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Presymptomatic testing for Huntington's disease: a world wide survey*

The World Federation of Neurology Research Group on Huntington's Disease†

Abstract

World wide data on presymptomatic testing for Huntington's disease using closely linked DNA markers show that 1479 persons at risk received completed test results up to the end of 1991. Testing has been carried out in 19 countries, with at least 88 centres involved, and numbers have levelled off after a peak in 1990. Only 5% of those at risk have been tested in six countries with the longest established programmes. Continued monitoring of international data will be of value in assessing the spread and impact of genetic testing, not only for Huntington's disease, but for other serious genetic disorders of later life.

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Since the detection of a genetic marker linked to Huntington's disease (HD) in 1983,[1] it has been recognised that genetic prediction for this disorder is feasible and that presymptomatic detection of the gene for this serious and currently incurable autosomal dominant disorder would raise important ethical, social, and practical problems for those being tested, their family members, and for professionals. The necessity for providing an appropriate framework of preparation and support for those undergoing testing was one reason why centres involved with HD families delayed the clinical application of this discovery; another was the need to exclude genetic heterogeneity[2] and to obtain closer genetic markers.[3]

In 1986 presymptomatic testing began as a carefully controlled evaluation in a small number of centres[4–7] and during subsequent years the numbers of tests performed and of centres involved increased rapidly. The fact that most centres in the world have been in close contact with one another and have used similar counselling protocols, initially in a research framework, has given the opportunity for collecting basic HD prediction data on an international basis (appendix). In some countries only a single testing centre exists, while in others, such as Canada[6] and Britain,[8] national data have been collected on a collaborative basis. In 1991 the joint meeting of the World Federation of Neurology Research Group on HD and the International Huntington's Association encouraged collection of international data on presymptomatic testing.

The data presented here include the great majority of HD presymptomatic tests undertaken up to the end of 1991, as well as information on almost all testing centres involved during this time. While the detailed analysis of outcomes, in particular the consequences for those predicted as being at high or low risk of having the HD gene, will follow from specific studies in individual centres, the present data should be of value in illustrating the experience, development, and spread of a new form of genetic testing that is likely to become common for a wide range of late onset disorders. The collaborative collection and analysis of data should also facilitate continued contact between centres and promote high standards of testing and associated counselling, factors which will become of even greater importance now that the HD gene itself is isolated and laboratory aspects are becoming simplified.

Methods

Following the international workshop on HD in July 1991, when this project was discussed, all centres involved in presymptomatic testing (most of whom were represented at the workshop) were circulated with a protocol to provide the data for their own country for each year up to and including 1990, as well as to give details on the number of testing centres. Preliminary data were presented at the International Human Genetics Congress, Washington, USA, in November 1991, and were subsequently updated to include 1991 results. All tabular data were returned to the individual centres for verification. Results are considered to be essentially complete for all countries except for the USA, where a significant proportion of testing takes place in the private sector.

Results

Table 1 shows that 1479 completed presymptomatic tests for HD had been undertaken world wide by the end of 1991, with 14 countries having carried out more than 20 tests each. A further five countries had carried out a smaller number of tests. In 1991 the 14 principal countries contained 44 molecular genetics laboratories undertaking the tests, while 83 centres were responsible for the counselling (data for the USA are known to be incomplete).

The figure indicates the overall growth of testing during the past five years. Data from the USA, where several large research series were carried out during 1986, have been omitted from this figure, but are included in table 1.

A levelling off of testing activity is shown for

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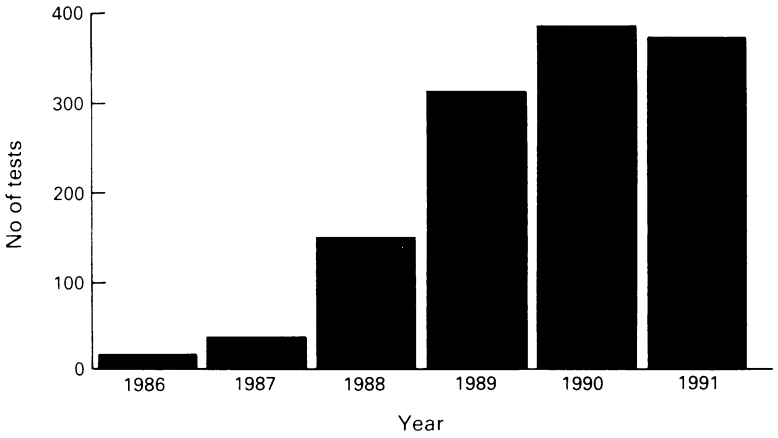
Table 1 Completed presymptomatic tests for HD up to the end of 1991.

Country	1986	1987	1988	1989	1990	1991	Total
Australia	0	2	4	8	19	35	68
Belgium	0	0	5	11	12	13	41
Canada	0	15	37	99	87	54	292
Denmark	0	0	0	16	23	12	51
Finland	0	0	0	4	2	2	8
France	0	0	0	0	26	7	33
Germany	0	0	0	3	13	12	28
Greece	0	0	0	17	25	12	54
Holland	0	0	12	21	40	63	136
Italy	0	0	15	9	18	31	73
Japan	15	10	14	15	0	0	54
Norway	0	0	0	0	0	41	41
New Zealand	0	0	0	0	0	2	2
South Africa	0	0	0	0	0	3	3
Sweden	0	0	0	0	4	3	7
Switzerland	0	8	20	2	12	11	53
United Kingdom	0	2	43	110	100	71	326
USA							201*
USSR	0	0	0	0	6	2	8
Total	15	37	150	315	387	374	1479

*Figure for USA represents tests performed up to the end of 1990.



Number of tests performed per year (excluding USA).

the years 1990 to 1991; a comparable pattern was seen when the analysis was confined to those countries that had begun testing before 1989.

No attempt was made in this survey to estimate the precise risk resulting from each prediction, but of the 1257 test results giving a significant risk alteration, 460 (36·6%) gave a raised risk, while in 797 (63·4) the risk was reduced. In 249 cases (16·5% of the overall total), no risk alteration was possible.

Discussion

It is clear from the data given here that presymptomatic testing for HD has now become an established service in many countries, with around 1500 persons from 19 countries having completed testing. This figure is likely to be a relatively small proportion of those who have requested testing initially, many of whom may have decided against proceeding with testing during the counselling process, while others will have had a pedigree structure not permitting testing by linked markers. It also represents an even smaller proportion of the total adults at risk for HD. If a mean prevalence of 4·0 per 100 000 is accepted, equivalent to a heterozygote frequency of around 10 per 100 000, the frequency of first degree relatives at risk for HD will be about twice this (20 per 100 000). In the total population of around 170 000 000 covered by the six countries where systematic testing had started before 1989, and including only those between the ages of 20 and 60 years (just over half the total population from UK data), this would suggest a total number of around 18 000 persons at risk. Only 5% have so far actually completed testing (table 2). The 2:1 ratio of low risk to high risk results corresponds with that already reported by individual centres and reflects the fact that many of those being tested have an age adjusted risk of considerably less than their 50% birth risk, though other factors could also be involved.

The proportion of 16% for test results where no risk alteration was possible is likely to represent an underestimate, since many subjects with an unsuitable pedigree structure will have been filtered out from testing programmes at an early stage, while data on uninformative results were not recorded for the UK and some other series.

The rapid spread of HD predictive testing across the world has been facilitated by the close links existing internationally between those working on the disorder, both clinicians and scientists. There has also been close cooperation between professionals and lay groups involved in framing protocols for testing and counselling,[11 12] and in undertaking continuing evaluation of the results of testing programmes.[13]

The apparent plateau in testing demand for countries where programmes have been longest established is likely to reflect the elimination of a 'backlog' of tests on those who had been waiting many years for the opportunity; it should be feasible to predict future demand if this steady state continues in future years. It is questionable whether the continuing growth in number of testing centres (table 3) is necessary or appropriate if experience and quality are to be maintained in the face of a constant total number of tests.

The HD gene has recently been isolated;[14] this may cause a further increase in demand for testing when residual uncertainty of risk because of recombination and the need for DNA samples from relatives is removed by the identification of a specific mutation. This development will undoubtedly simplify the laboratory testing process, but carries with it the risk that adequate counselling may not be offered if testing were to be performed by centres able to offer simple PCR based tests

Table 2 Completed tests for HD in relation to numbers at risk (approximate estimates).

Prevalence of HD	4·0 per 100 000
Heterozygote frequency	10·0 per 100 000
Total populations of countries involved	170 000 000
Proportion of population aged 20 to 59 years	90 000 000
Total at risk aged 20 to 59 years	18 000
Total number of tests in population involved	892
Proportion of those at risk actually tested	5·0%

The data cover those countries for which testing started before 1989, excluding the USA, where test data are incomplete, and Japan whose prevalence is around 10 times lower than most other populations. See Conneally[9] and Harper *et al*[10] for details of calculation.

Table 3 Results from testing centres.

Country	Risk				Centres	Laboratories
	Raised	Lowered	Uninform	Total		
Australia	21	47	21	89	4	4
Belgium	8	17	16	41	3	1
Canada	88	137	67	292	15	3
Denmark	21	18	12	51	1	1
Finland	2	8	0	10	1	1
France	10	15	8	33	1	1
Germany	7	21	8	36	2	2
Greece	11	28	15	54	1	1
Holland	50	77	9	136	1	1
Italy	15	45	9	69	2	2
Japan	9	23	22	54	1	1
Norway	11	22	8	41	1	1
New Zealand	1	1	0	2	1	0
South Africa	2	1	0	3	1	0
Sweden	4	2	1	7	2	2
Switzerland	11	19	23	53	5	2
United Kingdom	130	196	0	326	23	16
USA	56	115	30	201	23	8
USSR	3	5	0	8	2	1
Total	460	797	249	1506	90	48

but not expert in appropriate counselling. Those involved in HD presymptomatic testing are in general agreement that careful preparation and counselling should remain an essential and integral part of the testing process.

Most large centres currently involved in HD presymptomatic testing are undertaking long term follow up of those who have been tested, in particular those given a high risk result.[13] Even in extensive series, the number of such high risk subjects is limited, so the body of over 400 high risk outcomes world wide represents an important opportunity for collaboration in the monitoring of these subjects and for the detection, avoidance, and treatment of adverse responses. Such coordination of data will be of even greater importance when the possibility of effective therapy or prevention of onset exists for the disorder.

It is hoped that continued collection and analysis of these international data will be possible and that they will prove of value for those planning programmes of presymptomatic testing not only for HD, but for other important genetic disorders of later life for which presymptomatic testing will become possible.

Thanks are due to all the collaborating members from the various countries named in the appendix, and to the many others involved in the clinical and laboratory aspects of the testing programmes, as well as to the International Huntington's Association and World Federation of Neurology Research Committee for their encouragement to collect the data.

1 Gusella JF, Wexler NS, Conneally PM, *et al.* A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 1987;**306**:234–8.
2 Conneally PM, Haines J, Tanzi R, *et al.* No evidence of linkage heterogeneity between Huntington disease (HD) and G8 (D4S10). *Genomics* 1989;**5**:304–8.
3 Wasmuth JJ, Hewitt J, Smith B, *et al.* A highly polymorphic locus very tightly linked to the Huntington's disease gene. *Nature* 1988;**332**:734–6.
4 Meissen GJ, Myers RH, Mastromauro MSW, *et al.* Predictive testing for Huntington's disease with use of a linked DNA marker. *N Engl J Med* 1988;**318**:535–42.
5 Brandt J, Quaid KA, Folstein SE, *et al.* Presymptomatic diagnosis of delayed-onset disease with linked DNA markers. The experience of Huntington's disease. *JAMA* 1989;**261**:3108–14.
6 Fox S, Bloch M, Fahy M, Hayden MR. Predictive testing for Huntington's disease. I. Description of a pilot project in British Colombia. *Am J Med Genet* 1989;**32**:211–16.
7 Morris M, Tyler A, Lazarou L, Meredith L, Harper PS. Problems in genetic prediction for Huntington's disease. *Lancet* 1989;**ii**:601–3.
8 Tyler A, Ball D, Craufurd D, on behalf of the United Kingdom Huntington's Disease Prediction Consortium. Presymptomatic testing for Huntington's disease in the United Kingdom. *BMJ* 1992;**304**:1593–6.
9 Conneally PM. Huntington's disease: genetics and epidemiology. *Am J Hum Genet* 1984;**36**:506–26.
10 Harper PS, Morris M, Tyler A. Predictive tests in Huntington's disease. In: Harper PS, ed. *Huntington's disease.* London: Saunders, 1991:373.
11 World Federation of Neurology Research Group on Huntington's Disease. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J Neurol Sci* 1989;**94**:327–32.
12 World Federation of Neurology Research Group on Huntington's Disease. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. *J Med Genet* 1990;**27**:34–8.
13 Bloch M, Adam S, Wiggins S, Huggins M, Hayden MR. Predictive testing for Huntington's disease in Canada: the experience of those receiving an increased risk. *Am J Hum Genet* 1992;**42**:499–507.
14 The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;**72**:971–83.

Appendix List of persons and centres providing data on HD presymptomatic testing in different countries.

Australia	David Turner, Adelaide
Belgium	Gerry Evers-Kiebooms, Leuven
Canada	Michael Hayden, Vancouver
Denmark	Asger Sorenson, Copenhagen
Finland	Leena Peltonen, Helsinki
France	Yves Agid, Paris
Germany	Ulrike Thies, Gothagen
Greece	Christos Yapitzakis, Athens
Holland	Maria Vegter van der Vlis, Leiden
Italy	Paula Mandich, Genova
Japan	Ichiro Kanazawa, Tokyo
New Zealand	Caroline Lintott, Christchurch
Norway	Kare Berg, Oslo
South Africa	Trefor Jenkins, Johannesburg
Switzerland	Werner Schmidt, Zurich
Sweden	Maria Anvret, Stockholm
UK	Audrey Tyler, Cardiff
USA	Kim Quaid, Indianapolis
USSR	Oleg Evgrafov, Moscow