

Supplementary Table S1. Measured plasma biomarkers with lower detection limits and data classifications.

	Lower detection limit	Data classification
IL-12	5.869 pg/mL	Continuous
IL-5	0.646 pg/mL	Continuous
IL-17A	12.321 pg/mL	Continuous
IL-25	29.449 pg/mL	Continuous
IL-31	0.049 pg/mL	Continuous
IFN- α	6.629 pg/mL	Continuous
IL-10	2.066 pg/mL	Continuous
IL-1 α	4.912 pg/mL	Continuous
CCL11	16.358 pg/mL	Continuous
IL-4	0.65 pg/mL	Binomial
IL-22	12.336 pg/mL	Binomial
IL-6	0.478 pg/mL	Binomial

Supplementary Table S2. Baseline demographics of prurigo nodularis patients and healthy controls. PN – prurigo nodularis; SD – standard deviation; WI-NRS – Worst-Itch Numeric Rating Scale; IGA – Investigator’s Global Assessment.

	PN (n=20)	Healthy control (n=15)	P-value
Age, mean \pm SD	54.1 \pm 14.9	51.9 \pm 14.1	0.764
Sex, % (n)			0.911
Male	25% (5)	27% (4)	
Female	75% (15)	73% (11)	
Race, % (n)			0.686
Caucasian	40% (8)	33% (5)	
African American	60% (12)	67% (10)	
WI-NRS, mean \pm SD	9.0 \pm 1.2	0 \pm 0	< 0.001
IGA	3.3 \pm 0.7	0 \pm 0	< 0.001

Supplementary Table S3. Comparisons of plasma biomarkers between prurigo nodularis clusters. SD – standard deviation; IL – interleukin; IFN – interferon; CCL – C-C motif chemokine ligand

	Cluster 1	Cluster 2	P-value
Continuous variables, geometric mean \pm SD			
IL-12	4.36 \pm 0.45	4.64 \pm 0.45	0.1022
IL-5	1.54 \pm 0.55	1.98 \pm 0.44	0.0366
IL-17A	3.80 \pm 0.20	3.98 \pm 0.18	0.0366
IL-25	4.65 \pm 0.53	5.38 \pm 0.45	0.0016
IL-31	5.60 \pm 0.24	5.90 \pm 0.52	0.0798
IFN- α	3.49 \pm 0.19	4.19 \pm 0.40	0.0004
IL-10	1.44 \pm 0.94	2.68 \pm 0.56	0.0030
IL-1 α	1.35 \pm 0.55	2.49 \pm 0.57	0.0011
CCL11	3.74 \pm 0.95	4.17 \pm 0.59	0.2014
Binary variables, % positive (n)			
IL-4	22% (2)	91% (10)	0.0018
IL-22	11% (1)	82% (9)	0.0017
IL-6	33% (3)	82% (9)	0.0277

Supplementary Table S4. Comparisons of plasma biomarkers for prurigo nodularis clusters vs. controls. SD – standard deviation; IL – interleukin; IFN – interferon; CCL – C-C motif chemokine ligand

	Cluster 1	Cluster 2	Control	Cluster 1 vs. Control, P-value	Cluster 2 vs. Control, P-value
Continuous variables, geometric mean \pm SD					
IL-12	4.36 \pm 0.45	4.64 \pm 0.45	4.13 \pm 0.42	0.2965	0.0102
IL-5	1.54 \pm 0.55	1.98 \pm 0.44	1.44 \pm 0.57	0.7883	0.0169
IL-17A	3.80 \pm 0.20	3.98 \pm 0.18	3.61 \pm 0.61	0.6333	0.0292
IL-25	4.65 \pm 0.53	5.38 \pm 0.45	5.01 \pm 1.03	0.1348	0.0816
IL-31	5.60 \pm 0.24	5.90 \pm 0.52	5.06 \pm 2.44	0.5909	0.2124
IFN- α	3.49 \pm 0.19	4.19 \pm 0.40	3.70 \pm 0.60	0.1988	0.0355
IL-10	1.44 \pm 0.94	2.68 \pm 0.56	1.44 \pm 1.52	0.8554	0.0098
IL-1 α	1.35 \pm 0.55	2.49 \pm 0.57	1.87 \pm 0.88	0.0843	0.0945
Eotaxin	3.74 \pm 0.95	4.17 \pm 0.59	4.26 \pm 0.69	0.2384	0.6461
Binary variables, % positive (n)					
IL-4	22% (2)	91% (10)	47% (7)	0.2311	0.0191
IL-22	11% (1)	82% (9)	60% (9)	0.0187	0.2337
IL-6	33% (3)	82% (9)	60% (9)	0.2059	0.2337

Supplementary Table S5. Clinical characteristics of PN patients for each cluster. PN – prurigo nodularis; SD – standard deviation; WI-NRS – Worst-Itch Numeric Rating Scale; IGA – Investigator’s Global Assessment; DLQI – Dermatology Life Quality Index; BDI – Beck’s Depression Inventory

	Cluster 1 (n=9)	Cluster 2 (n=11)	P-value
Age, mean ± SD	53.7 ± 16.6	54.5 ± 14.2	0.7901
Sex, % (n)			0.1945
Male	11% (1)	36% (4)	
Female	89% (8)	64% (7)	
Race			0.0277
African American, % (n)	33% (3)	82% (9)	
Caucasian, % (n)	67% (6)	18% (2)	
WI-NRS, mean ± SD	8.3 ± 1.2	9.5 ± 0.9	0.0359
IGA, mean ± SD	3.0 ± 0.7	3.4 ± 0.7	0.2432
DLQI, mean ± SD	13.0 ± 4.1	21.9 ± 6.4	0.0152
BDI score, mean ± SD	8.0 ± 7.8	19.5 ± 12.8	0.0651
History of atopy, % (n)	11% (1)	27% (3)	0.3690
Spinal pathology, % (n)	67% (6)	18% (2)	0.0277
Inflammatory comorbidities, % (n)	44% (4)	55% (5)	0.9640
Immunomodulating drugs, % (n)	44% (4)	27% (3)	0.4231
Neuromodulating drugs, % (n)	55% (5)	27% (3)	0.1990

Supplementary Table S6. Major comorbidity profiles and medication use at the time of blood draw for prurigo nodularis (PN) and healthy control patients. Doses are represented as weekly for methotrexate, daily for gabapentin, and biweekly for dupilumab. CKD – chronic kidney disease; T2DM – type 2 diabetes mellitus; HIV – human immunodeficiency virus; CHF – congestive heart failure.

PN Cluster 1 (n=9)				PN Cluster 2 (n=11)				Healthy Control (n=15)			
Patient	WI-NRS	Comorbidities	Medications	Patient	WI-NRS	Comorbidities	Medications	Patient	WI-NRS	Comorbidities	Medications
1	10	Thoracic spinal stenosis	Gabapentin, Dupilumab	1	10	Cervical spinal stenosis	None	1	0	None	None
2	9	CKD	None	2	10	HIV	nbUVB	2	0	None	None
3	10	Cervical spinal stenosis	nbUVB, Methotrexate, Gabapentin	3	9	T2DM	None	3	0	None	None
4	9	T2DM, CKD, spinal trauma	Gabapentin	4	9	None	nbUVB, Gabapentin, Dupilumab	4	0	None	None
5	7	Spinal trauma	None	5	10	None	None	5	0	T2DM	None
6	8	Degenerative disc disease, multiple sclerosis	None	6	10	None	None	6	0	None	None
7	7	Crohn's disease	nbUVB, Methotrexate	7	10	T2DM, CHF	Methotrexate, Gabapentin	7	0	None	None
8	7	None	nbUVB, Gabapentin	8	10	T2DM, cirrhosis	None	8	0	None	None
9	8	Cervical spinal stenosis	Gabapentin	9	7	None	None	9	0	T2DM	None
				10	9	Hepatitis C	None	10	0	T2DM, CKD	None
				11	10	HIV, CHF, lumbar spinal stenosis	Gabapentin	11	0	None	None
								12	0	T2DM	None
								13	0	None	None
								14	0	CKD	None
								15	0	None	None