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Deficiency in mitochondrial aldehyde dehydrogenase increases the risk for late-onset Alzheimer's disease in the Japanese population.

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Mitochondrial aldehyde dehydrogenase 2 (ALDH2) deficiency is caused by a mutant allele in the Mongoloids. To examine whether genetic constitutions affecting aldehyde metabolism influence the risk for late-onset Alzheimer's disease (LOAD), we performed a case-control study in the Japanese population on the deficiency in ALDH2 caused by the dominant-negative mutant allele of the ALDH2 gene (ALDH2*2). In a comparison of 447 patients with sex, age, and region matched nondemented controls, the genotype frequency carrying the ALDH2*2 allele was significantly higher in the patients than in the controls (48.1% vs 37.4%, P = 0.001). Logistic regression analysis indicates that carriage of the ALDH2*2 allele is an independent risk for LOAD of the epsilon4 allele of the apolipoprotein E gene (APOE-epsilon4) (P = 0.002). Moreover, the odds ratio for LOAD in carriers of the ALDH2*2 allele was almost twice that in noncarriers, irrespective of status with regard to the APOE-epsilon4 allele. Among patients homozygous for the APOE-epsilon4 allele, age at onset of LOAD was significantly lower in those with than without the ALDH2*2 allele. In addition, dosage of the ALDH2*2 allele significantly affected age at onset of patients homozygous for the APOE-epsilon4 allele. These results indicate that the ALDH2 deficiency is a risk for LOAD, synergistically acting with the APOE-epsilon4 allele.

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