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Preservation of cognitive and functional ability as markers of longevity

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Abstract

Longevity is a complex biological process for which the phenotypes have not been established. Preservation of cognitive and physical function may be important and preservation of these functions is, in part, inherited. We investigated the relation between rate of change in cognitive and functional abilities in probands and risk of death in their siblings. Probands were classified as showing no decline, slow, medium, or rapid rate of decline, based on the slope of change in cognitive and physical/functional factors over three or more assessments. Siblings of probands who did not decline on measures of memory, visuospatial/cognitive function or ADL skills were approximately half as likely to die as siblings of probands who had the most rapid decline. The reduction in risk of death in siblings of probands who did not decline in was primarily observed among siblings of probands who were older than 75 years, suggesting that genetic influences on life span may be greater at older ages. There was no association between probands' rate of change in language, IADL skills, upper or lower extremity mobility and risk of death in siblings. The results of the present study identify phenotypes associated with preserved cognitive and functional abilities which may serve as markers for longevity.

Keywords: Longevity; Heritability; Phenotype; Memory; Function

1. Introduction

The heritability of longevity has been estimated from investigations of human twins, isolated and founder populations [11]. Monozygotic twins are twice as likely to be concordant for total years of life as dizygotic twins [23]. Overall, heritability of life span is approximately 20–30% [23,33,40]. Genetic influences on life span appear to be greater at extreme old age. Siblings of centenarians were four times as likely to live beyond 85 years as were siblings of individuals who did not survive past 73 years [43], and first degree relatives of individuals who lived beyond 95 years were twice as likely to survive to the same age as were relatives of controls [22,28].

The biological mechanisms mediating longevity are still unknown. Findings from centenarian and twin studies suggest that preservation of cognitive and physical function is important. In the New England Centenarian study, individuals who lived to extreme old age were found to have been healthy and independent for most of their lives [24]. Offspring of centenarians have favorable lipid profiles and lower relative prevalence of heart disease, hypertension and diabetes [1,12]. Genetic influences on general and specific cognitive function are substantial in studies of human twins [13,14,37,38,42,44,56]. About half the variance in cognitive function can be accounted for by genetic differences [42]. McClearn et al. [37] studied the heritability of cognitive function in Swedish twins 80 years of age and older and showed that genetic influences on cognitive performance continue into old age. Apolipoprotein E (APOE) has been proposed as one candidate gene consistently associated with longevity and memory function [31,34,36,45,50]. Data

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concerning the heritability of physical and functional ability are more limited, but support the hypothesis that genetic influences contribute to individual differences in function and that preservation of physical and functional ability may be associated with longevity [8,10,16].

Genetic factors may influence both the level as well as the rate of change in cognitive and physical functions [41]. Whether or not the genes that influence cognitive and physical function at a given age are the same as those that influence the rate of change in these functions remains unknown. In this study, preservation of cognitive and functional abilities was investigated in relation to survival in family members. We also investigated the relation between survival in families and the rate of change in cognitive and functional abilities in younger and older probands and across three ethnic groups.

2. Methods

2.1. Subjects and setting

Data were included from individuals participating in a prospective study of aging and dementia in 2126 Medicare recipients, 65 years and older, residing in northern Manhattan. A stratified random sample of 50% of all persons older than 65 years was obtained from the Health Care Finance Administration (HCFA) [57]. All persons were sent a letter from HCFA explaining that they had been selected to participate in a study of aging by investigators at Columbia University. The participation rate was 73% and did not differ by ethnic group. Each person received the same medical, neurological, and neuropsychological evaluations at regular 18-month intervals. At the baseline examination, 327 participants (15%) were found to be demented, leaving 1799 participants for the prospective study of incident AD. The cohort has been followed since 1992, but the data included in this analysis were gathered by 2001. Over the study period, the annual mortality rate has been 8.1%, the overall refusal rate has been 10% and the annual incidence rate of Alzheimer's disease (AD) has been 3%, leaving 1051 probands after the first follow-up [36]. To address the study aims, there were 961 of the 1051 probands in the cohort (91.4%) who had at least three measures of memory, cognitive, language or physical and function scores from which rates of change could be computed. Family history data were available for 734 of these 961 probands (76.4%). We then excluded all probands who developed dementia after the first follow-up ($n = 61$), leaving 673 nondemented probands with 2533 siblings to be included in the analysis (Fig. 1). The mean number of siblings was 4.74 per proband (range 1–18).

Ethnic group was classified by participants' self-report into white, African-American, and Hispanic. Participants were asked if they considered themselves white, African-American or other, and then asked if they were

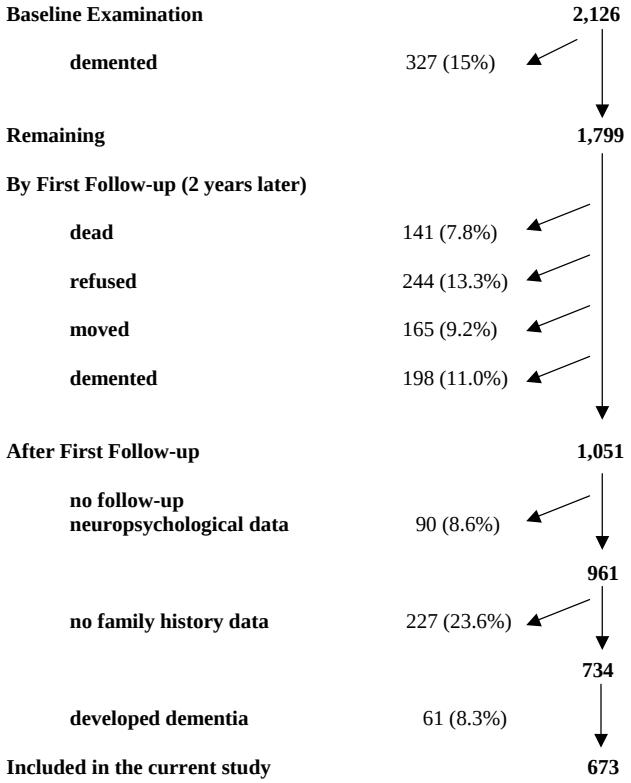

Fig. 1. Nondemented probands with family history.

Hispanic. If Hispanic, the country in which they were born was queried. Most of those classified as Hispanic were of Caribbean origin (84%), predominantly from the Dominican Republic, with the remainder from Mexico and Central America. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

2.2. Clinical evaluation

All participants (probands) received structured neurologic and functional assessments by physicians. Past medical history was recorded with specific attention to stroke, trauma, medications, recreational drug use and common age-related conditions such as heart disease, diabetes, thyroid disorders and cancer. All probands underwent a standardized neuropsychological battery [52] that included: orientation from the modified Mini-Mental State Examination [17]; language using the Boston Naming Test [25], the Controlled Word Association test [3], category naming, the Complex Ideational Material Subtest and the repetition of phrases from the Boston Diagnostic Aphasia Evaluation [21]; abstract reasoning from the WAIS-R Similarities subtest [59], and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale [35]; visuospatial ability using the Rosen Drawing Test [48] and the Benton Visual Retention