

## Historical Migration revealed through a Case of Autosomal Dominant Alzheimer's Disease

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**With the increasing geopolitical instability and environmental devastation occurring across the globe, human migration is increasing. We report a case that illustrates a migration pattern seen a century ago that is currently in the process of repeating itself. Using information from a neuropathological examination, genetic analyses, and historical sources, we linked a patient with autosomal dominant Alzheimer's disease in Hawai'i with her ancestors in Puerto Rico. In this patient we identified the G206A PSEN1 mutation, previously identified as being linked to a founder effect from Puerto Rico.**

**At the turn of the twentieth century, due to devastating hurricanes in Puerto Rico and the island's new status as a possession of the United States, over 5,000 Puerto Ricans, including the grandparents of our patient, migrated to Hawai'i. This short-term but historic migration has resulted in a significant population of Puerto Ricans in Hawai'i, today. As physicians we sometimes have the opportunity and privilege, through the patients who come to us for help, to be indirect witnesses to such historical events and movements. These occurrences can inform the present and also portend future developments in this rapidly changing world. [P R Health Sci J 2019;38:144-147]**

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Humanity's family tree is a complex lattice with branches that divide and re-connect, even after millennia (1). Modern genetics has increasingly made available knowledge of one's ancestry and propensity to develop a given genetic condition. People migrate and reproduce under the influence of a myriad cultural, economic, environmental, and political factors that historians strive to understand and document. As a result of migration to, from, and within the western hemisphere, Latinos are a genetically diverse population (2). Occasionally neurologists have the opportunity and privilege to witness, albeit second hand, historical migrations through the patients we serve. In this report we document a case of autosomal dominant Alzheimer's disease (ADAD) in a person living in Hawai'i bearing a mutation known to have resulted as a founder effect, or descent from a common ancestor, who is from Puerto Rico. The presence of this mutation coupled with our knowledge of her family history connects the patient with the historical migration that occurred in the early 1900s and, by extension, to the island of Puerto Rico.

### Methods

As the proband was deceased, her adult son signed a written consent and provided the following information regarding her case.

### Case Report

In the early 1990s, at age 48, a female nurse living in Honolulu, Hawai'i, began having difficulty operating computers and became uncharacteristically argumentative. By age 51, she was misplacing things, had become apathetic, and was obsessively collecting. She took leave from work at age 54 and began seeing a psychiatrist for stress and depression. At age 60, she had an automobile accident and was assessed by a neurologist for the first time. She had a Mini-Mental Status Examination score of 29/30 but was nonetheless thought to have suffered significant cognitive decline. At age 61 she retired permanently. At age 62 she was unable to cook or bathe herself and by age 63 had

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further difficulties with wandering and not recognizing family members or herself in a mirror. By age 64 she was unable to walk and required help with feeding and 24-hour assistance. She was admitted to hospice at age 66 and died at age 69.

A neuropathological examination revealed widespread diffuse and neuritic amyloid plaques by A $\beta$  immunoreactivity. A $\beta$  deposition was also evident in the molecular layer of the cerebellum. Neurofibrillary tangles were prevalent, with a Braak stage of VI. Using the ABC scoring system, the pathology was rated A3, B3, C2/C3, representing a high degree of AD neuropathological change. There was moderate to severe cerebral amyloid angiopathy.

The family history was positive: Her father had a similar illness, with onset occurring around age 49. A brother was also similarly affected, with his symptoms beginning at age 48; he died at age 60. Genetic testing of the index patient revealed a G to C nucleotide substitution at g.44636 in *PSEN1*, that causes a glycine to alanine substitution at codon 206 (G206A). This is a well-characterized pathogenic mutation, found to have originated in Puerto Rico, that causes autosomal dominant Alzheimer's disease (ADAD)(3). The patient's DNA had a CA dinucleotide repeat of 19 and GT repeat of 21 flanking the *PSEN1* gene. This normally variable stretch of DNA was identical between our patient and those previously reported with this mutation (3) and also among 4 other persons of Puerto Rican origin with the G206A mutation and from whom DNA was available. As it was absent in 2 persons from families in which this mutation ran but who had not inherited the mutation, there is strong evidence that it represents a common stretch of DNA, or haplotype, likely to have arisen by descent from a common ancestor as a founder effect.

### The index patient's plantation origins

Considering our patient's reported ethnic origins and shared haplotype with others carrying the G206A *PSEN1* mutation, the question arises as to how this haplotype came to be found in Hawai'i. The index patient's father was born in the Hilo district on the island of Hawai'i in 1914. The year 1900 marked the beginning of a small but influential migration of Puerto Ricans to the Hawaiian archipelago. At that time many Puerto Ricans were enduring dire circumstances in their home region under American rule, following the Spanish-American War of 1898 and subsequent Treaty of Paris. According to Kelvin Santiago-Valles, all levels of Puerto Rican society faced major economic and social problems at the turn of the twentieth century (4). In particular, the Puerto Rican working class faced a combination of starvation, inflation, unemployment, and land dispossession, due in part to the early U.S. economic policies implemented in the region.

To make matters worse, the devastating San Ciriaco hurricane hit the region on August 8, 1899. According to José Fernández-Partagas, writing in 1996, "the violent winds and torrential rains completely destroyed a coffee crop which value was estimated to be over 7 billion dollars, almost all banana crops were blown

down by the wind or washed away by river overflowing" (5). Puerto Rico was struck by another hurricane on August 22; after 28 days of continual rains and flooding, approximately 3,400 people had died and thousands more were left without homes, food, or work. In Adjuntas, starvation was rampant, with more than 200 people dying from it each month in 1900 (4). Some members of the destitute population resorted to thievery and, at times, murder: in Yauco an incident occurred in which an angry mob killed the owner of a coffee estate (4).

Seeing an opportunity, the Hawaiian Sugar Planters' Association (HSPA), an organization of Anglo-American sugar plantation owners whose goal was to act collectively in the industry's interest, hired agents in Puerto Rico to recruit workers to relocate and work on cane cultivation in Hawai'i. Many Puerto Ricans chose this course to escape their difficult circumstances (6, 7). Recruitment offices were established in the cities of San Juan, Ponce, Mayagüez, Arecibo, Adjuntas, and Aguadilla. Individuals as well as whole families, including children and pregnant women, were recruited. The majority of migrants came from the coffee-growing regions in southwestern Puerto Rico that had been particularly devastated after the hurricanes. Because hiring agencies were compensated on a per-recruit basis, the process was haphazard and agents neither provided accurate information regarding the venture nor did substantial vetting of the prospective migrants.

Puerto Rican and Filipino laborers were of particular interest to the HSPA because their home regions were now territories of the U.S., and the anti-immigration legislation of the time did not apply to them. In contrast, Chinese laborers had been banned from U.S. jurisdictions since 1882, Japanese and Korean labor would be banned by 1907, other Asiatic migration would cease by 1917, and most non-Western European labor would be severely restricted from 1924 to 1965.

Starting in November of 1900, 12 groups of persons traveled from San Juan to Honolulu. By most accounts, they were misled with regards to compensation and were underfed (6,8). Having a few persons die during the journey was not uncommon (8), and hunger was so severe that a rebellion by migrants led 1 ship to return to port for provisions (8). Nonetheless, during the period of 1900 to 1901, over 5,000 Puerto Rican men, women, and children ultimately made their way to new homes on the islands of Oahu, Hawai'i, Maui, and Kauai, where the "Big Five" companies were farming sugar.

Because of the difficult nature of sugar-plantation work, a constant need for help, and a lack of interest by native Hawaiians, the HSPA hoped Puerto Ricans and Filipinos would become major laborers in cane cultivation. While Filipinos became the bulk of workers for the HSPA by 1922, relatively few Puerto Ricans came, overall. Because the HSPA had a vested interest in keeping the laborers healthy and contented to perform the necessary work, landowners provided a minimum required salary, housing, and medical care. Many Puerto Rican migrants, however, were accustomed to more flexibility in work back

home, and thus found the labor difficult, their hours excessive, and their lives restricted. Their grievances to plantation owners were largely unaddressed. When news of harsh working conditions and poor treatment reached Puerto Rico, interest in boarding ships bound for Hawai'i ended. Nevertheless, the families that did migrate and settle in Hawai'i from 1900 to 1901 constitute an enduring segment of the population and continue to have a significant impact on the sugar industry and workforce in Hawai'i today.

As had his parents who had immigrated from Puerto Rico, the index patient's father worked in the cane fields of Onomea Sugar Company in Papaikou, just north of Hilo, ultimately becoming a supervisor. Because Puerto Ricans were racially categorized by the U.S. government and the HSPA as white migrants, members of this group could transition more easily from the hard manual labor of daily sugar cultivation work to mid-level management as field bosses. Some Puerto Ricans also trained for more skilled trades, such as blacksmithing (6). Despite efforts to keep the diverse workers separate, the index patient's father married a woman of Filipino origin who was also living on the islands as a U.S. colonial (6). He was thought to have been affected by AD at age 49, though he lived to be 84 years of age.

The paternal grandparents had been born in Yauco, Puerto Rico, and emigrated to Papaikou from Adjuntas in Puerto Rico in 1901. The paternal grandmother was age 6 and the paternal grandfather 16 when they came with their respective families. The paternal grandfather drove a truck for Onomea Sugar Company and died of cardiovascular disease at age 74. The paternal grandmother died from tuberculosis in Hawai'i at age 22. It is not known which of the grandparents carried the allele for ADAD.

### Today

The Jones Act of 1917 established Puerto Rico as a colony and gave all Puerto Ricans, including those living in Hawai'i, U.S. citizenship (9). Despite the relatively small number of Puerto Rican immigrants and their rare direct contact with their ancestral home, the Puerto Rican community is currently growing in Hawai'i (by 47% between 2000 and 2010). Puerto Rican food, ways, and music continue to symbolize important cultural aspects of this community (6,8). According to the 2010 census, there are 44,116 persons living in Hawai'i who describe themselves as being of Puerto Rican origin; they comprise over 3% of the population there (10). Throughout the twentieth century, traditional comfort foods such as pasteles, a dish similar to tamales cooked during the Christmas holidays, and gandules, or pigeon peas, and rice were and often still are, today, cooked. Caribbean-style music and instruments are played, with these last including the güiro, or ridged gourd, and the cuatro, a 10-string guitar. Maintaining traditions became a way for Puerto Rican intra-colonials (colonized people living in a second colonized space) to survive, cope with, and counter the physical, economic, and social harshness of migrant labor life in the Pacific.

### Perspective

The official death count from Hurricane Maria in 2017 in Puerto Rico was 64, although an estimate taking into account mortality from all causes and based on vital registration data calculated an excess of 1,191 to 2,975 deaths after the hurricane (11). According to the Florida Division of Emergency Management, more than 269,000 people arrived in Florida from Puerto Rico after the hurricane, from November to December 2017. The Center for Puerto Rican Studies in New York estimated that Puerto Rico would lose up to 470,335 residents by the end of 2019—about 14% of the population (12). This movement is only one example of the current worldwide refugee crisis, in which the number of persons forcibly displaced from their homes, estimated at 65.6 million, is the highest since World War II. Though this mobility may change migrants' cultural and environmental circumstances, we all carry our genes wherever we journey.

### Resumen

Con el aumento de la inestabilidad geopolítica y la devastación ambiental ocurriendo por todas partes del mundo, la migración humana es cada vez mayor. Reportamos un caso que ilustra una pauta de migración de hace un siglo que actualmente se encuentra en proceso de repetirse. Utilizando información de un examen neuropatológico, análisis genéticos, y fuentes históricas, vinculamos a un paciente con la enfermedad de Alzheimer autosómica dominante en Hawai'i con sus antepasados en Puerto Rico. En este paciente identificamos la mutación G206A en *PSEN1*, previamente identificada como resultado de un efecto fundador de Puerto Rico. Al principio del siglo XX, debido a los devastadores huracanes en Puerto Rico y al nuevo estatus de la región como una posesión de los Estados Unidos, más de 5,000 puertorriqueños, incluyendo los abuelos de nuestro paciente, emigraron a Hawai'i. Esta migración, corta pero histórica, ha resultado en una población significativa de puertorriqueños en Hawai'i hasta el día de hoy. Como médicos, a veces tenemos la oportunidad y el privilegio de ser testigos indirectos de tales eventos y movimientos históricos a través de los pacientes que servimos. Estas ocurrencias pueden informar el presente y también augurar desarrollos futuros en un mundo rápidamente cambiante.

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