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Typing *TREX1* gene in patients with systemic lupus erythematosus

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SUMMARY

An impaired expression of interferon-α regulated genes has been reported in patients with either systemic lupus erythematosus (SLE) or Aicardi-Goutières syndrome (AGS), a rare monogenic encephalopathy with onset in infancy. One of mutations causing AGS is located in the *TREX1* gene on chromosome 3. Heterozygous mutations in *TREX1* were reported in SLE patients. *TREX1* is a DNA exonuclease with specificity for ssDNA. An impairment of its activity may result in the accumulation of nucleid acid. A recent study described a significant association between a haplotype including several common single nucleotide polymorphisms (SNPs) of *TREX1* and neurological manifestations in European SLE patients.

Fifty-one SLE patients were screened for *TREX1* gene, and the corresponding data were collected from clinical charts.

A novel heterozygous variant (p.Asp130Asn) was identified in one patient and in none of 150 controls. A missense variation was located in one of the three active sites of the gene and was classified as probably damaging. Variations of SNP rs11797 were detected in 33 SLE patients and a variation of rs3135944 in one. A significantly higher rate of the minor allele (T nucleotide) of SNP rs11797 was found in SLE patients with neuropsychiatric manifestations [12/16 (75%) *vs* 28/86 (32.5%) O=0.002, odds ratio=6.42 95% confidence interval (1.7-26.2)]. Only 1 out of 8 patients (12.5%) with neuropsychiatric SLE carried the wild-type form in homozygosity.

Although we analyzed a small number of patients, we found a novel variation of *TREX1*, which may be pathogenic. The polymorphism of rs11797 was more frequent in SLE patients with neurological manifestations.

Key words: *TREX1, Novel variation, Neuropsychiatric systemic lupus erythematosus.*

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INTRODUCTION

TREX1 (3' repair exonuclease 1) is the most abundant intracellular 3'-5'exonuclease in mammalian cells (1). It is located on chromosome 3p21.31 and consists of a single exon encoding for a 314-amino acid polypeptide. DNA exonuclease proofreads DNA polymerase and potentially also functions as a DNA-degrading enzyme in granzyme-A-mediated apoptosis (2). Furthermore, *TREX1* is involved in the restriction of endogenous retroviruses. Mutations of this enzyme could impair DNA damage repair, leading to the accumulation of endogenous retroelement-derived DNA (3). A defective clearance of this DNA could induce interferon (IFN) production and an immune-mediated inflammatory response, promoting systemic autoimmunity. In fact, *TREX1*-deficient mice develop an inflammatory myocarditis and die of circulatory failure (4). In humans, mutations of the *TREX1* gene have been identified in patients with Aicardi-Goutierès syndrome (AGS) (5, 6) and also in several autoimmune diseases, namely familial chilblain lupus (7), systemic lupus erythematosus (SLE) (8, 9), Sjögren's syndrome and systemic sclerosis (10). AGS is a rare encephalopathy arising during the first year of life after an uneventful pregnancy (11).

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It is characterized by cerebral atrophy, acquired microcephaly, intracranial calcifications, leucodistrophy, lymphocytosis and raised level of INF-α in the cerebrospinal fluid. AGS is a genetic disease due to mutations in several genes, which are present in 90% of cases (12). Seven of these genes have been identified to date, namely: *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C* (which together encode for the ribonuclease H2 enzyme complex), *SAMHD1*, *ADAR1* and *IFIH1* (coding for MDA5). These mutations include null alleles, frameshift mutations and non-synonymous changes in the catalytic domains and the C-terminal region. In AGS, most *TREX1* mutations are autosomal recessive and diminish the exonuclease activity of enzymes (9). Patients with AGS can have autoimmune-like manifestations, such as lupus-like rash, chilblain lesions, arthritis, oral ulcers, thrombocytopenia, leukocytopenia and positive antinuclear antibodies that are frequently observed (13). For some patients with AGS a formal diagnosis of SLE according to the American College of Rheumatology (ACR) criteria for SLE was possible (14).
In SLE patients, most of the reported mutations of the *TREX1* gene are in heterozygosity and are usually located outside the catalytic domain in the C-terminal region. Previous studies have also analyzed the potential association of *TREX1* mutations and neuropsychiatric SLE (NPSLE). A relatively common risk haplotype of *TREX1* was described in European SLE patients with seizures (9) and a missense variant was identified in a patient with NPSLE (15).
A number of data highlight the relationship between SLE and AGS. As a consequence, we decided to genotype the *TREX1* gene in a cohort of SLE patients and evaluate possible associations between gene mutations and clinical and/or serological features.

MATERIALS AND METHODS

Patients

Fifty-one consecutive SLE patients attending the Rheumatology Unit of Brescia Hospital between 2011 and 2012 were enrolled in this study. The diagnoses were confirmed on the basis of the ACR criteria revised in 1997 (16) and the more recent Systemic Lupus International Collaborating Clinics classification (SLICC) criteria (17). Clinical and serological data were collected from clinical charts. The occurrence of clinical features was considered at any time during the follow-up. Data recorded in clinical charts were collected and classified in a database. Furthermore, we analyzed 150 healthy control subjects. This study was approved by the local Ethics Review Board.

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Mutation analysis

Genomic DNA from patients and controls was extracted from peripheral blood using automatic standard procedures (Maxwell® 16 Blood DNA - Promega, Milan, Italy). *TREX1* coding exon was amplified using primers located in adjacent intronic regions from genomic DNA by polymerase chain reaction (PCR). Primer sequences and PCR conditions are available upon request.
All amplicons were screened by direct sequencing using Big-Dye Terminator v3.1 sequencing kit (Applied Biosystems, Milan, Italy) and ABI 3130 Genetic Analyzer (Applied Biosystems). Each fragment was sequenced on both strands. The alignment to the reference sequence (NG_009820.1 RefSeqGene) was performed using Sequencher 4.8 software.
All the identified sequence variations were confirmed by sequencing forward and reverse independent PCR products. The presence of missense, synonymous and intronic variants was verified on the National Center for Biotechnology Information (NCBI) website and compared to literature data.

Bioinformatics analysis and modelling

Amplicon sequences were compared with the reference sequences in the NCBI database (http://www.ncbi.nlm.nih.gov). The *TREX1* database can also be found under Leiden Open Variation Database. The effect of mutations on the protein structure or function was analyzed with the prediction program PolyPhen (http://genetics.

bwh.harvard.edu/pph/) (18) and Project Hope software (http://www.cmbi.ru.nl/hope) (19).

Statistical analysis

The two-tailed Student's *t*-test for continuous variables and Fisher's exact test or Yates's χ^2 tests for categorical variables were used. $P<0.05$ was considered statistically significant, and correction for multiple testing was carried out using the Bonferroni adjustment when required. The odds ratio and the 95% confidence interval (CI 95%) were calculated.

RESULTS

All patients of the analyzed cohort (51 SLE cases) were females; the patients were unrelated and of Caucasian origin except one Chinese. All the controls were Caucasians.
In our cohort, we detected variants of the *TREX1* gene in 33 out of 51 (64.7%) patients. In particular we reported the presence of two synonymous variants: rs3135944 (NM_033629.4:c.462T>C, NP_338599.1:p.Asp154Asp) and rs11797 (NM_033629.4:c.531C>T, NP_338599.1:p.Tyr177Tyr), plus 1 non synonymous novel variant NM_033629.4:c.588G>A (NP_338599.1:p.Asp130Asn).
The heterozygous missense variant was found in an anti-dsDNA and anti-Ro/SSA positive female SLE patient (1.96%), with an age at disease onset of 25 years, followed in our Unit for 22 years with renal, hematological, thrombotic involvement. The mutation of GAC to AAC determined a substitution of aspartic acid with asparagine in the protein at position 130 (NP_338599.1:p.Asp130Asn). This residue is located in the highly conserved second exonuclease domain (Exo2), one of the three regions which form the catalytic site of the protein. This variation, which was never described before, was not found in any of the 150 Italian healthy subjects.
We used two different software applications to predict the potential functional role of the novel variation. Based on Polyphen scores, this mutation is probably damaging the protein (Hum Var 1/1 and Hum Div 1/1). This *de novo* mutation introduces an asparagine residue, which causes a charge variation.
The wild-type residue is negatively charged, whereas the mutant residue is neutral. Because the negative charge is lost, the interaction with the metal will be less stable, disturbing the domain.
The other two detected variations were synonymous. The rs11797 polymorphism is a common single nucleotide polymorphism (SNP), found in our cohort in 33 out 51 patients (64.7%), with a minor allele frequency of 39.2% in the patients and 39.6% in the controls. We reported both homozygous and heterozygous mutations of this SNP, with similar rates in patients and controls. The other SNP rs3135944 is a rare variant, and in our cohort was found in heterozygosity in one patient also carrying the rs11797 variation.
We then looked for clinical and serological differences among patients with the wild-type *versus* the mutated form of the gene (Tab. I), evaluating the difference in the rate of the minor allele. This analysis was possible only for the rs11797 SNP, due to the low prevalence of the other two mutations in our cohort.
As shown in Table II, we reported a significantly higher rate of the minor allele (T nucleotide) of SNP rs11797 in SLE patients with neuropsychiatric manifestations compared to those without. Moreover, the assessment of the genotype distribution in

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Table I - TREX1 variants observed in our cohort and their genotype frequency among patients and controls.

Nucleotide variation	Amino acid change	SLE HZ wild type	SLE HTZ	SLE HZ mutated	Control HZ wild type	Control HTZ	Control HZ mutated
c.462T>C	pAsp154Asp	50/51 (98%)	1/51 (2%)	0/51 (0%)	150/150 (100%)	0/150 (0%)	0/150 (0%)
c.531C>T	p.Tyr177Tyr	18/51 (35.3%)	26/51 (51%)	7/51 (13.5%)	50/150 (33%)	81/150 (54%)	19/150 (12.6%)
g.6214G>A	p.Asp130Asn	0/51 (0%)	1/51 (2%)	0/51 (0%)	0/150 (0%)	0/150 (0%)	0/150 (0%)

SLE, systemic lupus erythematosus; HZ, homozygous; HTZ, heterozygous.

Table II - Clinical features of our patients. We reported the frequency of the minor allele and the genotype distribution of the rs11797 SNP for each feature.

Manifestation (n. pts)	MAF (T) frequency in patient without the manifestation	MAF (T) frequency in patients with the manifestation	CC genotype frequency in patients with the manifestation	CT genotype frequency in patients with the manifestation	TT genotype frequency in patients with the manifestation	P value* (comparison MAF patient with vs without manifestation)
Artralgia/arthritis (45/51)	5/12 (41.6)	35/90 (38.8)	16/45 (35.5)	23/45 (51.1)	6/45 (13.4)	ns
Malar rash (19/51)	22/64 (34.3)	18/38 (50)	3/19 (15.8)	12/19 (63.1)	4/19 (21.1)	ns
Photosensitivity (18/51)	29/66 (43.9)	11/36 (30.59	7/18 (38.9)	11/18 (61.1)	0/18 (0)	ns
Oral ulcers (17/51)	25/68 (36.7)	15/34 (44.1)	3/17 (17.6)	13/17 (76.4)	1/17 (6)	ns
Chilblain lesions (6/51)	35/90 (8.8)	5/12 (41.7)	1/6 (16.7)	5/6 (83.3)	0/6 (0)	ns
Xerostomia (17/51)	24/68 (35.3)	16/34 (47)	3/17 (17.6)	12/17 (70.6)	2/17 (11.8)	ns
Xeropthalmia (11/51)	29/80 (36.2)	11/22 (50)	2/11 (18.2)	7/11 (63.6)	2/11 (18.2)	ns
Raynaud's phenomenon (15/51)	27/72 (37.5)	13/30 (43.3)	5/15 (33.3)	7/15 (46.7)	3/15 (20)	ns
Fatigue (34/51)	16/34 (47)	24/68 (35.9)	13/34 (38.2)	18/34 (52.9)	3/34 (8.9)	ns
Serositis (17/51)	29/68 (42.6)	11/34 (32.3)	8/17 (47)	7/17 (41.2)	2/17 (11.8)	ns
Glomerulonephritis (18/51)	27/66 (41)	13/36 (36.1)	6/18 (33.3)	11/18 (61.1)	1/18 (5.6)	ns
NPSLE (8/51)	28/86 (32.5)	12/16 (75)	1/8 (12.5)	2/8 (25)	5/8 (62.5)	0.002**
Leukopenia (19/51)	23/64 (35.9)	17/38 (44.7)	5/19 (26.3)	11/19 (57.9)	3/19 (15.8)	ns
Lymphopenia (11/51)	30/90 (33.3)	10/22 (45.4)	2/11 (18.2)	8/11 (72.7)	1/11 (9.1)	ns
Thrombocytopenia (8/51)	32/86 (37.2)	8/16 (50)	1/8 (12.5)	6/8 (75)	1/8 (12.5)	ns
Hemolytic anemia (6/51)	34/90 (37.7)	6/12 (50)	1/6 (16.7)	4/6 (66.6)	1/6 (16.7)	ns
Positive anti-dsDNA positivity (49/51)	3/4 (75)	37/98 (37.7)	18/49 (36.7)	25/49 (51)	6/49 (12.3)	ns
Positive antiphospholipid antibodies (28/51)	14/46 (30.4)	26/56 (46.4)	6/28 (21.4)	17/28 (60.7)	5/28 (17.9)	ns

MAF, minor allele frequency; NPSLE, neuropsychiatric systemic lupus erythematosus. *P value was considered significant if <0.0027 (adjusted with Bonferroni correction); **odds ratio=6.42 95% confidence interval (1.7-26.2).

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the NPSLE patients (8 patients) showed that only one had the homozygotic wild-type form of the rs11797, two were in heterozygosity for the mutated form and the majority of them (5 out of 8) had the SNP mutation in homozygosis.
Cerebrovascular events were the most frequent manifestation among our patients, occurring in 4 of them, followed by seizure disorders in 2 patients, multiplex mononeuropathy and psychosis in 1 patient, and a severe mood and anxiety disorder in 1 patient.

DISCUSSION AND CONCLUSIONS

Recent papers suggest several clinical, genetic and basic science similarities between AGS and SLE. A strong link between these two diseases is related to the role that IFN-α plays in them. In a recent paper (20), the author defined AGS as an interferonopathy due to an error of nucleic acid metabolism, consequently showing a strong similarity with SLE, where IFN-α is known to have a pathogenic role (21). *TREX1* is an exo-

nuclease and its impairment could result in excessive immune activation, triggering in particular the innate immune response and the IFN-α pathway. In this study we analyzed patients affected by SLE and controls mostly belonging to the Italian population. We identified a novel non synonymous mutation, which was not observed in the 150 controls analyzed in this study or in previously published papers. The substitution is located in a highly conserved functional region (one of the three motifs which form the catalytic site) and causes an amino acid change, with asparagine instead of an aspartic acid. Several mutations located in the same region, both missense and synonymous, have been reported in SLE, AGS, and familial chilblain lupus. A missense heterozygous variation pArg128His was described in a patient with neuropsychiatric SLE (15). The authors considered this novel mutation as potentially pathogenic because of its location in the ExoII and also due to the fundamental role of arginine in this position that provides single-strand DNA for the enzyme active site, as it disrupts the double strand.
The substitution found in our patient is considered as damaging by the prediction software. Each amino acid has its own specific size, charge, and hydrophobicity value. The original wild-type residue and the newly introduced mutant residue differ in these properties: the aspartic acid residue was negatively charged, whereas the mutant residue (asparagine) is neutral. The mutation is located in a crucial site for the normal enzyme activity, because it affects one of the four metal ion-binding residues of the *TREX1* gene: Asp-18, Glu-20, Asp-130 and Asp-200 (22). Mutations of the other three amino acids have been identified in patients with dominant familial chilblain lupus and AGS (7, 13, 23-25). An *in vitro* functional analysis has been performed for the pAsp200Asn mutation, revealing a strong decrease (200-fold) in the enzyme activity for the mutation also in heterozygosity. It can be speculated that also our newly described mutation is able to affect the physiological role of the enzyme, and that a defective *TREX1* may result in the impairment of the clearance of ssDNA or dsDNA.
We also confirmed the presence of two synonymous mutations, which were reported by our cohort with a similar rate among patients and controls and showed a frequency similar to that of a large multi-ancestral cohort (9). Synonymous SNPs do not cause an amino acid change, and the role of these mutations in the pathogenesis of diseases is still debated.
AGS and SLE share many similarities, for instance their neurological phenotype. Seizures represent a diagnostic criterion for SLE and are quite often observed in AGS patients. Moreover, neuroimaging findings in SLE patients include white matter lesions, calcifications and cerebral atrophy, which are commonly observed in patients with AGS. In a large multi-ancestral cohort the authors hypothesized that lupus patients with neuropsychiatric manifestations might be enriched for risk alleles in the *TREX1* gene. Indeed, the analysis of common SNPs revealed a relatively common risk haplotype among European lupus

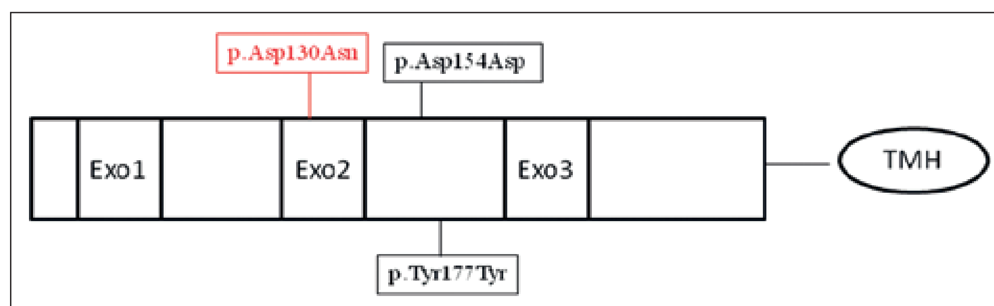

Figure 1 - Scheme of the TREX1 mutations found in this study. Exo1, 2, 3, exonic region; TMH, transmembrane domain.

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patients with seizures (58% in SLE patients with seizures compared with 45% in controls). We were not able to replicate these findings in our study for several reasons: firstly the risk haplotype includes SNPs belonging to the *TREX1* gene, but also the *ATRIP* gene, which is closely linked with the exonuclease that was not analyzed in the present study. Secondly we evaluated a relatively small sample of SLE patients, making it difficult to find all the SNPs of the risk haplotype. We reported, however, an association between the mutated common SNP rs11797, a SNP also included in the previously mentioned haplotype, and neurological manifestations. The risk allele was more frequently found among patients with neurological manifestations of SLE than in SLE patients without these manifestations. Moreover, among the 8 SLE patients with NPSLE, only one had the homozygous wild-type form of rs11797.
In conclusion the present study confirms the presence of *TREX1* mutations in SLE patients (Fig. 1). We reported a potentially pathogenic, novel variation in one of our patients. In our cohort, however, the *de novo* mutation was found in a patient without a history of neuropsychiatric SLE. We also confirmed the possible role of *TREX1* gene mutations in a subset of SLE patients with neurological manifestations. Further studies are required to assess the functional relevance of the detected variant and the potential association with SLE.

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Conflict of interest: the authors declare that there are no conflicts of interest.

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