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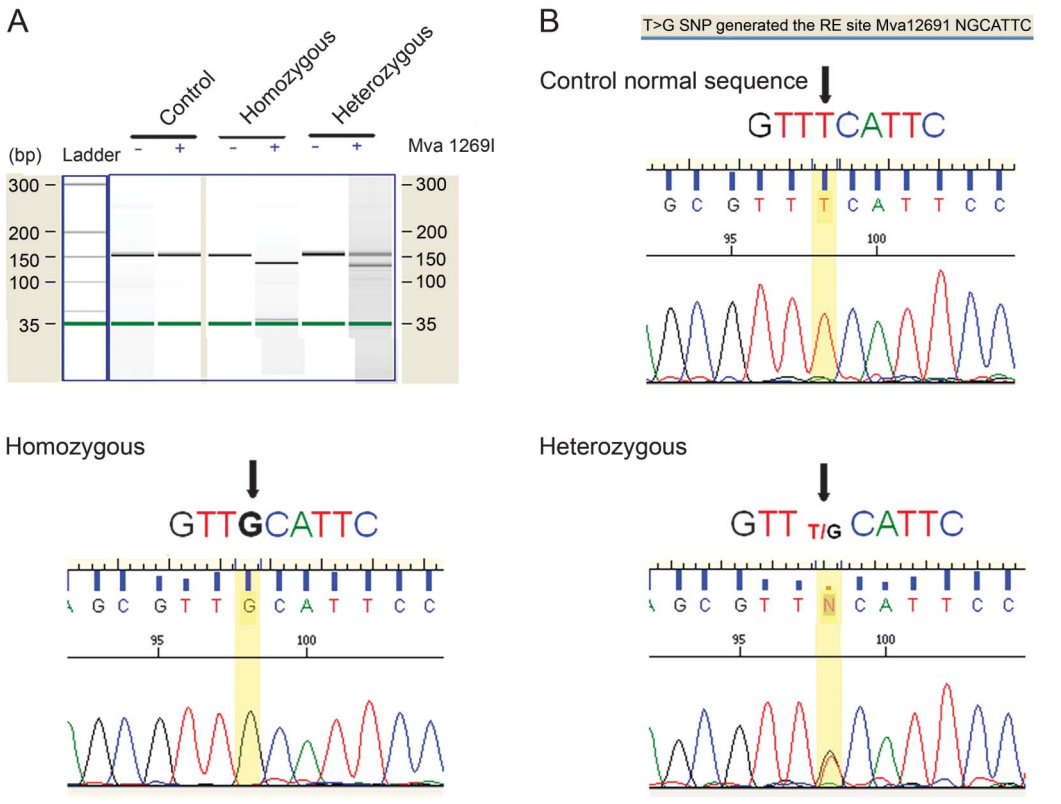
HOMOZYGOSITY OF THE AUTOSOMAL DOMINANT ALZHEIMER DISEASE PRESENILIN 1 *E280A* MUTATION

We identified several families in Antioquia, Colombia, with early-onset Alzheimer disease (AD) due to the mendelian autosomal dominant inheritance of a *PSEN1 E280A* gene mutation. Extended family members were interviewed and parish baptism certificates in Antioquian municipalities examined.[1] The size of these extended families (including carriers and noncarriers) approaches 5,000 individuals. Full genomes in carriers proved a single founder.[2] To support an AD prevention clinical trial, we established a registry in 2010 of all family members over age 8 years.[3] Since then we genotyped 3,407 family members and identified 823 (24%) carriers of the *PSEN1 E280A* mutation. The Comite de Bioetica de la Sede de Investigacion Universitaria, SIU Universidad de Antioquia, approved this study. All participants provided written informed consent. Despite the size of this exceptionally large family and frequent consanguinity, homozygosity at this gene locus had not been reported. The apparent absence of homozygous *PSEN1* mutations led to the speculation that *E280A* homozygosity

Figure **Genotype analysis**



(A) *PSEN1* was amplified using the following primers—forward AACAGCTCAGGAGAGGAATG3, reverse TGAACAGAGTAG—around the mutation site. We used 40 ng of PCR product for restriction digestion with 0.5 units of Mva1269I (Fermentas, Vilnius, Lithuania) for 16 hours at 37°C, and cleaned digestion products using the Qiagen clean up reaction kit. We ran the products on a Bioanalyzer DNA chip (Agilent, Santa Clara, CA). (B) In one patient, we confirmed the mutation by sequencing 20 ng of PCR product (sent to UCLA genotyping and sequencing core). The reported sequences were analyzed using Sequence scanner v1.0 (Applied Biosystems, Foster City, CA).

could be lethal. Generally, homozygous dominant mutations are more severely affected than heterozygotes in both humans and model systems.[4] However, human cases in which dominant point mutations are homozygous are rare.

We identified 6 individuals with homozygous *PSEN1 E280A* gene mutation (g.50024A>C) (figure). In all cases where ascertainable, the parents were mutation carriers. For determination of cognitive status, we utilized the behavior rating scale developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and a composite cognitive test consistent with National Institute on Aging criteria for mild cognitive impairment and dementia.[5] To preserve subject anonymity, we present key data in aggregate form. Two of the 6 subjects (age range, 44–46 years) had dementia for 1 to 7 years before the time of ascertainment (range of dementia onset 37–45 years). The age range of the remaining adults with dementia was 27–38 years; there was one child, aged 11 years, with mild mental retardation. Five of the 6 were female. We adjusted scoring on cognitive status tests for those individuals with minimal or no schooling by setting the cutoff at 1–1.5 SD below the population mean. Education and CERAD cutoffs were based on data for the Antioquia cohort. Most individuals with the homozygous mutation live in rural areas and had little or no schooling.

Discussion. There are no previous reports of individuals with homozygous mutations among familial AD patients. We demonstrate that individuals with the homozygous *PSEN1 E280A* can be viable; however, we have not excluded the possibility that other protective mutations may be present. Nor do these data apply to the viability of individuals with other AD mutations. Some subjects have children with a 100% likelihood of getting the disease. The small sample does not allow statistical conclusions as to whether homozygosity accelerates the age at AD onset. However, the *E280A* kindred at large have a very narrow range for mean age at onset, with very few individuals aged more than 1 SD different at onset.[6] Among 449 mutation carriers with symptoms, the mean age for MCI onset was 45 years and for AD was 50 years. Among the homozygotes, 2 individuals had AD dementia, which presented 5 and 13 years before the mean age at onset for the entire kindred. Data for other individuals were not informative for dementia due to younger age at the time of this study. *PSEN1* mutations affect both epsilon cleavage and subsequent carboxypeptidase-like processing of Aβ, resulting in longer Aβ peptides of 42, 43, or more amino acids and reduced peptide of 40 amino acids in length.[7] Therefore, the composition of the Aβ peptides in these individuals would be of interest. Nevertheless, even with homozygosity, disease onset did not occur until individuals were in their 40s. Notch, Syndecan, and *N*-cadherin are also γ-secretase substrates, and therefore we might expect a phenotype related to these non-APP substrates if homozygosity resulted in complete loss of function. However, the homozygous mutation was not associated with any obvious phenotype related to these substrates. Several individuals in this sample who were unschooled, but did not have dementia, scored at the lower boundary of normal on cognitive assessments. We do not know if this was due to their socioeconomic status or mild baseline cognitive deficits independent of amyloid deposition. The fact that 5 of the 6 patients are female is notable (probability of 5 females out of 6 independent births = 0.09375), but insufficient to draw conclusions regarding increased lethality among males or consequent deviation from Hardy-Weinberg equilibrium. *E280A* homozygotes are viable and the phenotypic consequence of homozygosity may be moderately accelerated age at onset relative to heterozygotes.

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