
Supplementary information

T and B cells recognize splicing-derived neutrophil neoantigens in lupus

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Supplemental material

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Suppl. Table S1. Patient data.

id	sex	SLEDAI	Age	Prednisone dose	Other medications	Major chronic comorbidities	ANA	dsDNA	SSA	SSB	Sm	Ribosomal P	RNP
SLE 1	M	2	58	-	hcq, mmf	history of DVTs, dyslipidemia, peripheral vascular disease, coronary artery disease	+	+	-	-	-	-	-
SLE 2	F	4	43	-	hcq	-	+	+	+	+	-	+	-
SLE 3	F	9	28	-	hcq	-	+	+	-	-	-	-	-
SLE 4	F	12	38	27.5mg	hcq, aza	-	+	-	-	-	+	-	+
SLE 5	F	16	63	-	hcq	-	+	-	-	-	-	-	-
SLE 6	F	5	49	2.5mg	hcq, tacrolimus	-	+	+	+	-	+	-	-
SLE 7	F	4	31	-	hcq, mtx	-	+	+	+	-	+	-	+
SLE 8	F	4	65	-	hcq	-	-	-	-	-	-	-	-
SLE 9	F	36	25	40mg	-	shrinking lung, thyroid disease, history of DVT	+	+	-	-	-	-	-
SLE 10	F	2	31	-	hcq, mmf	-	+	+	-	-	-	-	-
SLE 11	F	14	58	-	mtx	diabetes, dyslipidemia	-	-	n.a.	n.a.	n.a.	n.a.	n.a.
SLE 12	F	2	47	-	hcq, rtx	-	+	-	+	+	+	-	indet
SLE 13	F	4	30	-	hcq	-	+	-	-	-	+	-	+
SLE 14	F	12	65	-	hcq, mmf	-	+	+	+	-	-	+	+
SLE 15	M	2	42	-	hcq	-	+	-	+	-	-	-	-
SLE 16	F	2	31	-	hcq	-	+	-	-	-	-	-	-
SLE 17	F	5	34	-	hcq	-	+	+	+	+	+	n.a.	+
SLE 18	F	2	53	-	hcq	history of breast cancer	+	+	-	-	-	-	-
SLE 19	F	4	23	-	hcq, mmf	Libman Sacks endocarditis	+	+	+	-	-	-	-
SLE 20	F	8	22	5mg	hcq, aza	-	n.a.	+	n.a.	n.a.	+	n.a.	n.a.
SLE 21	F	19	49	-	hcq, aza	diabetes	+	-	-	-	-	-	-
SLE 22	F	4	40	-	hcq, mtx	-	+	+	-	-	-	n.a.	-
SLE 23	F	4	27	2.5mg	hcq, mmf	-	+	+	+	-	+	-	-
SLE 24	F	2	42	-	hcq, mtx	-	+	-	-	-	-	-	+
SLE 25	M	6	33	40mg	hcq, mmf	-	+	+	+	-	+	indet	+
SLE 26	F	2	42	-	hcq	-	+	+	-	-	+	-	indet
SLE 27	F	12	33	10mg	hcq, mmf	-	+	+	+	+	-	-	-
SLE 28	F	4	68	20mg	chloroquine, rtx	diabetes	+	-	+	-	-	-	-
SLE 29	F	0	33	-	hcq	-	+	-	+	+	-	-	-
SLE 30	F	2	36	3mg	hcq, benlysta	APS	+	+	+	-	-	-	-
SLE 31	F	17	38	-	benlysta	hisotry of malignancy, inflammatory bowel disease	+	+	+	-	-	+	-
SLE 32	F	4	47	-	hcq, mtx	-	+	+	+	-	-	-	-
SLE 33	F	4	26	-	hcq	-	+	-	-	-	-	-	-
SLE 34	F	1	32	-	hcq	thyroid disease	+	+	+	-	-	-	-

Suppl. Table S2. MHC haplotype of the SLE patients.

SLE 1	SLE 2	SLE 3	SLE 4	SLE 5	SLE 6	SLE 7	SLE 8	SLE 9	SLE 10	SLE 11	SLE 12
HLA-A*02:01	HLA-A*23:01	HLA-A*01:01	HLA-A*23:01	HLA-A*01:01	HLA-A*02:01	HLA-A*11:01	HLA-A*26:01	HLA-A*01:01	HLA-A*11:01	HLA-A*01:01	HLA-A*03:01
HLA-A*02:01	HLA-A*32:01	HLA-A*68:01	HLA-A*24:02	HLA-A*01:01	HLA-A*68:03	HLA-A*02:01	HLA-A*02:01	HLA-A*11:303	HLA-A*02:05	HLA-A*01:01	HLA-A*02:01
HLA-B*07:02	HLA-B*07:02	HLA-B*39:01	HLA-B*15:03	HLA-B*08:01	HLA-B*35:01	HLA-B*07:02	HLA-B*15:01	HLA-B*18:01	HLA-B*18:01	HLA-B*07:02	HLA-B*27:05
HLA-B*44:02	HLA-B*07:02	HLA-B*08:01	HLA-B*45:01	HLA-B*14:02	HLA-B*35:01	HLA-B*35:01	HLA-B*38:01	HLA-B*27:05	HLA-B*18:01	HLA-B*08:01	HLA-B*14:02
HLA-C*07:631	HLA-C*07:02	HLA-C*07:01	HLA-C*06:02	HLA-C*07:970N	HLA-C*07:02	HLA-C*04:01	HLA-C*12:03	HLA-C*02:02	HLA-C*04:30	HLA-C*07:970N	HLA-C*08:02
HLA-C*05:01	HLA-C*15:05	HLA-C*12:03	HLA-C*02:10	HLA-C*08:02	HLA-C*04:01	HLA-C*07:02	HLA-C*03:03	HLA-C*12:03	HLA-C*12:03	HLA-C*07:02	HLA-C*01:02
DPA1*02:01	DPA1*02:01	DPA1*02:01	DPA1*02:01	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03
DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:01
DPB1*01:01	DPB1*01:01	DPB1*01:01	DPB1*18:01	DPB1*04:01	DPB1*677:01	DPB1*04:01	DPB1*06:01	DPB1*04:01	DPB1*104:01	DQB1*06:04	DPB1*14:01
DPB1*03:01	DPB1*04:02	DPB1*04:01	DPB1*11:01	DPB1*04:01	DPB1*04:01	DPB1*02:01	DPB1*04:02	DPB1*04:01	DPB1*02:01	DQB1*06:118	DPB1*03:01
DQA1*01:02	DQB1*06:113	DQA1*01:03	DQA1*02:01	DQB1*05:01	DRA*01:02	DQB1*05:01	DQB1*05:01	DQA1*03:01	DQB1*06:112N	DRA*01:02	DQA1*03:03
DQA1*05:01	DQB1*06:02	DQA1*05:01	DQA1*01:02	DQB1*05:01	DRA*01:02	DQB1*05:01	DQB1*06:03	DQA1*05:05	DQB1*06:02	DRA*01:02	DQA1*03:03
DQB1*06:04	DRA*01:02	DQB1*06:112N	DQB1*06:114	DRA*01:01	DRB1*08:02	DRA*01:01	DRA*01:01	DRA*01:01	DRA*01:01	DRB1*03:01	DQB1*03:01
DQB1*06:118	DRA*01:02	DQB1*06:03	DQB1*06:02	DRA*01:01	DRB1*08:02	DRA*01:01	DRA*01:01	DRA*01:01	DRA*01:02	DRB1*13:02	DQB1*02:01
DRA*01:02	DRB1*03:01	DRA*01:01	DRA*01:01	DRB1*01:03	DPB1*01:03- DPB1*677:01	DRB1*01:03	DRB1*01:02	DRB1*04:04	DRB1*15:01		DRA*01:01
DRA*01:02	DRB1*15:01	DRA*01:02	DRA*01:01	DRB1*04:01	DPA1*01:03- DPB1*04:01	DRB1*01:01	DRB1*13:01	DRB1*11:01	DRB1*11:02		DRA*01:01
DRB1*03:01	DRB5*01:01	DRB1*03:01	DRB1*15:03	DPA1*01:03- DPB1*04:01		DPA1*01:03- DPB1*04:01	DPA1*01:03- DPB1*06:01	DPA1*01:03- DPB1*04:01	DPA1*01:03- DPB1*104:01		DRB1*04:07
DRB1*13:02	DRB5*01:01	DRB1*13:01	DRB1*07:01			DPA1*01:03- DPB1*02:01			DPA1*01:03- DPB1*02:01		DRB1*03:01
DRB3*03:01	DPA1*02:01- DPB1*01:01	DRB3*01:01	DRB5*01:01								DRB3*02:02
DRB3*01:01	DPA1*02:01- DPB1*04:02	DRB3*02:02	DRB5*01:01								DRB3*02:02
DPA1*02:01- DPB1*01:01	DPA1*01:03- DPB1*01:01	DPA1*02:01- DPB1*01:01	DPA1*02:01- DPB1*18:01	DPA1*02:01- DPB1*18:01	DPA1*02:01- DPB1*11:01						DPA1*01:03- DPB1*14:01
DPA1*02:01- DPB1*03:01	DPA1*01:03- DPB1*04:02	DPA1*02:01- DPB1*04:01	DPA1*02:01- DPB1*11:01	DPA1*02:01- DPB1*11:01	DQA1*02:01- DQB1*06:114						DPA1*01:03- DPB1*03:01
DPA1*01:03- DPB1*01:01		DPA1*01:03- DPB1*01:01	DPA1*01:03- DPB1*18:01	DPA1*01:03- DPB1*18:01	DQA1*02:01- DQB1*06:114						DPA1*02:01- DPB1*14:01
DPA1*01:03- DPB1*03:01		DPA1*01:03- DPB1*04:01	DPA1*01:03- DPB1*11:01	DPA1*01:03- DPB1*11:01	DQA1*02:01- DQB1*06:114						DPA1*02:01- DPB1*03:01
DQA1*01:02- DQB1*06:04		DQA1*01:03- DQB1*06:112N	DQA1*01:03- DQB1*06:114	DQA1*01:03- DQB1*06:114	DQA1*02:01- DQB1*06:02						DQA1*03:03- DQB1*03:01
DQA1*01:02- DQB1*06:118		DQA1*01:03- DQB1*06:03	DQA1*01:03- DQB1*06:02	DQA1*01:02- DQB1*06:114	DQA1*01:02- DQB1*06:02						DQA1*03:03- DQB1*02:01
DQA1*05:01- DQB1*06:04		DQA1*05:01- DQB1*06:112N	DQA1*05:01- DQB1*06:114	DQA1*01:02- DQB1*06:114	DQA1*01:02- DQB1*06:02						
DQA1*05:01- DQB1*06:118		DQA1*05:01- DQB1*06:03	DQA1*05:01- DQB1*06:02	DQA1*01:02- DQB1*06:02	DQA1*01:02- DQB1*06:02						

SLE 13	SLE 14	SLE 15	SLE 16	SLE 17	SLE 18	SLE 19	SLE 20	SLE 21	SLE 22	SLE 23	SLE 24
HLA-A*01:01	HLA-A*31:01	HLA-A*24:02	HLA-A*02:01	HLA-A*02:01	HLA-A*33:01	HLA-A*34:01	HLA-A*24:02	HLA-A*01:01	HLA-A*68:03	HLA-A*33:03	HLA-A*02:686
HLA-A*03:01	HLA-A*11:01	HLA-A*31:01	HLA-A*02:01	HLA-A*11:01	HLA-A*02:01	HLA-A*03:01	HLA-A*02:06	HLA-A*68:02	HLA-A*02:06	HLA-A*03:01	HLA-A*01:01
HLA-B*38:01	HLA-B*35:01	HLA-B*51:01	HLA-B*15:01	HLA-B*51:01	HLA-B*14:02	HLA-B*15:21	HLA-B*35:14	HLA-B*49:01	HLA-B*35:17	HLA-B*58:01	HLA-B*08:143
HLA-B*15:01	HLA-B*27:05	HLA-B*13:02	HLA-B*18:01	HLA-B*13:01	HLA-B*52:01	HLA-B*07:02	HLA-B*40:02	HLA-B*08:01	HLA-B*39:05	HLA-B*38:01	HLA-B*51:01
HLA-C*03:03	HLA-C*02:02	HLA-C*14:02	HLA-C*07:01	HLA-C*03:04	HLA-C*08:02	HLA-C*07:02	HLA-C*04:01	HLA-C*07:01	HLA-C*07:02	HLA-C*03:02	HLA-C*07:01
HLA-C*12:03	HLA-C*04:01	HLA-C*06:02	HLA-C*03:04	HLA-C*14:02	HLA-C*03:03	HLA-C*04:03	HLA-C*15:02	HLA-C*07:01	HLA-C*04:01	HLA-C*12:03	HLA-C*04:01
DPA1*02:01	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:02	DPA1*02:02	DPA1*02:02	DPA1*01:03	DPA1*01:04	DPA1*01:03	DPA1*02:02	DPA1*02:01
DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:01	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:01	DPA1*01:03	DPA1*01:03	DPA1*02:01
DPB1*04:01	DPB1*04:02	DPB1*02:01	DPB1*04:01	DPB1*14:01	DPB1*05:01	DPB1*01:01	DPB1*04:01	DPB1*15:01	DPB1*04:02	DPB1*02:01	DPB1*13:01
DPB1*14:01	DPB1*04:02	DPB1*04:02	DPB1*04:01	DPB1*05:01	DPB1*04:02	DPB1*16:01	DPB1*04:02	DPB1*01:01	DPB1*04:02	DPB1*05:01	DPB1*01:01
DQA1*01:10	DQA1*03:02	DQA1*04:01	DQA1*05:05	DQA1*06:01	DQA1*03:01	DQA1*01:02	DQB1*03:01	DQA1*05:01	DRA*01:01	DQA1*02:01	DRA*01:01
DQA1*01:01	DQA1*01:01	DQA1*02:01	DQA1*03:01	DQA1*03:02	DQA1*01:01	DQA1*01:02	DQB1*03:02	DQA1*01:02	DRA*01:02	DQA1*01:03	DRA*01:02
DQB1*05:01	DQB1*05:01	DRA*01:01	DQB1*03:02	DQB1*03:01	DQB1*05:01	DQB1*05:02	DRA*01:01	DQB1*06:04	DRB1*08:02	DQB1*06:01	DRB1*03:01
DQB1*06:03	DQB1*03:03	DRA*01:02	DQB1*03:01	DQB1*03:03	DQB1*03:02	DQB1*06:02	DRA*01:02	DQB1*06:118	DRB1*04:07	DQB1*02:02	DRB1*04:02
DRA*01:01	DRA*01:01	DRB1*08:02	DRA*01:01	DRA*01:01	DRA*01:01	DRA*01:01	DRB1*16:02	DRA*01:01	DPA1*01:03- DPB1*04:02	DRA*01:01	DPA1*02:01- DPB1*13:01
DRA*01:02	DRA*01:01	DRB1*07:01	DRA*01:01	DRA*01:02	DRA*01:01	DRA*01:02	DRB1*14:06	DRA*01:02		DRA*01:03	DPA1*02:01- DPB1*01:01
DRB1*01:03	DRB1*09:01	DPA1*01:03- DPB1*02:01	DRB1*04:01	DRB1*12:02	DRB1*01:02	DRB1*15:02	DRB5*02:02	DRB1*03:01		DRB1*07:01	
DRB1*13:01	DRB1*01:01	DPA1*01:03- DPB1*04:02	DRB1*11:04	DRB1*09:01	DRB1*04:11	DRB1*15:01	DRB5*02:02	DRB1*13:02		DRB1*08:03	
DRB3*01:01	DPA1*01:03- DPB1*04:02		DRB3*02:02	DRB3*03:01	DPA1*02:02- DPB1*05:01	DRB5*01:01	DPA1*01:03- DPB1*04:01	DRB3*03:01		DPA1*02:02- DPB1*02:01	
DRB3*01:01	DQA1*03:02- DQB1*05:01		DRB3*02:02	DRB3*03:01	DPA1*02:02- DPB1*04:02	DRB5*01:01	DPA1*01:03- DPB1*04:02	DRB3*01:01		DPA1*02:02- DPB1*05:01	
DPA1*02:01- DPB1*04:01	DQA1*03:02- DQB1*03:03		DPA1*01:03- DQB1*04:01	DPA1*02:02- DPB1*14:01	DPA1*01:03- DPB1*05:01	DPA1*02:02- DPB1*01:01	DPA1*02:02- DPB1*01:01	DPA1*01:04- DPB1*15:01		DPA1*01:03- DPB1*02:01	
DPA1*02:01- DPB1*14:01	DQA1*01:01- DQB1*05:01		DQA1*05:05- DQB1*03:02	DPA1*02:01- DPB1*05:01	DPA1*01:03- DPB1*04:02	DPA1*02:02- DPB1*16:01	DPA1*01:03- DPB1*01:01	DPA1*01:04- DPB1*01:01		DPA1*01:03- DPB1*05:01	
DPA1*01:03- DPB1*04:01	DQA1*01:01- DQB1*03:03		DQA1*05:05- DQB1*03:01	DPA1*02:01- DPB1*14:01	DQA1*03:01- DQB1*05:01	DQA1*01:03- DQB1*05:01	DPA1*01:03- DPB1*01:01	DPA1*02:01- DPB1*15:01		DQA1*02:01- DQB1*06:01	
DPA1*01:03- DPB1*14:01			DQA1*03:01- DQB1*03:02	DPA1*02:01- DPB1*05:01	DQA1*03:01- DQB1*05:01	DQA1*03:02- DQB1*05:01	DPA1*01:03- DPB1*16:01	DPA1*02:01- DPB1*01:01		DQA1*02:01- DQB1*06:01	
DQA1*01:10- DQB1*05:01			DQA1*03:01- DQB1*03:01	DQA1*06:01- DQB1*03:01	DQA1*03:01- DQB1*05:01	DQA1*01:02- DQB1*05:02	DQA1*01:02- DQB1*05:02	DQA1*05:01- DQB1*06:04		DQA1*01:03- DQB1*02:02	
DQA1*01:10- DQB1*06:03				DQA1*06:01- DQB1*03:03	DQA1*01:01- DQB1*03:02	DQA1*01:02- DQB1*06:02					
DQA1*01:01- DQB1*05:01				DQA1*03:02- DQB1*03:01							
DQA1*01:01- DQB1*06:03				DQA1*03:02- DQB1*03:01							

SLE 25	SLE 26	SLE 27	SLE 28	SLE 29	SLE 30	SLE 31	SLE 32	SLE 33	SLE 34
HLA-A*02:06	HLA-A*01:01	HLA-A*01:01	HLA-A*25:01	HLA-A*02:01	HLA-A*32:01	HLA-A*30:01	HLA-A*02:11	HLA-A*11:303	HLA-A*24:02
HLA-A*11:01	HLA-A*01:01	HLA-A*02:01	HLA-A*02:01	HLA-A*02:01	HLA-A*01:01	HLA-A*31:01	HLA-A*68:02	HLA-A*02:11	HLA-A*02:01
HLA-B*38:02	HLA-B*37:01	HLA-B*08:01	HLA-B*18:01	HLA-B*18:01	HLA-B*40:01	HLA-B*13:02	HLA-B*35:49	HLA-B*40:10	HLA-B*39:06
HLA-B*40:01	HLA-B*08:01	HLA-B*08:01	HLA-B*18:01	HLA-B*07:02	HLA-B*38:01	HLA-B*52:01	HLA-B*15:09	HLA-B*40:06	HLA-B*48:01
HLA-C*07:02	HLA-C*07:1000	HLA-C*07:01	HLA-C*07:01	HLA-C*07:02	HLA-C*07:01	HLA-C*06:02	HLA-C*04:01	HLA-C*15:02	HLA-C*08:03
HLA-C*03:04	HLA-C*06:02	HLA-C*07:01	HLA-C*12:03	HLA-C*07:01	HLA-C*03:04	HLA-C*03:03	HLA-C*07:04	HLA-C*04:03	HLA-C*07:02
DQB1*05:01	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:02	DPA1*01:03	DPA1*02:01	DPA1*01:03	DPA1*02:01	DRA*01:01
DQB1*05:01	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*01:03	DPA1*02:02	DRA*01:01
DRA*01:01	DRA*01:01	DPB1*04:01	DPB1*02:01	DPB1*04:01	DPB1*04:01	DPB1*14:01	DPB1*04:01	DPB1*01:01	DRB1*04:07
DRA*01:02	DRA*01:02	DPB1*04:01	DPB1*23:01	DPB1*05:01	DPB1*02:01	DPB1*04:01	DPB1*04:02	DPB1*13:01	DRB1*09:01
DRB1*04:03	DRB1*03:01	DQB1*06:02	DQB1*06:02	DQB1*06:02	DQA1*01:03	DQA1*03:03	DQB1*03:92	DQB1*05:02	
DRB1*15:02	DRB1*04:01	DQB1*06:02	DQB1*06:02	DQB1*03:01	DQA1*03:01	DQA1*01:02	DQB1*03:01	DQB1*06:03	
		DRA*01:02	DRA*01:02	DRA*01:02	DQB1*06:03	DQB1*06:04	DRA*01:01	DRA*01:01	
		DRA*01:02	DRA*01:02	DRA*01:02	DQB1*06:112N	DQB1*06:118	DRA*01:02	DRA*01:02	
		DRB1*03:01	DRB1*15:01	DRB1*15:01	DRA*01:01	DRA*01:01	DRB1*16:02	DRB1*15:02	
		DRB1*15:01	DRB1*08:01	DRB1*12:01	DRA*01:02	DRA*01:02	DRB1*11:01	DRB1*13:01	
		DRB5*01:01	DRB5*01:01	DRB3*02:02	DRB1*04:01	DRB1*04:11	DRB3*02:02	DRB5*01:01	
		DRB5*01:01	DRB5*01:01	DRB3*02:02	DRB1*13:01	DRB1*13:02	DRB3*02:02	DRB5*01:01	
		DPA1*01:03- DPB1*04:01	DPA1*01:03- DPB1*02:01	DRB5*01:01	DRB3*01:01	DRB3*03:01	DRB5*02:02	DPA1*02:01- DPB1*01:01	
			DPA1*01:03- DPB1*23:01	DRB5*01:01	DRB3*01:01	DRB3*03:01	DRB5*02:02	DPA1*02:01- DPB1*13:01	
				DPA1*02:02- DPB1*04:01	DPA1*01:03- DPB1*04:01	DPA1*02:01- DPB1*14:01	DPA1*01:03- DPB1*04:01	DPA1*02:02- DPB1*01:01	
				DPA1*02:02- DPB1*05:01	DPA1*01:03- DPB1*02:01	DPA1*02:01- DPB1*04:01	DPA1*01:03- DPB1*04:02	DPA1*02:02- DPB1*13:01	
				DPA1*01:03- DPB1*04:01	DQA1*01:03- DQB1*06:03	DPA1*01:03- DPB1*14:01			
				DPA1*01:03- DPB1*05:01	DQA1*01:03- DQB1*06:112N	DPA1*01:03- DPB1*04:01			
					DQA1*03:01- DQB1*06:03	DQA1*03:03- DQB1*06:04			
					DQA1*03:01- DQB1*06:112N	DQA1*03:03- DQB1*06:118			
						DQA1*01:02- DQB1*06:04			
						DQA1*01:02- DQB1*06:118			

Suppl. Table S3. Overview of SLE patients (n=35) by disease activity index (SLEDAI), ISG expression, ISG status, cryptic splicing of ISGs, and ISG-derived peptides (red) found by immunopeptidomics.

Patient	SLEDAI	avg_ISG	ISG status	cryptic ISG	neoAg on MHC-I by mass spec (ISG)
1	2	14781	ISG_high	yes	MX1, ANXA3, FCGRT PHF, XAF1, OAS1, OAS3
2	2	4206	ISG_low	yes	
3	5	17262	ISG_high	yes	
4	2	14035	ISG_high	yes	
5	17	8869	ISG_high	no	
6	12	13405	ISG_high	yes	
7	2	5852	ISG_high	no	
8	8	8880	ISG_high	no	
9	4	16439	ISG_high	yes	
10	12	17871	ISG_high	yes	
11	0	17871	ISG_high	yes	
12	2	26772	ISG_high	yes	
13	19	2388	ISG_low	no	
14	9	17098	ISG_high	yes	
15	4	2987	ISG_low	no	
16	36	6958	ISG_high	yes	
17	4	21636	ISG_high	yes	
18	2	12305	ISG_high	yes	
19	6	12981	ISG_high	no	
20	2	15516	ISG_high	yes	
21	2	14207	ISG_high	yes	
22	4	10714	ISG_high	yes	
23	4	2632	ISG_low	no	
24	2	10939	ISG_high	yes	USP18, RSAD2, MYO15B, ADAMTSL4
25	5	24823	ISG_high	yes	
26	16	4318	ISG_low	yes	
27	0	5679	ISG_high	no	
28	14	4105	ISG_low	no	
29	12	4317	ISG_low	yes	OGG1, IFI44L, TRAPPC10
30	4	15119	ISG_high	yes	
31	4	30574	ISG_high	yes	
32	4	6936	ISG_high	no	OAS1, ABCG1
33	4	12726	ISG_high	yes	
34	1	3744	ISG_low	no	
35	4	3686	ISG_low	no	

HC 95%ile =4828

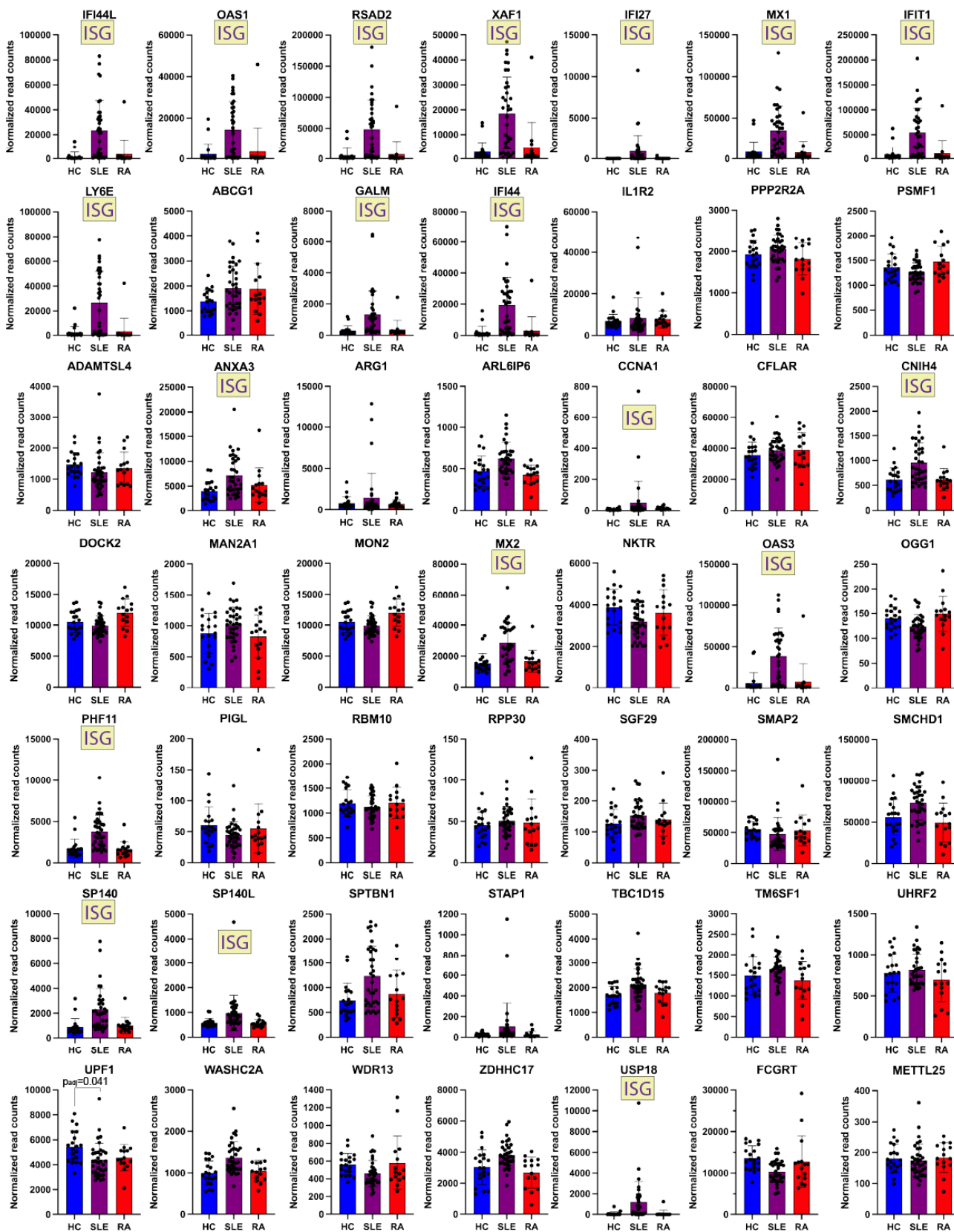
active

Suppl. Table S4. All p-values for panels h and i in Fig. 5.

Tcell_activation_stats_CD4_CD8

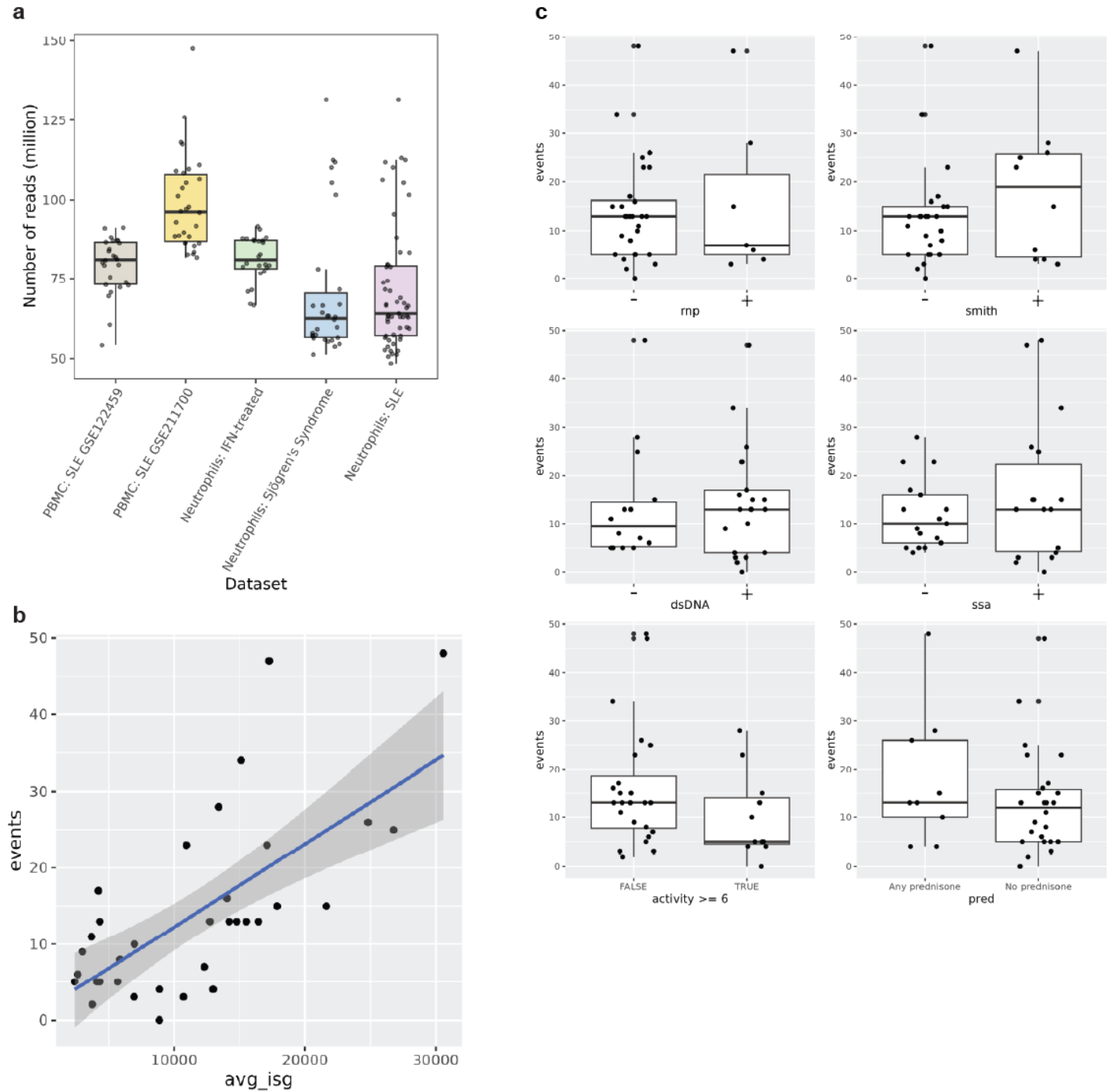
Stim	Activated_CD4	Total_CD4	Activated_CD8	Total_CD8	Chi_CD4_Fpadj	Chi_CD8_padj
IF44-1	886	17059	477	10541	1.23019563409832E-49	3.13703358289728E-33
IFI44L-1	236	13949	254	10396	0.00888340909127954	0.000511882246753642
IFI44L-2	466	11169	328	9812	7.73351080455585E-22	2.02470860282823E-13
MX1-1	277	12745	232	9274	0.931323111652439	0.000283566250395503
MX1-2	275	11410	221	8730	0.212678580116946	0.000216226366359737
MX1-3_1	207	9604	197	8996	0.980192791641372	0.0332045883905966
MX1-3_2	568	21430	246	9367	0.00378623905393877	2.84117618837999E-05
MX1-4	308	11528	273	9280	0.00888340909127954	3.02684056461585E-08
MX1-5	342	14158	243	9386	0.183447774242871	5.73066982785197E-05
OAS1-1	360	16281	218	9761	0.794476450639903	0.0165594282409951
OAS1-2	170	14658	169	9049	5.73419938238872E-11	0.569323605242885
RSAD2-1	305	16078	178	9417	0.184336870297428	0.499887173395512
RSAD2-2	332	14920	244	8448	0.788572730709479	1.88371100096388E-07
TBC1D15	293	11747	262	8432	0.0913237205582633	9.76625836814958E-10
IFIT1	509	19281	285	10556	0.00547079444494672	3.14071554771974E-06
RSAD2-3	362	13692	232	9318	0.00888340909127954	0.000329414746646229
SERPING1	339	9823	224	7760	3.88893008185145E-10	3.02448392189273E-07
IFI44L-3	357	13919	307	8719	0.0279499914585584	5.04420448734645E-15
FCGRT_1	127	13582	131	8810	6.03552132177342E-16	0.185872067136131
FCGRT_2	208	12518	204	8833	0.0078671847922347	0.00692817815777953
FCGRT_3	295	14260	209	8666	0.794476450639903	0.0015478110865489
FCGRT_4	155	13819	137	9096	2.24308179926397E-11	0.214291213813226
ABCG1_1	334	15777	276	9616	0.931323111652439	1.28623465403876E-07
ABCG1_2	274	13691	302	8859	0.524539629117833	1.11689490680431E-13
ABCG1_3	86	11803	128	8212	2.12453627693638E-20	0.35367481504016
ABCG1_4	147	13807	134	8407	1.21243702708608E-12	0.435790656638094
OAS3_1	155	12032	169	8542	2.23169658239002E-07	0.301842545134272
OAS3_2	364	15582	204	8617	0.35082322863239	0.00312198224737477
OAS3_3	306	15396	259	9070	0.461019860102735	2.25685789038616E-07
OAS3_4	222	18433	261	10446	2.24308179926397E-11	0.000216226366359737
OAS3_5	321	15209	152	9595	0.931323111652439	0.393689117542041

Supplemental Fig. S1



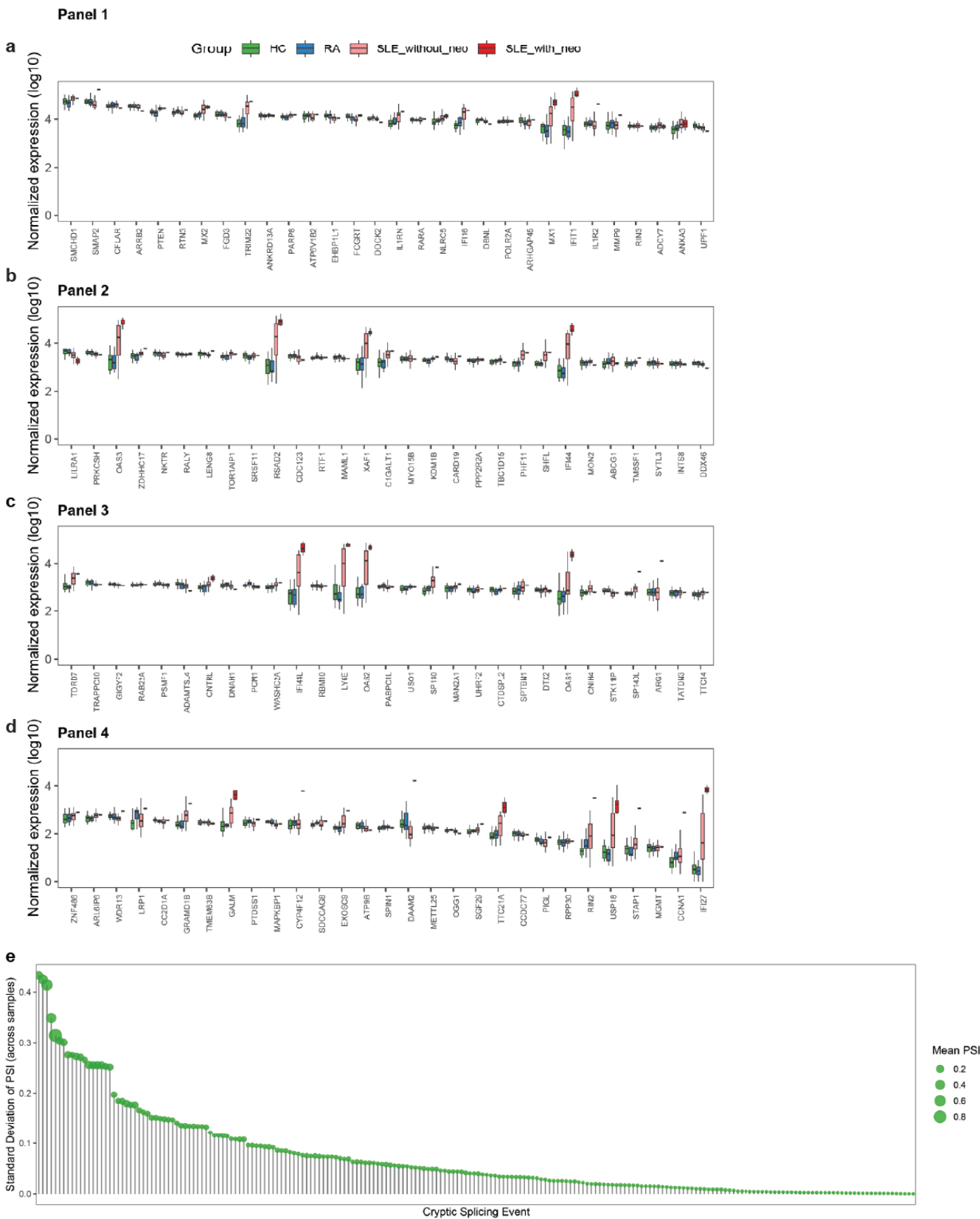
Suppl. Fig. S1 | Expression of the top genes (as in Fig. 1h, plus 3) whose transcripts are subjected to cryptic splicing in SLE neutrophils. Read counts from the same RNAseq of neutrophils used for the analysis of cryptic splicing in 20 healthy controls (HC; blue bars), 35 SLE patients (purple bars), and 15 RA patients (red bars). ISG, interferon-inducible gene.

Supplemental Fig. S2



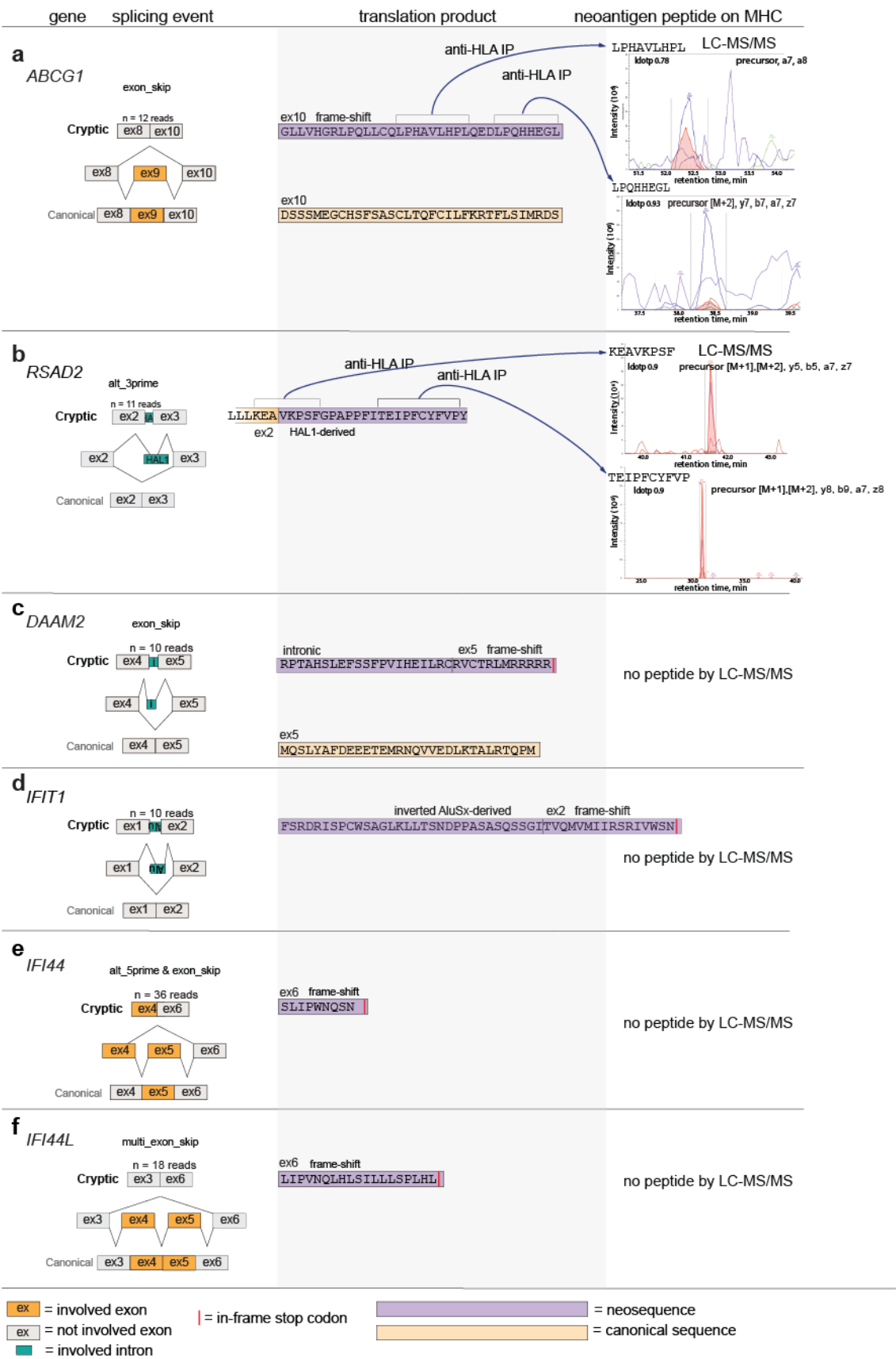
Suppl. Fig. S2 | RNA sequencing depth of comparator data sets and testing for clinical correlations. **a**, sequencing depth by patient sample of the publicly available PBMC data sets, as well as our IFN-treated healthy neutrophils, Sjögren's disease neutrophils, and the SLE neutrophil data set that forms the basis of the present paper. **b**, correlation of the number of cryptic splicing events and average expression of 111 ISGs. **c**, Lack of correlation of the number of cryptic splicing events and RNP, Smith, dsDNA, SSA autoantibodies, active (SLEDAI>6), or prednisone use.

Supplemental Fig. S3



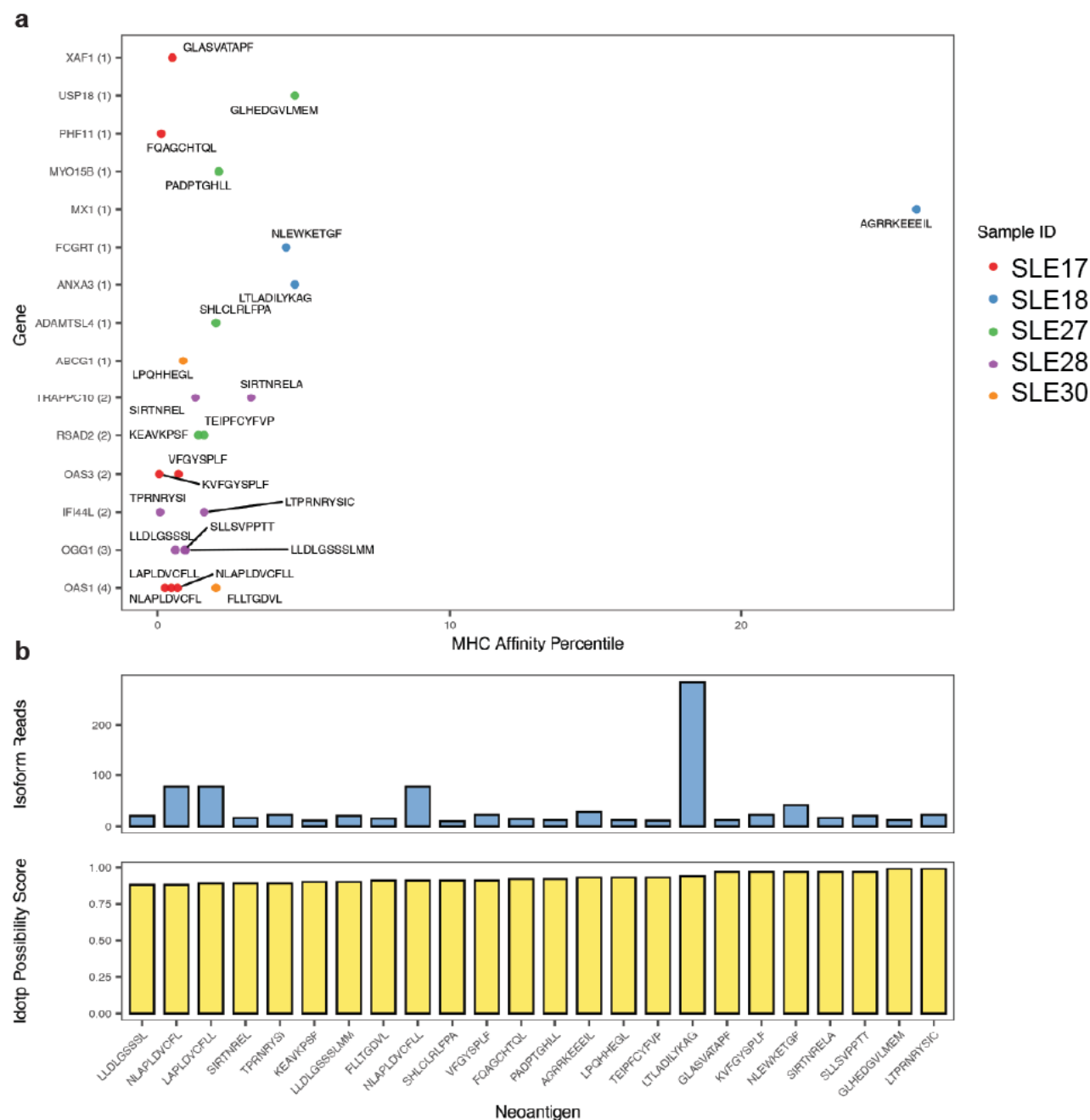
Supl. Fig. S3 | Expression levels in relation to percent spliced-in (PSI) of genes subjected cryptic splicing events in SLE neutrophils. a-e, Normalized read counts of the indicated genes in neutrophils from healthy donors, RA patients, SLE patients who did not have cryptic splicing of the indicated gene, and SLE who did have cryptic splicing of the indicated gene. **a,** Standard deviation of PSI for the cryptic variant of the same genes.

Supplemental Fig. S4



Suppl. Fig. S4 | Six additional examples of cryptic splicing events, some of which produced neoantigen peptides detected on HLA. Representation same as in Fig. 3.

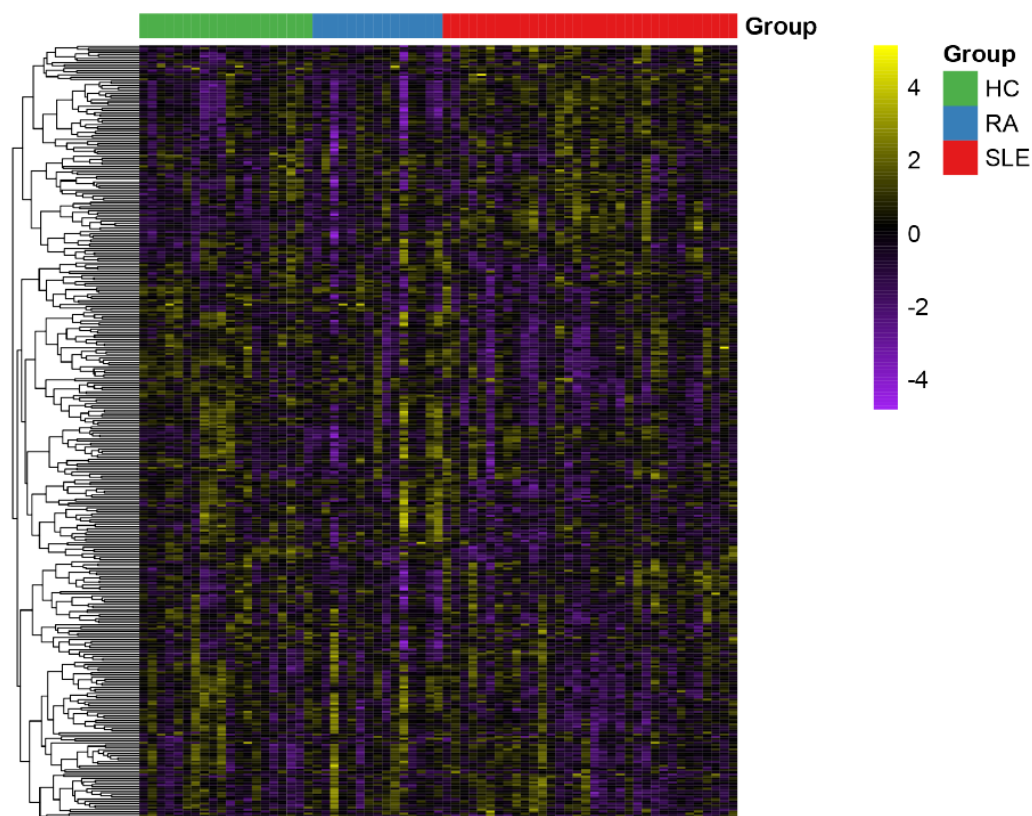
Supplemental Fig. S5



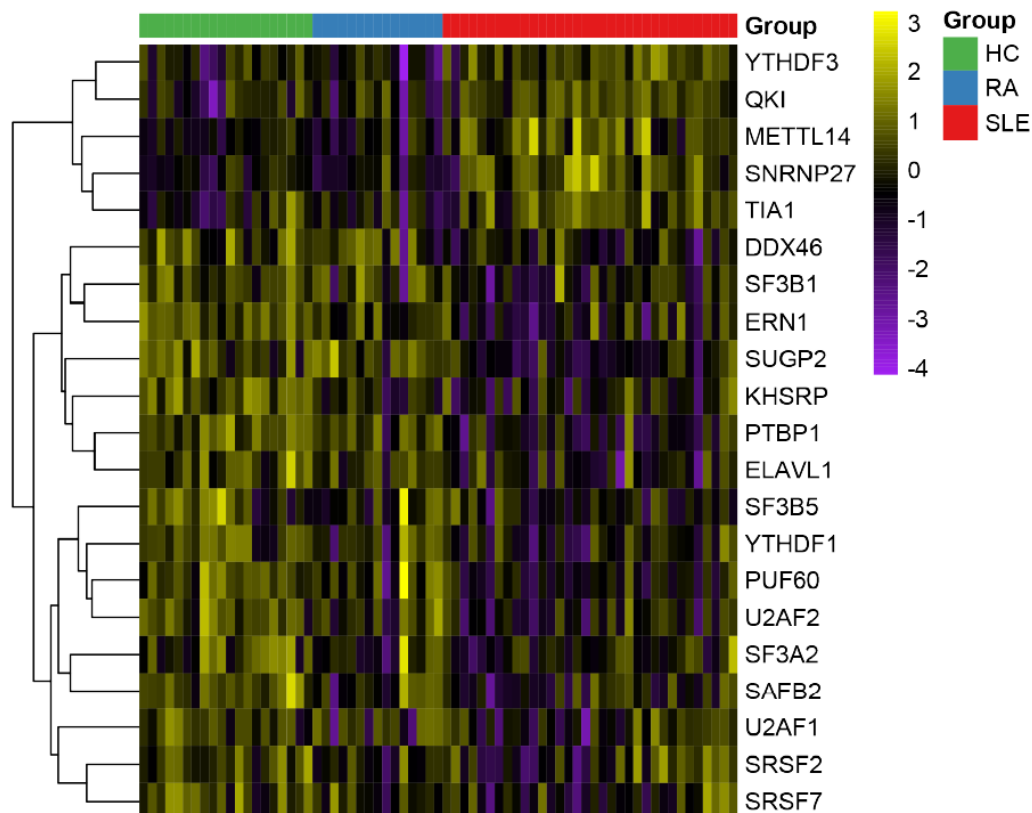
Suppl. Fig. S5 | Predicted affinities of the neoantigen peptides identified by immunopeptidomics for the class I MHC alleles unique to each patient. Top panel, the affinities by which the detected peptides are predicted to bind the patients MHC allele. Note that only the AGRRKEEEIL peptide derived from a cryptic splice event in MX1 is predicted to have a lower affinity of binding. Middle panel, read counts for the cryptic splice isoforms that generated these peptides. Bottom panel, the sequences and idop values for each peptide.

Supplemental Fig. S6

a

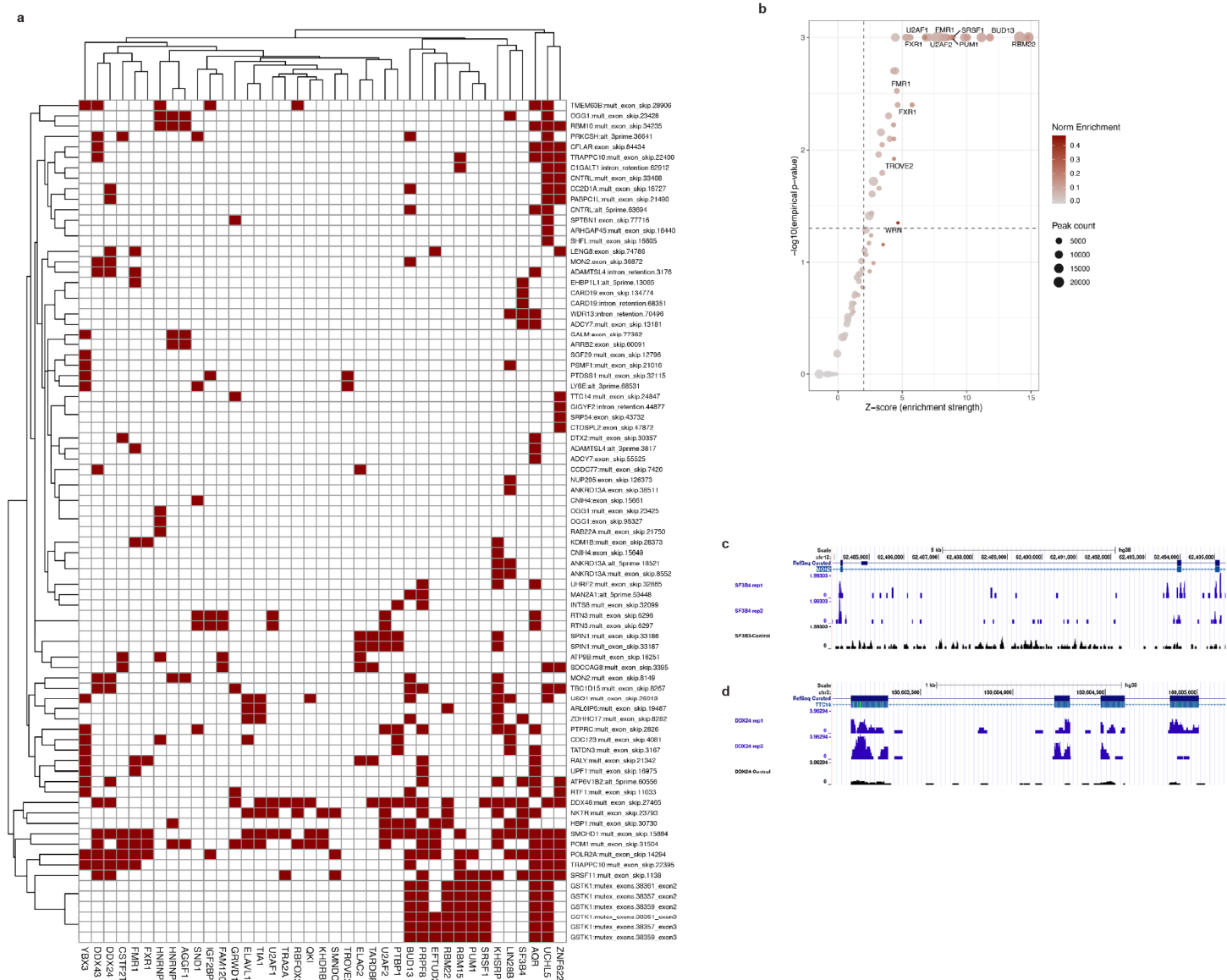


b



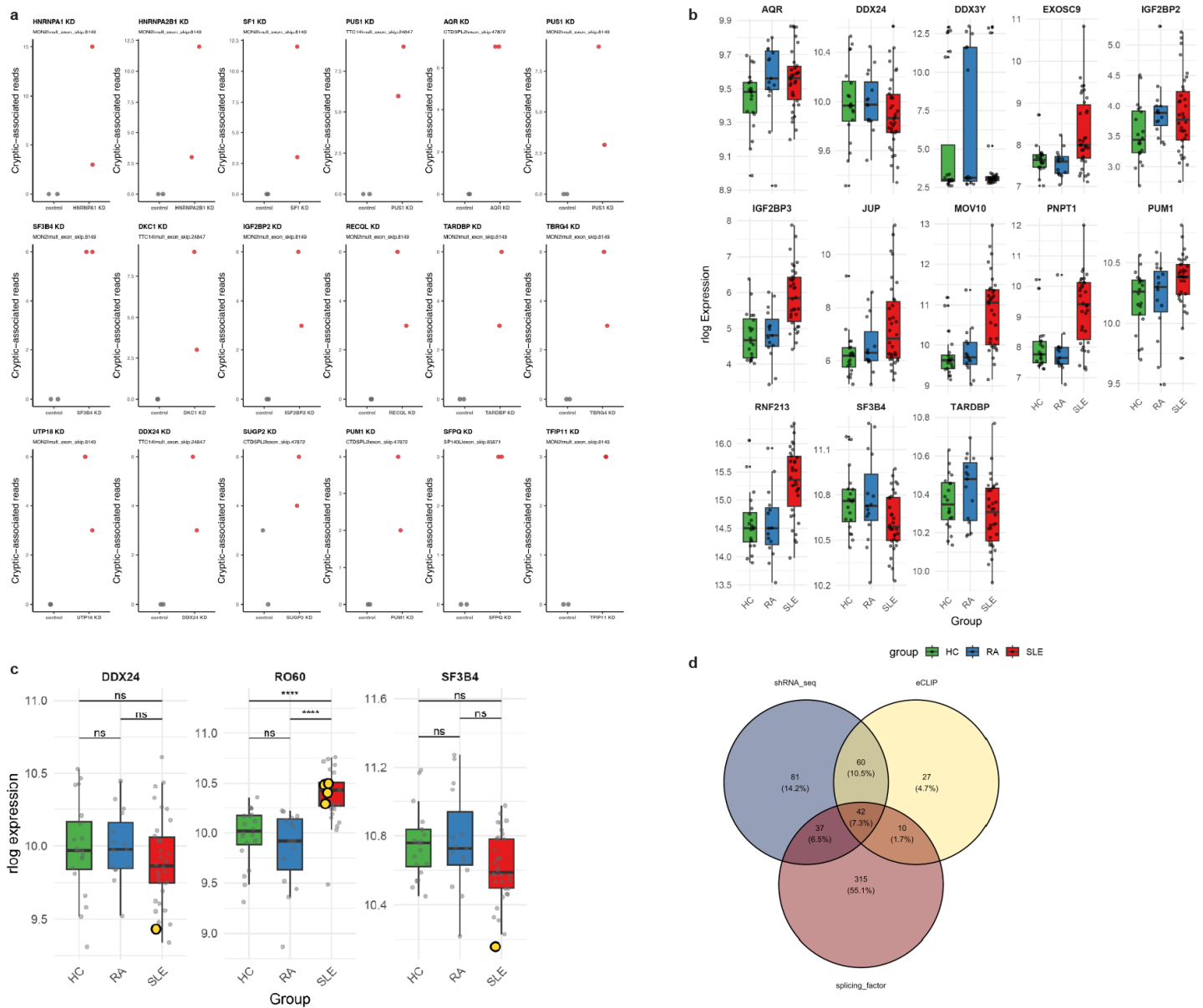
Suppl. Fig. S6 | Heat maps of expression of spliceosome components and mRNA splicing factors. a, all spliceosome and RBPs involved in splicing. b, Focus on the statistically significantly altered ones.

Supplemental Fig. S7



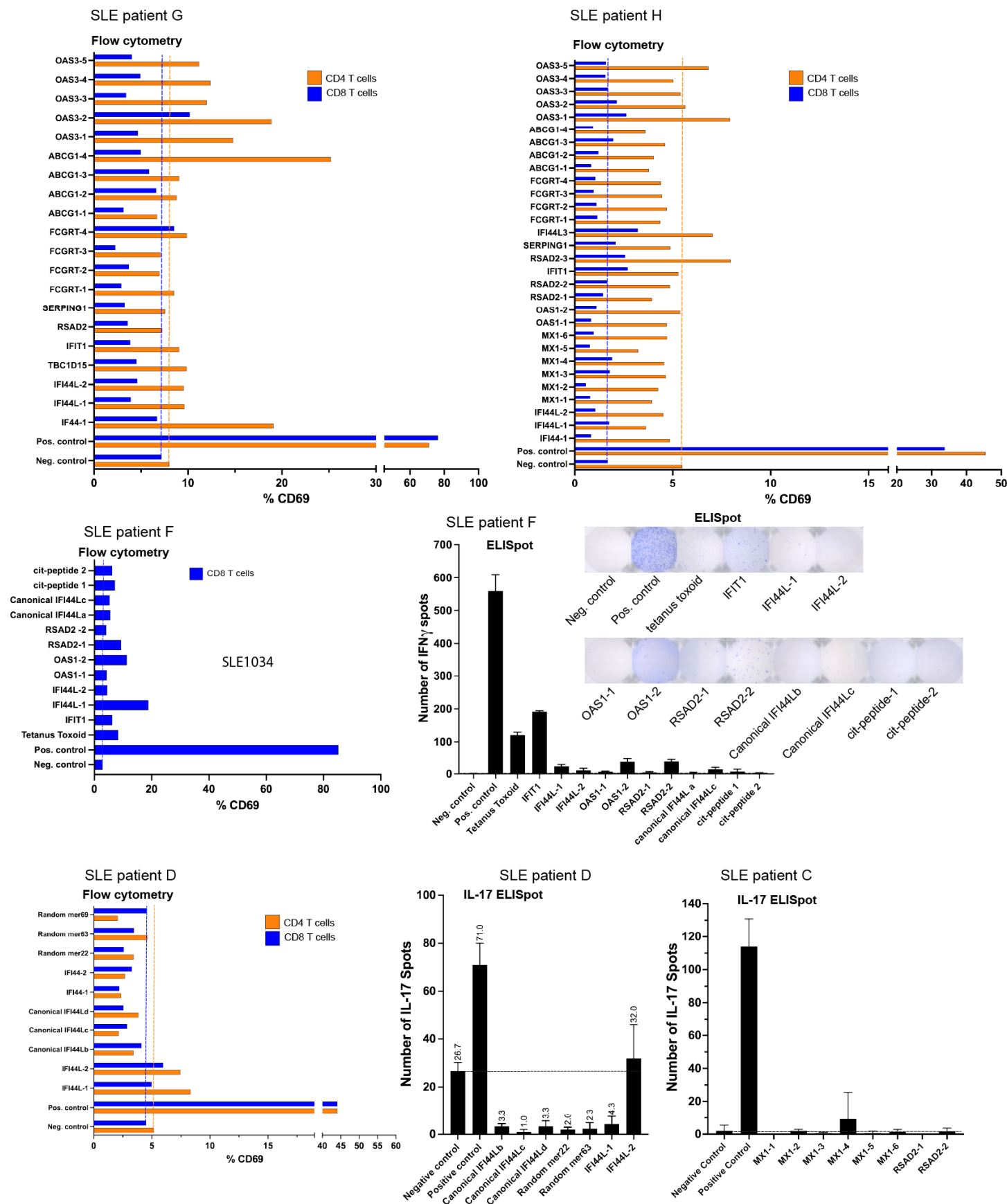
Suppl. Fig. S7 | RBP-binding pattern and cryptic splicing events based on Encode. a, RBPs binding at sites of cryptic splicing events. Each red square indicates that at least one significant eCLIP peak overlaps the ± 300 bp regulatory window around a given cryptic splice site. **b**, Enrichment analysis by Z-score and empirical p-value derived from the shuffle-based null model (see Supplemental Methods). The dotted lines indicate the statistical thresholds (empirical $p < 0.05$ and $Z\text{-score} > 2$). In total, 46 RBPs pass these thresholds, and the top 10 are labeled. **c** and **d**, Representative genome browser examples for DDX24 and SF3B4 to illustrate locus-level binding near specific transcripts with cryptic splicing.

Supplemental Fig. S8



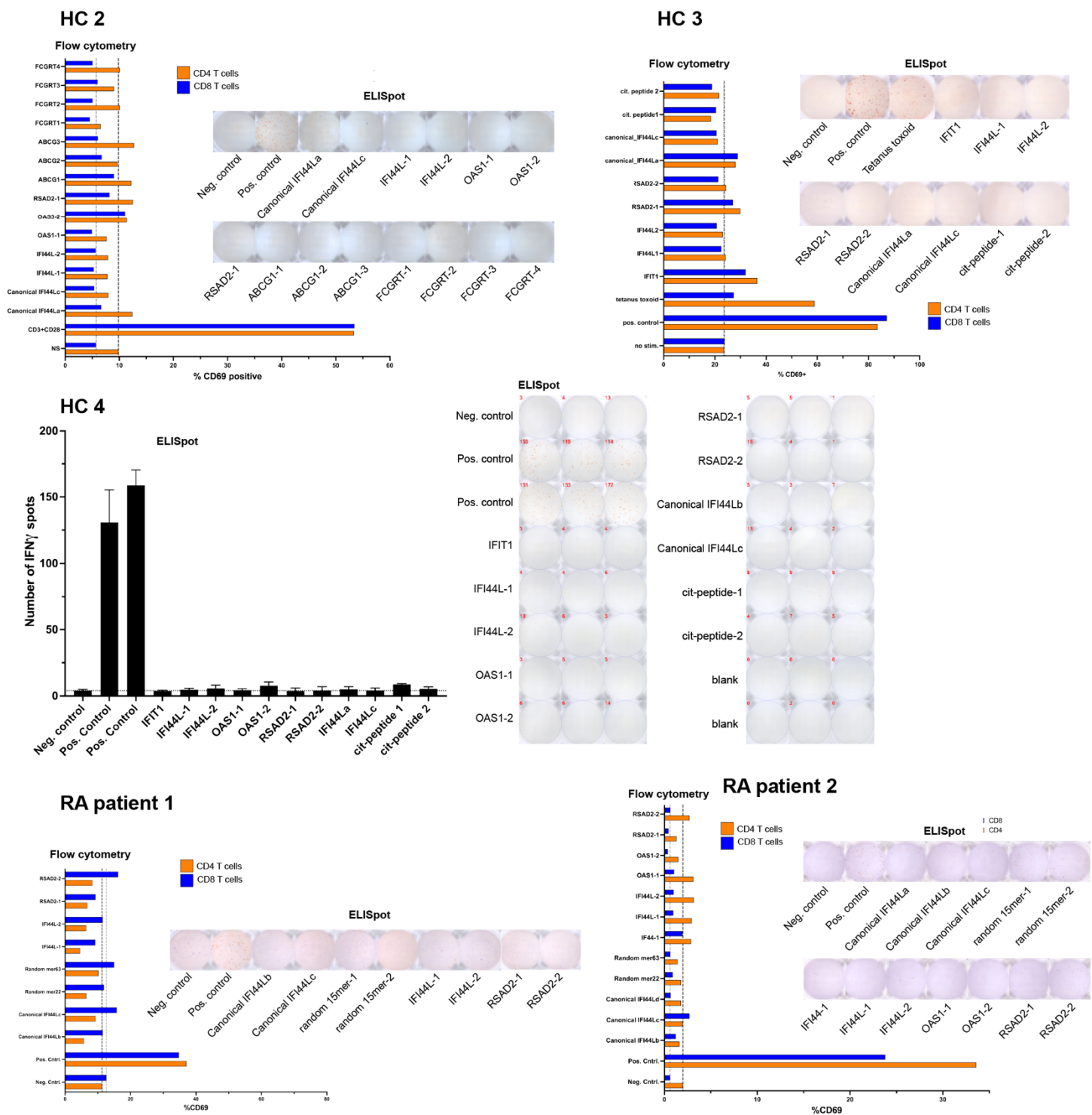
Suppl. Fig. S8 |shRNAi of RBPs in K562 in Encode that result in cryptic splicing events observed in SLE neutrophils. a, Reads of cryptic splicing events detected in K562 cells after knockdown of the indicated RBPs. **b,** expression levels in our neutrophil dataset of RBPs that overlap between the eCLIP and shRNA analyses and are differentially expressed in SLE neutrophils (7 are differentially expressed; 6 are in the overlap). **c,** Same as panel b but with the individual patient with a cryptic splicing event implicating DDX24 or SF3B4 indicated with a yellow-filled circle. **d,** The expression of TROVE2 (Ro60) in the 4 SLE patients with cryptic splicing events implicating TROVE2; 3 of these 4 were positive for SSA (anti-Ro) antibodies. **e,** the overlap between shRNA RBPs, eCLIP RBPs, and a curated list of known splice factors ([https://www.cell.com/cell-reports/fulltext/S2211-1247\(18\)30152-9](https://www.cell.com/cell-reports/fulltext/S2211-1247(18)30152-9)).

Supplemental Fig. S9



Suppl. Fig. S9 | 14-day assay with additional SLE patients F, G, and H and additional data for patients C and D (see Fig. 5). Tetanus toxoid was included with patient F as a comparator positive stimulus.

Supplemental Fig. S10



Suppl. Fig. S10 | 14-day assay with 3 additional healthy donors HC 2, HC 3, and HC 4, as well as two RA patients. Note that there is no response to SLE neoantigens or canonical IFI44L peptides. However, as a positive control, HC 3 responded to tetanus toxoid.

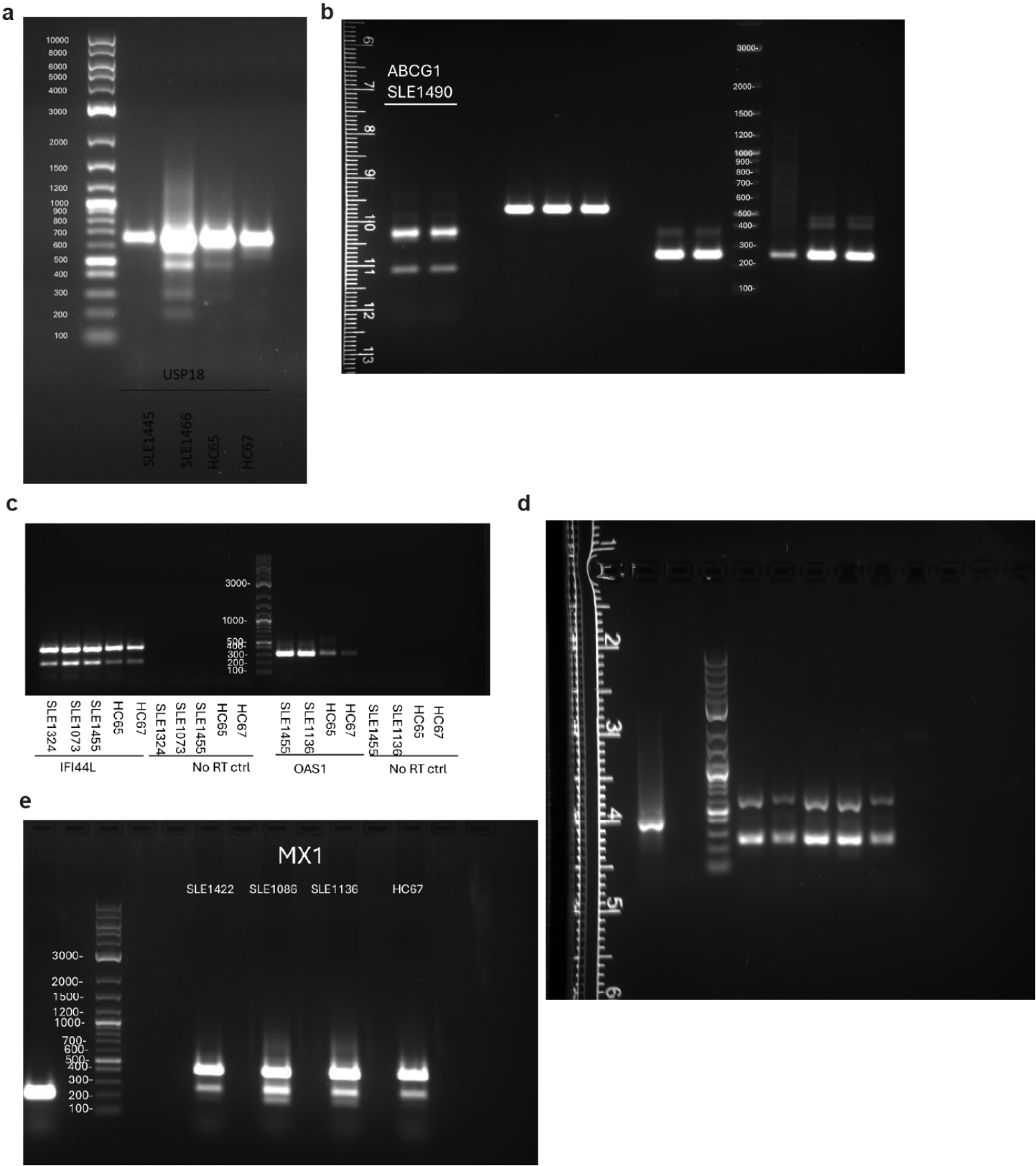
a



Suppl. Fig. S11 | Neoantigen response and TCRB sequencing of T cells from SLE patient I. **a**, PBMC were cultured for 14 days without added peptide, neoantigen IFI44L-1, or IFI44L-2. Flowcytometry was performed after overnight restimulation with the same peptides. Note the increase in CD69 and CD134 (OX40) expression by CD4 T cells stimulated by IFI44L-2 (red circles). **b**, Clonoseq™ results of TCRB sequencing (Adaptive Biotechnologies, Seattle, WA) shown as the 10 top clonotypic (unique) TCRB sequences from T cells stimulated as in panel a. **c**, TCR V gene utilization and CDR1-3 amino acid sequences from the top 10 TCRs in panel b.

Supplemental Fig. S12

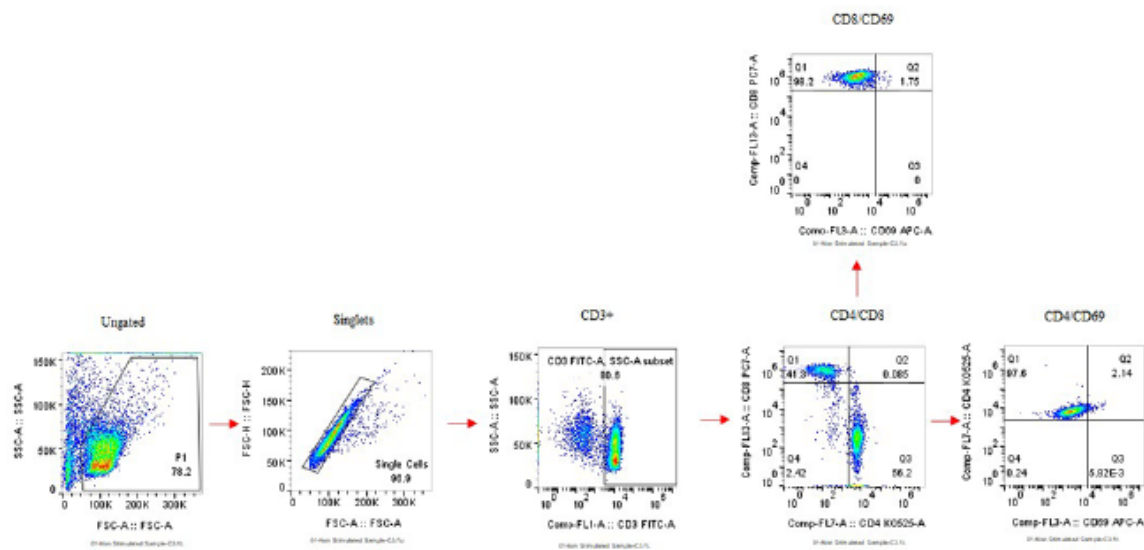
RAW IMAGES OF AGAROSE GELS IN Fig. 2



Suppl. Fig. S12 | RAW images of the gels in Fig. 2.

Supplemental Fig. S13

No Stim Sample



Supl. Fig. S13 | Gating strategy for flow cytometry in Fig. 5 and Supplemental Figs. S9, S10, and S11.

SUPPLEMENTAL METHODS

Analysis of cryptic splicing in SLE neutrophil using ENCODE (National Human Genome Research Institute, <https://www.encodeproject.org>)

The purpose of these analyses was to find connections between specific RNA-binding proteins (RBPs) and the cryptic splicing events present in neutrophils our cohort of SLE patients. The Encode data set use K562, a transformed hematopoietic cell line representing a precursor of granulocytic and erythrocyte lineages (erythroleukemia). We used enhanced crosslinking immunoprecipitation (eCLIP) and short hairpin RNA interference (shRNAi) data sets.

a. eCLIP-based enrichment analysis of RBPs on cryptic splicing events

ENCODE eCLIP peak data generated in K562 cells were used to evaluate the physical association between RBPs and cryptic splicing events. For each RBP, biological replicates were merged to obtain a single reproducible peak set. Peaks were filtered using stringent criteria, requiring both high statistical significance and binding enrichment ($-\log_{10} p\text{-value} \geq 3$ and $\log_2 \text{fold-enrichment} \geq 3$), and only peaks with valid genomic coordinates were retained.

For each alternative splicing event, event-specific binding regions were defined to capture the genomic window where RBPs are most likely to influence splice-site choice. These regions were centered on the relevant splice junctions or exon bodies depending on event type (e.g., donor or acceptor sites for alternative splice sites, exon boundaries for exon skipping, intron boundaries for intron retention), using a uniform ± 300 bp window.

For each RBP, the observed number of target cryptic event regions overlapping at least one filtered eCLIP peak was calculated using *bedtools intersect*, counting each target region only once. To assess whether the observed overlap exceeded what is expected by random chance, a shuffle-based null model was constructed. Cryptic event regions were randomly shuffled across the genome 1,000 times using *bedtools shuffle*, preserving chromosome assignment and preventing overlapping intervals. For each shuffle iteration, the number of overlaps between shuffled target regions and the RBP's filtered peaks was computed, generating a null distribution of overlap counts.

From this null distribution, the mean and standard deviation of expected overlaps were estimated. An empirical p -value was calculated as the proportion of shuffled overlap counts greater than or equal to the observed overlap count, with a pseudocount added to avoid zero values. A z-score was computed to quantify the deviation of the observed overlap from the null expectation. To account for differences in overall binding abundance across RBPs, the total number of filtered peaks per RBP was recorded, and additional normalization metrics were derived, including peak density and a normalized enrichment score obtained by scaling the z-score by the square root of the peak count.

Empirical p -values were adjusted for multiple hypothesis testing using the Benjamini–Hochberg procedure. RBPs were prioritized based on a combination of empirical significance, enrichment strength, and normalized enrichment. For enriched RBPs, event-level binding was further examined by intersecting filtered peaks with individual cryptic event regions. When multiple peaks overlapped the same event, peak-level statistics were summarized using the maximum $\log_2$ fold-enrichment and maximum $-\log_{10} p$ -value. These summaries were used for downstream visualization, event–RBP matrix construction, and network-based analyses.

b. shRNA-seq analysis of cryptic splicing regulation

The ENCODE shRNA-seq data in K562 were used to assess the regulatory effects of RNA-binding proteins (RBPs) on cryptic splicing. Only paired-end, strand-specific polyadenylated mRNA libraries were included. Reads were aligned using STAR, and alternative splicing events were quantified using SplAdder. Then we looked for overlap in these splicing events with the cryptic splicing observed in SLE neutrophils, based on genomic coordinates.

To ensure appropriate controls, each shRNA knockdown (KD) sample was paired with its matched non-targeting control samples using the ENCODE metadata field “Controlled by”. Control matching was performed at the sample level, and controls were not pooled across experiments. Instead, only explicitly matched control samples were used for each KD replicate.

For each cryptic splicing event and RBP, knockdown effects were evaluated using a replicate-aware, read-based framework. Let KD_i denote the cryptic-associated read metric for the i -th KD biological replicate, and let C_i denote the set of matched control samples for that replicate. A replicate-level effect size was defined as

$$\Delta_i = KD_i - \text{mean}(C_i).$$

Each biological replicate contributed one independent estimate of knockdown-induced cryptic splicing change. For each event–RBP pair, replicate-level effects were summarized by the mean effect size and assessed for directional consistency across replicates. Given the limited number of biological replicates per RBP, formal hypothesis testing was not used as a primary criterion. Instead, candidate regulatory effects were defined based on consistent directionality across replicates and a minimum effect size threshold. Event-level results were subsequently aggregated at the RBP level to summarize the number of cryptic splicing events affected by each knockdown.