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Risk Reversals in Predictive Testing for Huntington Disease

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Summary

The first predictive testing for Huntington disease (HD) was based on analysis of linked polymorphic DNA markers to estimate the likelihood of inheriting the mutation for HD. Limits to accuracy included recombination between the DNA markers and the mutation, pedigree structure, and whether DNA samples were available from family members. With direct tests for the HD mutation, we have assessed the accuracy of results obtained by linkage approaches when requested to do so by the test individuals. For six such individuals, there was significant disparity between the tests. Three went from a decreased risk to an increased risk, while in another three the risk was decreased. Knowledge of the potential reasons for these changes in results and impact of these risk reversals on both patients and the counseling team can assist in the development of strategies for the prevention and, where necessary, management of a risk reversal in any predictive testing program.

Introduction

The discovery of the first DNA marker linked to Huntington disease (HD) (Gusella et al. 1983) led to the development of a predictive test for HD. Subsequently, additional markers were identified (Gilliam et al. 1987; Hayden et al. 1988; Wasmuth et al. 1988) that enhanced the informativeness of the test. The recombination rate, which could result in inaccurate assignment of risk, was estimated as 1%–5%, depending on the proximity of the markers to the putative site of the HD mutation. Incorrect assignment of risk is most likely identified when new and more tightly linked markers to the gene are developed, when new information concerning family members is acquired, when the mutation underlying the disease is identified and direct mutation analysis is possible when misdiagnosis has occurred, or when persons at low risk unexpectedly manifest the signs and symptoms of the disease. In addition, human error may cause an incorrect risk result. As a result, risk reversals are possible in any predictive testing program that depends only on linked DNA polymorphisms.

Inaccuracy of the test and the absence of any effective treatment were two of the major concerns that were raised when predictive testing for HD first became available in 1986 (Bird 1985; Wexler 1985; Craufurd and Harris 1986; Farrer 1986; Kessler 1987; Smurl and Weaver 1987). With these concerns, a consensus developed that tests should be offered only under the guidelines of a protocol recommended by the World Federation of Neurology and the International Huntington Association (1990). The identification of the mutation in the HD gene in 1993 (Huntington's Disease Collaborative Research Group 1993) enabled predictive testing to be done more accurately, using direct detection of the CAG expansion, which should eliminate all but human error as a cause for incorrect assignment of risk.

A pilot project for predictive testing started in Vancouver, British Columbia, in 1986 (Bloch et al. 1989; Fox et al. 1989) and expanded in 1988 to include 16 genetics centers across Canada. Approximately 300 at risk individuals have received informative results through linkage analysis, and >1,000 individuals through direct assessment for the mutation. Of those receiving results via linkage, six individuals have been identified as receiving an incorrect risk result.

Here we report in detail on the risk reversals experienced in our program, which highlight its impact not only on the patient but also on the counseling team. These case reports reinforce the recognition that results of linkage testing are very much dependent on the technology and information available at the time. In addition, the importance of rigorous quality control measures to diminish the likelihood of human error is emphasized.

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We are unaware of reports of errors in genetic testing for HD, even though they are likely to have occurred. Forthright discussion of these issues provides an opportunity to learn from these experiences, which will hopefully reduce their likelihood of recurrence and also highlight approaches to deal with these difficult situations.

Methods

Eligibility criteria and recruitment methods for the Canadian Collaborative Study on Predictive Testing for HD have been described in detail elsewhere (Fox et al. 1989). The protocol includes at least two preresults sessions, a results session, and at least three follow-up sessions over a minimum period of 1 year after the patient receives test results.

Predictive testing was initially performed using DNA analysis of genetic markers linked to HD. Between 6 and 13 RFLPs were used to determine the informativeness of the test. The risk estimate was then calculated using the MLINK (version 3.5) subprogram of the LINKAGE program (Hayden et al. 1988), which takes into account age at onset, age of the candidate, penetrance, and recombination frequency between the marker and the gene. Once the gene was identified (Huntington Disease Collaborative Research Group 1993), direct assessment of the CAG repeat was performed by PCR amplification (Goldberg et al. 1993; Kremer et al. 1995). All data are kept confidentially in a master pedigree file in a locked cabinet. When a particular family is being assessed, a confidential working pedigree file is created. Normal individuals have CAG repeat sizes <29, while individuals affected with HD have CAG repeat sizes >35 (Kremer et al. 1994; Rubinsztein et al. 1996; Brinkman et al. 1997). Repeat sizes of 29–35 CAG are called "intermediate alleles." This designation has important clinical implications, because although individuals with repeat sizes in this range are not at risk of developing HD themselves, males are potentially at increased risk of having offspring with HD (Goldberg et al. 1995; Chong et al. 1997).

Case Histories

A Change from a Decreased to an Increased Risk Result

Individual 1: new information on family members.— At the time Mr. G requested predictive testing in 1989, blood was available from only two affected family members—his father and his aunt. (Every effort has been made to protect the confidentiality of patients by altering some details that do not distort the clinical presentation.) After some preliminary DNA analysis, he was informed that the accuracy of the risk estimate would be reduced because of the particular family structure and DNA available for assessment. He still wished to receive his results and was later told that he had a 17% risk of having inherited the gene for HD (fig. 1*A*). The large degree of uncertainty was due to the fact that both his father and his aunt had identical haplotypes. Therefore, the only way to determine which of the two chromosomes carried the HD gene was by assessment of the likelihood of homozygosity (based on the allele frequencies) for the polymorphisms comprising the different haplotypes.

Mr. G felt relieved and said that this was "great news." He talked about changing some things in his life, such as reducing his life insurance coverage and possibly having children. He stated that he felt "light" and "different." "I used to keep things bottled-up, especially my HD things." His marriage was also improving for various reasons, only one of which was the predictive test result.

Two years later, Mr. G's sister entered the predictive testing program and received a decreased risk estimate of 2%. Our patient wanted to know why his own decreased risk was so much higher and requested retesting. Since the assessment 2 years earlier, new highly poly-

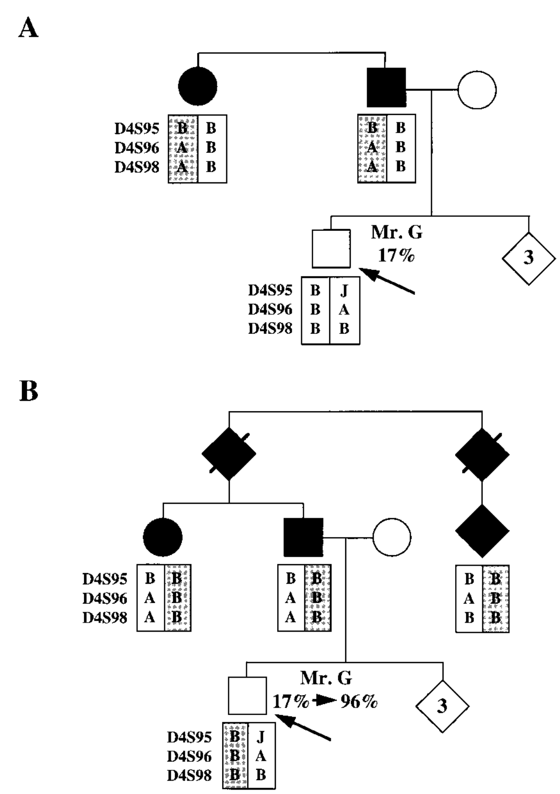

Figure 1 Pedigree of individual 1, showing the alleles for three different polymorphic markers (D4S95, D4S96, and D4S98) below the gender symbols. This represents a subset of all markers assessed, as it does for all figures that follow. The chromosome most likely carrying the HD mutation is colored gray.

morphic and informative DNA markers had been discovered that increased the likelihood of informativeness in this family. Furthermore, with DNA from a recently ascertained third affected relative, clear identification of the affected chromosome in the family was now possible (fig. 1*B*). Preresults counseling focused on the fact that there was a 17% chance that his risk estimate could be altered. The wife admitted that the 17% risk had felt the same as 50% to her. They were both anxious about the upcoming results. When he received his revised risk, he was informed that he had a 96% chance of having inherited the gene for HD (fig. 1*B*). Both he and his wife were upset. His wife attempted to focus on the 4% of hope that he had not inherited the gene, but he would not let her, saying "This is bad news." He never expressed anger with the counseling team or doubted these results. In follow-up sessions, he did admit to being more irritable and not sleeping as well. His wife felt he was not adjusting well to the results, citing his moodiness and depression and said they were having serious marital problems.

Two years later, Mr. G indicated that his life was on an "upswing." His relationship with his wife had improved, and they had decided against having children. He had bought the company where he was working and was attempting to plan his future financial security. When the direct test became available, he did not wish to be tested again.

Individual 2: the issue of quality control.—Mr. A was in his mid-30s when he first entered the predictive testing program in 1989. Many of the necessary blood samples from affected relatives had already been banked, and a working DNA file was begun. The counselor learned that two of the individuals in the family had the same name and notified the DNA Bank. The master pedigree was changed accordingly. However, the pedigree in the working file was not corrected. The DNA results revealed that Mr. A had a 3% risk of having inherited the gene for HD (fig. 2*A*). He was elated, and he and his fiancée made plans to marry and to have a reversal of his vasectomy. At the 2-mo follow-up appointment, Mr. A reported that "every day feels like Christmas."

A few months later, another relative applied for predictive testing. It was then discovered that Mr. A's result had been assessed using the uncorrected pedigree. The laboratory contacted the counselors immediately, and it was indicated that this error invalidated the results that he had been given. This was explained to Mr. A and his fiancée and it was emphasized that retesting could produce an altered result. Initially the couple appeared stunned. Mr. A stated that he understood "mistakes happen." His fiancée however was visibly upset. They both indicated that they wanted the new results as soon as possible.

Two weeks later, Mr. A contacted the genetics center

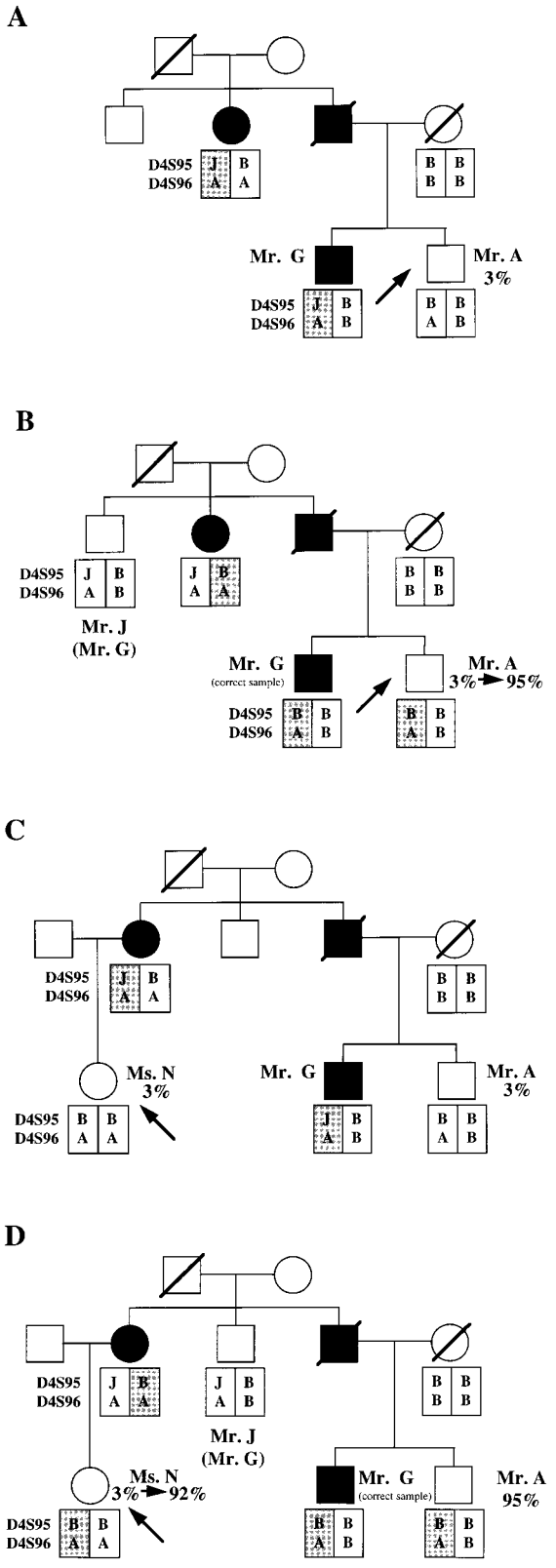

Figure 2 Pedigrees of individual 2 (*A* and *B*) and individual 3 (*C* and *D*). Alleles for two of the polymorphic markers (D4S95 and D4S96) analyzed are shown below the gender symbols. The chromosome most likely carrying the HD mutation is colored gray.

and explained that he had decided to delay receiving the new results because he was in the middle of moving and planning his wedding. Also, he had recently started a new job and wanted to establish his benefits there in case he was at increased risk. Seven months later, Mr. A contacted the genetics center to request the new results. The couple, who had been married in the interim, wanted the results for planning their family. Both Mr. and Mrs. A were prepared for the possibility that he might receive an increased risk result. At the results session, Mr. A was informed that his risk was increased to 95% (fig. 2*B*). Mr. A expressed no anger, blame, or regret about the test results, although he wistfully stated that he was glad to have had the opportunity to know what it felt like to live without the burden of risk.

During the following year, Mr. A did not complain of any problems and appeared in remarkably good spirits. He and his wife were planning to build their own home. He appeared to be determined to present an "all is well" view to the world. The counselor suspected that Mr. A was not acknowledging his fears about the future but noted that this coping mechanism seemed to be working for him.

Eighteen months after his revised results, Mr. A telephoned the genetics center on several occasions reporting periods of incapacitating anxiety. Twice an emergency referral to an anxiety disorder clinic was made, but on neither occasion did he attend. He also declined additional genetic counseling appointments but did call to report that he was doing better. At the 2-year follow-up, Mr. A was convinced that he was manifesting symptoms of HD. His neurological examination, however, was normal. He was also feeling tremendously guilty about ruining his wife's life and was unable to accept her reassurances. Soon thereafter, the home that Mr. A had built was burned accidentally. Immediately following this traumatic event, Mr. A needed lengthy psychiatric admissions during which he was diagnosed as having HD.

Individual 3: the issue of quality control.—While the DNA analysis for Mr. A's first test was being done, he did not know that a cousin, Ms. N also entered the predictive testing program. She had recently separated from her husband. At her results session, she was given a 3% risk of having inherited the gene for HD, which was based on the same pedigree as for individual 2 (fig. 2*C*). She appeared ecstatic with her results.

Two months later, the counseling center was informed about the laboratory error that could have influenced her results. The genetic team contacted the patient immediately. She understood that a major change in the risk estimate was possible. She did not appear angry with the unexpected turn of events and said that her life had not changed much since she received her initial result. Ms. N wished to receive the new results as soon as possible. After counseling, she returned to learn that her new risk was 92% (fig. 2*D*). She was devastated and could not understand how such a dramatic shift could have occurred.

At the follow-up session a week later, Ms. N expressed anger and frustration. She wanted to "exercise her rights," and be retested. She wanted to gather new blood samples from the entire family and start again. The counselors expressed the laboratory's confidence in the new results but agreed to her request to redo the analysis. She felt she had been "slugged in the gut" and that 92% was as good as being told she had the gene.

During the following few weeks, the patient gradually underwent a transition. She gave up the idea of collecting new blood samples and being retested. However, she still reported having crying outbursts at work and feeling "out of control." She declined additional counseling appointments with the genetics team but said that she would call her psychologist or go to the emergency room if needed. She stated that the worst part for her was having had the 2 mo of freedom from HD and then having that taken away. She said she would not have been so "shattered" if her first result had been an increased risk. The predictive testing team lost contact with Ms. N 6 mo after the new results, because she moved to another part of the country to be closer to her family. She did not respond to follow-up phone calls and letters.

A Change from an Increased to a Decreased Risk

Individual 4: new information on family members.—Mr. D was single and in his late 30s when he requested testing in 1987. His mother was the only living family member affected with HD. She had five unaffected siblings who were in their 50s or 60s. Since there was only one affected individual in the family, Mr. D was informed that his results would not be highly informative and that only a small shift in his prevailing risk would be possible.

At his results session, he was informed that he had a 80% risk of having inherited the gene for HD, on the basis of the haplotype of his affected mother, her age at onset, and the haplotypes and current ages of unaffected aunts and uncles (fig. 3*A*). He stated that he had always expected that he would get HD and that knowing was a relief. Two months later, some other family members attending follow-up sessions for their own predictive testing results indicated that Mr. D's sister was clearly showing signs of HD. However, she did not wish a medical examination. The counseling team had never seen the sister, and she resisted any efforts on the part of the family to even talk about HD.

One year later, when the sister requested predictive testing, she had concerns about her clinical status. A

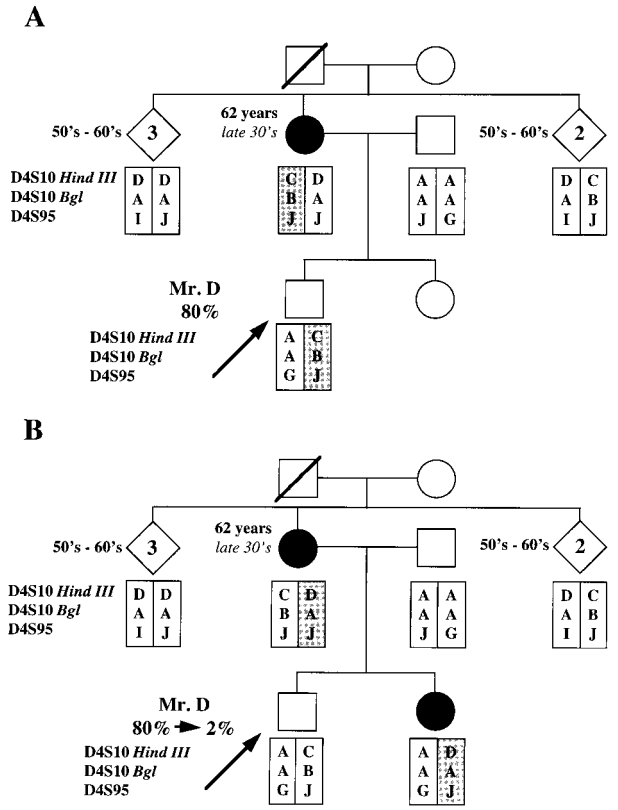

Figure 3 Pedigree of individual 4, showing the alleles for a subset of three polymorphic markers (D4S10 *Hind*III, D4S10 *Bgl* and D4S95) below the gender symbols. The chromosome most likely carrying the HD mutation is colored gray. Current age at the time of the linkage analysis is printed in boldface, and age at onset is printed in italics.

neurological examination confirmed the diagnosis of HD. Shortly thereafter, Mr. D attended his 2-year follow-up session and was keen to know whether his risk had been altered because of the availability of DNA from his affected sister. Repeat genetic analysis indicated that he had a 2% risk of having inherited the gene for HD (fig. 3*B*). He was delighted to receive this information. He talked of reversing his vasectomy and having children, of quitting his habit of frequent marijuana use, and of getting his debt load under control. At the same time, he expressed concern for his sister and some guilt feelings that he was the survivor of the two. Three years after the risk reversal, he was in a committed common-law relationship and had undergone a reversal of his vasectomy. He expressed no interest in having direct gene testing.

Individual 5: possible recombination event.—Mrs. K was in her mid 20s, had recently married and had a baby, and was contemplating having more children when her mother told her that she was at risk for HD. For some years she had been told incorrectly that her father, who had HD, was not her biological father and that her brother's problems were due to drug abuse, not HD. Soon after this new information, she requested predictive testing. She indicated that she wished she had known before her child was born, since she probably would have had prenatal testing if she had an increased risk.

Mrs. K was accompanied to the results session by her mother. She was given a 90% risk of having inherited the gene for HD (fig. 4*A*). They were both upset. At follow-up sessions, Mrs. K appeared to be more hopeful for the future and was trying to get pregnant again. Fifteen months after her results session, Mrs. K came in excited because she was 8 wk pregnant and the gene for HD had just been cloned. She wanted to have retesting immediately. However, after some discussion it was evident that she was not going to make any decisions regarding this pregnancy on the basis of the results and thus she decided to delay the direct testing until after the baby was born. One year later, Mrs. K and her mother returned to begin the process of retesting. The counseling focused on all the possible outcomes, with the most likely being that she had definitely inherited the mutation associated with HD.

Direct testing was carried out, and Mrs. K was shown to have inherited two normal alleles (fig. 4*B*). In all

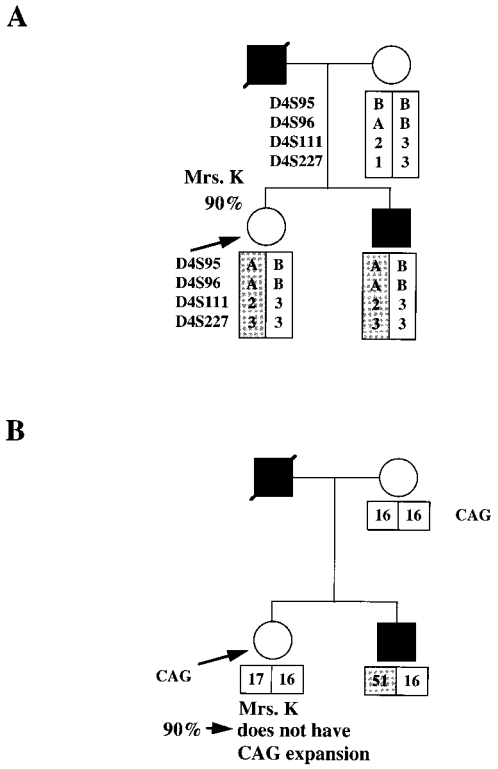

Figure 4 Pedigree of individual 5. Alleles for four of the polymorphic markers (D4S95, D4S96, D4S111, and D4S227) analyzed are shown below the gender symbols. The chromosome most likely carrying the HD mutation is colored gray.

likelihood, a recombination event had occurred between the markers and the HD gene, now leading to a decreased risk result. Another explanation for this result was that the affected father was homozygous for all markers tested; however, this possibility was very unlikely. The reaction to the new results was one of disbelief and shock. Slowly, Mrs. K began to realize the impact this was going to have on her family and that her children were no longer at risk. She wanted to have a copy of the results, and at the end of the session requested to go to the lab and see the actual raw data.

The months following the results were a happy time for this family. Mrs. K stated that the issue of HD had faded for her and that she rarely thought about it. She was considering changing her job and having another child, options that she would not have considered if she had inherited the mutation for HD.

Individual 6: new scientific information.—Mrs. D requested predictive testing because her sister was diagnosed with HD. There was no other known family history of HD. Mrs. D's father was 82 years of age and in good health, while her mother had died at the age of 44 years from Hodgkin disease. Testing to rule out alternative diagnoses and nonpaternity was undertaken on her sister.

Mrs. D was anxious to proceed with predictive testing, since she felt that her life, and that of her children's, were on hold until they could have some modification of her risk. Thus, after lengthy counseling, which stressed the limits of the test results and the fact that haplotype analysis could only indicate whether Mrs. D shared haplotypes with her affected sister, we proceeded with the DNA analysis. Mrs. D was informed that she did share a maternal haplotype with her sister and that she therefore had a 85% risk of having inherited the gene for HD (fig. 5*A*). She was very disappointed, not so much for herself as for the serious implications for her children.

At each follow-up over the next 5 years, Mrs. D continued to be healthy. When the gene for HD was identified, she requested retesting. At her second results session, she was told that her risk of developing HD was now very low (fig. 5*B*). In fact, she had inherited an intermediate allele with a CAG repeat size of 35. Her father also had a CAG size of 35, which had expanded on transmission to her sister. Mrs. D had in fact inherited exactly the same chromosome as her sister but with different CAG lengths. Thus, while she was no longer at risk of developing HD herself, this intermediate allele had the small possibility of expanding into the HD range, in particular on transmission through the male germ line. She acknowledged that it was indeed good news for her that we had never seen anyone with 35 CAG repeats or less develop HD. However, her primary focus had always been her offspring, and we were not able to completely eliminate the risk for HD to them.

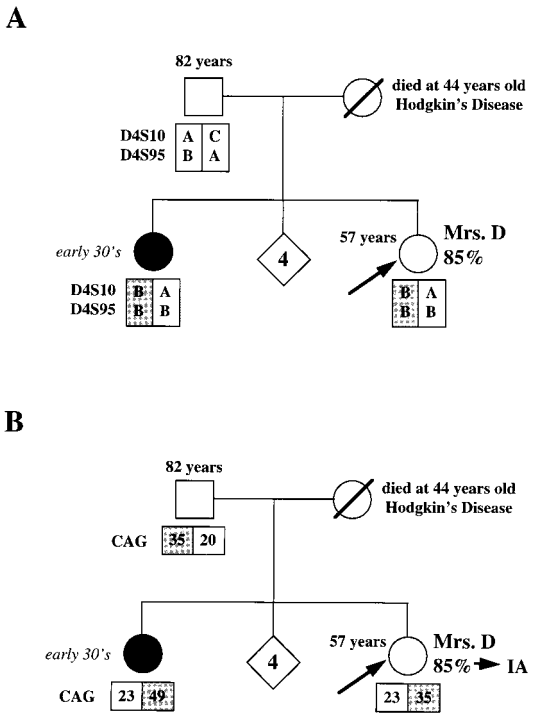

Figure 5 Pedigree of individual 6, showing the alleles for a subset of two polymorphic markers (D4S10 and D4S95) below the gender symbols (*A*). The chromosome most likely carrying the HD mutation is colored gray. Current age at the time of the linkage analysis is printed in boldface, age at onset in italics. The CAG repeat size in the HD gene is shown in panel *B*, and intermediate allele size is abbreviated as IA.

Discussion

More than 300 persons have received informative DNA results through linkage analysis in the predictive testing program for HD in Canada. Here we describe six individuals who had disparity between results of direct and linkage testing. Even though these events are rare, if a disparity is detected, a plan has to be developed as to how to provide this information. Risk reversals are likely to occur in any predictive testing program using linkage analysis, e.g., multiple endocrine neoplasia type 1 (Sandelin et al. 1994), breast cancer (Radford and Zehnbauer 1996), and spinocerebellar ataxia type 3 (Verschuuren-Bemelmans et al. 1995), and therefore considerations for how to deal with this have relevance for these genetic disorders.

A risk reversal may have significant impact on individuals receiving this modified risk. The most demanding risk reversals for both the patient and the counseling team were those that were due to human error (individuals 2 and 3). These two individuals both went from a

decreased risk to an increased risk and had long-term difficulties. For individual 2, however, difficulties appeared to coincide with the onset of the disease. Following that, associated with the experience with individuals 2 and 3, a more rigorous laboratory protocol of sample verification and clinical/laboratory communication was instituted.

The case history for individual 2 illustrates the importance of offering a choice to the candidate as to whether to proceed or not with the new risk estimate. In this situation, even though the counselors thought that the client would want the most accurate information, he chose not to receive it at that time. This has influenced our approach in dealing with change of risk detected with different technologies. We first inform the test candidate that new information has become available and, second, explore with them whether they wish to have this new information.

The unpredictability of individual responses is illustrated by individual 1, who was not only accepting of his increased risk result but appeared to make more positive adjustments in his life in the position of being at increased risk than when he believed he was at decreased risk. Similar narratives have been reported elsewhere, illustrating the unexpected responses that some individuals have with adjusting to their new risk status (Bloch et al. 1992; Huggins et al. 1992).

It is noteworthy that four of the six risk reversals occurred for individuals whose initial risk estimates ranged from 10%–20%, or 80%–90% likelihood of having inherited the mutation for HD. By definition, it was more likely that these persons would have a higher risk of an inaccurate result. This highlights the importance of patients' understanding the limitations of linkage analysis, particularly for a partially informative test result. It is also important to inform individuals in any predictive testing program that the interpretation of their results are based on the current knowledge and that this might change in the future as new scientific findings become available. This is shown in the case of individual 6, who received an increased risk but, after the HD gene was identified, was found to have a CAG repeat length in the intermediate range, which reduced her risk even though she had inherited the same chromosome 4 as her affected sister.

Given the difficulty with which individuals may experience risk reversals, the question arises whether linkage testing should be offered when only partially informative risk estimations are possible (<90% certainty in risk assessment). This situation is analogous to genetic testing for breast cancer, which also provides patients with partial risk estimates for developing cancer (Foulkes and Narod 1995). Clearly, it is important that the individual who requests testing is fully informed, that consent is voluntary, and that long-term counseling is provided. In our program, we discussed these issues with each candidate on a case-by-case basis and gave patients the option to pursue testing or not. This may, however, be a place for a more directive approach, primarily because it might be difficult for patients to understand fully a partial modulation of risk. On the basis of these experiences, despite urging by predictive testing participants, a more conservative approach that postpones testing until more clinical or scientific information becomes available might be warranted.

An important ethical and legal question can be raised whether the geneticist has a duty to recontact their patients when new information for a genetic test becomes available. This issue has been discussed by Pelias (1991) who suggested that the physician "has a continuing obligation to re-contact former clients when he receives new information that could be material in their lives" (p. 352). This would suggest that a patient who has participated in genetic testing must be informed of the availability of a direct test. As to our knowledge, different approaches have been used to deal with this particular issue in predictive testing for HD. Some test centers informed their participants about the direct test through the newsletter of the lay organization for HD, while other centers wrote a personal letter to the test candidates who had linkage testing. However, clearly one could argue that the patient also has a responsibility to keep themselves informed about new discoveries that might have implications on their lives (Pelias 1991). The physician-patient relationship imposes duties on both patient and counselor, including recommendations for further contact and, where necessary, follow-up visits to ascertain new information. At the present time, we would favor an approach that takes into account appropriate confidentiality while providing participants with new information in general about the latest scientific information and the availability of counseling.

As identification of genetic risk moves from linkage analysis to direct mutation testing for this and other diseases, further risk reversals will occur. Knowledge of the impact of these reversals is important to developing approaches for delivery of this new information to the patient.

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