研究用

EUROLINE ANA Profile 23 (IgG)

ORDER NO.	ANTIBODIES AGAINST	IG CLASS	SUBSTRATE	FORMAT
DL 1590-1601-23 G DL 1590-5001-23 G DL 1590-6401-23 G	dsDNA, nucleosomes, histones, SS-A, Ro-52, SS-B, nRNP/Sm, Sm, Mi-2α, Mi-2β, Ku, CENP A, CENP B, Sp100, PML, Scl-70, PM-Scl100, PM-Scl75, RP11, RP155, gp210, PCNA, DFS70	IgG	Ag-coated immunoblot strips	16 x 01 (16) 50 x 01 (50) 64 x 01 (64)

Indications: The EUROLINE test kit provides qualitative in vitro determination of human autoantibodies of the immunoglobulin class IgG to the 23 different antigens **dsDNA, nucleosomes, histones, SS-A, Ro-52, SS-B, nRNP/Sm, Sm, Mi-2α, Mi-2β, Ku, CENP A, CENP B, Sp100, PML, Scl-70, PM-Scl100, PM-Scl75, RP11, RP155, gp210, PCNA and DFS70** in serum or plasma to support the diagnosis of Sharp syndrome (MCTD), systemic lupus erythematosus (SLE), Sjögren's syndrome, progressive systemic sclerosis, poly-/dermato-myositis, overlap syndrome, the limited form of progressive systemic sclerosis (CREST syndrome) and primary biliary cholangitis.

Sensitivity and specificity:
dsDNA: For the detection of autoantibodies against dsDNA a sensitivity of 93% with reference to the ELISA method was determined using 36 samples of patients with SLE. The specificity was 100% for healthy blood donors (n = 50) and for a panel of non-SLE rheumatic diseases (Sjögren's syndrome n = 14, systemic sclerosis n = 18).

Nucleosomes: For the detection of autoantibodies against nucleosomes a sensitivity of 97% with reference to the EUROIMMUN Anti-Nucleosomes ELISA (IgG) method was determined using 34 samples of patients with SLE. The clinical prevalence determined by the ELISA (CE-notified test, coated with native mononucleosomes free from histone H1 and non-histone proteins, patent EP1476750B1/US7566545 (B2)) amounts to 53%. The specificity was 100% for healthy blood donors (n = 50) and in a panel of non-SLE rheumatic diseases (Sjögren`s syndrome n = 14, systemic sclerosis n = 18).

Histones: For the detection of autoantibodies against histones a sensitivity of 75% with reference to the ELISA method was determined using 40 samples of patients with SLE. The specificity was 100% for healthy blood donors (n = 50) and 97% in a panel of non-SLE rheumatic diseases (Sjögren's syndrome n = 14, systemic sclerosis n = 18).

SS-A: For the detection of autoantibodies against SS-A a sensitivity of 100% with reference to the ELISA method was determined using 14 samples of patients with Sjögren's syndrome. The specificity was 100% for healthy blood donors (n = 50) and 97.4% in a panel of non-SLE rheumatic diseases (systemic sclerosis n = 18, MCTD n = 22).

Ro-52: For the detection of autoantibodies against Ro-52 a sensitivity of 100% with reference to the westernblot method was determined using 103 samples of patients with SLE and Sjögren's syndrome (SLE n = 23, Sjögren's syndrome n = 77 and neonatal lupus erythematosus n = 3). The specificity was 100% for healthy blood donors (n = 65). Antibodies against Ro-52 are not disease specific and can be detected in samples from patients suffering from myositis, systemic sclerosis and other rheumatic diseases. For example, sera from patients with systemic sclerosis (n = 20) showed a prevalence of 31.6% for autoantibodies against Ro-52.
Criteria for the interpretation of isolated positive reactions of the Ro-52 band: isolated antibody reactions with Ro-52 should not be evaluated as anti-SS-A positive or specific for SLE or Sjögren's syndrome, since anti-Ro-52 antibodies may also occur in other autoimmune diseases.

We recommend interpreting the EUROLINE with reference to the ANA screening test (HEp-2 cells/primate liver) as follows:

IIFT	**EUROLINE**		**Result**
HEp-2 cells	**Ro-52 (52 kDa)**	**SS-A (60 kDa)**	
ANA negative	positive	negative	Anti-SS-A negative

ANA positive	positive	negative	Anti-SS-A negative
ANA positive	positive or negative	positive	Anti-SS-A positive

It has been shown in various studies that anti-SS-A positive sera always contain antibodies against native SS-A (60 kDa protein) and may additionally exhibit antibodies against Ro-52. For example, in a Japanese study (EUROIMMUN) sera from 103 patients with SLE and Sjögren's syndrome (SLE n = 26, Sjögren's syndrome n = 77), which were characterised as anti-SS-A positive by double immunodiffusion, were investigated. 102 sera reacted with native SS-A, and 90 sera reacted additionally with the Ro-52 band. But no serum showed only a reaction with the Ro-52 band. This study demonstrates that anti- bodies against native SS-A can be reliably detected using the native SS-A. In rare cases and in suspected cases of neonatal lupus syndrome, the Ro-52 band may provide important supplementary information.

SS-B: For the detection of autoantibodies against SS-B a sensitivity of 100% with reference to the ELISA method was determined using 14 samples of patients with Sjögren's syndrome. The specificity was 100% for healthy blood donors (n = 50) and 100% in a panel of non-SLE rheumatic diseases (systemic sclerosis = 18, MCTD n = 22).

nRNP/Sm: For the detection of autoantibodies against RNP/Sm a sensitivity of 100% with reference to the ELISA method was determined using 22 samples of patients with MCTD (mixed connective tissue disease). The specificity was 100% for healthy blood donors (n = 50) and 98% in a panel of non-SLE rheumatic diseases (Sjögren's syndrome n = 14, systemic sclerosis n = 18, polymyositis n = 25).

Sm: For the detection of autoantibodies against Sm a sensitivity of 100% with reference to the ELISA method was determined using 45 samples of patients with SLE. The specificity was 100% for healthy blood donors (n = 50) and 100% in a panel of non-SLE rheumatic diseases (Sjögren's syndrome n = 14, systemic sclerosis n = 18, polymyositis n = 25).

Mi-2α: Sera from 264 patients with clinically characterised myositis and 120 control samples were investigated for antibodies against Mi-2α. The prevalence amounted to 7%, at a specificity of 100%.

Mi-2β and Ku: Sera from 153 patients with clinically characterised myositis (50 patients with dermatomyositis, 89 patients with polymyositis, 4 patients with juvenile dermatomyositis and, 10 patients with inclusion body myositis) and 77 sera from control patients (26 patients with Sjögren syndrome, 26 patients with SLE and 25 patients with systemic sclerosis) were investigated for antibodies against Mi-2β and Ku. There were prevalences of 3% each, at a specificity for myositis of 100% and 97%, respectively.

Scl-70, CENP A, CENP B, RP11, RP155, PM-Scl100 and PM-Scl75: 129 sera from patients with clinically characterised systemic sclerosis (SSc, diffuse and limited form) as well as 202 sera from control patients (50 patients with dermato/polymyositis, 50 with systemic lupus erythematosus, 42 with rheumatoid arthritis and 60 healthy blood donors) were tested for antibodies against Scl-70, CENP A, CENP B, RP11 and RP155 (RNA Polymerase III subunits), PM-Scl100 and PM-Scl75. Sensitivities and specificities were calculated by ROC analysis at the given cut-off value of 10 intensity units of the EUROLINEScan program.

Anti-	**Sensitivity [%]**	**Specificity [%]**
Scl-70	65.1	98.5
CENP A	10.9	98.5
CENP B	13.2	98.5
RP11	5.4	99.5
RP155	7.0	100.0
PM-Scl100	6.6	99.0
PM-Scl75	11.8	98.0

Sp100, PML and gp210: Sera from 170 patients with clinically characterised primary biliary cholangitis (PBC), 49 sera from patients with autoimmune hepatitis (AIH), 200 sera from patients with viral hepatitis (HCV or HBV) were investigated for the presence of antibodies against Sp100, PML and gp210. Based on this study, four patients from the AIH patient panel were diagnosed with PBC/AIH overlap syndrome.

Anti-	Sensitivity [%]	Specificity [%]
Sp100	20.6	99.2
PML	12.9	98.8
gp210	26.5	98.8

PCNA: In 13 of 20 patient sera, having a cyclin I-positive pattern in the indirect immunofluorescence (HEp-2-cells/primate liver), autoantibodies against PCNA were detected. The specificity was 100% for healthy blood donors (n = 50) and 100% in cyclin I-negative sera of patients with SLE (n = 83).

DFS70: The investigation of sera from 198 healthy blood donors showed a prevalence of 3.5% (n = 7) for autoantibodies against DFS70. All positive samples showed a granular ANA pattern and a granular colouring of the chromosomes (typical of anti-DFS70) in the indirect immunofluorescence test with HEp-2 cells. The investigation of sera from 50 samples with positive, partly unclear ANA pattern showed, with respect to the reference method ELISA, a sensitivity of 92.3% at a specificity of 91.7% for the detection of autoantibodies against DFS70. With respect to the reference method Westernblot (whole cell lysate from HEp-2 cells with specific detection of the DFS70 band), the investigation showed a sensitivity of 100% at a specificity of 85.7% in the same samples (n = 49).

Reference range: The reference range was determined by incubating samples from healthy blood donors (n = 50). All blood donors were negative (exception see DFS70).

Clinical significance

Antibodies against nuclear antigens (ANA) are directed against various cell nuclear components (biochemical substances in the cell nucleus). These encompass nucleic acids, cell nuclear proteins and ribonucleoproteins. The serological detection of autoantibodies against individual or several cell nuclear autoantigens is an essential element in the diagnosis of autoimmune diseases, particularly rheumatic diseases. The frequency (prevalence) of anti-nuclear antibodies in inflammatory rheumatic diseases is between 20% and 100% (in rheumatoid arthritis between 20% and 40%). Therefore, differential ANA diagnostics to detect autoantibodies against different nuclear antigens is indispensable for the identification of individual rheumatic diseases. ANA analysis is also helpful in the diagnosis of other autoimmune diseases, such as primary biliary cholangitis (PBC) or autoimmune hepatitis (AIH).

The ANA profiles offer innovative test combinations based on the lineblot technology (EUROLINE). Positive test results provide important serodiagnostic information for the diagnosis of the rheumatic diseases below, as well as further autoimmune diseases such as PBC.

1. Systemic lupus erythematosus (SLE)

   SLE is a chronic inflammatory autoimmune disease which occurs in phases and mainly affects the connective tissue and various organic systems. Worldwide, women are ten times more frequently affected by collagenosis than men, whereby there are regional differences, e.g. 12.5 in 100,000 women in central Europe and up to 100 in 100,000 women in the US have SLE. The predilection age is between 15 and 30 years. The clinical symptoms vary greatly and can include butterfly erythema, discoid hyperkeratotic skin changes, purpura, arthralgia, myalgia, kidney insufficiency, neuropsychiatric abnormalities, polyneuropathy, pericarditis, cardiomyopathy, pleuritis, lung fibrosis, anaemia, hepatomegaly and splenomegaly. An SLE attack is often accompanied by fever.

   In drug-induced lupus around 50 to 75% of patients treated with procainamide and 25 to 30% of those treated with hydralazine develop ANA without symptoms of SLE during long-term therapy. A third of these patients demonstrate autoantibodies against histones and after varied duration of therapy show polyarthalgia, pleuritis and pericarditis. These ANA persist for years after the drugs have been discontinued and the symptoms have abated.

2. Sharp syndrome (mixed connective tissue disease = MCTD)

   Sharp syndrome is a multi-symptomatic and multiform MCTD combining symptoms of rheumatoid arthritis (RA), SLE, systemic sclerosis (SSc) and polymyositis. It has not yet been clarified if it is an independent disease.

3. Sjögren's syndrome (primary Sjögren's syndrome, SS)

   SS is a chronic inflammatory autoimmune disease of the exocrine glands which can be found in one to four million people in the US alone. Nine out of ten patients are women. The main clinical feature of primary SS is ocular and oral dryness as a result of the destruction of lachrymal and salivary glands by lymphocytic infiltration. The pancreatic glands, the mucous secreting glands of the intestine, bronchia or vagina and the sudoriferous glands may also be affected. Around 5% of SS patients develop malignant lymphoma. In secondary SS the disease signs of primary SS occur as accompanying symptoms of RA, SSc, SLE, polymyositis/dermatomyositis, PBC and AIH.

4. Systemic sclerosis (systemic scleroderma, SSc)

   SSc is an autoimmune connective tissue disease, which affects the skin and the inner organs. It affects around 2 to 50 in 100,000 persons worldwide (USA: 25 in 100,000), and is around three to four times more common in women than in men.

   Shortening of the lingual frenum and Raynaud's syndrome are early symptoms of SSc. In the following phase oedema of the hands and feet develop. The skin becomes stiff and in later stages atrophic, waxy and thin. Finally, deformation of the hands occurs. The fingers become fixed in a bent position (claw hand) and are highly tapered at the ends (Madonna fingers). Furthermore, the characteristic masklike face with rigid mimic develops. Finally, callosity of the inner organs, particularly of the digestive tract, lungs, heart and kidneys occurs. At present, lung involvement is the most frequent cause of death from SSc. Manifest SSc is the collagenosis with the highest vital risk for the patient. The 10-year survival rate is 55%.

   SSc is divided into limited and diffuse forms, depending on the cutaneous distribution. In the limited form, skin involvement is limited to the distal extremities. In the diffuse form (also proximal systemic sclerosis) the symptoms are diffusely distributed over the trunk, the proximal and distal extremities and the face.

5. Myositis (poly-/dermatomyositis)

   The autoimmunogenic myositides (idiopathic inflammatory myopathies) are systemic autoimmune diseases with inflammation of the skeletal musculature, symmetric and proximal accentuated pain and muscle weakness. They occur with an incidence of 0.1-1 per 100,000 per year, a prevalence of 1-6 per 100,000 and ratio of men to women of 1 to 2. They can be divided into polymyositis of adults (around 30%), dermatomyositis of adults (around 30%), paraneoplastic polymyositis of the lungs, ovaries, mammary glands, gastrointestinal tract and in myeloproliferative diseases (around 8%), infantile myositis/dermatomyositis with accompanying vasculitis (around 7%), as well as myositides in association with autoimmune diseases such as RA, lupus erythematosus, MCTD and rare forms such as granulomatosis, eosinophile, focal and inclusion body myositis (around 20%). It should be noted that dermato-/polymyositis is often of paraneoplastic origin, particularly in elderly patients. Dermatomyositis symptoms can occur before the tumour is even diagnostically detectable.

   Polymyositis (PM) is a systemic inflammatory disease of the skeletal muscles of unknown aetiology with perivascular lymphocytic infiltration. When the skin is involved, the disease is known as dermatomyositis (DM). Clinical symptoms of PM are recurring bouts of fever, muscle weakness, arthralgia, possibly Raynaud's syndrome, trouble with swallowing and involvement of the inner organs. In DM, skin symptoms appear as purple-coloured exanthema on the eye lids, nose bridge and cheeks, periorbital oedema, local erythema and scaly eczema dermatitis.

6. Rheumatoid arthritis (RA)

   RA is both one of the most common autoimmune disorders and the most common chronic inflammatory joint disease. The disease affects around 1% of the world population, whereby 75% of patients are female. It is characterised by inflammation of the synovial membrane, which spreads symmetrically from the small to large joints leading to the destruction of the joints in the late phase accompanied by a systemic involvement of the soft tissue. Initial symptoms include painful swelling of basic finger joints with morning stiffness in the joints. Reliable and earliest possible diagnosis is indispensable to keep the disease under control with suitable therapy and to avoid irreversible joint damage.

7. Primary biliary cholangitis (PBC)

   PBC is a chronic non-suppurative destructive cholangitis with progressive inflammatory destruction of the small biliary ducts and liver cirrhosis in the final stage. In 80 to 90% of cases the patients are female, mainly between 20 and 60 years of age. In rare cases, the disease also affects children. In Germany the prevalence is around 3 to 4 cases per 100,000 inhabitants. Demographic differences (Caucasians, Africans, etc.) are minimal.

   PBC can be subdivided into various stages based on liver biopsy results. In around 6% of cases there is an increased risk of hepatocellular carcinoma. In the final stage of PBC (decompensated cirrhosis) only liver transplantation will save the patient's life. In around 75% of cases the transplant patients recover fully from PBC. Some patients, however, suffer a PBC relapse after transplantation, but only with a very slow disease course.

   In addition to the typical PBC histological characteristics, specific serodiagnostic parameters are important for confirming suspected cases of PBC: 1. Biochemical markers of cholestasis, such as increased levels of alkaline phosphatase (AP) and gamma-glutamyl transferase (γGT) in serum. 2. Presence of PBC-specific autoantibodies, in particular autoantibodies against mitochondria (AMA) which are directed against the component M2 (family of oxo-acid dehydrogenases) 3. Additional determination of ANA, in particular against nuclear granules (nuclear dots, sp100 and PML) and against nuclear membrane (gp210), which are also pathognomonically relevant. Autoantibodies against centromere proteins are found regularly in a proportion of patients with overlap syndrome with SSc.

Overview

Autoantibodies against	**Autoimmune disease**	**Prevalence**
nRNP/Sm	MCTD	95%
Sm	SLE	5% - 40%
SS-A	SS or SLE Neonatal lupus erythematosus	40% - 95% or 20% - 60% 95% - 100%
Ro-52	SS or SLE SSc or idiopathic inflammatory myopathy	70% - 90% or 40% - 60% 20% or 20% - 40%
SS-B	SS or SLE Neonatal lupus erythematosus	40% - 95% or 10% - 20% 75%
Scl-70	SSc Diffuse or limited form of SSc	25% - 75% 40% - 65% or 5% - 15%
PM-Scl	SSc including overlap syndrome PM/SSc overlap syndrome SSc (anti-PM-Scl75 positive) SSc (anti-PM-Scl100 positive)	10% - 20% or 5% - 20% 18% 24% - 50% 7%
Jo-1	Myositis (polymyositis/dermatomyositis)	25% - 35%
CENP A	SSc - limited form or SSc - diffuse form	80% - 95% or 5% - 10%
CENP B	SSc - limited form or SSc - diffuse form PBC	80% - 95% or 8% 10% - 30%
PCNA	SLE	3%
dsDNA	SLE	40% - 90%
Nucleosomes	SLE	40% - 70%
Histones	Drug-induced SLE SLE or RA	95% - 100% 50% or 15% - 50%

Autoantibodies against	Autoimmune disease	Prevalence
Ribosomal P-protein	SLE	10%
AMA-M2	PBC or other chronic liver diseases SSc	up to 96% or 30% 7% - 25%
DFS70	Atopic dermatitis Rheumatic diseases	4% - 10% 5% - 10%
Mi-2α	DM	approx. 20%
Mi-2β	DM, associated with neoplasia (e.g. colon or breast carcinoma)	approx. 10%
Ku	SLE/myositis/SSc	up to 10%/40%/5%
RP11	SSc	5%
RP155	SSc	7%
Sp100	PBC	21%
PML	PBC	13%
gp210	PBC	26%

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