ORIGINAL CONTRIBUTION

Genome-Wide Analysis of the Parkinsonism-Dementia Complex of Guam

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Background: Parkinsonism-dementia complex (PDC) is a neurofibrillary tangle degeneration involving the deposition of Alzheimer-type tau, predominantly in the medial temporal cortex, brainstem, and basal ganglia. It occurs in focal geographic isolates, including Guam and the Kii peninsula of Japan. The familial clustering of the disease has suggested that a genetic factor could be important in its etiology.

Objective: To determine whether a genetic locus could be identified, linked, or associated with PDC.

Design and Patients: We performed a genome-wide association study of 22 Guamanian PDC and 19 control subjects using 834 microsatellite markers with an approximate genome-wide marker density of 4.4 centimorgans.

Results: Two-point association analysis identified 17 markers ($P < .015$). Each of these markers then underwent conventional linkage analysis in 5 families with PDC. One marker, D20S103, generated a logarithm of odds score of greater than 1.5. Multipoint association analysis also highlighted 2 other areas on chromosome 14q (adjacent to D14S592, 59.2 megabases [M]) and chromosome 20 (adjacent to D20S470, 17.4 M) with multipoint association logarithm of the odds scores of greater than 2. The areas around D20S103, D14S592, and D20S470 were further analyzed by association using additional microsatellite markers and by conventional linkage analysis. This did not provide further evidence for the role of these areas in PDC.

Conclusions: This study has not identified a single gene locus for PDC, confirming the impression of a geographic disease isolate with a complex genetic, a genetic/environmental etiology, or a purely environmental etiology.

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After World War II, US military physicians assigned to Guam and National Institutes of Health (NIH) scientists recognized that familial amyotrophic lateral sclerosis (ALS) and atypical parkinsonism with dementia (parkinsonism-dementia complex [PDC]) were common among Chamorro living on Guam. These diseases had been present on Guam for more than a century and were known as lytico, for paralysis, and bodig, for parkinsonism. It was hoped that finding the cause of these diseases would help to explain the causes of neurodegenerative diseases in the rest of the world. During the past 50 years, cycad neurotoxicity, infectious agents, and calcium deficiency have been investigated as possible causes for PDC but not been proved to be relevant.

In recent years, the etiology of familial Alzheimer disease, Parkinson disease, and frontotemporal dementia (FTD) has been clarified by the identification of genetic mutations in affected autosomal dominant families. These genetic advances and the continuing familial occurrence of PDC on Guam led to the consideration of a genetic approach to this disease. A number of observations suggest that PDC may have a genetic etiology. The disease clusters in some Guamanian Chamorro families but spares others. The disease has different prevalences in different villages. The adjacent villages of Umatac and Merizo in southern Guam have similar environments and their residents have identical lifestyles, yet from 1956 to 1965, the prevalence of PDC in Umatac was 274 per 100,000 population and only 42 per 100,000 population in Merizo. Traditionally, the populations of these villages did not intermarry. The disease may occur in Chamorro migrants many years after they have left Guam. The disease often occurs in successive generations and affects first-degree relatives. One
Chamorro family in Umatac, southern Guam, is recorded to have experienced the disease in every generation since the late 1700s. Furthermore, a recent 40-year follow-up of a National Institutes of Health case-control cohort shows that having an affected first-degree relative remains a risk factor for development of PDC. Parkinsonism-dementia complex occurs in Guamanian Chamorros, but it does not seem to have affected the other ethnic groups who have immigrated to Guam since World War II. Thus, among the many hundreds of pathologically verified cases of this disease in Chamorros during the past 50 years, there is only 1 clinicopathologic report of possible PDC in a Filipino migrant. In recent decades, the prevalence of PDC has steadily declined and the age at onset has increased.

This may support an exposure to a causal environmental factor with a cohort effect. Alternatively, this may reflect increased social mobility and marrying out, thereby allowing a decline in the co-occurrence of recessive genetic factors, and/or a decrease in concurrence between a genetic predisposition and environmental cofactors. A previous report from our group has excluded the most likely candidate gene for PDC, tau, by means of direct sequencing and microsatellite marker association. In the present study, we have used linkage disequilibrium to search for a PDC locus.

Population-based disequilibrium studies involve mapping a disease locus by association at adjacent polymorphic genetic markers. They depend on a single gene mutation arising on a founder chromosome, accounting for a given disease in the population under study. This approach has been used successfully in genetically isolated populations, because they are more likely to have a single disease/single gene and mutation relationship (genetic and allelic homogeneity). They are also more likely to have a sufficiently large shared chromosomal segment around any given marker and around a single disease gene mutation, depending on the age of the population and time of introduction of the mutation. An isolated population is defined as a population that is derived from a limited number of founder members and has expanded through growth rather than immigration. The Chamorro population of Guam originated from a small number of immigrants from the Indo-Malay peninsula. By the time of Magellan’s arrival in Guam in 1521, the population was 100,000. However, with Spanish colonization in the late 17th century, the native population was severely reduced to just 1608 by the early 1700s. The survivors, mostly women and children, were relocated to Catholic parishes on Guam, the largest and southernmost island in the Mariana archipelago. Subsequently, the remaining Chamorro population mixed with Filipinos, Mexican, and Spanish immigrants who acted as administrators for the government of Guam and European sailors who visited the island during Pacific explorations. This new population numbered 10,000 when Guam was ceded to the United States by Spain in 1899, and 30,000 at the time of World War II and Japanese occupation of the island in 1941. Since World War II, the Chamorro population has rapidly increased to 120,000, and a large and continuing migration of Filipino, white, Asian, and other ethnic groups to Guam has resulted in an immigrant population that now numbers 80,000. Contemporary Chamorros are descended from a genetic "bottleneck" occurring 300 years (approximately 13 generations) ago, although a substantial part of the subsequent population growth relates to immigration. Genetic analysis of this disease assumes that a common founder introduced a pathogenic mutation at an ancestrally distant point. The founder’s affected descendants would share the pathogenic mutation and an adjacent chromosomal region. Genotyping of cases and control subjects to determine shared alleles among cases should identify the area in which the pathogenic mutation lies. The strength of the association depends on the background frequency of the disease-associated allele in the control population and decays with increasing distance from the disease mutation, owing to meiotic recombination. The background allele frequencies are unknown a priori and may depend on whether the mutation has arisen on an indigenous chromosome or has been introduced by an immigrant to the population.

The evidence suggesting a genetic cause for PDC and the population structure of the affected Guamanian Chamorro population led us to further investigate a genetic cause for PDC using an association analysis method. The overlap between PDC and ALS is debated, but ALS has declined in prevalence on Guam much more rapidly than PDC, such that there is only a handful of cases on the island at present, and ALS does not have a significantly greater prevalence of disease on Guam than elsewhere. Because of this, we decided to study PDC in isolation. We identified 22 apparently unrelated PDC cases and 19 unrelated, neurologically asymptomatic controls for the case-control study and selected 5 families for confirmatory linkage studies. Cases, controls, and family members underwent evaluation and selection by clinical neurologists (J.C.S., H.R.M., K.G.-H., and A.J.L.), and autopsy confirmation of PDC was subsequently obtained in 3 cases.

CASE ASCERTAINMENT

All 22 cases were Chamorros with neurodegenerative symptoms beginning at ages that ranged from 54 to 74 years (detailed demographic and clinical material on the 22 cases is available from the authors on request). Eleven presented with dementia, and of these parkinsonism subsequently developed in 10. Ten presented with parkinsonism, and of these dementia subsequently developed in 6. In the remaining case, dementia (with paranoia) and parkinsonism occurred simultaneously. The parkinsonism usually had atypical features for Parkinson disease (ie, unresponsive to levodopa and involving rigidity without rest tremor). In 10 of the 22 cases, features of supranuclear gaze palsy, pseudobulbar palsy, and prominent axial rigidity were also seen. In the late stages of PDC, most cases had profound dementia and severe, disabling parkinsonism. Only 2 of the 22 patients had features suggesting motor neuron disease such as amyotrophy and limb spasticity. Eleven cases were from Umatac, a village at the epicenter of the disease, and 11 were residents of other Guam villages largely in the south of the island (which is 29 miles long and 4-10 miles wide). All had a family history of PDC or ALS, and in 20 cases a first-degree family member was affected. Thirteen of the 22...
had pathological confirmation of PDC in themselves (n=3) or in a family member (n=10). Fifteen cases died during the time from recruitment into the study to July 31, 1999. Genealogical research after patient recruitment indicated that most of the 22 PDC case-control subjects were more closely related and could be formed into 3 kindreds (ie, 6 cases had a common great-grandfather; 2 cases, a grandparent; 3 cases, a great-grandparent; and 2 cases, a grandfather). Nineteen control subjects were selected (age range, 65-88 years; 13 women) and, after clinical assessment by one of us (J.C.S.), were established to have no motor or cognitive features suggestive of PDC. They were the spouses of patients with PDC or healthy unrelated controls. Their average age at the time of sample was 76 years, compared with a recently estimated average age of onset for PDC of 68 years.25

GENOTYPING
Peripheral blood leukocytes from cases and controls were immortalized to provide a robust DNA source. Using purified DNA extracted from these cell lines, 834 fluorescent microsatellite markers were genotyped from the standard Perkin-Elmer versions 1 and 2 linkage mapping sets (Applied Biosystems, Foster City, Calif) and from the Research Genetics (Huntsville, Ala) MapPairs version 8 set. Perkin-Elmer, Inc (Wellesley, Mass) and Research Genetics microsatellite markers were amplified according to the manufacturers' instructions and analyzed using the ABI 377 DNA sequencer. We analyzed one third (276/ 834) of the markers using a DNA pooling technique in the first-pass genome-wide screen. To ensure that pooling was giving reliable results, we retested several markers in pooled and individual samples. In addition, we reanalyzed potentially associated pooled markers using individual genotypes before further analysis in the familial section of the study. Individual analysis always confirmed the analysis of the pooled samples.

ALLELIC ASSOCIATION STUDY
Eight hundred thirty-four microsatellite markers were analyzed and compared in the case-control study. The average marker spacing was 4.4 centimorgans (cM). The allele frequencies in cases and controls were compared in a first-pass genome-wide search using a 2-point (diseq) and multipoint (dismult) association analysis package.36 This analysis package uses a likelihood method and facilitates the use of multiallelic microsatellite markers in association studies, avoiding the loss of power that occurs in conventional χ² testing with sparsely populated tables (ie, a large number of degrees of freedom with some very infrequently occurring genotypes). Overall, the genome-wide significance level for a positive association is set at P<.0001 (equivalent to a logarithm of the odds [LOD] score of >3), and for a positively associated marker, λ indicates the strength of the association. Within the disequilibrium analysis, the disease allele frequency was set at 0.001, and for the multipoint association analysis, the intermarker distances were taken form the Marshfield Medical Genetics Web site (available at: http://www.marshfieldclinic.org/research/genetics/Map_Markers/maps/IndexMapFrames.html; all Web sites listed in “Methods” accessed October 1, 2004).

FAMILY ASCERTAINMENT
Five separate Chamorro families with PDC were identified, and DNA was collected from 19 individuals. Some of these individuals overlap with those used in the association study (Figure 1). The largest family was from Umatac. This family was traced back 4 generations to a single ancestor, born around 1840. We have traced 153 direct descendants, 37 of whom were affected by neurodegenerative disease (ALS and/or PDC). Generation II contained 8 members born during the time from 1865 to 1884. One may have had PDC and 2 may have had ALS, as indicated by death certificate diagnoses of “senility,” “muscle wasting,” and “paralysis,” respectively. Subsequent generations deriving from individuals II:1 and II:8 have been documented as completely as possible. Other affected members have derived from II:3, II:5, and II:6. Generation III contained 30 individuals, born during the years from 1879 to 1926. Five had ALS and 5 had PDC. Generation IV contained 114 individuals, born during the years from 1912 to 1955. Two had ALS and 22 had PDC. Autopsies in 5 of the 37 neurologically affected members of this family confirmed the findings of PDC.

None of the markers adjacent to known loci for neurodegenerative disease showed any evidence of association with PDC, with the exception of D3S2406 adjacent to the FTD3 locus (Table 1).36 Seventeen markers of the 834 studied reached the level of significance we determined as the threshold for further study (P<.015) in a 2-point analysis using diseq (Table 2). Each of the 17 markers identified in the first-pass 2-point association study was then genotyped in a conventional 2-point linkage analysis study in the 5 families and analyzed using MLINK. None generated a LOD score greater than 3, although marker D20S103 generated a maximum LOD score of 1.82, close to the maximum predicted by simulation (Table 3). Reanalysis of the first-pass association genotype data using a multipointlike approach with dismult revealed 2 areas of interest with a multipoint association LOD score greater than 2 (Figure 2 and Figure 3). One area had already been detected on the 2-point (diseq) analysis on chromosome 14q adjacent to marker D14S592 (59.2 megabases [Mb]), and a new area on chromosome 20 close to marker D20S470 (17.36 Mb) was also identified. These areas were reexamined with an increased marker density for 2-point and multipoint allelic association, and in a conventional family-based linkage analysis (Table 4). In addition to these areas, the telomeric chromosome 20 marker D20S103 (0.5 Mb) was included as a third area of interest because of the LOD score obtained in the 2-point linkage analysis. Addition of further markers for association and linkage around D14S592, D20S470, and D20S103 did not provide further evi-

RESULTS

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COMMENT

Although there have been a number of candidate gene studies of PDC and ALS on Guam, this study is, to our knowledge, the first genome-wide screen for neurodegenerative disease on Guam, which was thought by the earliest investigators to be primarily genetic in etiology. Parkinsonism-dementia complex shows no evidence of association with markers corresponding to known neurodegenerative disease loci, with the exception of the marker adjacent to $FT33$. However, the $FTD3$ locus was not linked to PDC in the family study, and pathological differences between PDC and FTD-3 suggest that these are unlikely to be allelic disorders. Confirming the earlier study from our group, we have not found evidence for an association between PDC and tau.

Figure 1. Five families used for genetic linkage studies. ALS indicates amyotrophic lateral sclerosis; PDC, parkinsonism-dementia complex; circles, females; question mark, diagnosis uncertain; slashes, deceased; squares, males; and diamonds, male or female subjects, disguised to preserve confidentiality.
Recently, another group has reported an association between a microsatellite marker within the tau region and PDC. However, they confirm that most markers in the tau region, including tau intragenic markers, are not associated with PDC. Furthermore, no associated or linked haplotype is related to PDC, and thus, these findings are of uncertain significance. Our study has provided evidence of areas of possible association between PDC and areas on chromosomes 20p, 20q, and 14. However these associations do not reach a level consistent with genomewide significance. In addition, a family-based replication study looking at the areas identified has not confirmed the results obtained in the case-control analysis.

A number of factors may limit the present study. Although the extent and mode of inheritance of the genetic influence on PDC is unknown, a recent follow-up case-control analysis of PDC confirms the previously reported excess risk in first-degree relatives of patients with PDC compared with their spouses. The relationship between PDC and ALS remains unclear. This study confirms the previous findings that some patients with PDC may have a family history of ALS, suggesting that there may be some common genetic or environmental factor/cause. There are also grounds for believing that PDC and ALS may be separate diseases, because the prevalence of ALS has declined much more rapidly than that of PDC. The decline in the prevalence of both PDC and ALS and the co-occurrence of an ocular and probably infective disease (Guam retinal pigmentary epitheliopathy) are compatible with the notion that an environmental factor may be important in the etiology of PDC. A genetic risk factor may be widely distributed in the population of Guam, and in these circumstances an association study may not detect a genetic locus. Also, our sample may have been underpowered in both the association and the family analyses. In fact, the power to detect an association between an allele of a microsatellite marker and PDC is about 59% in the best-case scenario ($\alpha = .015$; frequency of the associated allele, 0.05; assuming a relative risk conferred by the risk allele of 5.0, frequency of the disease of 0.15, and the extent of linkage disequilibrium between the marker and the disease [D'] of 0.9). The family population collected may also be underpowered. The simulations performed show that the LOD score that could be obtained for a linked marker would be around 1.5 for the marker density used in this study (Table 3).

Table 1. Two-Point Association Study and Familial Linkage Analysis for Markers With LRT $P < .015$

<table>
<thead>
<tr>
<th>Locus</th>
<th>Association Analysis</th>
<th>Linkage Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>LRT</td>
<td>$\lambda$</td>
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<tr>
<td>D14S592</td>
<td>11.41</td>
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<tr>
<td>ATAS9H06 (chr9)</td>
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<td>0.25</td>
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<tr>
<td>D23S260</td>
<td>8.20</td>
<td>0.44</td>
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<td>D18S976</td>
<td>7.13</td>
<td>0.33</td>
</tr>
<tr>
<td>D3S2406</td>
<td>6.44</td>
<td>0.25</td>
</tr>
<tr>
<td>D1S468</td>
<td>6.38</td>
<td>0.52</td>
</tr>
<tr>
<td>D16S2624</td>
<td>6.16</td>
<td>0.49</td>
</tr>
<tr>
<td>D12S375</td>
<td>6.15</td>
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<tr>
<td>D3S1271</td>
<td>6.10</td>
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<td>D22S103</td>
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<td>0.52</td>
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<td>D23S191</td>
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<td>D5S2505</td>
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<td>D2S180</td>
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<td>D2S403</td>
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<td>D2S170</td>
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<tr>
<td>D11S908</td>
<td>4.74</td>
<td>0.31</td>
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</table>

Abbreviations: chr9, chromosome 9; likelihood ratio; LOD, logarithm of odds; LRT, likelihood ratio test ($\chi^2$ value); $\theta$, recombination fraction.

*No marker identified in the association study as being possibly associated reached a LOD score level ($>3$) consistent with linkage.

Table 2. Two-Point Association Analyses (dislamb) of PDC and Existing Loci for Neurodegenerative Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Locus</th>
<th>Gene</th>
<th>Ch</th>
<th>STS Map Position on Ch</th>
<th>Marshfield Map Position Locus, cM</th>
<th>Marker Analyzed</th>
<th>Marshfield Map Position Locus, cM</th>
<th>LRT</th>
<th>$P$ Value</th>
<th>$\lambda$</th>
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<tbody>
<tr>
<td>PARK-1</td>
<td>SNCA</td>
<td>4</td>
<td>87</td>
<td>M</td>
<td>99</td>
<td>D4S414</td>
<td>101</td>
<td>0.0</td>
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<tr>
<td>PARK-2</td>
<td>Parkin</td>
<td>6</td>
<td>170</td>
<td>M</td>
<td>179</td>
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<td>PARK-3</td>
<td>2</td>
<td>67</td>
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<td>M</td>
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<td>PARK-5</td>
<td>UCHL1</td>
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<td>42</td>
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<td>PARK-6</td>
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<td>M</td>
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<td>D15S52</td>
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<td>PARK-7</td>
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<td>5.4</td>
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<td>M</td>
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<tr>
<td>APP</td>
<td>APP</td>
<td>21</td>
<td>24</td>
<td>M</td>
<td>21</td>
<td>D21S253</td>
<td>20</td>
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<td>.50</td>
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<tr>
<td>PS-1</td>
<td>PS1</td>
<td>14</td>
<td>67</td>
<td>M</td>
<td>85</td>
<td>D14S53</td>
<td>86</td>
<td>0.0</td>
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<td>0.0</td>
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<tr>
<td>PS-2</td>
<td>PS2</td>
<td>1</td>
<td>234</td>
<td>M</td>
<td>245</td>
<td>D15S2504</td>
<td>252</td>
<td>0.0</td>
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<td>0.0</td>
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<tr>
<td>FTD-3</td>
<td>3</td>
<td>74</td>
<td>103</td>
<td>M</td>
<td>103</td>
<td>D3S305</td>
<td>102</td>
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<td>FTD-9</td>
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<td>M</td>
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<td>D9S22</td>
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<tr>
<td>FTD-17</td>
<td>TAU</td>
<td>17</td>
<td>45</td>
<td>M</td>
<td>65</td>
<td>D17S791</td>
<td>64</td>
<td>0.0</td>
<td>.50</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviations: APP, amyloid precursor protein; Ch, chromosome; cM, centimorgans; FTD, frontotemporal dementia; $\lambda$, relative risk to siblings; LRT, likelihood ratio test ($\chi^2$ value); M, megabases; PARK, Parkinson disease locus; PS, presenilin; STS, sequence-tagged site; UCHL1, gene for ubiquitin C terminal hydrolase 1.
defined in the association study may still be relevant to the etiology of PDC. In this study, the LOD obtained with marker D20S103 was 1.82. Simulation analysis suggests that the probability of an unlinked marker reaching a LOD of this level would be less than 0.1%. Despite the lack of linkage or association with markers adjacent to D20S103, this may still emerge as an important area in the pathogenesis of PDC.

Another limitation of this study may arise from the marker density used and the size of the shared chromosomal segment in PDC cases. The power of genome-wide association studies is difficult to predict, because it depends on unknown factors such as the number of generations since the mutation arose or was introduced into the population and the background frequency of associated alleles in the normal population. Because of the severe reduction of the Chamorro population by 1720, we assume that the mutation has propagated in the population for approximately 13 generations. Under a free-mating scheme, the average genetic separation between the most distant relations who share a single ancestor from 1730 is approximately 26 meioses. This indicates an average shared chromosomal region of around 4 cM (at this distance recombination events occurring 4 times in every 100 meioses), which falls within the density used in the genome screen. The genealogical studies illustrate that cases studied in the genome screen are more closely related than 22 meioses, introducing the possibility that false-positive regions may exist because of kinship, although it is unlikely that this would prevent the detection of truly associated areas.

Identifying the cause of this disorder is complicated by the virtual disappearance of ALS from Guam and the delayed onset and decline of the PDC syndrome. An ill-defined entity termed Marianas dementia occurs on Guam, but unlike PDC and ALS, this entity is not

Table 3. Simulation of Family Linkage Analysis of Guam Families With PDC

<table>
<thead>
<tr>
<th>Summed LOD Probability</th>
<th>Mean Maximum LOD Score</th>
<th>Summed 1 2 3 4 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9 0.6 0.2 0.1 0.1</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>1.6 0.3 0.2 0.1 0.1</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>1.2 0.3 0.2 0.1 0.1</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>1.0 0.3 0.2 0.1 0.1</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td></td>
</tr>
<tr>
<td>0.8 0.3 0.2 0.1 0.1</td>
<td>0.0 0.0 0.0 0.0 0.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LOD, logarithm of odds; ρ, recombination fraction.

*Indicates disease penetrance of 0.4 by 75 years of age in autosomal dominant linked marker LOD score analysis.

Figure 2. First-pass genome-wide multipoint association study of parkinsonism-dementia complex for chromosomes 1 through 12. cM indicates centimorgans; χ², likelihood ratio; LOD, logarithm of odds; triangles, χ² association; and straight line, LOD score.
Figure 3. First-pass genome-wide multipoint association study of parkinsonism-dementia complex for chromosomes 13 through 22 and X. cM indicates centimorgans; λ, likelihood ratio; and LOD, logarithm of odds.

Table 4. Detailed Analysis of Areas of Interest Identified in the Study

<table>
<thead>
<tr>
<th>Markers</th>
<th>Mb</th>
<th>2-Point Linkage Maximum LOD Score</th>
<th>Multipoint Linkage SIMWALK2* Location Score, log10 U</th>
<th>2-Point Association LRT, χ²</th>
<th>P Value</th>
<th>λ</th>
<th>Multipoint Association, LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>D14S274</td>
<td>55.4</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D14S601</td>
<td>57.2</td>
<td>−0.074</td>
<td>−13.75</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
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<tr>
<td>D14S1038</td>
<td>57.3</td>
<td>1</td>
<td>−13.70</td>
<td>ND</td>
<td>ND</td>
<td>ND ND</td>
<td></td>
</tr>
<tr>
<td>D14S994</td>
<td>58.5</td>
<td>−0.085</td>
<td>−13.80</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D14S592</td>
<td>59.2</td>
<td>0.4</td>
<td>−13.92</td>
<td>11.4</td>
<td>.0004</td>
<td>0.4966 2.48</td>
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<tr>
<td>D14S589</td>
<td>61.6</td>
<td>−0.001</td>
<td>−13.95</td>
<td>1.25</td>
<td>.13</td>
<td>0.252 2.27</td>
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<tr>
<td>D14S1012</td>
<td>61.3</td>
<td>−0.056</td>
<td>−14.4</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
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<tr>
<td>D20S1155</td>
<td>0.071</td>
<td>−0.018</td>
<td>−13.91</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
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<tr>
<td>D20S103</td>
<td>0.547</td>
<td>1.82</td>
<td>−13.91</td>
<td>5.9</td>
<td>.008</td>
<td>0.52 0.005</td>
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<tr>
<td>D20S117</td>
<td>0.643</td>
<td>−0.11</td>
<td>−13.98</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0.006</td>
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<tr>
<td>D20S113</td>
<td>2.023</td>
<td>−0.021</td>
<td>−13.53</td>
<td>3.3</td>
<td>.04</td>
<td>0.44 0.002</td>
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<tr>
<td>D20S193</td>
<td>3.301</td>
<td>−0.12</td>
<td>−11.27</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0.003</td>
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<tr>
<td>D20S875</td>
<td>16.64</td>
<td>0.66</td>
<td>−4.28</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
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<tr>
<td>D20S48</td>
<td>17.3</td>
<td>0.12</td>
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<td>0</td>
<td>0.007</td>
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<tr>
<td>D20S470</td>
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<td>0.48</td>
<td>−9.91</td>
<td>4.6</td>
<td>.02</td>
<td>0.32 0.395</td>
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<tr>
<td>D20S475</td>
<td>18.11</td>
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<td>−7.21</td>
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<td>0</td>
<td>0</td>
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<td>D20S40</td>
<td>19.22</td>
<td>0.64</td>
<td>−6.60</td>
<td>0</td>
<td>.50</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: λ, relative risk to siblings; LOD, logarithm of odds; LRT, likelihood ratio test (χ² value); Mb, megabases; ND, analysis not done.

particularly common in the south of the island in Uma-
tac, and so its relationship to ALS and to PDC is even
more obscure than their relation to each other. The
number of remaining cases of PDC on Guam is esti-
mated to be around 100. Although this study could be
extended to a larger living affected population at this
stage, it is likely to be more rewarding to define the
relationship of Marianas dementia to PDC. If this dis-
ease’s pathologic characteristic is a neurofibrillary
tangle only, similar to that seen in PDC, then this
observation would identify a much larger pool of
affected subjects for genetic studies. The shifts in preva-
ience provide compelling evidence of an environmental
role, but they do not explain the strong familial rela-
tionships. We failed to find evidence of a single genetic
locus, which seems very unlikely given the data pre-
sented in the current study. It does not rule out more
complex genetic or genetic-environmental causes. How-
ever, further studies are needed that may require analy-
sis of archival material and identification of additional
cases of PDC or within a broader phenotypic group.
The classic diseases lyticó and bodig have essentially dis-
appeared.

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Critical revision of the manuscript for important intellec-
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