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# Inbreeding among Caribbean Hispanics from the Dominican Republic and the Effects on the Risk of Alzheimer's Disease

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## Abstract

**Background—**Inbreeding can be associated with a modification in disease risk due to excess homozygosity of recessive alleles impacting a wide range of phenotypes. We estimated the inbreeding coefficient in Caribbean Hispanics and examined its effects on risk of late-onset Alzheimer's Disease (LOAD).



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**Methods—**The inbreeding coefficient was calculated in 3392 subjects (1451 LOAD patients and 1941 age-matched healthy controls) of Caribbean Hispanic ancestry using 177,997 nearly independent SNPs from genome-wide array. The inbreeding coefficient was estimated using the excess homozygosity method with and without adjusting for admixture.

**Results—**The average inbreeding coefficient in the Caribbean Hispanics without accounting for admixture was F=0.018 (±0.048) suggesting a mating equivalent to second cousins or second cousins once removed. Adjusting for admixture from 3 parent populations, the average inbreeding was found to be 0.0034 (±0.019) or close to third cousin mating. Inbreeding coefficient was a significant predictor of AD when age, sex and *APOE* genotype was used as adjusting covariates (p=0.03).

**Conclusions—**The average inbreeding in this population is significantly higher than the general Caucasian populations in North America. The high rate of inbreeding resulting in increased frequency of recessive variants is advantageous for the identification of rare variants associated with LOAD.

## Introduction

Inbreeding can lead to rare heritable illnesses conferred by homozygous recessive alleles. Reduced early survival of children from first cousin marriages and similar observations in other organisms emphasize the presence of an increased number of homozygous deleterious alleles in the genome[1,2]. Inbreeding is highly prevalent across the world and differences in disease prevalence between populations can be partially attributed to extent of inbreeding[1,3].

Conservative estimates of prevalence of consanguineous marriages (defined as a union between individuals related as second cousins or closer) range between 1-10% among 2,811 million people studied globally. [3] Previous studies have seen a strong association between extent of inbreeding and reproductive health as well as childhood mortality and rare Mendelian disorders[1,2,4,5]. However a multi-population meta-analysis found only a moderate 1.1% increase in the infant death rate of 1.1% in the progeny of first cousins[6]. Biological consequences of inbreeding are known to get worse with aging in non-human species[7,8]. Studies examining the effects of inbreeding on late-onset complex diseases have found conflicting trends. Longer stretches of homozygosity have been observed in patients of breast, prostate, head and neck and colorectal cancer[9,10] but these findings have not been consistently replicated[11-14]. A recent study examining the concordance of AD raised the possibility that as much as 90% of early-onset cases with AD are likely the result of autosomal recessive inheritance[15]. Multiple risk loci for AD[16] were detected in a consanguineous Israeli-Arab community from WadiAra (Israel). Unaffected healthy controls were found to be more inbred than cases in the WadiAra population suggesting higher frequency of protective alleles as a result of inbreeding.[17] In an autopsy-confirmed AD dataset comprised of subjects from the Saguenay region of Quebec (Canada) subjects with late-onset AD and having at least one *APOE ε4* allele were observed to have higher levels of inbreeding (equivalent to first cousin genomic sharing) compared to healthy controls[18]. Recent studies have found the presence of long runs of homozygosity (ROHs) in Caribbean Hispanic LOAD patients compared to healthy controls[19]. In contrast, two ROH studies of outbred Caucasian populations did not yield any significant associations with LOAD[20,21]. In

current study we estimated the level of inbreeding in the Caribbean Hispanic families that are known to have higher rates of LOAD[22]; and investigated the association between inbreeding and risk of LOAD. Potential association between inbreeding and risk of LOAD may aid next-generation sequencing studies in mapping of disease-related genes.

## Methods

### Study Population

Study participants were identified from two source populations of Caribbean Hispanic ancestry. The two-parent studies include: the Washington Heights-Inwood Columbia Aging Project (WHICAP)[23] and the *Estudio Familiar Influencia Genetica en Alzheimer* (EFIGA) family study[24] . The WHICAP study is a longitudinal cohort study that has examined a multi-ethnic cohort of elderly residing in northern Manhattan, New York. We recruited Medicare recipients who were at least 65 years of age, without dementia, and lived in three contiguous ZIP codes in northern New York City. The EFIGA study is a family-based study comprising Dominican families with multiple persons affected with LOAD and a case-control study that included unrelated patients with LOAD and similarly aged unaffected and unrelated controls. Study participants were recruited from multiple sources including clinics in the Dominican Republic, as well as the Alzheimer's Disease Research Center Memory Disorders Clinic at Columbia University in New York City. To augment family recruitment, we advertised in local newspapers and media in Dominican Republic and New York. In addition, we recruited probands from the WHICAP study when the informant reported family members with dementia. Families were recruited as follows: once probands were identified, structured family history interviews were conducted to determine whether siblings and more distant relatives were affected with dementia. When probands had AD and also had other family members with dementia, we interviewed and neurologically evaluated all siblings and more relatives. We assessed and corrected for cryptic relatedness by using genetic markers. The Caribbean Hispanic case-control study complements the EFIGA study in that the sampling frame was the same as the EFIGA study; however, recruitment was restricted to affected and unaffected persons who were unrelated and did not have family history of dementia. For these participants, we performed the same extensive medical, neurological, and neuropsychological evaluations at each visit. Clinical diagnoses were made in a consensus diagnostic conference by a panel of neurologists, neuropsychologists and psychiatrists. The presence of LOAD was assessed based on NINCDSADRDA criteria[25]. Additional demographic and epidemiological information was available for all genotyped individuals. For estimating inbreeding in Caribbean Hispanics in this study, we selected age-matched unrelated cases and controls from the WHICAP and the EFIGA studies and one case per family from the EFIGA study.

### Genotyping

Previously, a HumanOmni-650Y SNP chip was used for genome wide association study (GWAS) of 1,094 Caribbean Hispanics[26]. This study consisted primarily of samples from whole blood with 0.16% samples from saliva. Blood samples were extracted using the Qiagen method and saliva samples were extracted using the Oragene method. Samples were genotyped in batches corresponding to 96-well plates. Each plate contained one or two

HapMap controls, as well as an average of two study sample duplicates. The DNA samples were genotyped at the Center for Inherited Disease Research (CIDR) using the Illumina HumanOmni1-Quad Quad v1 0 H array (http://www.illumina.org) and using the calling algorithms GenomeStudio version 2011.1, Genotyping Module 1.9.4 and GenTrain version 1.0. The genome build is 37/hg19. We combined the previously published GWAS data with the samples genotyped on Illumina HumanOmni1-Quad chip to create a large dataset for estimating the degree of inbreeding in the Caribbean Hispanic population.

### GWAS Quality Control

We used the QA/QC described by Laurie et al[27] to ensure consistency of the data. We excluded from the analyses the samples missing 2% of the SNPs from the GWAS panel and SNPs with genotype missingness rate of 5% or SNPs with minor allele frequency <0.05.

### Statistical Analyses

: We pruned the genome-wide SNP data based on linkage disequilibrium (LD) to retain 177,997 tagging SNPs from GWAS data at pairwise $r^2<0.3$ using PLINK[28]. We estimated the inbreeding coefficient in the sample set using the GCTA software [29]. GCTA gives two estimates for the relationship between haplotypes within an individual: one based on the variance of additive genetic values (diagonal of the SNP-derived GRM) and the other based on SNP homozygosity (implemented in PLINK)[28]. Here we report the second measure of inbreeding (the two metrics on average gave similar results). In the context of inferring relatedness in GWAS with population structure, relatedness-estimation methods that assume population homogeneity can give extremely biased estimates. We used the Relatedness Estimation in Admixed Populations (REAP) software[30] to estimate the average inbreeding in the Caribbean Hispanic population by adjusting for their admixed ancestry. REAP takes as input the proportion of parental populations for each sample and estimates autosomal kinship coefficients and identity-by-descent (IBD) sharing probabilities using SNP genotype data in samples with admixed ancestry. We estimated proportion of ancestry from each parental population using ADMIXTURE software[31] by assuming that the admixture in the Caribbean Hispanics is conferred by 2, 3, 4 and 5 parent populations. . This software provided a maximum likelihood estimation of individual ancestries from multi-locus SNP genotype datasets. We then used the estimates of parental population proportions and allele frequencies for each sample as input to the REAP software to compute admixture adjusted inbreeding coefficients.

## Results

The average inbreeding coefficient in the Caribbean Hispanics without accounting for admixture (computed using GCTA software) was 0.018 (±0.048) suggesting significant inbreeding. 1372 (40.4%) out of the 3392 subjects had an inbreeding coefficient greater than 0.02 (Supplementary Figure 1). We computed the inbreeding coefficient accounting for admixture conferred to Caribbean Hispanics from 2, 3, 4 and 5 parent populations (Supplementary Figure 2). Traditional methods assume homogeneity of population which can significantly inflate inbreeding estimates. By using REAP, we adjust for sub-population frequencies at sites to calculated admixture-adjusted inbreeding coefficients. It can be

argued that Caribbean Hispanics are derived from Caucasians, Africans, Asians and American Indian ancestries and exact number of parental populations is unknown. Hence we used 3 to 5 ancestral populations as input to adjust for admixture in the Caribbean Hispanics (Supplementary Table 1). Adjusting for admixture the average inbreeding coefficient decreased ranging from 0.0034 (±0.019) for 3 parent populations to 0.002 (±0.018) for 5 parent populations. 329 out 3392 samples (9.7%) were highly inbred with an inbreeding coefficient F>0.02 assuming admixture from 3 parent populations. Supplementary Figure 3 shows the admixture in the Caribbean Hispanics originating from Caucasian, African and Asian ancestry. We used the admixture-adjusted inbreeding coefficient values for samples obtained from REAP software in subsequent analyses. 47.4% of the samples in the dataset have a predominantly Caucasian ancestry (Supplementary Figure 3). The mean inbreeding coefficient was highest among those of Caucasian ancestry (F=0.0066; equivalent to second cousin once removed mating), followed by those with African ancestry (F=0.0014) (Table 2). Supplementary Figure 4 shows the overall distribution of the inbreeding coefficients in the samples by computed ancestry. Samples with African ancestry were less inbred than individuals having a significant proportion of the other two ancestries. Among those of Caucasian ancestry 14% had a high inbreeding coefficient of >0.02 compared to 4.8% for individuals of Asian and 4.8% individuals of African ancestry.

We then tested the association of the inbreeding with age LOAD status and age at onset of the disease using logistic and linear regression models wherever suitable (Table 3). For each sample we used the proportion ancestry from Asian and African parent population (Caucasian ancestry was the reference value) as covariates. Age was weakly inversely correlated with the inbreeding coefficient but not statistically significant.

Inbreeding was a significant predictor of LOAD adjusted for age and sex and population covariates (p=0.034) (Table 3). The presence or absence of the *APOE ε4* allele when used as a covariate in the model strengthens the association of inbreeding coefficient with LOAD (p=0.03). This could possibly imply that of the level of inbreeding is correlated with APOE ε4 status and the residual effect of inbreeding level on LOAD risk after adjusting for APOE genotype could be attributable to other recessive loci. To test the relationship of APOE with inbreeding and its association with AD, we regressed inbreeding coefficient on APOE ε4 status on cases and controls separately. Inbreeding is associated with number of ε4 alleles in unaffected subjects (Supplementary Table 2) but not in affected subjects. Also the direction of effect was in the opposite direction in cases vs controls. Alternatively, extent of inbreeding tended to increase the ε4 copies in cases but decrease ε4 in controls. This prompted us to test an interaction model between APOE and inbreeding with LOAD status. We found significant association between the interaction term of inbreeding and APOE with LOAD status (p=4.04e-03).

Higher inbreeding was associated with an increased risk of LOAD, which is consistent with findings in other complex diseases including Coronary Heart Disease, Stroke, Cancer, Depression, Asthma, Type-2 diabetes and Gout [32]. Contrary to the study in other complex diseases, inbreeding, doesn't significantly affect the age at onset of the LOAD but tendency for lower age at onset was observed with increased inbreeding in the dataset (Table 3 and 4).

## DISCUSSION

Our findings of the extent of inbreeding in Caribbean Hispanics were consistent with previous reports in this population[19]. Accounting for admixture we show that the true extent of inbreeding is less than second cousin mating but greater than outbred populations where consanguineous marriages occur at a low frequency. Range of inbreeding rates in Canada (Roman Catholics) is 0.00004-0.00007, in the US (Roman Catholics) it is 0-0.0008, in Latin America it is 0-0.003, in southern Europe 0.001-0.002, and in Japan approximately 0.005[33]. Compared to the Samaritans (F=0.04), a 3000 year old genetic-isolate population comprising of only 500 people, the observed inbreeding in Caribbean Hispanics is at an intermediate level[34]. Despite the higher risk that inbreeding might confer in complex late onset traits[7,8], it has not been well studied in LOAD. In this study we demonstrate a statistically significant association of the extent of inbreeding on conferring AD risk. This is consistent with the hypothesis that a significant proportion of risk in complex diseases such as LOAD could be mediated through multiple causal recessive loci resulting from increased homozygosity in inbred subjects. This is also consistent with our earlier finding of larger and higher number of runs of homozygosity (ROH) in LOAD patients (n=559) vs. controls (n=554)[19] from the same population. In the Caribbean Hispanic population, the authors detected an association between LOAD and a larger genome-wide mean ROH size ($P = .0039$), which was stronger with familial LOAD ($P = .0005$); while studies of Caucasian datasets have not reported an increased burden of ROH in AD[20,35]. A likely explanation is that the significant inbreeding in the Caribbean Hispanics as detailed in this report increases the likelihood of recessive of alleles in affected subjects resulting in longer and higher number of ROH in the genome. Interestingly, the authors also noted that total ROH size was twice as long in the European Hispanic subset vs. the African Hispanic subset which is corroborated by our observation of a higher inbreeding coefficient in the Caucasian subset of the data (Table 2). The higher inbreeding in the Caucasians is likely to render larger regions in the genome homozygous compared to the African subset of this population.

The high degree of inbreeding and presence of long stretches of ROH combined with higher frequency of AD in the Caribbean Hispanic population compared to Caucasians[36] suggests that there may be one or more recessive loci mediating AD risk in this population. Low-frequency mutations are hypothesized to confer greater risk for disease than common variants by collectively accounting for substantial fractions of a common disease heritability[37]. Inbred populations with few founders such as the Caribbean Hispanics share large chromosomal segments recurring among relatives and otherwise rare alleles can be observed repeatedly in multiple individuals. This reduces false positive findings due to sequencing errors that can be difficult to identify in isolated cases from outbred populations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Demographic Information

| Characteristics | Caribbean Hispanic (n = 3392) |
|---|---|
| Age, year, mean (SD) | 75.75 (9.41) |
| Education, year, mean (SD) | 6.4 (4.99) |
| Women, % | 68% |
| Cases (%) | 1532 (45.4) |

**Table 2**

Inbreeding Coefficient by ancestry of the samples. Samples are classified as Asian, Caucasian or African if they showed >60% admixture from the parent population (the differences between unaffecteds and affecteds were not statistically significant in any of the three ethnic groups).

| | N | Unaffected | Affected | Mean Inbreeding Coefficient in all samples | Mean Inbreeding Coefficient in unaffecteds | Mean Inbreeding Coefficient in affecteds |
|---|---|---|---|---|---|---|
| ASIAN | 41 | 30 | 11 | −0.0134 | −0.0146 | −0.0100 |
| BLACK | 356 | 153 | 202 | 0.0014 | 0.0018 | 0.0011 |
| CAU | 1520 | 672 | 847 | 0.0066 | 0.0062 | 0.0069 |
| MIXED | 1375 | 623 | 745 | 0.0005 | 0.0001 | 0.0007 |

**Table 3**

Association of Inbreeding with age

| TEST | BETA | SE | Z | P |
|---|---|---|---|---|
| AGE (in unaffecteds greater than 60 years) ~ F | −24.17 | 12.86 | −1.88 | 6.05E-02 |
| AGE AT ONSET (in cases) ~ F | −15.13 | 9.43 | −1.6 | 1.09E-01 |
| AGE AT ONSET ~ F + SEX + APOE (0,1,2) | −12.28 | 9.24 | −1.33 | 1.84E-01 |

Effects of Inbreeding on age in unaffected subjects and age at onset in affected LOAD cases were tested using a linear regression model

**Table 4**

Association of Inbreeding with LOAD status

| TEST | BETA | SE | Z | P |
|---|---|---|---|---|
| LOAD ~ F | 3.88 | 2 | 1.95 | 5.17E-02 |
| LOAD ~ F + AGE + SEX | 4.25 | 2.01 | 2.11 | 3.44E-02 |
| LOAD ~ F + AGE + SEX + *APOE* (0,1,2) | 4.39 | 2.02 | 2.17 | 3.02E-02 |

Effects of Inbreeding on LOAD were tested using a logistic regression framework.

All tests in table 3A and 3B are adjusted for covariates measuring proportion of ancestral population (Caucasians, Asians, Africans). Proportion of Caucasian ancestry was used as the base and two variables were used for to specify proportion of Asian and African ancestry.

F= Inbreeding Coefficient in Tables 3 and 4