

Journal Pre-proof

Anti-Saccharomyces cerevisiae Immunoglobulin G and Immunoglobulin A antibodies are associated with systemic inflammation and advanced disease in hidradenitis suppurativa

Florence Assan, MD, Jeremy Gottlieb, MD, Florence Tubach, MD, PhD, Said Lebbah, MD, Nicolas Guigue, Pharm.D, Geoffroy Hickman, MD, Emeline Pape, MD, Marine Madrangé, Emmanuel Delaporte, MD, PhD, Boualem Sendid, MD, PhD, François Aubin, MD PhD, Francis Derouin, MD PhD, Stéphane Bretagne, MD, PhD, Pascal Richette, MD, PhD, Asma Smahi, MD, PhD, Emilie Sbidian, MD, PhD, Hervé Bachelez, MD PhD

PII: S0091-6749(20)30188-3

DOI: <https://doi.org/10.1016/j.jaci.2020.01.045>

Reference: YMAI 14413

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 23 October 2019

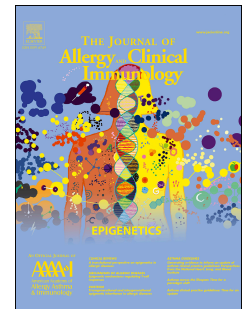
Revised Date: 26 January 2020

Accepted Date: 31 January 2020

Please cite this article as: Assan F, Gottlieb J, Tubach F, Lebbah S, Guigue N, Hickman G, Pape E, Madrangé M, Delaporte E, Sendid B, Aubin F, Derouin F, Bretagne S, Richette P, Smahi A, Sbidian E, Bachelez H, Anti-Saccharomyces cerevisiae Immunoglobulin G and Immunoglobulin A antibodies are associated with systemic inflammation and advanced disease in hidradenitis suppurativa, *Journal of Allergy and Clinical Immunology* (2020), doi: <https://doi.org/10.1016/j.jaci.2020.01.045>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 American Academy of Allergy, Asthma & Immunology



Anti-Saccharomyces cerevisiae Immunoglobulin G and Immunoglobulin A antibodies are associated with systemic inflammation and advanced disease in hidradenitis suppurativa

Florence Assan, MD * ^{1,2}, * Jeremy Gottlieb, MD * ^{1,3}, Florence Tubach, MD, PhD ⁴, Said Lebbah, MD⁴, Nicolas Guigue, Pharm.D^{1,5}, Geoffroy Hickman, MD^{1,3}, Emeline Pape, MD^{6,7}, Marine Madrangé^{1,8}, Emmanuel Delaporte, MD, PhD^{6,7}, Boualem Sendid, MD, PhD^{7,9}, François Aubin, MD PhD¹⁰, Francis Derouin, MD PhD^{1,5}†, Stéphane Bretagne, MD, PhD^{1,5} Pascal Richette, MD, PhD^{1,11,12}, Asma Smahi, MD, PhD^{1,8}, Emilie Sbidian, MD, PhD^{12,13,14}, Hervé Bachelez, MD PhD ^{1,2,3}

¹ Université de Paris, Paris, France

² INSERM UMR 1163, Laboratory of Genetic Skin Diseases, Institut Imagine, Paris,

³ Department of Dermatology, Hôpital Saint-Louis, APHP, Paris

⁴ Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP.Sorbonne Université, Hôpital Pitié Salpêtrière, Département de Santé Publique, CIC-1422, F75013, Paris, France

⁵ Department of Mycology and Parasitology, Hôpital Saint Louis, APHP, Paris

⁶ Department of Dermatology, CHRU Lille

⁷ Université Lille, LIRIC - Inserm UMR 995- Team 2, Lille, France

⁸ INSERM UMR 1163, Laboratory of Genetics of Monogenic Auto-inflammatory Diseases, Imagine Institute, Paris, France

⁹ Department of Mycology and Parasitology, CHU Lille

¹⁰ Department of Dermatology, Hôpital de Besançon, France

¹¹ Département de Rhumatologie, Hopital Lariboisiere, Paris, France.

¹² INSERM U1132 Bioscar

¹² Department of Dermatology, Hôpital Henri Mondor, APHP, Créteil

¹³ Inserm, Centre d'Investigation Clinique 1430, Créteil, F-94010, France.

¹⁴ Paris Est Créteil University (UPEC), Créteil, France

*These authors equally contributed to this work

Corresponding author : Hervé Bachelez, MD, PhD

Laboratoire de Génétique des Maladies Cutanées, INSERM UMR1163, Institut Imagine, 24 boulevard du Montparnasse, 75015, Paris, France

e-mail address : herve.bachelez@aphp.fr

Phone number: +33 1 42 75 43 67

Conflicts of interest statement: JG has potential competing interest as follow: clinical research sponsored by Janssen, Boehringer-Ingelheim and Amgen + consultant arrangements with UCB, Janssen, Novartis, Abbvie, Celgene, Lilly and Sanofi; HB paid consulting activities for Abbvie, Almirall, Amgen, Biocad, Biogen, Boehringer-Ingelheim, Celgene, Janssen, Leo Pharma, Lilly, Mylan, Novartis, Pfizer, UCB et Sun Pharmaceuticals

The rest of the authors declare that they have no relevant conflicts of interest.

Capsule Summary.

This is the first prospective study showing that ASCA are biomarkers for HS, especially in severe inflammatory forms, but not in PV, supporting the contribution of a gut fungal dysbiosis to HS pathogenesis.

Key words : Hidradenitis suppurativa ; Psoriasis ; Anti-Saccharomyces *Cerivisiae* antibodies ; dysbiosis

Words: 1107

Tables: 1

Figures: 1

To the editor :

Hidradenitis suppurativa (HS) is a skin chronic inflammatory disease affecting 1 to 4% of western population and associated with major impact on quality of life. Its pathogenesis, combining hair follicle dysregulation and both skin and systemic inflammation, involves a genetic background interacting with environmental factors (e.g. bacterial skin dysbiosis, overweight, smoking) (1). TNF- α , enhanced in HS, is upregulated in other inflammatory and immune-mediated diseases (IMIDs) such as severe psoriasis vulgaris (PV), inflammatory bowel diseases (IBD), and spondyloarthritis (Sp) (2). Evidences for an increased prevalence of IBD and Sp in HS patients raised the issue of the commonalities across these IMIDs (3). Recently, serological detection of anti-*Saccharomyces cerevisiae* antibodies (ASCA) was identified as a biomarker for Crohn's disease (CD) (4) and in spondylarthropathy (Sp) (5). Therefore, we prospectively investigated the seroprevalence of ASCA respectively in patients with HS and with severe PV.

A multicentric national transversal study was conducted between 2012 and 2017, in three major French Dermatology tertiary centres for skin IMIDs (Saint-Louis Hospital Paris, and university hospitals respectively from Lille and Besançon). Patients were consecutive adult (≥ 18 years) outpatients candidate for systemic therapy, presenting with HS or PV (see Figure E1 in this article's Online Repository). Exclusion criteria were: medical history of IBD or of any systemic immunomodulatory or immunosuppressive treatment. All HS patients were candidate for systemic therapy (antibiotics, TNF inhibitors), while patients with PV were candidate to conventional or biological therapy approved in France. Sera from healthy blood donors were collected (Etablissement Français du Sang, Hôpital Saint-Louis) during the same time period, after filling a questionnaire in order to exclude individuals with personal history of psoriasis, HS, IBD, systemic immunomodulatory or immunosuppressive treatment. (see Methods in this article's Online Repository)

The characteristics of the 469 individuals are summarized in **Table E1** (in this article's Online Repository). PV patients had a longer median duration of disease compared to HS patients (19 vs 9 years), their median psoriasis area severity index (PASI) score at the time of inclusion was 10.2 (range: 7.7-14.5). On the other hand, 38 (25.7%) HS patients were Hurley stage I, e.g. with mild disease, while the 110 others were either stage II (n=55, 37.2%), or stage III (n=55, 37.2%). Therefore, 74.4% of HS patients had moderate-to-severe disease at the time of inclusion, in line with the recruitment of tertiary care centres.

A positive serological detection of ASCA IgG and/or IgA was significantly more frequent in HS compared with both PV and HC groups, which did not significantly differ (respectively 24.3% [17.4-31.2] vs 4.4% [1.2-7.6] and 4.3% [1.2-7.5], $p < 10^{-4}$ for both comparison). (**Figure 1A**). This association, evidenced across all Hurley stages, was more frequent in elevated stages (see **Table E2** in this article's Online

Repository). Among HS patients, IgA isotype seroprevalence tended to be higher than IgG one (16.9% [11.6-23.9], vs 12.9% [8.3-19.3], $p=0.33$), while the IgA⁺/IgG⁻ pattern was more frequently observed than the IgG⁺/IgA⁻ one among HS patients showing a positivity for one single isotype, (11.5% [7.2-17.8], vs 7.4% [4.1-13.0], $p=0.23$), but results were not significant (**Figure 1B**).

In univariate analysis, ASCA detection within HS group was significantly associated with the absence of active smoking, inflammatory rheumatic disease, HS-related autoinflammatory syndrome, and Hurley stage III (**Table 1**). In addition, absence of ASCA was significantly associated with a C-Reactive Protein (CRP) plasmatic level inferior or equal to 5 mg/L (**Table 1**). All of the 10 patients with HS-related autoinflammatory syndromes, in which 5 were previously described (6), had a serological detection of ASCA. Of note, a personal history of antibiotherapy did not influence ASCA prevalence in HS patients. In multivariate analysis, factors associated with a serological detection of ASCA in HS were Hurley stage III and CRP serum level above 10 mg/L (see **Table E3** in this article's Online Repository). During a median time of 17 months (5.2-47.3), 49 (34%) HS patients were followed-up, especially for any sign of IBD or Sp, and none of them newly developed any other inflammatory disease. Twelve of these patients (24%) had a serological detection for ASCA. In a subgroups analysis, 52 HS patients had their γ -secretase (GS) complex encoding genes sequenced. Among those, only one patient with a familial form of HS showed a previously unreported heterozygous mutation of the *NCSTN* gene, and a negative detection for ASCA. Among the 51 other patients free of mutation in any of the four GS genes, 19 (36.5%) had a positive serological detection for ASCA.

This study identifies serological detection of ASCA as a biomarker for HS, mainly in its severe and inflammatory forms. The association between ASCA seropositivity and high HS tissular and/or systemic inflammatory burden, provides support for a link between systemic inflammation in the absence of IBD and the development of ASCA. Interestingly it has been showed in Crohn's disease that positive ASCA is associated with more severe disease and higher need for surgery (7). In the similar way in our study, ASCA detection was associated with Hurley stage III in multivariate analyses. On another hand, the value of ASCA in Hurley stages I/II is more uncertain, and the hypothesis that it might have prognostic significance requires further investigations.

Moreover, the presence of ASCA in all patients with HS-related autoinflammatory syndromes, regardless of joint involvement, supports this latter model. All but one tested patients were free of GS genes mutation, supporting that known genetic abnormalities in HS are not major a key driver of ASCA production.

The high prevalence of IgA isotype among HS population argues for a gastrointestinal tropism of deregulated inflammatory responses. Likewise, although none of our patients reported gastrointestinal symptoms, nor developed any sign of IBD during follow-up, previous observations reporting histopathological inflammatory changes of the digestive mucosa (7) are in line with this latter hypothesis, raising ASCA as a candidate biomarker for inflammatory burden in the

absence of IBD, and for putative digestive dysbiosis, a hypothetic pattern which still needs to be established by investigations of the gut microbiome.

As the association of ASCA detection with gut dysbiosis and gastrointestinal *Candida* colonization is established in CD (8) such signature might reflect similar perturbations in HS. Likewise, animal models of transtissular inflammation after modulating intestinal microbiome provide support for this hypothesis (9). 2/13/2020 3:13:00 AM Therefore, the present data appeal further investigations of the gut mycobiome in HS, as a potential promoting factor for tissular inflammation. Moreover, given the major role of IL-17 in intestinal barrier immunity and homeostasis, they also the interest to investigate the incident risk of in the ongoing the development of IL-17 inhibitors in severe HS.

In conclusion, this study identifying ASCA as a biomarker for inflammatory HS paves the way for further explorations of gut mycobiome in different disease subsets.

Florence Assan *^{1,2,*}, Jeremy Gottlieb *^{1,3}, Florence Tubach⁴, Said Lebbah⁴, Nicolas Guigue^{1,5}, Geoffroy Hickman^{1,3}, Emeline Pape^{6,7}, Marine Madrange^{1,8}, Emmanuel Delaporte^{6,7}, Boualem Sendid^{7,9}, François Aubin¹⁰, Francis Derouin^{1,5,†}, Stéphane Bretagne^{1,5}, Pascal Richette^{1,11,12}, Asma Smahi^{1,8}, Emilie Sbidian^{12,13,14}, Hervé Bachelez^{1,2,3}

¹ Université de Paris, Paris, France

² INSERM UMR 1163, Laboratory of Genetic Skin Diseases, Institut Imagine, Paris,

³ Department of Dermatology, Hôpital Saint-Louis, APHP, Paris

⁴ Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP. Sorbonne Université, Hôpital Pitié Salpêtrière, Département de Santé Publique, CIC-1422, F75013, Paris, France

⁵ Department of Mycology and Parasitology, Hôpital Saint Louis, APHP, Paris

⁶ Department of Dermatology, CHRU Lille

⁷ Université Lille, LIRIC - Inserm UMR 995- Team 2, Lille, France

⁸ INSERM UMR 1163, Laboratory of Genetics of Monogenic Auto-inflammatory Diseases, Imagine Institute, Paris, France

⁹ Department of Mycology and Parasitology, CHU Lille

¹⁰ Department of Dermatology, Hôpital de Besançon, France

¹¹ Departement of Rheumatology, Hopital Lariboisiere, Paris, France.

¹² INSERM U1132 Bioscar

¹² Department of Dermatology, Hôpital Henri Mondor, APHP, Créteil

¹³ Inserm, Centre d'Investigation Clinique 1430, Créteil, F-94010, France.

¹⁴ Paris Est Créteil University (UPEC), Créteil, France

*These authors equally contributed to this work

References

1. Frew JW, Vekic DA, Woods J, Cains GD. A systematic review and critical evaluation of reported pathogenic sequence variants in hidradenitis suppurativa. *Br J Dermatol.* oct 2017;177(4):987-98.
2. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model. *Frontiers in Immunology* [Internet]. 14 déc 2018 [cité 8 févr 2019];9. Disponible sur: <https://www.frontiersin.org/article/10.3389/fimmu.2018.02965/full>
3. Egeberg A, Jemec GBE, Kimball AB, Bachelez H, Gislasen GH, Thyssen JP, et al. Prevalence and Risk of Inflammatory Bowel Disease in Patients with Hidradenitis Suppurativa. *Journal of Investigative Dermatology.* mai 2017;137(5):1060-4.
4. Quinton JF, Sendid B, Reumaux D, Duthilleul P, Cortot A, Grandbastien B, et al. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut.* juin 1998;42(6):788-91.
5. Maillet J, Ottaviani S, Tubach F, Roy C, Nicaise-Rolland P, Palazzo E, et al. Anti-Saccharomyces cerevisiae antibodies (ASCA) in spondyloarthritis: Prevalence and associated phenotype. *Joint Bone Spine.* déc 2016;83(6):665-8.
6. Gottlieb J, Mdrange M, Gardair C, Sbidian E, Frazier A, Wolkenstein P, et al. PAPASH, Ps APASH and PASS autoinflammatory syndromes: Phenotypic heterogeneity, common biological signature and response to immunosuppressive regimens. *Br J Dermatol.* 13 avr 2019;bjd.18003.
7. Kim BC, Park S, Han J, Kim JH, Kim TI, Kim WH. Clinical significance of anti-Saccharomyces cerevisiae antibody (ASCA) in Korean patients with Crohn's disease and its relationship to the disease clinical course. *Dig Liver Dis.* juill 2007;39(7):610-6.
8. Standaert-Vitse A, Sendid B, Joossens M, François N, Vandewalle-El Khoury P, Branche J, et al. Candida albicans colonization and ASCA in familial Crohn's disease. *Am J Gastroenterol.* juill 2009;104(7):1745-53.
9. Scher JU, Littman DR, Abramson SB. Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases. *Arthritis & Rheumatology (Hoboken, NJ).* janv 2016;68(1):35-45.

Legends

Figure 1

A : Total ASCA detection among each group. Percentages of total ASCA detection among HS, PV and control groups (%; CI95%). Errors bars are based on confidence interval of 95%

B : ASCA isotypes repartition among each group. Each bar defines the respective prevalence rates of IgG, IgA, IgG and IgA, IgG without IgA, IgA without IgG, and of total ASCA across the three study groups. (%; CI95%)

ASCA : Anti *Saccharomyces Cerevisiae* antibodies

HS : hidranenitis suppurativa ; PV : psoriasis vulgaris ; HC : healthy controls

IgG+ : Patient presenting IgG ASCA isotype, associated or not with IgA; IgA+ : Patient presenting IgA ASCA isotype detected, whether associated with IgG or not ; IgG+/IgA- : Patient presenting IgG

ASCA isotype without association of IgA isotype ; IgG-/IgA+ : Patient presenting IgA ASCA isotype without association of IgG isotype ; IgG+/IgA+ : Patient presenting ASCA IgG and IgA isotypes; IgG+ and/or IgA+ : Patient presenting ASCA whether isotype is IgG and/or IgA

Table 1

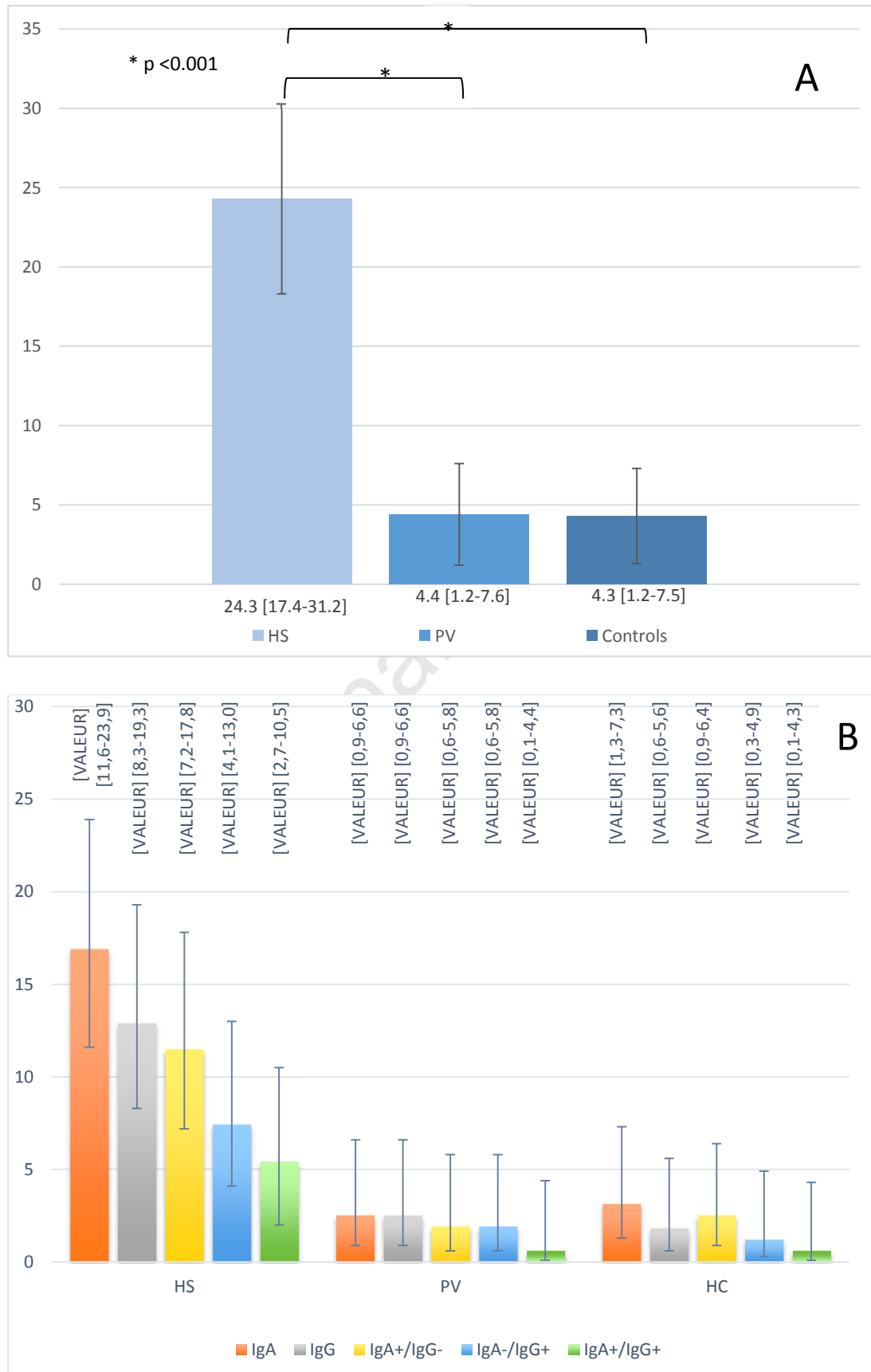
HS : hidradenitis suppurativa ; NA : not available ; IQR : interquartile range ; BMI : body mass index *p-values using Pearson's or Fisher chi-squared test as appropriate for categorial variables and wilconxon test for continuous variables

Table 1: HS patients characteristics respectively in the ASCA seropositive and seronegative groups

	ASCA -	ASCA +	P*
Sociodemographic characteristics			
Female, n (%)	68 (60.7)	24 (66.7)	0.522
Age, median (IQR)	30 (25.75-38)	33 (26-38.5)	0.442
Clinical features			
BMI, median (IQR)	26.1 (23.2-31.5)	27.5 (23.7-35.3)	0.296
Active smoking, n (%)	73 (65.8)	14 (40)	0.007
Associated inflammatory rheumatic disease, n (%)	5 (4.5)	6 (16.7)	0.025
HS-related autoinflammatory syndromes, n (%)	0 (0)	10 (27.8)	0.001
PASH		3	
PASS		2	
PAPASH		4	
PsAPASH		1	
Topography, n (%)			
Axillary	81 (72.3)	33 (91.7)	0.016
Inguinoperineal	102 (91.1)	33 (91.7)	1.00
Others	39 (34.8)	15 (41.7)	0.458
Locations number, n (%)			
1	27 (24.1)	3 (8.3)	0.123
2	52 (46.4)	20 (55.6)	
≥3	33 (29.5)	13 (36.1)	
Disease duration (years), median (IQR)	9 (4.5-13.5)	10 (5-17.5)	0.324
Hurley stages, n (%)			
- I	33 (29.5)	5 (13.9)	<0.001
- II	47 (42)	8 (22.2)	
- III	32 (28.6)	23 (63.9)	
C Reactive Protein serum level ≤ 5 mg/L	63 (64.95)	8 (25)	<0.001
Previous antibiotherapy, n (%)	32 (28.83)	12 (34.29)	0.53

HS : hidradenitis suppurativa ; NA : not available ; IQR : interquartile range ; BMI : body mass index *p-values using Pearson's or Fisher chi-squared test as appropriate for categorial variables and wilconxon test for continuous variables

Figure 1: Seroprevalence of anti *Saccharomyces Cerevisiae* antibodies (ASCA) and their isotypes in HS, PV and control study groups (% , CI95%)



Journal Pre-proof

Table E1: Patients baseline characteristics and seroprevalence of ASCA across the 3 study groups

	HS (n=148)	PV (n=159)	HC (n=162)	P* HS vs HC	P* PV vs HC	P* HS vs PV
Female, n (%)	92 (62.2)	65 (40.9)	88 (54.3)	0.016	0.163	<10 ⁻⁴
Age at inclusion, years, median (IQR)	31.5 (26-39)	45 (33-56)	33 (26-47.8)	<10 ⁻⁴	0.035	<10 ⁻⁴
Age at disease onset, years, median (IQR)	20 (16-27)	27 (18-40)				
Disease duration, years, median (IQR)	9 (5-14.75)	19 (12-29)				
BMI, kg/m², median (IQR)	26.5 (23.2-33.0)	26.6 (24.0-30.2)	23.6 (21.5-25.8)	<10 ⁻⁴	<10 ⁻⁴	0.134
Active smoking, n (%)	87 (59.6)	63 (40.4)	35 (21.7)	<10 ⁻⁴	<10 ⁻⁴	0.005
Hurley grades, n (%)						
I	38 (25.7)					
II	55 (37.2)					
III	55 (37.2)					
PASI, median (IQR)		10.2 (7.7-14.5)				
Inflammatory rheumatological disease, n (%)	11 (7.4)	30 (19)				

HS : hidradenitis suppurativa ; PV : psoriasis vulgaris ; HC : healthy controls ; IQR : Interquartile Range 25-75 ; BMI : body mass index ; CI : confidence interval

*p-values using Pearson's or Fisher chi-squared test as appropriate for categorial variables and wilcoxon test for continious variables

Table E2: ASCA seropositivity odds ratio among all HS patients and for each stage of Hurley vs controls

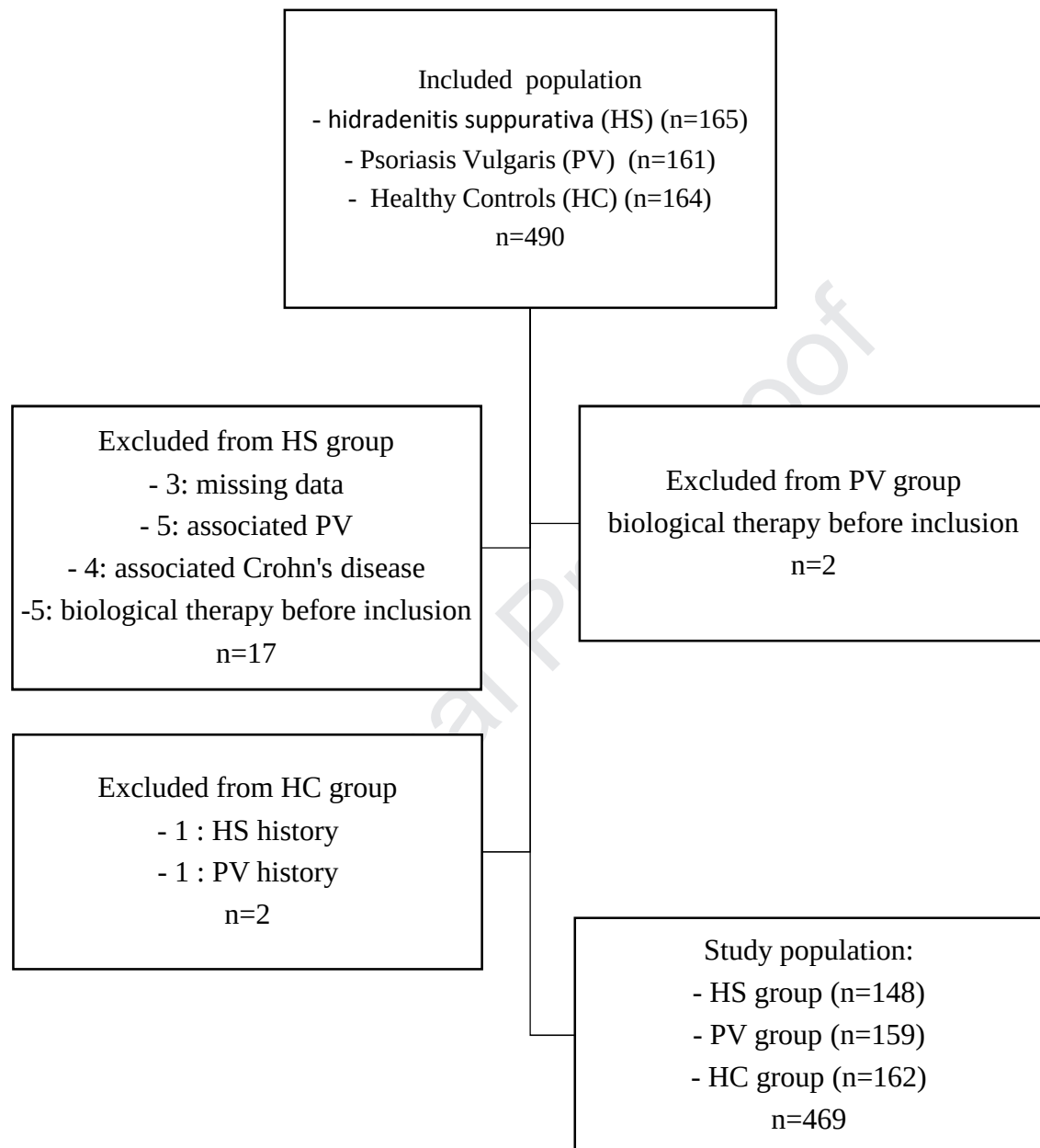
Sub-group population	N	OR	CI95%	P
HS all Hurley stages	148	7.12	3.24-17.98	<0.01
Hurley I	38	3.35	0.94-11.17	0.049
Hurley II	55	3.77	1.29-11.28	0.015
Hurley III	55	15.92	6.59-43.09	<0.001

OR: Odd Ratio; CI: confidence interval

Table E3: Factors associated with positive serological detection of ASCA among HS patients in multivariate analysis

	OR	CI95%	P
Hurley III	3.54	1.6 – 8.1	0.003
CRP > 10 mg/L	2.58	1.1-5.9]	0.02

CRP : C Reactive Protein ; OR : Odd Ratio ; CI : confidence interval

Figure E1: Study flow chart

Supplementary Materials

Patients

A multicentric national transversal study was conducted between 2012 and 2017, in three Dermatology departments known as major French tertiary care centres for skin IMIDs including HS, respectively located in Saint-Louis Hospital in Paris, and the university hospitals respectively from Lille and from Besançon.

Patients were consecutive adult (aged over 18) outpatients candidate for systemic therapy requiring a blood analysis, presenting with a diagnosis of either HS (n=148), or PV (n=159), ascertained by an expert physician in these diseases (HB, JG, GH, FA, ED). Given the known high prevalence of ASCA in IBD, patients with a personal history of CD or UC were excluded, in order to avoid a major confounding factor. Other exclusion criteria included a personal history of any systemic immunomodulatory or immunosuppressive treatment, e.g. methotrexate, ciclosporine, azathioprine, all biologics including tumor necrosis alpha inhibitors. All HS patients were candidate to systemic therapy including antibiotics and/or TNF inhibitors, while patients with PV were candidate to either conventional or biological antipsoriatic therapy approved in France. Sera from healthy blood donors were collected (Etablissement Français du Sang, Hôpital Saint-Louis, Paris, France) during the same time period, after filling a questionnaire in order to exclude individuals with psoriasis, HS, CD and UC history, or personal history of any systemic immunomodulatory or immunosuppressive treatment (e.g. methotrexate, ciclosporine, azathioprine, all biologics including TNF inhibitors). The information collected from these autoquestionnaires were the smoking status, the gender, age, and lastly, weight and height, in order to calculate body mass index (BMI). All patients and healthy donors were enrolled after written informed consent. The study protocol was approved by the Comité de Protection des Personnes Ile-de-France II. The research was conducted in compliance with the Helsinki Declaration.

Demographic and clinical data collection

We collected demographic and dermatological features such as age, gender, weight and height, smoking status, severity assessment of the diseases (Hurley stages, localization of the disease for HS, Psoriasis Area Severity Index/PASI for PV), previous antibiotherapy, as well as the eventual established association with other IMIDs, especially inflammatory rheumatic disease which have been shown to be more prevalent in patients with HS and with PV, spondyloarthritis in the former, and psoriatic arthritis (PsA) in the latter (11,12).

Biological data collection

Serological detection of ASCA and their IgG and/or IgA isotypes was performed using D-Tek Kit (Bluewell IgA-IgG Screen ELISA "ASCC02-96", Mons, Belgium). According to the manufacturer, positivity for ASCA was defined by a serum concentration of at least 25 UA/ml for IgG or for IgA.

Genetic studies

DNA was extracted from 52 HS patients' peripheral blood leukocytes using the Illustra DNA extraction kit BACC3 (GE Healthcare, Piscataway, NJ), following manufacturer's instructions. All exons and at least 100 base pair of flanking intronic sequences of the *PSENEN* (NM_001281532) *PSEN1* (NC_000014), *NCSTN* (NM_015331) and *APH1* (NM_016022) were amplified by PCR using specific primers. Both DNA strands were sequenced using the Big Dye® Terminator Cycle Sequencing Ready Reaction Kit version 3.1 (Applied Biosystems, Bedford, MA).

Statistical Analysis

Qualitative variables were expressed as frequencies (%), continuous variables as median (IQR) and were compared using Chi-squared or exact Fischer test and Wilcoxon rank sum test as appropriate. Pairwise tests were performed between HS, Psoriasis and healthy controls two by two. Multivariate analysis was performed using logistical regression. To identify the ASCA serological positivity determinants, a multivariate logistic regression was performed using all variables significant at 0.20 level in univariate analysis. A stepwise forward procedure was used to derive the multivariate model. The odds ratio (OR) were computed with their 95% confidence intervals. Statistical significance was defined as $p \leq 0.05$. Analysis was computed with Stata 14.0 software and R version 3.5.1.

Legends

Figure E1

ASCA : anti-*Saccharomyces cerevisiae* antibodies, HS : hidradenitis suppurativa, HC : healthy controls

Table E1

HS : hidradenitis suppurativa ; PV : psoriasis vulgaris ; HC : healthy controls ; IQR : Interquartile Range 25-75 ; BMI : body mass index ; CI : confidence interval

*p-values using Pearson's or Fisher chi-squared test as appropriate for categorial variables
and wilcoxon test for continious variables

Table E2

OR: Odd Ratio; CI: confidence interval

Table E3

CRP : C Reactive Protein ; OR : Odd Ratio ; CI : confidence interval