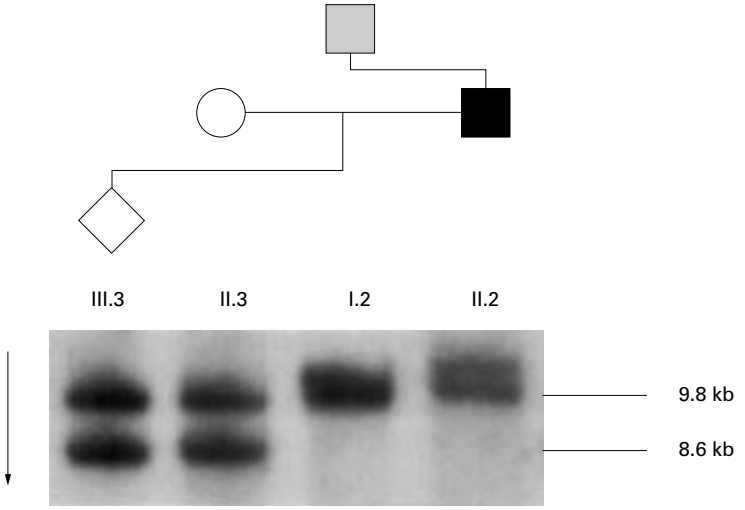

Figure 3 Southern blotting (EcoRI/ PM10M6) in patients III.3, II.3, I.2, and II.2. The expanded allele in II.2 is not found in his offspring III.3.

approximately half of the offspring who inherited a contracted allele showed clinical anticipation despite the reduced CTG repeat size. In all these cases, however, the size of the contracted allele remained above the normal range. Moreover, Southern blot analysis showed some overlap between the boundaries of the "smear" in some parent-offspring pairs. Conversely, in the four cases where the transmitted DM allele reverted to the normal range, the clinical phenotype seemed to be normal, taking into account the absence of data regarding long term follow up in these cases.[9–12]

Taken together, these data strengthen the well known fact that direct analysis of fetal DNA should be used as the primary approach in PND, since a reliable prediction of the seriousness of the phenotype cannot be based upon haplotyping using polymorphic markers linked to the *DMPK* locus. Moreover, the detection of a contraction event in a fetus by Southern blotting warrants further molecular investigations in order to assess the size of the CTG repeat accurately. Indeed, while detection of a DM allele remaining above the normal range does not preclude clinical anticipation, the observation of a contracted allele back to normality should allow reassurance of couples at risk for transmitting DM.

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Psychological studies in Huntington's disease: making up the balance

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EDITOR—Huntington's disease (HD) is an incurable neurodegenerative disease, characterised by involuntary movements, changes in behaviour and personality, and cognitive impairment, leading to death 15 to 20 years after its onset.[1] HD is an autosomal dominantly inherited disorder, the gene for which is localised on the short arm of chromosome 4.[2] Subjects carrying the gene will develop the disease in the absence of other causes of death. The mean age of onset is 40 years, by which time gene carriers may have passed on the gene to their offspring. The age of onset ranges from 2 to 75 years[3] so that those at risk (that is, risk carriers at 50% or 25% genetic risk) can never be sure of having escaped HD.

Since 1986, presymptomatic DNA testing using genetic linkage analysis has made it possible for risk carriers to have their risk modified to approximately 98% or 2%. After

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identification of the HD gene mutation in 1993, CAG repeat size analysis of the huntingtin gene allowed complete certainty of either having or not having HD.[2]

Risk carriers, being raised in a family in which HD played a major role, could be expected to have specific adjustment problems. Yet, only one study addressed the psychological functioning of people at risk for HD before presymptomatic testing was introduced. Most psychological studies were started when clinicians and researchers became concerned about the effects of a presymptomatic test on people at risk.

The aim of this article is to review studies addressing psychological and psychiatric adjustment of people at risk for HD. The methods used by the studies (that is, objectives, inclusion and exclusion criteria, recruitment, assessment, design, and statistical analyses) and their results are presented. General trends and limitations of the present work are described and a direction for future research is presented.

The term "carriers" is used to designate all subjects who underwent linkage or mutation analysis and were found to have an increased risk or were identified with a pathological repeat length of the *IT15* huntingtin gene. The term "non-carriers" denotes those with a decreased risk result or those having a normal repeat size of the *IT15* gene.

Methods

A search of published reports was conducted in the MEDLINE and PsycLIT databases using the keywords "Huntington's disease", "psychological", "psychiatric", "predictive testing", "adjustment", and "family". Cross references in identified papers were also used. Quantitative studies on the psychological wellbeing of those at risk were included; this could be conducted by questionnaire or by interview. Studies addressing attitudes are included when they indirectly refer to wellbeing in the pre- and/or post-test period. Case descriptions or clinical impressions were excluded from this analysis as well as neurological and pharmacological studies.

Results

A total of 18 articles provided a quantitative analysis on the wellbeing of subjects at risk for HD.[4–21] Characteristics of the studies are summarised in table 1.

STUDY OBJECTIVES

Before predictive testing became possible, Folstein *et al*[11 12] analysed psychological characteristics and psychiatric disorders among the offspring of HD patients and other at risk people. The pre- to post-test adjustment of carriers and non-carriers was evaluated in seven studies.[5 9 14 15 19–21] Attitudes, indirectly referring to wellbeing, before test disclosure[4] or in the post-test period were addressed in four studies.[4 6 16 18] A few studies also compared adjustment in test applicants with adjustment in their partners.[15 16 18 20] In order to identify those subjects who were at risk for poor adjustment after the test, predictive studies were introduced.[7 8 10 13 17]

INCLUSION AND EXCLUSION CRITERIA

In the study of Folstein,[12] subjects at 50% and 25% risk were included. Folstein *et al*[11] included offspring (aged 15 years and older) of HD patients. Exclusion criteria were not reported in these studies.

Studies on adaptation after testing for HD had comparable criteria for inclusion in pre- and post-test studies: people aged over 18 years and at risk for HD. Exclusion criteria were: having symptoms of HD, a severe depression or

Table 1 Studies of psychological functioning of HD risk carriers

Study	*Sample size*	*Carrier/ non-carrier/ uninformative**	*Mean age*	*Measurement time*	*Objective*	*Statistical methods*
Boston						
Meissen *et al*[14]	15	4/7/5	—	Baseline, 3 mth, 9 mth		Percentages
Vancouver						
Bloch *et al*[4]	51	NA	39.3	Before test	Description	Percentages
Wiggins *et al*[21]†	135	37/58/40	37.5	Baseline, 1 wk, 6 mth, 12 mth	Course	ANOVA, Kruskal-Wallis test
Lawson *et al*[13]†	135	37/58/40	37.5	Baseline, 1 wk, 6 mth, 12 mth	Prediction, description	*t* tests or Mann-Whitney U tests, chi-square test
Baltimore						
Folstein *et al*[11]	112	NA	26.7	NA	Description	Percentages, chi-square test
Brandt *et al*[5]	55	12/30/13	35.4	Baseline, 3 mth, 6 mth, 9 mth, 12 mth	Description, baseline, course	Percentages
Folstein[12]	147/161	NA	—	NA	Description	Clinical impressions
Codori and Brandt[6]	68	17/51	37.7	8 visits in 3 y after test	Description	Percentages
Codori *et al*[7]	160	52/108/—	34.4	Baseline, 3 mth, 6 mth, 9 mth, 12 mth	Prediction	F tests
Rotterdam/Leiden						
Tibben *et al*[16]	18	9/9	35.9	12 mth	Description	Percentages, clinical impressions
Tibben *et al*[17]‡	63	29/44	31.6	Baseline, 6 mth	Prediction	Backward regression analysis
Tibben *et al*[18]‡	63	24/39	31.6	6 mth	Description	Percentages
Tibben *et al*[19]‡	73	29/44	32.1	Baseline, 1 wk, 6 mth	Course	MANOVA
Tibben *et al*[20]‡	49	20/29	32.2	Baseline, 1 wk, 6 mth, 3 y	Course	MANOVA
DudokdeWit *et al*[9]§	25	9/16	39.5	Baseline, 1 wk, 6 mth	Course	MANOVA
DudokdeWit *et al*[10]§	25	9/16	39.5	Baseline, 6 mth	Prediction	Multiple regression analysis
Leuven						
Decruyenaere *et al*[8]	53	22/31	34	Baseline, 1 mth, 12 mth	Prediction, course	Multiple regression analysis, *t* tests
Indianapolis						
Quaid and Wesson[15]	19	5/14	36.9	Baseline, 3 mth, 6 mth, 9 mth, 12 mth	Comparison of groups	Mann-Whitney U test

*Genetic status not assessable in linkage test.
†‡§Same population.
NA: not applicable.

Table 2 Descriptive/course studies: used questionnaires

Study	*Questionnaires*
Vancouver	
Bloch *et al*[8]	SCL-90-R (GSI), BDI, GWS (MHI), Behaviour Survey, Reasons for Living Scale, AQ
Wiggins *et al*[21]	SCL-90-R (GSI), BDI, GWS
Baltimore	
Brandt *et al*[5]	SCL-90-R, BDI, BHS, MCMI-2
Codori and Brandt[6]	Nine items regarding effects of test result
Folstein[12]	EPI, GHQ-30
Folstein *et al*[11]	—
Boston	
Meissen *et al*[14]	BDI
Rotterdam/Leiden	
Tibben *et al*[16]	AQ, BHS
Tibben *et al*[18]	AQ
Tibben *et al*[19]	BHS, GHQ-60, IES
Tibben *et al*[20]	BHS, IES
DudokdeWit *et al*[9]	IES
Indianapolis	
Quaid and Wesson[15]	SCL-90-R (GSI, PSDI, PST), BDI, BHS, GWS (MHI), Life Satisfaction Index

Abbreviations are shown in the Appendix.

other major psychiatric illness, or, by history, being at risk for suicide (Baltimore Group, USA,[23] Boston, USA,[14] Indianapolis, USA,[24] Leuven Group, Belgium,[25] Rotterdam/Leiden Group, The Netherlands,[26] Vancouver Group, Canada[27]). In the study by Meissen *et al*,[14] secondary exclusion criteria were: a recently experienced stressful event, moderate depression, a suicide attempt more than 10 years before testing, or a family history of suicide.[14] The Leuven group included risk carriers with a psychiatric history, provided that social support was available and that the risk carriers were receiving psychiatric treatment (M Decruyenaere, 1999, personal communication).

Postponement or exclusion from testing were reported for various reasons: because of manifest symptoms of HD (n=4[4] and 10[5]), severe depression (n=3,[6] 1,[14] and 3[23]), and evaluation by a psychiatrist (n=2[14]). These exclusion criteria were not applied in any of the studies of Decruyenaere, DudokdeWit, and Tibben *et al* (personal communications, 1999).

RECRUITMENT

In the studies unrelated to presymptomatic testing, offspring of patients were asked to participate in the study and were identified either through a survey of HD patients in Maryland[11] or when they visited the Baltimore Huntington's Disease Project Research Clinic with questions concerning their own and/or parents' future.[12]

Psychological pre- and post-test follow up was offered on a research basis, by requesting informed consent from presymptomatic test participants. Information on the availability of the presymptomatic testing reached risk carriers through the Newsletters of the HD Society, the general practitioner, neurologist, clinical genetics service, relatives, or the public networks. Pre-test written information was provided in several centres. General information was mailed to all 50% risk carriers in one group.[15] The Vancouver Group mailed a description of the research project to all families on the HD registry, requesting them to contact the researcher.[27]

ASSESSMENT OF PSYCHOLOGICAL ADAPTATION

Wellbeing was assessed through self-report questionnaires and by means of interviews. The questionnaires used are summarised in tables 2 and 3. Folstein *et al*[11] performed psychiatric examination by means of a structured interview, the Diagnostic Interview Schedule (DIS), which yields diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III); an independent psychiatric interviewer validated these diagnoses. In other studies, the interviews provided additional information to the self-report questionnaires. Brandt *et al*[5] administered the Schedule of Affective Disorders and Schizophrenia (SADS)-Change Interview[28] to assess at least moderate to severe symptoms in one or more domains. Lawson *et al*[13] asked counsellors and clinicians to indicate participants who had experienced adverse events, for example, a suicide attempt or the formulation of a suicide plan, psychiatric hospitalisation, depression lasting longer than two months, a marked increase in substance abuse, or the breakdown of important relationships. Tibben *et al*[16] evaluated feelings and cognition in carriers and non-carriers and their partners.

The design and statistical analyses of the investigated studies are summarised in table 1.

Results of reviewed studies

STUDIES UNRELATED TO PRESYMPTOMATIC TESTING

Children of HD patients had a high rate of psychiatric disorder (25% conduct disorder or antisocial personality disorder, 18% major depression).[11] Most conditions (anxiety and depression) were mild or occurred only in adolescence (conduct disorder).[12] Introversion/

Table 3 Outcome variables and predictor variables in studies predicting psychological well being

Study	*Predictor variables*	*Outcome variables*
Tibben *et al*[17]	Intrusion (IES), avoidance (IES), hopelessness (BHS), psychopathological states (GHQ), social support (SSQ)	Intrusion (IES), avoidance (IES), hopelessness (BHS)
Decruyenaere *et al*[8]	General anxiety (STAI trait), situational anxiety (STAI state), depression (BDI), ego strength (MMPI), coping styles (UCL)	General anxiety (STAI trait), situational anxiety (STAI state), depression (BDI), ego strength (MMPI)
Codori *et al*[7]	Genetic status, gender, marital status, parenting status, risk perception, estimated years to onset of HD in those testing positive	Hopelessness (BHS), depression (BDI)
Lawson *et al*[13]	Global Severity Index (SCL-90), depression (BDI), social support (SSQ), adverse events questionnaire	Adverse events*
DudokdeWit *et al*[10]	Intrusion (IES), avoidance (IES), anxiety (HADS), depression (HADS), psychological problems (SCL-90), hopelessness (BHS), loneliness (loneliness scale), social support (SSQ), family functioning (FACES), gender, age, religion, marital status, parenting status	Intrusion (IES), avoidance (IES)

*A suicide attempt or the formulation of a suicide plan, psychiatric hospitalisation, depression lasting longer than two months, a marked increase in substance abuse, the breakdown of important relationships, increases on BDI and or GSI (SCL-90).
For abbreviations see table 2.

extraversion and neuroticism were similar to those in the general population.[12]

DESCRIPTIVE STUDIES RELATED TO PRESYMPTOMATIC TESTING

Psychological wellbeing of test applicants before disclosure of test result

The mean scores of psychological wellbeing and Huntington specific distress before disclosure of the test result (baseline level) fell within the normal range.[4 5 7 9 19–21] In the Dutch studies,[19 29] the mean scores of risk carriers indicated mild signs of hopelessness; this could not be confirmed in other studies.[7 15] Approximately 20% of the risk carriers scored at mild levels of depression and hopelessness, whereas very few scored at the level of moderate or severe depression.[4] For about 20% of the risk carriers, their scores on the GHQ-60 indicated the possible presence of psychiatric morbidity.[19 30]

Most test applicants had a normal psychological profile.[31] In comparison to the general population, they were more socially extraverted, had higher ego strength, and reacted more with active coping, palliative coping, social support seeking, and comforting ideas.

Later identified carriers and non-carriers did not differ in general wellbeing and Huntington specific distress.[5 8 9 15 19–21]

Course of psychological wellbeing after the test result

General measures of psychological wellbeing and Huntington specific distress

Analysis of distress in identified gene carriers at seven days post-test showed more depression, hopelessness, and a decrease in general wellbeing.[5 8 19–21] However, their mean scores remained in the mild range. A return to baseline levels of anxiety and depression occurred in the first month.[8] Hopelessness, depression, and general wellbeing returned to baseline level within six months[5 19 21] and remained there one and three years post-test.[8 20 21] Although not differing from baseline, Wiggins *et al*[21] found linear declines for distress and depression over a 12 month period. Only Brandt *et al*[5] reported a slight increase in general distress after one year. However, because the dropout rate in their sample was extremely high (75%), this finding should be interpreted with caution.

The non-carriers were more optimistic regarding their future at seven days post-test; however, this more positive view of the future disappeared after six months and three years.[18 20] On the other hand, anxiety and depression decreased from baseline one month and one year after the test result.[8] Also, general distress, assessed by means of the GSI index, decreased in the first year after the test result.[5 21]

In comparison to carriers, non-carriers reported less general distress, less depression, less hopelessness, and a greater sense of wellbeing one week after the test result.[19 21] This difference disappeared in the first year. At six months follow up, only general wellbeing was significantly greater for the non-carriers, but this difference disappeared at 12 months up to three years after the test result, returning to baseline level.[8 21 32] Only Quaid and Wesson[15] found a higher general wellbeing for carriers than non-carriers after 12 months.

In comparison to a "no change" group, consisting of 23 subjects who did not want to take the test and 17 subjects for whom the test was uninformative, both carriers and non-carriers scored lower for depression and higher for wellbeing.[21] However, it cannot be inferred from these findings that testing has benefits, since particularly an uninformative result can lead to an increase in distress, the wish for certainty about carrier status being frustrated.

A subgroup of both carriers and non-carriers had difficulties adjusting to their new carrier status. About 10-20% of both carriers and non-carriers showed psychological problems in the post-test period.[8 13 16 19 21 32 33] Interviews with carriers, three months after the result, indicated that half of the carriers had periods of severe depression, whereas the other half had suffered moderate depression.[14] Therapists identified a minority of carriers and non-carriers as having psychiatric symptoms in the first year after the test.[5] However, very few people committed or attempted suicide or needed psychiatric hospitalisation after predictive testing.[34]

With regard to Huntington specific distress, carriers showed a slight increase of avoidance behaviour in the first six months, which returned to baseline level after three years.[20] Non-carriers showed a decrease in avoidance during the first six months post-test,[9 19] which returned to baseline level at the three year follow up.[20] For both groups, intrusive thoughts decreased in the first six months,[9 19] whereas these increased to baseline level at the three year follow up.[20]

The observations by Lawson *et al*[13] underline the general impression that both carriers and non-carriers have problems in adapting to the test result, but at different moments in time. The number of adverse events was similar for carriers and non-carriers. For the carriers, adverse events took place within 10 days after the test result, whereas for non-carriers adverse events occurred six months after the result or later. Seventy percent of these events were identified by clinical criteria, that is, suicidal ideation, depression lasting longer than two months, substance abuse, or a breakdown of an important relationship, either alone or in conjunction with a raised score on one or more questionnaires.[13]

Attitudinal studies regarding the test result

Before a test result was given, risk carriers expressed concern about the future and guilt about the possibility of passing on the gene.[4] After six months, half of the carriers stated that the results had not influenced their lives and half of them also rarely thought of the result, indicating that denial plays a role.[18] The non-carriers expressed relief in the first weeks after the test result was given, but after six months half of the non-carriers appeared to

deny the impact of the test result, as was reflected by absence of relief and emotional numbness.[18] Some of them have expressed survivor guilt.[6 16]

Comparison of at risk population and partners
At baseline, spouses reported more depression than their at risk partners,[15] whereas hopelessness was comparable for carriers and their partners.[16] During the three year follow up, carriers and their partners showed similar patterns of avoidance, intrusion, and hopelessness, whereas non-carrier partners reported less avoidance, intrusion, and hopelessness than the non-carriers.[32] After three years, partners of carriers were still showing more avoidance than partners of non-carriers. In contrast, Quaid and Wesson[15] found comparable distress for carrier partners and non-carrier partners in the first year after disclosure of the test result.

Whereas distress was similar for carriers and their partners, their attitudes towards the test result differed. Carriers did not report an increase in problems after they received an unfavourable test result. Their partners did mention having problems, but expressed reluctance to seek help or to talk about it with their spouse, owing to feelings of guilt and not wanting to hurt them. This was especially the case for those who became aware of the risk for HD at a later stage, for example, after marriage. For the non-carriers, most of them did not experience relief, whereas their partners did.[16 18]

Having children proved to be an additional stress factor for partners during and after the test procedure.[20] At baseline, partners with children were significantly more hopeless than partners without children. One week after the test, carrier partners with children reported significantly more hopelessness, avoidance thoughts, and intrusive feelings than carrier partners without children. At six months and three years after the test, this difference in avoidance thoughts and intrusive feelings was sustained.

Prediction of wellbeing
Five studies aimed to identify pre-test variables that predict the way subjects adapt to their test result[7 8 10 13 17] (for the variables see table 3).

Test result
In general, test outcome did not predict psychological adjustment. Only Codori *et al*[7] found carriers to be more likely to be pessimistic about their future than non-carriers.

General and Huntington specific distress
The level of psychological adaptation after the test (anxiety, depression, hopelessness, intrusion, and avoidance) was predicted by the same measures at baseline.[7 8 10 17] The more depressive symptoms reported at baseline, the more distress subjects reported at the one year follow up, and the greater the chances that they were rated as having experienced an adverse event, as defined by Lawson *et al*.[13] Pessimism, a low avoidance, and dissatisfaction with available support at the moment of testing predicted pessimism at six months.[17] Those severely anxious before the test were more likely to show low intrusion six months after disclosure.

Biographical variables
Having children predicted post-test intrusion and hopelessness.[7 10] Women showed more intrusion and avoidance than men six months after disclosure of the test result.[10] For carriers, being married or having children predicted hopelessness, as did the estimated years to onset of HD.[7]

Social support
Subjects who were satisfied with the perceived quality of support of others felt less hopeless after either test result.[17] The more pre-test avoidance and the less satisfaction with available support, the more avoidance behaviour was reported six months post-test.[17] However, the larger the number of persons perceived as being supportive before the test, the more avoidance was reported post-test.[10]

Risk perception
Risk perception refers to the expectations one has about the test result. No support was found for the hypothesis that for identified carriers, those with a low perceived risk of being a carrier would have a less favourable adjustment than persons with a high perceived risk.[7]

Personality measures and coping strategies
Ego strength was associated with a lower general anxiety and depression level one year after the test. Moreover, ego strength in combination with the coping strategy "comforting ideas" predicted a lower general anxiety.[8]

Discussion

Reviewing psychological research on wellbeing in Huntington patients and those at risk showed only a few studies that were unrelated to presymptomatic testing. HD in a parent proved to have a profound impact on adolescence. A high rate of psychiatric disorders in adolescents was seen, but not among adults. Most of the research was carried out as part of the presymptomatic testing protocol. In general, wellbeing of the group of test applicants was normal before test disclosure. Both carriers and non-carriers had difficulties in adapting to the test result, but at different moments in time. Distress in carriers increased in the first weeks post-test, which returned to baseline level within one year. The relief non-carriers expressed in the first weeks disappeared afterwards; they experienced most distress at six months. Within one year, non-carriers seemed to be somewhat less distressed than they were before test disclosure, but they had not developed more optimistic future expectancies.

A subgroup of both carriers and non-carriers had long lasting adaptation problems. Those reporting to be distressed before test disclosure most often had problems in adapting to the test result. Although wellbeing seemed to be independent of test outcome, wellbeing was

related to having children, certain personality traits (ego strength, coping), and the subjective estimation of the number of years before onset of HD.

These findings have been shown to be helpful in guidance and counselling of risk carriers in testing programmes. However, the research still has some serious limitations that need to be overcome for progress to be made in this research field. Limitations and a promising new direction will be discussed below.

STUDY POPULATION

In the study of Folstein *et al*,[11] 60% were not willing to participate in the study, leading to a possible underestimation of the problems of risk carriers. The study population in other studies consisted of risk carriers who visited a genetic centre and/or applied for a predictive test. The percentage of those at risk who requested testing when approached by registries or testing centres varied from 9% in Wales, 10% in Indiana, 16% in the Manchester area, to 20% in the Vancouver area.[35] In The Netherlands, 752 out of 1032 subjects at risk, applying for presymptomatic testing in the period 1987 to 1997, decided to be tested, which is 24% of the at risk persons registered in the Leiden Roster for HD.[36] It was suggested[37] and confirmed[4 31] that persons who participate in the studies on testing form a resourceful self-selected group. Those who decided not to be tested had more frequent expectations of unfavourable emotional reactions and showed more hopelessness than tested subjects.[6 38] On the other hand, the level of anxiety, ego strength, and coping strategies were not different between the tested and untested groups.[39] Also, the untested participants form a self-selected resourceful group; both tested and untested participants had a higher ego strength in comparison to the general population.[31] Little is known about the wellbeing of those who do not seek testing and who do not participate in psychological studies. Therefore, bias seems to be involved in the estimation of adaptation in HD risk carriers.

Although we need to be careful to generalise the findings to the whole HD population, we should take into account that differences were observed within the group of test applicants. Some subjects acknowledged the burden of HD, but saw themselves as being able to face the truth. Others denied a burden of HD in their lives and disagreed that the results had a profound impact on their lives.[4 40]

Moreover, the dropout rates in most follow up studies are high. Information from relatives about the wellbeing of these dropouts suggest that those who declined participation in follow up research, both carriers and non-carriers, often have serious problems they do not want to disclose, indicating that risk carriers applying for the test may have more problems than the studies suggest.

SELF-REPORT MEASUREMENT

Adjustment was usually assessed by means of self-report questionnaires. Interpretations of findings based on self-reporting may be problematical because low scores on mental health questionnaires may indicate that people deny problems, trying to maintain an illusion of mental health.[41] Since denial may arise in reaction to stressful or traumatic experiences,[42] this can be expected in a testing procedure for HD. Tibben *et al*[16] found that some carriers did not mention having had depressive periods in the post-test period, whereas their partners reported the opposite about them.[16] Moreover, test applicants were more defensive when filling out the MMPI than the general population. Also, female participants obtained a higher lie score than women in the general population.[31]

DudokdeWit *et al*[29] introduced the possibility of assessing the manner in which participants discuss the disease, the test, and its implications in terms of coherence. Coherence refers to the ability to discuss and to reflect upon emotions, feelings, and ideas without becoming entangled in it or avoiding discussion of the subject.[43] DudokdeWit *et al*[29] found that one third of the participants spoke incoherently about their possible inherited disease, the majority of them (two thirds) using an avoidance (dismissing) strategy, one third being entangled. It turned out that those showing avoidance reported fewer problems than those being entangled did. Dismissing subjects generally have more psychological and psychiatric problems than others do.[44]

These findings support the impression of clinicians and counsellors that a group of HD risk carriers who report themselves to be functioning well are in fact having difficulty with being aware of the impact of their experiences with HD on their lives, reflected in sustained numbness.[10 45] This numbness may reflect warding off a variety of guilt feelings, anger, resentment, and hostility towards the family and its HD history and the inability to create new life perspectives. When the reality of a situation is avoided, it cannot be integrated into one's personal life, which might lead to adaptation problems. To gain more insight into the psychological dynamics, denial and other psychological defences need to be studied; since defences are unconscious, more subtle measures are required.

GLOBAL MEASUREMENT

Another problem is that most measures used are global ones. The IES is the only Huntington specific questionnaire that provides insight into the process of a person's working through the situation. Research with more specific and sensitive measures is needed for assessment of the process of adjustment between and within test applicants in the post-test period.

THEORETICAL FRAMEWORK

Tibben *et al*[19] and DudokdeWit *et al*[9] used the stress response theory of Horowitz *et al*[46] to formulate their hypotheses. In other studies, it is unclear which underlying theoretical assumptions are used, the design and statistics not being guided by clear hypotheses. A theoretical framework is needed to provide more insight into the observations.[37 47] A

psychological model or theory will contribute to our understanding about the psychological dynamics that characterise this study population.

LACK OF FAMILY PERSPECTIVE ON WELLBEING OF RISK CARRIERS

HD is a family disease.[12] The initial onset of symptoms is usually between 30 and 50 years, a period when people are raising a family. People at risk were generally familiar with the disease from early childhood, knowing the symptoms in the parent and/or other family members. Clinicians have shown how the presence of HD in a family can affect the family dynamics.[48–51] In some of the reviewed studies, the influence of HD on family dynamics can be inferred. Post-test studies indicated the difficult and different processes test participants and their partners go through. Marriage and career need to be reconsidered[14] and the necessary social support may no longer be available. Having children is an additional stress factor for both carriers and their partners.[20]

However, wellbeing in HD risk carriers has rarely been related to their childhood experiences. Folstein *et al*[11] investigated how childhood experiences contribute to a more or less favourable adaptation in later life. They found conduct disorder in adolescents and antisocial personality disorder in adults to be related to experiences of having lived in a disorganised household. No relation was found between anxiety or depression and family factors. Recently, Decruyenaere *et al*[52] found a low but significant correlation between the participants' age at which the parent showed the first symptoms and psychological functioning before test disclosure. Psychological adjustment to the test result was not correlated with the age of the participant at onset of HD in the parent.

To identify adjustment problems in adult risk carriers, childhood experiences and family dynamics need to be taken into account. In our opinion, the attachment theory[53] provides a meaningful theoretical framework for describing childhood experiences in HD families and generating hypotheses concerning the influence of childhood experiences on later adaptation.

ATTACHMENT THEORY

Attachment theory, developed by John Bowlby, postulates a universal human need to form close affectionate bonds. It is a normative theory of how the "attachment system" functions in all humans.[54] The attachment theory concerns the nature of early experiences of children, and the impact of these experiences on aspects of later functioning. The central assumption of attachment theory is that individual social behaviour may be understood in terms of generic mental models of social relationships constructed by the person.[55] These models, although constantly evolving and subject to modification, are strongly influenced by the child's experiences with the primary caregivers. The attachment system serves as a primary mechanism for the regulation of infant safety and survival and is highly activated in times of danger.[53] An infant is considered securely attached if he or she regards the parents as people to rely on when facing a frightening situation. A responsive and sensitive way of parenting generally gives rise to a secure attachment pattern. Secure infants are able to explore new situations and to experience proximity and comfort in times of distress, illness, or tiredness. Insecure attachment is often found in those who in childhood have experienced rejection or neglect by one or both parents, or who were asked to take care of the parent instead of being taken care of.[56] Insecure attachment in either infancy or adulthood is related to the occurrence of psychopathology in adulthood.[57]

Three types of insecure attachment can be discerned. An avoidant (dismissing) attached infant shifts attention away from rejecting caregivers and minimises displays of distress. An ambivalent (preoccupied) attached infant is highly focused on the caregiver and maximises distress through insistent demands for care and attention. A third group of infants appear to exhibit a range of seemingly undirected behavioural responses giving the impression of disorganisation and disorientation.[58] These infants may display (momentarily) bizarre and contradictory behaviour. Frightening experiences with caregivers who behaved in threatening, frightened, or dissociated ways and experiences of loss and trauma may lead to a disorganised attachment pattern.[59 60] It is generally held that for such infants the caregiver has served both as a source of fear and as a source of reassurance, thus the arousal of the attachment behavioural system produces strong conflicting motivations. Not surprisingly, a history of severe neglect or physical or sexual abuse is often associated with the manifestation of this pattern.[61 62] It is generally held that the patterning of attachment related behaviour is underpinned by different strategies adopted by children to regulate their emotional reactions.[63] As affect regulation is acquired with the help of the child's primary caregiver, the child's strategy will be inevitably a reflection of the caregiver's behaviour towards him/her. Established attachment patterns or working models guide a person's response to frightening situations and interpretation of the caregiver's response.

The stability of early childhood attachment patterns is well demonstrated. During development from infancy to childhood, attachment working models become difficult to change. However, current experiences with attachment figures continue to influence the attachment working model.[64–66]

How can the attachment theory be relevant for people dealing with Huntington's disease? We speculate that the presence of HD in a family involves specific stressors, which might influence the attachment relationship between parents and their children for different reasons. First, the affected parent in the onset phase of HD may become preoccupied with the diagnosis, their own future, and the frightening recollections of his/her parent or other relatives going through the HD disease progression. As

the disease progresses, the patient is less receptive to the questions of the children and may become depressive or aggressive. These mood and personality changes, together with the choreic movements, may frighten or alienate their offspring.[67] Second, the disease may lead to changes in the family system. The unaffected parent will experience a change in responsibilities and dependency of the spouse in the relationship; the affected spouse becomes a person who insidiously needs care. Some healthy partners may feel unable to take up this task and will leave the household. Changes in the household may lead to neglect of the children. Some children may take up the care of the ill parent. The unaffected parent may seek one of the children as a substitute partner.[48]. Third, the fact that the children are at risk for developing HD also puts stress on parent-child bonding. The parents may be concerned about the carrier status of the child and may have feelings of guilt by having passed on the gene. Knowing that their children may get the disease can also create an emotional distance.[67] Some parents also have predictions or even fantasies about their children, thinking that they may or may not develop HD.[68] The healthy parent often has the difficult task of rearing these children and informing them about their risk without the help of the partner.[69 70] With regard to testing, having children is an additional stress factor for the healthy parent.[20] To summarise, a family burdened by a genetic disorder may have to deal with several types of loss: loss of the physical capacity of the affected person, loss of his or her own personality, loss of the old family system, and loss through death. This may be accompanied by shame, secretiveness, and social isolation.

Mental representations of attachment in adults are assessed by means of the Adult Attachment Interview (AAI).[71] The AAI asks subjects about childhood attachment relationships and the meaning which a person currently gives to attachment experiences. The instrument is rated according to the scoring system developed by Main and Goldwyn[72] which classifies people into Secure/Autonomous, Insecure/Dismissing and superimposed on these Insecure/Preoccupied, Unresolved/Disorganised with respect to loss or trauma, categories according to the structural qualities of their reports of early experiences. The assessment of attachment by means of coherence[43] may help to overcome problems with self-report measures in previous studies. Next to the attachment representation, the Adult Attachment Interview generates information about the psychodynamics and defences in a person.

Although Huntington's disease is a highly dramatic disorder with an increased chance for children to become traumatised, we speculate that the findings are also important for other genetic disorders that have been passed on to consecutive generations. This does not need to be restricted to autosomal dominant, late onset diseases with full or partial penetrance, but also for X linked disorders and diseases with recessive inheritance patterns. There is further important evidence that attachment relationships may play a key role in the transgenerational transmission of hardship and deprivation. People categorised as secure are three or four times more likely to have children who are securely attached to them.[60] This turns out to be true even in prospective studies where parental attachment is assessed before the birth of the child.[55 73–75] These findings also emphasise the importance of quality of parenting in determining the child's attachment classification. Investigation of the attachment relationship in HD families and its influence on adult functioning may contribute to a greater understanding of earlier research findings and serve to improve genetic counselling and intervention.

Appendix

AQ, Attitude Questionnaire
BDI, Beck Depression Inventory (BDI)[76]
BHS, Beck Hopelessness Scale (BHS)[77]
EPI, Eysenck Personality Inventory
FACES, Family Adaptability and Cohesion Evaluation Scales
GHQ, General Health Questionnaire[30]
GSI, Global Severity Index
GWS, General Wellbeing Scale[78]
HADS, Hospital Anxiety Depression Scale[79]
IES, Impact of Event Scale[46]
MCMI-2 , Millon Clinical Multiaxial Inventory II[80]
MHI, Mental Health Index
MMPI, Minneapolis Multiphasic Personality Inventory[81]
PSDI, Positive Symptom Distress Index (SCL-90)
PST, Positive Symptom Total (SCL-90)
SCL-90, Symptom Checklist 90[82]
SSQ, Social Support Questionnaire
STAI, State Trait Anxiety Questionnaire[83]
UCL, Utrecht Coping List[84]

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A novel 3' mutation in the *APC* gene in a family presenting with a desmoid tumour

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EDITOR—Desmoid tumours, also known as infiltrative fibromatoses, are rare benign tumours which often recur after local resection and can cause death through local infiltration of vital structures.[1] The estimated incidence in the general population of such tumours is 1-2 per million but in familial adenomatous polyposis (FAP) they occur in up to 15% of cases.[2] Likely precipitating factors include trauma and female sex hormones, since females are more often affected than males.[3] The majority of desmoid tumours in FAP (over 90%) arise in the mesentery of the bowel or in the abdominal wall musculature. In recent years, several families have been described where the predominant phenotype is of desmoid disease and where the colonic phenotype is minimal.[3–6] We describe another such family with a novel protein truncating mutation in the 3' end of the *APC* gene.

Methods and results

CLINICAL DETAILS

The index case presented at 29 years of age with a firm, slightly tender swelling within the right rectus abdominus muscle. A 6 x 5 cm tumour was locally excised and conventional histological examination showed infiltrative fibromatosis. The tumour recurred after six years and was resected again along with 30 cm of adherent small bowel. A year later, a further abdominal wall recurrence was resected and on this occasion fresh tissue was submitted for cytogenetic analysis. Full colonoscopy before referral to the genetics service showed no evidence of colonic adenomas throughout the colon. Repeat colonoscopy after the gene mutation was identified still failed to show any colonic pathology, although contrast dye spray was not undertaken on either occasion. The only relevant family history was that her father had a previous history of a sigmoid colectomy carried out at 56 years of age for a carcinoma of the colon. He had been discharged from follow up after seven years during which endoscopy had shown no further pathology and he has remained well and symptom free since. He had never had any palpable lumps. Review of the histopathology from the resection specimen showed a Dukes B adenocarcinoma of the colon with six adenomas in the surrounding colonic mucosa.

CYTOGENETIC ANALYSIS

Fresh desmoid tumour was subjected to cytogenetic analysis which showed normal fibroblasts mixed with abnormal cells showing an interstitial deletion involving chromosome 5q22.

MOLECULAR ANALYSIS

DNA from the index case was examined for mutations in the APC gene using denaturing high performance liquid chromatography (DHPLC). A single base substitution G>A was identified at nucleotide position 7511, codon 2504, which changes tryptophan (TGG) to a stop codon (TAG). The mutation was present in both the index case and her father.