APOE Genotype Disclosure for Risk of Alzheimer's Disease: The REVEAL Study

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ABSTRACT

Background: APOE genotype provides information on risk of developing Alzheimer's disease (AD), but disclosure is discouraged. We examined the impact of APOE disclosure in a prospective randomized controlled trial: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study.

Methods: We randomly assigned 162 asymptomatic adult children of AD patients to Genotype Disclosure (GD) or Genotype Non-Disclosure (GND) groups. We measured anxiety, depression symptoms and test-related distress 6 weeks, 6 months and 1 year after disclosure.

Results: Changes in time-averaged measures of anxiety ($p = 0.84$), depression symptoms ($p = 0.98$) and test-related distress ($p = 0.61$) did not differ between GD and GND groups. Secondary comparisons between those with higher risk (GDε4+) and the GND group revealed no significant differences. The GDε4- group showed a significantly lower level of test-related distress in comparison with the GDε4+ group ($p = 0.01$). Persons with clinically meaningful changes in psychological outcomes were distributed evenly among the GND, GDε4+ and GDε4- groups. Baseline scores of anxiety and depression symptoms were strongly associated with post-disclosure scores of these measures ($p < 0.0001$ for each).

Conclusion: Disclosure of *APOE* genotype to adult children of persons with AD did not result in significant short-term psychological risks to those who received genotype information or to those who learned they were *APOE* ε4+; distress was reduced among those who learned they were *APOE* ε4-. Persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure. (ClinicalTrials.gov number NCT00571025.)

Risks of genetic susceptibility testing include anxiety, depression or other types of distress. Nevertheless, gene variants providing risk information are being rapidly discovered for common diseases, and genetic testing is now marketed to consumers.[1-3] Apolipoprotein E (APOE) testing for Alzheimer's disease (AD) is a useful paradigm to evaluate the impact of genetic risk assessment since persons with the APOE ε4 allele have a well-characterized increased risk for AD.[4] By consensus, APOE testing for asymptomatic individuals is not currently recommended, with a major concern being the emotional impact of risk disclosure.[5-8]

We report results of a clinical trial to evaluate the benefits and safety of APOE genotype disclosure. We hypothesized that persons learning their genotype through a structured education and disclosure protocol would not show greater anxiety, depression symptoms or test-related distress than those not receiving APOE disclosure.

METHODS

Study Population and Instruments

Participants were adult children of a living or deceased parent with AD, recruited through self-referral or telephone calls to families in research registries.[9] Potential participants were interviewed and were excluded if, before randomization, they scored 1.3 standard deviations below norms on the Repeatable Battery for the Assessment of Neuropsychological Status (a test of cognitive ability) or the Wide Range Achievement Test-3 (a test of academic achievement), higher than 20 on the Beck Anxiety Inventory (BAI), or higher than 26 on the Center for Epidemiological Studies-Depression Scale (CES-D).

The BAI[14, 15] is a 21-item scale designed to distinguish symptoms of anxiety from depression, and to be sensitive to change. This test is based on self-reported severity of a given anxiety symptom over the past week (clinical cut-off score (moderate anxiety) = 16). The CES-D[16, 17] is widely used to measure depressive symptoms in studies of non-clinical populations (clinical cut-off score > 16-20).[18, 19] We estimated that 5 point differences on either the CES-D or BAI would be a sensitive indicator of clinically meaningful change and that a sample of 46 persons per group would have 80% power to detect this on either scale. The Impact of Event Scale (IES) is a 15-item self-report instrument assessing test-related distress,[20, 21] that is commonly used in genetics research.[22-29] A total score of 20-40 may indicate significant distress, and a 5 point difference is a conservative measure of clinically meaningful change. We also designed original questions on (1)

change in risk perception, (2) positive and negative impact of the disclosure and (3) whether or not the participant would "do it again."

Study Design

The REVEAL Study was designed by an interdisciplinary team of experts in clinical trials, neurology, genetics, genetic counseling, health psychology, biostatistics and bioethics and drew upon surveys conducted with relatives of AD patients.[10-12] Age and gender-specific risk curves were created for the disclosure process illustrating lifetime cumulative incidence of AD and remaining risk of AD (cumulative incidence from current age to age 85).[13]

The study was conducted between 2000-2003 at sites in Boston, Cleveland and New York with IRB approval and a board certified/eligible genetic counselor (GC) coordinating at each site. Informed consent was obtained first by telephone, then in writing (Figure 1). A 90-minute semi-scripted group session led by the GC described the limitations of *APOE* testing, the absence of medical benefit and the format for risk communication. Participants and GCs later met individually for the drawing of blood samples which were sent to Athena Diagnostics, Inc. (Worcester, MA), a CLIA-certified laboratory, for *APOE* genotyping by PCR. After phlebotomy, participants were randomized to genotype disclosure (GD) or genotype non-disclosure (GND) arms. In individual sessions, GND participants were shown two incidence curves: (1) general population risk of AD; (2) gender and age-specific incidence of AD among first-degree relatives of AD cases.[13] GD participants were shown the same curves with an additional line for their genotype-specific risk (Supplemental Figure 1). The lifetime cumulative incidence risk (LCIR) by age 85 was also communicated. Participants were told their APOE genotype and given written reports of their LCIR and remaining incident risk.[13]

Outcome Measures

We pre-specified co-primary outcomes to be changes in participants' anxiety and depression symptoms as measured by BAI and CES-D, respectively. We prespecified test-related distress, as measured by the IES, as a secondary outcome.

We administered the BAI and CES-D prior to randomization, at 6 weeks, 6 months and 1 year following risk disclosure. The IES was measured at 6 weeks, 6 months and 1 year. The primary analysis compared the two randomized arms (GD vs GND), with a secondary analysis comparing those learning that they had at least one ε4 allele (GDε4+) with those learning they had no ε4 alleles (GDε4-) and with the GND group.

Safety and Data Monitoring

Throughout the study, GCs monitored participants for adverse psychological effects. We created an independent external Ethics and Safety Board (ESB) to review the protocol, monitor study progress and establish criteria for adverse event reporting to site IRBs. For example, participants whose BAI or CES-D was elevated over a score of 16, or whose scores increased by 15 points, was immediately interviewed, with referral as appropriate. Adverse and unanticipated events were reviewed annually by the ESB chair.

Statistical Analysis

Baseline variables were compared with 2-sided t tests or chi-square tests between randomization groups (GD vs GND) and among the 3 disclosure groups (GND, GDε4+ and GDε4-). Withdrawals were compared across groups to assess differential drop-out. Pre-specified primary analyses compared scores on BAI and CES-D between the GD and GND groups and included data from all time points, using longitudinal analysis mixed effects models adjusted for age, gender, years of education, time and baseline outcome score (if available). Missing data were multiply imputed using Markov chain Monte Carlo methods with PROC MI (SAS 9.1) for intention-to-treat analysis. To assess trends over time, interaction terms between group and time were added as covariates to longitudinal models. The model for primary analysis was also run separately for each time point. This process was repeated for the IES scores. All 3 outcomes were then examined in the same manner for the 3 disclosure groups. Although the study was not originally powered for equivalence testing, equivalence was demonstrated post-hoc when a confidence interval for a group difference did not include 5 points in either direction.[30] We examined raw change scores on each outcome measure to calculate the percentage of individuals whose change score exceeded clinically significant thresholds (Supplemental Figure 3).

RESULTS

Flow of participants through the study is shown in Figure 1. Of those participating in the informational interview and educational session, 60.8% and 83.8%, respectively, progressed to phlebotomy. After phlebotomy but before randomization, 12 persons changed their minds and withdrew, and we excluded 5 persons with low neuro-cognitive scores and 2 persons with high depression scores. The remaining 162 participants (mean age 53.0, SD 9.8, range 30-78 years; 72.2% female, 93.8% white) were randomized in a 2:1 ratio into GD or GND groups.

Table 1 presents characteristics of randomized persons. After randomization, 14 withdrew citing study burden. Of variables in Table 1 only baseline BAI showed a trend toward association with withdrawal (those less anxious were more likely to withdraw, p = 0.067). Some participants in the GND arm were dissatisfied at not receiving their genotype and 8 (15.7%) of these withdrew; while 6 participants (5.4%) in the GD arm withdrew (p = 0.038). Among those receiving disclosure, 3 (5.7%) withdrew from the GDε4+ group and 3 (5.2%) from the GDε4- group. Of the 111 participants randomized to the GD group, 3 (2.7%) were ε4/ε4, 46 (41.4%) were ε3/ε4, 53 (47.7%) were ε3/ε3, 5 (4.5%) were ε2/ε3, 4 (3.6%) were ε2/ε4 and none were ε2/ε2. Those disclosed to be ε4/ε4 were given higher risk estimates,[13] but included within the GDε4+ group in analyses. Data collected after randomization but prior to withdrawal were included in the analyses.

For the endpoints of BAI and CES-D, adjusted group means for the GD and GND groups were not significantly different using the time-averaged longitudinal model, or at any individual time point (Table 2). Interaction analysis indicated that differences between scores were stable over time. We designed the pre-specified analyses to allow detection of statistically significant differences, and observing none, we then carried out *post-hoc* analysis for equivalence by examination of confidence intervals. Confidence intervals excluded a difference of 5 points or more with 95% confidence for both the BAI (all intervals within 3 points) and CES-D (all intervals within 2 points). Post-disclosure scores on BAI and CES-D were strongly associated with respective baseline scores on these measures (p < 0.0001 for each). We observed no significant differences between any of the 3 groups (GND, GDε4+ and GDε4-) in the overall model on BAI or CES-D at any time point (Tables 3 and 4), with all intervals excluding a difference of 5 points or more with 95% confidence. There were no significant differences between GND and GDε4+ groups over time using the longitudinal model or at any time point. In these analyses, adjusted means gave very similar results to unadjusted means (tables show only adjusted means, raw means are shown in Supplemental Figure 2).

Adjusted means of the IES scores for GD and GND groups were not significantly different at any time point or over time. All confidence intervals excluded clinically meaningful differences of 5 points or more with 95% confidence, except the 6 month time point which showed a trend toward less distress in the GD group. Adjusted IES scores in the GDε4- group were lower than those of the GND group at 6 months (p = 0.01), with a trend over time (p = 0.09). Comparison of IES scores of GDε4- and GDε4+ groups showed significant differences over time and at 6 weeks and 6 months, with a marginally significant difference at 12 months. On the IES in the 3-group comparison only, we could not demonstrate equivalence to within 5 points with 95% confidence at

any time point for comparisons of GND and GDε4+ groups against the GDε4- group. Comparison of GND and GDε4+ groups revealed no significant differences over time or at any time point. A difference of 5 points could be excluded with 95% confidence at 6 months, 12 months and over time, but not at 6 weeks where there was more distress in the GDε4+ group. The results of all ITT analyses were similar to results using only "completers" (data not shown).

Our findings in Tables 2-4 were not meaningfully changed after adding variables listed in Table 1 as covariates. Lower overall BAI scores were associated with lower baseline BAI scores ($p < 0.001$) and also with self-referral to the study ($p = 0.002$). Lower overall CES-D scores were associated with lower baseline CES-D scores ($p < 0.0001$), with lower age of onset of the parent's AD symptoms ($p = 0.003$) and with self-referral ($p = 0.008$). Lower overall IES scores were associated with male gender ($p = 0.01$). No other covariates were significantly associated with outcome.

Compared to the GND and GDε4- participants, the GDε4+ group reported higher risk perception and were more likely to report an overall negative impact upon learning their genotype (Supplemental Table 1), suggesting that they understood the risk communication and experienced some negative feelings about receiving their results. Nevertheless, those in the GDε4+ group were no less likely than those in the GDε4- group to say that they would repeat the experience.

We compared the distribution of change scores within each of the 3 disclosure groups; these showed the distribution to be similar among the groups at all time points (see Supplemental Figure 3 for data at 6 weeks). Outcome scores for 13 individuals combined with pre-specified safety criteria triggered examination. Three persons were in the GND group, 4 were in the GDε4- group, and 6 were in the GDε4+ group (4 were ε3/ε4 and 2 were ε4/ε4). None attributed their psychological state to concerns about disclosure, but cited non-study-related personal events such as family illness or job-related stress.

DISCUSSION

This is the first randomized trial evaluating the impact of disclosing a susceptibility polymorphism for a common disease among adult children of persons with that disease. Those randomized to receive risk assessment with APOE disclosure did not have greater anxiety, depression or test-related distress than those randomized to receive risk assessment without APOE disclosure. Post-hoc equivalence within 5 points was demonstrated at all visits over time for

all outcomes with the exception of the 6 month time-point on the secondary outcome of the IES, which showed a trend toward less distress in the genotype disclosure group.

Those who learned they were ε4+ and at increased risk for AD showed no more anxiety, depression symptoms or test-related distress than those without genotype disclosure, although strict equivalence could not be demonstrated for test-related distress at 6 weeks, indicating a possibility of transient test-related distress among ε4+ participants that resolved by 6 months. Comparing ε4+ to ε4- participants revealed statistically significant (but clinically non-meaningful) differences on test-related distress, driven by *reduced* distress among ε4- individuals, again with the possible exception of result obtained at 6 weeks. On all outcome measures, mean scores in each disclosure group were well below clinical cut-offs for concern. Participants with outcome scores above pre-specified safety thresholds were evenly distributed among the GND, GDε4+, GDε4- groups and did not cite genotype disclosure as contributing to their psychological distress.

Additional questions about risk perception and "impact" 6 weeks after disclosure suggested that participants understood their risk was higher or lower due to genotype, and experienced negative and positive feelings about this news in the expected directions. Thus, participants were not immune to negative implications of learning that they had increased risk, but these feelings were not associated with clinically significant psychological distress.

These data support the psychological safety of disclosing genetic risk information with genetic counseling protocols to screened adult children of AD patients who request it, despite the frightening nature of the disease and the fact that disclosure has no clear medical benefit. Larger studies that follow participants for more than one year are required to detect uncommon and long-term effects, such as delayed emotional repercussions and injudicious life decisions. If APOE genotyping were provided without screening by the GC, the results might be different. The responses of persons who did not have a parent with AD might well differ.

APOE is the most robust risk marker available for AD,[4] and is associated with poorer memory among unaffected persons[31] and with progression to AD among persons with mild cognitive impairment.[32] Surveys by our group[33] and others[34, 35] indicate that *APOE* genotyping is of interest to the public and that 15% of community physicians who treat AD have already received genotyping requests. Should *APOE* genotype be discovered to predict treatment efficacy or risk of side effects, the level of interest is likely to increase.

While visions of personalized medicine suggest that genetic risk markers will empower individuals to improve their health through preventive practices and early interventions,[36] there is also concern that understanding of risk among both lay public and medical professionals is exceedingly poor,[37] that genetic tests offering probabilistic estimates for common diseases in the

absence of family history or environmental risks may be misunderstood, and that the psychological harm of such misunderstanding may outweigh the benefits, particularly with diseases like AD where no medical interventions are available.[38-40] These concerns are amplified by the recent emergence of direct-to-consumer genetic testing companies (with most providing SNPs that reflect APOE genotype)[1-3] in an environment without guidelines for deciding which gene-disease associations have sufficient clinical validity and utility to justify disclosure, or what impact such disclosures will have. In the absence of such guidelines, caution is warranted and empirical data are valuable. Our study was conducted in persons with a family history, around a single polymorphism, with genetic counseling and in the context of more robust clinical validity than is available with most susceptibility genes and so the extent to which our findings can be generalized is limited. Within these constraints, our results suggest that genotype information may be a benefit for those who test "negative", while only transiently and modestly distressing for those whose test is "positive".

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References

1. Wolfberg AJ. Genes on the Web--direct-to-consumer marketing of genetic testing. New Eng J Med 2006;355(6):543-5.

2. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle - will we get our wish? New Engl J Med 2008;358(2):105-7.

3. Offit K. Genomic profiles for disease risk: predictive or premature? JAMA 2008;299(11):1353-5.

4. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex and ethnicity on the association between apolipoprotein E genotype and Alzheimer's Disease: A meta-analysis. JAMA 1997;278(16):1349-56.

5. Farrer LA, Brin MF, Elsas L, et al. Statement on use of Apolipoprotein E testing for Alzheimer's Disease. JAMA 1995;274(20):1627-9.

6. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer's Disease: An ethical perspective. JAMA 1997;277(10):832-6.

7. McConnell LM, Koenig BA, Greely HT, Raffin TA. Genetic testing and Alzheimer disease: Has the time come? Nature Med 1998;5(7):757-9.

8. Relkin NR, Tanzi R, Breitner J, et al. Apolipoprotein E genotyping in Alzheimer's disease. Lancet 1996;347(9008):1091-5.

9. Roberts JS, Barber M, Brown TM, et al. Who seeks genetic susceptibility testing for Alzheimer's disease: Findings from a multisite, randomized clinical trial. Genet Med 2004;6(4):197-203.

10. Roberts JS. Anticipating response to predictive genetic testing for Alzheimer's disease: A survey of first-degree relatives. Gerontologist 2000;40:43-52.

11. Roberts JS, Connell CM, Cisewski D, Hipps V, Demissie S, Green RC. Differences between African Americans and White Americans in perceptions of Alzheimer's disease. Alz Dis Assoc Dis 2003;17(1):19-26.

12. Hipps YG, Roberts JS, Farrer LA, Green RC. Differences between African Americans and Whites in their attitudes toward genetic testing for Alzheimer's disease. Genetic Testing 2003;7(1):39-44.

13. Cupples LA, Farrer L, Sadovnick D, Relkin N, Whitehouse P, Green RC. Estimating risk curves for first-degree relatives of patients with Alzheimer's disease: The REVEAL Study. Genet Med 2004;6(4):192-6.

14. Beck AT, Steer RA. Beck Depression Inventory. New York: The Psychological Corporation, Harcourt Brace Javanovich, Inc.; 1987.

15. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consulting and Clinical Psychology 1988;56:893-7.

16. Radloff LS. The CES-D Scale: A self report depression scale for research in the general population. Applied Psychological Measurement 1977;1:385-401.

17. Santor DA, Zuroff DC, Ramsay JO, Cervantes P, Palacios J. Examining scale discriminability in the BDI and CES-D as a function of depressive severity. Psychological Assessment 1995;7:131-9.

18. Vernon SW, Gritz ER, Peterson SK, et al. Correlates of psychologic distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. Health Psychol 1997;16(1):73-86.

19. Lerman D, Narod S, Schulman K, et al. BRCA1 testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes. JAMA 1996;275(24):1885-92.

20. Horowitz M, Wilner N, Alvarez MA. Impact of event scale: A measure of subjective distress. Psychosom Med 1979;41(3):209-18.

21. Zilberg NJ, Weiss DS, Horowitz MJ. Impact of Event Scale: A cross-validation study and some empirical evidence supporting a conceptual model of stress response syndromes. J Counsult Clin Psychol 1982;50:407-14.

22. Payne K, Nicholls S, McAllister M, Macleod R, Donnai D, Davies LM. Outcome measurement in clinical genetics services: A systematic review of validated measures. Value in Health 2008;11:497-508.

23. DudokdeWit AC, Tibben A, Duivenvoorden HJ, Niermeijer MF, Passchier J. Predicting adaptation to presymptomatic DNA testing for late onset disorders: Who will experience distress? J Med Genet 1998;35(9):745-54.

24. Michie S, Bobrow M, Marteau T. Predictive genetic testing in children and adults: A study of emotional impact. J Med Genet 2001;38:519-26.

25. Thewes B, Meiser B, Hickie IB. Psychometric properties of the Impact of Event Scale amongst women at increased risk for hereditary breast cancer. Psychooncology 2001;10(6):459-68.

26. Meiser B, Butow P, Friedlander M, et al. Psychological impact of genetic testing in women from high-risk breast cancer families. Eur J Cancer 2002;38(15):2025-31.

27. Schwartz MD, Peshkin BN, Hughes C, Main D, Isaacs C, Lerman C. Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. J Clin Oncol 2002;20(2):514-20.

28. Smith CO, Lipe HP, Bird TD. Impact of presymptomatic genetic testing for hereditary ataxia and neuromuscular disorders. Arch Neurol 2004;61(6):875-80.

29. Meiser B, Collins V, Warren R, et al. Psychological impact of genetic testing for hereditary non-polyposis rectal cancer. Clin Genet 2004;66:502-11.

30. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: The importance of rigorous methods. Brit Med J 1996;313:36-9.

31. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. Psychology and Aging 2004;19(4):592-600.

32. Petersen RC. Mild cognitive impairment: current research and clinical implications. Seminars in Neurology 2007;27(1):22-31.

33. Roberts JS, LaRusse SA, Katzen H, et al. Reasons for seeking genetic susceptibility testing among first-degree relatives of people with Alzheimer's Disease. Alz Dis Assoc Dis 2003;17(2):86-93.

34. Neumann PJ, Hammitt JK, Mueller C, et al. Public attitudes about genetic testing for Alzheimer's disease. Health Aff 2001;20:252-64.

35. Chase GA, Geller G, Havstad SL, Holtzman NA, Bassett SS. Physicians' propensity to offer genetic testing for Alzheimer's disease: Results from a survey. Genet Med 2002;4(4):297-303.

36. Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research. Nature 2003;422(6934):835-47.

37. Julian-Reynier C, Welkenhuysen M, Hagoel L, Decruyenaere M, Hopwood P. Risk communication strategies: state of the art and effectiveness in the context of cancer genetic services. Eur J Hum Genet 2003;11(10):725-36.

38. Khoury MJ, McCabe LL, McCabe RB. Population screening in the age of genomic medicine. New Engl J Med 2003;348:50-8.

39. Haga SB, Khoury MJ, Burke W. Genomic profiling to promote a healthy lifestyle: Not ready for prime time. Nature Genetics 2003;34(4):347-50.

40. Burke W, Psaty BM. Personalized medicine in the era of genomics. JAMA 2007;298:1682-4.