Monogenic models of migraine : from clinical phenotypes to pathophysiological mechanisms

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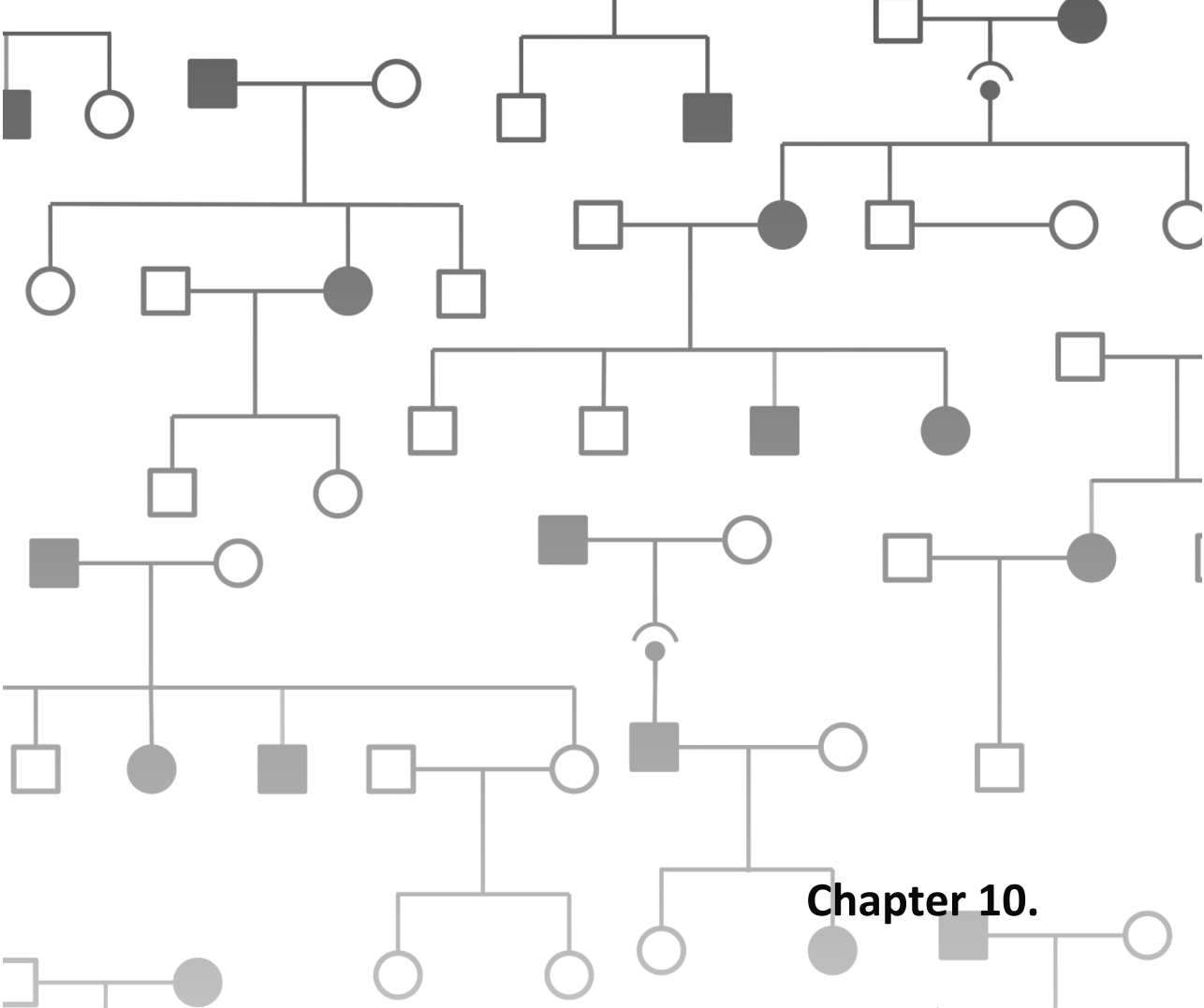

Chapter 10.

Heterozygous *TREX1* mutations in early-onset cerebrovascular disease

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Dear Sirs,

We report on 100 patients suspected of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[1] who were analyzed in our international CADASIL referral center, but in whom no *NOTCH3* mutations were found. *TREX1* was considered an excellent next disease gene candidate because of its link with Aicardi-Goutières syndrome (AGS),[3] the small vessel disease retinal vasculopathy and cerebral leukodystrophy (RVCL),[8] and (neuropsychiatric) systemic lupus erythematosus (SLE).[4–6] Screening of our patient cohort yielded heterozygous *TREX1* mutations in two patients with early-onset cerebrovascular disease. This expands the clinical spectrum of diseases associated with *TREX1* mutations, and offers a differential diagnosis for CADASIL-like phenotypes.

Patient A, a 53-year-old woman with a history of hypertension, hyperlipidemia and alcohol abuse presented with otherwise unexplained presenile dementia. MRI demonstrated basal ganglia and pontine lacunar infarcts and bilateral confluent white matter lesions (Fig. 1a–c). An extensive analysis for causes of dementia and stroke, including serum autoantibodies (ANCA, ANA) was negative. Her severe retinopathy was labeled as hypertensive. Severely demented, she died at the age of 55 of an aspiration pneumonia. Direct sequencing of the *TREX1* gene detected a heterozygous mutation c.1079A>G; p.Tyr360-Cys (p.Tyr305Cys on TREX1 isoform B).

Patient B, a 42-year-old heavily smoking man with a past medical history including a splenic artery aneurysm at age 29, hypertension, hyperlipidemia and vascular claudication presented with progressive cognitive dysfunction. His family history was positive for (cardio)vascular disease. MRI showed a cortico-subcortical infarct in the right frontal lobe, ischemic lesions in the basal ganglia, brainstem and corpus callosum, and focal T2 white matter hyperintensities (Fig. 1d–f). Extensive diagnostic work-up did not reveal other causes for his cognitive decline. CSF showed a mononuclear pleocytosis with normal protein levels, but angiography was not suggestive of a cerebral vasculitis. CSF culture was negative and serum autoantibodies (ANCA, ANA, cardiolipines) were absent. He had a deep venous thrombosis in the leg at age 44. At age 46 and 47 he suffered from new brainstem infarcts. Direct sequencing detected a heterozygous *TREX1* mutation c.506G>A; p.Arg169His (p.Arg114His on TREX1 isoform B).

The two patients described were referred for CADASIL screening because of extensive white matter hyperintensities and infarcts and progressive early-onset (cerebro)vascular disease. No *NOTCH3*

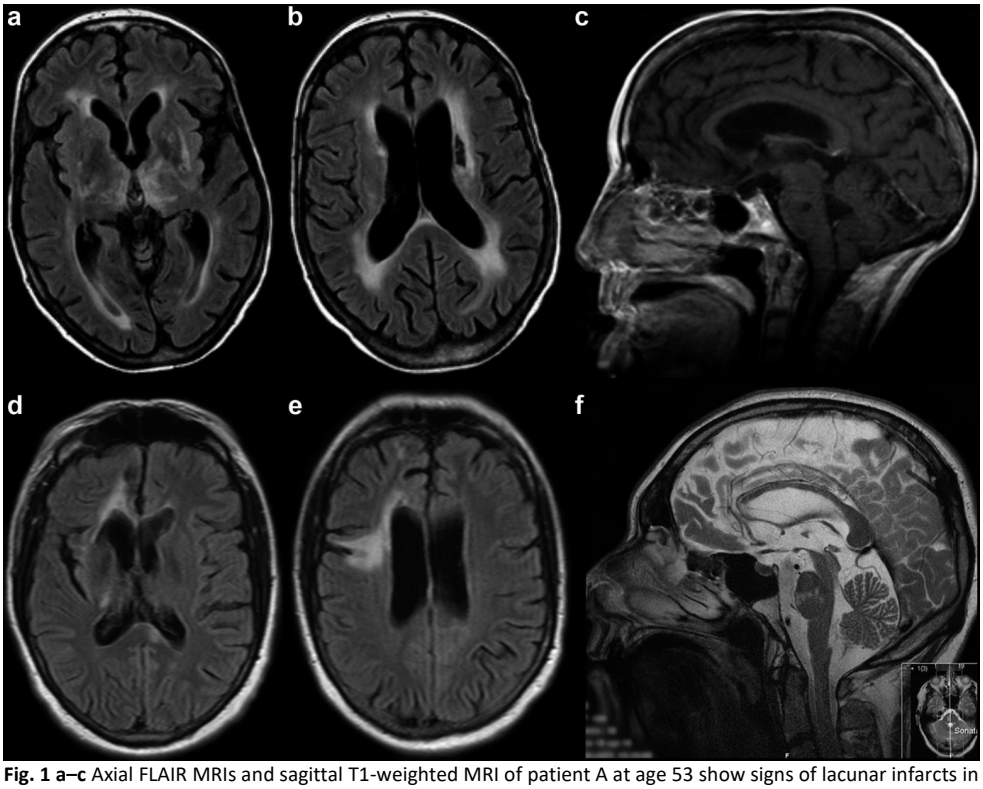

Fig. 1 a–c Axial FLAIR MRIs and sagittal T1-weighted MRI of patient A at age 53 show signs of lacunar infarcts in the basal ganglia, bilateral periventricular white matter lesions, and a pontine infarct; **d–f** Axial FLAIR MRIs and sagittal T2-weighted MRI of patient B at age 47 show right frontal, basal ganglia, brainstem and corpus callosum infarcts.

mutations were found. Screening of the *TREX1* gene revealed heterozygous mutations p.Tyr305Cys and p.Arg114His, which were both previously reported in SLE patients.[5,6] The p.Tyr305Cys mutation affects a highly conserved residue andwas not found in large cohorts of healthy controls.[5,6] The heterozygous p.Arg114His mutation, however, has also been identified in six controls.[5,6] Nonetheless, when homozygous, this mutation is quite common in AGS.[2,5] Mutation p.Arg114His affects a highly conserved residue in the catalytic domain of TREX1 and severely decreases enzymatic activity, suggesting pathogenicity.[5,7] Enzymatic activity was also (mildly) decreased when co-expressed with wildtype TREX1 protein, mimicking the situation in heterozygotes.[7] Mutated TREX1 protein seems to cause accumulation of cytosolic nucleic acids and subsequent abnormal innate immune responses, which may have damaging effects on the circulatory system.[2]

Clinical features and MRI abnormalities in our patients were not suggestive of RVCL or AGS. Absent

autoantibodies made SLE unlikely. Nevertheless, we hypothesise that *TREX1* mutations may have caused these phenotypes with adult onset. Even the phenomena referred to as 'vascular risk factors' may be part of the phenotypic spectrum of *TREX1* mutations.

We suggest that early-onset cerebrovascular disease can be caused by heterozygous *TREX1* mutations. Further elucidation of pathogenetic mechanisms of *TREX1* mutations may reveal new cerebrovascular disease mechanisms.

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Conflicts of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard: This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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