Genetic susceptibility for Alzheimer's disease: Why did adult offspring seek testing?

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Abstract

This study explored why adult offspring of individuals with Alzheimer's disease (AD) sought genetic susceptibility testing for AD. Participants (N = 60) were a subset of subjects from the first randomized controlled clinical trial to offer such testing. Qualitative analysis revealed two central constructs: altruism and learning. Planning for the future, hoping to prevent AD, and need to know were concepts that explained the value of learning. These results add important contextual information into why people might seek information on their genetic risk for a severe neurodegenerative disease for which there are, as yet, no preventative treatments. As genetic susceptibility testing for numerous other diseases enters clinical medicine, these findings can enhance the knowledge and sensitivity of researchers and clinicians when they are asked by participants or patients whether they should be tested.

Key words: Alzheimer's disease, genetics, susceptibility testing, qualitative research

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Introduction

Many persons are concerned with their own or their offspring's risk of inheriting Alzheimer's disease (AD).[1] While early-onset AD inherited as a dominant trait accounts for a very small percentage of cases,[2] the most robust genetic risk factor for developing AD is the ε4 allele of the apolipoprotein (APOE) gene on chromosome 19.[3,4] There are three common APOE alleles—ε2, ε3, and ε4. Individuals with one copy of the ε4 allele are approximately two to four times more likely to develop AD compared to those who have the ε3/ε3 genotype,

while ε4 homozygotes are five to 30 times more likely to do so.[5,6] These findings have raised the possibility of using APOE genotyping in a predictive manner to help evaluate risk for AD.

Although there has been research on motivation to seek genetic testing for other diseases with known genetic markers, such as Huntington's disease[7-10] and breast and ovarian cancers,[11-13] research in the AD field is just beginning. The use of the ε4 allele for predictive purposes in asymptomatic individuals is not recommended,[14-18] due to the possibility of psychological harm or discrimination in an environment where no preventative treatments are currently available. Moreover, because APOE genotype confers increased risk, but not definite information whether or not someone will develop AD, there is considerable complexity and potential for misunderstanding in seeking to use APOE to estimate personal risk. APOE testing is not available clinically for asymptomatic individuals.

Nonetheless, there have been consistent reports from clinicians and researchers that some individuals do wish to learn their own APOE genotypes. Until the first randomized controlled clinical trial to offer APOE testing, the Risk Evaluation and Education in Alzheimer's Disease (REVEAL) Study,[19] knowledge about seeking APOE testing was limited to the use of survey research methods and hypothetical scenarios.[20,21]

The REVEAL Study was the first National Institutes of Health (NIH)-funded randomized clinical trial to explore the impact of APOE disclosure in asymptomatic individuals, enrolling adult offspring of patients with AD to 1) learn the characteristics and motivations of those who chose to obtain risk assessment, 2) determine the psychological consequences of genetic risk assessment, and 3) examine real-life changes in health behaviors and insurance purchases made after learning one's personal risk for AD. After enrollment, subjects completed a packet including a 12-item survey in which they responded to proposed reasons for seeking risk assessment. In this first nonhypothetical study, the three most commonly endorsed reasons were 1) to contribute to research (93.9 percent), 2) arrange personal affairs (87.4 percent), and 3) hope that effective treatment will be developed (86.8 percent).[22]

The purpose of this qualitative phase was to enrich our understanding about participants' perspectives, beliefs, and motivating factors for seeking genetic susceptibility testing for AD. This article builds on previously published reports of reasons for seeking genetic susceptibility testing[22,23] using stories told in semistructured interviews that describe, in depth, why adult offspring of individuals with AD participated in the REVEAL Study.

Methods

We followed Glaserian methods of Grounded Theory[24,25] and a process of basic content analysis of narrative data[26] to conduct this sequential phase of research. The methods of Grounded Theory are derived from social process theory and symbolic interactionism,[27] and are appropriate here because a basic tenet of symbolic interactionism is that human beings' actions are purposeful and based on the meanings that the individual has for them. Process research has been suggested as a way to examine the dynamic psychoeducational process of genetic counseling,[28] and qualitative investigation after a quantitative phase of study allows for more detailed exploration of the results.[29]

Institutional review board approval was obtained at all three REVEAL Study sites (Boston, Cleveland, and New York). Genetic data were protected by an NIH Certificate of Confidentiality. REVEAL Study genetics counselors, who had met with potential interviewees several times during the conduct of the REVEAL Study, invited participants to be interviewed. Unlike probability sampling in a quantitative study,[30] participants were not randomly determined but identified by counselors as potentially being a "good informant." In qualitative research, appropriate participants have both experienced the phenomena and can articulate their experiences.[31] REVEAL subjects who conversed easily about their beliefs and feelings and who would be available when the interview team was in that city constituted the qualitative sample. A semistructured interview guide was used to elicit information about background, personal experiences, reasons for initial participation and continuation in the REVEAL Study, beliefs about AD causes and risk factors, and genetic knowledge and beliefs regarding AD. Tape-recorded interviews were conducted after participants had concluded their participation in the quantitative phases of REVEAL.

Interview tapes were transcribed into a word processing package, any identifying information was removed, and pseudonyms were substituted for names. These data were then entered into The Ethnograph to facilitate coding and analysis by allowing us to retrieve, organize, and ultimately classify segments of text.[32] Data were examined for instances of "why" participants enrolled, contrasted across participants, and combined into descriptive categories[33] to discover new perspectives from the verbatim accounts in participants' stories. Validity was achieved by two independent reviewers agreeing on what was heard when coding the transcripts and by grounding concepts in the respondents' words.

Results

Sample demographics

Demographic data were collected immediately after enrollment, approximately 18 months before participating in the interview phase. Participants were of high social economic status based on income and education (Table 1). Their income and gender differed slightly from the overall REVEAL Study sample. Most had first-hand knowledge of the clinical progression of AD through caring for their affected parent, 50 percent of whom were living at the time. One-half of the participants had more than one relative with a memory disorder. Almost 75 percent self-referred themselves to be in REVEAL, while the remainder were approached through their family's participation in a research registry and agreed (see Roberts et al.[22] for details).

Qualitative findings

Analysis and coding of 60 interview transcripts yielded 157 stories classified as why a participant volunteered for the REVEAL Study. There were elaborate accounts with intricate thoughts, as well as terse descriptions such as the following: "Well, it was the first one anybody was doing with the children of Alzheimer's patients. And I was, like, here I am." Also, the concern about potential lack of privacy of genetic information was expressed by Donald, who worked in the field of molecular biology:

> DONALD: I was probably drawn to it from a personal interest in wanting to know my genotype in an off-record situation, off-medical record situation. Well, basically because I figured if I was randomized into the group that I would receive it, it would be off record and I would know and have a sense of what that was. I had actually thought about doing it myself in my lab. That will give you an answer that you're probably not going to hear from too many other people.

These stories yielded data bits describing reasons why participants sought genetic testing, albeit through a research study. We achieved increasingly higher levels of abstraction, culminating in two constructs—altruism and learning. Segments of participants' quotes are used to help illustrate the constructs.

Altruism. Altruism was defined as helping others by advancing science.

GABE: When I came here, it was strictly because I realized that I was the prime candidate that might be able to help.

MARY: I mean, it's like you are willing to do anything you can if you feel that you could make a mark or contribution.

REGINA: I thought maybe it might help somebody, because we had the two people in our family. But the driving force seemed to be maybe I can help somebody else.

ZEUS: To do something to contribute to find out how you could help in solving the problem, because they must need thousands and thousands and thousands of people to put all these facts together. And there has to be a common thread somewhere that somebody's got to find, and want to see something done about it. So, I figure I'm helping.

ADELE: I just think that our family would be a great group because they did have the brain autopsy. They did know that was her cause of death, and if it was genetic or whatever, if I could help in any way, I just wanted to return that favor.

URI: For her. Yeah. I think, knowing Mom, I mean we knew that she would want to do anything that could help. Which is also why I'm doing this.

DORIS: I was feeling—and I still feel—if there's something I can do to try to help advance the knowledge, or the treatment, or the understanding, or some greater good, if there's any greater good that can come from my father's illness, I'm happy to try to help get to that.

PAUL: I thought if I can help in any way to do anything to participate in this study, that's all that was important to me. And I said, anything I could do to help. I still feel that way. I have an interest in the disease because my mother has it.

XYLONA: And because my mom had Alzheimer's and I kind of feel that research does help, maybe not in the short term but in the long term. And so maybe it wouldn't be of help for me, but it might be of help for my children or grandchildren, so therefore why not do something that might help somebody else down the line?

Table 1. Demographics for the REVEAL Study and interview phase participants		
Factor	**REVEAL (N = 206)**	**Interview (N = 60)**
Mean (SD) age, range (yr)	52.8 (9.5); 30 to 78	54.2 (10.2); 37 to 76
Gender (percent female)	72.3	86.7
Race (percent white)	94.7	95
Mean (SD) years of education	16.5 (2.3)	16.9 (2.1)
Median household income	$70,000 to 99,999	> $100,000
Status of affected person (percent living)	52.5	50.0
Diagnosis of affected parent (percent)		
Autopsy-confirmed AD	16.9	26.3
Formal clinical diagnosis of AD	74.0	71.9
Suspected AD	9.1	1.8
Number of relatives with memory problems (percent)		
One	40.8	50.0
Two	31.6	28.3
Three	16.5	15.0
Four or more	11.1	6.7
Served as caregiver for relative with AD (percent yes)	74.8	71.7
Recruitment source (percent)		
Self-referred	70.9	74.0
Systematically ascertained	29.1	26.0
Study site (percent)		
Boston	33.5	41.7
New York	35.0	25.0
Cleveland	31.5	33.3
AD, Alzheimer's disease; REVEAL, Risk Evaluation and Education in Alzheimer's Disease; SD, standard deviation.		

> DANNY: And then I had the genetic testing, which showed that I had every possibility of having it, and thought I would continue with this and help me and help somebody else. Well, I guess for my benefit, and my family's.

Participants' reasons for their altruism included notions of "I/we can help," a gesture of thanks for care provided to the AD-affected parent, believing the parent would want it, or for one's own family. Thus, societal and personal interests, implied or explicitly stated, were embedded in altruism. Being a stakeholder in AD research because of being an offspring of a person with AD (participants were well aware of the hereditary nature of AD) implied a notion of self-interest for the participant and/or for future generations.

Learning. Learning was defined on a continuum from curiosity for self and/or a scientific detached inquisitiveness to a search for information. Three concepts seemed to explain the reasons for learning or seeking information: planning, prevention, and need to know.

Planning was defined as thinking ahead to consider/make future arrangements for self while preparing/not burdening others. Participants considered future actions they might take for themselves and/or for others. Organizing one's self for the future while not burdening others may have been in the forefront for many participants, because 34 of 60 had or were presently caring for their parent with AD (Table 1).

> ROBERTA: When they wanted to know if I wanted to do the program, I go, sure, I want to see where I'm at. Because I can make some decisions in my life that I could take care of everything before and not have everybody else stress about it. I figured I needed to know because what if I get it? Who's going to take care of me?
>
> HENRIETTA: Because I wanted to know. Because if I have a high risk for Alzheimer's, there are a lot of things that I want to get in order that I might just let slide. There are some things that I haven't done that I may want to start doing, and also to inform my spouse that if he starts seeing signs of this, let me know so I can speed up the schedule, you know, of getting my will done and that sort of thing.
>
> OLAF: I think probably for the future of my family and my kids because I know I've had to play a big part in my mother's care, so I'd like to be prepared and really have all the ducks in a row and know what's going to happen. That's why I was interested.
>
> EDWARD: Well, I think it can only help you. If you really knew, then perhaps you better take out this insurance so that my care wouldn't deplete the family resources or whatever.
>
> ELINOR: My mother's was early onset. I've still got 20 years. That's 20 years for them to do something about it. Twenty years for me to protect myself, 20 years for me to decide if I'm going to spend my money or put it in an IRA. So, you know, that's been the one thing that probably made it easier for me to actually go ahead and do it.

Prevention was defined as reducing one's risk for AD. In the absence of a currently known preventative for AD, at-risk persons thought about deterring AD as they considered genetic susceptibility testing. Some participants believed that contact with the REVEAL Study team might increase their likelihood of gaining access to new therapeutics for possible prevention.

> ALBERT: To see if we could find out anything. And if there was something that they came up with that said, well, now, you know if you do this, maybe there would be a chance that you could reduce your possibility of having Alzheimer's. By all means, you'd try it.
>
> QUINT: Because of things like HRT [hormone replacement therapy]. Things that I would consider under certain circumstances and absolutely not consider under others.
>
> KARA: I got a flu shot today. I'd rather go with that and getting a vaccine, prevention being the key.
>
> PEGGY: My thought at doing this was to know so that if something comes down the pipe, that I could take that could circumvent it or prevent it, that I would be the first in line. That was my premise.

Need to know was defined as a heightened sense of wanting information. Some participants expressed the need to know because of fear of developing AD or worrying about already having symptoms that may mean early onset AD. Cecelia concluded her drive was curiosity, stating a detached "academic curiosity," but immediately wondered about having incipient symptoms of AD—a need to know, a strong reason to join the REVEAL Study for the opportunity of obtaining genetic risk assessment that would otherwise be unavailable.

> ORA: Just desire to know.
>
> QUINSELLA: Oh, I suppose I've always had the nagging thought in the back of my mind if my mother had dementia of whatever sort, it would be kind of interesting to find out. But also, I'm just plain interested in it from a totally scientific view. I really do love science.
>
> FRANCINE: I guess I wanted to know, like, what my chances were. And as I said, well, maybe it will make me look at my life in a different way.
>
> KEN: You know, I wanted to find out if I was susceptible, you might say, based on genetics. That's why I took the test, to find out.

IRENE: But I got scared to death that I inherited this, and that's why I was anxious to get in the study and see. I wanted to know if I had the gene.

CLAIRE: And I'd just as soon know it now rather than later.

ICARUS: Because I felt I was already doomed, so nothing that I could be told could be worse than what I already thought.

FRANK: And that's how I got involved in this, because my father was very sick and my stepmother got involved in this, so the family was involved. Well, I'm very much in the category of wanting to know. So I figured it was a win-win for me, since I was worrying some anyway without knowing. So for me, it was a fairly easy decision to want to do it.

CECILIA: Then I became more focused on, obviously, my own probabilities. And I did what I tend to do, which is start seeking information, and a large amount of it. Some of it I think is generated by an academic curiosity, which I've always had, whether it's personally driven or nonpersonally driven. And I realized that just going to a neurologist to do genetic testing was not going to do it. That, and, again, with the diagnosis and having been enveloped in my mother's Alzheimer's, her diagnosis, and also my focus, my cognizance of knowing. My memory has never been very strong. I'm bright, so I compensate. But my memory has never been very strong and my word finding, once I turned 50, seemed to become more pronounced. So I began thinking about, what does predisposition mean? Obviously with my family members, onset was in the 70s. But, at what point do you start—you begin thinking about—am I predisposed? Has it already begun, but it's being buried? Whatever. So I became—again, I was driven by personal curiosity, but also by an academic curiosity. It was entirely personally driven.

Discussion

Altruism was a prominent theme, which was consistent with "to participate and contribute to AD research," the most commonly endorsed quantitative reason for seeking testing in the REVEAL Study.[22] The altruism that emerged from stories was not solely an unselfish regard for or devotion to others, but included a notion of exchange; either a thanks for care provided to the AD-affected parent or hope for benefit for self and family. The notion of action was also embedded in altruism, as participants wanted "to do something" or "to see something done about it." An additional interpretation is that action may overcome feelings of helplessness. If an adult offspring of a person with AD cannot change one's genes and risk for developing AD, a coping mechanism to overcome helplessness may be to take action against AD.

Learning and concepts that explained learning (i.e., planning, prevention, and need to know) are consistent with the second most strongly endorsed reason found in the REVEAL Study, "to arrange my personal affairs."[22] Seeking information is common when persons are faced with making healthcare decisions. Persons differ with respect to the amount of information they want[34] and their coping processes influence their decision. Preference for information is a coping strategy that adds insight to the learning construct because information seeking is a common coping strategy of persons facing a stressful event, such as thinking about developing AD or having incipient AD symptoms.

Segments of participants' stories illustrate the ability of interview data to express the complex, varied, and multifaceted reasons for joining the REVEAL Study and seeking genetic risk information for AD. Within the altruism and learning constructs, participants' stories reflected an active, information-seeking coping style that can give a sense of control. These findings confirm and extend prior published results of survey research using hypothetical scenarios about genetic testing[20,21] and when, in the REVEAL Study, participants rated survey items in as close to real-life situation as possible.[22,23] Interviews took place after participants had concluded their final quantitative data collection phase, between 12 and 18 months after disclosure. Thus, participants had more time to reflect on their reasons for joining the REVEAL Study. The retrospective nature of obtaining the data should actually enhance the accuracy of the data, because a person cannot reflect in the present[35] and consolidation of perspective becomes clearer on reflection.

Our participants are not representative of the general population, and findings need to be interpreted with caution. For example, most of the participants had firsthand knowledge of the clinical progression of AD as a result of personal caregiving experiences, had actively sought out the opportunity to participate in the REVEAL Study, and had a high socioeconomic status (see education and income, Table 1). We also recognize that there were more women among the 60 interview participants and their incomes were higher than in the REVEAL Study sample. This sample included mostly whites and only

one African American. Because African Americans have a high incidence of AD,[36] their voices could potentially have brought different perspectives to motivation.

As the public considers genetic testing for this complex late-onset disease with no currently known preventative treatment, these findings may better shape the way in which clinicians respond to family members' questions about future testing for their risk of developing AD. Clinicians can understand that people who seek information are more likely to seek genetic testing. With this information, clinicians can explore the best coping strategies and provide advice accordingly. Research participants in the REVEAL Study preferred to receive information to make future plans. Clinicians can be particularly attuned to helping such individuals plan for the future, which is useful even without a heightened risk of developing AD.

Participants wanted to contribute to science and to the efforts to find a cure for future generations. Being in the REVEAL Study allowed participants to do something to combat AD, which in turn may have been a coping strategy for managing helplessness. Because some clinical trials of therapeutics for treating AD may be enriched by including persons who are ε4+, knowing motivating factors for becoming a research participant may serve to help in recruitment and maintaining participation in longitudinal research.

New discoveries of therapeutic agents to prevent or slow the progression of AD could add urgency to the need to identify at-risk individuals, making the use of genetic testing and disclosure clinically relevant. Recent reports suggest that the presence of the ε4 allele may be associated with increased risk of converting from mild cognitive impairment to AD[37] and a possible marker for who may benefit from specific therapeutics.[38] As hoped for by participant Claire, "Well, I realized that genetic information is going to be more valuable and there may be treatments that come down the pike if you know that you have it." These findings can make research teams more sensitive and responsive to the complex motivating factors surrounding participation in AD genetics research.

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