The evolving genetic and pathophysiological spectrum of migraine

Vries, B. de

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TREX1 gene variant in neuropsychiatric systemic lupus erythematosus

B de Vries[1], G M Steup-Beekman[2], J Haan[3,4], E L Bollen[3], J Luyendijk[5], R R Frants[1], G M Terwindt[3], M A van Buchem[5], T W J Huizinga[2], A M J M van den Maagdenberg[1,3] & M D Ferrari[3]

[1]Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[3]Department of Neurology, Leiden University Medical Center, The Netherlands
[4]Department of Neurology, Rijnland Hospital, Leiderdorp, The Netherlands
[5]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a complex genetic background. Some 14–75% of SLE patients report neurological and psychiatric symptoms and are diagnosed with neuropsychiatric-SLE (NPSLE).[1] Many of these patients also have cerebral white matter hyperintensities (WMH). The aetiology and genetic background of NPSLE is largely unknown.

In 2007, mutations in the *TREX1* gene, encoding the major mammalian 3′-5′ DNA exonuclease, were identified in nine out of 417 SLE patients.[2] In addition, *TREX1* has been associated with disorders that are often associated with cerebral WMH, migraine(-like symptoms) and other manifestations of brain disease.[3,4] Consequently, we considered *TREX1* an excellent candidate for NPSLE.

Results

We scanned genomic DNA of 60 NPSLE patients (table 1) for exonic *TREX1* mutations using direct sequencing,[5] and identified a novel heterozygous p.Arg128His mutation in one NPSLE patient. This DNA belonged to a postmenopausal woman who was admitted to our hospital because of lethargy and progressive migraine-like headache for 2 weeks. Previously, she was diagnosed with SLE[6] associated with pleuritis, Coombs positive autoimmune haemolytic anaemia, thrombopenia, and tested positive for antinuclear antibody (ANA) and anti-dsDNA antibodies. SLE manifestations were successfully treated with corticosteroids. Two years before admission, she was treated with prostacyclin infusions, corticosteroids and azathioprine for severe Raynaud's phenomenon with imminent gangrene of the fingers. On admission, she became increasingly confused and obtunded. Neurological examination revealed aphasia and bilateral Babinski signs. General physical examination and cerebrospinal fluid analysis were normal. Laboratory tests for ANA, anti-ENA, anticardiolopin IgM, anti-SSA and anti-SSB were positive. Brain MRI showed generalised atrophy, extensive symmetric cerebral WMH and cerebellar infarcts (figure 1A,B) without evidence for recent ischaemia. She was diagnosed with NPSLE[7] and treated for 3 days with daily doses of 1000 mg intravenous methylprednisolone and recovered after a few days. One year later she developed lupus nephritis class IV as confirmed by kidney biopsy.

Table 1 *Characteristics of neuropsychiatric systemic lupus erythematosus patients (n=60), of which 25 patients had white matter hyperintensities*

	n (%)		n (%)
Female	56 (93)	APS	16 (27)
Age (years)		aCL_IgM*	29 (48)
Mean±SD	37.2±13.4	aCL_IgG*	39 (65)
Median	37.1	LAC†	16 (27)
SLE duration (years)		Active NPSLE	45 (75)
Mean±SD	6.4±5.5	Inactive NPSLE	15 (25)
Median	5.2	Aseptic meningitis	2 (3)
NPSLE duration (years)		Cerebrovascular disease	24 (40)
Mean±SD	1.9±3.8	Headache	15 (25)
Median	0.1	Mononeuropathy	2 (3)
Malar rash	21 (35)	Movement disorder	1 (2)
Discoid rash	26 (43)	Myelopathy	3 (5)
Photosensitivity	18 (30)	Cranial neuropathy	4 (7)
Oral ulcers	12 (20)	Plexopathy	1 (2)
Arthritis	42 (70)	Polyneuropathy	1 (2)
Serositis	33 (55)	Seizures	12 (20)
Renal disorder	28 (47)	Acute confusional state	4 (7)
Haematological disorder	36 (60)	Cognitive dysfunction	19 (32)
Immunological disorder	57 (95)	Mood disorder	4 (7)
ANF	58 (97)	Psychosis	4 (7)

**Data unavailable for one patient, †data unavailable for seven patients. aCL, anticardiolipin; ANF, antinuclear factor; APS, antiphospholipid syndrome; LAC, lupus anticoagulans; NPSLE, neuropsychiatric-SLE; SLE, systemic lupus erythematosus.*

Discussion

We suggest that mutation p.Arg128His is causing NPSLE in the patient for several reasons. The mutation was not found in 400 control chromosomes, nor in 1712 healthy individuals, previously screened by Lee-Kirsch *et al*.[2] Furthermore, the mutation is located within the highly conserved second exonuclease domain (figure 1C). Notably, a crystallisation study of TREX1 by de Silva and colleagues[8] showed that specific hydrogen bonds of Arg^{128} are involved in the destabilisation of double-stranded DNA to provide single-stranded DNA for the enzyme active site. Ultimate proof of pathogenicity should be provided by future functional studies.

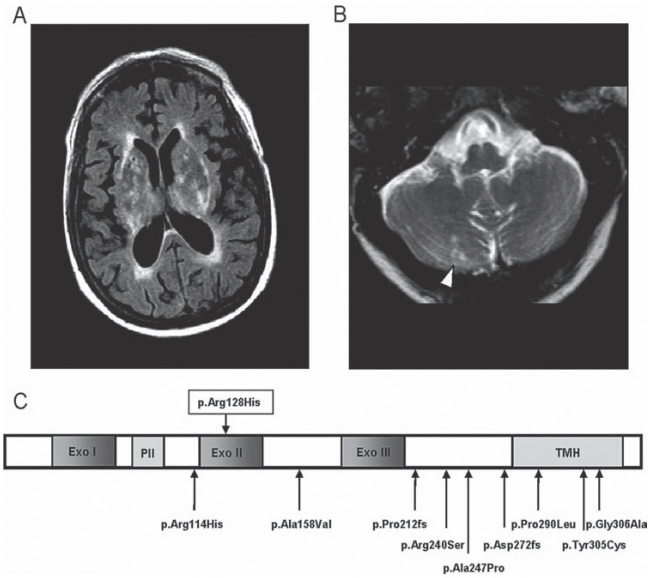

Figure 1 *MRI abnormalities in the p.Arg128His TREX1 mutation carrier with neuropsychiatric systemic lupus erythematosus.* (**A**) *FLAIR image shows symmetric white matter hyperintensities in the capsula interna, capsula externa and periventricular white matter.* (**B**) *T2-weighted image shows three small infarcts in the right cerebellar hemisphere as indicated by the white arrow.* (**C**) *Schematic representation of the TREX1 protein, showing the position of p.Arg128His as well as previously identifi ed SLE mutations. 2 Exo I, II and III represent the exonuclease regions. PII represents the polyproline II motif and TMH the transmembrane helix.*

Here we confirm *TREX1* as a genetic factor in SLE. Moreover, we were able to show involvement of *TREX1* in one out of 60 NPSLE patients, of which 25 had extensive WMH. Clinical characteristics of NPSLE patients with or without WMH were not different, except perhaps for a higher occurrence of cognitive dysfunction in the group with WMH (52 vs 17%) (data not shown). No exonic *TREX1* DNA variants were identified in the other 59 NPSLE patients refl ecting the genetic heterogeneity in NPSLE.

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