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The A431E mutation in *PSEN1* causing Familial Alzheimer's Disease originating in Jalisco State, Mexico: an additional fifteen families

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Abstract Nine families with autosomal dominant Alzheimer's disease (AD), all of whom had the Ala431Glu substitution in the PSEN1 gene and came from Jalisco State in Mexico, have been previously reported. As they shared highly polymorphic flanking dinucleotide marker alleles, this strongly suggests that this mutation arose from a common founder. In the current letter, we expand this observation by describing an additional 15 independent families with the Ala431Glu substitution in the PSEN1 gene and conclude that this mutation is not an uncommon cause of early-onset autosomal dominant AD in persons of Mexican origin.

Keywords Presenilin-1 · Mexican · Founder effect · A431E · Ala431Glu · Alzheimer's disease

We read with interest the article by Yescas et al. [1] reporting nine families from Jalisco State in Mexico with early-onset autosomal dominant Alzheimer's Disease (AD), all of whom harbored the Ala431Glu substitution in the PSEN1 gene. The identity of polymorphic dinucleotide polymorphisms flanking this gene in all mutation carriers that was absent in most non-carriers strongly suggests the descent of these persons from a common founder. In the course of our clinical and research activities in Mexico and the U.S., we have identified an additional 20 patients from 15 families with similar clinical presentations who also carry the Ala431Glu mutation and, therefore, extend the finding of a founder effect.

The 15 families were identified in Guadalajara ($n=2$), Chicago ($n=1$), and Southern California ($n=12$). Fourteen families were of Mexican mestizo descent and nine of these could trace the illness in their family to ancestors from Jalisco State. The remaining proband, originally from Arizona, appeared as, and identified herself as, a non-Hispanic Caucasian. Her sister, however, stated that the side of the family through whom the illness was inherited originated in Mexico though the specific location was

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unknown. None of the 15 families was known to be related to each other nor to any of the families evaluated by Yesca et al. in Mexico. Cognitive [2] and affective [3] changes occurring in the preclinical stage of the illness have previously been reported in at-risk members of a subset of these families and the neuropathologic findings from family N (Table 1) have been presented in abstract form [4].

Using techniques similar to those employed by Yesca et al. [5], 10 of the 20 mutation carriers, 19 related persons “at risk”, and 56 Mexican and Mexican-American controls with no history of dementia were genotyped for the polymorphic dinucleotide repeats (CA and GT) flanking the PSEN1 gene. All the samples that had the Ala431Glu mutation shared the same dinucleotide repeat alleles, (CA)₁₉ and (GT)₁₅. Analyses of the families showed that the Ala431Glu mutation, (CA)₁₉, and (GT)₁₅ always segregated together. None of the seven non-mutation carriers from the families had these alleles and only one of the 56 normal controls had the (CA)₁₉ allele and another had the (GT)₁₅ allele. None of the controls had both (CA)₁₉ and (GT)₁₅ alleles.

The age of disease onset in these families was similar to that reported by Yescas et al. (mean age of 39.5 years with the range in our sample of 33 to 44; see Table 1). All 20 affected persons presented with cognitive changes, particularly involving memory [2]. One patient had significant depression at presentation (case M1) [3], one presented

with predominant personality changes (case F1), and one patient’s early cognitive deficits included a substantial aphasia (case D1). In contrast to only one of nine patients having spastic paraparesis in the report by Yesca et al., nine of our 20 probands had significant spastic paraparesis within 5 years of symptom onset. Of note, all affected persons examined at a moderately advanced stage of the illness demonstrated some degree of pyramidal rigidity in all limbs and, thus, the presence of such spasticity appears to be a matter of degree rather than simply being present or absent. A pathological diagnosis of A.D. was proven on autopsy in members of five of these families [4].

Our independent finding of 15 additional families with autosomal dominant AD associated with the Ala431Glu substitution in PSEN1, all of those in whom the flanking CA and GT repeats were tested having shared alleles, and the fact that nine of these families could trace their roots to Jalisco confirm the findings of Yescas et al. [1] regarding a likely founder effect. Furthermore, we extend their observations by showing a higher prevalence of spastic paraparesis and describe an apparently non-Hispanic Caucasian with this mutation. This mutation is, therefore, not an infrequent cause of early-onset autosomal dominant AD in persons of Mexican descent in the U.S., most likely due to migration patterns.

Table 1 Summary of cases

Family	Case	Age at first symptom	Age at dementia diagnosis	Age at death	Early spastic paraparesis?	Able to trace roots to Jalisco?	Pathologically confirmed diagnosis of AD in family?
A	1	39	43	–	+	Yes	No
B	1	39	42	–	–	Yes	No
B	2	43	44	–	–	Yes	No
B	3	41	42	50	++	Yes	No
C	1	42	44	–	+	Yes	No
D	1	39	40	–	++	No	No
E	1	44	?	–	+	Yes	No
F	1	34	37	–	–	No	Yes
G	1	40	44	–	–	Yes	No
H	1	37	38	–	+	No	Yes
I	1	Early 40 s	N/A	48	–	Yes	Yes
J	1	42	N/A	–	++	Yes	No
K	1	36	44	–	–	Yes	No
L	1	44	46	–	++	Yes	No
M	1	39	46	–	–	No	No
N	1	N/A	35	42	–	N/A	Yes
N	2	N/A	39	48	–	N/A	Yes
N	3	N/A	44	–	+	N/A	Yes
O	1	40	42	44	–	N/A	Yes
O	2	33	37	43	–	N/A	Yes

++ Spastic paraparesis present within 1–2 years of initial symptom, + spastic paraparesis present within 2–5 years of initial symptom, – feature absent or late (>5 years of initial symptom), N/A not available

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