



The  
**Ehlers  
Danlos**  
Society™



**EDS ECHO SUMMIT SERIES**

**PRESENTATION**

# **Autoimmune Disease And the Ehlers-Danlos Syndromes**

**SPEAKER**

**Clair A. Francomano MD**  
**Indiana University School of Medicine**

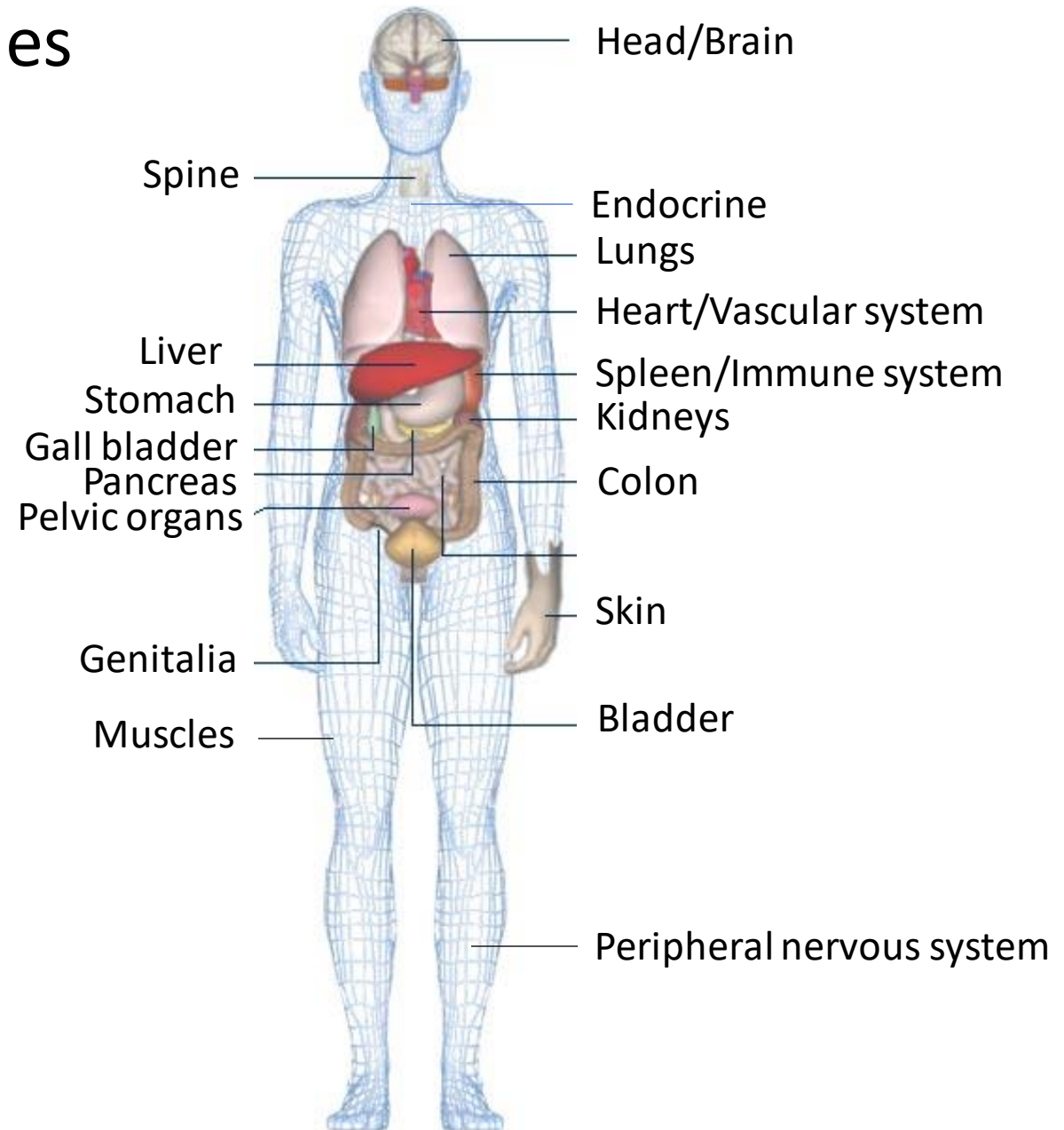
ECHO SUMMIT

# Disclosures

Dr. Francomano is a consultant to Acer Therapeutics and serves on the Scientific Advisory Board for Kyani International.

If you can't connect the issues  
Think Connective Tissues!

Heidi Collins, MD



# SCIENTIFIC REPORTS



**OPEN**

## **Ehlers-Danlos syndrome hypermobility type is associated with rheumatic diseases**

Received: 21 July 2016

**Kyla R. Rodgers<sup>1</sup>, Jiang Gui<sup>2,3,4</sup>, Mary Beth P. Dinulos<sup>5,6,7</sup> & Richard C. Chou<sup>1,8</sup>**

## Significantly higher prevalence in hEDS compared to the General Population

Primary Hypogammaglobulinemia

Hereditary Angioedema

Fibromyalgia

Erythromelalgia

Tumor necrosis factor-receptor associated periodic syndrome (TRAPS)

Systemic lupus

Rheumatoid arthritis

Psoriatic arthritis

Psoriasis

Pernicious anemia

Inflammatory eye disease

Crohn's Disease

Autoimmune Thyroiditis

Ankylosing spondylitis

Rodgers, K. R. *et al.* Ehlers-Danlos syndrome hypermobility type is associated with rheumatic diseases. *Sci. Rep.* **7**, 39636; doi: 10.1038/srep39636 (2017)

➤ [Arthritis Care Res \(Hoboken\)](#). 2021 Nov 17. doi: 10.1002/acr.24819. Online ahead of print.

# **Prescription Claims for Immunomodulator and Anti-Inflammatory Drugs among Persons with Ehlers-Danlos Syndromes**

Radha Dhingra<sup>1</sup>, Alan Hakim<sup>2 3</sup>, Rebecca Bascom<sup>1 2</sup>, Clair A Francomano<sup>4</sup>, Jane R Schubart<sup>1 5</sup>

Affiliations + expand

PMID: 34788905 DOI: [10.1002/acr.24819](#)

Table 1. Classification of Immunomodulator and Anti-Inflammatory Drugs

Drug Groups	Drug Class	Names of Drugs included from the claims
Non-Biologic DMARDs	Conventional DMARDs (Disease-modifying anti-rheumatic drugs)	Hydroxychloroquine, Leflunomide, Methotrexate, Sulfasalazine
	Other Non-Biological DMARD	Azathioprine, Cyclosporine, Mycophenolate
	Separate (Special use DMARD)	Minocycline
Biologic Agents	Anti-TNF-alpha Biologics	Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab
	Other Biologics	Abatacept, Rituximab
	JAK Inhibitor	Tofacitinib
Immunoglobulin Therapy	Non-RA Biologics	Canakinumab, Ranibizumab, Ustekinumab, Sirolimus, Tacrolimus
		Immune globulin (IVIG)
Anti-inflammatory Agents	NSAIDs	Aspirin, Celecoxib, Choline Magnesium Trisalicylate, Diclofenac, Diflunisal, Etodolac, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Salsalate, Sulindac, Tolmetin, Valdecoxib
	Injectable Steroids	Hydrocortisone Sodium Succinate, Methylprednisolone Acetate, Methylprednisolone, Triamcinolone Acetonide
	Oral Steroids	Prednisone, Prednisolone, Prednisolone Sodium Phosphate, Prednisolone Acetate
	Less common Steroids	Dexamethasone, Dexamethasone Sodium Phosphate, Betamethasone Sodium Phosphate, Betamethasone Dipropionate, Betamethasone Valerate, Betamethasone/Calcipotriene, Betamethasone/Clotrimazole, Hydrocortisone, Hydrocortisone Acetate, Amcinonide, Alclometasone, Clobetasol, Clocortolone, Diflorasone, Desoximetasone, Difluprednate, Desonide, Flurandrenolide, Fluocinonide, Fluocinolone, Halobetasol, Halcinonide, Hydrocortisone/Iodoquinol, Hydrocortisone/Lidocaine, Hydrocortisone/Pramoxine

Dhingra R et al., Prescription claims for immunomodulator and anti-inflammatory drugs among persons with Ehlers-Danlos Syndromes. Arthritis Care Res 2021 Nov 17. doi: 10.1002/acr24819. PMID: 34788905



**Table 2. Percentage of Persons with EDS (Cases=3484) and Matched Controls (N=3484) with Prescription Claims for Immunomodulator Medications. Conditional Odds Ratio (95% CI) are also Reported**

Medication Classes	Cases N (%; [95% CI]) %F, %M %P, %A	Controls N (%; [95% CI]) %F, %M %P, %A	P-value*	Conditional Odds Ratio for the Entire Cohort** (95% CI)
At least One Immunomodulator Medication	2280 (65.4; [63.8, 67.0]) 69.7, 53.1 50.1, 71.9	1853 (47.4; [45.7, 49.1]) 50.6, 38.2 34.6, 52.8	<0.0001	2.2 (2.0, 2.4)
Non-Biologic Agents (DMARDs)	197 (5.65; [4.9, 6.4]) 6.8, 2.3 1.4, 7.4	53 (1.52; [1.1, 1.9]) 1.9, 0.3 0.2, 2.0	<0.0001	4.2 (3.0, 5.8)
Biologic Agents	49 (1.41; [1.0, 1.8]) 1.4, 1.3 0.9, 1.5	36 (1.03; [0.7, 1.4]) 1.0, 1.1 0.7, 1.1	<0.0001	1.3 (0.8, 2.0)
NSAIDs	1438 (41.2; [39.6, 42.9]) 46.2, 27.6 25.0, 48.1	857 (24.6; [23.1, 26.0]) 24.2, 15.1 11.5, 30.1	<0.0001	2.3 (2.0, 2.5)
Injectable Steroids	709 (20.3; [19.0, 21.7]) 22.9, 12.9 11.7, 23.9	452 (12.9; [11.8, 14.1]) 14.2, 9.2 8.9, 14.6	<0.0001	1.7 (1.5, 2.0)
Oral Steroids	805 (23.1; [21.7, 24.5]) 24.8, 18.8 21.0, 23.9	462 (13.2; [12.1, 14.4]) 13.9, 11.3 10.6, 14.3	<0.0001	2.0 (1.7, 2.2)

-EDS: Ehlers-Danlos Syndromes

-DMARDs: Disease-modifying anti-rheumatic drugs

-NSAIDs: Non-steroidal anti-inflammatory drugs

-\*P value is from the McNemar's test comparing overall proportions between cases and controls.

-sex-stratified percentages are shown under overall percentages (%F, %M), and represent percentages for female cases versus female controls (N=5164); and male cases versus male controls (N=1804).

-age group stratified percentages (%Pediatric, %Adult) are shown under sex-stratified percentages, and represent percentages for pediatric cases versus pediatric controls (N=2074); and adult cases versus adult controls (N=4894).

-\*\*Conditional Odds ratio and 95% Confidence Interval (CI) were calculated using Conditional Logistic Regression Analyses to account for the matching.

Dhingra R et al., Prescription claims for immunomodulator and anti-inflammatory drugs among persons with Ehlers-Danlos Syndromes. Arthritis Care Res 2021 Nov 17. doi: 10.1002/acr24819. PMID: 34788905



BRIEF COMMUNICATION

## **Autoimmune postural orthostatic tachycardia syndrome**

Mari Watari<sup>1</sup>, Shunya Nakane<sup>1,2</sup>, Akihiro Mukaino<sup>1</sup>, Makoto Nakajima<sup>1</sup>, Yukiko Mori<sup>1</sup>, Yasuhiro Maeda<sup>3,4,5</sup>, Teruaki Masuda<sup>1</sup>, Koutaro Takamatsu<sup>1</sup>, Yanosuke Kouzaki<sup>6</sup>, Osamu Higuchi<sup>3</sup>, Hidenori Matsuo<sup>4</sup> & Yukio Ando<sup>1</sup>

### **Abstract**

The aim of this study was to evaluate the association between postural orthostatic tachycardia syndrome (POTS) and circulating antiganglionic acetylcholine receptor (gAChR) antibodies. We reviewed clinical assessments of Japanese patients with POTS, and determined the presence of gAChR antibodies in serum samples from those patients. Luciferase immunoprecipitation systems detected anti-gAChR $\alpha$ 3 and  $\beta$ 4 antibodies in the sera from POTS (29%). Antecedent infections were frequently reported in patients in POTS patients. Moreover, autoimmune markers and comorbid autoimmune diseases were also frequent in seropositive POTS patients. Anti-gAChR antibodies were detectable in significant number of patients with POTS, and POTS entailed the element of autoimmune basis.

Received: 20 March 2018 | Revised: 23 November 2018 | Accepted: 3 February 2019

DOI: 10.1002/ccr3.2070

**CASE REPORT**

WILEY [Clinical Case Reports](#) Open Access

# **Hypermobile type Ehlers-Danlos syndrome associated with hypogammaglobulinemia and fibromyalgia: A case-based review on new classification, diagnosis, and multidisciplinary management**

Wei Zhang<sup>1</sup>  | Kevin Windsor<sup>2</sup> | Richard Jones<sup>1,3</sup> | David Oscar Taunton<sup>1</sup>

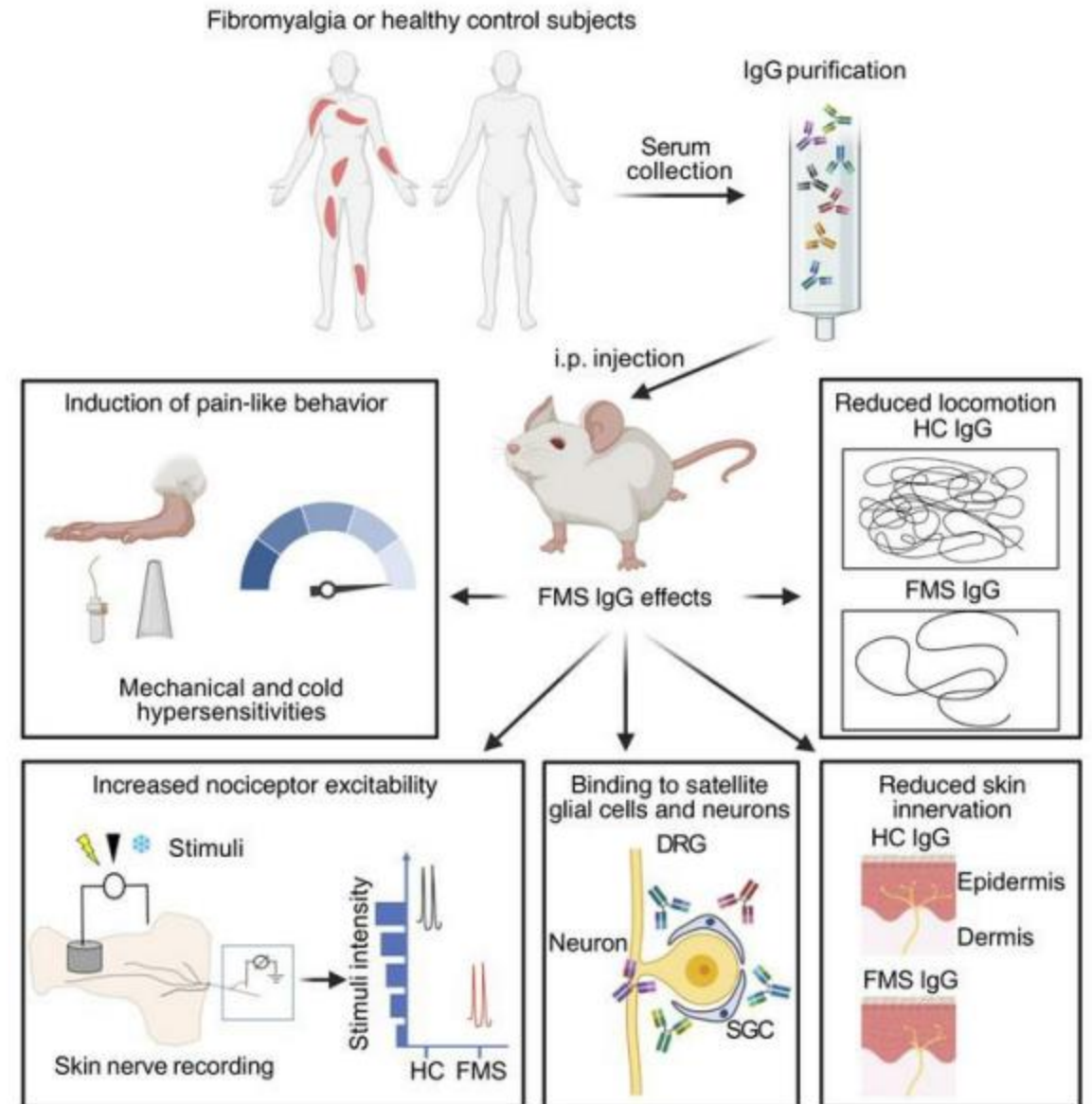
## Passive transfer of fibromyalgia symptoms from patients to mice

Andreas Goebel, ... , Camilla I. Svensson, David A. Andersson

*J Clin Invest.* 2021;131(13):e144201. <https://doi.org/10.1172/JCI144201>.

IgG from patients with fibromyalgia was injected into mice and caused:

- Increased pain-like behavior
- Mechanical and cold hypersensitivity
- Reduced locomotion
- Increased nociceptor excitability
- Reduced skin innervation
- Binding to satellite glial cells and neurons



*Case Review*

# **Autoimmune Small Fiber Neuropathy Associated With Ehlers–Danlos Syndrome Treated With Intravenous Immunoglobulins**

*Melissa K. Cook, MD and Morgan Jordan, DO*

➤ [Rev Med Suisse](#). 2021 Apr 7;17(733):697-701.

## [Small fiber neuropathy in systemic autoimmune diseases]

[Article in French]

Gautier Breville <sup>1 2</sup>, Damien Fayolle <sup>1</sup>, Agustina M Lascano <sup>1 3</sup>, Patrice Lalive <sup>1</sup>, Jörg D Seebach <sup>2</sup>

Affiliations [+](#) expand

PMID: 33830702

### **Abstract** in English, [French](#)

Small fiber neuropathy (SFN) causes damage to small-calibre nerve fibers (unmyelinated C fibers and myelinated A-delta fibers). The symptoms of SFN usually are sensitive including paresthesia, dysesthesia or burning pain, and protopathic deficits, sometimes associated with dysautonomia. The causes of SFN can be classified in six main groups: idiopathic, toxic, metabolic, immunological, infectious and hereditary. In this article, we present the diagnostic approach to SFN, the most common autoimmune aetiologies, as well as elements of their therapeutic management.



## Alimentary Tract

## Nationwide population-based cohort study of celiac disease and risk of Ehlers-Danlos syndrome and joint hypermobility syndrome



Monika Laszkowska<sup>a,1</sup>, Abhik Roy<sup>a,1</sup>, Benjamin Lebwohl<sup>a,b</sup>, Peter H.R. Green<sup>a</sup>,  
Heléne E.K. Sundelin<sup>c</sup>, Jonas F. Ludvigsson<sup>b,d,e,\*</sup>

<sup>a</sup> Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA

<sup>b</sup> Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

<sup>c</sup> Department of Pediatrics, Linköping, University Hospital, Linköping, Sweden

<sup>d</sup> Department of Pediatrics, Örebro University Hospital, Örebro, Sweden

<sup>e</sup> Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK

. The incidence of EDS or JHS was 14 per 100,000 person-years in CD, compared with 9 per 100,000 person-years in the reference cohort. This corresponded to a HR of 1.49 (95%CI = 1.07–2.07;  $p = 0.018$ ).

**Table 1**

Characteristics of patients with celiac disease and matched controls.

Characteristic	CD ( $n = 28,361$ ) <sup>a</sup>	Controls ( $n = 139,832$ ) <sup>a</sup>
Age at study entry (years)		
Median/range	29/0–95	29/0–95
0–19	11,776 (41.5)	58,517 (41.8)
20–39	5262 (18.6)	26,051 (18.6)
40–59	6338 (22.3)	31,380 (22.4)
≥60	4985 (17.6)	23,884 (17.1)
Male	10,694 (37.7)	52,505 (37.5)
Female	17,667 (62.3)	87,327 (62.5)
Calendar period of study entry		
≤1989	3681 (13.0)	17,647 (12.6)
1990–1999	11,762 (41.5)	57,967 (41.5)
≥2000	12,918 (45.5)	64,218 (45.9)
Born in the Nordic countries	27,423 (96.7)	131,770 (94.2)
Developed EDS/JHS <sup>a</sup>	45 (0.15)	148 (0.11)

<sup>a</sup> Number with percentages within brackets where not otherwise stated. EDS, Ehlers-Danlos syndrome; JHS, joint hypermobility syndrome.

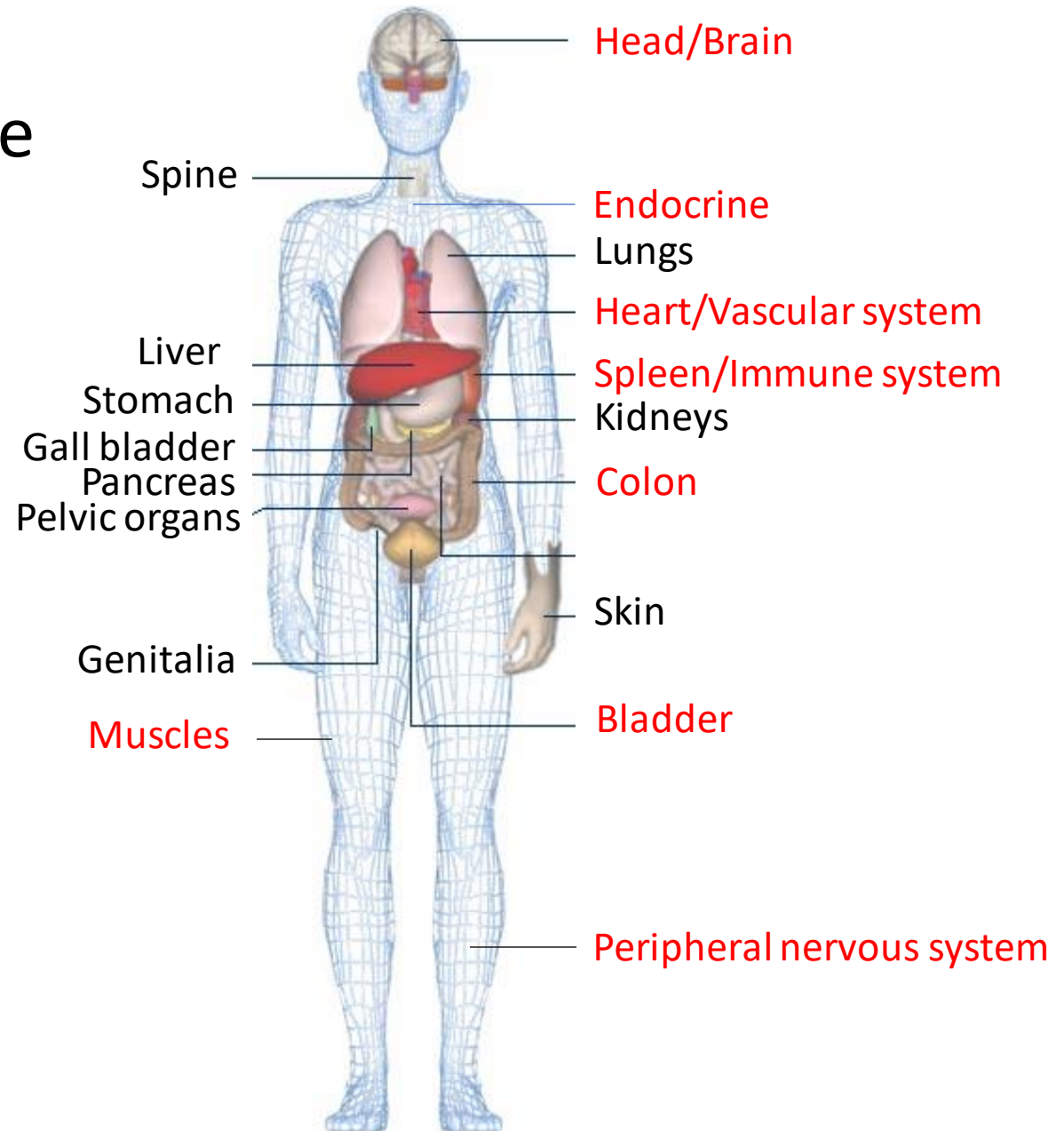
# Conditions Considered as Co-morbid with Autoimmune Disease

- Chronic fatigue syndrome
- Complex regional pain syndrome
- Eosinophilc esophagitis
- Gastritis
- Raynaud's phenomenon
- Primary immunodeficiency

These conditions are highly represented in the Ehlers-Danlos population as well



Organs in which there is  
at least preliminary evidence  
of an autoimmune process  
associated with EDS



Why might people with EDS be at increased risk for autoimmune conditions?

- Immune Dysregulation
- Maternal-fetal cell trafficking
- ??????

# EDS and Autoimmune Conditions: State of the Science



# Thanks

- Dr Alan Hakim
- Lara Bloom
- The Ehlers-Danlos Society