Impact of DNA Testing for Early-Onset Familial Alzheimer Disease and Frontotemporal Dementia

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Background: DNA testing of persons at risk for hereditary, degenerative neurologic diseases is relatively new. Only anecdotal reports of such testing in familial Alzheimer disease (FAD) exist, and little is known about the personal and social impact of such testing.

Methods: In a descriptive, observational study, individuals at 50% risk for autosomal dominant, early-onset FAD or frontotemporal dementia with parkinsonism linked to chromosome 17 underwent DNA testing for the genetic mutations previously identified in affected family members. Individuals were followed up for 1/2 to 3 years and were interviewed regarding attitudes toward the testing process and the impact of the results.

Results: Twenty-one (8.4%) of 251 persons at risk for FAD or frontotemporal dementia requested genetic testing. The most common reasons for requesting testing were concern about early symptoms of dementia, financial or family planning, and relief from anxiety. Twelve individuals had positive DNA test results, and 6 of these had early symptoms of dementia; 8 had negative results; and 1 has not yet received results. Of 14 asymptomatic individuals completing testing, 13 believed the testing was beneficial. Two persons reported moderate anxiety and 1 reported moderate depression. As expected, persons with negative test results had happier experiences overall, but even they had to deal with ongoing anxiety and depression. Thus far, there have been no psychiatric hospitalizations, suicide attempts, or denials of insurance.

Conclusions: Genetic testing in early-onset FAD and frontotemporal dementia can be completed successfully. Most individuals demonstrate effective coping skills and find the testing to be beneficial, but long-term effects remain unknown.

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DNA testing for genetic diseases is a relatively new and controversial enterprise. The benefits of relieving anxiety and being better able to plan for the future must be weighed against the potential risks of emotional depression, compromise of insurance and employment, and social isolation.1,2 Formal evaluation of such testing is largely available only for breast cancer and Huntington disease (HD). However, even with these diseases, follow-up is relatively short and the outcomes are only partially evaluated. There is an urgent need for additional information in this field.3

The University of Washington Alzheimer Disease Research Center, Seattle, has ascertained several families with specific mutations associated with autosomal dominant early-onset familial Alzheimer disease (FAD) and frontotemporal dementia (FTD) with parkinsonism linked to chromosome 17. Several individuals in these families requested detailed genetic counseling and DNA testing. We evaluated the impact of this testing on their lives.

RESULTS

The 251 mailed letters prompted 58 specific inquiries about DNA testing (23.1%); 21 persons (8.4%) decided to proceed with genetic counseling and testing. Of this group, 16 persons from 9 families were at risk for FAD (10 with presenilin 2 and 6 with presenilin 1 mutations) and 5 persons from 2 families were at risk for FTD with parkinsonism linked to chromosome 17 tau mutations. The mean age of disease onset in these families was 51.8 years (range, 30-75 years). There were 11 women and 10 men, with an average age of 42.5 years and an average of 14 years of education. All persons had an affected parent and were at 50% risk for inheriting the disease gene. Additional demographic data are shown in Table 1.

Six persons requesting DNA testing were considered by their families and physicians to probably be in the early stages of
PARTICIPANTS AND METHODS

In the course of our research on inherited dementia, we ascertained more than 20 families with specific mutations in the following genes: amyloid precursor protein, presenilin 1, presenilin 2, and tau. Many of the pedigrees have been published. Lifetime penetrance is known to be greater than 95% in affected members of these kindreds. A follow-up study of persons at risk for the disease genes in these families was approved by the University of Washington Human Subjects Review Committee. Two hundred fifty-one family members received a letter describing the genetic findings in the family, discussing the availability of DNA testing, and requesting that individuals contact the University of Washington Alzheimer Disease Research Center for further information. Those requesting further information received a telephone call from one of us (E.J.S.) and a booklet describing the potential risks and benefits of genetic testing. This booklet followed the format of a booklet about genetic testing in HD. It was indicated that the DNA testing must be done in the context of formal genetic counseling according to a previously published protocol. Persons unable to travel to Seattle (n=11) had professional genetic counseling locally. Two of us (E.J.S. and T.D.B.) communicated directly with the local counselors through all phases of the testing.

To assess the effects of DNA testing, 11 persons completed a 5-page questionnaire that provided demographic information and included questions about attitudes toward the testing and the impact of the results on their lives. The Impact of Event Scale (IES) and the Hospital Anxiety and Depression Scale were also administered. The latter contains 14 questions, 7 relating to anxiety and 7 relating to depression. The sum of the individual scores indicates an overall anxiety (range, 0-21) and depression (range, 0-21) score. A score of 8 or 9 on either subscale is an indication of borderline anxiety or depression, and a score of 10 or higher in either subscale is an indication of definite anxiety or depression. The validity and reliability of the Hospital Anxiety and Depression Scale have been demonstrated previously. The IES classifies stress into 2 major categories: intrusion and avoidance. Intrusion refers to constantly experienced ideas, images, feelings, or dreams. Avoidance refers to conscious denial of certain ideas, feelings, or situations. The IES is a reliable self-report scale that can be anchored to any specific life event, such as DNA testing for a neurogenetic disease. Seven items form the intrusion subscale, with a maximum score of 21, and 8 items form the avoidance subscale, with a maximum score of 24. The items are scored by choosing 1 of 4 indicators of occurrence of the specified event (never, seldom, often, and continuously). The IES is especially useful in determining how much a person worries about a disease process and the degree of denial concerning the disease that is experienced by the individual. This test has been particularly useful in assessing the distress experienced by individuals undergoing DNA testing for HD.

The small number of participants in this study and the subjectivity of the data did not warrant statistical analysis. DNA mutation screening for presenilin 1, presenilin 2, and tau were performed by previously described methods. A positive test result indicates that the individual carries the disease gene mutation and has a greater than 95% chance of developing the condition at some point in their lifetime.

Dementia. DNA testing was performed in collaboration with the physicians, and all 6 individuals had a positive test result. In 6 of 6 cases the results were considered useful in helping to explain the cause of the early dementia and in allowing the family and health care providers to tailor the diagnostic evaluation and plan for the future. The mean ± SD age of the symptomatic individuals was 48.0 ± 8.2 years.

The mean ± SD age of the 15 asymptomatic individuals was 40.3 ± 11.3 years. Test results followed up ranged from 2 to 3 years. One of these persons received genetic counseling and completed a questionnaire but decided to postpone testing for 1 year; the testing process has not yet been completed. Two persons received genetic counseling and had a blood sample taken but postponed receiving their results for 2 years. Of 14 individuals receiving results, 8 had negative results and 6 had positive results.

In the 12 asymptomatic persons completing a questionnaire, the 3 most common reasons for requesting DNA testing were financial planning (n=10), family planning (n=8), and relief from worry and anxiety (n=9). Other less frequently given reasons included travel or retirement planning, career planning, possible effect on family relationships, and possible eligibility for future treatment trials.

When asked, “Would you advise other persons in your situation to have such testing?” 4 individuals with negative results and 1 with positive results replied yes. All others said that they would give no specific advice and that it would “be up to the individual.” No person answered the question no. However, as noted later herein, 1 individual with positive test results refused all further follow-up evaluations.

All 8 persons receiving negative results expressed relief or gratefulness. As expected, individuals with positive results were disappointed, but they expressed the following feelings: this was an “important and necessary life decision,” “glad I know result for planning,” “ambivalent but glad to have knowledge,” and “gives me clear choices for the future.” One person stated that the positive test results “confirmed what I thought.”

Three individuals scored moderately high on the anxiety subscale of the Hospital Anxiety and Depression Scale (1 with positive and 2 with negative DNA test results) (Table 2). One person had a moderately high score on the depression subscale. This person had a negative DNA test result but a past history of depression.

On the IES, 5 persons had relatively high intrusion scores, suggesting frequent daily thoughts about the disease. Four of these 5 persons had negative DNA test results, 1 of whom still cares for an affected mother.

Four persons had relatively high scores on the avoidance subscale of the IES, suggesting a strong tendency to avoid thinking about the disease. Two of these persons had a positive DNA test. The 2 individuals with the highest avoidance scores include one who postponed receiving results for 2 years and another who has not yet received results after a 1-year postponement.
The testing affected the marriages of 3 persons. An individual with positive test results separated from his or her spouse. A person with negative test results proceeded with a divorce, and another with negative results proceeded with plans for a second marriage. All 3 persons stated that the test results were a factor in these decisions.

The testing affected family planning in 3 individuals. A woman with positive test results proceeded to have a first child. Another person with positive test results had 1 child and decided not to have additional children. Another person had a first child during a 2-year hiatus between having the blood sample drawn and deciding to receive the test information.

Thus far, no asymptomatic person with a positive DNA test result has lost employment or been denied insurance, to our knowledge. There have been no psychiatric hospitalizations and no suicide attempts.

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Two years after receiving a negative test result for FAD, 1 person had high anxiety and intrusion scores on the IES. These scores were associated with ongoing concerns and worries about AD in the family, which had affected the father, a deceased brother, and a living brother.

One individual who had positive test results for a tau mutation was distressed with the result and requested no further evaluation or contact from study personnel.

One individual had counseling and a blood sample drawn and then postponed receiving the results for 2 years while “emotionally preparing.” When the result proved to be negative he or she stated, “I was so convinced I carried the (abnormal) gene that I have to retrain my mind to think differently. . . . Now I have a future—I take less of my anti-anxiety pills—my closest friends cried with happiness.”

A 57-year-old woman who had negative test results for FAD subsequently wrote a one-woman play about her life that has been publicly performed on several occasions. A major theme of this play is her family history of AD and the impact of genetic testing on her life.

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Detailed information about the psychosocial impact of genetic testing is primarily available for only 2 diseases, namely, HD and breast cancer.3 Testing for inherited forms of breast cancer is different from testing for either HD or dementia. Treatment and prevention options are available for persons with positive test results for a BRCA (breast cancer gene) mutation, and breast cancer does not cause degenerative brain disease. A large worldwide follow-up study19 of persons undergoing genetic testing for HD showed that persons generally coped reasonably well with the results. However, in persons with positive test results for HD there was a 2% frequency in approximately 2 years of serious psychiatric distress, such as depression requiring hospitalization or a suicide attempt.19,20 These adverse events usually did not occur immediately after testing but rather at a later date, when the individual began to experience early symptoms of the disease.

There are several similarities among early-onset FAD, FTD, and HD. All 3 are inherited, autosomal dominant, progressive, degenerative neurologic diseases for which there are no dramatically effective treatments. However, there are important differences that could affect the perspective of family members toward these diseases. Huntington disease has been known to be a genetic disease for more than 100 years, and the potential risks and benefits of genetic testing have been discussed in the HD community for at least 25 years. Specific genetic knowledge about FAD and FTD is much more recent. Huntington disease has a prominent movement disorder, is usually not associated with early dementia, and has an average disease duration of approximately 15 years. Familial Alzheimer disease and FTD do not commonly have a movement disorder, always begin as a dementing or aberrant personality disorder, and typically have a shorter disease duration than HD. Also, AD is a heterogeneous disease such that everyone in the general population has a risk of eventually developing the disorder even if he or she has negative test results for a specific FAD mutation. This is a confounding variable not present in the genetic counseling of families with HD. For all of

Table 1. Genetic Testing for Familial Dementia*

<table>
<thead>
<tr>
<th>Genes, No.</th>
<th>Disease, No.</th>
<th>Married, No.</th>
<th>Time since tested, mean ± SD, y</th>
<th>Impact on family planning</th>
<th>Impact on marriage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS2</td>
<td>FAD</td>
<td>6</td>
<td>2.1 ± 1.0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PS1</td>
<td>TAU</td>
<td>4</td>
<td>2.2 ± 0.9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TAUP</td>
<td>FTD</td>
<td>6</td>
<td>2.2 ± 1.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>6</td>
<td>2.1 ± 1.0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Positive</td>
<td>10</td>
<td>16</td>
<td>2.2 ± 1.0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Impact of Genetic Testing on 14 Asymptomatic Persons*

<table>
<thead>
<tr>
<th>DNA Test Results</th>
<th>Negative (n = 8)</th>
<th>Positive (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact on marriage</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Impact on family planning</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HAD Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression score ≥9</td>
<td>1 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety score ≥9</td>
<td>2 (10 and 13)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>IES Avoidance score ≥5†</td>
<td>1 (12)</td>
<td>2 (8 and 9)</td>
</tr>
<tr>
<td>Intrusion score ≥9</td>
<td>4 (9, 10, 18, and 20)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

*Data are given as number of patients; actual scale scores are shown in parentheses. HAD indicates Hospital Anxiety and Depression; IES, Impact of Event Scale.
†The individual with the highest IES avoidance score (14) postponed the testing and is not included in this table.
these reasons, attitudes toward genetic testing in FAD and FTD cannot be assumed to be identical to or even similar to those in HD.

Although the potential for genetic testing of asymptomatic persons in families with FAD has been discussed, only 2 anecdotal studies actually reported such testing. In a family from Sweden, a person with positive test results for an amyloid precursor protein mutation experienced more than 6 months of severe depression. In an American family with an amyloid precursor protein mutation, 2 siblings had negative and 1 had positive test results. The individual with the positive test result wrote a personal statement describing her anxiety and difficulty coping with the results.

Results of the present study should be considered preliminary because of the small number of participants and the relatively short follow-up. However, the following observations can be made:

1. A relatively small number of persons at risk decide to actually pursue DNA testing (8% in this study). This is similar to recent experience with HD testing. Thus, persons who pursue genetic testing are a highly self-selected group, possibly biased toward those most able to deal with the process and results.

2. DNA testing can be of diagnostic benefit in evaluating persons at risk for early-onset FAD who are in the initial stages of memory loss and dementia and are from families with known autosomal dominant mutations.

3. Persons with negative DNA test results experience considerable relief and have an affirmative attitude toward the testing. However, even persons with negative test results might continue to experience anxiety, depression, or both because of previous personal history or ongoing involvement with the disease in the family. Negative test results can affect future behavior.

4. Persons with a positive test result often display strong coping abilities, are able to carry on with their lives, and might express affirmative attitudes toward the testing. However, there is no doubt that the testing can have a major personal impact, especially on marriage and family planning. The long-term effect of a positive test result is unknown, including its effect on the recognition of or concern about possible early symptoms of dementia.

5. Deciding to proceed with genetic testing can be associated with considerable ambivalence, and individuals may postpone receiving test results at the last minute.

In summary, we conclude that DNA testing in autosomal dominant early-onset FAD and FTD with parkinsonism linked to chromosome 17 can be successfully accomplished in appropriate families in the context of formal genetic counseling with ongoing follow-up and monitoring. The testing has benefits and risks for persons with positive or negative results. The overall impact of such testing, especially on marriage and family planning, should not be underestimated, and further longitudinal studies are required to fully appreciate the long-term effects of genetic testing.

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REFERENCES


