Original Investigation

Age-Specific Incidence Rates for Dementia and Alzheimer Disease in NIA-LOAD/NCRAD and EFIGA Families

National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD) and Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA)

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IMPORTANCE Late-onset Alzheimer disease (LOAD), defined as onset of symptoms after age 65 years, is the most common form of dementia. Few reports investigate incidence rates in large family-based studies in which the participants were selected for family history of LOAD.

OBJECTIVE To determine the incidence rates of dementia and LOAD in unaffected members in the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD) and Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) family studies.

DESIGN, SETTING, AND PARTICIPANTS Families with 2 or more affected siblings who had a clinical or pathological diagnosis of LOAD were recruited as a part of the NIA-LOAD/NCRAD Family Study. A cohort of Caribbean Hispanics with familial LOAD was recruited in a different study at the Taub Institute for Research on Alzheimer's Disease and the Aging Brain in New York and from clinics in the Dominican Republic as part of the EFIGA study.

MAIN OUTCOMES AND MEASURES Age-specific incidence rates of LOAD were estimated in the unaffected family members in the NIA-LOAD/NCRAD and EFIGA data sets. We restricted analyses to families with follow-up and complete phenotype information, including 396 NIA-LOAD/NCRAD and 242 EFIGA families. Among the 943 at-risk family members in the NIA-LOAD/NCRAD families, 126 (13.4%) developed dementia, of whom 109 (86.5%) met criteria for LOAD. Among 683 at-risk family members in the EFIGA families, 174 (25.5%) developed dementia during the study period, of whom 145 (83.3%) had LOAD.

RESULTS The annual incidence rates of dementia and LOAD in the NIA-LOAD/NCRAD families per person-year were 0.03 and 0.03, respectively, in participants aged 65 to 74 years; 0.07 and 0.06, respectively, in those aged 75 to 84 years; and 0.08 and 0.07, respectively, in those 85 years or older. Incidence rates in the EFIGA families were slightly higher, at 0.03 and 0.02, 0.06 and 0.05, 0.10 and 0.08, and 0.10 and 0.07, respectively, in the same age groups. Contrasting these results with the population-based estimates, the incidence was increased by 3-fold for NIA-LOAD/NCRAD families (standardized incidence ratio, 3.44) and 2-fold among the EFIGA compared with the NIA-LOAD/NCRAD families (1.71).

CONCLUSIONS AND RELEVANCE The incidence rates for familial dementia and LOAD in the NIA-LOAD/NCRAD and EFIGA families are significantly higher than population-based estimates. The incidence rates in all groups increase with age. The higher incidence of LOAD can be explained by segregation of Alzheimer disease–related genes in these families or shared environmental risks.

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Late-onset Alzheimer disease (LOAD), defined as onset of symptoms after 65 years of age, is the most common form of dementia.[1] A history of LOAD or dementia in the family is one of the strongest risk factors. The lifetime risk for family members of patients may be as high as 50%, which suggests an age-dependent autosomal dominant mode of inheritance.[2] Mutations in the amyloid precursor protein (*APP* [HGNC 620]), presenilin 1 (*PSEN1* [HGNC 9508]) and presenilin 2 (*PSEN2* [HGNC 9509]) genes are associated with familial early-onset Alzheimer disease (AD) but account for only a small proportion (approximately 0.1%-1.0%) of all cases of AD and are rarely associated with LOAD.[3] The ε4 variant in the apolipoprotein E (*APOE* [HGNC 613]) gene increases susceptibility to sporadic and familial LOAD, and additional susceptibility genes have been identified in genome-wide association studies, mostly among unrelated cases and control participants.

Genetic investigation of multigenerational families affected by LOAD to uncover risk genes rests on the hypothesis that these families are enriched for risk-raising alleles and that the occurrence of disease exceeds that in the general population. With multiple cases in a family, incidence rates among previously unaffected family members would provide the best measure of disease occurrence. Few reports exist of incidence rates in large family-based studies in which the participants were selected for family history of LOAD. In 2002, the National Institute on Aging (NIA) launched the Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease (NIA-LOAD/NCRAD) to expand resources needed to identify the remaining genes contributing to the risk for LOAD. The goal of the NIA-LOAD/NCRAD Family Study was to identify and recruit families with 2 or more affected siblings with LOAD and unrelated, nondemented control participants similar in age and ethnic background. The clinical data, DNA, genotyping results, and preliminary analyses have been made available to investigators worldwide and are widely used. The underlying hypothesis was that families multiply affected by LOAD would be enriched for alleles increasing disease risk.

Caribbean Hispanics are one of the most rapidly increasing ethnic groups in the United States, and an 11-fold increase is expected in the elderly Caribbean Hispanic population.[4] Caribbean Hispanics and Mexican Americans have an increased prevalence and incidence of LOAD.[5-7] To study the underlying genetic architecture of LOAD in Caribbean Hispanics, the Estudio Familiar de Influencia Genetica en Alzheimer (EFIGA) was initiated, and recruitment began in 1998. Since then, large multiplex families with multiple individuals at risk of LOAD have been recruited. Thus, we estimated the annual incidence rates of LOAD in previously unaffected individuals in the NIA-LOAD/NCRAD and EFIGA families and assessed the effects of demographic variables, such as age at onset, sex, and *APOE* genotype, on those rates.

Methods

Participants and Sample

NIA-LOAD/NCRAD Study

Unaffected individuals were from families with a history of AD. All participants were recruited after providing written informed consent and with approval by the relevant institutional review boards. Family inclusion criteria required 1 member to have had a diagnosis of definite or probable LOAD[8] with onset after age 60 years and to have a sibling with definite, probable, or possible LOAD with a similar age at onset. A third biologically related first-, second-, or third-degree relative of the affected sibling pair who was 60 years or older if unaffected or was diagnosed as having LOAD or mild cognitive impairment at 50 years or older was also required.[9] In these families, additional relatives older than 50 years were also recruited regardless of cognitive status. Persons deemed unaffected were required to have undergone documented cognitive testing and clinical examination to verify this clinical designation.

Phenotypes | A minimal data set was available for each person and consisted of demographic variables, diagnosis, age at onset for cases, method of diagnosis, Clinical Dementia Rating Scale score,[10] and the presence of other relevant health problems. Each recruitment site used standard research criteria for the diagnosis of LOAD.[8] Participants with advanced disease or those living in a remote location who could not complete a detailed in-person evaluation contributed a blood sample, and the site investigator conducted a detailed review of medical records to document the presence or the absence of LOAD based on the same criteria. The age at onset for patients with LOAD was the age at which the family first observed signs of impaired cognition. For unaffected family members, we used their age at the time of their examination confirming the absence of dementia. For deceased family members who had undergone a postmortem evaluation of the brain, results of the neuropathological examination were used to document the diagnosis. In total, neuropathological documentation was available for 306 cases from 199 families and 25 unrelated controls. For the purpose of analyses, a clinical case was defined as any individual meeting criteria from the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible LOAD.[8] We used the NINCDS-ADRDA criteria for definite LOAD when clinical and pathological criteria were met or pathological criteria of the Consortium to Establish a Registry for Alzheimer's Disease[11] for LOAD when based on postmortem information alone. Individuals with other forms of dementia, mild cognitive impairment, or uncorroborated family reports of LOAD were treated as unaffected by AD but still contributed to person-years in the incidence rate calculations.

Follow-up | Many families were followed up after the initial examination to establish the most current clinical status of all participating family members by conducting a standardized, telephone-administered cognitive, psychiatric, and functional assessment. The present study focused on individuals determined to be free of dementia who were examined after the proband in the family was recruited. We used the date of the initial examination in which the absence of dementia was confirmed as the beginning of follow-up. When an individual was found to have become demented, we assumed that the age at onset occurred at the midpoint between the previous and last date of examination as the date to affix the age at

onset of disease. For individuals who remained unaffected, we used the date of the last examination as the end point age.

Analyses | Analyses were restricted to 396 of 607 families (65.2%) with complete phenotype information and individuals with at least 1 follow-up examination or a confirmed diagnosis of LOAD or those deemed cognitively normal. Family members who were diagnosed as having dementia at the first examination (assumed to be prevalent cases) were excluded. Only members with at least 1 diagnosis free of dementia or LOAD were included in the study. The analysis cohort consisted of 943 at-risk participants at baseline. Among these, 126 (13.4%) developed dementia, which converted to LOAD in 109 (85.6%). Age-specific incident rates of LOAD for family members were calculated starting when the proband was recruited to the last examination of a member of the pedigree.

Apolipoprotein E Gene | For all NIA-LOAD/NCRAD samples, genotyping of *APOE* (based on single-nucleotide polymorphisms rs7412 and rs429358) was performed at Prevention Genetics (http://preventiongenetics.com) or at LGC Genomics (http://www.lgcgenomics.com/). Genotyping was performed on a commercially available platform (Array Tape; Douglas Scientific) using allele-specific polymerase chain reaction analysis with universal molecular beacons. Sequencing of DNA from positive control samples was completed to ensure correct assignment of alleles.

Estudio Familiar de Influencia Genetica en Alzheimer

Recruitment for the EFIGA began in 1998 and was restricted to families of Caribbean Hispanic ancestry. Patients with familial LOAD were recruited from Taub Institute for Research on Alzheimer's Disease and the Aging Brain in New York City using local newspapers, the local Caribbean Hispanic radio station, and postings throughout the Washington Heights-Inwood neighborhood. A system of recruitment was also set up in the Dominican Republic with the help of several local physicians, including the president of the Dominican Society of Geriatrics and Gerontology. Once patients with LOAD were identified, their illnesses were documented with standardized neurological and neuropsychological evaluations. Structured family history interviews were then conducted with available family members to determine whether patients had living siblings or relatives with the disease. If the family history interview revealed a living sibling with suspected LOAD, that individual was also interviewed and examined. If a sibling of the proband had dementia, all other living siblings and available relatives underwent evaluation with the same examinations. The recruitment included younger family members (<65 years) who were followed up over time. Medical and neurological examinations were completed for all family members. As with the NIA-LOAD/NCRAD families, a case was defined as any individual meeting NINCDS-ADRDA criteria for probable or possible LOAD.[8] The Clinical Dementia Rating[10] was used to rate the severity of dementia. Brain imaging and other laboratory study results were reviewed, when available, to ensure full implementation of the NINCDS-ADRDA criteria. A modification[12] of the methods described by Hixson and Vernier[13] was used to determine *APOE* genotypes. Brains of participants with dementia and history of stroke were administered magnetic resonance imaging scans to exclude patients with comorbid cerebrovascular disease.

Statistical Analysis

Incidence rates were calculated by dividing the number of cases with onset of dementia in each age group by the number of person-years of observation[14] in that group. Person-years were calculated from the time of study entry (ie, first examination results as unaffected) for each individual until the time of dementia or LOAD onset or until the date of the last examination for those who remained unaffected (including dates of death, loss to or unavailability for follow-up, or the most recent contact). Incidence rates were also calculated within 3 age categories (65-74, 75-84, and ≥85 years). For each 10-year age group, a 95% confidence interval for the incidence rate was computed assuming a Poisson distribution for the number of new cases in each age group. We used the extent of overlap of 95% confidence intervals to compare point estimates of incidence rates in different subgroups.

We used a standardized incidence ratio (SIR) to estimate the magnitude of increase in the expected number of cases, adjusting for age and using the population-based incidence rates from the Rochester Epidemiology Project[15] as the referent. We calculated SIRs as the ratio of observed to expected numbers of cases and then generated a 95% confidence interval[16] using a χ^2 distribution.

Family members examined once but never followed up were excluded. All family members with dementia at their first examination were treated as prevalent cases and were not included in the calculation of incidence rates. Patients with incident LOAD who had test results positive for pathogenic early-onset AD mutations in *APP*, *PSEN1*, *PSEN2*, *GRN* (HGNC 4106), *MAPT* (HGNC 6893), and other genes listed in the Alzheimer Disease and Frontotemporal Dementia Mutation Database[17] were excluded from the incidence rate calculations. One incident LOAD case carried the pathogenic R5H mutation in the *MAPT* gene and was excluded from the incident rate calculations.

Results

The demographic characteristics of the participants at risk are shown in **Table 1**. Caribbean Hispanic elderly individuals from the EFIGA were slightly younger and significantly less educated than white elderly individuals. These observations are consistent with previous findings.[6] The *APOE* allele distribution is similar in both data sets, but the ε4 allele is significantly enriched in the large families compared with population-based estimates.[7]

NIA-LOAD/NCRAD Families

The incidence rate of dementia was estimated from 943 unaffected individuals (344 men and 599 women aged ≥55 years) in 396 pedigrees contributing a total of 3634 person-years of follow-up. Annual incidence rates for dementia in the NIA-LOAD/

NCRAD families (**Table 2** and **Table 3**) were 0.03 for those aged 65 to 74 years, 0.07 for those aged 75 to 84 years, and 0.08 for those 85 years or older. We observed 649 at-risk participants (aged ≥65 years) in 341 families, with 194 from as many families being the only individuals at risk in their family. The remaining 455 participants belonged to 147 families with more than 1 family member at risk of dementia. We calculated the incidence rates separately for families with 1 or multiple individuals at risk (data not shown). The point estimates of incidence rates between the 2 sets vary by age group, but 95% confidence intervals overlap in each age band. The incidence rate of LOAD for family members in the group aged 65 to 74 years was 0.03 per person-year; in the group aged 75 to 84 years, 0.06; and in the group 85 years or older, 0.07 per person-year. We did not observe any sex differences in incidence rates except in the group aged 75 to 84 years, in which men had twice the incidence rate of women (**Table 4**). A similar trend for sex was observed in the population-based Mayo Clinic study[15] from 1990 through 1994 for the group aged 80 to 84 years, which we used to standardize the incidence rates in the NIA-LOAD/NCRAD families.

Table 1. Demographic Characteristics of 1666 Individuals at Risk

Characteristic	NIA-LOAD/NCRAD Families (n = 983)	EFIGA Families (n = 683)
Age, mean (SD), y[a]	71.0 (9.9)	69.6 (9.1)
Educational level, mean (SD), y[b]	14.1 (10.9)	7.9 (5.3)
Women, %	63	65
Person-years at risk, mean (SD)	3.9 (2.0)	4.3 (2.9)
APOE allele distribution, ε2/ε3/ε4, %	5.0/69.0/26.0	4.5/69.5/26.0

Abbreviations: EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer; NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

[a] The NIA-LOAD/NCRAD individuals were significantly older than the EFIGA individuals ($P = .004$).

[b] The NIA-LOAD individuals had significantly more years of education than the EFIGA individuals ($P < 2 \times 10^{-16}$).

EFIGA Families

The EFIGA included 683 individuals known to be free of dementia at the start of follow-up in 242 families. Among these individuals, 174 had incident dementia, of whom 145 (83.3%) met criteria for LOAD. The annual incidence rates for dementia in the EFIGA families were higher than those for the NIA-LOAD/NCRAD families in every age group, including 0.06 for the group aged 65 to 74 years, 0.10 for the group aged 75 to 84

Table 2. Incidence Rate of All Dementia in NIA-LOAD/NCRAD Families

Age Group, y	No. of Cases	No. of Person-years at Risk	Incidence Rate (95% CI)	Characteristic, Mean (SD)	
				Educational Level, y[a]	Person-years at Risk[b]
65-74	36	1262	0.03 (0.02-0.04)	13.8 (11.7)	4.0 (2.0)
75-84	58	894	0.07 (0.05-0.08)	14.4 (14.1)	3.7 (2.0)
≥85	24	302	0.08 (0.05-0.12)	13.0 (10.2)	3.2 (1.9)

Abbreviation: NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

[a] We observed no significant difference between the education levels between the age-groups (F test, $P = .60$)

[b] We observed no significant difference between the person-year distribution within the age groups (F test, $P = .13$).≥

Table 3. Incidence Rate of LOAD in NIA-LOAD/NCRAD Families

Age Group, y	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)
65-74	31	1200	0.03 (0.02-0.04)
75-84	46[a]	820	0.06 (0.04-0.08)
≥85	23	324[b]	0.07 (0.05-0.11)

Abbreviation: NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

[a] One individual with incident Alzheimer disease (AD) had positive test results for the R5H mutation in *MAPT* and was excluded from the incident rate calculation.

[b] Includes individuals who were diagnosed as having dementia in the first examination (prevalent dementia) but who did not experience conversion to AD after multiple examinations. These individuals contribute person-years to AD incidence rate calculations but were excluded from dementia subgroup.

Table 4. Sex-Specific Dementia Rates in NIA-LOAD/NCRAD Families

Age Group, y	Women			Men		
	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)
65-74	21	808	0.03 (0.02-0.04)	15	454	0.03 (0.02-0.05)
75-84	27	575	0.04 (0.03-0.07)	31	319	0.10 (0.07-0.14)
≥85	11	158	0.07 (0.04-0.12)	13	144	0.09 (0.05-0.15)

Abbreviation: NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

years, and 0.10 for the group 85 years or older (**Table 5**). The annual incident rates for LOAD were also higher in these age groups, at 0.05, 0.08, and 0.07, respectively, in the EFIGA families (**Table 6**). The dementia incidence rate in men was higher than that in women 85 years or older, but the 95% confidence interval overlapped in the 2 groups (**Table 7**). The other age groups had similar incidence rates for men and women.

APOE ε4 and LOAD Incidence Rates

Incidence rates were recalculated by stratifying for *APOE* status for the NIA-LOAD/NCRAD and EFIGA families (**Table 8**). As expected, in NIA-LOAD/NCRAD families, the incidence rate of LOAD was higher among *APOE* ε4 carriers than noncarriers, and the incidence of LOAD was more pronounced in the older groups. However, in the EFIGA families, although the LOAD incidence rate was higher among *APOE* ε4 carriers than noncarriers, the rates were similar in the older groups. Moreover, the increased incidence rate of LOAD within each age group among *APOE* ε4 carriers in the EFIGA families was not as pronounced as in the NIA-LOAD/NCRAD families, suggesting that *APOE* has a significant but weaker influence on LOAD incidence in the EFIGA families compared with the NIA-LOAD/NCRAD families. Alternatively the effects of *APOE* ε4 may be overwhelmed by other factors, possibly environmental, that are not associated with increasing incidence rates with age.

Comparison With Population-Based Rates and SIR

As hypothesized, the NIA-LOAD/NCRAD and EFIGA family cohorts were found to have higher incidence rates of dementia and LOAD compared with data from published studies.[18-23]

Table 5. Incidence Rate of All Dementia in EFIGA Families

Age Group, y	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)	Characteristic, Mean (SD)	
				Educational Level, y[a]	Person-years at Risk
55-64	22	895	0.03 (0.02-0.04)	10.3 (5.3)	3.2 (1.8)
65-74	68	1148	0.06 (0.05-0.08)	7.1 (4.9)	4.4 (3.0)
75-84	65	634	0.10 (0.08-0.13)	6.4 (5.2)	4.2 (3.1)
≥85	19	188	0.10 (0.06-0.16)	5.3 (4.3)	4.5 (3.3)

Abbreviation: EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer.

[a] We found no significant difference between the education levels among the age groups (*F* test, *P* = .14).

Table 6. Incidence Rate of LOAD in EFIGA Families

Age Group, y	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)
55-64	19	898	0.02 (0.01-0.03)
65-74	56	1161	0.05 (0.04-0.06)
75-84	54	716	0.08 (0.06-0.10)
≥85	16	223	0.07 (0.04-0.12)

Abbreviations: EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer; LOAD, late-onset Alzheimer disease.

Table 7. Sex-Specific Dementia Rates in EFIGA Families

Age Group, y	Women			Men		
	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)
65-74	43	757	0.06 (0.04-0.08)	25	392	0.06 (0.04-0.09)
75-84	36	378	0.10 (0.07-0.13)	29	256	0.11 (0.05-0.11)
≥85	12	130	0.09 (0.05-0.16)	7	59	0.12 (0.05-0.25)

Abbreviation: EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer.

Table 8. *APOE*-Stratified Incidence Rate of AD

Age Group, y	No *APOE* ε4 Allele			1 or 2 Copies of *APOE* ε4 Allele		
	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)	No. of Cases	Person-years at Risk	Incidence Rate (95% CI)
NIA-LOAD/NCRAD Families						
65-74	10	558	0.02 (0.01-0.03)	21	543	0.04 (0.002-0.06)
75-84	13	409	0.03 (0.02-0.05)	30	340	0.09 (0.06-0.13)
≥85	10	221	0.05 (0.02-0.08)	9	81	0.11 (0.05-0.21)
EFIGA Families						
55-64	9	551	0.02 (0.01-0.03)	10	347	0.03 (0.01-0.05)
65-74	25	600	0.04 (0.03-0.06)	31	55	0.06 (0.04-0.08)
75-84	28	396	0.07 (0.05-0.10)	26	309	0.08 (0.06-0.12)
≥85	10	152	0.07 (0.03-0.12)	6	72	0.08 (0.02-0.16)

Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E; EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer; NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

Table 9. Calculation of Standardized Incidence Ratio in the NIA-LOAD/NCRAD Families Using Population-Based Rates Published in the Mayo Clinic Study[a]

Age Group, y	Mayo Clinic Rochester Rates[b]	Person-years at Risk in NIA-LOAD/NCRAD Study	No. of Incident Cases	
			Expected	Observed
65-74	0.005	1262	6.4	36
75-84	0.017	894	15.6	58
≥85	0.041	302	12.4	24
All			**34.4**	**118**

Abbreviation: NIA-LOAD/NCRAD; National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

[a] The overall standardized incidence ratio for the NIA-LOAD/NCRAD families compared with the Mayo Clinic Rochester population-based rate was 3.44 (95% CI, 2.82-4.06), indicating that the incidence was at least 3-fold higher.

[b] Data are found in Knopman et al.[15]

Table 10. Comparison of Cumulative Incidence of LOAD in First-Degree Relatives in Family-Based Studies

Study by Participants	No. of Cases	No. of Controls	Cumulative Incidence (95% CI)
Relatives of NIA-LOAD/NCRAD probands	101	448	0.18 (0.15-0.22)[a]
Relatives of EFIGA probands	119	331	0.26 (0.22-0.30)
Steffens et al[24]			
First-degree relatives of concordant twins	16	60	0.21 (0.12-0.30)
First-degree relatives of discordant twins	38	362	0.10 (0.06-0.12)
Green et al[25]			
First-degree relatives, white	1323	16 316	0.08 (0.07-0.80)
First-degree relatives, African American	220	2061	0.10 (0.08-0.11)

Abbreviations: EFIGA, Estudio Familiar de Influencia Genetica en Alzheimer; LOAD, late-onset Alzheimer disease; NIA-LOAD/NCRAD, National Institute on Aging Genetics Initiative for Late-Onset Alzheimer Disease/National Cell Repository for Alzheimer Disease.

[a] The 95% confidence interval was calculated using a normal approximation method of the binomial confidence interval.

Incidence of dementia in the NIA-LOAD/NCRAD was increased 3-fold (SIR, 3.44 [95% CI, 2.82-4.06]) (**Table 9**) compared with the incidence in Rochester, Minnesota, from 1990 through 1994.[15] When we compared the incident rate in the EFIGA families with that of the NIA-LOAD/NCRAD families, we observed a SIR of 1.71 (95% CI, 1.43-1.97).

We also compared the cumulative incidence of AD in the NIA-LOAD/NCRAD and EFIGA families with 2 studies of familial aggregation of LOAD[24,25] (**Table 10**). The cumulative incidence in the NIA-LOAD/NCRAD and EFIGA families are comparable (overlapping 95% confidence intervals of the point estimate) to the incidence of AD in first-degree relatives of concordant AD twins and much higher than that in the first-degree relatives of discordant twins[24] and in the study by Green et al.[25]

Discussion

Published estimates of LOAD incidence rates in the literature have been variable owing to underlying differences in populations, varying case ascertainment, or different study designs.[26] Unaffected members of families multiply affected by LOAD are assumed to have an increased risk of dementia. Family studies tend to be biased because recruitment strategies favor large, multiplex families. Most previous studies of familial risk of LOAD have included a small number of families or families with specific genetic variants, making it difficult or impossible to estimate incidence rates. The goal of this study was to determine whether the incidence rate for new-onset dementia, specifically LOAD, in multiplex families exceeded that in the general population.

The results here suggest that the incidence rate of LOAD in the NIA-LOAD/NCRAD families, who are multiply affected by the disease, exceed published population incidence rates[18-23] by 3-fold or more. Despite the lack of comparable studies, we elected to contrast the AD incidence rate estimates calculated from a family-based study design with those from population-based studies to emphasize and quantify the importance of familial aggregation studies. As expected, the incidence in the NIA-LOAD/NCRAD families was also higher than has been observed in families ascertained through a single individual with LOAD, owing to multiple NIA-LOAD/NCRAD individuals who have had LOAD. Higher rates of incidence in such families could be partially attributed to relatives of affected individuals who might be recruited with early signs of mild cognitive impairment and who might be more likely to develop dementia or AD in subsequent visits. The increased incidence rate may result from enrichment for the rare and common variants currently the subject of large-scale investigations in these families. Alternatively, these families may also have an increased frequency of certain environmental exposures or behaviors associated with increased risk. We also observed no differences in rates between men and women, but the incidence increased with advancing age.

The EFIGA began 20 years ago to identify the cause or causes of the high frequency of LOAD among Caribbean Hispanics living in New York and the Dominican Republic. Compared with white populations residing in the same communities, the incidence rate of LOAD is approximately twice as high

in Caribbean Hispanics, leading to a considerable burden is this population group.[6] The increased incidence rate of LOAD could be explained by common ancestry and inbreeding within the isolated population. In addition, common risk factors that are known to be associated with LOAD risk, such as diabetes mellitus, obesity, hypertension, low levels of education, and an unhealthy diet, are also more frequent in this ethnic group.[6] Although recently identified genetic associations in non-Hispanic populations have been replicated in Caribbean Hispanics, the specific single-nucleotide polymorphism variants can differ.[27] This variation results in part from differences in allele frequency and linkage disequilibrium structure. The population-based estimates of incidence rates among African Americans have been reported to be 2-fold greater than those for whites and are comparable to but slightly higher than those for Caribbean Hispanics.[6] Dominicans and Puerto Ricans share strong genetic African ancestry,[28] which resulted from the large influx of African slaves into the islands of the Caribbean basin after the mid-16th century, when European settlers imported them for agricultural production. We also estimated a strong African ancestry in Caribbean Hispanics from genome-wide single-nucleotide polymorphism data.[27] These observations suggest that Caribbean Hispanics who are most closely related to Western Africans among the broad Hispanic populations might share common risk factors for LOAD with African Americans.

The incidence rate among unaffected family members in the EFIGA was at least twice as high as that observed in the NIA-LOAD/NCRAD families. The frequency of *APOE* alleles in the NIA-LOAD/NCRAD individuals at risk is similar to that of EFIGA individuals (Table 1) but substantially enriched compared with some population estimates among the white individuals. The higher incidence of AD in Caribbean Hispanics is not attributable to enrichment of *APOE* ε4 alleles and could be due to familial clustering or other genetic risk variants. Socioeconomic factors, such as low rates of literacy and occupational attainment, have been shown to increase the risk of developing AD.[29] However, results relating AD risk to educational level are inconclusive in the literature,[29-33] which might indicate that educational level captures the effect of yet unknown early life factors. The educational levels attained among individuals in the NIA-LOAD/NCRAD and EFIGA families are significantly different ($P < 2 \times 10^{-16}$) (Table 1), which could increase the risk of LOAD in the EFIGA cohort.

The sex bias in AD has conflicting evidence in the literature. An increased prevalence of AD among women has been reported in many studies.[34-41] However, incidence studies have generally found no significant sex difference,[18,23,42-44] which could be explained by lack of sample size and by low recruitment at the highest ages of incidence for men. Remarkably, we observed a more than 2-fold increase in the incidence of AD in men in the group aged 75 to 84 years within the NIA-LOAD/NCRAD data set, but the incidence rates were similar in the other age categories. We believe that this estimate might be biased by a limited number of observations and requires replication in other studies. In the EFIGA data set, we observed small sex differences in incidence rates within the 3 age groups, with overlapping 95% confidence intervals consistent with the previous findings in the literature. This study suggests that the family-based incident rates of dementia and AD are higher than in the general population and that Caribbean Hispanics have significantly a higher rate than the white population.

Conclusions

As hypothesized, the incidence rates for familial dementia and LOAD in the NIA-LOAD/NCRAD and EFIGA families are significantly higher in than population-based estimates. The incidence rates in all groups increase with age. The higher incidence of LOAD can be explained by segregation of AD-related genes in these families or shared environmental risks.

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