 2 months and had the feeling of being already ill. One component of her depressive state, however, was also the changed attitude toward the test of her children, who decided not to be tested. This led

her to consider her decision to undergo the test as a useless "sacrifice". After several interviews with the psychologist during which they worked on her image of the disease and on the importance for the children of knowing that it is possible to cope with it, she gradually recovered from her depression in order to provide her offspring with an example of courage in facing HD.

Case 3

DM is a 30-year-old male, married and without children who underwent the test by linkage analysis in 1987, with a non-informative result. After 8 years he decided to undergo CAG typing, which showed that he was a gene carrier. At the test disclosure he did not want to accept the result and refused the psychological interview. His complete refusal to accept the results was evident at the first follow-up phone call. Seven months later he came spontaneously to the centre with his wife in order to discuss his carrier status. He clearly demonstrated "search for symptoms" behaviour and needed to be reassured that his neurological examination was normal. At his last meeting with the team, he demonstrated a new ability to cope with his status and was planning his future with his wife; in particular they were buying a house and thinking about having a child.

All 87 subjects with low risk (non-gene carrier) had an initial period of disbelief and needed a few months time to become confident with their new genetic status. As reported in the following case history, only one subject who underwent linkage testing had a fear of being a gene carrier which persisted for several years.

Case 4

FA is a 31-year-old married man. He first came to the Genetic Centre in 1991 and underwent presymptomatic linkage testing which resulted negative. He kept in touch with the team after the end of the follow-up and, in 1994, asked for a direct test. In spite of the negative result of CAG typing he contacted the centre when his wife became pregnant in order to perform a prenatal test. After being refused prenatal diagnosis and undergoing exhaustive counselling he was finally convinced of his negative non-carrier status.

Long-term problems most frequently observed were:

a) "Survivors syndrome", i.e. feeling guilty toward relatives who are gene carriers or are already affected. It has been frequently observed that subjects with favourable results tend to withhold the good news from their untested sibs ("I could not boast about my luck with them.");
b) a search for reasons for their good fortune, which frequently led these subjects to becoming actively involved in lay associations in order to help less fortunate people; and
c) an increase in self-esteem which leads to regret for decisions taken when, being still at risk, they were less confident. In three cases of this type, problems with the partner arose, leading, in two of them, to divorce, as exemplified by the following case history.

Case 5

MA is a 27-year-old married woman without children who had a low-risk test result. Before testing she had always considered being at risk as her major problem. She was almost certain she was a gene carrier. For those reasons she had given up every opportunity for taking control of her life, becoming totally dependent upon her husband. The disclosure of her actual status gave her no sense of relief and she needed continuous psychological support. Some months later she realised that her low self-esteem was due more to the absence of a maternal figure in her life than to her at-risk status. The psychological support increased her self-esteem, allowed her to make personal plans for the future, and to divorce her husband.

Discussion

The above results further confirm that predictive HD testing can safely be offered to subjects at risk who wish to know if they will develop the disease, provided that a time consuming and complex protocol is strictly followed. In our experience, some aspects of the protocol have a major relevance in avoiding harmful consequences after test disclosure. First, the considerable length of time required to complete the test (at least 2-3 months) leaves the applicant sufficient time to reconsider the decision to undergo testing. Secondly, through the pre-counselling sessions with the psychologist and their colloquial nature, the applicant is induced to analyse in-depth all possible consequences of a test result at a personal, emotional and cognitive level. In this process, it appears crucial that the applicant feels free to communicate thoughts and feelings to the psychologist. This led both groups to avoid psychometric tests and questionnaires which can provide information to counsellors but do not favour a trusting relationship with the psychologist, which is the base of an effective psychological counselling. The importance of these pre-counselling sessions is also shown by the high percentage of applicants who decide to withdraw from testing. Most subjects do so because of a more realistic consideration of the test consequences. In our experience it has frequently been observed that subjects at risk ask for predictive testing in order to avoid uncertainty about the future or to solve life problems erroneously attributed to the genetic risk, but do not sufficiently consider what will happen if the test brings them bad news. A final relevant aspect of the pre-counselling sessions is the thorough information about all possible test approaches and

about alternatives to definitive presymptomatic testing, such as prenatal exclusion testing with linked markers. Among the motivations for HD testing, reproductive choice is one of the most frequent. The prenatal exclusion test provides information on children who have not inherited the gene, leaving the parental risk unchanged. Some of those who withdrew from testing have chosen this alternative.

The follow-up of subjects who completed the test showed that none of them had severe long lasting consequences. Coping with a high risk result was achieved in all cases usually within a short period of time from the disclosure. Some "adverse" consequences, in terms of a readjustment of life and personal goals, were observed for a variable period of time in subjects with a low risk result, as already reported [18, 19].

The successful process of coping with test results observed in our centres should be viewed in the context of the preliminary results of a world-wide survey on the frequency of catastrophic events (suicide, suicide attempts, psychiatric hospitalisation) following predictive testing for HD. A very low frequency (0.7%, 40/5781) of catastrophic events (CE) among all testees is reported [20]. CE occurred in 1.4% of 2299 gene carriers, in 0.2% of 3318 non-carriers and in 1.2% of 164 uninformative cases. In our series, no CE was observed among 140 testees, while 1 case should be expected on the basis of a 0.7 % frequency. Although our data are still too scanty to provide meaningful frequencies, a confirmation of this result on a higher number of cases could suggest that the protocol in use is particularly efficient in preventing CE.

A last aspect of the above data deserves further consideration, namely the low carrier to non-carrier ratio in the group of subjects who completed the test, already reported in previous papers. The low proportion of HD gene carriers has partly been attributed to the age of applicants who have already passed through a significant part of their risk period [21]. However, it has also been suggested that the protocol itself induces a sort of self-selection by which only those subjects with particular ego strength and psychological stability, heralding a non-carrier condition, actually make it to the test disclosure [22].

In conclusion, presymptomatic HD testing does not appear to have adverse consequences when performed in the conditions described above. However, these conditions require skilled personnel and, in particular, psychologists trained in genetic counselling, working a considerable number of hours per HD test performed (overall, at least 10-15 hours). This implies that the cost of offering presymptomatic HD testing freely, as recommended by the World Federation of Neurology guidelines [9, 16], will be extremely high for the National Health Service or in general for the community. This will limit the possibility of offering the presymptomatic HD test freely outside expressly designed research projects.

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Sommario *Dal dicembre 1987 è disponibile presso i Centri di Roma e Genova il test presintomatico per la corea di Huntington, inizialmente mediante l'analisi di linkage di marcatori del DNA e, dalla metà del 1993, mediante l'analisi diretta della mutazione. A tale scopo è stato utilizzato un approccio multidisciplinare e un protocollo in accordo con le Linee Guida per il Test Presintomatico per la Corea di Huntington (Ethical Issue Policy Statement on Huntington's Disease Molecular Genetics Predictive Test). Nel periodo descritto, 332 soggetti hanno richiesto il test, di questi, 288 sono stati inclusi nel protocollo e circa la metà lo hanno concluso. Centoquarantotto soggetti si sono ritirati durante il protocollo per diverse ragioni, ma la più frequente è stata una più realistica valutazione delle possibili conseguenze psicologiche del risultato del test, indotta dalla consulenza psicologica. Centoquaranta soggetti hanno completato il protocollo e il rapporto portatori/non portatori della mutazione è risultato 0.46:1. Nessuno dei portatori del gene malato ha avuto reazioni quali suicidio, tentativo di suicidio o gravi disturbi psichiatrici. Tutti hanno avuto un simile quadro di reazione al risultato di portatore e nessuno di essi ha mostrato di essersi pentito di aver effettuato il test. In conclusione, il test presintomatico per HD può essere considerato una procedura priva di rischi e non appare avere conseguenze negative quando viene inserito in un protocollo integrato presso centri di genetica qualificati.*

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