Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a familial autosomal recessive vascular disorder characterized by nonhypertensive cerebral small-vessel disease with early adulthood onset of subcortical infarcts, cognitive impairment, alopecia, and spondylosis. Until recently, this disorder was almost exclusively reported in the Asian population.

Methods—Description of the clinical, imaging, and genetic study of 2 siblings with CARASIL, with a brief comparative review of published non-Asian cases of the disease.

Results—Both patients exhibited the typical phenotype: cerebral small-vessel disease, spondylosis, and abnormal hair lost.

Mutation screening was performed for NOTCH3 and HTRA1 genes. No mutations were found in NOTCH3. The study revealed the presence of a homozygous c.496C>T substitution in HTRA1 in both siblings.

Conclusion—This report highlights the need of considering this entity in the differential diagnosis of cerebral small-vessel disease in young patients, even in the non-Asian populations. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.006735.)

Key Words: CARASIL  ■  HTRA1
The complementary investigation, including extensive study for genetic and acquired thrombophilic disorders, was negative in both patients. The brain magnetic resonance imaging showed diffuse leukoencephalopathy involving periventricular and deep white matter with multiple lacunar infarcts in the deep white and gray matter of both brain hemispheres and brain stem in both siblings (Figures 1A and 2B). Spine magnetic resonance imaging showed multilevel degenerative changes causing moderate to severe stenosis of the cervical canal, more severe in the male patient (Figure 1B and 2C). At the last examination, the female patient presented complaints of hair lost, and some incipient baldness could be seen (Figure 2D).

Both patients have 2 healthy children. There was no history of consanguinity or any psychiatric or neurological illness in the rest of the large family (parents, grandparents, and 8 siblings).

No mutations were found in NOTCH3. The genetic study revealed the presence of a homozygous c.496C>T substitution in HTRA1 (Figure 3A) in both patients. This substitution replaces a highly conserved positively charged arginine by a neutral cysteine (p.R166C; Figure 3B) predicted to be probable damaging by different bioinformatic analysis softwares (PolyPhen-2, SIFT, and MutationTaster). Additionally, this mutation was not present in dbSNP131 or in the 1000 genomes database. The remaining family members, including the parents, refused or were not available to be studied clinically or genetically.

**Discussion and Conclusion**

Because the first report in 1976, there has been an increase in the number of reported cases, although almost exclusively in the Asian population. The first white case was reported in 2010 in a patient of Spanish ancestry. Since then, only 5 cases, including the present 2, have been published.

The characteristics of non-Asian patients are similar to those described in the Asian population (Table in the online-only Data Supplement).

Although being highly suggestive in its full bloom phenotype, the clinical characteristics of CARASIL are not necessary consensaneous or present at the time of the diagnosis. Alopecia, for instance, one of the classical signs of CARASIL, maybe absent in some patients with genetic confirmation, especially females.

The signal changes in the anterior temporal lobes and the involvement of the external capsule, believed to be radiological markers of CADASIL, are frequently present in CARASIL patients. Extensive temporal lobe involvement was present in our male patient but not in the sibling (Table and Figures I and II in the online-only Data Supplement).

Although exceptionally described in association with CARASIL, occurrence of cerebral hemorrhage in other monogenic cerebral small-vessel disease, such as CADASIL, and particularly in type IV collagen α1 (COL4A1)–related diseases, is well recognized. Therefore, inclusion of cerebral hemorrhage in the clinical spectrum of CARASIL seems reasonable.

Until now, 9 different homozygous HTRA1 mutations were identified and 1 compound heterozygous patient has been reported. The p.R166C missense mutation described here for the first time is located in the trypsin-like serine protease domain. The proteolytic activity of this serine protease has been shown to be reduced in the presence of...
p.R274Q, p.A252T, and p.V297M mutations, all located in the same functional domain of this new mutation. Despite the limitation that the remaining family members refused to be studied, we have strong arguments supporting the pathogenicity of this newly described missense mutation: (1) presence in 2 affected family members, (2) consistent bioinformatic analysis prediction of pathogenicity by several softwares, (3) absence of the mutation from normal variant databases, (4) location in the trypsin-like serine protease domain, and, most importantly, (5) a clinical phenotype highly compatible with mutations in HTRA1.

The fact that some of the typical CARASIL characteristics may not be present at the time that patients seek medical counseling, combined with a low level of suspicious in the non-Asian population, precludes or delays the diagnosis. Indeed, the long interval of time before the diagnosis in our patients confirms the notion of the under diagnosis of monogenic causes of stroke. It seems reasonable to test for CARASIL in NOTCH3 negative patients, particularly if spondylosis and baldness coexist in patients with unexplained cerebral small-vessel disease.

In conclusion, this report highlights the need of considering CARASIL in the differential diagnosis of cerebral small-vessel disease in young patients, even in the non-Asian populations.

Disclosures
None.

References