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ORIGINAL RESEARCH

Perceptions of Familial Risk in those Seeking a Genetic Risk Assessment for Alzheimer's Disease

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Abstract Perceived risk is a complex concept that influences the genetic counseling process and can affect client coping and behavior. Although the association between family history and risk perception is well recognized in the literature, no studies have explored this relationship specifically in those seeking genetic susceptibility testing for a common chronic condition. REVEAL is a randomized trial assessing the impact of APOE disclosure and genetic risk assessment for Alzheimer's disease (AD). Using baseline REVEAL data, we hypothesized that there would be a significant association between the degree of AD family history and risk perception of AD, and that this relationship would be stronger in those who believed that genetics is a very important AD risk factor. In our sample of 293 participants, we found that a higher self-perceived risk of AD was associated with strength of family history of AD ($p<0.001$), belief in genetics as an important AD risk factor ($p<0.001$), being female ($p<0.001$) and being Caucasian ($p=0.02$). These results are the first to demonstrate the association between family history and risk perception in persons volunteering for genetic susceptibility testing for a common complex disease.

Keywords Risk perception · Alzheimer's disease · APOE · Genetic susceptibility testing · Risk assessment

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Introduction

Family history is one of the most significant, consistent, and efficient ways to evaluate genetic disease risk (Bennett 2004; DiLorenzo et al. 2006). It can inform both personal and reproductive risks (Bennett 1999) and can be used to assess risk for diseases with Mendelian inheritance, as well as multifactorial conditions that depend on both genetic and environmental contributions (Wattendorf & Hadley 2005; Yoon et al. 2003). Family history is a known risk factor for many common chronic diseases including heart disease, cancer, diabetes and Alzheimer's disease (DiLorenzo et al. 2006; Green et al. 2002; Scheuner et al. 1997; Yoon et al. 2003), and is being promoted for wide-spread use in risk assessment and preventive medicine (Centers for Disease Control and Prevention, National Office of Public Health Genomics).

There is a high general awareness of the increased risk conferred by a family history of disease; those with cancer,

heart disease and diabetes in their family tend to have significantly higher risk perceptions for these diseases than those without such a family history (Absetz 2000; DiLorenzo et al. 2006; Donovan & Tucker 2000; Facione 2002; Katapodi et al. 2004; Montgomery et al. 2003). However risk perception, as defined as the risk perceived before any education, counseling, or testing, is a complex concept encompassing acknowledgement of family history as well as personal experience and perceived disease burden (d'Agincourt-Canning 2005; Frich et al. 2006; Henderson & Maguire 2000; McAllister 2003; Walter & Emery 2005). Beliefs about inheritance and disease causation also inform risk perception, and lay understandings of genetics and heredity often differ from those held by clinicians (Henderson & Maguire 2000; McAllister 2003; Richards & Ponder 1996). In addition, demographic factors of age, sex, race, education and income have been reported to have varying effects on perceived risk of complex disease (DiLorenzo et al. 2006; Katapodi et al. 2004; Lipkus & Hollands 1999; Lipkus et al. 1999).

Perceived risk is an important predictor of the reactions to and outcomes of genetic counseling. It affects disease-specific worry (Price et al. 2007), coping (Gooding et al. 2006; McAllister 2003) and engagement in health behaviors such as cancer screening and uptake of preventative therapies (Katapodi et al. 2004; Marteau & Weinman 2006; Matloff et al. 2006). Perceived risk can be more influential than objective risk estimates (Meiser et al. 2001), and inaccuracies have been shown to persist even after genetic counseling (Cull et al. 1999). Most previous studies exploring family history and risk perception have been conducted from samples of the general population, or have been targeted to women seeking BRCA1/2 testing for breast cancer risk assessment. No studies to date have explored the association between family history and risk perception specifically in those seeking genetic susceptibility testing for a common chronic condition. The discovery of genetic markers associated with complex disease continues to increase (Couzin & Kaiser 2007) contributing to the growing availability of genetic susceptibility testing both clinically and through direct-to-consumer private companies (Pollack 2006). This paradigm shift in clinical genetics from diagnosis and treatment to risk assessment and prevention (Collins 1997) provides a compelling reason to re-examine this relationship in those seeking genetic susceptibility testing for complex disease.

The purpose of this study was to explore the association between family history and risk perception in those seeking genetic susceptibility testing for Alzheimer's disease (AD) risk, and to assess how a belief in genetics may influence this relationship. We hypothesized that (1) strength of family history of AD would be significantly associated with risk perception and (2) this association would be stronger for those who endorsed genetics as an important AD risk factor.

Background

The REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Study is a multi-site clinical trial that provides genetic susceptibility testing for Alzheimer's disease. Family history is a well-established risk factor for AD (Lautenschlager et al. 1996; Silverman et al. 1994), with risks ranging from 18–41%, depending on gender and race, for first-degree relatives of AD patients, compared to the general population risk of 10–15% (Green et al. 2002; Lautenschlager et al. 1996). The apolipoprotein E gene (APOE) is a susceptibility marker for Alzheimer's, with the ε4 allele conferring a 3-15X greater risk, depending on whether it is in the homozygous or heterozygous state (Farrer et al. 1997). There are several consensus statements recommending against the use of APOE testing for AD risk assessment due to the potential for misunderstanding of the probabilistic information, and the absence of treatment and prevention options for the disease (Brodaty et al. 1995; American College of Medical Genetics 1995; Relkin & Gandy 1996). However, there is evidence that relatives of persons with AD are concerned about their own risk and want to better understand this risk (Green 2002). Those volunteering for such testing are motivated by the potential to make personal, family, and financial plans in response to the results, as well as a desire to contribute to research (Roberts et al. 2003b). In the first funding cycle of REVEAL, trial results suggested that AD genetic susceptibility testing could be provided safely using an extended education and counseling protocol by a trained genetic counselor (Roberts et al. 2005). The current study sought to examine the impact of providing this information in a condensed, more clinically feasible protocol.

Methods

Study Design

First-degree relatives of individuals with AD were ascertained largely through self-referral, learning of the study through website and pamphlet advertisements, as well as through physician referral and community outreach efforts. Exclusion criteria included persons with current, untreated anxiety or depression, those experiencing cognitive difficulties, those with a family history of AD-onset of less than 60 years of age, and those with more than one affected first-degree relative. Participants completed a phone interview

and mailed pre-educational survey which elicited demographic information as well as attitudes towards and knowledge about AD, genetics, and genetic testing. Participants were then randomized into the Condensed study arm, which received a mailed educational brochure, or Extended study arm, which had an in-person educational session. All participants had genetic testing and disclosure of their APOE genotype with AD genetic risk assessment by either a physician or genetic counselor. Participants received lifetime risks for developing AD depending on APOE genotype, gender, race, and age, with risk estimates ranging from 13–77%. Follow-up measures included a one week follow-up phone call, two in-person visits at 6 weeks and 6 months post-disclosure, and a 12 month post-disclosure mailed survey. Results of the primary analysis will be published separately. For the purposes of this analysis, only baseline measures elicited prior to the education session were examined. The study was conducted at four sites: Boston University, Weill Medical College of Cornell University, Case Western Reserve University, and Howard University, and received Institutional Review Board approval at each of the study sites.

Study Measures

Dependent Variable

The main outcome measure for this study was baseline perceived risk of developing AD, which was ascertained in the pre-educational survey using a rating scale of 0–100%. This method has been used to measure disease risk perception in previous studies and has demonstrated good reliability (0.85) and validity (Durfy et al. 1999; Erblich et al. 2000; Montgomery et al. 2003).

Independent Variables

Demographics Age, sex, race (African American versus Caucasian), education and income, as well as current status as a caregiver for someone with AD were included in our analyses.

Family History The number of family members with AD, living and deceased, for each participant, was elicited during the intake with the questions "Do you have any living or deceased family members—related to you by blood—who have been affected by Alzheimer's disease?" and "If yes, please tell me how you are/were related to each of your family members." Although medical records were not required to confirm this report, a set of standardized questions were asked in order to obtain more details about age and nature of onset of symptoms for verification purposes. For analyses, family history was classified as having one relative versus having more than one relative with AD.

Perceptions of AD Causation Belief in genetics as an important AD risk factor was quantified using the question "How important do you believe the following factors are in increasing one's risk of Alzheimer's disease?" Genetics/heredity was listed as one of the factors, with a five point Likert scale ranging from "not important" to "very important."

Data Analyses

All analyses were conducted using SAS 9.1 software. For analysis, the family history variable was dichotomized into one affected relative versus more than one affected relative. In the pre-educational survey, participants rated the importance of genetics/heredity to increasing one's risk for AD on a 5 point Likert scale. For purposes of analysis, responses 1, 2, and 3 were collapsed and responses 4 and 5 were collapsed, creating a dichotomous variable. Student's t-tests were used to analyze differences between those with one relative with AD versus those with more than one affected relative. Bivariate linear regression analyses were used to assess predictors of baseline risk perception. These variables included family history of AD, age (continuous variable), sex, race (White versus African American), income (≤50 K versus >50 K), education level (< high school versus ≥high school), and current status as a caregiver for a relative with AD. In addition, two multivariate models were run. The first included all predictor variables except for belief in genetics as an important AD risk factor. A second full model was run including this variable. An interaction analysis of family history and belief in genetics was also conducted.

Results

Participant Characteristics

Of our 293 participants, 53% entered the study through self-referral, with 38% recruited through physician referral or other research studies, and 9% from community outreach efforts. Over half of the sample (56%) reported having only one relative with AD, and 24%, 12%, 4%, 1%, and 3% reported two, three, four, five, and six affected relatives respectively. Majority of the sample was Caucasian, female, with a high level of income and education (Table 1). Ninety-two percent of participants reported their affected

Table 1 Participant Characteristics

Characteristic (N=293)	n (%)
Family history of AD: n (%) 1 affected relative	163 (56%)
Age (mean ± SD)	57.9±10.6
Sex: n (%) Female	208 (71%)
Race: n (%) Caucasian	232 (79%)
Income: n (%) >50 k	204 (70%)
Education: n (%) > college	124 (42%)
Serve as a caregiver for a relative w/ AD: n (%) yes	38 (13%)
Belief in genetics as an AD risk factor: n (%) important/very important	229 (78%)

first-degree relative to be a parent and 8% reported an affected sibling (data not shown). Those with more than one relative with AD had a higher baseline risk perception (p<0.001), were younger (p=0.001), and had a stronger belief in genetics as an important AD risk factor (p=0.017) than those with only one affected relative. These groups did not differ significantly in sex, race, income, education level, or current status as a caregiver for someone with AD (Table 2).

Risk Perception Analyses

Family history (i.e. having one affected relative versus having more than one affected relative) was significantly associated with risk perception in our multivariate regression analysis (38.5% vs 46.5%, β=8.0, p<0.001) after adjusting for age, sex, race, income, education level, caregiver status, and belief in genetics as an important AD risk factor (Table 3). Thus those with more than one relative with AD had on average an 8% higher baseline risk perception than those with only one relative with AD. In this model, sex, race, and belief in genetics remained significant predictors of baseline risk perception as well. An evaluation of whether the association between family history and risk perception varied by one's belief in genetics was not significant, suggesting that the effect of family history on baseline risk perception was not dependent on the strength of an individual's belief in genetics as an AD risk factor.

Discussion

The purpose of this study was to test the hypothesis that strength of AD family history is significantly associated with risk perception in those seeking genetic susceptibility testing for AD. Our results support this finding. We also believed that for those who placed more importance on genetics, family history would be more meaningful and would have a stronger impact on risk perception. However this hypothesis was not supported in our results. We found that having more affected relatives predicts a higher risk perception, regardless of how strongly one believes in genetics.

Similar findings were reported by Drossaert et al. (1996) who demonstrated that breast cancer risk perception was increased by being aware of family history as a risk factor, but was also influenced by personal experience with breast cancer. Perceptions of disease risk are informed by the number of affected relatives and age of onset in their family, in addition to personal factors such as the nature of the relationship with the affected family member, perceived resemblance to that individual, and personal experience with the disease (Walter et al. 2004). Lock et al. (2007) extend this interpretation of familial risk in the description of "blended inheritance." Interviews with relatives of AD patients revealed that many believe that the disease "runs in the family," but conflate genotype and phenotype in explaining disease inheritance. Participants often cited the number of traits shared with the affected individual in explaining their own personal risk. With complex conditions such as AD, where inheritance patterns are less precise, there is more latitude for personal interpretation of family history and disease risk.

Different causal attributions can also affect risk perception. We found that those who believed more strongly in genetics as an AD risk factor had a higher perceived risk of

Table 2 Participant Characteristics: 1 vs. >1 Relative with AD

Variable	1 relative with AD (n=163)	>1 relative with AD (n=130)	p-value
Risk perception, % mean ± SD	*46.4±23.2*	*57.8±19.1*	*<0.001*
Age, mean ± SD	*59.7±10.8*	*55.7±10.0*	*0.001*
Sex, n (%) Female	115 (71)	93 (72)	0.853
Race, n (%) White	123 (76)	109 (84)	0.079
Income, n (%) >50 K per year	107 (66)	97 (75)	0.097
Education, n (%) > college	68 (42)	56 (43)	0.269
Belief in genetics as an AD risk factor, n (%) very important	*119 (73)*	*110 (85)*	*0.017*
Serve as a caregiver for a relative with AD, n (%) yes	25 (15)	13 (10)	0.177

*Significant differences (p<0.05) indicated in italic

Table 3 Effect of Participant Characteristics on Risk Perception: Multivariate Regression Analyses

	Effect on risk perception (beta value)	p-value
Family history of AD (>1 relative vs. 1 relative)	*8.0*	*0.001*
Age (per year)	−0.2	0.054
Sex (female vs. male)	*6.7*	*<0.001*
Race (white vs. AA)	*7.4*	*0.019*
Income (≤50 K vs. >50 K)	1.7	0.536
Education (≤college vs. >college)	0.7	0.774
Serve as a caregiver for a relative with AD (No vs. Yes)	6.6	0.075
Belief in genetics as an AD risk factor (v. impt. vs. not v. impt)	*13.2*	*<0.001*

*Significant relationships ($p<0.05$) indicated in italic

AD. Genetic disease is often believed to be more severe and uncontrollable, and genetic information may be valued more than other types of health information (Green & Botkin 2003; Shiloh 2006). This could explain the stronger feelings of vulnerability in this group. Given that REVEAL is presented as a genetic risk study, it was surprising that there was some variability, albeit relatively little, in how strongly participants rated genetics as an important AD risk factor. It seems that even in those seeking genetic testing to inform their risk of Alzheimer's disease, there is not uniform agreement on how important this test may be in determining their risk. Although not specifically addressed in our study, it is likely that a belief in shared environmental risk factors may also impact interpretations of familial risk, and should be explored in future studies.

Caucasian participants were more likely to have a higher risk perception than African Americans. Other studies support this finding of racial distinctions between Caucasians and African Americans in their attitudes towards AD and genetic testing, with African Americans generally anticipating less negative consequences from a positive test result, indicating less perceived threat of AD, and showing less awareness about AD (Hipps et al. 2003; Roberts et al. 2003a; Sadler et al. 2005). This is in contrast to current research suggesting that African American relatives of AD patients actually have a higher risk of developing dementia than Caucasians (Green et al. 2002). This contrast highlights the need for better education of the public regarding various risk factors for AD. Women also had significantly higher risk perceptions than men, which is in line with current scientific evidence (Farrer et al. 1997), but may be reflective of a general gender difference in perception of disease risk (Gustafson 1998).

Our results were limited by the fact that we only enrolled those with a family history of AD, and therefore could not assess self-perceived risk in those with no family history. In addition, our single measure of belief in genetics as an AD risk factor could not be assessed for validity. Although the generalizability of our study was strengthened by the inclusion of over 20% African Americans in our sample, future research should be directed towards samples with more diverse racial backgrounds.

Conclusions

This is the first study to present quantitative data on the relationship between family history and risk perception in those seeking genetic susceptibility testing for a common disease polymorphism. Unlike previous studies examining risk perception for complex disease, our results are reflective of those actually enrolled in a genetic testing protocol, rather than in response to a survey or hypothetical scenario, and thus may be more applicable to the clinical setting. We also focused on measures that were collected prior to education and counseling, providing insights into baseline perceptions of risk and family history.

With the number of genetic tests offered for disease risk assessment rapidly increasing, there is a need to better understand personal interpretations of familial risk in those seeking this testing. Clinicians are now being faced with the challenge of interpreting personal genetic profiles obtained from the many emerging direct-to-consumer genetic testing companies (Offit 2008). Among the various considerations concerning the evaluation of this industry is the test's clinical utility, or how it can be translated into clinical practice (Hunter et al. 2008). Gaining insight into perceived risk for complex disease can impact clinical utility by improving risk communication, optimizing coping strategies, and encouraging the uptake of preventive health behaviors. Future studies should be directed towards replicating these findings in those seeking genetic risk assessment for other complex diseases as this testing becomes more widely available.

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