



# Clinical significance of rare serum autoantibodies in rheumatic diseases: a systematic literature review

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**Abstract:** The identification of serum autoantibodies is central in the diagnosis of systemic autoimmune rheumatic disease (SARD), and an increasing number of specificities have been detected in the past years. This allows an early diagnosis in the active phases of diseases, with the identification of specific disease subsets that may ultimately improve the disease outcomes. Thanks to the use of old and new laboratory techniques that are becoming increasingly available worldwide, the number of rheumatic patients with a specific autoantibody is increasing and this is improving also our knowledge of disease trigger mechanisms. The paradigmatic example is the plethora of serum autoantibodies described in polymyositis and dermatomyositis, coined myositis-specific antibodies (MSA) which include antibodies directed against tRNA synthetases, anti-SRP, anti-Mi-2, and anti-TIF-1 $\gamma$  and can discriminate disease subtypes, particularly when associated with the risk of cancer. As a further example, anti-HMGCR antibodies have been reported in several studies in association with necrotizing autoimmune myositis that may follow statin use. To clarify the current knowledge on these rare specificities, we performed a systematic literature review. We focused on the main features associated to specific autoantibodies that are rarely identified in rheumatic disease, to increase the awareness and scientific knowledge on these autoantibodies in different ethnic groups worldwide.

**Keywords:** Immune tolerance; autoimmunity; systemic lupus erythematosus (SLE); systemic sclerosis (SSc); cancer

Received: 13 August 2018; Accepted: 25 September 2018; Published: 23 October 2018.

doi: [10.21037/jlpm.2018.09.13](https://doi.org/10.21037/jlpm.2018.09.13)

**View this article at:** <http://dx.doi.org/10.21037/jlpm.2018.09.13>

## Introduction

Serum autoantibodies (autoAbs) represent the hallmark of systemic autoimmune rheumatic diseases (SARD) (1), and can be detected years before the development of clinical manifestations and diagnosis (2). Currently, a high number of autoAbs are routinely detected worldwide to assist the clinicians in the diagnosis of SARD and their importance is related to the fact that they correlate with disease phenotype

and severity, independently from their frequency. However, some patients are still defined “seronegative” when no known or specific autoAb is detected (3).

Patients affected by SARD can develop various disease manifestations, which share in most cases serum ANA positivity, and they may be diagnosed as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjögren’s syndrome (SjS), polymyositis and dermatomyositis (PM/DM) and mixed connective tissue disease (MCTD). The

clinical manifestations of SARD may also overlap in some cases (4), and the identification of serum autoAbs is of major importance not only for SARD diagnosis but also for their prognosis, as they may predict internal organ involvement and/or cancer coexistence, as for anti-TIF1 $\gamma/\alpha$  in inflammatory myositis associated with cancer (5). Moreover, anti-dsDNA and anti-Sm antibodies are classic serological markers of SLE, with increased titers of anti-dsDNA associated with a more active and severe disease such as lupus nephritis (6). Anti-topoisomerase I/Scl-70 and anti-RNA polymerase I/III antibodies are both associated with diffuse scleroderma (dcSSc) with increased mortality rates due to interstitial lung disease (ILD) and renal crisis, while anti-centromere antibodies (ACA) are commonly detected in the limited cutaneous form of SSc (lcSSc), which may be related to the onset of pulmonary arterial hypertension (7).

Myositis-specific antibodies (MSA) include autoAbs directed against tRNA synthetases, anti-SRP, anti-Mi-2, and anti-TIF-1 $\gamma$ . Among the anti-tRNA synthetases antibodies, anti-Jo-1 is the most frequently reported and this class of autoAbs is commonly associated with the occurrence of arthritis, myositis, ILD, Raynaud's phenomenon (RP), fever and mechanic's hands (8).

Recently, a novel ANA specificity defined by dense fine speckled (DFS) pattern has been reported but it is now considered the most frequent ANA pattern in healthy individuals, thus it may have a protective role towards the development of SARD (9).

As described, the identification of a specific autoAb is important to define the diagnosis and the prognosis of specific SARDs such as SLE and SSc. However, the diagnosis of SARD might be challenging when clinical manifestations are weak, heterogeneous and uncommon, and in those patients without detectable autoAb, therefore patients do not fulfill classification criteria (10-13). The identification of rare or non-diagnostic serum autoAbs might be challenging as well and in most cases the search for these autoAbs cannot be performed routinely but only by research laboratories in a few centers worldwide. Furthermore, novel rare autoAbs with unknown clinical associations are detected in a small number of patients with CTD, and only few observational studies have addressed these infrequent serological markers and published data that mostly derive from single case reports. Therefore, the diagnostic and prognostic value of these markers, as well as their potential role in monitoring disease activity and predicting specific organ involvement, still remains unknown.

## Systematic literature review for the identification of rare autoAbs in rheumatic diseases

Based on the principles described above, we conducted a systematic literature review to identify the prevalence and clinical significance of rare autoAbs in SARD. The systematic review procedures we adopted are in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). The structured literature research was conducted as of January 20<sup>th</sup> 2017 in the following databases: The Cochrane Library, PubMed/MEDLINE and EMBASE. Search terms included the medical subject headings (MeSH) or Emtree terms for "systemic sclerosis", "systemic lupus erythematosus", "sjögren's syndrome", "dermatomyositis", "polymyositis", "mixed connective tissue disease", "connective tissue disease", "anti-synthetase syndrome", "autoantibodies", "rare", "prevalence", and "clinical significance". Titles and abstracts were screened to determine if they met the inclusion criteria and if they were of potential interest, then two independent reviewers (Bianca Palermo and Elena Generali) selected relevant abstracts. Articles of seminal importance were included in the final analysis.

### Inclusion criteria

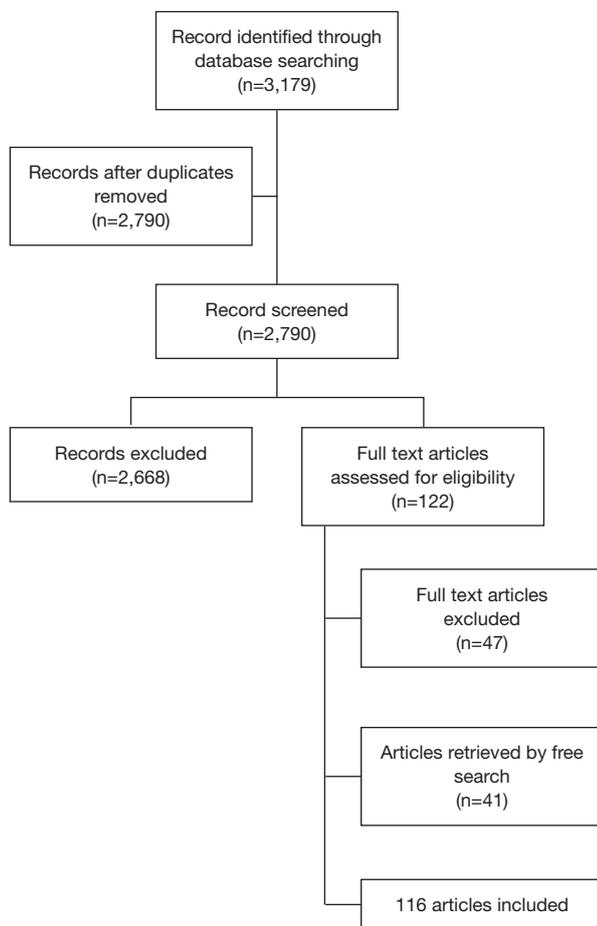
Observational studies, case reports and clinical trials were included.

### Exclusion criteria

Articles not concerning SARD, and reviews or editorials in languages different from English, if including children or animals, were excluded to limit the literature review to adults and because no funding was available for translation. The selection process was performed by two authors, based on titles, abstracts and subsequently full text papers. *Figure 1* represents the flowchart of the selection process of this systematic literature review.

### Data extraction

The year of publication, study design, number of patients and demographic data were recorded. The outcome was defined by the identification of rare autoAbs and their prevalence and clinical significance in SARD. Articles were divided into categories depending on the disease.



**Figure 1** Flowchart of the articles selection process reporting autoAbs in SARD, then described in the present review.

## Results of the systematic literature review

The literature search allowed us to identify articles (n=116) that are described in the Tables below, that show the prevalence and clinical significance of autoAbs in each specific SARD.

### *AutoAbs in SLE*

SLE is a chronic systemic autoimmune disease characterized by the positivity of specific autoAbs, namely anti-dsDNA and anti-Sm, but several other rare autoAbs have been reported in association with SLE as described in *Table 1*. The appearance of the autoAbs in SLE has been demonstrated to start years before the clinical onset of the disease, thus autoAbs in SLE patients have are fundamental for early diagnosis and treatment (2).

Among the rare autoAbs identified in SLE patients, anti-RNP antibodies are frequently detected in SLE patients (15,19,20,22-26,28-30) with a prevalence ranging from 9.5% to 30% (15,19,20,22,24,31). They have been reported in association with neuropsychiatric SLE (NPSLE), and in case reports in association with anti-CASPR2 antibodies (32), shrinking lung syndrome (30) and Crohn's disease (28). Anti-Ku antibodies have been detected in the sera of 18 (11.6%) African American SLE patients, while they were not found in SLE Caucasian patient (25,33). Anti-NKG2A antibodies have been detected in one patient with SLE, in particular in association with vascular involvement and deep venous thrombosis, renal involvement, progressive alveolitis and increased levels of interferon  $\alpha$  (17). Anti-replication protein A antibodies (anti-RPA) have been found in 1.4% of SLE patients (and in 2.5% of SjS patients), with a subset of SLE without other autoAbs commonly found in SLE (27). Very high titers of antibodies to glucose-6-phosphate isomerase (anti-GPI) were reported in one patient with SLE with articular involvement (21). Anti-neuronal antibodies are being evaluated in NPSLE, i.e., anti-VGCK, CASPR2, NMDA-R, LGI1, GAD, AMA-R, GABA<sub>B</sub>-R antibodies; however, Karaaslan *et al.* found that, in a cohort of eighteen SLE patients with epilepsy, only one female patient had anti-GAD, one female patient with hippocampal sclerosis on magnetic resonance imaging was CASPR-2 antibody positive, whereas four female patients showed hippocampal neutrophil staining reflecting antibodies against unknown neuronal cell surface antigens (18). One case of anti-VGKC positive antibodies in a SLE patient followed by acquired neuromyotonia development was reported (29). Another autoAb described in SLE patients is represented by anti-GW182 autoAbs that have been detected in SLE and SjS patients, mostly female, and interestingly, six patients manifested neurological disease (16).

### *AutoAbs in SSc*

Serological markers of SSc are shown in *Table 2*. AutoAbs to nucleolar antigens (ANoA) have been reported to occur in 8–47% of sera from patients with SSc (41,43,52), and they include PM-Scl (57), RNA polymerase I (41), Th/To (43,57,58), and small nucleolar RNP particles, such as U3 RNP/fibrillarin (51,52).

The prevalence of anti-U3 RNP/fibrillarin antibodies ranges between 1.1–18% in SSc patients, who are more likely to be African American male patients with dcSSc and younger age at disease onset (35,36,43,46,47,51-53,

**Table 1** Prevalence and clinical significance of rare serum autoAbs in systemic lupus erythematosus (SLE)

Study	Year	Disease	Study design	Number of cases/controls	Autoantibody	Methods	Main clinical associations
Black (15)	2002	SLE (12.5%) and SCLE (1.3%)	Case-control	24/76	Anti-U1RNP	Review of medical records	More prevalent in SLE than SCLE patients
Eystathioy (16)	2003	SLE, SjS	Cohort	200	Anti-GW182	Laser bead IF	Eighteen subjects, mostly women (17, 94.4%), 4 with SLE and 5 with SjS; 6 patients had neurological disease
Hagberg (17)	2013	SLE	Case-control	SLE [94]; SjS [60]; HC [30]	Anti-NKG2A	Flow cytometry	Vasculitis, skin rashes, renal involvement, and progressive alveolitis in 1 patient with increased levels of IFN- $\alpha$ ; anti-Sm and anti-RNP were also present
Karaaslan (18)	2017	NPSLE	Case-control	SLE [18]; HC [50]	Anti-neuronal antibodies (VGKC, CASPR2, NMDA-R, LGI1, GAD, AMA-R, GABAB-R)	ELISA and RIA	SLE patients with epilepsy, hippocampal neuronal staining (4/18)
Lee (19)	2002	SLE	Cohort	175	Anti-RNP	N/A	Lupus enteritis
Lin (20)	2012	Late-onset SLE ( $\geq$ 50 years)	Cohort	158	Anti-U1RNP; Anti-RibP	IIF (Hep-2), Crithidia luciliae	Hematological (61.4%), renal (57.0%) and articular (53.2%) involvement most common, CNS affection was rare (3.2%)
Matsumoto (21)	2003	SARD	Case-control	578 (RA 291, PsA 20, JRA 4, SpA 46, UA, 80, arthralgia 16, viral arthritis 3, SLE 38, SjS 20, sarcoidosis 20, CD 40); 136 HC	Anti-glucose-6-phosphate isomerase (anti-GPI)	ELISA with recombinant and native GPI, IB	Very high titers were found in 1 SLE, 1 seronegative RA, and 1 RA with severe extraarticular manifestations
Patsinakidis (22)	2016	SLE, SCLE, CLE	Cohort	402 (CLE 296, SLE with CLE 58, SLE w/o CLE 48)	Anti-U1RNP; Anti-histone; Anti-Jo-1	IIF, ELISA	Presence of anti-U1RNP as positive predictor for CLE in SLE patients (38.6% vs. 16.7% in SLE without CLE patients)
Su (23)	2014	SLE with LN	Cohort	559	Anti-RNP Anti-Jo-1	N/A	Numbness and functional gastrointestinal problems were the most common symptoms. Only anti-Ro/SSA was independently associated with peripheral neuropathy in SLE-LN patients
Van Venrooij (24)	1990	SLE	Cohort	118	Anti-U1snRNA	CIE, RNA-IP, IB	SLE or SLE overlap syndromes
Wang (25)	2001	SLE	Cohort	African American [155]; Caucasian [126]	Anti-Ku; Anti-nRNP	IP	Anti-Ku were detected in sera from 18/155 African American patients with SLE (12%) vs. 0/126 Caucasian patients. Anti-nRNP (63% vs. 16%) and anti-Sm (23% vs. 7%) were also more common in African American patients

Table 1 (continued)

Table 1 (continued)

Study	Year	Disease	Study design	Number of cases/ controls	Autoantibody	Methods	Main clinical associations
Xi (26)	2016	SjS, SLE, RA, UCTD, DM	Cohort	180	Anti-MSA; Anti-RNP	IIF and IB	The most frequent clinical symptoms in anti-MSA (+) patients were arthralgia (35.7%) and sicca (28.5%)
Yamasaki (27)	2006	SLE, PM/DM, SjS, SSc, RA	Cohort	1,119 (276 SLE, 43 PM/DM, 47 SSc, 40 SjS, 35 RA)	Anti-RPA	IP, ELISA, IIF, WB	Anti-RPA-positive patients may form a unique group of SLE patients (interstitial lung disease, autoimmune thyroiditis/hepatitis C virus/pernicious anemia) without other autoantibodies commonly found in SLE

DM, dermatomyositis; ELISA, enzyme linked immunosorbent assay; IB, immunoblotting; IIF, indirect immunofluorescence; IP, immunoprecipitation; LN, lupus nephritis; MSA, mitotic spindle apparatus; N/A, not available; NPSLE, neuropsychiatric lupus; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; RIA, radioimmunoassay; RPA, replication protein A; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease; WB, western blot.

56,59,60). In contrast, Tormey *et al.* found a high proportion of Caucasian patients with lcSSc and anti-U3 RNP/fibrillarin positivity (61). In additional reports, anti-U3 RNP/fibrillarin antibodies are associated with higher prevalence of hypo/hyper- skin pigmentation (51,53), calcinosis (51), digital pitting scars and/or ulcers (51,53), digital amputation (62), myositis (47,51,60,61), PAH (51,53,61), pulmonary fibrosis (35,46,52,61), diarrhea and gastric antral vascular ectasia (GAVE) (59,62), cardiac and renal involvement (35,59,61). Arnett *et al.* found a significant association between anti-U3 RNP/fibrillarin and the HLA class II haplotype DRB1\*1302, DQB1\*0604; in addition, one or more HLA-DQB1 alleles \*0604, \*0301, \*0602, and/or \*0302 were detected in all anti-U3 RNP/fibrillarin positive patients who joined the study (35). Furthermore, anti-U3 RNP/fibrillarin may be more frequently related to the rare occurrence of SSc/ANCA-associated vasculitis (AAV) than the other scleroderma-specific antibodies. Glomerulonephritis, renal arteritis, and pulmonary fibrosis occur more frequently than expected in SSc/AAV overlap (38), and a case of nodular scleroderma with positive anti-U3RNP/fibrillarin antibodies has been reported (63,64).

Anti-RNA polymerase (RNAPol) antibodies are directed towards the antigens called RNA polymerase I-III, and anti-RNAPolIII antibodies are the most relevant as they have been recently included in the SSc classification criteria (65). Their identification has been possible in the past thanks to a time and labor consuming technique called

“immunoprecipitation” until the late 90's when a specific RNAP ELISA was developed and validated as described by Chang *et al.* (33). This allowed the large scale and rapid identification of anti-RNAPol antibodies in a clinical diagnostic laboratory setting to identify SSc patients who are at risk for developing SSc with these autoAbs (66,67). Anti-RNAPol antibodies are found in 1.1% to 15% of SSc patients (33,36,37,40,41,45,47,49,52,54,68) and anti-RNA polymerase I/III positive patients are more likely to develop dcSSc with pulmonary involvement, joint and tendon involvement, myositis, and a significantly increased risk of scleroderma renal crisis (33,37,40,45,47,49,50,52,62). However, patients with anti-RNA polymerase III antibodies have lower risk of gastrointestinal (GI) manifestations and esophageal dysmotility compared to patients with anti-topo I/Sc170 (40,62), as well as a lower incidence of pulmonary disease (40). A subset of anti-RNA polymerase III positive patients may have an atypical clinical presentation with the onset of scleroderma prior to Raynaud's phenomenon (36). In 2010, Shah *et al.* (69) first reported a possible association of anti-RNA polymerase I/III with the development of malignancy that occurred concomitantly to SSc onset in a small number of US patients. Subsequently, the higher frequency of synchronous cancer cases in SSc patients with anti-RNA polymerase III antibodies has been validated in independent SSc patients of European, Australian and Japanese populations (34,48,50,54).

Autoantibodies to U1RNP are commonly detected in scleroderma overlap syndromes, with frequency ranging

**Table 2** Prevalence and clinical significance of rare serum autoAbs in systemic sclerosis (SSc)

Study	Year	Disease	Study design	Number of cases/ controls	Autoantibody	Methods	Main results
Airo' (34)	2011	SSc	Cohort	466	Anti-RNAP III	ELISA, IIF, CIE	Malignancies more frequent in the anti-RNAP III group (7/16) than in the anti-topo I (11/101) and ACA groups (21/243)
Arnett (35)	1996	SSc	Cohort	335	Anti-U3 RNP/ fibrillarin	IIF, IB, IP	More frequent in male African American SSc patients with cardiac, renal, gut involvement and pulmonary fibrosis
Ceribelli (36)	2011	SSc/disease controls (SLE,PM/DM) and HC	Case-control	SSc [119]; SLE [434]; PM/DM [85]	Anti-RNAP III	IP (K562), ELISA	Rapidly progressive diffuse SSc prior to Raynaud's phenomenon in 5/16 (31%) anti-RNAP III (+) patients
Chang (33)	1998	dcSSc, lcSSc, SLE, MCTD, HC	Case-control	dcSSc [36]; lcSSc [53]; SLE [42]; MCTD [49]; HC [125]	Anti-RNAP I/II/III	IP (HeLA), ELISA	Diffuse SSc with highly prevalent esophageal (62%) and pulmonary involvement (75%) and myositis (62%)
Codullo (37)	2009	SSc	Cohort	46	Anti-RNAP I/III	ELISA	All developed scleroderma renal crisis, and anti-RNAP II had dcSSc with pulmonary involvement in 3/7 (43%)
Derrett-Smith (38)	2013	SSc	Cohort	2,200	Anti-U3RNP/fibrillarin	N/A	Overlap SSc/ANCA-associated vasculitis
Hudson (39)	2016	SSc	Case-control	306	Anti-HMGCR	ALBIA, ELISA	Significantly lower levels of CPK, higher frequency of heart involvement, no history of statin use
Jaeger (40)	2016	SSc	Cohort	695	Anti-RNAP III	N/A	Lower risk of lung disease and gastrointestinal manifestations, 4.6 times higher incidence of renal crisis (95% CI: 1.6–12.4) than anti-topo I
Kipnis (41)	1990	SSc	Cohort	112	Anti-U1RNP, RNAP I, U3RNP/fibrillarin, PM-Scl, Th/To RNP, Ku, NOR90	IP	Nine sera had multiple specificities
Krzyszczak (42)	2011	SSc	Cohort	105 (75 Caucasian, 24 African-American, 6 others)	Anti-topo I; Anti-RNAPIII; Anti-U3RNP/fibrillarin; Anti-Th/To; Anti-PM-Scl; Anti-U1RNP	IIF, IP	Rare coexistence of more than one SSc-related autoantibody except for anti-U1RNP and topo I
Kuwana (43)	1994	SSc	Cohort	275 Japanese	Anti-topo I; ACA; Anti-U1 RNP; Anti-RNAP I/II/III; Anti-U3RNP/fibrillarin; Anti-PM-Scl; Anti-Ku	IIF, DID, IP	Anti-U1RNP significantly higher in Japanese than in Caucasian patients

Table 2 (continued)

Table 2 (continued)

Study	Year	Disease	Study design	Number of cases/controls	Autoantibody	Methods	Main results
Lega (44)	2010	PM/DM, UCTD, ISSc, amyopathic DM, amyopathic DM/SjS/SSc overlap	Cohort	9 anti-PM-Scl, 12 anti-ARS (7 anti-Jo1, 3 anti-PL7, 1 anti-EJ, 1 double-positive for anti-EJ and anti-OJ), 1 anti-PM-Scl and anti-ARS	Anti-PM-Scl; Anti-ARS	ELISA, IP	Prevalence of respiratory symptoms, pulmonary function test results and HRCT patterns did not significantly differ
Maes (45)	2010	SSc, PM/DM, SLE, SjS, RA, MCTD, chronic fatigue syndrome and HC	Prevalence case-control	242 (70 SSc, 13 PM, 23 DM, 66 SLE, 35 SjS, 24 RA, 11 MCTD). 36 controls (9 HC, 27 chronic fatigue syndrome)	Anti-PM-Scl 100; Anti-RNAPIII	ELISA, IIF, dot blot	At high levels, anti-PM-Scl100 were exclusively found in SSc (4.3%), DM (4.3%) and PM (6.1%)
McNearney (46)	2007	SSc	Cohort	203 (104 Whites, 39 African Americans, 60 Hispanics)	Anti-U3RNP/fibrillarin; Anti-RNP	IIF, ID, IP	Factors independently associated with early pulmonary involvement included African American ethnicity, skin score, serum creatinine and CPK levels, hypothyroidism and cardiac involvement.
Mierau (47)	2011	SSc	Cohort	863 (lcSSc 513, dcSSc 173, scleroderma overlap syndrome 108, UCTD with scleroderma 64, SS sine scleroderma 5)	Anti-U1RNP; Anti-PM-Scl; Anti-M2; Anti-RNAP I/II; Anti-Ku; Anti-U3RNP/fibrillarin; Anti-Th/To; Anti-NOR-90; Anti-ARS; Anti-p25/p23	IIF, line immunoassay, IP, ID	Anti-p25/p23 characterise a subset within the ACA + group strongly associated with SSc (71.4%)
Moinzadeh (48)	2014	SSc	Cohort	2,177	Anti-RNAPIII; Anti-topo I; Anti-ACA	N/A	Patients who developed cancer (7.1%; breast (42.2%), haematological (12.3%), gastrointestinal (11%), and gynaecological (11%) had higher frequency of anti-RNAPIII
Motegi (49)	2015	SSc	Cohort	246	Anti-RNAP III	ELISA	High skin score and risk of renal crisis
Nikpour (50)	2015	SSc	Cohort	451	Anti-RNAPIII	ELISA	Independently associated with renal crisis (OR 3.8), diffuse disease (OR 6.4), joint contractures (OR 2.5) and malignancy diagnosed within 5 years of onset of SSc skin disease (OR 4.2)

Table 2 (continued)

Table 2 (continued)

Study	Year	Disease	Study design	Number of cases/ controls	Autoantibody	Methods	Main results
Okano (51)	1992	SSc	Case-control	416 cases; 264 controls	Anti-U3RNP/fibrillarin	IIF, IP	More frequent in African American patients with dcSSc
Okano (31)	1996	SSc, PM/DM, SLE, overlap syndromes, SjS	Cohort	1,171 (SSc 548, PM/DM 193, overlap syndromes 164, SLE 194, SjS 72)	Anti-U5snRNP	IP, IIF, IB	Identified in a patient with SSc/PM overlap syndrome and with RP, sclerodactyly, puffy fingers, esophageal hypomotility and inflammatory myopathy
Reimer (52)	1988	SSc	Cohort	646	Anti-RNAP I; Anti-U3RNP/fibrillarin; Anti-PM-Scl	IIF, IB, IP	Anti-RNAP I were associated with dcSSc of short duration, joint and tendon involvement, higher prevalence of renal crisis
Reveille (53)	2001	SSc	Cohort	GENISOS (54 Hispanics; 28 African Americans; 79 White Americans). HLA analysis (77 Hispanics; 77 African Americans; 192 White Americans)	Anti-U3RNP/fibrillarin	IIF, IP, ID	HLA-DQB1*0301 was significantly associated with SSc in all 3 ethnic groups
Saigusa (54)	2015	SSc	Cohort	261	Anti-RNAP III	ELISA	The prevalence of malignancy was significantly higher in patients with anti-RNAP III (7/22, 31.8%) than in those with anti-topo I (2/82, 2.4%) and ACA (8/137, 5.8%)
Sujau (55)	2015	SSc and HC	Case-control	SSc [31]; HC [11]; SLE [6]; RA [5]; SjS [A]; IIM [1]; MCTD [1]; SpA [2]; PsA [1]	Anti-PM-Scl-100/-75; Anti-Ku; Anti-Ro-52; Anti-RNAP III (RP11 and RP155); Anti-fibrillarin (U3RNP); Anti-NOR 90 Anti-Th/To; Anti-PDGFR	Immunoblot	Anti-PM-Scl75 was associated with overlap syndrome, and anti-CENP A with vasculitic rash
Yang (56)	2003	SSc	Cohort	220 (59 ANoA+, 161 ANoA-)	Anti-hU3-55K; Anti-U3RNP/fibrillarin; Anti-Mpp10	IIF, IB, IP	The 74% (23/31) of the anti-U3RNP/fibrillarin + sera also had anti-Mpp10, but only 32% (10/31) were positive for anti-hU3-55K

ACA, anti-centromere antibodies; ANoA, antinucleolar autoantibodies; ARS, aminoacyl-tRNA synthetases; CIE, counterimmunoelectrophoresis; DID, double immunodiffusion; ELISA, enzyme-linked immunosorbent assay; dcSSc, diffuse cutaneous systemic sclerosis; HC, healthy controls; IB, immunoblotting; IIF indirect immunofluorescence; IIM, idiopathic inflammatory myopathy; IP, immunoprecipitation; lcSSc, limited cutaneous systemic sclerosis; MCTD, mixed connective tissue disease; N/A, not available; OR, odds ratio; PM/DM, polymyositis/dermatomyositis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RNAP, RNA polymerase; RP, Raynaud's phenomenon; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

from 4.8% to 10.7% in SSc patients (41,47). Specific autoantibodies to U5snRNP represent a rare finding (2.4%) in patients with SSc-PM overlap syndrome (31). Anti-Ku and anti-PM-Scl antibodies, when found in SSc patients (about 1.2–1.8% and 4.0–4.9%, respectively), are often related to overlap syndromes with muscular manifestations, including creatine phosphokinase (CPK) elevation (45). Antibodies to p25/p23 characterize a subset within the ACA-positive SSc patients, which is strongly associated with SjS symptoms (47). A case report of nephrotic syndrome in a patient with lcSSc and anti-ribosomal P antibodies was found (70). The association of anti-HMGCR antibodies and necrotizing autoimmune myositis (NAM) is well-known (71,72). Such autoAbs have been identified in 1.3% of SSc patients; these subjects show significantly lower levels of CPK, a higher frequency of heart involvement and pulmonary hypertension, and no history of statin use (39).

A DFS pattern at IIF and anti-DSF70 antibodies have been reported to be less frequent in SSc patients than healthy controls (73–76).

#### *AutoAbs in polymyositis/dermatomyositis (PM/DM) and in the anti-synthetase syndrome*

As described in the results shown in *Table 3*, anti-synthetase antibodies identified in myositis patients have a variable prevalence, and this depends on each single specificity. In particular, anti-Jo-1 antibodies have the highest prevalence ranging from 0.5% to 54.7% (82,88), while other anti-synthetase antibodies have lower prevalence, as for anti-PL-7 0.5–9.3% (82,90), anti-PL-12 1.5–19.2% (82,88), anti-OJ 0.5% (82,88), anti-EJ 1–3% (82,88). Antibodies to asparaginyl-tRNA synthetase (anti-KS) occur in 0.3–0.5% of patients with CTD—especially in Japanese patients (62.5%)—most of them presenting ILD (88%)—while an association with myositis was rarely found, as it was detected in 0% of Japanese subjects with PM/DM and in 25% of all positive patients. Interestingly, cancer history was reported in 25% of anti-KS positive patients (83), thus it may be very important to be able to identify this rare autoAb not only for diagnostic but also for prognostic evaluations. With regard to clinical manifestations, overall anti-synthetase antibodies are more frequent in female patients with diffuse cutaneous involvement similarly to limited SSc, arthralgia, joint deformities, high CK levels (88), and overlap myositis (90). Lung involvement is a common manifestation of anti-synthetase syndrome, and anti-Jo-1 antibodies have been reported in association with ILD (91,92), even though a

larger study reported that anti-Jo-1 (+) patients have higher rates of myositis and arthralgia than ILD, as well as higher CK levels compared to anti-PL-12 and PL-7 (+) patients (81). Anti-synthetase antibodies have also been detected in a case of cryptogenic organizing pneumonia (93) and in association with uncommon clinical manifestations such as aphthous-like ulcerations and xerostomia (94). As for their prognostic significance, anti-PL-12 and PL-7 antibodies are related to lower survival rates (81,82), and anti-EJ antibodies have been reported in a case of fatal myocarditis in anti-synthetase syndrome (95).

Rare autoAbs reported in PM/DM patients include anti-Mi-2 (5%) (90), anti-SRP (2.8%) (90), anti-Ku (1–1.7%) (90,96) and anti-HMGCR (3%) (96,97). In particular, anti-Mi-2 and anti-SRP antibodies are more common in female patients affected by DM, while DM skin manifestations are less frequently seen in anti-Ku and anti-SRP positive patients. Anti-SRP antibodies have been associated with higher CK levels (90) in clinically relevant myositis (86), and more severe clinical symptoms, such as rapidly developing muscle weakness and atrophy, dysphagia, ILD complicated by massive pleural effusion and respiratory insufficiency (89,98–100) with poor response to immunosuppressive treatments (101).

Anti-HMGCR antibodies have been reported in several studies (77,78,102–106), in particular in association with necrotizing autoimmune myositis (NAM) (44.9%), followed by PM (4.4%) and DM (1.9%) (107). The titer of anti-HMGCR antibodies seems to correlate with CPK levels (106) and their association with statin therapy is controversial since some studies report that less than 50% of patient have used statins (77,80,97,105), while other reports suggest a strong association in a higher percentage of cases (89,104,107,108). A case of NAM associated with anti-HMGCR antibodies with severe head and neck involvement, resembling a retropharyngeal abscess, has also been reported (71).

As for anti-TIF1 $\gamma$  antibodies, they have been detected mainly in cases of paraneoplastic myositis associated in particular with solid tumors such as breast cancer (109), thus they have not only a diagnostic but also a prognostic value for myositis patients.

When histology is considered, anti-Mi-2 and anti-synthetase antibodies are more frequent in cases with typical DM involvement, while unspecified myositis is the most frequent pathologic finding in patients with anti-Ku antibodies, and NAM is present in 75% of anti-SRP positive subjects (90).

**Table 3** Prevalence and clinical significance of rare serum autoAbs in polymyositis/dermatomyositis (PM/DM) and anti-synthetase syndrome

Study	Year	Disease	Study design	Number of cases/controls	Autoantibody	Methods	Main results
Allenbach (77)	2014	Necrotizing myopathy	Cohort	206	Anti-HMGCR	ALBIA	Statin exposure was present in 44.4% [20] of patients
Alvarado-Cardenas (78)	2016	Statin-associated autoimmune myopathy	Cohort	23/135	Anti-HMGCR	ELISA	23 cases, 14 (82%) were exposed to statins, 15 (88%) had IMNM at muscle biopsy
Coppo (79)	2002	Myositis	Cohort	5	Anti-U1snRNP	ELISA, CIE, dot blot, DID	Muscle weakness is present since the onset, with pulmonary manifestations, neurological symptoms, and symmetric arthritis involving distal joints
Drouot (80)	2014	Necrotizing myopathy	Case-control	150 NAM; 142 SARD; 100 HC	Anti-HMGCR	IP, ALBIA, WB	Positive in 24% (37 cases), with higher CPK levels and only 40% exposed to statins
Hervier (81)	2012	Anti-synthetase syndrome	Cohort	233	Anti-synthetase antibodies (anti-Jo-1, anti-PL-7, anti-PL-12)	N/A	Anti-PL7 and PL12 are very similar and clearly distinct from anti-Jo1 patients for reduced survival (P=0.012) and had higher frequency of ILD (98%)
Hervier (82)	2013	Anti-synthetase syndrome	Cohort	203	Anti-synthetase antibodies (anti-Jo1, anti-PL-7, anti-PL-12)	Immunodot	Anti-PL7 and PL12 were associated at multivariate analysis to increased risk of death (OR 6.3, 95% CI: 1.1–35.4, P=0.038).
Hirakata (83)	2007	CTD (including myositis and ILD)	Case-control	2,500	Anti Asparaginyl-tRNA synthetase (anti-KS)	IP	Identified in the sera of 8 patients (5 Japanese, 1 American, 1 German and 1 Korean). Two patients had DM, but 7/8 (88%) had ILD, 4 arthritis, 1 RP. 2 patients had history of cancer (ovarian and prostate). 7/8 were women; all patients were middle-aged or elderly. Anti-KS were found in 3% of patients with idiopathic ILD
Lega (44)	2010	PM/DM, UCTD, IctSSc, amyopathic DM, overlap syndrome amyopathic DM/SSc/SjS	Cohort	9 anti-PM-Scl, 12 anti-ARS (7 anti-Jo1, 3 anti-PL7, 1 anti-EJ, 1 double-positive for anti-EJ and anti-OJ), 1 anti-PM-Scl and anti-ARS	Anti-PM-Scl; Anti-ARS	ELISA, immunodot, IP	Extrapulmonary manifestations of CTD in all patients, except 1 with anti-PM-Scl
Nakashima (84)	2010	SARD	Case-control	192/21	Anti-CADM-140/MDA5	IP	11/13 patients positive for anti-CADM-140/MDA5 were diagnosed with CADM. Anti-CADM-140/MDA5 antibodies are strongly associated with rapidly progressive ILD

**Table 3** (continued)

Table 3 (continued)

Study	Year	Disease	Study design	Number of cases/ controls	Autoantibody	Methods	Main results
Neri (85)	2014	PM/DM, cancer-associated myopathy (CAM)	Cohort	162 (PM 80, 55 DM, CAM 27)	Anti-Jo-1; Anti-RNP	IIF, CIE	CAM were observed in 27 patients (17%). Breast and ovarian cancers were the more common (8 and 6 patients). CAM were strongly associated with DM (24.6% vs. 10.1 % in PM), older age and dysphagia at disease onset (37% vs. 18.5% in IIM)
Pinal-Fernandez (86)	2016	IMNM	Cohort	666	Anti-SRP; Anti-HMGCR	ELISA, IP	Anti-SRP positive patients were younger and more commonly under immunosuppressive therapy than anti-HMGCR (38.4 vs. 53.3 years old, $P < 0.001$ ; 68% vs. 40%, $P = 0.03$ )
Pluk (87)	2013	Sporadic inclusion body myositis, PM/DM and HC	Case-control	94 sIBM, 24 DM, 22 PM, 94 NDM, 32 HC	Anti-Mup44	IB, cDNA cloning and expression of Mup44, IP, microarray-based epitope mapping	The Mr 44,000 polypeptide (Mup44) was identified as cytosolic 50-nucleotidase 1A (cN1A). Anti-Mup44 was detected in 60% of the sIBM sera at high titer. The 3 major autoepitope regions of cN1A suggest that relatively small fragments of this protein can be used to detect anti-Mup44 in patient sera. One of these regions (aa221–243) were recognized by all of the anti-Mup44 positive sIBM sera, but not by the sera from HC
Watanabe (88)	2011	Anti-synthetase syndrome	Cohort	198	Anti-Jo-1; Anti-PL7; Anti-PL12; Anti-OJ; Anti-EJ; Anti-KS	RNA IP	Anti-EJ antibodies were positive in 3%, anti-PL12 in 1.5%, and anti-Jo-1, KS, OJ, and PL7 in 0.5%
Watanabe (89)	2016	IMNM	Cohort	460	Anti-SRP; Anti-HMGCR	ELISA, RNA IP	Anti-SRP antibodies are associated with more severe muscle involvement compared to anti-HMGCR (63% vs. 24%, $P < 0.001$ ), who had more frequently statin exposure (18% vs. 4%, $P = 0.019$ )

ARS, aminoacyl-tRNA synthetases; ALBIA, addressable laser bead immunoassay; CAM, cancer-associated idiopathic inflammatory myopathy; CIE, counterimmunoelectrophoresis, CTD, connective tissue disease; DID, double immunodiffusion; DM, dermatomyositis; ELISA, enzyme linked immunosorbent assay; dcSSc, diffuse cutaneous systemic sclerosis; HC, healthy controls; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IB, immunoblotting; IIF, indirect immunofluorescence; ILD, interstitial lung disease; IMNM, immune-mediated necrotizing myopathy; IP, immunoprecipitation; lcSSc, limited cutaneous systemic sclerosis; N/A, not available; PM/DM, polymyositis/dermatomyositis; SARD, systemic autoimmune rheumatic diseases; SRP, signal recognition particle; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease; WB, western blot.

A distinct subset of DM, called clinically amyopathic DM (CADM), has been associated with anti-CADM-140/MDA5 antibodies which are strongly related to rapidly progressive ILD (84) and in cases of anti-CADM-140/MDA5 positive patients with idiopathic pulmonary fibrosis (110).

### *AutoAbs in MCTD, Sjögren's syndrome (SjS) and other rheumatic diseases*

MCTD is characterized by the overlap of SSc, SLE and RA diagnosis in the presence of autoAbs such as anti-synthetase antibodies, described in previous sections of this review. Other undefined autoAbs directed towards tRNA were identified in about 1.9% of sera from patients with SARD, and nearly all the positive sera belonged to patients affected by either SLE or SjS. Subjects with both anti-tRNA synthetase antibodies and anti-RoSSA/LaSSB (57.1%) develop annular or papulosquamous recurrent erythema in 37.5% of cases (111). Antibodies to NOR 90 were first described in a patient with SSc by Rodriguez-Sanchez *et al.*, who identified a novel 90-kDa protein recognized by autoantibodies that selectively stained the nucleolus-organizing region (NOR) of chromosomes 13, 14, 15, 21, and 22 (112). The 90-kDa autoantigen was later shown to be identical to human upstream-binding factor (hUBF), an RNA polymerase I-specific transcription factor which plays a central role in transcriptional regulation of rRNA (113). In search for the NOR 90 specificity among 254 patients with various autoimmune rheumatic diseases, Rodriguez-Sanchez *et al.* concluded that anti-NOR 90 antibodies were associated with SSc. By contrast, Kipnis *et al.* did not detect anti-NOR 90 in sera from 112 patients with SSc (41), while Imai *et al.* (114) and Dick *et al.* (115) reported the presence of antibodies to NOR 90 in patients with heterogeneous conditions, including SSc, SLE, RA, SjS, UCTD and other non-rheumatic diseases..

Among patients with SjS, the occurrence of several rare autoAbs and uncommon clinical presentations (such as severe motor-dominant weakness in the lower extremities, depression, cerebellar ataxia) have been described, for example in a patient with anti-neuronal antibodies (116) and in a patient with antibodies to Ma2/Ta with progressive spastic paresis without evidence of cancer over a 4-year follow-up (117). One case of anti-aquaporin 4 antibodies positivity had tetraparesis due to recurrent central nervous system demyelination, together with distal renal tubular acidosis, hypokalemia, medullary nephrocalcinosis, respiratory failure, and secondary anti-phospholipid

syndrome (118). Vandergeynst *et al.* report the occurrence of anti-PM-Scl antibodies in one patient with SjS and ILD, without features of SSc or myositis (99).

AutoAbs against the mitotic apparatus (MA) represent a subtype of ANA rarely detected in sera from patients with SARD. Different MA antigens have been identified so far: mitotic spindle apparatus (MSA), centrosome (CE), midbody (MB/MSA-2), and centromere-F (CENP-F) (119). After the description of anti-MSA antibodies by McCarty *et al.* in 1981 (120), two major classes were identified: autoAbs against the nuclear mitotic apparatus protein (NuMA) and the kinesin-like protein HsEg5 (121,122). Their prevalence is estimated to be less than 1%, with anti-HsEg5 being less frequently detected than anti-NuMA (123,124). Anti-mitotic spindle apparatus antibodies appear to be primarily associated with SjS, SLE and UCTD (26,121-124), and the most frequent clinical symptoms are arthralgia and sicca syndrome (26).

## Discussion

SARD are characterized by the presence of serum autoAbs directed against cellular components belonging to different tissues and organs, and in this view the first step to recognize the presence of an autoimmune response in a specific clinical setting is the identification of autoAbs. However, autoAbs and serum ANA are not disease specific for rheumatic diseases and they can be present also in a significant proportion of healthy people (3), as well as in other autoimmune conditions, i.e., autoimmune thyroid disease (125). AutoAbs specific for SARD have been identified and described since the 1990s, and albeit the most known (i.e., anti-dsDNA and anti-RoSSA/LaSSB), which are also included in the disease classification criteria (126,127) and easily tested in routine assays (128), many others are rare and they are not available for the routine testing. In this view, rheumatologists treating SARD should know also the prevalence and clinical associations of rare autoAbs, especially for particular rheumatic disease subsets and their possible association with malignancy (129). The results of the present systematic literature summarize the main features of rare serum autoAbs identified in SARD, as described in *Tables 1-4*, and a few novel findings have been identified. For example, the number of autoAbs targeting the nervous system, as well as the field of neuroimmunology, have enormously increased (131). In the present work, we have retrieved several articles regarding anti-neuronal antibodies in NPSLE (17,18,29,32), however, most of them

**Table 4** Prevalence and clinical significance of rare serum autoAbs in mixed connective tissue disease (MCTD), Sjögren's syndrome (SjS) and other connective tissue diseases (CTDs)

Study	Year	Disease	Study design	Number of cases/controls	Autoantibody	Methods	Main results
Andrade (121)	1996	SjS	Cohort	37	Anti-NuMA1; Anti-NuMA2	IIF, IB, IP	Anti-NuMA1 react with a 210-kd protein previously described as NuMA antigen. 17 patients with anti-NuMA1 (53%) had clinical and lip biopsy findings that met the criteria for SjS
Bonaci-Nikolic (123)	2006	SjS UCTD	Cohort	6,270	Anti-NuMA1; Anti-NuMA2 (HsEg5); Anti-CENP F; Anti-CENP F/ centrosome	IIF, ELISA	Anti-NuMA1 antibodies were found in 23 (41%) and -NuMA2 in 7 patients. Most of the positive patients had CTD (22/43, 51.1%), UCTD (7/22) and SjS (6/22) being the most common. Anti-NuMA1 positivity was associated with SjS, while patients with -NuMA2 had various diseases (1 SSc, 2 AIH, 1 infection, 1 vasculitis)
Fujii (130)	1996	SjS, SSc, SLE, RA, UCTD	Cohort	91 (SjS 13, SLE 21, SSc 21, RA 14, UCTD 10)	Anti-NOR 90	IIF, IB	Anti-NOR 90 antibodies were present in 7 (77.7%) patients with SjS, RA [4] and SSc [3], no patient with SLE or UCTD
Mozo (124)	2008	SjS, UCTD, SLE	Cohort	47	Anti-NuMA; Anti-HsEg5	IIF, IB, ELISA, chemiluminescence, radioimmunoassay	NuMA positivity was mainly associated with SjS/sicca syndrome and UCTD. Anti-HsEg5 antibodies were detected in 7 patients, not associated with a specific SARD
Owada (116)	2002	SjS	Case report	1	Anti-neuronal antibodies	Immunohistochemistry, WB	Severe motor-dominant weakness in the lower extremities, depressive state, cerebellar ataxia, bladder disturbance were present in this patient
Piccolo (117)	2011	SjS	Case report	1	Anti-Ma2/Ta	Line blot assays	Co-occurrence of anti-Ma2 antibodies and SjS in a patient presenting with a progressive spastic paresis mainly involving lower limbs and no tumour over a 4-year follow-up
Rajagopala (118)	2015	SjS	Case report	1	Anti-aquaporin-4 antibodies	ELISA	SjS with distal renal tubular acidosis, hypokaliemia, medullary nephrocalcinosis, recurrent central nervous system demyelination with tetraparesis, respiratory failure, secondary anti-phospholipids with intravenous catheter thrombosis
Whitehead (122)	1996	SLE, SjS	Cohort	51 MSA- positive sera (43 NuMA, 7 HsEg5); 52 SLE sera	Anti-NuMA2 (HsEg5)	IIF, IB, IP	Five of the 7 HsEg5-positive sera had SLE, 1 had possible SLE, and 2 had SjS. The anti-HsEg5 activity did not decrease in titer over time, and there was no apparent association with disease activity

CTD, connective tissue disease; ELISA, enzyme linked immunosorbent assay; IB, immunoblotting; IIF, indirect immunofluorescence; IP, immunoprecipitation; MSA, myositis specific antibodies; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SjS, Sjögren's syndrome; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

are case reports or small case series, thus estimating the prevalence of these autoAbs remains difficult. Lastly, we confirm that an autoAb called “anti-DFS70” which stands for diffuse speckled pattern at IIF has been associated negatively with SARD, as it is more frequent in healthy subjects (73-76,132-135) and it is rare in SLE patients (132), thus maybe representing a protective pattern.

We must acknowledge that a large variability is found when searching for rare autoAbs in SARD, and additional unsolved problems are represented by the lack of validation, the small number of cases described with different prevalence in different ethnic groups and the use of different laboratory methods for autoAb identification. Further research is needed to strengthen evidence for the role of such autoAbs in the clinical assessment of specific diseases.

### Acknowledgements

This project has been supported by the contribution of the Italian Ministry of Foreign Affairs (Ministero degli Affari Esteri e della Cooperazione Internazionale, Direzione Generale per la Promozione del Sistema Paese).

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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doi: 10.21037/jlpm.2018.09.13

**Cite this article as:** Ceribelli A, Isailovic N, De Santis M, Generali E, Gorlino C, Palermo B, Selmi C. Clinical significance of rare serum autoantibodies in rheumatic diseases: a systematic literature review. *J Lab Precis Med* 2018;3:89.