R54C mutation of NOTCH3 gene in the first Rungus family with CADASIL

Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts andleukoencephalopathy (CADASIL) is a rare hereditary stroke caused by mutations in NOTCH3 gene.We report the first case of CADASIL in an indigenous Rungus(Kadazan-Dusun) family in Kudat, Sabah, Malaysia confirmed by a R54C (c.160C>T,p.Arg54Cys) mutation in the NOTCH3. This mutation was previously reported in a Caucasian and two Korean cases of CADASIL. We recruited two generations of the affected Rungus family (n=9) and found a missense mutation (c.160C>T) in exon 2 of NOTCH3 in three siblings.Two of the three siblings had severe white matter abnormalities in their brain MRI (Scheltensscore33and50respectively),one of whom had a young stroke at the age of 38 .The remaining sibling ,however, did not show any clinical features of CADASIL and had only minimal changes in her brain MRI (Scheltensscore 17).This further emphasized the phenotype variability among family members with the same mutation in CADASIL.This is the first reported family with CADASIL in Rungus subtribe o fKadazan-Dusun ethnicity with a known mutation at exon 2 of NOTCH3.The penetrance of this mutation was not complete during the course of this study