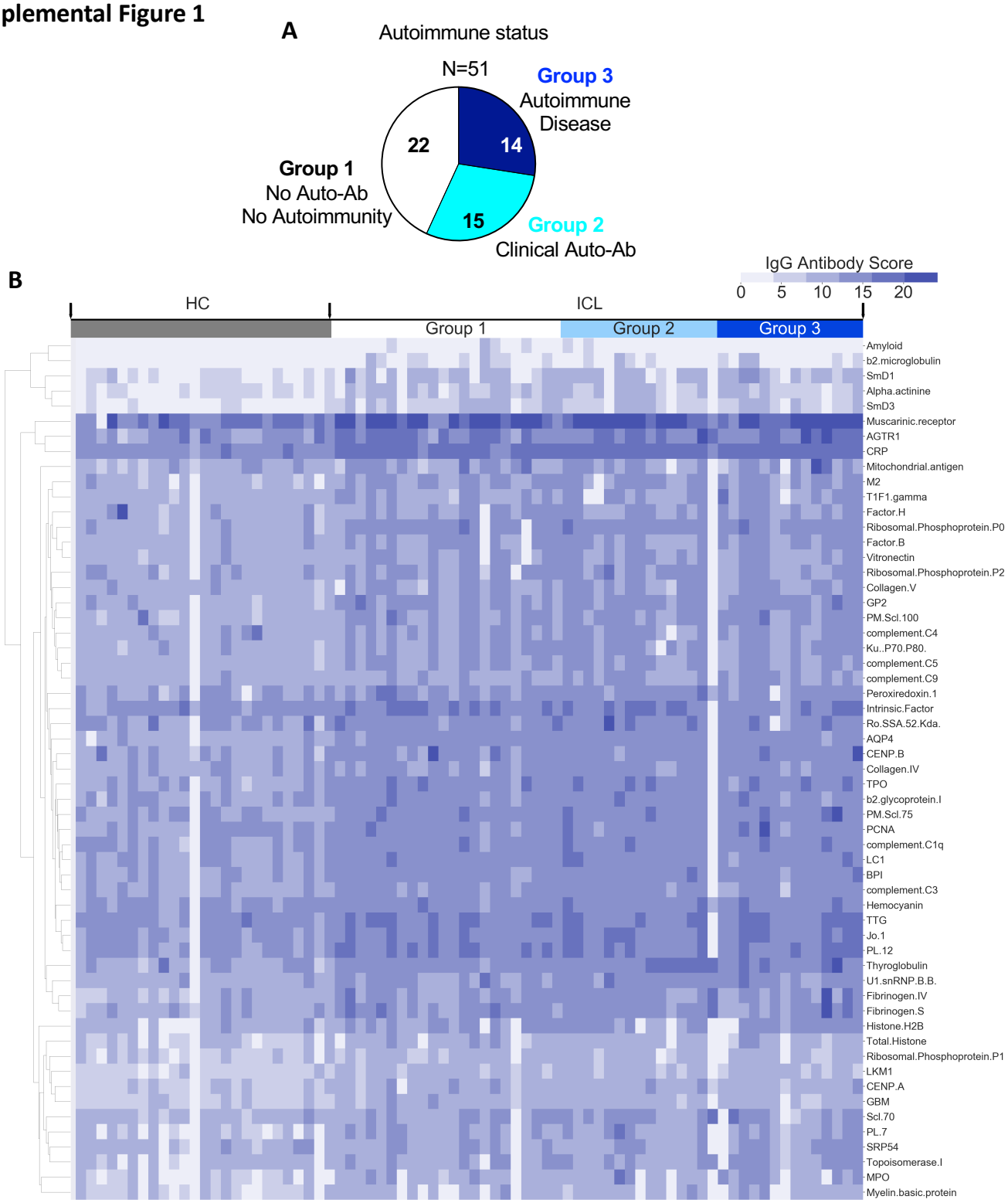
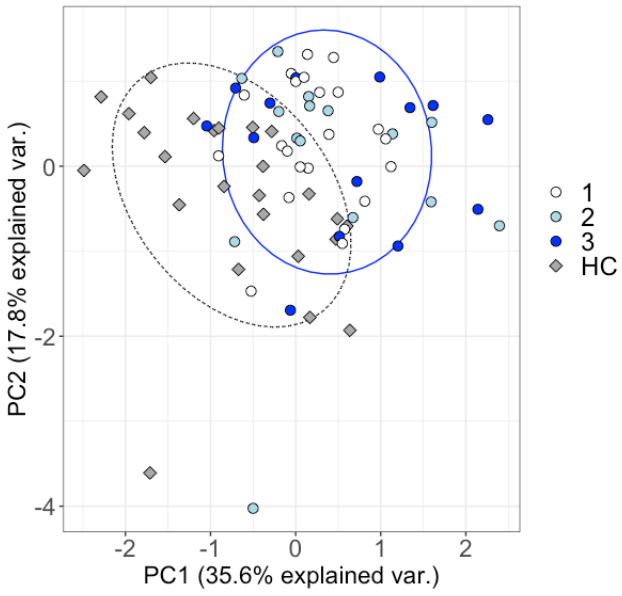
Supplemental Figure 1



Supplemental Figure 1. High prevalence of autoantibodies in ICL patients regardless of clinical autoimmunity status. (**A**) Distribution of the ICL patients, analyzed by the autoantigen array, based on autoimmunity category. Group 1, in white, patients with no autoimmune disease and no clinical autoantibodies. Group 2, in cyan, patients with clinical autoantibodies but no specific autoimmune diagnosis. Group 3, in blue, patients with autoimmune disease. (**B**) Cluster showing the Ab scores of the 57 IgG auto-antibodies found in the ICL patients. Data were supervised at the sample level (x-axis) and unsupervised at the autoantibody level (y-axis). (Cont.)

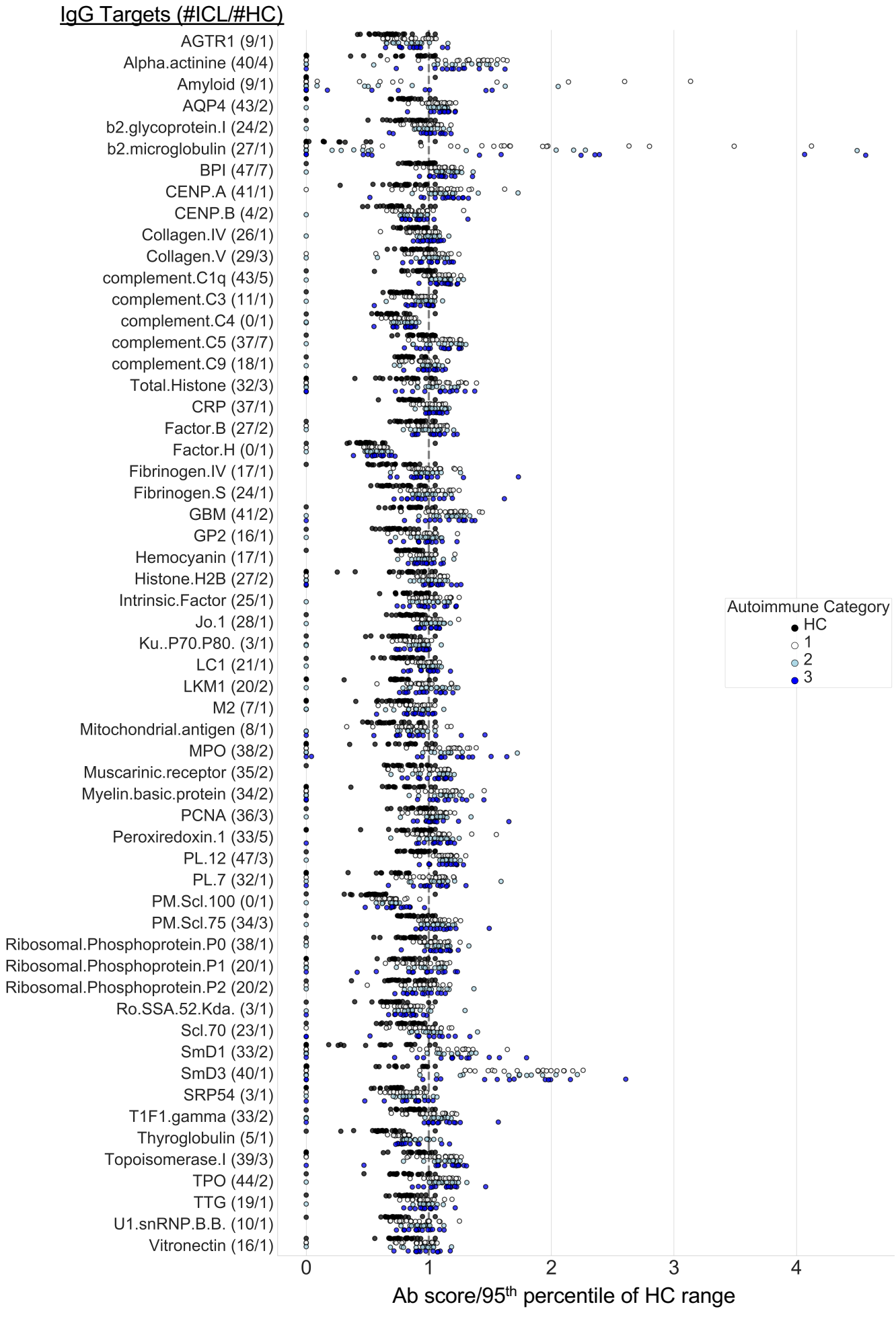
Supplemental Figure 1C

Supplemental Figure 1D

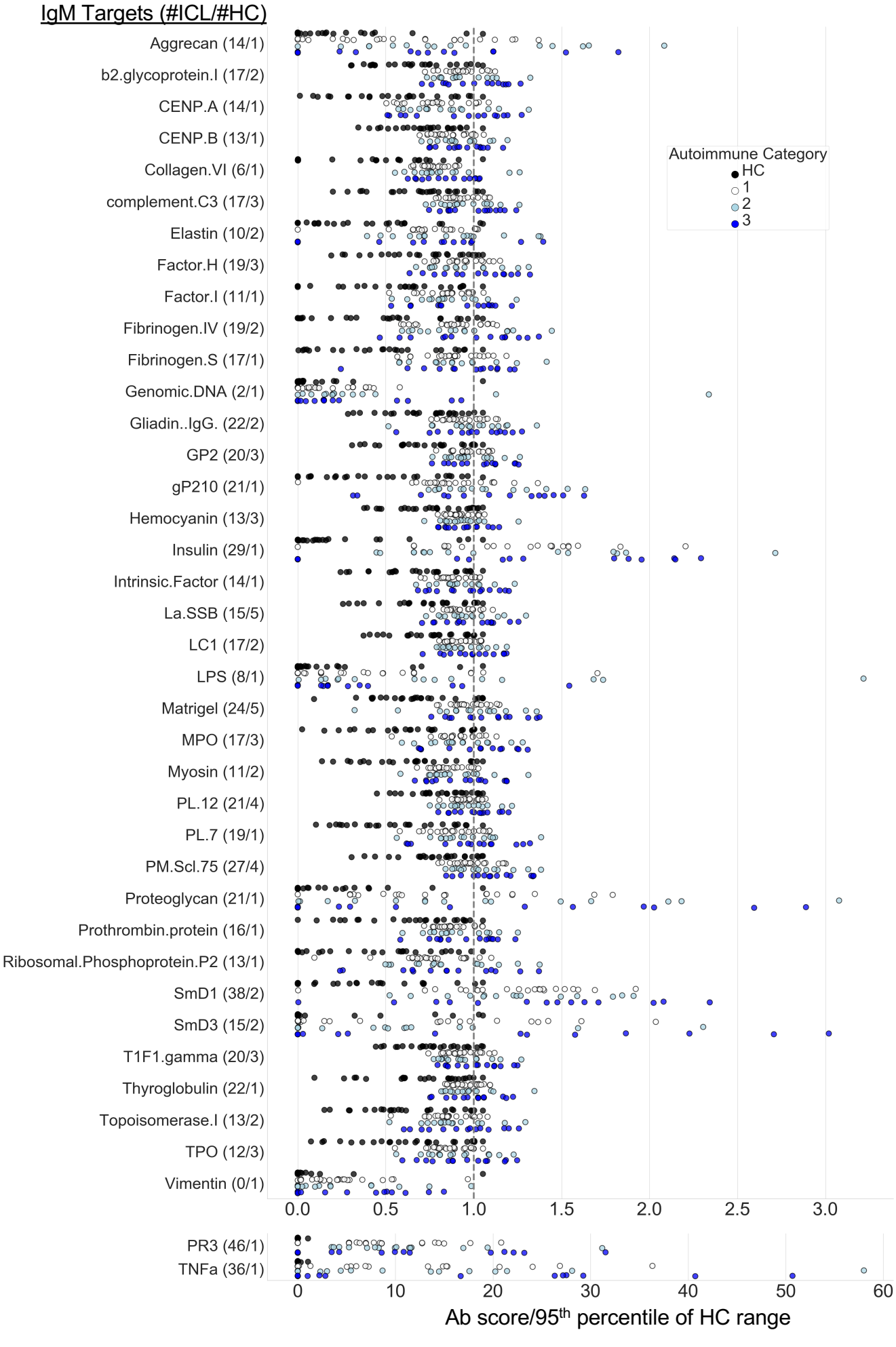


(Cont.) Supplemental Figure 1. High prevalence of autoantibodies in ICL patients regardless of clinical autoimmunity status. (**C**) Cluster showing the Ab scores of the 39 IgM auto-antibodies found in the ICL patients. Data were supervised at the sample level (x-axis) and unsupervised at the autoantibody level (y-axis). (**D**) Principal Component Analysis using the combined IgG and IgM Ab scores for each patient. Each symbol represents one patient. ICL patients cluster (blue circle) separately from HC cluster (black discontinuous circle), and the three ICL subgroups cluster together. Pairwise Adonis test with adjusted p values for FDR: $p<0.001$ for all three comparisons, HC vs group 1, HC vs group 2 and HC vs group 3. Differences within the three ICL subgroups by autoimmunity status were not statistically significant. (cont).

Supplemental Figure 1E

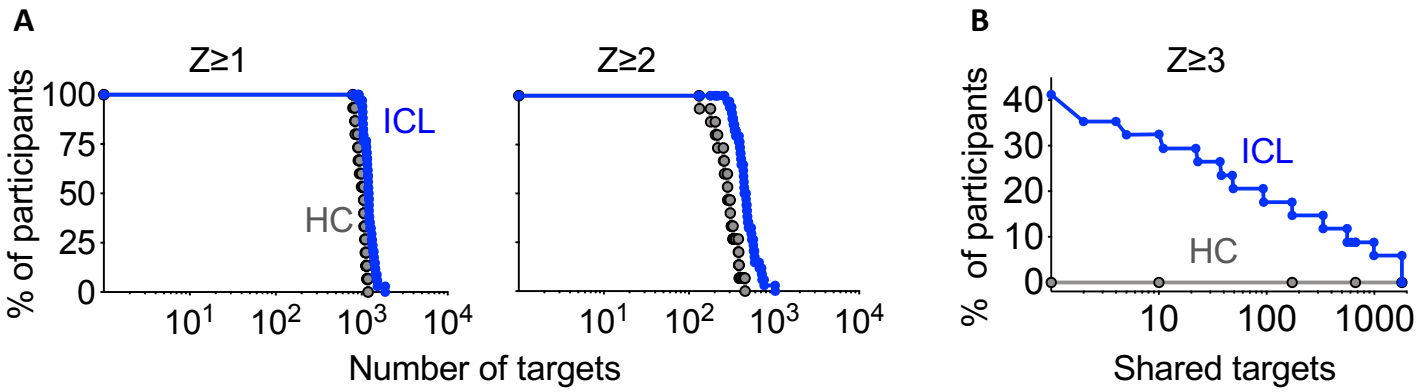


Supplemental Figure 1F



(Cont.) Supplemental Figure 1. High prevalence of autoantibodies in ICL patients regardless of clinical autoimmunity status. (**E**) Strip plot showing the targets of the 57 IgG autoantibodies found in ICL patients. For each target, the range of the Ab score of healthy controls (HC) was calculated and its 95th percentile was used to set up the threshold for positivity. For each sample and target, the ratio of Ab score to the respective HC 95th percentile is shown with HC in black and the three different ICL autoimmune categories in white, light blue and dark blue. Ratio >1 was considered positive (grey discontinuous line). The number of positive samples in the ICL and HC groups, respectively, are shown in parenthesis next to the targets' name. (**F**) Strip plot showing the targets of the 39 IgM autoantibodies found in ICL patients with Ab scores ratios calculated as described in E. PR3 and TNF-α are shown separately due to higher values found in ICL patients.

Supplemental Figure 2



C

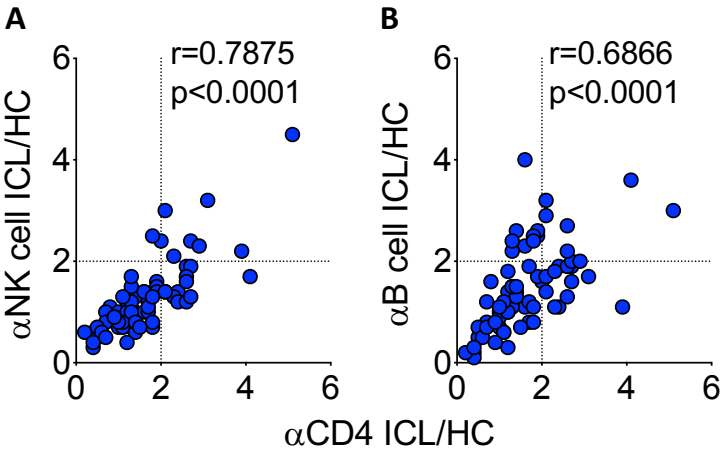
Top Upstream Regulators

Name	p-value
HNF4A *	4.09E-12
beta-estradiol	5.38E-09
CD3	6.26E-08
TCR	9.46E-08

*Hepatocyte Nuclear Factor 4 Alpha

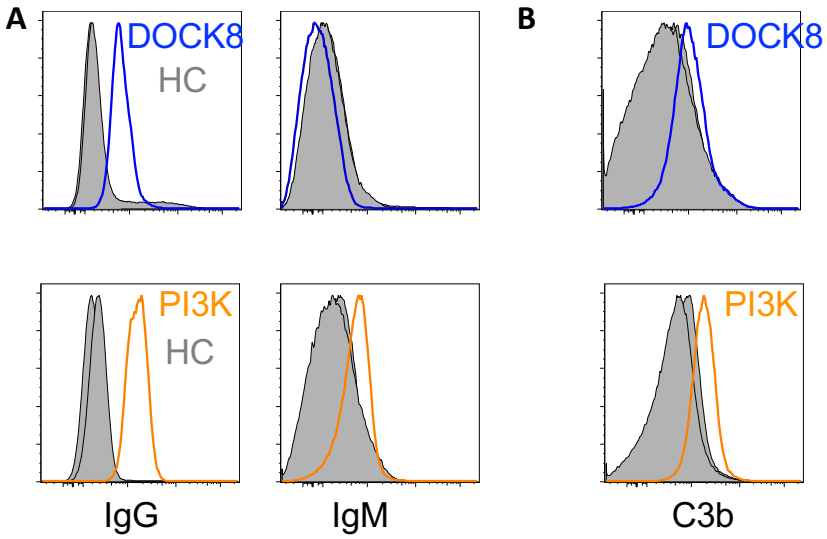
Supplemental Figure 2. Z scores and top upstream regulators from protoarray data analysis. (**A**) Z-scores were calculated as the number of standard deviations of antibody score from the mean of HC. At Z≥1 and Z≥2 there was no discrimination between HC and ICL groups. **(B**) Percentage of participants (HC, grey; ICL, blue) that shared any of the 3,418 and 668 targets found in the ICL and HC groups, respectively, at Z≥3. (**C**) Top upstream regulators of the 2,159 proteins targeted by ICL antibodies at Z≥4, using the Ingenuity Pathway Analysis. Data pooled from three independent experiments.

Supplemental Figure 3



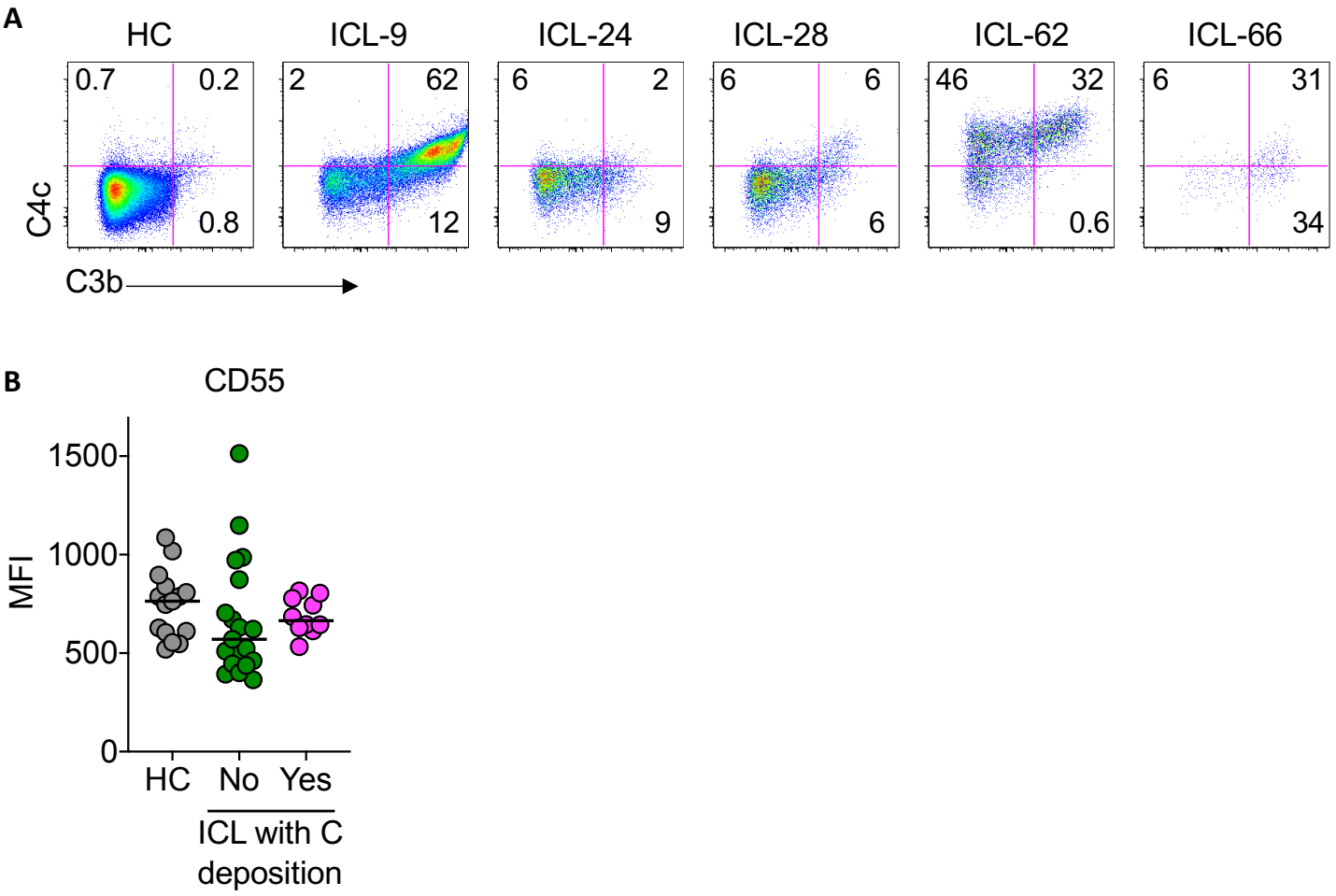
Supplemental Figure 3. Correlation of IgG antibodies against different cell subsets. Correlation of IgG anti-CD4-cell Ab versus either NK cells (A) or B cells (B) found in the same individual patient**.** Data were pooled from 17 independent experiments done on 71 ICL patients and 30 HC as described on Figure 3A. A ratio ≥2 (dotted lines) was considered as positive antibody deposition. R and p values obtained by a two-tailed Spearman correlation.

Supplemental Figure 4



Supplemental Figure 4. Lymphopenias associated with primary immune deficiencies (PID) exhibit similar anti-lymphocyte antibodies that can lead to complement activation. (**A**) Anti CD4 T cell antibody detection measured as in Figure 3A. One patient (in blue) with bi-allelic *DOCK8* mutations had IgG Ab and a second patient (in orange) with a *PI3KCD* mutation had both IgG and IgM. (**B**) Complement deposition induced by patients' sera measured as in Figure 5A.

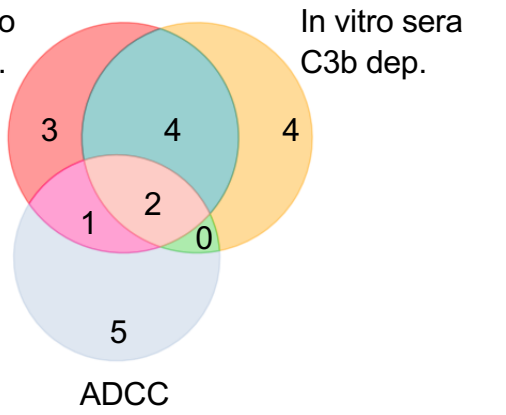
Supplemental Figure 5



Supplemental Figure 5. Deposition of C4c and levels of complement inhibitor CD55 on ICL CD4 T cells. (**A**) Staining for C4c and C3b on one HC PBMC and five ICL PBMC tested positive previously for C1q and C3b, directly ex vivo without any further incubation or manipulation. Numbers in the quadrants represent the percentage of positive cells out of the CD4 T cell gate. (**B**) MFI of complement inhibitors CD55 on CD4 T cells from HC or ICL patients with and without ex vivo complement (C) deposition as described in Figure 6. Circles represent individual donors and the horizontal lines the median value for each group.

Supplemental Figure 6

A



B

EPIC #	Ig (aCD4)	ADCC	C3b dep.	Ex vivo C dep.	#CD4	Autoimmunity
10						
11						
18						
27						
30						
34						
42						
48						
56						
72						
86						
90						
92						
93						
97						
2						
5						
21						
40						
45						
46						
54						
59						
64						
66						
71						
74						
78						
84						
1						
37						
44						
53						
63						
67						
81						
98						
23						
26						
33						
38						
41						
60						
69						
76						
77						
80						
87						
88						
89						
7						Sarcoidosis, Vitiligo, Autoimmune Thyroid Disease
9						Autoimmune Hemolytic anemia, atopic dermatitis
12						ITP
25						Autoimmune Thyroid Disease
39						Psoriatic Arthritis, Autoimmune Thyroid Disease
43						Sarcoidosis
51						Autoimmune Thyroid Disease
58						Ulcerative colitis
73						Autoimmune Thyroid Disease
79						Psoriasis
94						Ankylosing spondilitis
99						Ulcerative colitis
15						Sarcoidosis
16						SLE
24						Autoimmune Thyroid Disease
28						Psoriatic Arthritis
49						Autoimmune Thyroid Disease
50						Autoimmune Thyroid Disease, Psoriasis
62						Vitiligo, ITP
83						Autoimmune Thyroid Disease
91						Psoriatic rash, Alopecia totalis
96						Sarcoidosis

Supplemental Figure 6. Venn diagram of the three functional autoreactivities found in ICL patients and table with the individual information organized by autoimmune status. (**A**) Venn diagram representing the number of patients with complement deposition on their CD4 T cells observed directly ex vivo (ex vivo C dep., n=10), whose sera induced complement deposition on HC CD4 T cells (in vitro sera C3b dep., n=10), whose sera induced ADCC on HC CD4 T cells (ADCC, n=8) and overlap generated by any combination of these three functional autoreactivities. All 28 patients shown in this graph had antibodies against lymphocyte membrane proteins. (**B**) Table showing in green, the presence of anti-CD4 Ab (either IgG or IgM) (Ig αCD4); in orange, the presence of Ab with ADCC activity, Ab with complement deposition activity in vitro (C3b dep.), or complement activation on the T cells in vivo (Ex vivo C dep.), and in red CD4 numbers <75 for each ICL patient, and how they relate to their autoimmune status. Autoimmune status color coded as in Supplemental Figure 1. The specific autoimmune diseases are listed.

Supplemental Table 1. Clinical and laboratory characteristics of ICL participants.

ICL	Sex[A]	Age[B]	Autoimmune disease	Infectious Complications	CD3[C, D] (cells/ µL)	CD4 (cells /µL)	CD8 (cells /µL)	NK (cells /µL)	B (cells /µL)	IgG[E] (mg/ dL)	IgM (mg/d L)
1	M	33	None (2)	HPV	**375**[F]	**139**	216	**91**	125	1127	141
2	F	58	None (1)	HPV/Histoplasma	**50**	**18**	**26**	**99**	*419*[G]	833	105
5	M	51	None (1)	HPV/VZV	**279**	**40**	**168**	**77**	**54**	**531**	58
7	F	51	Sarcoidosis, Vitiligo, Autoimmune Thyroid Disease (3)	Histoplasma	**197**	**150**	**42**	267	244	1286	150
9	M	68	Autoimmune Hemolytic anemia, Atopic dermatitis (3)	NO	**305**	**158**	**144**	**88**	**20**	745	*291*
10	M	62	None (1)	VZV	**689**	**100**	558	211	144	**675**	48
11	M	44	None (1)	NO	**617**	**242**	280	**87**	**43**	1025	42
12	M	69	ITP (3)	NO	**278**	**172**	**105**	159	**30**	1011	48
15	M	56	Sarcoidosis (3)	Cryptococcus	**131**	**66**	**61**	160	81	802	75
16	F	31	SLE (3)	HPV/Molluscum	**111**	**13**	**47**	**118**	250	1070	*245*
18	F	60	None (1)	NO	**261**	**149**	**109**	**89**	**55**	**524**	74
21	F	55	None (1)	VZV	**80**	**11**	**35**	130	*392*	1010	53
23	F	59	None (2)	HPV/Cryptococcus	1432	**63**	*1344*	137	134	902	57
24	F	61	Autoimmune Thyroid Disease (3)	HPV/VZV/Cryptococcus	**101**	**44**	**40**	**74**	106	**563**	149
25	M	66	Autoimmune Thyroid Disease (3)	NO	**437**	**255**	**163**	334	164	928	92
26	F	39	None (2)	HPV/Cryptococcus	829	**59**	651	161	211	942	120
27	M	27	None (1)	NO	962	**143**	769	176	156	1088	68
28	F	39	Psoriatic Arthritis (3)	HPV/VZV	**233**	**34**	**118**	**90**	*434*	871	187
30	M	62	None (1)	Candida	**408**	**240**	**158**	177	176	797	92
33	F	33	None (2)	HPV	848	**70**	761	**102**	127	**685**	*239*
34	M	62	None (1)	VZV	**420**	**168**	240	177	69	1083	60
37	M	45	None (2)	HPV/VZV/Cryptococcus	**364**	**127**	**132**	128	221	1170	72
38	M	58	None (2)	HPV/VZV/Cryptococcus	**100**	**33**	**30**	**68**	130	842	80
39	F	62	Psoriatic Arthritis, Autoimmune Thyroid Disease (3)	NO	**570**	**133**	435	178	153	1288	120
40	F	54	None (1)	Cryptococcus	**560**	**46**	453	134	101	758	129
41	F	31	None (2)	HPV	**138**	**22**	**72**	193	182	1096	85

42	M	32	None (1)	NO	**459**	**250**	**145**	128	**39**	807	74
43	F	51	Sarcoidosis (3)	NO	**440**	**272**	188	**116**	64	**686**	90
44	F	64	None (2)	HSV-1	**251**	**205**	**53**	**104**	**59**	1558	41
45	M	36	None (1)	Molluscum	**157**	**15**	**55**	137	*322*	720	58
46	F	36	None (1)	HPV/HSV-1/Cryptococcus	**642**	**76**	460	246	96	739	128
48	F	38	None (1)	HPV	**458**	**203**	217	132	97	**669**	87
49	F	57	Autoimmune Thyroid Disease (3)	NO	**127**	**41**	**69**	323	*368*	828	91
50	F	61	Autoimmune Thyroid Disease, Psoriasis (3)	PML	**108**	**11**	**21**	258	**42**	740	62
51	F	66	Autoimmune Thyroid Disease (3)	NO	**416**	**282**	**145**	129	110	926	*239*
53	M	50	None (2)	Cryptococcus	**428**	**160**	**170**	**106**	99	1553	139
54	F	58	None (1)	Cryptococcus	843	**71**	732	129	134	**544**	56
56	M	77	None (1)	KSHV	**192**	**138**	**45**	**77**	**14**	842	47
58	M	63	Ulcerative colitis (3)	NO	**417**	**230**	**175**	176	**20**	**633**	97
59	M	75	None (1)	Cryptococcus	**168**	**24**	**118**	165	187	1190	72
60	M	54	None (2)	VZV/Molluscum/MAC	**41**	**6**	**8**	138	*339*	979	**22**
62	M	41	Vitiligo, ITP (3)	HPV/Cryptococcus	**324**	**49**	214	447	123	1165	45
63	F	60	None (2)	NO	**109**	**78**	**20**	129	234	1362	129
64	M	48	None (1)	Cryptococcus/Molluscum	**105**	**32**	**40**	213	222	891	90
66	F	35	None (1)	HPV	**41**	**9**	**13**	139	223	850	167
67	F	27	None (2)	HPV	**467**	**145**	258	365	*327*	**590**	110
69	M	53	None (2)	Cryptococcus	**133**	**2**	**25**	211	306	949	71
71	M	50	None (1)	Cryptococcus	**186**	**2**	**58**	**50**	144	736	61
72	M	66	None (1)	NO	**640**	**268**	291	**70**	78	771	46
73	M	65	Autoimmune Thyroid Disease (3)	CMV	**713**	**190**	495	173	**20**	*1697*	41
74	F	62	None (1)	PML	875	**71**	800	**88**	*363*	**545**	**32**
76	M	43	None (2)	NO	**113**	**26**	**46**	**78**	158	1113	81
77	M	39	None (2)	HPV	**71**	**32**	**42**	**46**	**3**	1218	52
78	M	71	None (1)	Cryptococcus/Aspergillosis/CM\	**155**	**17**	**111**	**18**	**56**	**638**	**32**
79	M	30	Psoriasis (3)	HPV	**474**	**118**	294	276	275	1149	98
80	F	66	None (2)	VZV	**263**	**74**	**123**	186	109	**653**	230
81	M	47	None (2)	HPV	**345**	**166**	**156**	**78**	259	**665**	71
83	F	48	Autoimmune Thyroid Disease (3)	HPV/VZV/Cryptococcus	**132**	**23**	**82**	260	102	719	56
84	F	46	None (1)	NO	**133**	**41**	**58**	**96**	212	936	65

86	F	35	None (1)	HPV/Molluscum	991	**126**	801	203	175	704	64
87	M	29	None (2)	HPV/Molluscum/Cryptococcus	**576**	**24**	518	**99**	114	1531	77
88	F	46	None (2)	NO	**213**	**58**	**94**	138	81	1287	92
89	M	31	None (2)	Molluscum/Histoplasma	**357**	**26**	194	**110**	161	968	125
90	F	38	None (1)	NO	**689**	**111**	545	**102**	92	1242	51
91	F	20	Psoriatic rash, Alopecia totalis (3)	HPV/Molluscum	**142**	**50**	**28**	176	163	1037	140
92	M	61	None (1)	NO	**168**	**105**	**50**	**120**	72	802	89
93	M	37	None (1)	HPV/Cryptococcus/Coccidiodes	984	**79**	792	192	193	**529**	53
94	M	70	Ankylosing spondilitis (3)	NO	**441**	**183**	236	342	72	**633**	76
96	M	36	Sarcoidosis (3)	PCP	**118**	**42**	**68**	**37**	**56**	823	185
97	F	37	None (1)	NO	934	**93**	782	**87**	149	**693**	223
98	F	34	None (2)	HPV	**372**	**187**	**150**	**92**	101	827	189
99	M	52	Ulcerative colitis (3)	MAC	**197**	**121**	**60**		100	**674**	53

[A]F=Female, M=Male

[B]Age at time of enrollment

[C]Laboratory values on the day of anti-CD4 T cell membrane autoantibody testing by flow

[D]Range of normal values (cells/µL): CD3 714-2266, CD4 359-1565, CD8 178-853, NK 126-729 and B cells 61-320

[E]Range of normal values for serum immunoglobulins (mg/dL): IgG 700-1600 and IgM 40-230

[F]In red and bold, values below the normal range

[G]In blue and italic, values above the normal range

Supplemental Table 2. Top molecules targeted by IgG Ab found in ICL sera.

	Targets of IgG AutoAb	p-value[A]	log2(fc)[B]
1	AGTR1[C]	9.76E-06	3.37
2	Alpha.actinine	5.98E-07	3.44
3	Amyloid	9.18E-05	1.16
4	AQP4	2.94E-10	3.88
5	b2.glycoprotein.I[D]	6.63E-06	2.47
6	b2.microglobulin	4.96E-06	2.82
7	BPI	1.75E-09	2.60
8	CENP.A	1.02E-08	2.88
9	CENP.B	5.82E-06	2.26
10	Collagen.IV	2.79E-05	1.06
11	Collagen.V	1.14E-04	1.09
12	complement.C1q	4.20E-09	2.60
13	complement.C3	7.96E-07	2.22
14	complement.C4	1.04E-04	1.37
15	complement.C5	6.63E-06	1.93
16	complement.C9	7.73E-05	1.61
17	Total.Histone	3.46E-05	2.44
18	CRP	2.37E-10	3.10
19	Factor.B	2.85E-05	1.48
20	Factor.H	2.75E-04	1.40
21	Fibrinogen.IV	8.98E-09	3.82
22	Fibrinogen.S	7.28E-08	3.34
23	GBM	1.41E-08	2.65
24	GP2	4.57E-08	3.07
25	Hemocyanin	1.05E-07	2.39
26	Histone.H2B	2.87E-05	2.65
27	Intrinsic.Factor	5.71E-05	1.93
28	Jo.1	6.68E-09	2.76
29	Ku.P70.P80.	7.54E-06	1.87
30	LC1	4.57E-08	2.89
31	LKM1	2.44E-08	2.43
32	M2	3.80E-06	2.83
33	Mitochondrial.antigen	2.87E-04	1.87
34	**MPO[E]**	**2.61E-07**	**4.80**
35	**Muscarinic.receptor[E]**	**2.90E-07**	**4.73**
36	Myelin.basic.protein	2.23E-04	2.17
37	PCNA	1.32E-06	2.26
38	Peroxiredoxin.1	3.42E-06	2.94
39	PL.12	3.51E-10	3.41

40	**PL.7[E]**	**8.93E-09**	**4.94**
41	PM.Scl.100	7.06E-08	2.98
42	PM.Scl.75	1.66E-08	2.84
43	Ribosomal.Phosphoprotein. P0	1.55E-08	2.72
44	Ribosomal.Phosphoprotein. P1	2.11E-04	1.89
45	Ribosomal.Phosphoprotein. P2	2.12E-04	2.02
46	Ro.SSA.52.Kda.	3.38E-05	2.11
47	Scl.70	5.58E-05	1.78
48	SmD1	1.70E-05	3.93
49	SmD3	7.03E-07	4.50
50	SRP54	3.94E-04	1.99
51	T1F1.gamma	4.01E-06	1.65
52	Thyroglobulin	1.20E-09	4.26
53	Topoisomerase.I	3.80E-07	3.65
54	TPO	2.64E-10	4.04
55	TTG	1.65E-07	2.56
56	U1.snRNP.B.B.	6.43E-08	2.89
57	Vitronectin	1.58E-05	1.74

[A]Bonferroni correction

[B]fc= fold change ICL/HC.

[C]List organized by alphabetical order

[D]In pink background, targets recognized by both IgG and IgM autoAb

[E]In bold, top three targets mentioned in the text.

Supplemental Table 3. Top molecules targeted by IgM Ab found in ICL sera.

	IgM autoantibodies	p-value[A]	log2(fc)[B]
1	Aggrecan[C]	9.55E-06	1.51
2	b2.glycoprotein.I[D]	7.31E-07	3.31
3	CENP.A	2.03E-04	2.81
4	CENP.B	3.38E-05	2.40
5	**Collagen.VI[E]**	**6.16E-07**	**4.53**
6	complement.C3	4.24E-06	3.06
7	Elastin	9.73E-06	2.41
8	Factor.H	1.43E-04	2.63
9	Factor.I	2.29E-05	3.21
10	Fibrinogen.IV	1.21E-06	3.76
11	**Fibrinogen.S[E]**	**1.60E-06**	**3.78**
12	Genomic.DNA	7.53E-05	1.31
13	Gliadin..IgG.	2.48E-06	2.58
14	GP2	2.62E-06	3.24
15	gP210	1.28E-06	3.51
16	Hemocyanin	3.41E-04	2.45
17	Insulin	5.32E-08	2.67
18	Intrinsic.Factor	4.30E-05	2.73
19	La.SSB	8.29E-05	2.71
20	LC1	5.71E-05	2.57
21	LPS	2.09E-04	1.08
22	Matrigel	1.36E-06	3.02
23	MPO	5.71E-05	2.77
24	Myosin	7.92E-05	2.65
25	PL.12	7.92E-05	2.21
26	PL.7	1.28E-06	3.37
27	PM.Scl.75	8.66E-07	2.96
28	PR3	1.33E-11	2.33
29	Proteoglycan	5.30E-07	1.10
30	Prothrombin.protein	1.56E-04	2.92
31	Ribosomal.Phosphoprotein.P2	1.43E-04	2.45
32	**SmD1[E]**	**8.46E-10**	**3.84**
33	SmD3	4.69E-05	1.39
34	T1F1.gamma	4.96E-05	2.18
35	Thyroglobulin	2.92E-06	3.06
36	TNFa	3.43E-11	1.29
37	Topoisomerase.I	2.12E-04	2.58
38	TPO	2.12E-04	2.71
39	Vimentin	9.14E-08	1.12

[A]Bonferroni correction
[B]fc= fold change ICL/HC.
[C]List organized by alphabetical order
[D]In pink background, targets recognized by both IgG and IgM autoAb
[E]In bold, top three targets mentioned in the text.

Supplemental Table 4. List of most frequently shared targets among ICL patients at Z≥4.

	Symbol	Name	% (N) ICL patients	Cellular compartment
1	UGT3A1	UDP glycosyltransferase 3 family	35.3 (12)	Intracellular
2	CDCA7	Cell division cycle associated 7	26.5 (9)	Intracellular
3	ZCCHC17	Zinc finger CCHC domain containing 17	26.5 (9)	Intracellular
4	KLHL32	Kelch-like family member 32 (Drosophila)	23.5 (8)	Intracellular
5	NME3	Non-metastatic cells 3	23.5 (8)	Intra and extracellular
6	PDGFB	Platelet-derived growth factor beta polypeptide	23.5 (8)	Extracellular
7	SPSB3	SplA/ryanodine receptor domain and SOCS box containing 3	23.5 (8)	Intracellular
8	USF1	Upstream transcription factor 1	23.5 (8)	Intracellular
9	BMF	Bcl2 modifying factor	20.6 (7)	Intracellular
10	CFHR2	Complement factor H-related 2	20.6 (7)	Extracellular
11	CREM	CAMP responsive element modulator	20.6 (7)	Extracellular
12	DKK4	Dickkopf WNT signaling pathway inhibitor 4	20.6 (7)	Intracellular and plasma membrane
13	EIF2B1	Eukaryotic translation initiation factor 2B subunit alpha	20.6 (7)	Intracellular
14	HMGB2	High mobility group protein B2	20.6 (7)	Intra and extracellular
15	ISCA2	Iron-sulfur cluster assembly 2	20.6 (7)	Extracellular
16	NPY	Neuropeptide Y	20.6 (7)	Intracellular
17	NUP133	Nuclear pore complex protein Nup 133	20.6 (7)	Extracellular
18	PNLIPRP1	Pancreatic lipase-related protein 1	20.6 (7)	Intracellular
19	PRELID1	PRELI domain containing 1	20.6 (7)	Intracellular
20	RNF128	Ring finger protein 128	20.6 (7)	Extracellular
21	RP11-49G10.8	BASE	20.6 (7)	Extracellular

Supplemental Table 5. List of the most frequently shared targets in ICL group 3 that are the least shared by the rest of patients at Z≥3.

Symbol	% Group 3	% Group (1+2)	Description
LETM1	64	13	leucine zipper-EF-hand containing transmembrane protein 1 (LETM1)
AASDHPPT	45	9	aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase (AASDHPPT)
SPRED1	36	0	Sprouty-related, EVH1 domain containing 1 (SPRED1), mRNA
PRSS33	36	0	protease, serine, 33 (PRSS33)
MGC39821	36	4	Sorting nexin-18
CIAPIN1	36	4	cytokine induced apoptosis inhibitor 1 (CIAPIN1)
MX1	36	4	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) (MX1)
KCNIP2	36	4	Kv channel interacting protein 2 (KCNIP2), transcript variant 2
PTPRC	36	4	Leukocyte common antigen
XAF1	36	4	XIAP associated factor-1 (XAF1), transcript variant 1
LOC100128510	36	4	cDNA clone MGC:59959 IMAGE:4137660, complete cds
CDC7	36	4	Cell division cycle 7-related protein kinase
OSM	27	0	oncostatin M (OSM)
C5orf39	27	0	Annexin-2 receptor
MINA	27	0	MYC-induced nuclear antigen
C9orf163	27	0	Uncharacterized protein C9orf163
WWC2	27	0	Protein WWC2
NRN1L	27	0	Neuritin-like protein
NUS1	27	0	Nogo-B receptor
NR2E3	27	0	Photoreceptor-specific nuclear receptor
ACSM3	27	0	acyl-CoA synthetase medium-chain family member 3 (ACSM3), transcript variant 1
IL-19	27	0	Interleukin-19
ODF2L	27	0	outer dense fiber of sperm tails 2-like (ODF2L)
LOC649946	27	0	ribosomal protein L23a pseudogene (LOC649946)
LOC401068	27	0	PREDICTED: Homo sapiens hypothetical LOC401068 (LOC401068)
C13orf24	27	0	chromosome 13 open reading frame 24 (C13orf24)
LOC400849	27	0	PREDICTED: Homo sapiens hypothetical LOC400849 (LOC400849)

Supplemental Table 6. Serum and plasma complement related measurements from ICL and HC donors.

Marker	ICL	N	HC	N	P-value[A]
C1q (µg/mL)	78.6 (65.7-97.5)	57	87.8 (66.3-109)[B]	20	ns
C5a (ng/mL)	16 (10.1-39)	40	78 (18-152)	19	0.0003
C9 (µg/mL)	4 (2.5 – 5.1)	57	4.7 (1.8-6.4)	8	ns
CIC[C] C1q (µg EQ/mL)	41 (29-136)	42	68 (30-136)	8	ns
CIC[C] C3d (µg EQ/mL)	138 (95-222)	57	174 (101-217)	8	ns
CH50 U EQ/mL	169 (112-206)	66	147 (116-179)	37	ns
BLD[D] C5a (pg/mL)		16		0	0.0079*
BLD[D] CIC[2] C1q (µg EQ/mL)		13		0	0.0160*

[A]Mann-Whitnney or Fischer's Exact test
[B]Median values with IQR in parenthesis
[C]Complement Immune complex
[D]Below limit of detection

Suppplemental Table 7. Antibodies used for flow cytometry analysis.

Antigen	Clone	Fluorochrome	Supplier
C1q	polyclonal	FITC	Dako
C3b	1H8	PE	BD Biosciences
CD19	SJ25C1	BV510	BD Biosciences
CD19	SJ25C1	BV510	BD Biosciences
CD19	SJ25C1	APC	BD Biosciences
CD3	SK7	BUV395	BD Biosciences
CD3	SK7	PE-cy7	BD Biosciences
CD3	OKT3	Percp-cy5.5	Biolegend
CD4	SK3	PE	BD Biosciences
CD4	SK3	BUV737	BD Biosciences
CD4	L200	BV605	BD Biosciences
CD4	OKT-4	BV711	Biolegend
CD56	HCD56	BV421	Biolegend
CD56	NCAM	BV421	Biolegend
CD56	B159	V450	BD Biosciences
CD8	SK1	BV711	Biolegend
CD8	RPA-T8	Pacific Blue	BD Biosciences
Ig	Polyclonal	FITC	Biolegend
IgG	polyclonal	FITC	Jackson ImmunoResearch
IgG1	HP6001	PE	Southern Biotech
IgG2	HP6002	PE	Southern Biotech
IgG3	HP6005	AF647	Southern Biotech
IgG4	HP6025	AF647	Southern Biotech
IgM	polyclonal	APC	Jackson ImmunoResearch
CD55	IA10	APC	BD Biosciences
CD59	P282(H19)	BV711	BD Biosciences

Supplemental figure legends

Supplemental Figure 1. High prevalence of autoantibodies in ICL patients regardless of clinical autoimmunity status. (A) Distribution of the ICL patients, analyzed by the autoantigen array, based on autoimmunity category. Group 1, in white, patients with no autoimmune disease and no clinical autoantibodies. Group 2, in cyan, patients with clinical autoantibodies but no specific autoimmune diagnosis. Group 3, in blue, patients with autoimmune disease. (**B**) Cluster showing the Ab scores of the 57 IgG auto-antibodies found in the ICL patients. Data were supervised at the sample level (x-axis) and unsupervised at the autoantibody level (y-axis). (**C**) Cluster showing the Ab scores of the 39 IgM auto-antibodies found in the ICL patients. Data were supervised at the sample level (x-axis) and unsupervised at the autoantibody level (y-axis). (**D**) Principal Component Analysis using the combined IgG and IgM Ab scores for each patient. Each symbol represents one patient. ICL patients cluster (blue circle) separately from HC cluster (black discontinuous circle), and the three ICL subgroups cluster together. Pairwise Adonis test with adjusted p values for FDR: $p<0.001$ for all three comparisons, HC vs group 1, HC vs group 2 and HC vs group 3. Differences within the three ICL subgroups by autoimmunity status were not statistically significant. (**E**) Strip plot showing the targets of the 57 IgG autoantibodies found in ICL patients. For each target, the range of the Ab score of healthy controls (HC) was calculated and its 95th percentile was used to set up the threshold for positivity. For each sample and target, the ratio of Ab score to the respective HC 95th percentile is shown with HC in black and the three different ICL autoimmune categories in white, light blue and dark blue. Ratio >1 was considered positive (grey discontinuous line). The number of positive samples in the ICL and HC groups, respectively, are shown in parenthesis next to the targets' name. (**F**) Strip plot showing

the targets of the 39 IgM autoantibodies found in ICL patients with Ab scores ratios calculated as described in E. PR3 and TNF-α are shown separately due to higher values found in ICL patients.

Supplemental Figure 2. Z scores and top upstream upregulators from protoarray data analysis. (**A**) Z-scores were calculated as the number of standard deviations of antibody score from the mean of HC. At Z≥1 and Z≥2 there was no discrimination between HC and ICL groups. **(B**) Percentage of participants (HC, grey; ICL, blue) that shared any of the 3,418 and 668 targets found in the ICL and HC groups, respectively, at Z≥3. (**C**) Top upstream regulators of the 2,159 proteins targeted by ICL antibodies at Z≥4, using the Ingenuity Pathway Analysis. Data pooled from three independent experiments.

Supplemental Figure 3. Correlation of IgG antibodies against different cell subsets. Correlation of IgG anti-CD4-cell Ab versus either NK cells (**A**) or B cells (**B**) found in the same individual patient. Data were pooled from 17 independent experiments done on 71 ICL patients and 30 HC as described on Figure 3A. A ratio ≥2 (dotted lines) was considered as positive antibody deposition. R and p values obtained by a two-tailed Spearman correlation.

Supplemental Figure 4. Lymphopenias associated with primary immune deficiencies (PID) exhibit similar anti-lymphocyte antibodies that can lead to complement activation. (**A**) Anti CD4 T cell antibody detection measured as in Figure 3A. One patient (in blue) with bi-allelic *DOCK8* mutations had IgG Ab and a second patient (in orange) with a *PI3KCD* mutation had both IgG and IgM. (**B**) Complement deposition induced by patients' sera measured as in Figure 5A.

Supplemental Figure 5. Deposition of C4c and levels of complement inhibitor CD55 on ICL CD4 T cells. (**A**) Staining for C4c and C3b on one HC PBMC and five ICL PBMC which tested positive previously for C1q and C3b, directly ex vivo without any further incubation or manipulation. Numbers in the quadrants represent the percentage of positive cells out of the CD4 T cell gate. (**B**) MFI of complement inhibitor CD55 on CD4 T cells from HC or ICL patients with and without ex vivo complement (C) deposition as described in Figure 6. Circles represent individual donors and the horizontal lines the median value for each group.

Supplemental Figure 6. Venn diagram of the three functional autoreactivities found in ICL patients and table with the individual information organized by autoimmune status. (A) Venn diagram representing the number of patients with complement deposition on their CD4 T cells observed directly ex vivo (ex vivo C dep., n=10), whose sera induced complement deposition on HC CD4 T cells (in vitro sera C3b dep., n=10), whose sera induced ADCC on HC CD4 T cells (ADCC, n=8) and overlap generated by any combination of these three functional autoreactivities. All 28 patients shown in this graph had antibodies against lymphocyte membrane proteins. (**B**) Table showing in green, the presence of anti-CD4 Ab (either IgG or IgM) (Ig aCD4); in orange, the presence of Ab with ADCC activity, Ab with complement deposition activity in vitro (C3b dep.), or complement activation on the T cells in vivo (Ex vivo C dep.), and in red CD4 numbers <75 for each ICL patient, and how they relate to their autoimmune status. Autoimmune status color coded as in Supplemental Figure 1. The specific autoimmune diseases are listed.