Discovery and validation of dominantly Inherited Alzheimer’s Disease mutations in populations from Latin America.

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Abstract

Background: More than 300 variants in the presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) genes have been reported to cause Dominantly Inherited Alzheimer Disease (DIAD). However, most of these reports come from non-Hispanic whites and the full extent of DIAD remains understudied in Latin American (LatAm) countries. Here we describe five AD affected families from LatAm carrying novel DIAD variants.

Methods: Five novel variants in the presenilin1 (PSEN1) gene were identified in Brazilian (p.Val103_Ser104delinsGly, p.Lys395Ile, p.Pro264Se and p.Ala275Thr) and Mexican families (p.Ile414Thr). To assign the likelihood of pathogenicity among these variants of unknown significance, we report pedigree information, frequency in control populations, in silico predictions, and cell-based models.

Result: The mean age at onset in newly identified families was 43.5 years (range 36-54). The novel variants were absent from gnomAD genome and exome databases. Two PSEN1 variants (p.Val103_Ser104delinsGly and p.Lys395Ile) showed segregation with the disease status; segregation studies were not possible in the other three families. Additionally, PSEN1 p.Val103_Ser104delinsGly, p.Lys395Ile, p.Pro264Se, p.Ala275Thr produced Aβ profiles consistent with known AD pathogenic mutations (i.e. increased extracellular Aβ42/40); thus, we consider them as likely pathogenic. PSEN1 p.Ile414Thr did not alter Aβ in a manner consistent with a known pathogenic mutation; therefore, PSEN1 p.Ile414Thr likely represents an AD risk factor or benign polymorphism.

Conclusion: Our study provides further insights into the genetics of AD in LatAm by identifying novel DIAD pathogenic variants in Brazil and Mexico, two countries with distinct genetic admixtures. Expanding the families eligible to participate in observational and clinical trials of DIAD enhances the generalizability of diagnosis and treatment approaches.