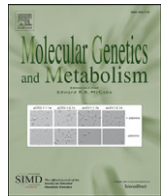




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Experience over fifteen years with a protocol for predictive testing for Huntington disease

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ABSTRACT

Objective: To compile a comprehensive profile of the participants who had predictive testing from Huntington disease (HD) between 1994 and 2008 in Montreal, Canada.

Method: This is a retrospective cohort study. The predictive testing protocol consisted of a telephone interview to give information about predictive testing and collect demographic data; a psychological assessment and counseling session; a session focused on medical and family history of HD; a session reserved for genetic counseling; a session where results were given to participants; and a follow-up telephone interview.

Results: A total of 181 applicants requested presymptomatic testing. 135 applicants (77 women and 58 men) completed the protocol and received test results while 40 withdrew. Of the latter, 3 manifested symptoms of the disease and were referred to a neurologist or psychiatrist, and 3 had previously been tested by linkage analysis. Participants usually mentioned more than one reason for requesting predictive testing but the most frequent was to put an end to uncertainty concerning their risk of illness. The proportion of positive and negatives test results was 40% and 54.1% respectively, significantly different from the expected 50% ($p < 0.01$). Prenatal testing was not frequently requested.

Conclusion: All the participants expressed satisfaction regarding their decision to be tested. None to our knowledge had a catastrophic reaction (major depressive disorder or psychiatric hospitalization, declared suicide attempt or suicide). Our study highlights that preparation for receiving test results is a psychologically complex process for which appropriate support in a timely fashion is critical. We feel that a cautious and ethical case by case approach remains essential and that high standards of testing should be maintained because of the far reaching impact of test results.

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1. Introduction

Huntington disease (HD), named after George Huntington, the physician who described this hereditary form of chorea in 1872, is a devastating degenerative neuropsychiatric disorder characterized by involuntary movements, personality changes, cognitive impairment, and depression [1–3]. It is an autosomal dominant disorder, and each offspring of a person carrying a mutation in the HD gene has a 50% risk of inheriting the mutation and eventually becoming affected with the disease. There is currently no means of prevention or medical treatment for this progressive and eventually fatal disorder [4]. The mean age of onset is 35 to 44 years [2], although the age of onset can vary from early childhood to as late as the eighth decade [5–7]. Symptoms progress without remission until death occurs, usually 15 to 20 years after onset [8]. The average age at death is 54 to 55 years

[9]. The prevalence of HD is estimated to be between 3 and 7 per 100,000 in populations of western European descent [2].

The discovery that the HD gene is located on the short arm of chromosome 4 in 1983 opened up the possibility of predictive testing and confirmation of diagnosis using linkage analysis (sensitivity 96% to 99%) [10]. After considerable debate and consultation among scientists, families and the lay organizations that represent patients and their families, a predictive testing program was developed and the first predictive test for the disease was offered in 1986 [11] in the context of a research protocol. In 1993, expansion of a CAG trinucleotide repeat in the HD gene (*IT15*) was identified as the pathogenic mutation [12]. This discovery allowed direct mutation testing and led to highly accurate predictive testing and confirmation of diagnosis, with sensitivity and specificity of virtually 100%. Direct mutation testing also obviated the need for family participation in predictive testing and allowed individuals greater autonomy and privacy [13].

Alleles of the HD gene can be subdivided into four main categories according to the size of the CAG trinucleotide expansion, reflecting the level of risk that they confer. Disease-causing alleles have ≥ 40

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CAG repeats and the normal alleles have ≤ 26 CAG repeats. In this article, the term «positive» refers to a CAG expansion causing disease and the term «negative» refers to an allele with a CAG number of repeats in the normal range. Alleles with 27–35 repeats are considered to be mutable because of instability in the CAG tract and thus may expand when transmitted to an offspring. These mutable alleles do not cause disease in the carrier but a child may inherit a disease causing allele if expansion occurs and the expanded number of repeats is in the disease causing range [14]. Alleles in the 36–39 CAG repeat range are mutable and can also cause disease, with reduced penetrance. Carriers of such alleles may pass on alleles with a greater number of repeats and they may develop the disease themselves, but in rare cases individuals will remain asymptomatic throughout their lives [6,15,16].

Diagnostic testing confirms that the clinical symptoms and signs of the disease observed in a patient are due to a mutation in the HD gene whereas predictive testing provides information about an individual's future [17]. Predictive testing for HD is now a worldwide accepted clinical application, allowing individuals from HD families to clarify their HD status. With predictive testing uncertainty remains concerning the moment when carriers of the HD gene will become symptomatic and how fast the disease will progress [17]. A therapy or a cure does not exist presently to modify the course of the disease. However, new approaches to treatment are being actively pursued [18].

As clinicians and researchers can learn from accrued experience and gain deeper insight into the complexity of the psychological issues related to predictive testing, we deemed it important to report our 15 years of experience with predictive testing for HD in the Montreal Predictive Testing Program. This was the only comprehensive predictive testing protocol using a multidisciplinary approach offered in the Greater Montreal Metropolitan area and immediate surroundings serving a population of approximately 3½ million. The aim of this paper is to present the data on all participants who completed the protocol, to report and analyse the uptake, the social and demographic characteristics, the reasons given by participant for requesting predictive testing, the test outcome, the emotional reactions of an unexpected nature or intensity to test results and to explore how best to fulfill participants' perceived needs.

2. Methods

2.1. Study design

This is a retrospective cohort analysis. Data on all consecutive participants who underwent predictive testing for HD at our centre between January 1994 and June 2008 were included in the study. Information was obtained through a detailed chart review performed by the psychologist who acted as clinical coordinator throughout the study period and was responsible for conducting and documenting the semi-structured interviews.

Our protocol for predictive testing for HD was conceived as a service protocol, taking into account the recommendations concerning the use of predictive testing for the detection of the HD gene drawn up in 1994 by a committee consisting of members of both the International Huntington Association (IHA) and the World Federation of Neurology (WFN) and the ethical conditions required for the application of predictive testing. As for the Canadian Collaborative Study of Predictive Testing for Huntington disease, four main ethical principles guided our approach to designing the protocol: autonomy, beneficence, nonmaleficence, and justice [19].

The test was offered to anyone with a documented family history of HD, without financial discrimination. It was offered to individuals who had reached the legal age of consent (age 18 in Quebec, Canada) who could attest that the decision to undergo testing was their own personal decision and whose decision was based on accurate

knowledge of the disease and its genetic determinants. Predictive testing was not offered to minors because of the absence of preventive or therapeutic benefit and in order to preserve their autonomy concerning an eventual desire to know or not to know their carrier status. Stigmatization within the family and in other social settings is a distinct possibility as well as serious educational and career consequences resulting from this knowledge [20]. All members of the professional team involved in the protocol made sure that the results of the test would be given to individuals whom the team felt were psychologically and emotionally equipped to safely deal with the predictive testing result. During counseling, great care was taken to avoid disclosing any information concerning related individuals. Participation in the protocol and test results could only be disclosed to a third party after specific written consent had been obtained from the participant.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. A family history of at least one case of confirmed HD and an *a priori* risk of 50% (parent affected or carrier) or 25% (grandparent or other second degree relative affected)
2. Age 18 or over
3. Capacity to give informed consent
4. Absence of outside pressure for testing
5. Willingness to follow the protocol.

Exclusion criteria for participation in the program were as follows:

1. Obvious neurological signs compatible with the presence of HD
2. Significant risk/declared intention of suicide
3. Current mental illness.

2.3. Professional team

The protocol was supervised by the same medical geneticist throughout the study and the same psychologist who performed all psychological evaluations and acted as clinical coordinator. Both had extensive experience with predictive testing for HD gained through prior participation in the Canadian Collaborative Study for Predictive Testing for Huntington disease. Genetic counseling was provided by a certified genetic counselor and test results were given by physicians with experience dealing with HD patients and their families. Service was provided in both French and English.

2.4. Interventions

The first contact had to be initiated by the patient. Although members of the professional team participated in educational presentations to both professional and lay groups, no attempt was made to initiate contact with individuals who had expressed interest for predictive testing in the past.

2.5. Phone contact with the psychologist

The initial call from applicants was referred to the psychologist who explored the applicant's knowledge and motivation for seeking predictive testing and who collected basic demographic information. General information about predictive testing and the protocol was given during this first telephone interview with the psychologist. Applicants who expressed a desire to undergo testing and requested an appointment were encouraged to be accompanied by a supportive partner, usually a relative and often a spouse, or a close friend throughout the protocol. However, some participants preferred to go through testing alone and their wish was respected.

2.6. First visit – psychological assessment and counseling

The primary objective of this two hour semi-structured clinical interview conducted by the psychologist was to evaluate the participant's psychological needs which were deemed to require attention prior to the disclosure of the test result. Participants were also invited to share how and when they became aware of the presence of HD in the family and of their personal risk, its emotional and psychological impact and how the presence of the disease in the family had affected their close relatives and influenced family dynamics (for instance: Was it a taboo subject? Was it a source of solidarity or of conflicts? Had they lived in the same household as an affected HD family member and, if so, how had it affected their emotional and family life?).

Participants were also invited to express their representations of the disease and their reasons for taking the test, along with the way they felt concerning the possibility of developing HD. They were encouraged to focus on their personal feelings and were asked with whom they would share the information whether or not they were gene carriers. Each participant was encouraged to identify his/her coping strategies and the extent of his/her social support. Any personal or family history of psychiatric illness was documented. Special attention was paid to any history of depression or suicidal ideation or attempted suicide in participants and attempted or completed suicide in relatives, as it is known that the suicide rate among persons with HD is estimated to be at least twofold higher than that observed in the general population [21–23]. Participants who exhibited suicidal symptoms or who contemplated suicide in the event of an unfavorable result were referred for professional help and excluded from the protocol.

Participants were asked to think out loud about what it might be like to experience predictive testing. This first visit with the psychologist provided an opportunity for the patient to anticipate losses, to grieve, to rehearse his/her possible reactions, to envision how their role within the family and society in general could change, and to draw realistic plans that would enable him/her to cope better whatever the test result turns out to be. The aim of this intervention was to avoid as much as possible catastrophic, albeit very rare, reactions after the result of the test was given to the participant [24]. For individuals who expressed some hesitation concerning predictive testing, participation in the protocol was delayed and they were referred to an appropriate support service. Those with obvious neurological signs compatible with the presence of HD were referred to a neurologist and those with evidence of a serious psychiatric condition were referred to a psychiatrist and a neurologist if warranted.

2.7. Second visit – interview with the physician and the psychologist

This one hour session took place about 4 weeks after the first visit except for prenatal testing where participants were seen within one week of phone contact and material usually covered in the first, second and third sessions was covered during the same visit for obvious reasons. The aim of this visit was for the physician to document the participant's medical history and any personal health issues, to review the family history of HD and to obtain confirmation of the diagnosis in affected key relatives. Often a next of kin had to be contacted by the participant in order to obtain medical confirmation of HD in an affected relative. The participant's exposure to the disease in affected relatives was explored and the medical features of the disease were explained. The participant was encouraged to discuss his/her personal concerns about the disease with the physician.

2.8. Third visit – genetic counseling

This two hour session took place 4 weeks after the second visit for most participants, but up to 8 weeks for a few participants because of

a delay in obtaining confirmation of the HD diagnosis in the family, for the participant's convenience or because of perceived emotional turmoil in the participant. It was conducted by a genetic counselor who gave information about HD inheritance, DNA testing and its reliability. A nondirective presentation of all options was given. The counselor informed participants that there was always a possibility that paternity might be an issue if HD was present in the paternal family. Worries regarding psychological harm and social discrimination were addressed as well as the possibility of insurance and employment discrimination. Although, a recent study based on data from Canada has found that genetic testing does not increase the risk for discrimination; perceived genetic risk is more due to family history of HD regardless of the gene status [25]. The genetic counselor made sure that the participants understood that after receiving their test result, their possibility of qualifying for life and disability insurance could be compromised. The family history was reviewed and additional counseling sessions were offered on an *ad hoc* basis.

After documenting informed consent, a blood sample was drawn for molecular testing. The participant was advised that the test result would only be ready in 4 to 6 weeks in order to conduct the necessary lab work and quality control tests. A personalized letter summarizing the information about the test was sent home so that the participant could review this information at leisure. When the lab team informed the clinical personnel that the test result was available, the psychologist contacted the participant to schedule the result visit at the participant's convenience. Throughout the protocol, participants were informed that they could delay the next session or withdraw from the protocol at any time, up to the moment of disclosure of the result of their test. The test results were only communicated to the physician and to the psychologist one day before or on the day of disclosure to the participant in case he/she withdrew from the protocol before receiving the result of the test, and to ensure that the professional team maintained a neutral attitude towards the participant.

2.9. Fourth visit – disclosure of test result

This session took place 4 to 6 weeks after the participant's blood was drawn. The participant was informed of the test result by the physician who was accompanied by the psychologist in a face-to-face interview. They made sure that the participant understood the result and its implications. Disclosure of test results by telephone, which was sometimes requested by participants, was always denied. Results were delivered in a supportive manner and the participants were given the opportunity to ask questions and express their feelings about the results. If the test revealed the participant to be a carrier of the HD gene, he/she was given the opportunity to be referred to a neurologist for assessment.

2.10. Follow-up

A follow-up session by phone was held one week after disclosure of the test result. During this session, the psychologist assessed the participant's emotional state and explored his/her initial reaction. A longer follow-up by the psychologist was available upon request by the participant.

2.11. Source of applicants

Applicants had usually heard about predictive testing for HD through family members, the Huntington Society of Quebec, the lay press or were referred to the program by their family physician, a neurologist or a psychiatrist. Most participants lived in the Greater Montreal Metropolitan Area and followed the protocol as described above. For those who lived at a significant distance from Montreal, a physician of their choice was provided with information about HD,

predictive testing and its results. Because of the complexity of the test and of the importance of optimal adjustment of participants to their new status revealed by predictive testing, sessions 1 and 3 were held in Montreal. The participant's physician was responsible for obtaining confirmation of HD in the family and for informing the participant of his/her test result. The psychologist conducted the follow-up session by phone as usual and the participant's physician provided additional support as needed.

2.12. Funding

Initially, establishment of the program and genetic testing was funded by a grant from Hydro-Quebec/FRSQ to encourage transfer of new technologies to clinical practice. Subsequently, the cost of genetic testing, including the visits leading to the result session and lab work, was covered by the provincial health insurance plan and private funding from the Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone.

3. Results

Between January 1st 1994 and July 1st 2008, 181 individuals (applicants) at risk for HD requested predictive testing. Among those who requested testing, 135 (participants), all of whom were of western European descent, completed the protocol and received test results. 40 withdrew from testing for various reasons at different stages of the testing protocol: 18 before the first visit, 21 after psychological counseling or later in the protocol up to the fourth visit (result session) where 1 individual did not show up at the result session in spite of the fact that she had confirmed her intention to attend the day before. Although reasons for withdrawal were not systematically compiled, some participants expressed their fear of being unable to cope with an eventual positive result as their reason for withdrawal. Some were deterred by the length of the protocol. Others withdrew after realizing that they had entered the protocol only because they felt pressured by family members or a health professional. Participants who thought that they were showing signs of HD and were seeking a medical diagnosis were referred to a neurologist and dropped out of the predictive testing protocol. Some participants were showing signs compatible with HD, but lacked awareness of the presence of early signs of the disease. Three participants were referred to a neurologist or a psychiatrist because they were showing clear signs of HD or were medically unfit to participate. If participants did not wish to learn that they were already affected, it was construed as a form of psychological defense and predictive testing was carried out. In such cases, predictive testing helps to prepare the participant for an eventual clinical diagnosis [26]. Individuals displaying symptoms of depression were referred for treatment before undergoing predictive testing. A personal history of psychiatric disease warranted subsequent rigorous follow-up. Three applicants had undergone linkage-testing previously and requested direct testing to confirm the linkage test findings and improve the level of accuracy of the previous test result (Table 1).

3.1. Social and demographic characteristics

The social and demographic characteristics of the 135 participants who completed the protocol are summarized in Table 2. It offers information regarding gender, age at time of psychological counseling, marital and family status, occupation, schooling, self-reported psychiatric history and use of psychotropic drugs.

The gender distribution was 58 men (43%) and 77 women (57%) – a statistically non significant gender difference (z statistic). The mean age of participants was 36.4 years ($SD = 10.3$, range: 18–67 years, median 36.2), 36.2 years for men (median 35.3) and 36.6 years for women (median 37.0). Most participants were either married or lived in a

Table 1

Distribution of the total number of applicants with respect to the outcome of their participation.

	N	%
Applicants	181	100
Tested (participants)	135	74.6
Dropped out	37	20.4
Prenatal testing (dropped out)	3	1.7
Referred to a neurologist or a psychiatrist (withdrawn)	3	1.7
Retested by direct lab method (withdrawn)	3	1.7

Table 2

Social and demographic characteristics of participants.

Variable	
<i>Gender</i>	
Women	77 (57.0%)
Men	58 (43.0%)
Total	135
<i>Age</i>	
18–30	44 (32.6%)
31–40	48 (35.6%)
41–50	32 (23.7%)
51–60	10 (7.4%)
61–70	1 (0.7%)
<i>Average age</i>	
Male	36.2 years
Female	36.6 years
Overall	36.4 years (SD: 10.3)
<i>Marital status</i>	
Single	26 (19.3%)
Married/common-law	95 (70.4%)
Separated/divorced	14 (10.4%)
<i>Number of children</i>	
None	58 (43.0%)
One or more	77 (57.0%)
<i>Occupation</i>	
Academic/professional	35 (25.9%)
Skilled worker	36 (26.7%)
Unskilled worker	43 (31.9%)
Student	6 (4.4%)
Homemaker/unemployed	15 (11.1%)
<i>Education</i>	
Some college and above	58 (43.0%)
High school and below	63 (46.7%)
Unknown	14 (10.4%)
<i>Self-reported history of mental health disorder</i>	
Positive	54 (40.0%)
Negative	81 (60.0%)
<i>Type of mental health disorder and number of episodes?</i>	
Major depressive disorder	21
Anxiety disorder	9
Substance-related disorders	7
Anxiety and depressive disorder	6
Adjustment disorders	3
Substance-related disorders associated with anxiety and depressive disorder	2
Schizophrenia	1
Substance-related disorders associated with major depressive disorder	1
Unspecified psychiatric illness	4
<i>Psychotropic medication</i>	
Antidepressants	12
Anxiolytics	4
Unspecified	8

common-law relationship (70.4%); 26 (19.3%) participants were single; 14 (10.4%) were either divorced or estranged from their spouse; 77 (57.0%) had one or more children. With regard to occupational status, 35 (25.9%) were academics or professionals, 36 (26.7%) were skilled workers, 43 (31.9%) were unskilled workers, 6 (4.4%) were students and 15 (11.1%) were homemakers or unemployed.

Data on the level of education was available for 90% of the participants (52 men and 69 women). Among men, 31 (60%) had a college or university education. This proportion dropped to 33 (48%) out of 69 for women participants. The difference between the proportions of men and women with a college or university education was not statistically significant.

3.2. Reasons given for requesting predictive testing

There was usually more than one reason given for undergoing predictive testing and the reasons were quite varied. The most frequent reason given was to put an end to uncertainty concerning their risk of illness (Table 3). The three other main reasons were: 1) to decide about having (any or more) children; 2) to plan their future in general; 3) to give their offspring more definitive estimates of their own personal risk and thus enable them to make informed decisions concerning family planning. Some reasons were less common but are however important to mention: to protect one's children against physical and psychological violence. These participants had been victims of violence from the affected parent and felt that it was his/her responsibility to ensure that the same situation would not befall his/her own children. One participant openly admitted that he/she was involved in supporting the cause for HD out of fear for his/her future welfare. If confirmed as a non-carrier, he/she intended to distance himself/herself from a perceived family burden and to tone down his/her participation in HD related activities. Another participant who experienced problems at work because of behavioural issues requested predictive testing to protect himself/herself from a wrongful dismissal.

3.3. A priori risk

All participants save one had a family history of HD. For participants with an *a priori* risk of 25%, the predictive test may modify the risk

status of other family members, such as an at-risk parent who may not wish to know of his or her status. In such cases, the applicant was encouraged to discuss this issue with the at risk parent. If the parent at 50% risk was alive and wished to undergo predictive testing, he/she was advised to go through the protocol and receive the test result before his/her offspring. If the parent declined to be tested, the rights of the individual at 25% risk to undergo testing prevailed. The *a priori* risk was 50% in 133 (98.5%) participants and 25% in one (0.7%) participant. One woman (0.7%) who had no family history of HD requested to be tested because her daughter had recently been diagnosed with HD. She wanted to make sure that she was not a carrier. She suspected that the HD gene came from her daughter's father with whom she had had no contact for many years.

3.4. Test outcome

Of the 135 participants who completed the protocol and received their test results, 73 (54.1%) carried 2 normal size alleles of which 40 were women (54.8%) and 33 were men (45.2%); 54 (40.0%) were gene positive of which 32 were women (59.3%) and 22 were men (40.7%); 5 (3.7%) had CAG repeat lengths in the intermediate zone of which 3 were women and 2 were men and 3 (2.2%) in the zone of reduced penetrance, 2 women and 1 man (Table 4). We did not routinely report the size of the CAG expansion to the participants because of the relative imprecision of this information and its potential misinterpretation by participants and eventual detrimental consequences. Even though there is a well-established inverse correlation between age of onset and repeat length [27,28], paternal versus maternal transmission [29,30], an interaction between the expanded CAG length and the length of the normal allele [31], and other genetic and environmental factors are also thought to contribute to the variance in age of onset of HD [32]. If requested specifically by individual participants, the information was given along with clear indications as to the uncertainty of predicting the age of onset based on the number of CAG repeats.

3.5. Reported psychiatric disorders or affective disturbances and psychotropic medications

With respect to self-reported past or present psychiatric history (one or a combination of the following psychiatric disorders or

Table 3
Reasons given for requesting predictive testing for Huntington disease and their frequency.

Reason given as	1st motivation	2nd motivation	3rd motivation	4th motivation	5th motivation	Total number of times expressed
To relieve uncertainty about the risk of illness	76	23	6	0	1	106
To decide about having (further) children	29	12	9	0	0	50
To plan future in general	11	23	9	4	0	47
To give their offspring a more definitive estimate of their personal risk and allow them to make an informed decision about family planning	8	23	13	2	0	46
To investigate their beliefs of having already developed HD	4	5	3	1	1	14
To decide about finance and prepare legal will	1	3	7	1	0	12
To look for guidance and start treatment in the event of a positive test	1	4	4	1	0	10
To make educational and career choices	1	3	3	0	0	7
To decide about marriage/relationship	0	3	0	2	0	5
To inform and prepare family with the disease	1	2	0	1	0	4
To satisfy a family member (spouse or relative) who experience difficulty with uncertainty	0	1	0	1	0	2
To enable subscription to a life or mortgage insurance	0	0	1	1	0	2
To protect oneself from an unfair dismissal	1	0	0	0	0	1
To take early arrangement for admission in a long-term care centre	0	1	0	0	0	1
To protect one's children against physical and psychological violence	0	1	0	0	0	1
To enable the identification of the first symptoms	0	1	0	0	0	1
To allow the spouse to make an enlightened choice about staying or leaving the relationship	0	0	1	0	0	1
To cease investing time in the HD cause if confirmed as a non-carrier	0	0	0	1	0	1
To request an abortion if she is a gene-carrier	1	0	0	0	0	0

Questions about reasons were open-ended; one to five reasons were given.

Table 4
Outcome of predictive testing for the 135 participants.

	Number of subjects	Relative size of group	Number of men	Number of women	Average age of men	Average age of women	Average age of group
Normal (CAG \leq 26)	73	54.1%	33	40	37.8	36.4	37.0
Intermediate (CAG 27–35)	5	3.7%	2	3	37.0	44.4	41.4
Reduced penetrance (CAG 36–39)	3	2.2%	1	2	58.7	33.2	41.7
Gene positive (CAG \geq 40)	54	40.0%	22	32	32.7	36.4	34.9
Total	135	100%	58	77	36.2	36.6	36.4

affective disturbances: anxiety, panic attacks, depression, suicide attempts, schizophrenia, alcoholism, drug addiction, adaptation or personality disorders) 51/132 (38.6% – missing information on 3 individuals) participants reported a previous psychiatric illness, 30/77 (39%) women and 21/55 men (38.2% – missing information on 3 individuals). The difference between the proportion of men and women reporting a psychiatric history was not statistically significant. We compared proportion of the HD gene carriers and carriers of normal alleles (intermediate and reduced penetrance carriers were excluded from the analysis). 23/53 (43.4% – missing data on 1 individual) were gene carriers and 27/71 (38% – missing data on 2 individuals) were carriers of normal alleles. The difference was not statistically significant. The same holds true if data is analysed separately for women and men. Moreover, the average age of carriers of the HD gene reporting a past or present psychiatric disorder or affective disturbance (40.15 years) was higher than the average age of the HD gene carriers without such a personal history (30.35 years), the same holds true if the data is analysed separately for women (43.58 versus 30.72 years) and men (34.83 versus 29.80 years).

Among the 135 participants, 15/77 (19.5%) women and 9/56 (16.1% – missing information on 2 individuals) men reported using psychotropic medications at the time of the evaluation. The difference between the proportion of women and men reporting use of psychotropic medications was not statistically significant. We then compared the proportion of HD gene carriers 14/53 (26.4% – missing information on 1) and carriers of normal alleles 8/72 (11.1% – missing information on 1 individual) reporting present use of psychotropic medications. The difference was statistically significant ($p=0.0132$). The same analysis on data analysed for women and men separately yielded a significant result for women ($p<0.05$) but not for men ($p=0.0764$).

3.6. Prenatal testing

Pregnant women were encouraged to postpone predictive testing for themselves until after their child was born unless prenatal testing was elected to determine the outcome of the pregnancy. Therefore, prenatal testing was offered only to couples who were considering termination of pregnancy as an option. We discussed with the couple the potential impact of knowing that this child is an HD carrier on raising the child and also their child's right to make his/her own decision about resorting to predictive testing eventually. One woman requested predictive testing for herself because she was pregnant and did not want to go through with the pregnancy if she was a carrier, regardless of the risk status of the fetus. She completed the protocol and thus is considered as a study participant. Three pregnant women with pregnancies at 25% risk started the protocol but later abandoned it for various reasons: one woman had felt pressured by her doctor to request testing and she realized that she did not really want to know her status. She dropped out after the counseling session. Another woman who requested exclusion testing abandoned the protocol after the counseling session because she considered that her pregnancy was too advanced and she did not wish to undergo an abortion if the fetus could not be confirmed as a non-carrier. The third pregnant woman did not show up for the counseling session.

4. Discussion

The data presented here reflect the experience of the Montreal Predictive Testing Program based at the McGill University Teaching Hospitals, from January 1, 1994 to July 1, 2008. The most important objectives of the predictive testing protocol were to help people make an informed decision regarding predictive testing, based on their own judgment and personal circumstances, and to prepare them to deal in a positive way with their test result. In light of the clinical and genetic knowledge about HD they have acquired through the program and considering their personal experience and emotions, each participant was invited to reflect on a very personal issue, namely if clarifying their genetic status was likely to improve their quality of life. Although for most participants the test eliminates uncertainty concerning their carrier status, it does not pinpoint the time of onset of the disease in carriers of the HD gene.

For persons at risk for HD, the decision to undertake predictive testing is complex and emotionally challenging [33]. Before the introduction of predictive testing, high interest towards such a test had been expressed by about two thirds of at-risk persons interviewed [34–36]. Since its introduction in 1986, it is estimated that uptake has been less than 20% among the at-risk population [37–40]. It has been suggested that those who opt for genetic testing are those who are best equipped emotionally to deal with the test results [33,41]. They have been described as a resourceful and self-selected group [42]. Conversely, there is evidence that some at-risk individuals avoid testing because of fear of being unable to cope with the result [33]. Other reasons given for choosing not to be tested were: the risk to relatives, the lack of treatment or cure, and fear of losing one's health insurance [43].

We estimated that 9.2% of the at risk population of the Greater Montreal Metropolitan Area requested predictive testing during the study period, a figure lower than that reported in a number of Canadian provinces, ranging from 12.5% to 20.7% [13] but higher than that reported in France (5%), Germany and Austria (3–4%), and South Africa (4.5%) [13,44]. The highest figure reported is that for the province of British Columbia, Canada, probably owing to the fact that the initial protocols for HD predictive testing were developed in Vancouver where there is ongoing research on HD and close links to the HD population. The total number of test participants was relatively stable throughout the study period, with a slightly larger number of applicants in 1994 and 1995 and a second surge between 2003 and 2005 (Fig. 1). There were probably more applicants during the first two years because a number of individuals may have been waiting for the direct mutation test. Up to 1993, presymptomatic testing was based on the use of closely linked genetic markers which required the collaboration of family members, a fact that may have deterred a number of at risk individuals. We do not anticipate a remarkable increase in demand for predictive testing until means of delaying the onset or treating the disease are found. Easier access to assisted reproductive technologies will undoubtedly increase the demand for presymptomatic testing.

A total of 181 applicants requested presymptomatic testing for HD over a 15 year period in Montreal. The gender ratio (61.9% women) corroborates preceding international reports of a female predominance among those tested [13,45–47]. Possible explanations for this

discrepancy include greater involvement of women in family and reproductive decisions [42] and a greater willingness of women to face up to difficult personal decisions and their consequences [48]. This gender difference in attitude concerning predictive testing could also be explained by the fact that women have a higher perception of their own ability to cope with an adverse result than men and they are more prone to share with others their genetic status [49].

Most participants who requested testing were in their mid-30s (mean age 36.4, for women 36.6 and for men 36.2) whereas the mean age reported in some previous studies is closer to 40 [46,50]. This age difference seems to us to be relatively important. A possible explanation could be that older individuals who wanted to know about their HD status had already availed themselves of predictive testing when it was first offered as a research protocol. Fifty seven percent of participants already had children by the time they requested predictive testing whereas in other studies a greater percentage of participants already had children (67%, 64.7%) [13,46] which is conceivably related to the older age of their study subjects. In the general Canadian population, 55.4% have children [Statistics Canada. CANSIM, 2001, <http://www.statcan.ca>], a figure similar to our finding. The level of education of participants, 52.9% having completed a college or university education (60% for men, 48% for women) is comparable to that of the general Canadian population at 50% [Statistics Canada. CANSIM, 2007, <http://www.statcan.ca>].

The rate of self-withdrawal in this study was 22.1% (40/181), a rate similar to that reported in other studies, namely in a United Kingdom study (25%) and one from Leiden, The Netherlands (23%), but notably different from an Australian study (14.3%), a Mexican study (12%) and an Italian study (51%) [38,46,51–53]. It is noteworthy that 21.5% of individuals abandoned testing after the first phone interview (for some, more than one phone interview was carried out) or the first visit. This high withdrawal rate early on during the protocol can be viewed as a form of last minute self-selection and reinforces the importance of the counseling process and of a pause between the first contact and the test result. In our view, counseling to explain the risks and benefits of testing is an essential prerequisite for a safe and efficient integration of predictive testing in the health-care system. For many individuals, the decision to undergo predictive testing is a difficult one. They experience an important degree of ambivalence when making the first contact with the professional team and this ambivalence can persist throughout the process. These individuals are torn between their desire to know and their desire not to know their status. The coexistence of these two desires and the motivational competition that plays out in their psyche is very strong. They are facing two possibilities which, in their eyes, entail as many advantages as disadvantages and the decision process can be a stressful experience.

The proportion of positive and negative test results in Montreal was 40% (54/135), and 54.1% (73/135) respectively, significantly different from the expected 50% ($p < 0.01$). This is similar to 38% and

56% positive to negative test results in Australia [54] and 45% and 55% in the Canadian study [55]. This could be explained by the fact that individuals born at 50% risk and who present for testing as adults have a significantly lower level of risk the longer they remain asymptomatic [56,57]. In Montreal, 3.7% (5/135) of test results were in the intermediate zone (27–35 CAG repeats) and 2.2% (3/135) in the zone of reduced penetrance (36–39 CAG repeats), which compares to 2.6% of the test results in Mexico [53], 6% in Australia which were in the intermediate or reduced penetrance zones, and higher than the 1.5% found in the UK study [45], even though in this study the “uncertain intermediate” zone was defined as 31–38 CAG repeats. In our study, only 0.7% (1/135) had a prior risk of 25%, which is lower than that of 6% reported in Australia [54], 6.9% in the UK, and 9% in the Dutch studies [13] and 9.8% in the Canadian study. Only one participant in our study came with an *a priori* 25% risk. It is well known that this situation may raise ethical and counseling dilemmas because of possibly conflicting interests of two related parties [52,58]. Fortunately, in our case, after counseling the parent agreed to be tested before the offspring.

Prenatal testing was not frequently requested. Reluctance to have prenatal testing for adult-onset disorders in general is thought to contribute to the low uptake [10]. We are aware of the fact that a number of cases of prenatal testing in our area are managed by obstetricians who send the blood samples to be tested directly to the lab and ultimately transmit the results to the patients. In our cohort, one woman requested testing for herself (not the fetus) early during her pregnancy because she did not wish to become a mother if she turned out to be a carrier. One man came in a rush to get tested because his spouse was pregnant. The couple had agreed to have the fetus tested if his test revealed that he was a carrier. As already noted in another study [59], women in our cohort sought prenatal testing when they were already pregnant. Four pregnant women requested prenatal testing and started the protocol, but abandoned it before the test was done on the fetus. Three were ambivalent concerning prenatal testing and the possibility of terminating the pregnancy. One of them mentioned that she would have had the test done on the fetus if she had entered the protocol earlier in the pregnancy. Two were uncomfortable with the idea of an abortion and came to us to explore their options. One of these two came to us on the advice of her physician. She stated that she had felt pressured by the physician to undergo testing and she eventually decided to forgo prenatal testing. The fourth woman's husband was at 50% risk and did not want to know his personal status, whereas his wife had assumed that he would be willing to be tested when she became pregnant. The couple was uncomfortable with exclusion testing, performed by linkage analysis without revealing the at-risk parent's status, because of the possibility of aborting a non-carrier fetus. After counseling she realized that she had to respect her husband's right not to know. They decided to go on with the pregnancy without resorting to prenatal testing. The interest for prenatal testing has also been very low in other centres, in the past because of reluctance to have prenatal testing for adult-onset disorders in general [10].

Uptake of predictive testing for refinement of their risk estimate by applicants who had already received results using DNA markers has been low. The 3 applicants were women with a low risk whose tests had been done by linkage analysis. Since they had already taken part in the Canadian Collaborative Study of Predictive Testing for Huntington disease, they did not participate in the service protocol and hence are not part of our study. The fact that these three individuals had a low risk is not consistent with the expectation that individuals with a low risk would resort again to predictive testing by the direct lab method in order to obtain a definitive level of risk because they have more to lose, since there is still a small possibility that their risk status will be reversed [51]. In our study, one woman who was at low risk according to linkage analysis was expecting a result that would eliminate any doubt for herself and her children. She

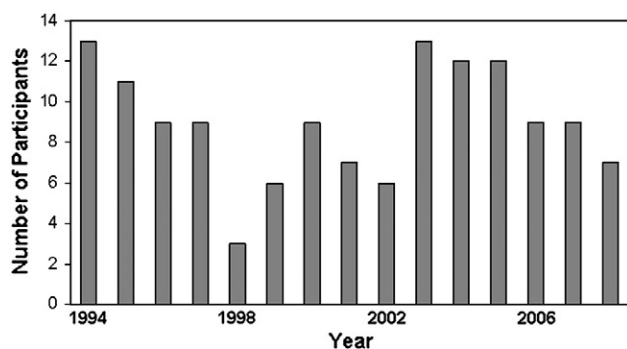


Fig. 1. The number of participants applying for presymptomatic testing during each year of the study period.

was found to be carrying an allele with an intermediate size repeat, inherited through the unaffected side of her family. She experienced confusion and disbelief at first and a period of distress following the revelation that she will be spared from HD, but that there is a small risk that her descendants may not be. She requested additional sessions with the genetic counselor and with the psychologist. It took time for her to adjust to her new status. Other authors have reported similar challenging counseling issues due to the difficulty of giving definite information to individuals about their risk of developing HD and of transmitting it to their descendants [54].

Our study reports the reasons expressed by participants during psychological counseling. The most frequent reason mentioned was to relieve uncertainty about the risk of illness. The fact that the first motivation reported was for personal benefit, namely ending the threat of loss of personal integrity, was reassuring. The test should be primarily for the benefit of the individual who is at risk and be requested without undue outside pressure. Unconscious as well as conscious motives underlie the reasons for requesting predictive testing [60]. Anxiety generated by the threat of loss of personal integrity can be compounded by uncertainty about the loyalty of the present life partner. Other important reasons were to decide about having children, to plan their future in general and to provide their offspring with a precise estimate of their own risk and enable them to make an informed decision about family planning. Several authors have mentioned the fact that the test applicants who bring up family planning as one of the major reasons for having predictive testing and who receive a positive test result are confronted with new decision difficulties and an additional emotional burden [60,61]. Carriers of the HD gene with the desire to have children have many options, namely using prenatal diagnosis, artificial insemination with donor sperm, IVF with donor eggs, preimplantation genetic diagnosis and adoption. These participants were invited to contact the genetic counselor at their convenience if they desired to explore these possibilities, to help them choose among these options and, if warranted, to refer them to appropriate services. Planning their future often included financial issues, career decisions and leisure activities such as traveling. We invited to expand on these issues, we noticed that for some individuals their planning was realistic, but for others it seemed more like an impossible dream, given their family and economic circumstances. When confronted, many realized that they could not fulfill certain wishes in the near future, like worldwide travel for instance, because of their present responsibilities.

Predictive testing for HD is likely to elicit anxiety and adapting difficulties among participants and their loved ones. It is difficult for anyone to prepare in advance for adverse events which have profound personal and interpersonal implications, are threatening to the person's health and integrity [41] and are likely to change the person's role in the family and society. Whatever approach the psychologist adopts, the participant is likely to experience some degree of stress [41]. Exposure to anxiety-provoking thoughts in a safe and supportive environment provides an opportunity for the individual to anticipate losses, to identify their personal coping mechanisms and to foresee their reactions [62]. Projecting themselves in the future allowed some participants to plan for it and work through some of the difficulties in advance as in anticipatory grief work [62]. Moreover, the amount of social support and psychological resources that people possess also influences their ability to cope. Social support serves as a moderator of life stress because the individual feels that he/she is loved, esteemed and a member of a close network and appears to protect people in crisis from a variety of pathological states [63]. Since intimate relationships are likely to be disturbed by the test result, sentimental partners may show distress and their plight is often ignored [53,64].

Regardless of the test outcome, some individuals may experience psychological difficulties and will need time to adjust to their new reality. Most participants who found out that they are not at risk for

HD feel relief, diminished anxiety and fear, and they are reassured concerning the future of their children. "Survivor guilt" [65,66], a guilt feeling elicited by the knowledge that they are spared from HD, can be a negative consequence of predictive testing for non-carriers and a source of psychological distress. This guilt is very strong in some individuals and can be a source of disruption in relationships. Paradoxically, some individuals will be relieved to learn about their own carrier status because they had anticipated feelings of guilt towards HD carriers or affected close family members. One individual in our cohort, who was informed of her HD carrier status, said that she felt that it would have been unfair if her sibling, a carrier, had been the only one receiving a bad news. She belonged to a closely knit family and said that this way they would stick together and be stronger to face illness and death.

The disclosure of a carrier status may lead to psychological distress and marital difficulties [67,68]. Many at-risk participants mentioned their fear of abandonment or rejection. We often witnessed participants who expressed fear that their partner might leave them after the result was known or when illness or major incapacity developed. Some participants who felt guilty to impose their eventual illness on their life partner verbalized in the presence of the latter that they would understand if he/she decided to leave the relationship. Others who felt that their partner was less committed to the relationship have also openly expressed their willingness to break off the relationship in the event of a positive result. The reluctance to disclose risk of HD to children may also be a manifestation of the fear of abandonment or rejection. This reluctance may also be motivated by shame, fear of ostracism and a tradition of secretiveness in the family. Some expressed feelings of guilt at the thought that they might have passed on a deleterious gene to their children and, under the pretext of "protecting" them, were tempted to hide their carrier status. Others perceived their teenaged or young adult children as emotionally fragile and feared destabilizing them and compromising their normal psychological development. The role of the psychologist is to enable the free expression of fear of abandonment and/or of rejection, facilitate open communication between partners and help them deal with painful emotions.

Fear of genetic discrimination was expressed by a number of participants. Genetic discrimination following predictive testing continues to be a concern [69]. Genetic discrimination against individuals who are at risk for HD is still perceived to be prevalent in insurance (29.2%), family (15.5%) and social settings (12.4%) [25]. In Canada public health insurance makes it less likely when compared to other countries, like the United States, to experience discrimination in health care [70]. Keeping their at risk status or test result private is a strategy often used by at risk individuals [25]. In fact, one of the participants was a foreign citizen who came to Montreal to undergo predictive testing for HD to ensure that she would not be a victim of discrimination from insurance companies in her country of origin and to minimize the possibility that family members and personal friends or employer would be aware of her participation.

It is worth mentioning that about 39.3% of participants reported a personal history of mental illness. Life-time prevalence of mental disorders in the general Canadian population is reported to be 20%, a figure similar to that generally reported for industrialized nations as "1 out of 5". Even though our study was not designed to evaluate the prevalence of psychiatric disorders in our cohort, we noted a high rate of self-reported past or present psychiatric disorders or affective disturbances in participants carrying an HD allele. The fact that the HD gene carriers with such a personal history were older than those without is compatible with the view that these individuals could have already entered the prodromal phase of HD which is thought to last from several months to years [71].

In our cohort, no participant has expressed regret for undergoing the test and none, to our knowledge, have had catastrophic reactions, such as a major depressive disorder or psychiatric hospitalization,

declared suicide attempt, or suicide. We feel that many aspects of the protocol have a major role in avoiding possible deleterious consequences of test results. Firstly, the inclusion and exclusion criteria were strictly followed. Secondly, the length of time between the first visit and the result leaves the participants enough time to re-evaluate the decision to go through testing and induces a sort of self-selection by which only those participants likely to possess adequate psychological stability and coping abilities make it to the test result disclosure. Thirdly, during the psychological counseling with the psychologist, the participants were invited to anticipate all possible consequences and evaluate carefully their ability to cope with all possible results. The importance of this session is revealed also by the high percentage of applicants who decided to withdraw from testing after this session because they realized they were not ready to cope with the many consequences of the test, the timing was not good for them or they realized that their anxiety and displeasure with life were only partly due to being at risk for HD. Fourthly, the fact that almost all participants were sharing the experience of the testing protocol with a person close to them gave them the opportunity to express feelings about the test and benefit from emotional support.

A number of participants spontaneously expressed reservations towards our predictive testing protocol. Some considered that the process was too long, entailed too many sessions, and they would have preferred to have their blood drawn at the first visit and receive their result the following week. In fact, one participant abandoned the protocol for this reason and resorted to services offered by the private sector. Others were anxious and unhappy to have to comply with the protocol and perceived the psychological assessment as menacing and the questions regarding their personal life as intrusive, threatening their liberty to choose what is good and suitable for themselves. They expressed fear that presymptomatic testing would be withheld because of their previous mental history or their current psychological state. The applicants who, because of their personality, were not in touch with their emotions and feelings, found that the sessions were difficult, particularly the clinical interview with the psychologist, because she urged them to reflect on their emotions and extrapolate their reactions to the test result. We have noticed that those who were more vulnerable had more difficulty going through our structured counseling and testing protocol. We are aware of the fact that some participants may have withheld information, given false information or hidden their true feelings because they feared that presymptomatic testing would be denied to them because of their psychological state or their motivations for taking the test. However, the majority of participants valued the personal approach. They understood the importance of every step of the protocol and considered it to be a responsible way of practicing of medicine. They considered the attention paid to the potential impact of the test as a mark of respect towards them, an opportunity to recognize strengths and skills and to develop coping strategies. Some took the opportunity to share personal and family issues related to HD, looking for professional support. It would have been interesting to systematically follow up on participants to evaluate satisfaction and impact of our predictive testing protocol through a questionnaire as was done for the Canadian Collaborative Study for Predictive Testing for Huntington disease [3]. Very few participants took advantage of the offer of a longer follow-up. However, it is known that some at risk persons, up to 19% in one study, may not accept professional help even when in crisis [72], presumably because of a lack of social skills, personality factors such as avoidant or schizoid tendencies, or a wish to distance themselves from a stressful experience. We also have very little information on the impact of predictive testing on the individual from a life cycle perspective, or on couples, the family, social relationships, employment and financial issues.

In predictive testing, the uniqueness of each person, their personality traits and personal history, their present aspirations and future projects confer them a different degree of sensitivity and

vulnerability and has an impact on their interpretation of situations and type of reactions to stressful events. Under such circumstances, some respond with anxiety, others with depression, guilt or anger. Individuals who had a close personal experience of HD, having lived with an affected parent, often had more apprehension about the future, particularly if the affected relative manifested behavioural problems such as aggressive traits, irrational ideas and poor judgment in decision-making. A person's mood and coping skills before testing are a better indication of how they will react to their test result than is the result of the test itself. Those who are distressed or who possess poor coping skills before they undergo genetic testing are particularly at risk of an adverse psychological outcome after testing, and they need to be identified and given additional support early on [73].

Our study highlights the fact that preparation for receiving test results is a psychologically complex process for which appropriate support in a timely fashion is critical to a favorable outcome. More research on the long term impact of predictive testing on the individual, their family and the socio-economic circumstances needs to be done in order to optimize the benefits to participants. Since the diagnosis of HD is based mainly on motor signs of the disease, further study of the psychological disturbances and psychiatric disorders occurring in HD gene carriers in the presymptomatic phase of the disease is warranted in order to offer a more adequate diagnosis and treatment and optimize their quality of life and that of their loved ones. We feel that a cautious and ethical case by case approach remains essential and that high standards of testing should be maintained because of the far reaching impact of test results particularly as integration of predictive testing to clinical practice is imminent. Predictive testing for HD has been established as a valuable integration of molecular biology technology to clinical practice and has often been used as a model for other genetic disorders. As research progresses towards preventative or therapeutic interventions for many genetic disorders, the integration of predictive testing to clinical practice is imperative. Hopefully, in the near future, predictive testing will become the first step leading to targeted clinical interventions in at risk individuals.

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References

- [1] S.M. Cox, Stories in decisions: how at-risk individuals decide to request predictive testing for Huntington disease, *Qual. Sociol.* 26 (2003) 257–280.
- [2] G. Bates, P.S. Harper, L. Jones (Eds.), *Huntington's Disease*, Oxford University Press, New York, 2002.
- [3] T.T. Copley, S. Wiggins, S. Dufrasne, M. Bloch, S. Adam, W. McKellin, M.R. Hayden, Are we all of one mind? Clinicians' and patients' opinions regarding the development of a service protocol for predictive testing for Huntington disease, *Am. J. Med. Genet.* 58 (1995) 59–69.
- [4] B. Meiser, S. Dunn, Psychological impact of genetic testing for Huntington's disease: an update of the literature, *J. Neurol. Neurosurg. Psychiatry* 69 (2000) 574–578.
- [5] R.A. Roos, V. Vegter-van der Vliet, J. Hermans, H.M. Elshove, A.C. Moll, J.J. van de Kamp, G.W. Bruyn, Age at onset in Huntington's disease: effect of line of inheritance and patient's sex, *J. Med. Genet.* 28 (1991) 515–519.
- [6] D.R. Langbehn, R.R. Brinkman, D. Falush, J.S. Paulsen, M.R. Hayden, A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length, *Clin. Genet.* 65 (2004) 267–277.

- [7] A. Coustasse, A. Pekar, A. Sikula, S. Lurie, Ethical considerations of genetic presymptomatic testing for Huntington's disease, *J. Hosp. Mark. Public Relations* 19 (2009) 129–141.
- [8] M.R. Hayden, *Huntington Chorea*, Springer Verlag, New York, 1981.
- [9] B. Harper, *Huntington disease*, *J. R. Soc. Med.* 98 (2005) 550.
- [10] J.F. Gusella, N.S. Wexler, P.M. Conneally, S.L. Naylor, M.A. Anderson, R.E. Tanzi, P.C. Watkins, K. Ottina, M.R. Wallace, A.Y. Sakaguchi, A polymorphic DNA marker genetically linked to Huntington's disease, *Nature* 306 (1983) 234–238.
- [11] M.R. Hayden, Predictive testing for Huntington's disease: a universal model? *Lancet Neurol.* 2 (2003) 141–142.
- [12] 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* 72 (1993) 971–983.
- [13] S. Creighton, E.W. Almquist, D. Macgregor, B. Fernandez, H. Hogg, J. Beis, J.P. Welch, C. Riddell, R. Lökkesmoe, M. Khalifa, J. MacKenzie, A. Sajoo, S. Farrell, A. Shugar, A. Summers, W. Meschino, D. Allingham-Hawkins, T. Chiu, A. Hunter, J. Allanson, H. Hare, J. Schween, L. Collins, S. Sanders, C. Greenberg, S. Cardwell, E. Lemire, P. MacLeod, M.R. Hayden, Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987 to 2000, *Clin. Genet.* 63 (2003) 462–475.
- [14] A. Semaka, S. Creighton, S. Warby, M.R. Hayden, Predictive testing for Huntington disease: interpretation and significance of intermediate alleles, *Clin. Genet.* 70 (2006) 283–294.
- [15] D.C. Rubinsztein, J. Leggo, R. Coles, E. Almquist, V. Biancalana, J.J. Cassiman, K. Chotai, M. Connarty, D. Craufurd, A. Curtis, D. Curtis, M.J. Davidson, A.M. Diffeo, C. Dode, A. Dodge, M. Frontali, N.G. Ranen, O.C. Stine, M. Sherr, M.H. Abbott, M.L. Franz, C.A. Graham, P.S. Harper, J.C. Hedreen, A. Jackson, J.C. Kaplan, M. Losekoot, J. C. MacMillan, P. Morrison, Y. Trottier, A. Novelletto, S.A. Simpson, J. Theilmann, S. E. J. Whittaker, C.A. Ross Folstein, M.R. Hayden, Phenotypic characterization of individuals with 30–40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36–39 repeats, *Am. J. Hum. Genet.* 59 (1996) 16–22.
- [16] S.M. McNeil, A. Novelletto, J. Srinidhi, G. Barnes, I. Kornbluth, M.R. Altherr, J.J. Wasmuth, J.F. Gusella, M.E. MacDonald, R.H. Myers, Reduced penetrance of the Huntington's disease mutation, *Hum. Mol. Genet.* 6 (1997) 775–779.
- [17] J.P. Evans, C. Skrzynia, W. Burke, The complexities of predictive genetic testing, *BMJ* 322 (2001) 1052–1056.
- [18] Y. Bombard, E. Penziner, O. Suchowersky, M. Guttman, J.S. Paulsen, J.L. Bottoff, M. R. Hayden, Engagement with genetic discrimination: concerns and experiences in the context of Huntington disease, *Eur. J. Hum. Genet.* 16 (2008) 279–289.
- [19] M. Huggins, M. Bloch, S. Kanani, O.W. Quarrell, J. Theilman, A. Hedrick, B. Dickens, A. Lynch, M.R. Hayden, Ethical and legal dilemmas arising during predictive testing for adult-onset disease: the experience of Huntington disease, *Am. J. Hum. Genet.* 47 (1990) 4–12.
- [20] S.C. Warby, R.K. Graham, M.R. Hayden, *Huntington Disease*, in: R.A. Pagon, T.C. Bird, C.R. Dolan, K. Stephens (Eds.), *GeneReviews*, University of Washington, Seattle, 2010.
- [21] S.A. Sorensen, K. Fenger, Causes of death in patients with Huntington's disease and in unaffected first degree relatives, *J. Med. Genet.* 29 (1992) 911–914.
- [22] L. Di Maio, F. Squitieri, G. Napolitano, G. Campanella, J.A. Trofatter, P.M. Conneally, Suicide risk in Huntington's disease, *J. Med. Genet.* 30 (1993) 293–295.
- [23] J. Marshall, K. White, M. Weaver, W.L. Flury, S. Hui, J.C. Stout, S.A. Johnson, X. Beristain, J. Gray, J. Wojcieszek, T. Foroud, Specific psychiatric manifestations among preclinical Huntington disease mutation carriers, *Arch. Neurol.* 64 (2007) 116–121.
- [24] C. Goizet, G. Lesca, A. Durr, Presymptomatic testing in Huntington's disease and autosomal dominant cerebellar ataxias, *Neurology* 59 (2002) 1330–1336.
- [25] Y. Bombard, G. Veenstra, J.M. Friedman, S. Creighton, L. Currie, J.S. Paulsen, J.L. Bottoff, M.R. Hayden, Perceptions of genetic discrimination among people at risk for Huntington's disease: a cross sectional survey, *BMJ* 338 (2009) b2175.
- [26] M.R. Hayden, Y. Bombard, Psychosocial effects of predictive testing for Huntington's disease, *Adv. Neurol.* 96 (2005) 226–239.
- [27] S.E. Andrew, Y.P. Goldberg, B. Kremer, H. Telenius, J. Theilmann, S. Adam, E. Starr, F. Squitieri, B. Lin, M.A. Kalchman, R.K. Graham, M.R. Hayden, The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease, *Nat. Genet.* 4 (1993) 398–403.
- [28] M. Duyao, C. Ambrose, R. Myers, A. Novelletto, F. Persichetti, M. Frontali, S. Folstein, C. Ross, M. Franz, M. Abbott, J. Gray, P. Conneally, A. Young, J. Penney, Z. Hollingsworth, I. Shoulson, A. Lazzarini, A. Falek, W. Koroshetz, D. Sax, E. Bird, J. Vonsattel, E. Bonilla, J. Alvir, J. Bickham Conde, J.H. Cha, L. Dure, F. Gomez, M. Ramos, J. Sanchez-Ramos, S. Snodgrass, M. de Young, N. Wexler, C. Mosecowitz, G. Penchaszadeh, H. MacFarlane, M. Anderson, B. Jenkins, J. Srinidhi, G. Barnes, J. Gusella, M. MacDonald, Trinucleotide repeat length instability and age of onset in Huntington's disease, *Nat. Genet.* 4 (1993) 387–392.
- [29] Y. Trottier, V. Biancalana, J.L. Mandel, Instability of CAG repeats in Huntington's disease: relation to parental transmission and age of onset, *J. Med. Genet.* 31 (1994) 377–382.
- [30] N.G. Ranen, O.C. Stine, M.H. Abbott, M. Sherr, A.M. Codori, M.L. Franz, N.I. Chao, A.S. Chung, N. Pleasant, C. Callahan, L.M. Kasch, M. Ghaffari, G.A. Chase, H.H. Kazazian, J. Brandt, S.E. Folstein, C.A. Ross, Anticipation and instability of IT-15 (CAG)_n repeats in parent-offspring pairs with Huntington disease, *Am. J. Hum. Genet.* 57 (1995) 593–602.
- [31] L. Djoussé, B. Knowlton, M. Hayden, E.W. Almquist, R. Brinkman, C. Ross, R. Margolis, A. Rosenblatt, A. Durr, C. Dode, P.J. Morrison, A. Novelletto, M. Frontali, R. J.A. Trent, E. McCusker, E. Gomez-Tortosa, D. Mayo, R. Jones, A. Zanco, M. Nance, R. Abramson, O. Suchowersky, J. Paulsen, M. Harrison, Q. Yang, L.A. Cupples, J.F. Gusella, M.E. MacDonald, R.H. Myers, Interaction of normal and expanded CAG repeat sizes influences age at onset of Huntington disease, *Am. J. Med. Genet. A* 119A (2003) 279–282.
- [32] A. Rosenblatt, R.R. Brinkman, K.Y. Liang, E.W. Almquist, R.L. Margolis, C.Y. Huang, M. Sherr, M.L. Franz, M.H. Abbott, M.R. Hayden, C.A. Ross, Familial influence on age of onset among siblings with Huntington disease, *Am. J. Med. Genet.* 105 (2001) 399–403.
- [33] A.M. Codori, R. Hanson, J. Brandt, Self-selection in predictive testing for Huntington's disease, *Am. J. Med. Genet.* 54 (1994) 167–173.
- [34] G. Evers-Kiebooms, J.J. Cassiman, H. Van den Bergh, Attitudes towards predictive testing in Huntington's disease: a recent survey in Belgium, *J. Med. Genet.* 24 (1987) 275–279.
- [35] R. Stern, R. Eldridge, Attitudes of patients and their relatives to Huntington's disease, *J. Med. Genet.* 12 (1975) 217–223.
- [36] B. Teltscher, S. Polgar, Objective knowledge about Huntington's disease and attitudes towards predictive tests of persons at risk, *J. Med. Genet.* 18 (1981) 31–39.
- [37] E.W. Almquist, M. Bloch, R. Brinkman, D. Craufurd, M.R. Hayden, A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease, *Am. J. Cardiol.* 64 (1999) 1293–1304.
- [38] P. Mandich, G. Jacopini, M.E. Di, G. Sabbadini, G. Abbruzzese, F. Chimirri, E. Bellone, A. Novelletto, F. Ajmar, M. Frontali, Predictive testing for Huntington's disease: ten years' experience in two Italian centres, *Ital. J. Neurol. Sci.* 19 (1998) 68–74.
- [39] R. Babul, S. Adam, B. Kremer, S. Dufrasne, S. Wiggins, M. Huggins, J. Theilmann, M. Bloch, M.R. Hayden, The Canadian Collaborative Group on Predictive Testing for Huntington Disease, Attitudes toward direct predictive testing for the Huntington disease gene. Relevance for other adult-onset disorders, *JAMA* 270 (1993) 2321–2325.
- [40] The World Federation of Neurology Research Group on Huntington's Disease, Presymptomatic testing for Huntington's disease: a world wide survey, *J. Med. Genet.* 30 (1993) 1020–1022.
- [41] S. Kessler, Predictive testing for Huntington disease: a psychologist's view, *Am. J. Med. Genet.* 54 (1994) 161–166.
- [42] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, J.J. Cassiman, T. Cloostermans, K. Demyttenaere, R. Dom, J.P. Fryns, H. Van den Berghe, Predictive testing for Huntington's disease: risk perception, reasons for testing and psychological profile of test applicants, *Genet. Couns.* 6 (1995) 1–13.
- [43] K.A. Quaid, M. Morris, Reluctance to undergo predictive testing: the case of Huntington disease, *Am. J. Med. Genet.* 45 (1993) 41–45.
- [44] M.J. Futter, J.M. Heckmann, L.J. Greenberg, Predictive testing for Huntington disease in a developing country, *Clin. Genet.* 75 (2009) 92–97.
- [45] P.S. Harper, C. Lim, D. Craufurd, Ten years of presymptomatic testing for Huntington's disease: the experience of the UK Huntington's Disease Prediction Consortium, *J. Med. Genet.* 37 (2000) 567–571.
- [46] M.K. Trembath, R.J. Tassicker, V.R. Collins, S. Mansie, L.J. Sheffield, M.B. Delatycki, Fifteen years of experience in predictive testing for Huntington disease at a single testing center in Victoria, Australia, *Genet. Med.* 8 (2006) 673–680.
- [47] F. Laccone, U. Engel, E. Holinski-Feder, M. Weigell-Weber, K. Marczinek, D. Nolte, D.J. Morris-Rosendahl, C. Zuhlke, K. Fuchs, H. Weirich-Schwaiger, G. Schluter, G. von Beust, A.M.M. Vieira-Saecker, B.H.F. Weber, O. Riess, DNA analysis of Huntington's disease: five years of experience in Germany, Austria, and Switzerland, *Neurology* 53 (1999) 801–806.
- [48] S.A. Simpson, J. Besson, D. Alexander, K. Allan, A.W. Johnston, One hundred requests for predictive testing for Huntington's disease, *Clin. Genet.* 41 (1992) 326–330.
- [49] S. Taylor, Gender differences in attitudes among those at risk for Huntington's disease, *Genet. Test.* 9 (2005) 152–157.
- [50] M. Bloch, M. Fahy, S. Fox, M.R. Hayden, Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates, *Med. Genet.* 32 (1989) 217–224.
- [51] C.M. Benjamin, S. Adam, S. Wiggins, J.L. Theilmann, T.T. Copley, M. Bloch, F. Squitieri, W. McKellin, S. Cox, S.A. Brown, H.P.H. Kremer, M. Burgess, W. Meschino, A. Summers, D. MacGregor, J. Buchanan, C. Greenberg, N. Carson, E. Ives, M. Frecker, J.P. Welch, A. Fuller, D. Rosenblatt, S. Miller, S. Dufrasne, M. Roy, E. Andermann, C. Prevost, M. Khalifa, K. Girard, S. Taylor, A. Hunter, C. Goldsmith, D. Whelan, D. Eisenberg, H. Soltan, J. Kane, M.H.K. Shokeir, A. Gibson, S. Cardwell, S. Bamforth, S. Grover, O. Suchowersky, M. Klimek, T. Garber, H.A. Gardner, P. Macleod, M.R. Hayden, Proceed with care: direct predictive testing for Huntington disease, *Am. J. Hum. Genet.* 55 (1994) 606–617.
- [52] A. Maat-Kievit, V. Vegter-van der Vlis, M. Zoetewij, M. Losekoot, A. van Heringen, R. Roos, Paradox of a better test for Huntington's disease, *J. Neurol. Neurosurg. Psychiatry* 69 (2000) 579–583.
- [53] M.E. Alonso, A. Ochoa, A.L. Sosa, Y. Rodriguez, M. Chavez, C. Boll, P. Yescas, R. Macias, A. Rasmussen, Presymptomatic diagnosis in Huntington's disease: the Mexican experience, *Genet. Test. Mol. Biomark.* 13 (2009) 717–720.
- [54] R.J. Tassicker, P.K. Marshall, T.A. Liebeck, M.A. Keville, B.M. Singaram, F.H. Richards, Predictive and pre-natal testing for Huntington disease in Australia: results and challenges encountered during a 10-year period (1994–2003), *Clin. Genet.* 70 (2006) 480–489.
- [55] G. Evers-Kiebooms, M. Welkenhuysen, E. Claes, M. Decruyenaere, L. Denayer, The psychological complexity of predictive testing for late onset neurogenetic diseases and hereditary cancers: implications for multidisciplinary counselling and for genetic education, *Soc. Sci. Med.* 51 (2000) 831–841.
- [56] P.S. Harper, R.G. Newcombe, Age at onset and life table risks in genetic counselling for Huntington's disease, *J. Med. Genet.* 29 (1992) 239–242.

- [57] B. Bonke, A. Tibben, D. Lindhout, A.J. Clarke, T. Stijnen, Genetic risk estimation by healthcare professionals, *Med. J. Aust.* 182 (2005) 116–118.
- [58] A.N. Lindblad, To test or not to test: an ethical conflict with presymptomatic testing of individuals at 25% risk for Huntington's disorder, *Clin. Genet.* 60 (2001) 442–446.
- [59] M.A. Nance, R.H. Myers, Trends in predictive and prenatal testing for Huntington disease 1993–1999, *Am. J. Hum. Genet.* 65 (1999) A406.
- [60] G. Evers-Kiebooms, K. Nys, P. Harper, M. Zoetewij, A. Durr, G. Jacopini, C. Yapijakis, S. Simpson, Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study, *Eur. J. Hum. Genet.* 10 (2002) 167–176.
- [61] S. Adam, S. Wiggins, P. Whyte, M. Bloch, M.H. Shokeir, H. Soltan, W. Meschino, A. Summers, O. Suchowersky, J.P. Welch, Five year study of prenatal testing for Huntington's disease: demand, attitudes, and psychological assessment, *J. Med. Genet.* 30 (1993) 549–556.
- [62] R.S. Lazarus, S. Folkman, *Stress, Appraisal and Coping*, Springer, New York, 1984.
- [63] S. Cobb, *Toward an Integrated Medicine — Classics from Psychosomatic Medicine 1959–1979*, American Psychiatric Press, 1995.
- [64] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, K. Demyttenaere, R. Dom, J.P. Fryns, Partners of mutation-carriers for Huntington's disease: forgotten persons? *Eur. J. Hum. Genet.* 13 (2005) 1077–1085.
- [65] R.J. Lifton, *The Broken Connection: On Death and the Continuity of Life*, Simon and Schuster, New York, 1979.
- [66] A. Tibben, M.F. Niermeijer, R.A. Roos, V. Vegter-van der Vliet, P.G. Frets, G.J. Van Ommen, J.J. van de Kamp, F. Verhage, Understanding the low uptake of presymptomatic DNA testing for Huntington's disease, *Lancet* 340 (1992) 1416.
- [67] V. Cina, F. Fellman, Implications of predictive testing in neurodegenerative disorders, *Schweiz. Arch. Neurol. Psychol.* 157 (2006) 8.
- [68] C.A. Taylor, R.H. Myers, Long-term impact of Huntington disease linkage testing, *Am. J. Med. Genet.* 70 (1997) 365–370.
- [69] B.M. Knoppers, Y. Joly, Physicians, genetics and life insurance, *CMAJ* 170 (2004) 1421–1423.
- [70] *The Double-Edged Helix, Social Implications of Genetics in a Diverse Society*, The Johns Hopkins University Press, Baltimore, 2002.
- [71] C.L. Julien, J.C. Thompson, S. Wild, P. Yardumian, J.S. Snowden, G. Turner, D. Craufurd, Psychiatric disorders in preclinical Huntington's disease, *J. Neurol. Neurosurg. Psychiatry* 78 (2007) 939–943.
- [72] S. Kessler, T. Field, L. Worth, H. Mosbarger, Attitudes of persons at risk for Huntington disease toward predictive testing, *Am. J. Med. Genet.* 26 (1987) 259–270.
- [73] T.M. Marteau, R.T. Croyle, The new genetics. Psychological responses to genetic testing, *BMJ* 316 (1998) 693–696.