Clinical manifestations, disease penetrance, and treatment in individuals with SOCS1 insufficiency: a registry-based and population-based study

Jerome Hadjadj, Anna Wolfers*, Oleg Borisov*, Derek Hazard, Ronan Leahy, Marie Jeanpierre, Alexandre Belot, Shahrzad Bakhtiar, Fabian Hauck, Pui Y Lee, Stefano Volpi, Serena Palmeri, Vincent Barlogis, Nathalie Aladjidi, Georg Ebetsberger-Dachs, Jerome Avouac, Fabienne Charbit-Henrion, Morgane Cheminant, Jean Donadieu, Sujal Ghosh, David P Hoytema van Konijnenburg, Julia Körholz, Jacinta Bustamante, Jeremie Rosain, Lisa Forbes Satter, Ingrid Selmeryd, Georgios Sogkas, Benedicte Neven, Frederic Rieux-Laucat, Stephan Ehl, on behalf of the SOCS1 Study Group†*

Summary

Background Suppressor of cytokine signalling 1 (SOCS1) insufficiency is an inborn error of immunity affecting the negative regulation of cytokine and growth factor signalling. We aimed to enhance the understanding of clinical manifestations, disease trajectories, disease penetrance, and the effect of Janus kinase (JAK) inhibition in individuals with SOCS1 insufficiency.

Methods This study used data from two independent cohorts: the European Society for Immunodeficiencies (ESID) registry and the UK Biobank. Participants from the ESID registry were from nine European countries (Austria, Belgium, France, Germany, Ireland, Italy, Portugal, Sweden, and Ukraine), China, Taiwan, and the USA. Participants from the ESID registry were eligible if they had heterozygous, functionally validated *SOCS1* variants; participants from the UK Biobank were included if they had any *SOCS1* variant detected in the ESID registry cohort or any other *SOCS1* variant that was classed as high-impact. Clinical manifestations of the underlying SOCS1 insufficiency were documented and summarised into nine subgroups, with ICD-10 diagnosis codes collected for participants from the UK Biobank. Participants from the ESID registry were tested for relevant autoantibodies in their local laboratory. Responses to JAK inhibitor treatment in participants from the ESID registry were assessed by the treating physician using a visual analogue scale. Descriptive statistics were used for analysis. People with lived experience were not involved in the study design.

Findings We included 119 participants with SOCS1 insufficiency: 67 from the ESID registry, enrolled between Feb 15, 2021, and Dec 31, 2023, and 52 from the UK Biobank. Of the 67 participants from the ESID registry, 39 (58%) were female, 28 (42%) were male, and the median age was 28 years (IQR 15–44, range 2–85). 27 different monoallelic *SOCS1* variants were identified in these participants. 62 (93%) of the 67 participants in the ESID registry cohort were symptomatic and five (7%) were asymptomatic family members; of the 62 participants with symptoms, allergy (33 [50%]), inflammatory gastrointestinal (22 [36%]) and skin (18 [29%]) manifestations, autoimmune cytopenia (24 [39%]), and lymphoproliferation (23 [37%]) were most frequent. Rheumatological manifestations (23 [37%]) included systemic lupus erythematosus, Sjögren's disease, and rheumatoid arthritis, with typical autoantibody profiles. 42 (68%) of the 62 symptomatic participants had at least three different manifestations. In the UK Biobank we found 52 participants carrying high-impact *SOCS1* variants; 29 (56%) were female, 23 (44%) were male, and the median age was 72 years (65–78, 57–86). Only 30 (58%) of these participants had developed manifestations that were potentially related to SOCS1 insufficiency. Allergy and rheumatological manifestations were more common in participants from the UK Biobank than the ESID registry. Female predominance (21 [70%] of 30 participants were female and nine [30%] were male) was also found among symptomatic participants from the UK Biobank. Treatment with JAK inhibitors showed promising results in 12 (92%) of 13 participants in the ESID registry.

Interpretation SOCS1 insufficiency differs from other genetic autoimmune lymphoproliferative disorders by the presence of frequent atopic and rheumatological manifestations. Penetrance is incomplete and is higher in females than in males. JAK inhibition is a promising targeted therapy for patients with SOCS1 insufficiency.

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*Contributed equally

†Members listed in the appendix (pp 2–4)

Sorbonne University, Department of Internal Medicine, Assistance Publique-Hôpitaux de Paris (AP-HP), Saint-Antoine Hospital, Paris, France (J Hadjadj MD PhD); **University Paris Cité, Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, INSERM UMR 1163, Paris, France** (J Hadjadj, M Jeanpierre MSc, Prof B Neven MD PhD, F Rieux-Laucat PhD); **Institute for Immunodeficiency, Center for Chronic Immunodeficiency** (A Wolfers, Prof S Ehl MD), **Institute of Genetic Epidemiology** (O Borisov PhD), **and Institute of Medical Biometry and Statistics** (D Hazard PhD), **Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany; Paediatric Immunology, Children's Health Ireland, Dublin, Ireland** (R Leahy MD PhD); **University of Dublin, Trinity College, Dublin, Ireland** (R Leahy); **CIRI, INSERM U1111, UMR5308, University of Lyon, Lyon, France** (A Belot MD PhD); **National Referee Centre for Pediatric-Onset Rheumatism and Autoimmune Diseases (RAISE), Lyon, France** (A Belot); **Hospices Civils de Lyon, Paediatric**

Introduction

Immune dysregulatory disorders are a diverse group of diseases affecting around 15–35% of the global population. Key manifestations of dysregulated immunity are allergy, autoimmunity, inflammatory diseases, lymphoproliferative manifestations, infectious diseases, and malignancies. The occurrence of several of these manifestations in one individual suggests a

Nephrology, Rheumatology, Dermatology Unit, Mother and Children University Hospital, Bron, France (A Belot); **Division of Stem Cell Transplantation and Immunology, Department of Pediatrics, Goethe University Hospital Frankfurt, Frankfurt am Main, Germany** (S Bakhtiar MD); **Division of Pediatric Immunology and Rheumatology, Department of Pediatrics, Dr von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität München, Munich, Germany** (F Hauck MD PhD); **Division of Immunology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, USA** (P Y Lee MD, D P Hoytema van Konijnenburg MD PhD); **Dipartimento Di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI), Università degli Studi di Genova, Genoa, Italy** (S Volpi MD PhD, S Palmeri MD); **UOC Reumatologia e Malattie Autoinfiammatorie, IRCCS Istituto Giannina Gaslini, Genoa, Italy** (S Volpi, S Palmeri); **Department of Pediatric Hematology, Immunology and Oncology, APHM, Hôpital de la Timone Enfants, CEReSS Research Unit EA 3279, Aix Marseille University, School of Medicine, Marseille, France** (Prof V Barlogis MD PhD); **Pediatric Haemato-Immunology, INSERM CICP 1401, National Reference Center for Autoimmune Cytopenias in Children (CEREVANCE), Bordeaux University Hospital, Bordeaux, France** (N Aladjidi MD); **Department of Paediatrics and Adolescent Medicine, Johannes Kepler University Linz, Kepler University Hospital, Linz, Austria** (G Ebetsberger-Dachs MD); **Service de Rhumatologie, Hôpital Cochin, AP-HP Centre-Université Paris Cité, Paris, France** (J Avouac MD PhD); **Université Paris Cité, Department of Genomic Medicine of Rare Diseases, Hôpital Necker-Enfants Malades, AP-HP, Paris, France** (F Charbit-Henrion MD PhD); **Université de Paris Cité/Necker-Enfants Malades University Hospital, AP-HP, Clinical Haematology, Paris, France** (M Cheminant MD PhD);

Research in context

Evidence before this study

The contribution of genetic factors to immune dysregulation in complex diseases is yet to be fully explored. Suppressor of cytokine signalling 1 (SOCS1) insufficiency, an inborn error of immunity that affects negative control of cytokine and growth factor signalling, was first described in 2020. We searched PubMed for records published in English from database inception to Sept 1, 2024, using the search terms "SOCS1" and "deficiency" or "haploinsufficiency" or "inborn error of immunity". We identified nine publications describing 33 patients. These case reports and small case series illustrate a broad clinical phenotype of immune dysregulation, but asymptomatic carriers of deleterious variants from the same pedigrees were also reported. To our knowledge, there has been no standardised and complete systematic analysis of individual disease trajectories, including treatment responses and robust data on disease penetrance, in individuals with SOCS1 insufficiency.

Added value of this study

Combining data from a patient registry with population-based data, we provide systematic disease and treatment information on 119 participants with relevant *SOCS1* germline variants. The evolving disease phenotype includes a large spectrum of immune dysregulatory disorders, manifesting across all ages. Compared with other autoimmune lymphoproliferative immunodeficiencies, allergic and rheumatological disease manifestations are particularly prominent in individuals with SOCS1 insufficiency, although considerable overlap in prevalence is observed. Population-based analysis of 52 participants predicts a disease penetrance of less than 60%, with a female predominance. Janus kinase inhibitors might be an important therapeutic option, with variable effects on different manifestations of SOCS1 insufficiency.

Implications of all the available evidence

SOCS1 insufficiency is a genetic disorder resulting in predisposition to autoimmunity, allergy, lymphoproliferation, inflammatory disease, and infectious disease, with moderate penetrance. Awareness of this condition across disciplines is required to ensure that targeted therapies and genetic counselling are made available for affected individuals.

potential genetic contribution. Monogenetic inborn errors of immunity can present with numerous different immune dysregulatory manifestations.[1] In addition to rare autosomal-recessive diseases, this group of diseases includes several more prevalent autosomal-dominant genetic diseases with overlapping autoimmune lymphoproliferative immunodeficiency phenotypes,[2] such as CTLA4 deficiency,[3] activated PI3K delta syndrome,[4] or STAT3[5] gain-of-function associated disease, and NF-κB1 insufficiency.[6]

In 2020, suppressor of cytokine signalling 1 (SOCS1) insufficiency was added to the group of monogenetic immune dysregulatory disorders.[7–9] SOCS1 is a crucial negative regulator of Janus kinase (JAK)-STAT signalling, downregulating the activity of more than 30 cytokines and growth factors involved in immune responses—particularly those that signal through the γc-chain (the IL-2 family) and interferons.[10] SOCS1 regulates several immune processes, such as T-helper lymphocyte lineage decisions, regulatory T-cell function, B-cell function, and inflammatory or allergic responses.[11] In line with these broad immunological implications, initial studies have documented a diverse range of immune dysregulatory manifestations associated with SOCS1 insufficiency, including autoimmune cytopenia, systemic lupus erythematosus (SLE), asthma, inflammatory bowel disease, and susceptibility to viral and bacterial infectious diseases.[7–9,12–17] Notably, there have been reports of individuals with manifestations of SOCS1 insufficiency having asymptomatic family members who carry deleterious *SOCS1* variants, suggesting that penetrance is incomplete.[7]

A detailed description of the natural history of SOCS1 insufficiency has been challenging because of small patient numbers and variable and incomplete information about individual disease trajectories and responses to therapy. With poor awareness of this rare condition, patients are mainly identified by physicians specialised in inborn errors of immunity, which can lead to considerable bias because patients presenting to other specialists might not be diagnosed. Moreover, the report of a few asymptomatic carriers of deleterious variants is a poor basis for judging disease penetrance.[7] Although collecting standardised information on rare diseases is the domain of patient registries, the availability of genetic information in large-scale population-based studies has opened up unprecedented opportunities to contribute additional data.[18]

Here we present an international cohort of participants with SOCS1 insufficiency, integrating data from the European Society for Immunodeficiencies (ESID) registry and the UK Biobank.[18] We describe the clinical, immunological, and genetic characteristics of SOCS1 insufficiency and provide detailed descriptions of disease trajectories and treatment, with particular focus on response to JAK inhibitors.

Methods

Study design and participants

For this study we used data from two independent cohorts: the ESID registry and the UK Biobank. Participants from the ESID registry were from nine European countries (Austria, Belgium, France,

Germany, Ireland, Italy, Portugal, Sweden, and Ukraine), China, Taiwan, and the USA.

The SOCS1 subregistry was implemented within the ESID registry in 2021. To find eligible participants, we contacted all clinicians (mostly paediatric and adult clinical immunologists) who contributed patient data to the ESID registry and advertised the study via a dedicated SOCS1 registry page on the ESID website. In addition, we invited authors of publications on patients with SOCS1 insufficiency to contribute data on their patients. People with lived experience were not involved in the study design.

The core data sheet capturing information on clinical manifestations, genetic findings, and findings of immunological investigations as well as specific case report forms on rheumatological manifestations and JAK inhibitor treatment are provided in the appendix (pp 26–47). Ethnicity data were available for less than 40% of the ESID registry participants and we therefore decided not to include this information. Study enrolment was initiated on Feb 15, 2021, and the cutoff date was Dec 31, 2023. All participants with heterozygous, functionally validated *SOCS1* variants were eligible. Assays used for functional validation are specified in the appendix (pp 16–17). Participants could be included without functional validation if they had a predicted loss-of-function variant (termed a high-impact variant; eg, a frameshift deletion or premature stop mutation).

The study and use of ESID data was approved by the ethics committee of the University of Freiburg (number 20/1309). Written informed consent was obtained from participants in the ESID registry, their parents, or both.

We also identified participants with SOCS1 insufficiency in the UK Biobank.[18] The UK Biobank has 502 655 participants who were recruited between March 13, 2006, and Oct 1, 2010, when aged between 40 and 69 years. On recruitment, participants completed touchscreen and nurse-led questionnaires on their medical history, had physical measurements taken, and provided biological samples. Whole-exome sequencing data for approximately 470 000 participants were released in July, 2022.[19] In addition to self-reported health conditions, hospital inpatient data are available for the full cohort, providing information on all diagnoses and underlying conditions coded in ICD-10 (England, Scotland, and Wales; since 1998) or ICD-9 (Scotland; since 1981). We included all participants from the UK Biobank for whom whole-exome sequencing data were available, except for those who withdrew their consent. Information on ethnicity was self-reported in the touchscreen questionnaires; we did not apply any inclusion or exclusion criteria on the basis of ethnicity.

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee; participants provided written informed consent for data collection, data analysis, and record linkage. This study was conducted using the UK Biobank resource under application number 103789.

Procedures

We searched the UK Biobank for participants with the *SOCS1* variants detected in the ESID registry cohort and with variants otherwise classified as high-impact by the Ensembl Variant Effect Predictor[20] (eg, frameshift deletions or premature stop mutations). We also investigated the variants catalogued in ClinVar. We extracted all ICD-10 diagnostic codes of participants carrying these variants, but we defined as potentially related to SOCS1 only the 198 ICD-10 codes that were also observed in participants from the ESID registry (appendix pp 5–9). Participants with at least one such manifestation were classified as symptomatic.

Any of the following diagnoses were considered as a manifestation of the underlying SOCS1 insufficiency: any autoimmune, inflammatory or allergic disease; lymphoproliferation; or any malignancy. Manifestations were categorised into nine subgroups (allergy, non-allergic skin, liver, gastrointestinal, rheumatological, lymphoproliferation, autoimmune cytopenia, lung, and other inflammatory manifestations); however, for some manifestations, this classification was not obvious. We decided to group eczematous skin disorders with allergic manifestations (rather than with non-allergic skin disease) and systemic lupus erythematosous (SLE)-associated skin lesions with rheumatological manifestation (rather than with inflammatory skin diseases). Allergic bronchopulmonary aspergillosis was classed as a lung manifestation and asthma was classed as a manifestation of allergy. Hypereosinophilic syndrome was listed among allergic manifestations, whereas eosinophilic oesophagitis was classed as a gastrointestinal manifestation. In the ESID registry cohort, the diagnoses of SLE and arthritis were evaluated in detail and accepted only if they met the 2019 European Alliance of Associations for Rheumatology–American College of Rheumatology (EULAR–ACR) criteria.[21] Allergic rhinitis was not a specified manifestation in the dataset but could be listed as other allergic manifestation, and was counted as a separate manifestation only in participants without asthma. A participant was classified as asymptomatic in the ESID registry if the responsible physician did not list any manifestations and in the UK Biobank if no manifestations possibly related to SOCS1 were documented. Infectious diseases requiring hospitalisation were also recorded and analysed. For immunological investigations, physicians reported the first results obtained. Therapy with subcutaneous or intravenous immunoglobulin replacement, systemic steroids, immunosuppressive drugs, or monoclonal antibodies, as well as splenectomy or organ transplantation, were captured in the ESID registry with the participants age at start of therapy and treatment status at the time of registration also recorded. Response to

Pediatric Hemato-Oncology Department, Trousseau Hospital, AP-HP, Paris, France (J Donadieu MD PhD); **Department of Pediatric Oncology, Hematology and Clinical Immunology, Medical Faculty, Center of Child and Adolescent Health, Heinrich-Heine-University and University Hospital, Düsseldorf, Germany** (S Ghosh MD); **Department of Pediatrics, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany** (J Körholz MD); **Université Paris Cité, INSERM UMR1163, Imagine Institute, Paris, France** (J Bustamante MD PhD, J Rosain PharmD PhD); **Study Center for Primary Immunodeficiencies, Necker-Enfants Malades Hospital – AP-HP, Paris, France** (J Bustamante, J Rosain); **Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France** (J Bustamante, J Rosain); **St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA** (J Bustamante, J Rosain); **William T Shearer Center for Human Immunobiology, Texas Children's Hospital, Houston, TX, USA** (L Forbes Satter MD); **Department of Pediatrics Immunology Allergy and Retrovirology, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA** (L Forbes Satter); **Department of Infectious Diseases, Västmanland Hospital Västerås, Västerås, Sweden** (I Selmeryd MD); **Rheumatology and Immunology** (G Sogkas MD PhD) **and Cluster of Excellence RESIST (EXC 2155)** (G Sogkas), **Hannover Medical School, Hanover, Germany; Université Paris Cité, IHU-Imagine, Paris, France** (Prof B Neven, F Rieux-Laucat); **Paediatric Immuno-Haematology and Rheumatology Department, Necker Hospital for Sick Children, AP-HP, Paris, France** (Prof B Neven)

Correspondence to:
Prof Stephan Ehl, Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, 79104 Freiburg, Germany
stephan.ehl@uniklinik-freiburg.de

For the **SOCS1 registry page** see https://esid.org/socs1-study-socs1-registry/

See Online for appendix

For **ClinVar** see https://ncbi.nlm.nih.gov/clinvar/

	ESID registry (n=67)	UK Biobank (n=52)
Sex		
Female	39 (58%)	29 (56%)
Male	28 (42%)	23 (44%)
Age, years		
Age at first manifestation	10 (5–15; 1–44)	48 (38–59; 0–79)
Age at inclusion	28 (15–44; 2–85)	72 (65–78; 57–86)
Country or region		
Europe	61 (91%)	52 (100%)
USA	4 (6%)	0
China	1 (1%)	0
Taiwan	1 (1%)	0
***SOCS1* variants**		
Validated variant	60 (90%)	40 (77%)*
Other severe variant	5 (7%)	11 (21%)
Unvalidated point mutation	2 (3%)	1 (2%)*
Clinical manifestations		
Asymptomatic	5 (7%)	22 (42%)
Female	2/5 (40%)	8/22 (36%)
Male	3/5 (60%)	14/22 (64%)
Symptomatic	62 (93%)	30 (58%)
Female	37/62 (60%)	21/30 (70%)
Male	25/62 (40%)	9/30 (30%)

Data are n (%), n/N (%), or median (IQR; range). Percentages might not total 100 owing to rounding. ESID=European Society for Immunodeficiencies. SOCS1=suppressor of cytokine signalling 1. *All mutations were also observed in the ESID registry cohort.

Table: **Demographics and characteristics of participants from the ESID registry and UK Biobank**

JAK inhibitor treatment was documented in detail (appendix pp 44–45). Overall treatment response was assessed by the treating physician using a non-standardised subjective global response assessment (ie, wellbeing of the participant on JAK inhibitor treatment compared with before treatment when considering all relevant disease manifestations) on a visual analogue scale (VAS), scored from 0 (no response) to 10 (complete response).

Participants from the ESID registry were tested for autoantibodies (antinuclear antibodies, antinuclear antigen antibodies, and anti-double-stranded DNA) in the local laboratory chosen by their treating physicians. Flow cytometry was done locally according to local diagnostic protocols using whole blood or purified peripheral blood mononuclear cells. Panels and instruments were not standardised. Naive CD4 T cells were defined as the proportion of $CD4^+$ cells that were $CD45RA^+CD4^+$, class-switched memory B cells as the proportion of $CD19^+$ cells that were $CD27^+IgD^-$, and $CD21^{low}$ B cells as the proportion of $CD19^+$ cells that were $CD21^{low}$. Results were compared with age-related normal values from the literature.[22]

Statistical analysis

The cutoff for recruitment in the ESID registry was Dec 22, 2023, with the aim of recruiting 100 participants with SOCS1 insufficiency. We expected this number of participants to sufficiently reflect the diversity of disease manifestations. Information given as unknown or not obtained was interpreted as missing. If the date of laboratory measurements was missing, the date of study inclusion was used instead. Data cleaning and analyses were done with R (version 4.2.3) and Microsoft Excel 2016. Descriptive statistics were used in the analysis. Because of the different recruitment approaches, data from the ESID registry and the UK Biobank were analysed separately.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In this study, we included 119 participants with SOCS1 insufficiency: 67 from the ESID registry and 52 from the UK Biobank. Between Feb 15, 2021, and Dec 31, 2023, 67 participants with heterozygous *SOCS1* variants from 33 pedigrees were reported to the ESID registry (table). Participants were from nine European countries (n=61), the USA (n=4), China (n=1), and Taiwan (n=1). 39 (58%) of the 67 participants were female and 28 (42%) were male, with a median age at registration of 28 years (IQR 15–44, range 2–85). Data on 32 of these participants have been published previously,[8–10,13–17] whereas data on 35 are reported here for the first time to our knowledge. Additional genetic findings were reported in five (7%) of the 67 participants, but none of these variants were in genes associated with inborn errors of immunity (appendix p 18). Of the 52 participants with high-impact *SOCS1* variants from the UK Biobank, 29 (56%) were female and 23 (44%) were male, and the median age was 72 years (IQR 65–78, range 57–86).

Of the 67 participants in the ESID registry cohort, 62 (93%) were symptomatic and five (7%) were asymptomatic family members. The ages at inclusion of the five asymptomatic participants were 3, 28, 32, 42, and 57 years. Sex distribution was unequal among the 62 symptomatic participants, 37 (60%) of whom were female and 25 (40%) male. The 67 participants carried 25 different variants spread across the *SOCS1* gene, two of whom had whole-gene deletions (appendix p 25). The p.Ala9fs*76 (ten variant carriers in one family) and p.Met161Alafs*46 (12 variant carriers in ten families) variants were most frequent. 40 participants had predicted loss-of-function frameshift mutations, deletions, or premature stop mutations and 27 had missense variants. Functional data were provided for all but seven participants: four with predicted loss-of-function mutations, one with a whole-gene deletion, and

two carrying missense variants. We included the two participants carrying missense variants on the basis of their plausible multi-immune dysregulation phenotype.

The spectrum of clinical manifestations in the ESID registry cohort was broad and overlapped with that of other autoimmune lymphoproliferative immunodeficiencies,[3] but with two characteristic differences (figure 1A). First, 33 (53%) of the 62 symptomatic participants had allergic symptoms that included unspecified eczematous skin disorders and 15 (24%) had at least two allergic manifestations. Seven (11%) of the 62 symptomatic participants had eosinophilic diseases: four (6%) had eosinophilic oesophagitis, two (3%) had hypereosinophilic oesophagitis, and one (2%) had hypereosinophilic syndrome without oesophagitis. One (2%) participant had eosinophilic granulomatosis with polyangiitis (classed as vasculitis in figure 1A). Second, 23 (37%) of the 62 symptomatic participants had at least one rheumatological manifestation: 16 (26%) had rheumatoid arthritis, nine (15%) had SLE or SLE-associated skin lesions, three (5%) had vasculitis, three (5%) had Sjögren's disease, one (2%) had chronic recurrent multifocal osteomyelitis, and one (2%) had myositis. Of the 16 participants with rheumatoid arthritis, eight (50%) were seronegative (all with polyarthritis but no radiological erosion), three (19%) fulfilled criteria for juvenile idiopathic arthritis, and one (6%) had spondyloarthritis. All nine participants with SLE had haematological and musculoskeletal manifestations, four had skin involvement, and three had renal involvement; neuropsychiatric manifestations were not observed. Autoantibodies were not systematically analysed in the whole cohort but were detected in 25 (64%) of the 39 participants tested: 22 (56%) of 39 participants had antinuclear antibodies, ten (63%) of 16 tested participants had extractable nuclear antigen antibodies, and all 11 (100%) tested participants were negative for anti-dense fine speckled 70 kDa. Of 24 participants screened for anti-double stranded DNA, nine (38%) were positive. Ten (63%) of 16 participants had a combination of an antinuclear antibody titre greater than 1:80 and at least one antibody to extractable nuclear antigen and five (31%) of 16 participants had an antinuclear antibody titre greater than 1:80 and antibodies to both extractable nuclear antigen and double stranded DNA. According to the treating physicians, disease activity did not seem different to that of participants in other paediatric autoimmunity cohorts.

Other autoimmune lymphoproliferative and inflammatory manifestations showed significant overlap with those of other autoimmune lymphoproliferative immunodeficiencies (figure 1A).[3] Of the 62 symptomatic participants, 24 (39%) had autoimmune cytopenia, of whom 22 (35%) had immune thrombocytopenic purpura, 13 (21%) had autoimmune haemolytic anaemia, and 11 (18%) were diagnosed with Evans syndrome. Reported lymphoproliferative manifestations were splenomegaly in 19 (31%) of 62 participants, lymphadenopathy in 14 (23%) participants, and hepatomegaly in ten (16%) participants. Gastrointestinal inflammatory manifestations extended along the whole gastrointestinal tract and, of the 62 symptomatic participants, nine (15%) had inflammatory bowel disease, eight (13%) had chronic diarrhoea, six (10%) had aphthae, five (8%) had eosinophilic oesophagitis, four (6%) had coeliac disease, and three (5%) had gastritis. Specific inflammatory skin diseases other than eczema were reported for 18 (29%) of 62 participants: 14 (23%) had psoriasis, three (5%) had skin granulomas, two (3%) had alopecia, two (3%) had panniculitis, one (2%) had bullous pemphigoid, and one (2%) had erythema nodosum. Liver disease occurred in 12 (19%) of 62 participants: eight (13%) had autoimmune hepatitis, three (5%) had cholangitis, two (3%) had nodular regenerative hyperplasia, two (3%) had hepatopulmonary syndrome, one (2%) had chronic liver disease, and one (2%) had portal hypertension and oesophageal varices. Hepatopulmonary syndrome was severe enough to justify liver transplantation in two (3%) of 62 participants. Lung disease was less pronounced than in other autoimmune lymphoproliferative immunodeficiency conditions. Granulomatous lymphocytic interstitial lung disease was reported in seven (11%) of 62 participants, five (8%) had bronchiectasis, and three (5%) had allergic bronchopulmonary aspergillosis. Eight (13%) of 62 participants had autoimmune thyroiditis, three (5%) had glomerulonephritis, two (3%) had recurrent fever of unknown origin, one (2%) had pancreatitis, and one (2%) had multiple sclerosis-like encephalitis. One (2%) of 62 participants had non-Hodgkin lymphoma at the age of 34 years and reached full remission. Most autoimmune, but not allergic, manifestations were more frequent in female than in male participants (appendix pp 19–21).

Immunological investigations revealed absolute $CD4^+$ T-cell counts below the age-related normal range in seven (14%) of 51 participants (figure 1B) and low naive CD4 T-cell proportions in 15 (36%) of 42 participants (figure 1C). Class-switched memory B-cell proportions were low in 21 (55%) of 38 participants (figure 1D) and proportions of $CD21^{low}$ B cells were elevated in 14 (56%) of 25 participants (figure 1E). These findings were accompanied by frequent bronchopulmonary bacterial infections in eight (12%) of 67 participants. Additional bacterial infections requiring hospitalisation affected the gastrointestinal tract (five [7%] of 67 participants; mostly protracted *Salmonella* infections), skin (four, 6%), and urinary tract (four, 6%), whereas the most frequent viral infections requiring hospitalisation were herpes zoster (six, 9%) and SARS-CoV-2 (four, 6%). Two (3%) of 67 participants were hospitalised for each of respiratory syncytial virus, cytomegalovirus, and herpes simplex virus infections and one (1%) was hospitalised for each of enterovirus, adenovirus, norovirus, and human polyomavirus 1 (also known as BK virus) infections. Two (3%) of 67 participants had systemic

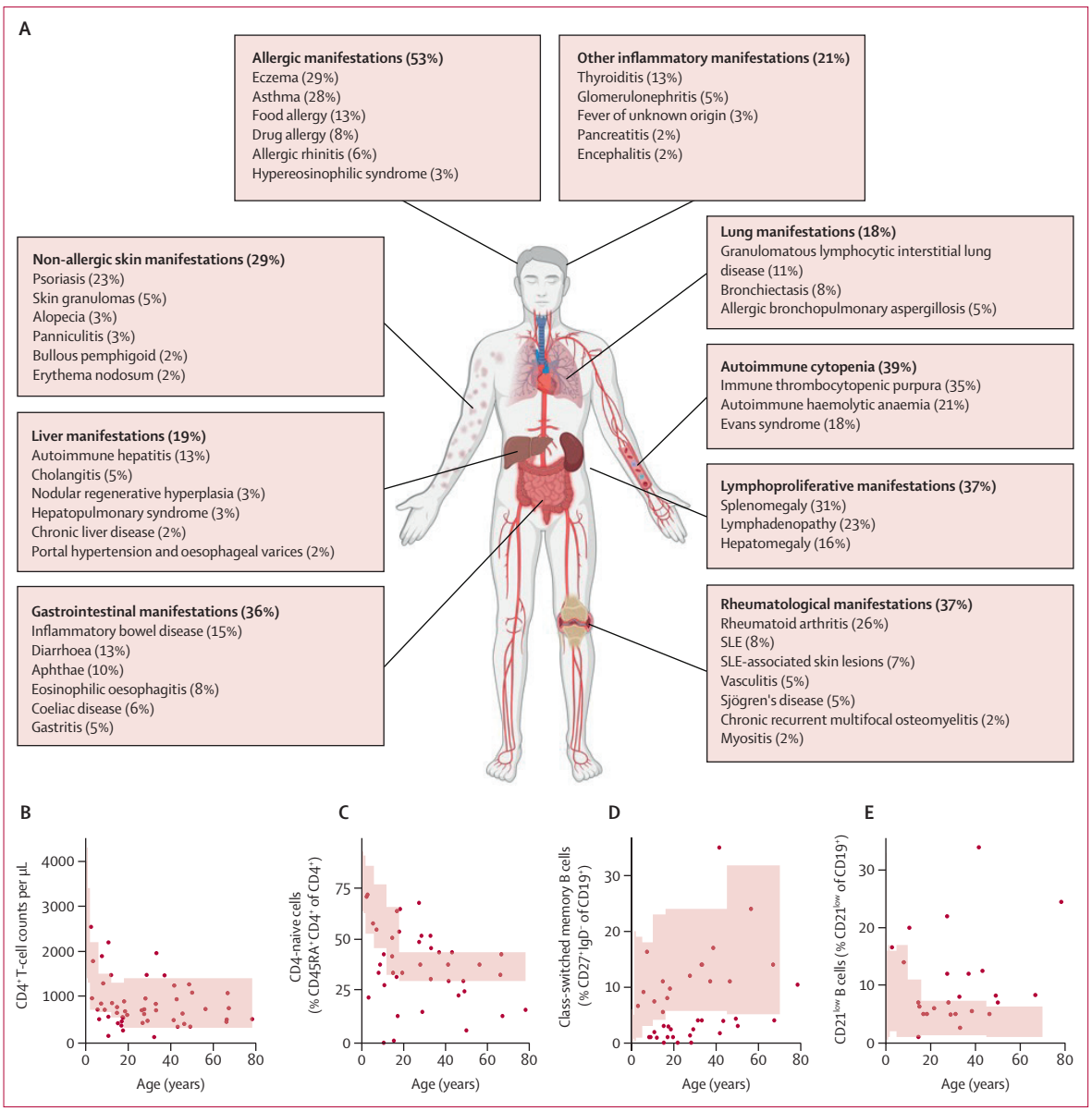

Figure 1: **Manifestations of immune dysregulation and immune alterations in 62 symptomatic participants with SOCS1 insufficiency in the ESID registry**
(A) Summary of clinical manifestations, classified into nine subgroups, observed in 62 symptomatic participants with SOCS1 insufficiency at the time of their inclusion in the ESID registry. (B) Absolute $CD4^+$ T-cell counts (per µL); values missing for 16 participants. (C) Proportion of naive CD4 T cells; values missing for 25 participants. (D) Proportion of class-switched memory B cells; values missing for 29 participants. (E) Proportion of $CD21^{low}$ B cells; values missing for 42 participants. In B–E, data points show values for individual participants in the ESID registry for the indicated lymphocyte subsets at the time of diagnosis. The red shading indicates age-related normal values (10th–90th percentile). ESID=European Society for Immunodeficiencies. SLE=systemic lupus erythematosus. SOCS1=suppressor of cytokine signalling 1.

Candida infections and one (1%) participant presented with pulmonary tuberculosis. Whether these infections occurred while participants were on immunosuppressive therapy was not documented.

Data on age of onset of individual health events were available for 247 (87%) of 284 of immune dysregulatory manifestations observed in the ESID registry (figure 2A). The median age at the first manifestation was 10 years (IQR 5–15, range 1–44), with no difference between male and female participants. Age of onset was earliest for allergic manifestations, autoimmune cytopenia, and lymphoproliferation, with almost half (25 [49%] of 51) of affected participants showing these manifestations by 10 years of age. Almost three-quarters (29 [74%] of 39) of participants with rheumatological, inflammatory skin, and gastrointestinal manifestations had onset by 20 years of age. Liver, lung, and other inflammatory manifestations frequently had an onset later into adulthood (aged

>18 years). However, new manifestations occurred across the whole lifespan—extending from the first year of life to older than 60 years (figure 2A)—which was also evident when looking at the individual disease trajectories (figure 2B). Initiation of steroids or immunosuppressive therapy did not prevent additional disease manifestations.

The release of whole-exome data for UK Biobank participants in June, 2022, enabled a comparison of ESID registry data (figure 3A) with data from an unbiased, population-based study (figure 3B). Seven *SOCS1* variants that were each reported in a single participant in the ESID registry were also found at variable frequencies in participants from the UK Biobank (appendix p 24). Of the 41 participants in the UK Biobank carrying these seven variants, 17 (41%) did not have any of the 198 ICD-10 diagnostic codes encoding the autoimmune lymphoproliferative or inflammatory manifestations observed in the ESID registry cohort. Of the remaining 24 participants, 11 (46%) had one manifestation, five (21%) had two, seven (29%) had three, and one (4%) had five manifestations (figure 3B). The single manifestations observed in the 11 participants in the UK Biobank (compared with nine participants in the ESID registry) included hypothyroidism, eczema, asthma, and drug allergy, which have a high prevalence in the general population. We did not observe any additional inflammatory, autoimmune, allergic, infectious, or lymphoma-related manifestations in participants from the UK Biobank that were not also observed in the registry cohort (appendix pp 10–11). In a second approach, we identified 11 additional participants from the UK Biobank with high-impact variants of *SOCS1* (ie, frameshift deletions or premature stop mutations) that were not observed in the ESID registry. Analysis of the UK Biobank data based on variants listed in ClinVar did not identify additional carriers of high-impact variants. Of these 11 participants, five (45%) were asymptomatic, two (18%) had one manifestation, and four (36%) had three to nine different manifestations. Figure 3B summarises the 41 participants from the UK Biobank with variants observed in the ESID registry and the 11 participants with other high-impact variants. Compared with controls from the UK Biobank, allergy, rheumatoid arthritis, inflammatory skin disease, and SLE were significantly enriched in participants carrying high-impact *SOCS1* variants (appendix p 12) after adjusting for multiple testing using the Benjamini–Hochberg procedure.

Overall, 62 (93%) of 67 participants with SOCS1 insufficiency in the ESID registry were symptomatic whereas only 30 (58%) of 52 were symptomatic in the UK Biobank cohort (figure 3A, B). Rheumatological and allergic manifestations comprised a higher proportion of total manifestations among the 54 manifestations in the UK Biobank (13 [24%] were rheumatological and 16 [30%] were allergic manifestations) than among the 179 manifestations in the ESID registry (23 [13%] were

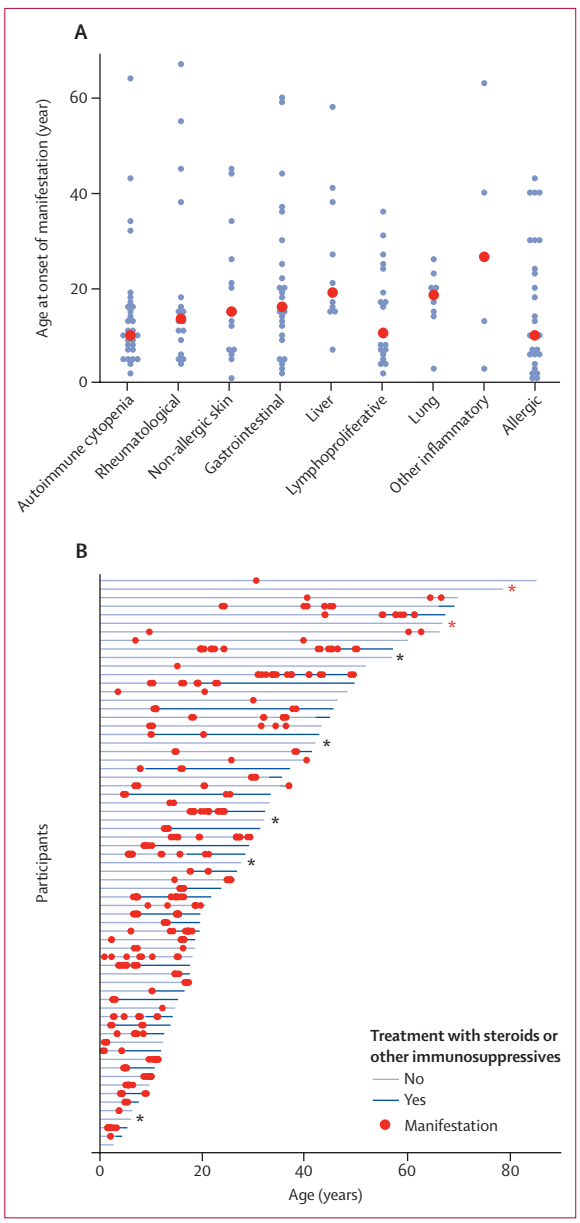

Figure 2: **Disease trajectories of participants with SOCS1 insufficiency in the ESID registry**

(A) Age at onset of manifestations of immune dysregulation in the indicated manifestation groups. Blue dots indicate individual manifestations; participants with several manifestations are represented by several dots. Red dots indicate the median age at onset of manifestations within a given group. Age of onset information was absent for 23 manifestations. (B) Individual disease trajectories for all 67 participants in the ESID registry. Each participant is represented by a horizontal line, which covers the time from birth to registration; participants are ordered vertically from young to old. Red dots indicate the occurrence of a disease manifestation. Lines turn from pale to dark blue when steroids or other immunosuppressive drugs were given. The five asymptomatic participants are marked by a black asterisk. The red asterisks indicate two participants who were symptomatic but for whom age at symptom onset was unknown. ESID=European Society for Immunodeficiencies. SOCS1=suppressor of cytokine signalling 1.

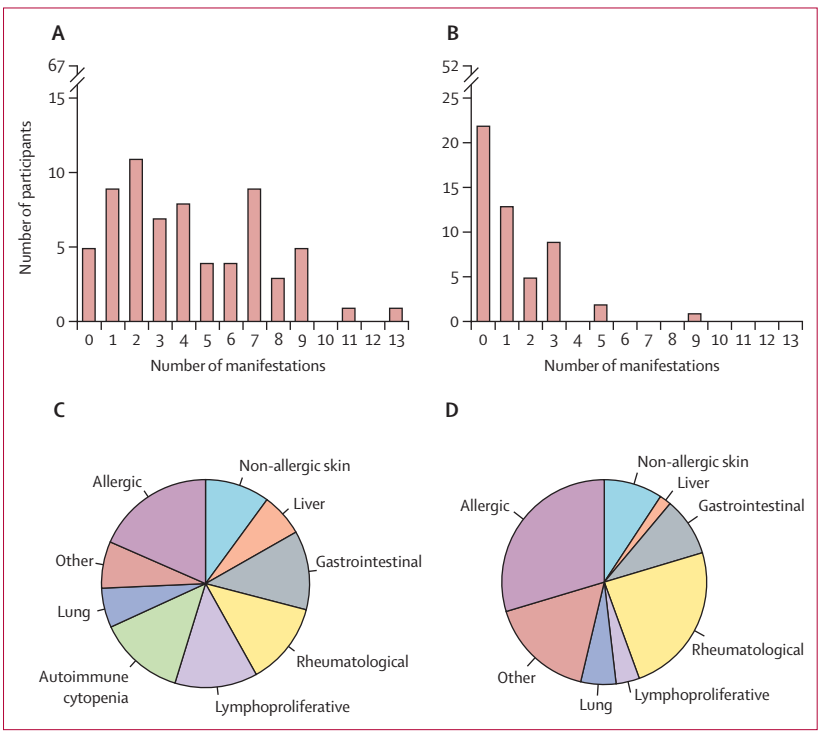

Figure 3: **Registry-based versus population-based pattern of disease manifestations in SOCS1 insufficiency**
Number of participants with a given number of manifestations of immune dysregulation in the ESID registry (A; 67 individuals, 62 symptomatic with 284 mainfestations) and the UK Biobank cohort (B; 52 individuals, 30 symptomatic with 69 manifestations). All manifestations were counted and were not grouped into subcategories. Contribution of manifestations of immune dysregulation, grouped in nine categories, to all 179 grouped manifestations observed in the 62 symptomatic participants in the ESID registry cohort (C) and 54 grouped manifestations observed in the 30 symptomatic participants in the UK Biobank cohort (D). ESID=European Society for Immunodeficiencies. SOCS1=suppressor of cytokine signalling 1.

rheumatological and 33 [18%] were allergic manifestations; figure 3C, D). Of all 92 symptomatic individuals, 58 (63%) were female and 34 (37%) were male.

The severity of autoimmune and inflammatory manifestations was reflected by the use of multiple immunosuppressive drugs among participants (figures 2B, 4A). Of 62 symptomatic participants from the ESID registry, 37 (60%) received systemic steroids, ten (16%) received azathioprine, nine (15%) received mycophenolate mofetil, seven (11%) received hydroxychloroquine, six (10%) received methotrexate, four (6%) received rapamycin, three (5%) received ciclosporin, two (3%) received cyclophosphamide, and one (2%) received tacrolimus. Monoclonal antibodies were frequently part of the treatment history: seven (11%) of 62 participants received TNF inhibitors, six (10%) received rituximab, three (5%) received mepolizumab, and one (2%) participant each received tocilizumab, ustekinumab, omalizumab, and dupilumab. Most participants receiving immunosuppressive treatment were receiving several different drugs. Liver disease was progressive and necessitated liver transplantation in two (3%) of 62 participants. Eight (13%) participants received immunoglobulin substitution. At the end of this study, no participants had been scheduled for bone marrow transplantation.

Ten children (aged 5–18 years) and three adults (aged 19–66 years) were treated with JAK inhibitors for at least 3 months (figure 4B). Of these participants, five (38%) received ruxolitinib, six (46%) received baricitinib, and two (15%) received tofacitinib. One additional child was treated with upadacitinib for 2 months to treat autoimmune haemolytic anaemia and developed non-tuberculous mycobacterial infection, leading to discontinuation of treatment. No other severe infections were observed in participants treated with JAK inhibitors. The overall response to treatment was regarded as very good (defined as a physician-rated score on the VAS of 8 or higher) in nine participants, good (VAS score 4–7) in three participants, and poor (VAS score <4) in one participant (figure 4C). The main targeted manifestation was autoimmune cytopenia in four participants, with complete response in two, partial response in one, and no response in one. Three participants each were treated for inflammatory bowel disease, inflammatory skin disease, and rheumatoid arthritis; each condition showed complete response in two participants and no response in one. Mixed responses were also observed in the treatment of hepatitis, lymphoproliferation, and pulmonary disease (figure 4D). At the end of this study, 12 (92%) of 13 participants remain on JAK inhibitor treatment. Notably, initiation of a JAK inhibitor enabled a reduction of steroids and other immunosuppressants in ten (77%) of 13 participants (figure 4E). No obvious difference in response was observed between treatment with different JAK inhibitors.

Discussion

By combining patient registry data (ESID) with population-based data (UK Biobank), we provide insights into the prevalence, penetrance, clinical spectrum, and genetic variability of SOCS1 insufficiency. This approach provides a more comprehensive understanding of the condition than would be possible through the use of either data source alone.

A key finding is the high prevalence of rheumatological manifestations (seen in 37% of symptomatic participants), including rheumatoid arthritis, SLE, vasculitis, and Sjögren's disease. This prevalence is notably higher in SOCS1 insufficiency than in other autoimmune lymphoproliferative immunodeficiency disorders.[2–6] This finding is consistent with the role of SOCS1 in regulating interferon signalling, a pathway known to be dysregulated in SLE.[14,23] The rheumatological manifestations of SOCS1 insufficiency, which are of childhood or adolescent onset in most patients, underscore the need for rheumatologists to consider this genetic disorder in their differential diagnosis, particularly in individuals for whom these manifestations

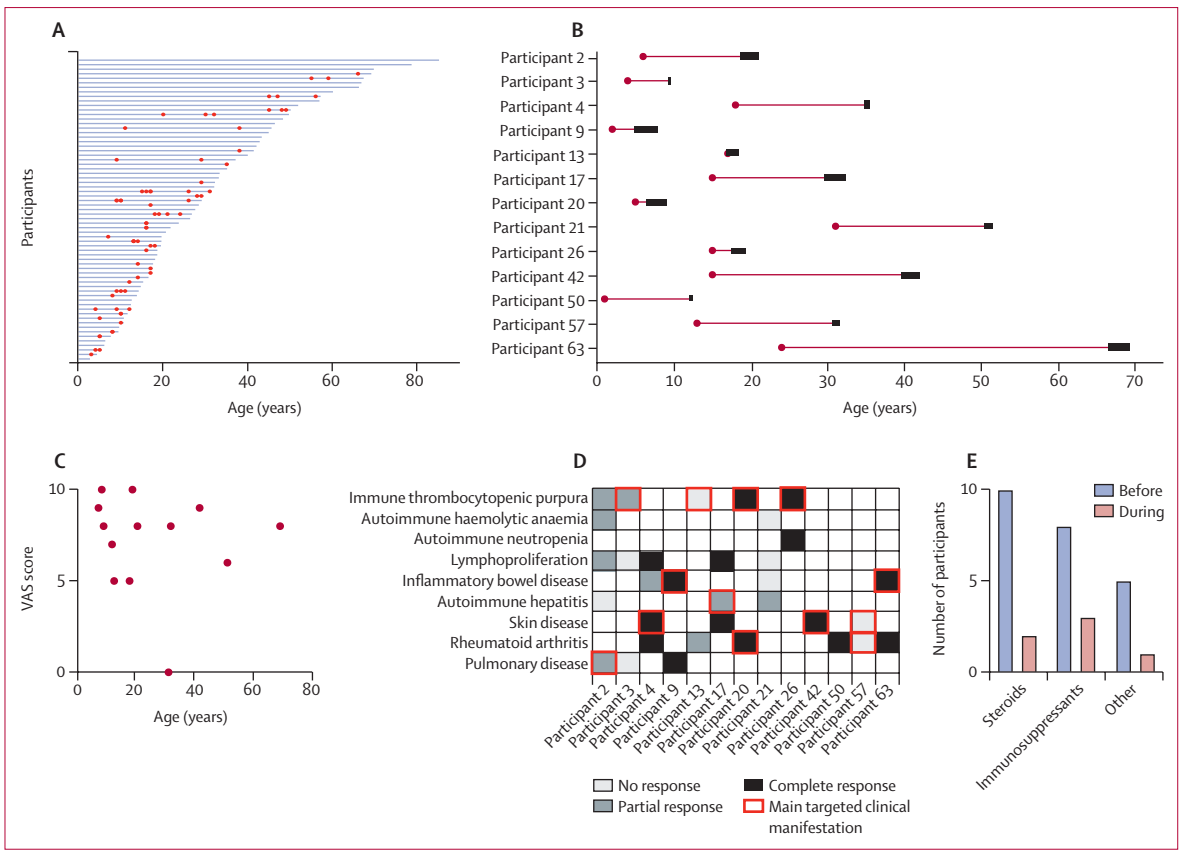

***Figure 4*: Treatment of SOCS1 insufficiency**

(A) Trajectories of immunosuppressive treatments of participants in the ESID registry. Each participant is represented by a line, which covers the time from birth to registration. Red dots indicate the start of immunosuppressive treatment (steroids are not included); each different drug is indicated by a participant dot. (B) Overview of JAK inhibitor treatment. Each participant is represented by a line, which covers the time from the first clinical manifestation to patient registration in the ESID registry. The line changes from thin to thick at the start of JAK inhibitor therapy. (C) Response to therapy of participants treated by JAK inhibitors, assessed subjectively by the treating physician using the VAS. The x-axis indicates the participants' age at the last observation. (D) Treatment responses of 13 participants treated with JAK inhibitors and their manifestations at the start of treatment. The main clinical manifestation targeted by the therapy is marked by a red box. Elsewhere in the Article, autoimmune neutropenia is grouped with Evans syndrome, because it occurred in combination with immune thrombocytopenia. (E) Concomitant treatment before and during treatment with JAK inhibitors. Other treatment refers to intravenous immunoglobulins, thrombopoietin receptor agonists, granulocyte colony stimulating factor, and parenteral nutrition. ESID=European Society for Immunodeficiencies. JAK=Janus kinase. SOCS1=suppressor of cytokine signalling 1. VAS=visual analogue scale.

are associated with other autoimmune, inflammatory, or allergic conditions. The association of *SOCS1* gene expression and polymorphisms with SLE and rheumatoid arthritis activity in previous studies supports this notion.[23–25] The analysis of high-impact *SOCS1* variants among independent cohorts of patients with autoimmune disorders will be of interest in future research.

The identification of frequent atopic manifestations—including eczema, asthma, and eosinophilic diseases but also severe food and drug allergies—in more than half of symptomatic participants underscores the unique immunological profile of SOCS1 insufficiency. The parallel occurrence of disorders driven by T-helper-1 and T-helper-2 cells within the same individuals is consistent with the broad regulatory role of SOCS1 in cytokine responses.[10,11] This regulatory role is also highlighted by the diversity of additional autoimmune, inflammatory, and lymphoproliferative manifestations. The increased susceptibility to some infections, particularly herpes zoster and severe SARS-CoV-2 infections, highlights the complex interplay between autoimmunity and immunodeficiency in SOCS1 insufficiency.[8,16]

The identification of 31 different *SOCS1* variants, all in coding regions, provides valuable information for genetic counselling and diagnosis. 19 (61%) of the 31 variants were classified as high-impact—comprising frameshift deletions, premature stop mutations, and whole-gene deletions—supporting that haploinsufficiency is the consequence of the majority of the disease-causing variants.[7] The functional validation of most variants strengthens the observed associations between genotype and phenotype.

Our analysis of the UK Biobank data offers an unbiased perspective on the penetrance and clinical spectrum of SOCS1 insufficiency. SOCS1 insufficiency is rare. The

population-based prevalence of participants carrying a high-impact variant, as defined in this study, was one in 9034—similar to data in the Genome Aggregation Database (appendix p 24). This estimate is conservative, as we focused on participants with variants observed in the ESID registry and high-impact variants and will have missed participants with other functionally relevant variants. The observation that only 30 (58%) of 52 participants with *SOCS1* variants in the UK Biobank cohort were symptomatic, compared with 62 (92%) of 67 participants in the ESID registry cohort, highlights the incomplete penetrance of SOCS1 insufficiency. The variable expressivity and incomplete penetrance of SOCS1 deficiency, even among individuals with the same variant, suggest that these variants are necessary, but not sufficient, to cause disease and that additional genetic (eg, non-coding variants and modifier genes), epigenetic, or environmental events (eg, infections) are required for manifestations to occur.[26]

The even higher prevalence of rheumatological and allergic manifestations in the UK Biobank cohort than in the ESID registry cohort is intriguing. This discrepancy probably reflects ascertainment bias in the ESID registry. A notable finding was the higher penetrance in female participants, evident from the female predominance among symptomatic participants but not asymptomatic carriers in both the ESID registry and the UK Biobank. The unequal distribution by sex aligns with the higher incidence of autoimmune diseases in females than in males and suggests a potential influence of sex hormones or sex-linked genetic factors on disease expression.[27] However, this finding contrasts with the 80% male bias observed in genetically undiagnosed autoimmune lymphoproliferative immunodeficiency disorders in childhood.[2] Further studies are needed to elucidate the factors influencing disease expression and severity in SOCS1 insufficiency.[28] The immunological abnormalities observed in our cohort—including low proportions of naive CD4 T cells and class-switched memory B cells—were variable, were not specific for SOCS1 insufficiency, and were not associated with disease severity. In a previous study, we reported immunological abnormalities in all four carriers of *SOCS1* variants, including a characteristic serum inflammatory cytokine signature similar to that in symptomatic participants.[7] The immunological phenotype might therefore be more penetrant than the clinical phenotype. From a diagnostic point of view, considering the genetic heterogeneity of autoimmune lymphoproliferative immunodeficiency conditions and the poor specificity of clinical manifestations and currently available biomarkers,[2] our current practice is to have a low threshold for trio whole-exome sequencing in patients with more than one organ affected by autoimmune, autoinflammatory, lymphoproliferative, or allergic manifestations.

The treatment history of symptomatic individuals reflects the complexity and severity of SOCS1 insufficiency, with many patients requiring multiple immunosuppressants. The promising results of JAK inhibitor treatment in 13 participants, with partial or complete response observed in most, suggest that JAK inhibition could be a viable targeted therapy for SOCS1 insufficiency, as documented for other inborn errors of JAK-STAT signalling.[29] These results need to be confirmed in a larger cohort and with validated activity scores for each clinical manifestation. SOCS1 insufficiency can result in severe disease, with two participants in this study requiring liver transplantation. The key manifestations of SOCS1 insufficiency could be treatable with haematopoietic stem-cell transplantation, raising the question of a potential role for this treatment. However, at present, we would suggest reserving stem-cell transplantation for patients who do not respond to JAK inhibition.

This study has several limitations. The ESID registry has substantial referral bias, requiring contact with physicians participating in the ESID registry network. Owing to the broad spectrum of clinical manifestations, many patients will be under the care of other specialists who do not participate in the registry. Because many participants were registered in childhood, there is a bias towards early-onset versus late-onset manifestations. The ESID registry contains few non-European participants. Because SOCS1 insufficiency was first described in 2020, many affected individuals probably remain undiagnosed. Although the UK Biobank addresses some of the limitations of the registry, considerable biases remain. UK Biobank participants are predominantly White and of European ancestry and they tend to be healthier, better educated, and less socioeconomically deprived than the general UK population. We decided to include only high-impact *SOCS1* variants and therefore will have missed missense variants with loss-of-function consequence among UK Biobank participants. By restricting diagnosis to ICD-10 codes, mapping of phenotypes is suboptimal and is sometimes subject to data inconsistencies between hospital records, primary-care data, and self-reported information. Participant histories relying on self-reporting are likely to be less complete than those obtained in a specialised immunology clinic. Finally, people with lived experience were not involved in the study design.

This study has several implications for clinical practice. First, it provides a rationale for considering genetic testing for inborn errors of immunity, including *SOCS1* variants, followed by functional evaluation of detected variants in participants with early-onset, multi-system autoimmune disease, particularly when associated with rheumatological and allergic manifestations. Second, it highlights the need for a multidisciplinary approach in managing individuals with SOCS1 insufficiency, involving rheumatologists, haematologists, allergists, immunologists, and other specialists. Third, the incomplete penetrance and female predominance highlight the need for personalised approaches to diagnosis and management. As our understanding of

SOCS1 insufficiency continues to evolve, it is likely to provide valuable insights into the broader field of immune dysregulation and autoimmunity.[30]

Contributors

JH, AW, FR-L, and SE designed and conducted the study. JH, AW, and SE curated the data. MJ, FH, FC-H, JB, JR, and OB did the genetic analysis. SE, AW, JK, and FH did the immunological analysis. JH, AW, SE, OB, and DH did the statistical analysis. JH, AW, SE, and OB drafted the manuscript. DH analysed the data and helped to draft the figures. SE, JH, AB, SB, FH, PL, SV, SP, VB, NA, JA, FC-H, MC, JD, SG, FH, DPHvK, JK, JB, JR, LFS, IS, GS, SG, BN, and FR-L collected patient data. All authors reviewed and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. JH, AW, and OB directly accessed and verified the underlying data.

Declaration of interests

SE is member of a data monitoring committee for leniolisib (Pharming). JK received honoraria and travel expenses from Pharming Group for a conference presentation at SFH Paris about leniolisib. PYL has received royalties or licenses from UptoDate. AB has received support from ANR LUMUGENE and consulting fees from Fresenius Kabi, Roche Chugai, GSK, AbbVie, Novartis, and Boehringer Ingelheim. LFS has received National Institutes of Health funding (1UG3TR003908-01) for a trial investigating the safety and efficacy of itacitinib in JAK/STAT disorders with activating mutations, is a council member of the Clinical Immunology Society, and Director of the Jeffrey Modell Foundation Center at Texas Children's Hospital. All other authors declare no competing interests.

Data sharing

The SOCS1 study data are held at The European Society for immunodeficiency (ESID) registry, currently hosted at the Medical Center – University of Freiburg, Freiburg, Germany. ESID encourages the optimal use of data by using a controlled access approach to data sharing. Requests for data can be made at any time and can be initiated by contacting the corresponding author or registry@esid.org. There is a formal application process, whereby the request will undergo review by the study team to ensure that the proposed research is both ethical and has a strong scientific rationale. Anonymised patient data, the data dictionary, the study protocol, the statistical analysis plan, and the informed consent form will be made available upon request with publication.

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