

## Unusually High Frequency of Autoantibodies to PL-7 Associated With Milder Muscle Disease in Japanese Patients With Polymyositis/Dermatomyositis

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**Objective.** Autoantibodies to aminoacyl transfer RNA synthetases, such as histidyl (Jo-1), threonyl (PL-7), alanyl (PL-12), glycyl (EJ), and isoleucyl (OJ), are closely associated with a subset of patients with polymyositis/dermatomyositis (PM/DM) complicated by interstitial lung disease (ILD). Anti-Jo-1 is by far the most common, found in 15–25% of patients with PM/DM, whereas the other types are found in only ~3% of these patients. In this study, the clinical associations of these autoantibodies in Japanese patients with PM/DM were investigated.

**Methods.** The diagnoses of PM/DM and amyopathic DM (ADM) were based on the Bohan and Peter criteria and Sontheimer's definition, respectively. Sera from 36 Japanese patients with PM/DM (13 with PM, 20 with DM, 3 with ADM) were screened by immunoprecipitation and by enzyme-linked immunosorbent assay (for Jo-1). Clinical and laboratory data were collected.

**Results.** The frequencies of autoantibodies to Jo-1 (22%) and to EJ, OJ, and PL-12 (3–6%) were similar to those found in previous studies, including studies of Japanese subjects. However, anti-PL-7 was found in 17% of patients, in contrast to a frequency of 1–4% in previous studies ( $P < 0.02$ – $0.0002$ ). The 6 anti-PL-7-positive patients were not related, and no skewing in

year or month of disease development, place of residence or work, or occupation was found. All patients had ILD, consistent with the clinical features of antisynthetase-positive patients. The patients with anti-PL-7 had lower serum muscle enzyme levels and milder muscle weakness ( $P < 0.05$ ) compared with anti-Jo-1-positive patients.

**Conclusion.** Anti-PL-7 was found at an unusually high frequency in this group of Japanese patients with myositis. Although anti-PL-7, similar to anti-Jo-1, is associated with PM/DM with ILD, muscle involvement in the patients with anti-PL-7 appeared to be milder than that in the anti-Jo-1 subset.

Certain autoantibodies, such as anti-Sm in systemic lupus erythematosus (SLE) and anti-topoisomerase I in systemic sclerosis (SSc; scleroderma), are associated with particular diagnoses and are useful clinical markers. In addition, some autoantibodies are tightly linked with a specific clinical subset of the disease. Anti-Jo-1 antibodies, which recognize the cytoplasmic amino acid-charging enzyme histidyl transfer RNA (tRNA) synthetase, are a disease marker of polymyositis/dermatomyositis (PM/DM) associated with a unique clinical subset, characterized by myositis, interstitial lung disease (ILD), arthritis, mechanic's hands, and Raynaud's phenomenon (1). Interestingly, autoantibodies to all other aminoacyl tRNA synthetases, including threonyl (PL-7), alanyl (PL-12), glycyl (EJ), isoleucyl (OJ), and asparaginyl (KS), are associated with the same syndrome, which has been designated antisynthetase syndrome (1).

Anti-Jo-1 antibodies, found in 15–25% of PM/DM patients, are by far the most common among the antisynthetase antibodies; all other types are usually

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found in only 0.5–6% of patients (1–6). Therefore, the clinical associations of other antisynthetase antibodies are based on case reports (2,7). Whether there is any difference in clinical manifestations between patients with different antisynthetase autoantibodies is not known. The production of certain autoantibodies depends heavily on genetic factors, resulting in strikingly different frequencies between races. However, the frequency of antisynthetase antibodies is reported to be very similar regardless of race, ethnicity, or nationality (3). In the present study, we found an unusually high frequency of anti-PL-7 in our cohort of Japanese patients with PM/DM. We therefore compared the clinical manifestations in these anti-PL-7-positive patients with those in a subset of anti-Jo-1-positive patients with inflammatory myopathies.

## PATIENTS AND METHODS

**Patients.** Sera from 36 Japanese patients with inflammatory myopathies (13 with PM, 20 with DM, and 3 with amyopathic DM [ADM]) were obtained from the rheumatology clinic at St. Marianna University Hospital (Kawasaki, Japan). These patients were enrolled in the PM/DM study at St. Marianna University during 1991 to 2002, and most of the patients have been followed up once a month. All except 2 patients were diagnosed as having PM/DM and started their treatment with glucocorticoid and/or immunosuppressive drugs at our hospital. Sera were collected in January through March 2004 from all patients who returned to the rheumatology clinic. The diagnoses of PM/DM and ADM were based on the Bohan and Peter criteria and Sontheimer's definition, respectively (8,9). Three patients also had SSc, 1 had SLE, 4 had rheumatoid arthritis, and 2 had Sjögren's syndrome, all based on standard criteria (10–13). Clinical and laboratory data from the patients were reviewed retrospectively. The protocol was approved by the appropriate institutional review board.

**Analysis of autoantibodies by immunoprecipitation.** The proteins recognized by human sera were evaluated by immunoprecipitation of radiolabeled K562 cell extract and sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), as previously described (14). Briefly, cells were labeled with  $^{35}\text{S}$ -methionine and cysteine, lysed in 0.5M NaCl, 2 mM EDTA, 50 mM Tris, pH 7.5, 0.3% Nonidet P40 (NET/NP40) buffer containing 0.5 mM phenylmethylsulfonyl fluoride and 0.3 TIU/ml aprotinin, and immunoprecipitated with protein A–Sepharose beads coated with 8  $\mu\text{l}$  of human sera. Immunoprecipitates were washed with 0.5M NaCl–NET/NP40 followed by SDS-PAGE and autoradiography. The specificity of the autoantibodies was confirmed using human reference sera (14).

The RNA components of the antigens recognized by human sera were analyzed by immunoprecipitation of unlabeled K562 cell extract. Nucleic acid components were extracted from immunoprecipitates using phenol–chloroform–

isoamyl alcohol (25:24:1), separated on 12% urea-PAGE, and identified with silver staining (Silver Stain Plus; Bio-Rad, Hercules, CA).

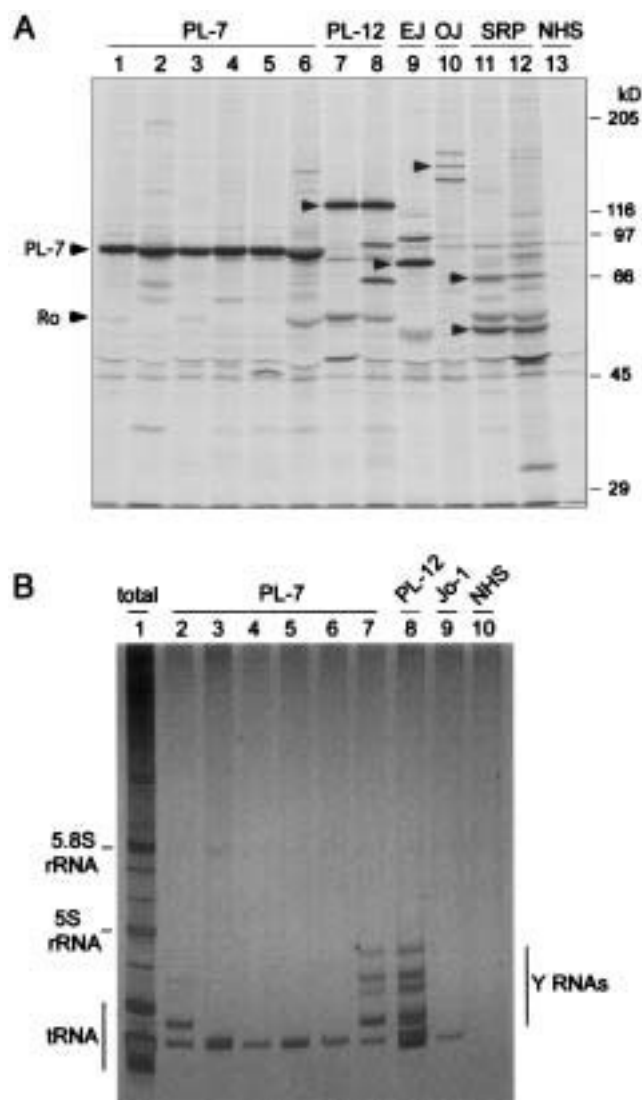
**Enzyme-linked immunosorbent assay (ELISA).** Antibodies to Jo-1 were tested by ELISA using histidine-tagged recombinant proteins expressed in *Escherichia coli* and purified on an Ni-NTA resin column. The wells on microtiter plates (Immobilizer Amino; Nunc, Naperville, IL) were coated with purified recombinant Jo-1 antigen. The plates were blocked with 0.5% bovine serum albumin (BSA)–NET/NP40 for 1 hour at room temperature. Patients' sera were diluted 1:500 with 0.5% BSA–NET/NP40. Goat anti-human IgG antibodies ( $\gamma$ -chain specific; Southern Biotechnology, Birmingham, AL) diluted 1:1,000 in 0.5% BSA–NET/NP40 were used as secondary antibodies. A standard curve was made with a serial 1:5 dilution of high-titer anti-Jo-1 antibody-positive serum. The optical density at 405 nm was converted to units using a standard curve.

**Clinical data.** Patients with PM/DM were grouped according to autoantibody specificities, and the clinical characteristics were compared between the groups. Muscle weakness was evaluated by standard manual muscle testing (MMT). Scoring of muscle weakness on MMT was based on the evaluation of 18 proximal muscle groups as previously described (15), comprising the right and left deltoid, biceps brachii, brachioradialis, triceps brachii, iliopsoas, gluteus maximus, quadriceps femoris, and hamstring muscles, and the neck flexors and extensors. The responses were rated according to the Medical Research Council (MRC) scale (0 = lowest score and 5 = highest score), with a maximum MRC score of 90. The normal range of creatine phosphokinase (CPK) (40–200 IU/liter in men, 20–160 IU/liter in women) and lactate dehydrogenase (LDH) (115–230 IU/liter) was not changed during the study period. The diagnosis of ILD was made according to the presence of bibasilar infiltrates on chest radiography and/or high-resolution computed tomography. Pericardial effusion was assessed by echocardiogram. Myocarditis was defined on the basis of new onset of abnormal electrocardiography findings (sinus tachycardia, ST-T elevation, conduction abnormalities), accompanied by evidence of left ventricular dysfunction (16) and elevation of cardiac troponin T (17). Since none of the cases was confirmed by biopsy or autopsy, these patients were classified as having suspected myocarditis.

**Statistical analysis.** Statistical analyses were performed by Fisher's exact test or Mann-Whitney U or Kruskal-Wallis tests, with corrections for multiple comparisons by Dunn's test.

## RESULTS

**Screening of autoantibodies by immunoprecipitation.** Six of 36 sera (17%) immunoprecipitated the 80-kd PL-7 (threonyl tRNA synthetase) protein from  $^{35}\text{S}$ -labeled K562 cell extracts (Figure 1A). Immunoprecipitation of threonyl tRNA by these sera was also confirmed by silver staining of the RNA component immunoprecipitated by the same sera (Figure 1B).



**Figure 1.** Immunoprecipitation analysis of autoantibodies to aminoacyl tRNA synthetases. **A**, Immunoprecipitation of  $^{35}\text{S}$ -labeled K562 cell extracts was carried out on sera from patients with polymyositis/dermatomyositis (lanes 1–12) or normal human serum (NHS) (lane 13). Threonyl (PL-7) (lanes 1–6), alanyl (PL-12) (lanes 7 and 8), glycyl (EJ) (lane 9), isoleucyl (OJ) (lane 10), and SRP (SRP70 and SRP54, lanes 11 and 12) proteins are shown by arrowheads. Sera in lanes 1, 3, 6–8, 11, and 12 were also positive for anti-Ro. **B**, Silver staining of tRNA immunoprecipitated by sera. K562 cell extracts were immunoprecipitated with sera and RNA was extracted, run on 12% urea-polyacrylamide gel electrophoresis, and silver-stained. Lane 1, Total RNA; lanes 2–7, anti-PL-7-positive sera; lane 8, anti-PL-12-positive serum; lane 9, anti-histidyl (Jo-1)-positive serum; lane 10, NHS. Sera in lanes 2, 7, and 8 also immunoprecipitated Y RNAs.

**Frequency of autoantibodies.** The frequencies of antisynthetase autoantibodies in the present study compared with the findings in previous studies that also

included anti-PL-7 are summarized in Table 1. No overlap of antisynthetase antibodies was found, consistent with previous studies (1). The frequency of autoantibodies to Jo-1 (22%), EJ (3%), OJ (3%), and PL-12 (6%) in our cohort was similar to that observed in other studies in the US, Europe, and Japan (2–6). In contrast, the 17% frequency of anti-PL-7 autoantibodies found in our cohort (6 of 36 sera) was much higher than the frequency of 1–4% reported in previous studies ( $P < 0.02$ – $0.0002$  by Fisher's exact test).

The 6 anti-PL-7-positive patients were not genetically related, and no skewing in their residence, workplaces, or occupations was found. Patients developed PM/DM during the months of January (2 patients), May (1 patient), June (2 patients), and November (1 patient). Analysis of disease development by year indicated the occurrence of 1 case each in 1991, 1992, 1993, 1995, 1999, and 2002. Thus, neither clustering in a particular year nor clustering in a particular time of year was found.

**Clinical characteristics.** The clinical characteristics of the patients with anti-PL-7 as compared with patients with anti-Jo-1, antisynthetase-positive patients, and antisynthetase-negative patients are summarized in Table 2. Consistent with observations in previous reports (1,2,7), anti-PL-7-positive patients had myositis with ILD, which are typical clinical features of the antisynthetase syndrome. The anti-PL-7-positive patients appeared to have milder muscle involvement compared with the anti-Jo-1-positive subset, based on 1) higher MMT scores (patients with scores  $>80$ , 100% of anti-PL-7-positive patients versus 50% of anti-Jo-1-positive patients;  $P < 0.05$  by Fisher's exact test), 2) lower levels of muscle enzymes ( $P < 0.05$  for CPK levels and  $P = 0.059$  for LDH levels, by Mann-Whitney U test, in the anti-PL-7 versus anti-Jo-1 subset), and 3) lower percentage of patients with very high levels of muscle enzymes (CPK  $>1,000$  IU/liter or LDH  $>700$  IU/liter) (33% of anti-PL-7-positive patients versus 100% of anti-Jo-1-positive patients;  $P < 0.05$ ).

Dysphagia has been reported to be associated with poor prognosis (18) and was noted in 2 of 8 anti-Jo-1-positive patients but in none of the anti-PL-7-positive group. Although a female predominance was seen overall in the patients with PM/DM (number of men:number of women 12:24), the percentage of male patients appeared to be higher in the antisynthetase-positive group compared with the antisynthetase-negative group (9 men to 9 women versus 3 men to 15 women, respectively;  $P = 0.08$ ). The male:female ratio among the anti-Jo-1-positive patients was 5:3. The

**Table 1.** Frequency of myositis-related autoantibodies in various studies compared with the present study\*

	Present study	Hirakata et al (ref. 5)	Arnett et al (ref. 3)	Love et al (ref. 6)	Targoff et al (ref. 2)	Mathews et al (ref. 7)	Bernstein et al (ref. 4)
Country	Japan	Japan	US	US	US	UK	UK
Year	2005	1992	1996	1991	1988	1984	1984
No. of patients	36	52	203†	212	109	84	36
Specificity, % of patients							
Jo-1	22	15	17	17	23	ND	25
PL-7	17‡	2	1	2	4	4	3
PL-12	6	ND	6	0.5	ND	ND	ND
EJ	3	3	0.5	2	ND	ND	ND
OJ	3	ND	1	1	ND	ND	ND
SRP	6	3	3	3	ND	ND	ND

\* Jo-1 = histidyl; ND = not described; PL-7 = threonyl; PL-12 = alanyl; EJ = glycyl; OJ = isoleucyl.

† Caucasian n = 89, African American n = 89, Mexican American n = 25 (21 Japanese subjects were excluded).

‡  $P = 0.0173$  versus Hirakata et al;  $P = 0.0002$  versus Arnett et al;  $P = 0.0009$  versus Love et al;  $P = 0.02$  versus Mathews et al;  $P = 0.1065$  versus Bernstein et al (all by Fisher's exact test).

frequency of ILD in the antisynthetase-positive group compared with the antisynthetase-negative group was significantly higher ( $P < 0.05$ ), as has been previously described (1,6).

## DISCUSSION

The etiology of PM/DM remains to be clarified. The current understanding is that it results from immune-mediated damage in response to environmental stimuli occurring in genetically susceptible individuals (19). The reported frequency of various antisynthetase antibodies was very similar in all previous studies, regardless of the race, ethnicity, or nationality of the subjects (3–6), except for a report suggesting clustering of anti-PL-12 in the southern US (20). Anti-Jo-1 has been by far the most frequently detected specificity in patients with PM/DM (15–25%); all other antisynthetase antibodies have been found in 0.5–6% of patients.

All antisynthetase antibodies are associated with myositis, ILD, Raynaud's phenomenon, mechanic's hands, and arthritis, and this is known as the antisynthetase syndrome (1). Although there are no studies that have directly compared the clinical features of patients with different antisynthetase antibodies, some differences in clinical manifestations according to the type of antisynthetase antibody have been described. Reports on anti-PL-12 and anti-KS suggest that these are common in patients with ILD without myositis (20). The majority of patients with anti-PL-7 have PM/DM and joint symptoms in common. ILD (20–100%) and Raynaud's phenomenon (25–100%) are also common, but the frequency of these features tends to vary (2,7,21). A high frequency (5 of 7 patients; 71%) of PM/DM-SSc overlap in anti-PL-7-positive Japanese

patients was recently reported (22). However, this was not the case in the present study (0 of 6 had overlap with SSc) and also is unusual in other studies (2,7).

The high frequency of anti-PL-7 in the present study allowed us to compare the clinical characteristics of the anti-PL-7-positive patients with those of anti-Jo-1-positive patients. Although the anti-PL-7-positive patients also had myositis plus ILD, more patients in this group had MMT scores of  $>80$ , and CPK levels in this group were lower (Table 2) as compared with the anti-Jo-1-positive group, suggesting that muscle involvement in patients with anti-PL-7 antibodies is milder than that in anti-Jo-1-positive patients. Whether this is generally true or a unique characteristic of our cohort needs to be verified in future studies.

The high frequency of anti-PL-7 in the present study (17% versus 1–4% in previous studies [Table 1]) cannot be attributed to differences in the detection techniques used, because our method was essentially the same as that used in other studies (2–7). Moreover, the frequency of anti-PL-7 in patients with PM/DM from the US, who were screened by us at the University of Florida using exactly the same technique, was 2% (1 of 43) (Yamasaki Y, et al: unpublished observations). One study comparing autoantibodies in Caucasian, African American, Mexican American, and Japanese patients with PM/DM showed that antisynthetase antibodies were produced at similar frequencies in patients with different racial/ethnic backgrounds (3).

The Japanese population is considered to be homogeneous, and the institution at which previous studies of Japanese subjects (3,5) were conducted is only 30 km away from our enrollment site at St. Marianna University Hospital. In addition, the 6 anti-PL-7-

**Table 2.** Clinical features of patients with antisynthetase antibodies\*

	Anti-PL-7	Anti-Jo-1	Antisynthetase positive	Antisynthetase negative
No. of patients	6	8	18	18
Followup, mean $\pm$ SD months	100 $\pm$ 49.9	70 $\pm$ 36.3	79 $\pm$ 43.3	83 $\pm$ 40.9
Age, mean $\pm$ SD years	49 $\pm$ 16.9	44 $\pm$ 12.3	48 $\pm$ 13.4	49 $\pm$ 12.2
Male:female, no.	2:4	5:3†	9:9‡	3:15
Malignancy, %	0	0	0	12
Diagnosis, no. with PM/DM/ADM	2/3/1	3/5/0	6/11/1	7/9/2
Positive result on biopsy, %	100	100	100	100
Myogenic on EMG, %	67	100	86	79
Muscle weakness, %	67	88	72	88
MMT score				
Mean $\pm$ SD	85 $\pm$ 3.9	80 $\pm$ 6.8	81 $\pm$ 6.5	71 $\pm$ 12.8
Score >80, %	100§	50	67	38
CPK				
Mean $\pm$ SD IU/liter	1,429 $\pm$ 2,016§	3,710 $\pm$ 609	2,238 $\pm$ 2,248	1,400 $\pm$ 1,957
>1,000 IU/liter, %	33§	100	56	39
LDH				
Mean $\pm$ SD IU/liter	663 $\pm$ 466¶	1,147 $\pm$ 609	811 $\pm$ 572	812 $\pm$ 523
>700 IU/liter, %	33§	100	56	50
ILD, %	100#	100**	94**	56
%VC, mean $\pm$ SD	68 $\pm$ 17.3	68 $\pm$ 17.4	68 $\pm$ 14.5	77 $\pm$ 14.1
FEV 1.0%, mean $\pm$ SD	77 $\pm$ 7.3	87 $\pm$ 7.0	83 $\pm$ 7.5	81 $\pm$ 5.8
DLco, mean $\pm$ SD	40 $\pm$ 11.5	53 $\pm$ 9.9	49 $\pm$ 11.4	56 $\pm$ 18.0
Arthralgia, %	50	88	61	44
Destructive arthritis, %	0	25	11	0
Rheumatoid factor, %	33	38	39	19
Raynaud's phenomenon, %	33	13	28	39
Pericardial effusion, %	17	13	11	6
Myocarditis, %	17	25	17	6
Dysphagia, %	0	25	12	29

\* All *P* values are by Fisher's exact test or Mann-Whitney U test. Antisynthetase antibodies comprise anti-PL-7/threonyl (*n* = 6), anti-Jo-1/histidyl (*n* = 8), anti-PL-12/alanyl (*n* = 2), anti-EJ/glycyl (*n* = 1), anti-OJ/soleucyl (*n* = 1). PM = polymyositis; DM = dermatomyositis; ADM = amyopathic DM; EMG = electromyography; MMT = manual muscle testing; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; ILD = interstitial lung disease; %VC = percent vital capacity; FEV = forced expiratory volume; DLco = diffusion capacity for carbon monoxide.

† *P* = 0.07 versus antisynthetase negative.

‡ *P* = 0.08 versus antisynthetase negative.

§ *P* < 0.05 versus anti-Jo-1.

¶ *P* = 0.059 versus anti-Jo-1.

# *P* = 0.066 versus antisynthetase negative.

\*\* *P* < 0.05 versus antisynthetase negative.

positive patients were not related and originated from various areas of Japan. Thus, the difference in frequency of anti-PL-7 between our study and previous Japanese studies is unlikely to be explained by genetic differences.

The frequencies of all other antisynthetase antibodies in our study were comparable with those in other studies, suggesting that environmental factors specifically associated with anti-PL-7 might play a role in our cohort. A possible association between PM/DM or specific autoantibodies and viral infection, chemicals, and other environmental factors has been suggested (19). Geographic clustering of myositis cases has been reported (23) and patients with different myositis-specific autoantibodies may develop the disease at different times of the year (24), consistent with the possibility of

an environmental effect (19). However, no seasonal clustering of anti-PL-7 was observed in our patients, nor were other environmental factors, such as viral infection or exposure to chemicals, identified.

Despite many reports suggesting the role of environmental factors in the development of PM/DM and the production of myositis-related autoantibodies (19,23,24), no single factor can explain their pathogenesis in a significant proportion of patients with PM/DM. It is likely that as-yet-unidentified environmental factors play a critical role in the pathogenesis of PM/DM. It is also possible that the critical environmental factors are difficult to identify, because the determining factor is an unusual immune response that confers susceptibility to a ubiquitous environmental factor.

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## Erratum

In the article by Navratil et al published in the February 2006 issue of *Arthritis & Rheumatism* (pp. 670–674), the disclosure of interest information provided by the authors was inadvertently omitted from the publication. The following disclosure paragraph should have been included: “Drs. Manzi and Ahearn have received consulting fees (more than \$10,000) from StageMark, Inc. Dr. Ahearn holds stock in Stagemark, Inc. Drs. Navratil, Manzi, Liu, and Ahearn have patent, licensing, and royalty agreements with StageMark, Inc.”

We regret the error.