

REVIEW

# Novel autoantibodies and clinical phenotypes in adult and juvenile myositis

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## Abstract

Autoantibodies targeting intracellular proteins involved in key processes are detected in patients with idiopathic inflammatory myopathies. These myositis-specific autoantibodies have been increasingly demonstrated to correlate with distinct clinical phenotypes within the myositis spectrum. This review highlights the clinical associations of the myositis-specific autoantibodies, with particular attention to the recently identified and characterized novel myositis autoantibodies: p155/140, p140 (MJ), CADM-140 (MDA5), SAE, and 200/100.

## Introduction

The idiopathic inflammatory myopathies (IIMs) polymyositis (PM) and dermatomyositis (DM) are heterogeneous conditions that are historically diagnosed by proximal muscle weakness, evidence of muscle inflammation or necrosis, and characteristic skin lesions [1,2]. However, it is now well recognized that patients can present with other overlapping features, including arthritis and systemic involvement (including interstitial lung disease, or ILD), and this has led to the proposal of alternative diagnostic criteria [3]. In recent years, it has become even more apparent that autoantibodies have a role in distinguishing between further subtypes of myositis patients, and clinico-serological classifications have been proposed. The myositis autoantibodies can be divided into myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs). The MAAs – anti-PMScl, anti-Ku, anti-U1RNP, and anti-U3RNP (fibrillarin) – are commonly found in myositis patients who have features of other connective tissue diseases (CTDs) (in particular, overlap with systemic sclerosis). In contrast, the MSAs are found exclusively in

IIM and are directed to specific proteins found in both the nuclear and cytoplasmic regions of the cell; these MSAs correlate with genotype and clinical manifestations [4,5]. Investigations into these specific autoantibodies help classify myositis patients into increasingly homogeneous subgroups, may guide specific treatment regimes, and importantly increase our understanding of the pathogenesis of IIM.

The ‘traditional’ MSAs – anti-Jo-1 (and the less common non-Jo-1 anti-synthetases), anti-SRP, and anti-Mi-2 – can be detected by routine commercial assays and are identified in approximately 40% to 50% of adult myositis patients and in less than 10% of juvenile dermatomyositis (JDM) patients [6]. More recently, a number of groups have reported the identification of novel MSAs, including anti-p155/140, anti-SAE, anti-CADM-140 (melanoma differentiation-associated gene 5, or MDA5), anti-p140, and anti-200/100, the clinical and genetic associations of which are described in this review. With the inclusion of the latter MSAs, it is now possible to identify a positive MAA or MSA in approximately 80% of myositis patients, allowing a clearer serological stratification of patients (Table 1 and Figure 1).

## Anti-synthetase syndrome

### Anti-synthetase autoantibodies

The most prevalent group of MSAs consists of the anti-synthetase autoantibodies. These autoantibodies target the amino-acyl-tRNA synthetases (ARSs) which catalyze the binding of amino acids to the corresponding tRNAs. Each amino acid has a separate ARS, and autoantibodies targeting 8 of the 20 ARSs have been identified. The most common of these is anti-Jo-1 (anti-histidyl tRNA synthetase), which is found in approximately 20% of adult IIM patients. The remaining anti-synthetases – PL-12 (alanyl), PL-7 (threonyl), EJ (glycyl), OJ (isoleucyl), KS (asparginyl), and the more recently identified Ha (tyrosyl) and Zo (phenylalanyl) – have been collectively described in a further 20% of patients, and the frequency of each individual autoantibody is between 1% and 5% [4]. In contrast, the prevalence of ASAs in juvenile myositis patients is much lower: less than 3% [7]. With a few exceptions, each ASA-positive patient develops

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**Table 1. Myositis-specific autoantibodies, target autoantigens, and clinical associations**

Autoantibody	Target autoantigen	Clinical associations	Frequency, percentage	
			Adults	JDM
Anti-ARS	Amino-acyl-tRNA synthetase	Anti-synthetase syndrome	Overall: 30-40	Overall: 1-3
- Jo-1	- Histidyl	Myositis	Jo-1: 15-20	
- PL7	- Theronyl	Interstitial lung disease	PL7: <5	
- PL12	- Alanyl	Raynaud phenomenon	PL12: <5	
- OJ	- Isoleucyl	Arthritis	OJ: <5	
- EJ	- Glycyl	Mechanic's hands	EJ: <5	
- KS	- Asparaginylyl	Fever	KS: <5	
- Ha	- Tyrosyl		Ha: <1	
- Zo	- Phenylalanyl		Zo: <1	
Anti-Mi-2	Nucleosome remodeling deacetylase complex (NuRD)	DM	<10	4-10
Anti-p155/140	Transcriptional intermediary factor 1 gamma (TIF1-γ)	JDM: DM and ulceration Adults: DM and malignancy	13-21	22-29
Anti-p140	Nuclear matrix protein 2 (NXP2)	JDM: DM and calcinosis Adults: DM and ILD	<5	23
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)	DM	<5	<1
Anti-CADM-140	Melanoma differentiation-associated gene 5 (MDA5)	CADM and ILD	50-73 CADM (not in Caucasians)	Not known
Anti-SRP	Signal recognition particle (SRP)	Necrotizing myopathy	5-10	<3
Anti-200/100	Unknown 100- and 200-kDa proteins	Necrotizing myopathy	<10 necrotizing myopathy	Not known

ARS, amino-acyl-tRNA synthetase; CADM, clinically amyopathic dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis.

autoantibodies to only a single ARS. Patients with these autoantibodies are classed as having the anti-synthetase syndrome (ASS) with clinical associations of myositis, ILD, non-erosive arthritis, mechanic's hands, Raynaud phenomenon, and fever, and some patients also have a DM rash.

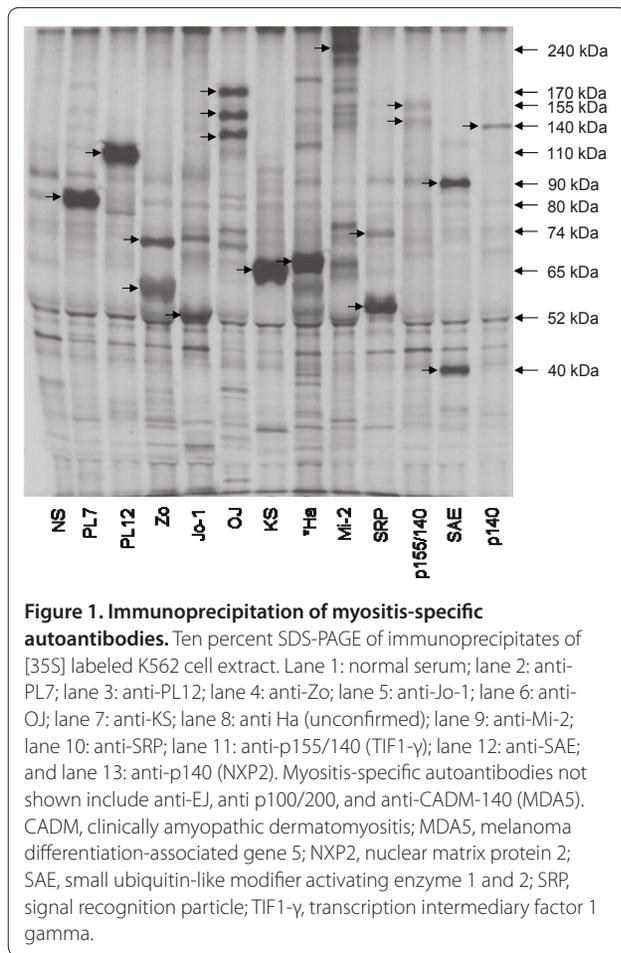
The presence of an ASA has also been shown to indicate response to corticosteroid treatment, particularly in the context of ILD, with ASA-positive patients responding better to initial therapy but having relapses more frequently than ASA-negative patients [8]. Furthermore, it has been demonstrated that titers of anti-Jo-1 autoantibodies moderately correlate with serum creatine kinase levels as well as joint and muscle disease activity [9], demonstrating that the presence and titer of MSAs can help predict disease course and treatment response.

Recently, it has been shown that, while the ASS covers all eight anti-synthetase autoantibodies, the precise clinical manifestations associated with each autoantibody are not identical. It has been reported that anti-Jo-1 autoantibodies are closely associated with what would be classically described as PM, with the majority developing clinically significant myositis over the full disease course [10]. In comparison, anti-OJ, anti-KS, and anti-PL-12 have been more closely associated with DM skin lesions

and are strongly associated with ILD. The development of clinically evident myositis in these patients is less frequent than with anti-Jo-1 and often occurs after the onset of ILD [11-13]. In addition, patients with anti-PL-7 may have lower serum muscle enzyme levels and milder muscle weakness in comparison with anti-Jo-1 patients [14].

Anti-Ha, the seventh ASA to be identified, was identified by means of a combination of immunoaffinity purification and mass spectrometry. So far, it has been demonstrated in only one patient who displayed clinical manifestations of ILD and myositis [15]. Anti-Zo, the most recent ASA to be identified, was identified by means of immunoprecipitation (IPP) and mass spectrometry. It was first detected in an index case with myositis and ILD [16] and has since been found in a further three patients with classic ASS features (ZEB and NJM, unpublished data).

Further studies have been completed on the pathogenic roles of the ASAs and their corresponding autoantigens. Seminal work by Casciola-Rosen and colleagues [17] has shown that Jo-1 autoantigen expression is enhanced in the muscle of myositis patients in comparison with normal controls, suggesting a role for autoantigens in the



**Figure 1. Immunoprecipitation of myositis-specific autoantibodies.** Ten percent SDS-PAGE of immunoprecipitates of [<sup>35</sup>S] labeled K562 cell extract. Lane 1: normal serum; lane 2: anti-PL7; lane 3: anti-PL12; lane 4: anti-Zo; lane 5: anti-Jo-1; lane 6: anti-OJ; lane 7: anti-KS; lane 8: anti Ha (unconfirmed); lane 9: anti-Mi-2; lane 10: anti-SRP; lane 11: anti-p155/140 (TIF1- $\gamma$ ); lane 12: anti-SAE; and lane 13: anti-p140 (NXP2). Myositis-specific autoantibodies not shown include anti-EJ, anti p100/200, and anti-CADM-140 (MDA5). CADM, clinically amyopathic dermatomyositis; MDA5, melanoma differentiation-associated gene 5; NXP2, nuclear matrix protein 2; SAE, small ubiquitin-like modifier activating enzyme 1 and 2; SRP, signal recognition particle; TIF1- $\gamma$ , transcription intermediary factor 1 gamma.

pathogenesis of IIM. This group has shown that certain ARSs can be cleaved by granzyme B which may reveal autoantigenic epitopes [18], and Levine and colleagues [19] demonstrated that the cleavable conformation of Jo-1 is found predominantly in alveolar cells, suggesting that the lung microenvironment is the site of disease initiation in the Jo-1 syndrome. Further work has shown that Jo-1, KS, and Ha autoantigens have chemoattractant properties and can induce leukocyte migration, hence potentially propagating the immune response [20]. A study by Barbasso Helmers and colleagues [21] demonstrated that serum from anti-Jo-1-positive patients had a significantly stronger effect on the expression of intercellular adhesion molecule 1 (ICAM-1) in human microvascular endothelial cell (HMVEC) lung tissue in comparison with serum from healthy controls or patients with other autoantibodies. Endothelial cell activation by increased ICAM-1 expression may contribute to the multiorgan involvement of myositis and ILD in anti-Jo-1-positive patients [21]. Finally, *in vitro* studies demonstrating the potential for anti-Jo-1 autoantibodies to induce type 1 interferon may suggest a direct pathogenic role in disease propagation [22].

## Dermatomyositis clinical phenotypes

### Anti-Mi-2

Targoff and Reichlin [23] first described anti-Mi-2 autoantibodies in 9% of adult myositis patients and more specifically in 20% of adult DM patients. Subsequent studies on JDM cohorts have shown that anti-Mi-2 may also occur albeit at a lower frequency (4% to 10%) [7,24,25]. This autoantibody has been associated with hallmark cutaneous DM lesions, including Gottron papules, heliotrope rash, cuticular overgrowth, and V-sign and Shawl sign rashes. Love and colleagues [26] reported a correlation between UV radiation exposure at myositis onset and the development of anti-Mi-2 autoantibodies, suggesting an influence of environmental features on the development of autoimmunity in this syndrome. Interestingly, *in vitro* studies have demonstrated that the Mi-2 protein is upregulated in UV-irradiated human keratinocytes, further highlighting potential disease mechanisms [27]. The autoantigen target, Mi-2, is a nuclear helicase protein that forms part of the nucleosome-remodeling deacetylase complex, which plays a role in gene transcription [28]. In work similar to studies on Jo-1 expression in target tissues, Mi-2 has been shown to be overexpressed in myositis muscle compared with normal muscle and in particular is upregulated in human DM myofibers expressing markers of regeneration [17,29]. Functionally, Mi-2 has been shown to be essential for the repair of skin basal epidermis [30]; collectively, these data indicate that the autoantigen may have a role in the pathogenesis of disease.

### Anti-p155/140 (TIF1- $\gamma$ )

Autoantibodies to a 155-kDa protein (in most cases with a weaker 140-kDa band) and a 155-kDa/140-kDa complex were first reported by Targoff and colleagues [31] and Kaji and colleagues [32]. Targoff and colleagues screened a cohort of 244 North American patients with IIM and found anti-p155/140 in 21% of the patients. Investigations into the clinical features of the anti-p155/140-positive patients showed an association with DM and cancer and also demonstrated that Caucasian patients with anti-p155/140 autoantibodies had a unique HLA risk factor: DQA1\*0301. The parallel study by Kaji and colleagues screened 52 Japanese patients with DM along with healthy controls and disease controls. The study found anti-p155/140 autoantibodies exclusively in 13% of patients with DM. Clinical manifestations of the p155/140-positive DM patients, including the significant association with malignancy as well as a more severe DM skin disease, were similar to those noted in the study by Targoff and colleagues. The strong link with cancer-associated myositis was confirmed in a larger cohort study of Caucasian adult patients from the UK (Adult Onset Myositis Immunogenetic Collaboration [AOMIC]

study group) [33]. In a recent review, Selva-O'Callaghan and colleagues [34] performed a meta-analysis of all published anti-p155/140 cohort studies to determine the accuracy of anti-p155/140 autoantibodies for predicting cancer in DM. Overall, anti-p155/140 autoantibodies have an 89% specificity and a 70% sensitivity for predicting malignancy and have a negative predictive value of 93% and a diagnostic odds ratio of 18 [34].

Studies investigating the occurrence of anti-p155/140 autoantibodies in JDM patients have also been completed. Gunawardena and colleagues [35] screened 116 JDM cases by radiolabeled IPP and found anti-p155/140 autoantibodies in 23% of the patients. Similarly, both Espada and colleagues [36] and Targoff and colleagues [31] have detected anti-p155/140 in 22% and 29% of patients with JDM, respectively. Interestingly, while the anti-p155/140 autoantibody has been demonstrated by radio-labeled immunodepletion experiments to target the same autoantigens as the adult anti-p155/140 autoantibody, there are some clinical differences. In particular, cancer was not associated with anti-155/140-positive JDM cases; however, both anti-p155/140-positive adults and children appear to have a more severe cutaneous disease [35].

In preliminary work, the 155-kDa autoantigen target was identified by immunoaffinity purification and mass spectrometry as transcription intermediary factor 1 gamma (TIF1- $\gamma$ ). This was confirmed by immunization of rabbits with a TIF1- $\gamma$  peptide with affinity purification of subsequent antibodies for use in sandwich enzyme-linked immunosorbent assays (ELISAs) [37]. The identity of the autoantigen detected as the associated 140-kDa band has yet to be established, although this is likely to be a degradation product of TIF1- $\gamma$  or possibly TIF1- $\alpha$ , an isoform that has a molecular weight of 140 kDa. TIF1- $\gamma$  is a nuclear protein involved in controlling DNA transcription. Moreover, TIF1- $\gamma$  has been shown to inactivate Smad-4, which regulates transforming growth factor-beta (TGF- $\beta$ ) signaling, thus promoting cell growth and differentiation (including malignant tumors) [38].

More recently, Hoshino and colleagues [39] developed a non-radiolabeled method for screening CTD patients for the presence of anti-p155/140. Biotinylated recombinant TIF1- $\gamma$  was produced from a cDNA vector and used as the antigen source in a non-radiolabeled IPP assay. Comparisons between the results of this screen and standard radiolabeled IPP using HeLa cell lysates were similar, with 10 DM patients being positive in both assays, 68 DM patients being negative in both assays, and 5 DM patients being positive in only one assay. The authors suggested that the differences in results between the two assays might have been due to differences in conformation, protein stability, or other factors of the autoantigens. Interestingly, while the biotinylated assay may not have been as sensitive for the detection of weakly

reactive anti-TIF1- $\gamma$  autoantibodies, the detection of anti-TIF1- $\gamma$  in cancer-associated DM was not reduced. The introduction of this novel, non-radiolabeled assay may therefore be extremely helpful in the setting of routine laboratories for the screening of DM patients [39].

#### **Anti-CADM-140 (MDA5)**

Autoantibodies to a 140-kDa cytoplasmic protein in Japanese adult patients with clinically amyopathic dermatomyositis (CADM) were first described by Sato and colleagues [40]. This novel autoantibody was shown to be associated with rapidly progressive ILD. Further investigation in Asian adult cohorts of CTD patients has shown anti-CADM-140 to be specific for DM, with most having CADM [39,41,42]. Furthermore, anti-CADM-140 has been associated with elevated serum ferritin concentrations, suggesting an association of anti-CADM-140 and macrophage activation syndrome. Patients with CADM-140 autoantibodies have also been shown to have a poor prognosis; one study demonstrated that 46% of anti-CADM-140-positive patients died of respiratory failure within 6 months of disease onset [42].

Studies investigating p155/140 autoantibodies, anti-CADM-140 autoantibodies, and anti-synthetase autoantibodies have shown that these autoantibodies are mutually exclusive [43]. Interestingly, while studies have shown that the incidence of ILD in CADM is greater in Asia, a systematic review of patients in North America and Europe has shown that approximately 15% of CADM patients develop ILD. The prevalence of anti-CADM-140 has been reported to be between 19% and 35% in Japanese patients with DM and between 53% and 73% in Japanese patients with CADM; however, to date, this autoantibody has not been described in European or American Caucasian cohorts, implying that either a genetic or an environmental factor is associated with anti-CADM-140 generation.

The CADM-140 autoantigen has been identified as MDA5 from a cDNA expression library [41]. This protein is one of the retinoic acid-inducible gene-1-like receptors and has a role in the recognition of viral RNAs as part of the innate immune system. The identification of this autoantigen may therefore provide insight into the pathogenesis of CADM and ILD and into the reported association between viral infections and myositis. The clinical utility and identity of this autoantigen have since been confirmed in further studies by a combination of immunoaffinity chromatography with mass spectrometry analysis, by immunoblot with a commercial antibody, and by IPP with a biotinylated recombinant MDA5 protein [39,42].

#### **Anti-p140 or anti-MJ (NXP-2)**

A different 140-kDa autoantigen target has also been described in DM patients. This autoantibody was originally

termed anti-MJ and was found in 18% of 80 American patients with JDM [44]. In a preliminary study by Targoff and colleagues [45], the MJ autoantigen was identified as NXP2 (nuclear matrix protein 2, also known as MORC3) by means of a K562 cDNA expression library. This protein is involved in transcriptional regulation [46]. Gunawardena and colleagues [47] demonstrated that anti-p140 autoantibodies are a major serological subset in children recruited to the UK JDM Cohort Study. After IPP studies, 23% of 162 children were anti-p140-positive and had a higher incidence of calcinosis. Immunodepletion experiments using a commercial anti-NXP2 antibody suggested that the p140 target in this study has the same identity as the MJ autoantigen. Recently, anti-MJ was also described in 25% of an Argentinean juvenile IIM cohort and was associated with muscle contractures, atrophy, and significant compromise of functional status [36]. Parallel studies on the European adult IIM cohort study (EuMyoNet) have also demonstrated the presence of what appears to be the same anti-p140 specificity, which was found exclusively in 5% of DM patients. Preliminary data suggest that the clinical associations in adults differ from JDM, with anti-p140 autoantibodies being associated with ILD in adults [48].

#### **Anti-SAE**

Betteridge and colleagues [49] first described the presence of novel autoantibodies targeting 40-kDa and 90-kDa proteins in DM patients with similar clinical manifestations. Using IPP and mass spectrometry, the authors identified these proteins as small ubiquitin-like modifier activating enzyme 1 and 2 (SAE) that are involved in the post-translational modification of numerous targets, including protein kinases and transcription factors [49]. Further work has confirmed that anti-SAE was found in 8% of DM patients from the AOMIC UK study. The majority of anti-SAE patients presented with cutaneous manifestations and progressed to myositis with systemic features, including dysphagia. This autoantibody was associated with a low frequency of malignancy and ILD. Furthermore, genetic studies found a strong association of the anti-SAE autoantibody with the HLA-DRB1\*04 DQA1\*03 DQB1\*03 haplotype [50]. This autoantibody has also been investigated in the UK JDM Cohort and, with the exception of one patient, has not been seen in JDM (HG and ZEB, unpublished data).

#### **Immune-mediated necrotizing myopathy**

##### **Anti-signal recognition particle**

Autoantibodies to the signal recognition particle (SRP) were first demonstrated in IIM by Reeves and colleagues [51]. SRP is a cytoplasmic protein with a role in the recognition and translocation of newly synthesized proteins across the endoplasmic reticulum. Anti-SRP

autoantibodies are present in approximately 5% of adult myositis patients and have been associated with acute-onset severe necrotizing myopathy and with systemic features that may be refractory to standard immunomodulatory treatments [52-54]. Muscle biopsies from anti-SRP patients classically demonstrate muscle fiber necrosis with minimal inflammatory cell infiltrate [53-55]. Conversely, anti-SRP autoantibodies are rarely detected in juvenile patients. A study by Rouster-Stevens and colleagues [56] detected anti-SRP in 3 of 123 children with clinical manifestations similar to those of anti-SRP adult patients. Interestingly, all of the anti-SRP-positive cases were of African-American origin, suggesting a specific immunogenetic association [56].

##### **Anti-200/100**

The most recent myositis autoantibody to be described, by Christopher-Stine and colleagues [57], is the anti-200/100 autoantibody. Muscle biopsies from 225 myositis patients were screened for necrotizing myopathy features. Thirty-eight patients demonstrated predominant necrosis without histological findings of perifascicular atrophy or red-rimmed vacuoles, and 26 of these patients had no known MSA. After radiolabeled IPP using HeLa cells, 16 (62%) of these MSA-negative patients were found to immunoprecipitate 200-kDa and 100-kDa proteins. Since both of these proteins were immunoprecipitated together in all cases, the authors suggested that the subunits are likely to be part of the same protein complex. This pattern was found in only one patient (from 187) without necrosis and in no healthy controls, indicating that this novel autoantibody is associated with immune-mediated necrotizing myopathy. Interestingly, 63% of patients with this autoantibody were found to have a history of exposure to statins. Further studies now need to be completed, identifying the 200/100-kDa doublet, assessing the frequency of this autoantibody in additional cohorts, and clarifying the potential association of this autoantibody with statin exposure.

#### **Conclusions**

In this review, we have highlighted the recent studies identifying and characterizing novel myositis autoantibodies and their associated autoantigens. The increasing number of patients with a known MSA aids the clinico-serological classification of myositis and may help to predict complications of disease, prognosis, and responses to treatment. The identification of these novel autoantibodies has led to an increasing demand for the development of commercial assays in order to allow the screening of patients in the routine clinical setting. The recent development and validation of a line blot assay containing a number of the MSAs demonstrate

progression in this field [58,59] and further work is currently in progress. Studies of MSAs and their corresponding targets have also provided insights into the pathogenesis of IIM, and links between environmental, immunogenetic, and autoantibody status have been described. Further studies are now required to identify novel targets in patients who are currently viewed as autoantibody-negative and to further elucidate the role of autoimmunity in the pathophysiology of IIM subtypes.

#### Autoimmune Basis of Rheumatic Diseases

This article is part of a series on *Myositis*, edited by Ingrid Lundberg, which can be found online at  
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#### Abbreviations

AOMIC, Adult Onset Myositis Immunogenetic Collaboration; ARS, amino-acyl-tRNA synthetase; ASS, anti-synthetase syndrome; CADM, clinically amyopathic dermatomyositis; CTD, connective tissue disease; DM, dermatomyositis; ICAM-1, intercellular adhesion molecule 1; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IPP, immunoprecipitation; JDM, juvenile dermatomyositis; MAA, myositis-associated autoantibody; MDA5, melanoma differentiation-associated gene 5; MSA, myositis-specific autoantibody; PM, polymyositis; SAE, small ubiquitin-like modifier activating enzyme 1 and 2; SRP, signal recognition particle; TIF-1 $\gamma$ , transcription intermediary factor 1 gamma.

#### Competing interests

The authors declare that they have no competing interests.

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