Identifying Families with Likely Genetic Protective Factors against Alzheimer Disease

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Summary

Elderly individuals who lived beyond the age of 90 years without dementia were hypothesized to have increased concentrations of genetic protective factors against Alzheimer disease (AD), conferring a reduced liability for this disease relative to less-aged nondemented elderly. However, testing this hypothesis is complicated by having to distinguish such a group from those who may lack genetic risk factors for AD, have had protective environmental exposures, or have escaped dementia for other reasons. Probands carrying genetic protective factors, however, should have relatives with lower illness rates not only for earlier-onset disease, when genetic risk factors are a strong contributing factor to the incidence of AD, but also for later-onset disease, when the role of these factors appears to be markedly diminished. AD dementia was assessed through family informants in 6,660 first-degree relatives of 1,049 nondemented probands aged 60–102 years. The probands were grouped by age (60–74, 75–89, and 90–102 years), and the cumulative survival from AD and 10-year–age-interval hazard rates of AD were calculated in their first-degree relatives. Cumulative survival from AD was significantly greater in the relatives of the oldest proband group (aged 90–102 years) than it was in the two younger groups. In addition, the reduction in the rate of illness for this group was relatively constant across the entire late life span. The results suggest that genetic factors conferring a lifelong reduced liability of AD may be more highly concentrated among nondemented probands aged ≥90 years and their relatives. Efforts to identify protective allele–bearing genes that are associated with very late–onset AD should target the families of nonagenarians and centenarians.

Introduction

A small number of genes (e.g., the apolipoprotein E [APOE] gene) have been associated with Alzheimer disease (AD) and possess alleles conferring different levels of risk for this disease. Whereas an allele may be considered a "genetic risk factor" when it increases the predisposition to disease relative to some other, usually more common allele for the same gene (e.g., APOE-ε4 relative to APOE-ε3 [Corder et al. 1993; Farrer et al. 1997]), a "genetic protective factor" is an allele associated with a reduction in risk relative to a more common reference allele. In AD, the only well-established genetic protective factor is APOE-ε2 (Chartier et al. 1994; Corder et al. 1994), but there may be other, as yet unidentified protective alleles against AD that are present at other loci.

Although investigative strategies such as association studies are available to examine specific candidate genes, a more general and powerful search for AD-related genes with protective alleles is hampered by the age at onset typical of the disease. The incidence of AD increases substantially with age. In the United States, the incidence appears to double approximately every 5 years, from ~0.6% at 65–69 years to 8.4% at ≥85 years (Hebert et al. 1995). Thus, the absence of the AD phenotype in individuals living well into the eighth or the early part of the ninth decade of life does little more than marginally increase the likelihood that such individuals carry a liability to AD less than that in the general population. Even in the very longest–lived nondemented individuals, assessing the possibility that they may carry particular alleles that are protective against AD is complicated by various other possibilities. For example, such individuals may lack genetic risk factors or exposure to environmental ones, or they may have had protective environmental exposures or escaped AD for other reasons.

The investigation of families of aged, nondemented probands may help to narrow these alternatives and aid in identifying individuals within families who are more likely to carry genetic protective factors against AD. In an earlier genetic epidemiological study, relatives of op-

timally healthy nondemented probands aged ≥85 years were found to have a reduced risk of dementia compared with the relatives of younger but still elderly random controls (Payami et al. 1994). This finding suggests that familial—likely genetic—factors help to explain these probands' freedom from AD (at least until the ages at which they were studied). However, detecting a difference between survival curves does not by itself help to distinguish between *increased* genetic protective factors and *decreased* genetic risk factors.

In the present study, we assessed the survival from AD in the relatives of a group of nondemented probands who had lived beyond age 90 years, that is, well into the ages of highest incidence of AD, and in relatives of other nondemented, but younger, probands. Similar to earlier investigators in this area, we compared survival curves among the relatives of probands from different age groups. These curves, however, represent the *cumulative* decreased survival from AD over time, and hence do not adequately reveal more age-specific risk patterns (Singer and Willett 1991). For this reason, we also examined the patterns of risk in relatives of proband groups at different age intervals to help identify the factors that likely underlie any detected differences in the overall curve. A reduced frequency of genetic risk factors should lead to lower rates of relatively earlier-onset illness, when such factors most strongly influence the expression of AD (Silverman et al. 1994). An increased frequency of genetic protective factors should lead to lower rates of later-onset illness as well, when the role of genetic risk factors appears to be greatly diminished.

Subjects and Methods

Index Subjects

Family histories were collected from 1,049 elderly probands who were nondemented and aged >60 years. The probands were recruited from the following sources: (1) the spouses of geriatric probands involved in studies at the Mt. Sinai Alzheimer's Disease Research Center ($n = 292$); (2) nondemented residents at the Jewish Home and Hospital for Aged (JHHA) ($n = 135$); (3) spouses of JHHA residents ($n = 200$); and (4) Jewish and Italian participants in New York City–sponsored senior centers ($n = 422$) (Silverman et al. 1992). Although the probands in the latter three groups were more ethnically homogeneous than those in the first group, the cumulative risk curves for AD in their relatives have been found to be almost identical (Silverman et al. 1994), justifying their inclusion in a single, nondemented proband group. Determination that these index subjects were free of dementia was made by evaluation with the Alzheimer's Disease Risk Questionnaire (ADRQ) (Breitner and Folstein 1984) and the Dementia Questionnaire

(DQ) (Silverman et al. 1986), described below, administered to one or two family informants. The probands were grouped, according to their age at the time of the interview, into three 15-year age intervals: 60–74, 75–89, and 90–104 years. All protocols used were approved by the Mt. Sinai Institutional Review Board.

Assessment of Relatives

We identified first-degree relatives of the probands by using the ADRQ, and we collected information on each relative concerning birth year, sex, current age (if alive), or (if not) age at, and cause of, death. Finally, the ADRQ was used to screen for possible dementia, cognitive impairment, or memory loss of any type. If any such condition was suggested, the DQ was administered for that relative. The DQ is a 50-item questionnaire focused on ascertaining whether a dementia is present and, if so, determining its specific type. AD was diagnosed according to previously published criteria (Silverman et al. 1986) that are similar to DSM-IV criteria for dementia of the Alzheimer type (American Psychiatric Association 1994) but designed for informant-based assessment. Previous studies have found this method to have very good interinformant (Silverman et al. 1986) and test-retest (Silverman et al. 1990) reliability. The DQ has demonstrated excellent sensitivity and specificity for identifying dementias independently ascertained through direct clinical assessment (Kawas et al. 1994). In addition, in a study of a series of former nursing home residents, informant-based DQ diagnoses were compared with independent neuropathological examinations; for AD, the family history method was found to be only slightly less sensitive than direct clinical assessment, and its specificity was virtually at the same level (Li et al. 1997).

Statistics

In addition to conventional χ^2 and analysis of variance, the actuarial life table method was used with 1-year intervals to generate survival curves for AD in relatives. Survival analysis provides an estimate of the cumulative rate of survival from AD over time and allows rates in different groups to be compared while differences in age structure are controlled for. As described more fully elsewhere (Silverman et al. 1994), in contrast to the Kaplan-Meier method, the actuarial method includes an estimation of within-interval censorship, which, when the interval is minimized, likely improves the survival estimate. The Mantel-Haenszel log-rank statistic was used to test the difference between curves. In addition to statistical comparisons of survival *curves,* the test of the difference between two proportions (z statistic) was used to determine whether groups differed in the cumulative survival *estimate* at a point on the curve, specifically at the age of 90 years. We also calculated

the 10-year–age-interval hazard rates for each group of relatives. This statistic provides an estimate of the risk of AD a relative faces per year during a given age interval, given that the relative is alive and at risk at the start of the interval. The hazard-rate ratio is a measure of the extent to which one hazard rate is increased or decreased in comparison to another (reference) hazard rate. The hazard-rate statistics and the hazard-rate ratios were calculated primarily as an internal diagnostic tool. Using the relatives of the youngest proband group (aged 60–74 years) as a reference group, we could inspect the set of decade-specific hazard-rate ratios for each of the other two groups. Examining the degree to which these ratios were similar across different age intervals would help reveal whether a difference in survival curves derived from proportionately similar levels of increased risk across the late life span or whether the overall difference might instead have been disproportionately driven by increased rates at particular age periods.

Results

Demographic and diagnostic information was assessed in 6,660 first-degree biological relatives of 1,049 nondemented elderly probands (table 1) aged 60–102 years (hence the oldest proband group was redesignated "90–102 years"). Across the three groups, the proportions of women among the probands and their relatives were similar. As expected, the relatives of these successively older proband groups were themselves successively older. Using the crude proportion of AD cases in each group of relatives (i.e., with no correction for age structure), we found no significant differences, nor did we find significant differences in mean age at onset.

The survival curves for the three groups of relatives (fig. 1) were significantly different (log-rank statistic = 9.8, df = 2, $P < .01$). In pairwise comparisons, the overall survival from AD observed in the relatives of the nondemented probands aged 90–102 years was signifi-
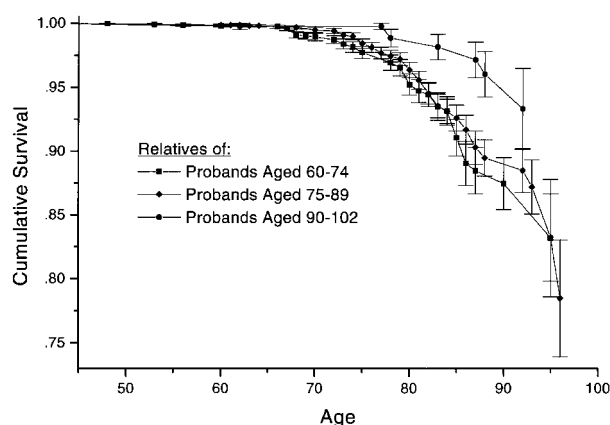

Figure 1 Cumulative survival of AD dementia in relatives of probands aged 60–74, 75–89, and 90–102 years.

cantly better than the survival observed both in the relatives of probands aged 60–74 years (log-rank statistic = 9.3, df = 1, $P < .005$) and in the relatives of probands aged 75–89 years (log-rank statistic = 7.9, df = 1, $P = .005$). In contrast, the survival curves associated with the two younger proband groups did not significantly differ (log-rank statistic = 0.8, df = 1, not significant [NS]). By the age of 90 years, cumulative survival from AD was 96.0% ± 1.7% SD among relatives of probands aged 90–102 years. This rate of survival was significantly better than that found in the relatives of probands aged 60–74 years (87.4% ± 2.0% SD; $z = 3.16$, $P < .005$) and in the relatives of probands aged 75–89 years (89.5% ± 1.4% SD; $z = 2.88$, $P < .005$). The latter two groups did not differ significantly ($z = 0.81$, NS).

In the fifth through ninth decades, there were new AD cases in one or more of the groups and sufficient numbers of relatives still at risk ($n > 100$ in each group) to provide a reasonably stable hazard-rate estimate (fig. 2). In the fifth and sixth decades, the hazard rate rose above

Table 1

Demographic Characteristics of Nondemented Probands and Their Relatives

Age Group	NONDEMENTED PROBANDS			FIRST-DEGREE RELATIVES				
	No. of Individuals	Mean Age (SD)	Women (n [%])[a]	No. of Individuals	Mean Age (SD)[b]	Women (n [%])[c]	AD Dementia (n [%])[d]	Age (SD) at Onset[e]
60–74	478	68.7 (3.9)	275 (57.5)	3,018	61.4 (19.1)	1,466 (48.6)	57 (1.9)	76.1 (9.1)
75–89	486	80.5 (3.9)	280 (57.6)	3,050	65.3 (18.9)	1,498 (49.2)	71 (2.3)	79.1 (7.9)
90–102	85	93.5 (3.1)	56 (65.9)	592	70.1 (18.2)	300 (50.8)	7 (1.2)	81.1 (9.9)
Total	1,049	76.2 (8.6)[f]	611 (58.2)	6,660	63.9 (19.1)[f]	3,269 (49.0)	135 (2.0)	78.0 (8.6)[f]

NOTE.—All ages are given in years.
[a] $\chi^2 = 2.22$, df = 2, NS.
[b] $F(2,6238) = 65.77$, $P < .001$.
[c] $\chi^2 = .96$, df = 2, NS.
[d] $\chi^2 = .45$, df = 1, NS.
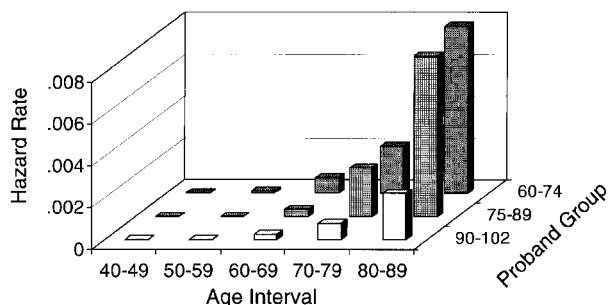[e] $F(2,131) = -2.47$, NS.
[f] Mean (SD).

Figure 2   Ten-year–age-interval–specific hazard rates of AD dementia in relatives of probands aged 60–74, 75–89, and 90–102 years.

zero only in the relatives of the probands aged 60–74 years. In subsequent decades, the hazard rate rose in each group with increasing steepness. In the seventh decade, the rates of AD were still noticeably higher in the relatives of the youngest proband group than in those of the two older groups, whose rates were similar to each other. The low base rates of AD at these ages reduce power, and these differences were not significant. In the eighth and ninth decades, the hazard rates of the relatives of probands aged 90–102 years were significantly lower than those of the relatives of probands aged 60–74 years (eighth decade, $z = -2.03$, $P < .05$; ninth decade, $z = -2.84$, $P < .005$) and those of relatives of probands aged 75–89 years (eighth decade, $z = -2.23$, $P < .05$; ninth decade, $z = 2.98$, $P < .005$).

Using the relatives of the probands aged 60–74 years as the reference group, we then assessed the 10-year–age-interval–specific hazard-rate ratios for the seventh, eighth, and ninth decades—the three age intervals for which these could be meaningfully calculated (fig. 3). Here we were primarily interested in the relatives of the oldest proband group, because only this group had a survival curve significantly different from the reference group's. Again, statistical power was low for these comparisons; only for the ninth decade was the hazard-rate ratio significantly different from 1.0 (hazard-rate ratio = 0.26; 95% confidence interval = 0.08–0.85). However, the primary purpose for calculating the hazard-rate ratios was to determine whether the overall difference observed in survival curves was driven by proportionately similar levels of decreased risk across different age periods. That this was so is indicated by the essentially flat line associated with the relatives of the oldest proband group. Although the survival curve for the relatives of probands aged 75–89 years was not significantly different from the reference group's, for comparison purposes, we also included their hazard-rate ratios. None of these were significantly different from 1.0, but, relative to each other, the hazard-rate ratio in the seventh decade was lower than those in the two subsequent decades.

The 15-year intervals for grouping the probands were relatively wide time periods. Might the familial characteristics of those probands with ages closer to the dividing point (age 90 years) be more similar to each other than was observed in the full group comparisons? To answer this question, we identified the subgroups of probands whose ages fell in the 5 years immediately below (85–89 years: $n = 92$) or above (90–94 years: $n = 63$) the dividing point of age 90 years and compared the risk of AD in their respective relatives (85–89 years: $n = 564$; 90–94 years: $n = 357$) with the risk in relatives of the probands aged 60–74 years and with that of each other's relatives. Compared with the reference group, the relatives of the probands aged 90–94 years (log-rank statistic = 5.3, df = 1, $P < .5$), but not those of the probands aged 85–89 years (log-rank statistic = 0.0, df = 1, NS), showed better survival from AD, and the latter two curves were also significantly different from each other (log-rank statistic = 4.2, df = 1, $P < .05$).

We were able to examine APOE genotypes in only a small subset of probands ($n = 133$), but we found no significant differences between groups ($\chi^2 = 7.3$, df = 10, NS). The allele frequencies of APOE-ϵ2 were roughly similar (0.11, 0.08, and 0.10 in probands aged 60–74, 75–89, and 89–102 years, respectively), as were the allele frequencies of APOE-ϵ4 (0.14, 0.13, and 0.11 in probands aged 60–74, 75–89, and 90–102 years, respectively).

Discussion

The relatives of nondemented probands who had lived to the 10th decade or beyond had a significantly lower risk of AD compared with relatives of two groups of successively younger, but still elderly, nondemented pro-
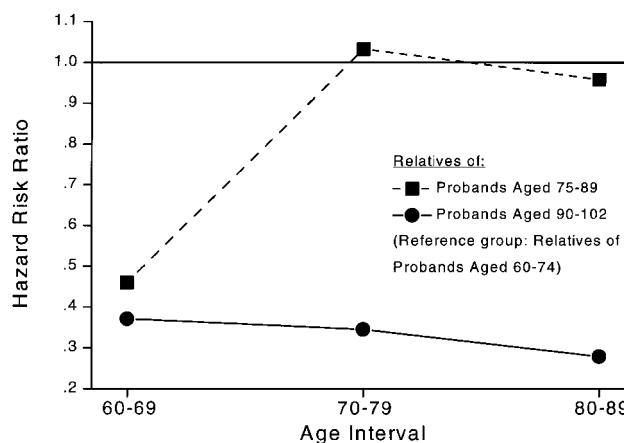

Figure 3   Ten-year–age-interval–specific hazard-rate ratios in relatives of probands aged 75–89 and 90–102 years compared with relatives of probands aged 60–74 years.

bands. In addition, the reduction in risk among the relatives of the oldest proband group encompassed virtually the entire late life span. In contrast, similar to nondemented probands' relatives described elsewhere (Payami et al. 1995; Mayeux et al. 1991; Hirst et al. 1994), AD in the relatives of the two younger groups of probands decreased to <90% by the age of 90 years.

Two different, but not mutually exclusive, possibilities provide the most obvious explanations for the reduction in risk of AD among relatives of the oldest nondemented probands. First, nonagenarian and centenarian probands have lived through more of the risk period for AD free of disease, and hence are less likely to carry alleles that might either directly cause AD (Goate et al. 1991; Levy-Lehad et al. 1995; Sherrington et al. 1997) or, more generally, increase the risk of AD (e.g., APOE-ε4) (Corder et al. 1993). This is especially likely since the pattern of risk among relatives of AD probands suggests that genetic risk factors are less influential with increasing age and that their effects are markedly diminished by the ages of peak incidence (Heun and Maier 1995; Li et al. 1995; Silverman et al. 1994; Lautenschlager et al. 1996). Consistent with this, several recent studies of APOE-ε4 (Scacchi et al. 1995; Sobel et al. 1995; Asada et al. 1996; Corder et al. 1996; Blacker et al. 1997; Farrer et al. 1997)—but not all (Brayne et al. 1996; Gessner et al. 1997; Payami et al. 1997)—have found that the effect of this allele on AD markedly diminishes at very late ages.

A second possible explanation for lower rates of AD among the relatives of long-lived nondemented probands is that such probands are more likely to carry genetic protective factors. Although some candidates (e.g., human leukocyte DR4 or DR6 antigens [Sandbrink et al. 1996; Curran et al. 1997]) have been suggested, the evidence seems strongest for the APOE-ε2 allele (Chartier et al. 1994; Corder et al. 1994; Higgins et al. 1997). A recent meta-analysis found the odds ratio for AD among individuals with ε2/ε2 or ε2/ε3 APOE genotypes was 0.6 compared with individuals carrying a ε3/ε3 genotype (Farrer et al. 1997). Yet, there may well be alleles on other genes, or possibly nongenetic familial factors, thus far unidentified, that confer protection against AD (Payami et al. 1994). If indeed genetic, such protective alleles, provided they are not positively associated with some competing fatal illness, will tend to be more highly concentrated among long-lived nondemented individuals, since these individuals have manifestly remained free of dementia over a very long stretch of the risk period, including many years of peak incidence. In turn, by Hardy-Weinberg equilibrium, their relatives will have a higher concentration of such genes than the relatives of nondemented probands who have not lived so long into the risk period.

The patterns of risk in the present study offer some useful clues for estimating the contribution of genetic protective factors to the observed reduced risk. Reduced rates of earlier-onset illness can be expected from a group that primarily lacks a high concentration of genetic risk factors for AD but does not possess a high concentration of genetic protective factors. The liability to later-onset disease in such a group would tend, with age, to increasingly resemble that of the general population. Such a pattern was observed for relatives of probands aged 75–89 years. It must be emphasized that the survival curve in this group did not significantly differ from that of the reference group, nor did any of the age-interval hazard rates. Thus, the pattern of hazard-rate ratios, suggestive of lower rates of earlier- but not later-onset AD, must serve strictly as an interesting hypothesis that requires further testing with a larger sample.

On the other hand, the statistically significant reduction of risk for AD in the relatives of the probands aged ≥90 years appeared to be essentially consistent over a 30-year span of late life. This suggests a reduced incidence not only of AD variants attributable to genetic risk factors, but also of those types of disease in which the role of genetic risk factors appears to be markedly diminished. Thus, the concentration of genetic factors that protect against AD is likely to be substantially increased among the families of nondemented individuals living into the 10th decade, particularly among those very old individuals themselves, compared with families of other, less aged individuals.

The cumulative survival differences observed in the present study are similar to those observed in an earlier study that compared relatives of optimally healthy, nondemented individuals aged ≥85 years with relatives of a younger group of random controls (Payami et al. 1994). The results of the present study, which used a sample that overall is >10 times as large as the nondemented proband sample used previously, extend the findings from the earlier study by examining age-interval–specific patterns of risk. Another difference in the present study was our choice of the age of 90 rather than 85 years as a dividing age. This was done to examine the families of individuals who had lived well into the years of peak incidence of AD without having developed the disease. Thus, it was informative to restrict the ranges of proband ages to 85–89 and 90–94 years and observe that the results in these more narrowly defined and adjacent age–determined subgroups were similar to the larger, more broadly based age groups. In a post hoc analysis (data not shown), we confirmed that using the age of ≥85 rather than ≥90 years as the dividing point would also have led to significant overall differences, more directly replicating the results of Payami et al. (1994), but the age-specific risk of AD in this more broadly defined proband group was disproportionately reduced at earlier ages and then rose during

later decades to levels more comparable to those of relatives of younger nondemented probands.

Several methodological issues require attention. First, it is possible that these results may have arisen from different levels of accuracy, associated with increased proband age, about AD among family members. Although such a bias cannot be ruled out, the particular pattern of results obtained does not readily lend itself to such an interpretation. For example, the survival curve of relatives of probands as old as 85–89 years was quite different from that of relatives of an only slightly older proband group but was similar to that of the relatives of the substantially younger proband group.

A second issue is whether APOE-ϵ2 alone can explain the reduced rates of AD in the relatives of the oldest probands—without having to posit other, yet to be identified, protective alleles of other genes. This possibility is refuted by the low and similar frequencies of APOE-ϵ2 in the smaller subgroups of probands that could be genotyped. At the same time, the failure to find differences in the ϵ2 allele frequency should not be interpreted as important evidence against this allele's protective properties. The absence of an age-related relationship in this relatively small sample must be weighed against the size and consistency of those studies associating APOE-ϵ2 with greater longevity and freedom from dementia (Corder et al. 1996; Helkala et al. 1996; Farrer et al. 1997). Even among centenarians, the absolute frequency of APOE-ϵ2 has been observed to be low, even though it is greater than in younger groups (Hirose et al. 1997). Hence, rather large samples are generally required, to detect differences between the oldest old and younger elderly groups.

Third, although our methods for determining the absence of dementia in probands have been shown to have very good to excellent reliability and validity, they are inevitably less certain than a full cognitive evaluation. Any misclassification of probands that might have occurred, however, would likely be strongly associated with age. This, in turn, would mean that the observed rate of survival from AD in the relatives of the oldest nondemented probands may have been unduly *deflated* by the inclusion of some relatives of probands with dementia; the true rate of survival might be even better in this group than what was observed.

The findings from the present study suggest that variation in familial liability to AD exists even at ages at which the role of genetic risk factors appears to be small. Some families have a relatively low risk of AD throughout the life span. If this is so, it presents opportunities to identify genes involved in the pathogenesis of some of the most common forms of AD that, perhaps because of the apparent ubiquity of the alleles associated with AD vulnerability at those ages, may be otherwise difficult to ascertain. In AIDS research, a mutation of the *CC-CKR-5* gene that is resistant to HIV has recently been identified by focusing on a group of individuals repeatedly exposed to HIV who yet remained free of infection (Dean et al. 1996; Liu et al. 1996). In a search for AD-associated genes with uncommon protective alleles, the present results suggest that it may be valuable to study probands who have lived at least to the 10th decade without developing dementia. Future genetic studies (e.g., an unaffected sibling pair approach in which both siblings are required to be free of AD) aimed at identifying such genes might benefit from targeting such probands and their families.

Acknowledgments

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