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LETTER TO THE EDITORS

High frequency of exon 10 mutations in the NOTCH3 gene in Italian CADASIL families: phenotypic peculiarities

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Sirs,

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebral small vessel disease due to mutations in the *NOTCH3* gene, characterized by recurrent stroke, cognitive deterioration, and MRI signal abnormalities of subcortical white matter (WM) [4, 8].

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CADASIL-causing mutations involve the EGF-repeats coding region of the *NOTCH3* gene. The majority of pathogenic mutations have been reported within exon 4, 3, and 11 even in Italian pedigrees [6, 8]. Exon 10 mutations have been reported in a few pedigrees, all but one of Italian origin [1, 2, 5, 10, 11].

Here we report clinical and molecular data of 18 patients from 10 unrelated families with exon 10 mutations (Fig. 1). The phenotypic spectrum included a high frequency of psychiatric symptoms (12/18) and peripheral vascular involvement (6/18).

Clinical information of presumably affected relatives were also collected. Family C details have been previously reported by Ragno et al. [13]. No family information was available for three patients.

Mutation analysis of the *NOTCH3* gene was performed according to standard methods (reference sequence of *NOTCH3* mRNA: GenBank accession no. NM_000435). Informed consent was obtained from all participants and the local medical ethical committee approved the study.

Table 1 summarizes the main clinical and genetic findings of our patients.

Exon 10 of the *NOTCH3* gene was rarely reported as a site of mutations in CADASIL patients. Clinical details are substantially lacking, with the exception of the family reported by Ragno et al. 2007, with predominant mood disorder and psychiatric symptoms (family C in Table 1; Fig 1).

Our experience suggests that exon 10 mutations are quite common, at least in Italian patients, with a frequency of 11.1% in our cohort of 90 families. Worth noting is the peculiar clinical phenotype, including the high frequency of psychiatric disturbances and peripheral vascular system involvement.

Psychiatric manifestations are listed in the classical CADASIL phenotype and have been reported in 10–20%