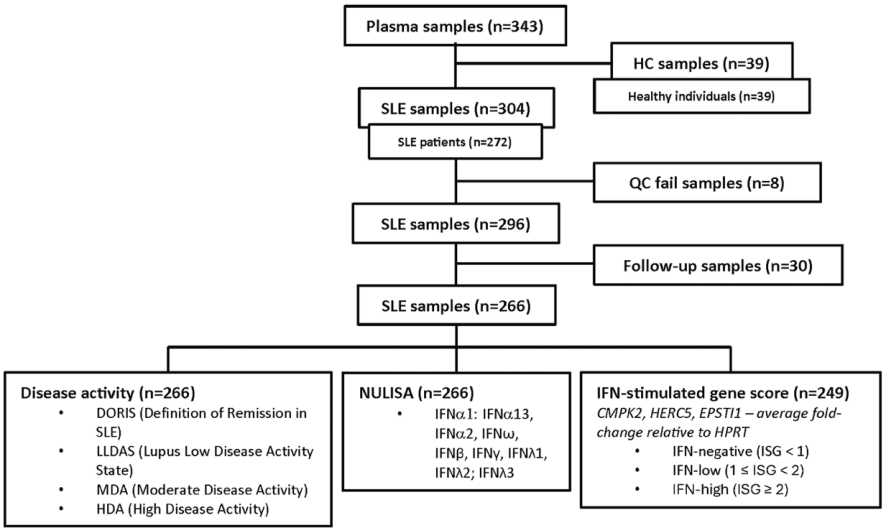
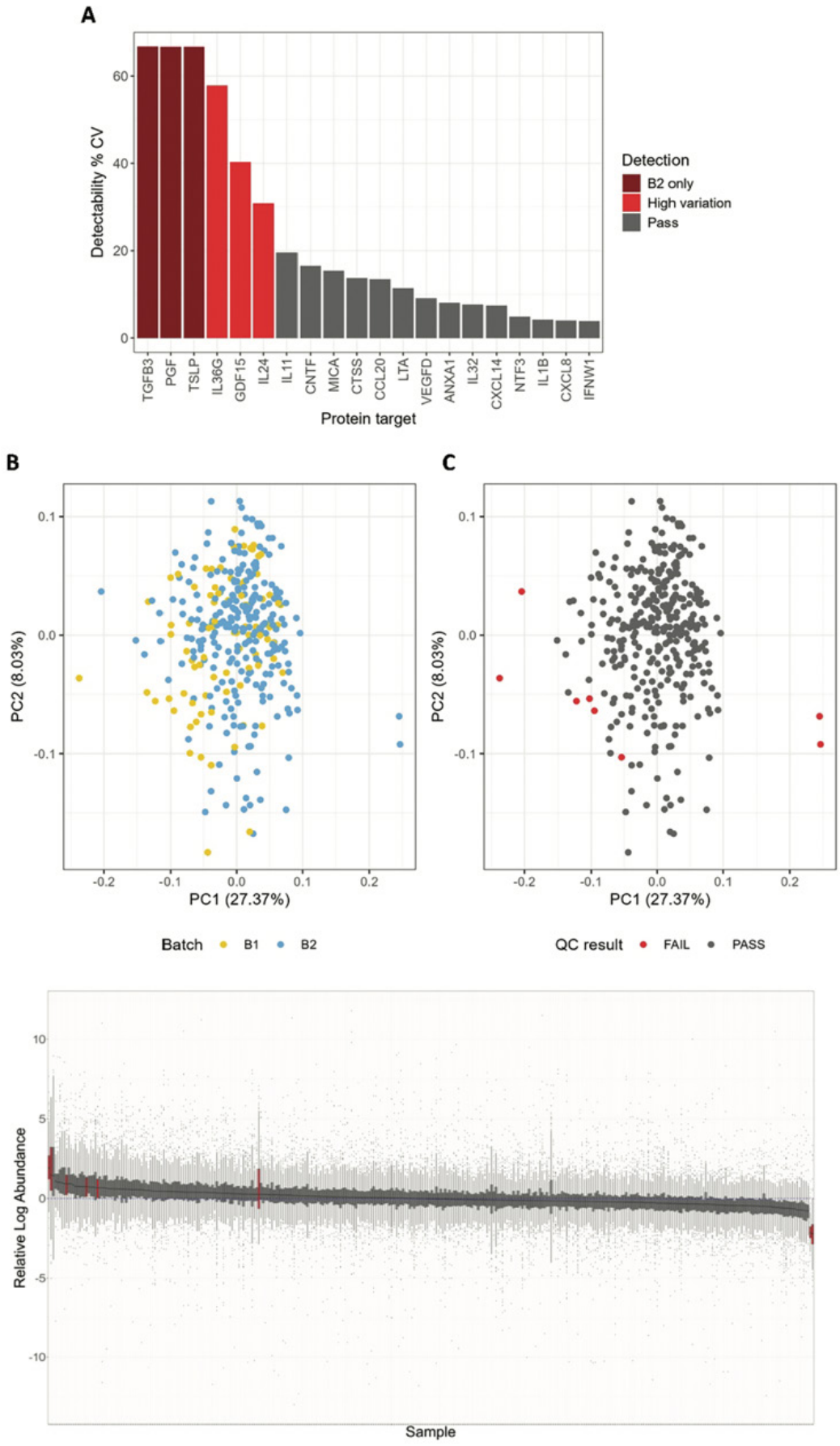


Supplementary Fig. S1. Study cohort n=343 plasma samples were sent for protein measurement, including n=39 healthy controls and n=304 SLE samples from n=272 patients. n=8 samples failed quality control analysis. The remaining n=296 SLE samples included n=30 repeat samples. The 30 repeat samples were reserved for longitudinal analysis. Matched RNA for n=249 plasma samples was measured by rtPCR for IFN-stimulated gene score quantification.

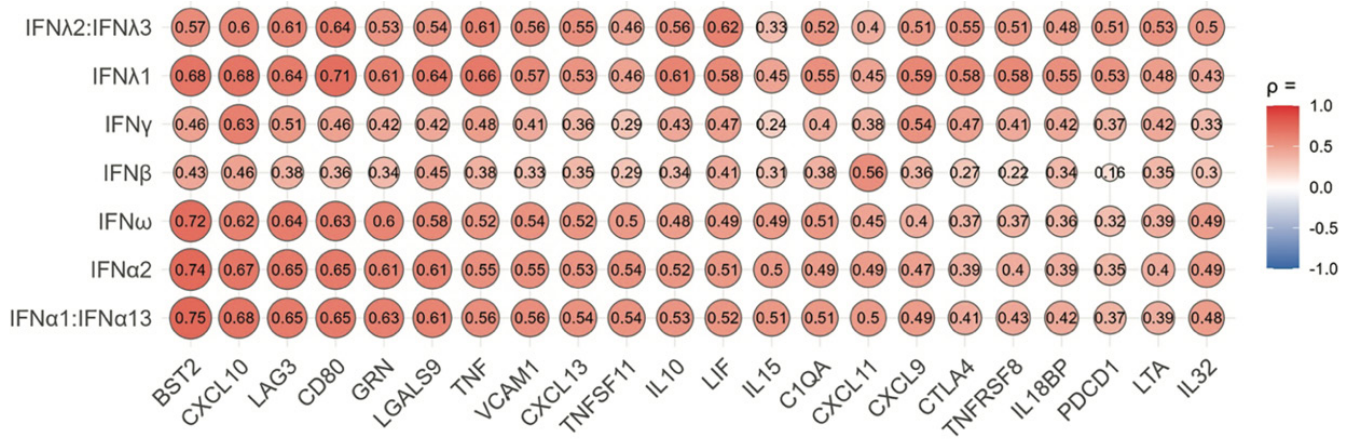
Supplementary Table S1. Active SLEDAI-2K manifestations in MDA and HDA patients.

SLEDAI component, n (%)	MDA	HDA
Arthritis	15 (17)	8 (73)
Myositis	0 (0)	2 (18)
Proteinuria	47 (53)	6 (55)
Rash	15 (17)	7 (64)
Alopecia	5 (6)	3 (27)
Mucosal ulcers	11 (13)	3 (27)

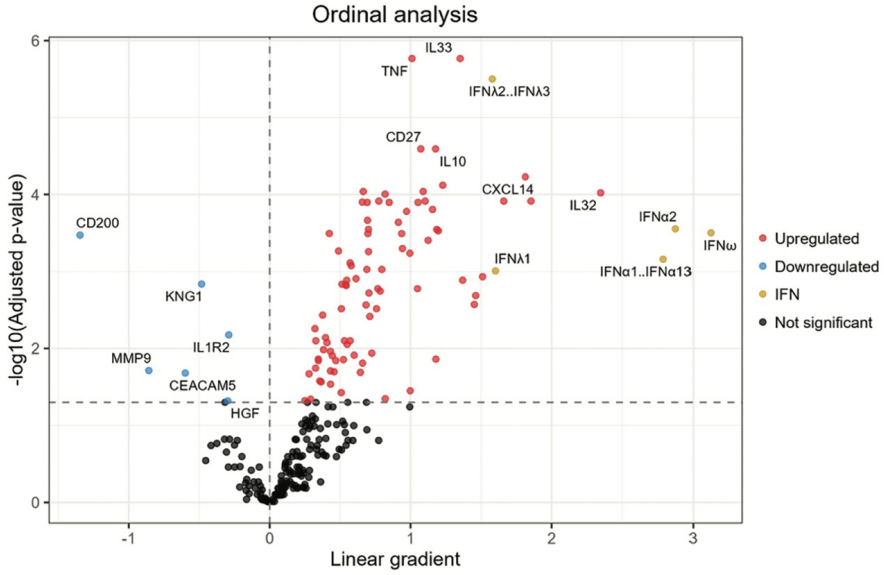
MDA: mild disease activity; HDA: high disease activity.



Supplementary Fig. S2.
Inter-plate variation of protein target detectability and Principal Component Analysis (PCA) of total sample cohort.
A: The top 20 protein targets with highest percentage coefficient of variation (CV) of detectability between four plates (B1; 1 plate. B2; 3 plates). Three proteins were assayed in B2 only, and three proteins had greater than 20% CV so were excluded from further analysis.
B: Principal Component Analysis (PCA) was performed on n=343 plasma samples to assess batch effect; and
C: to identify samples which failed QC (n=8).
Relative Log Expression (RLE) of plasma samples.
D: RLE analysis of n=343 plasma samples based on NPQ values. Boxplots represent median ± interquartile range.
Blue dashed line represents the NPQ global median across all samples.
Boxes highlighted in red indicate samples which failed QC and were removed from analysis (n=8)

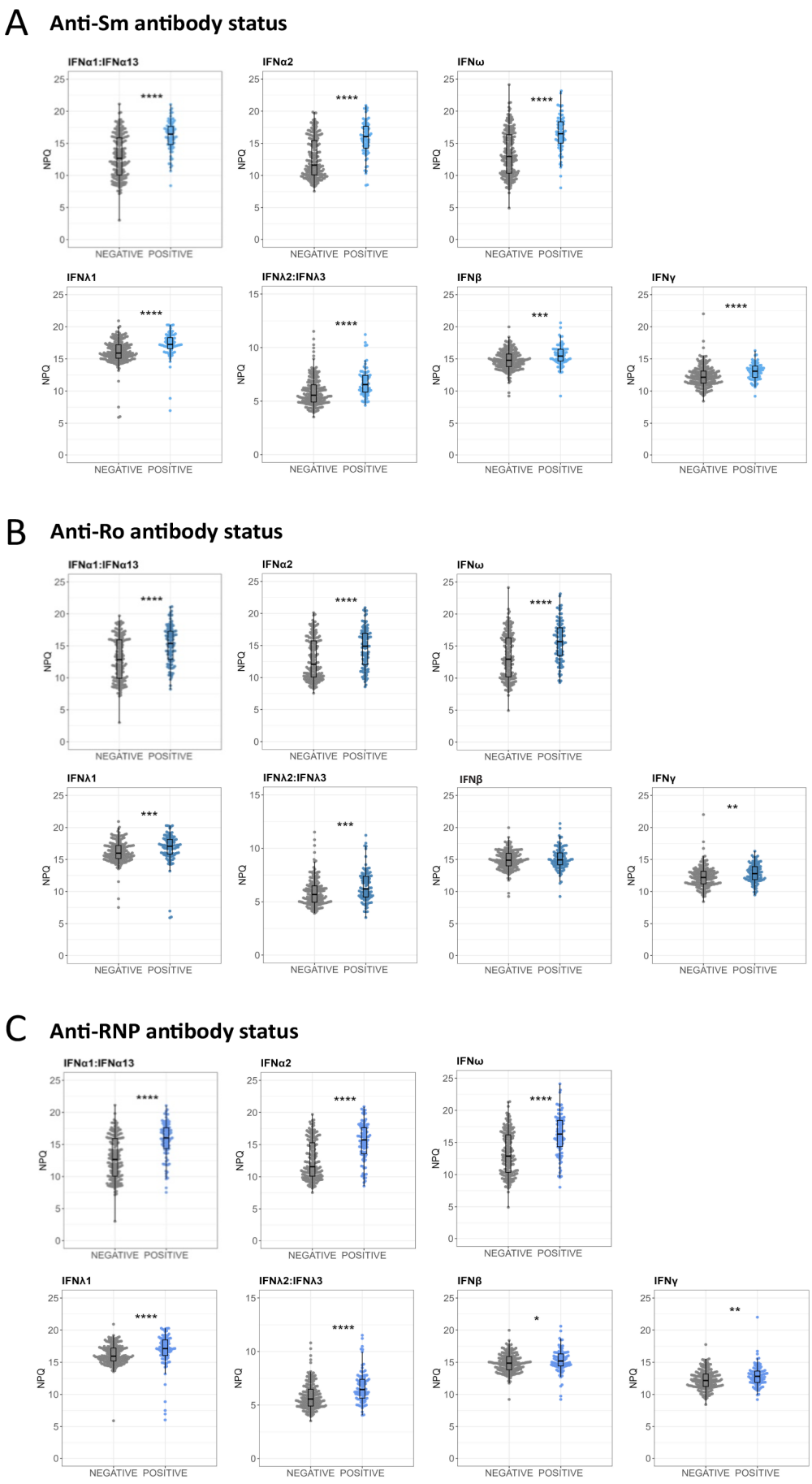


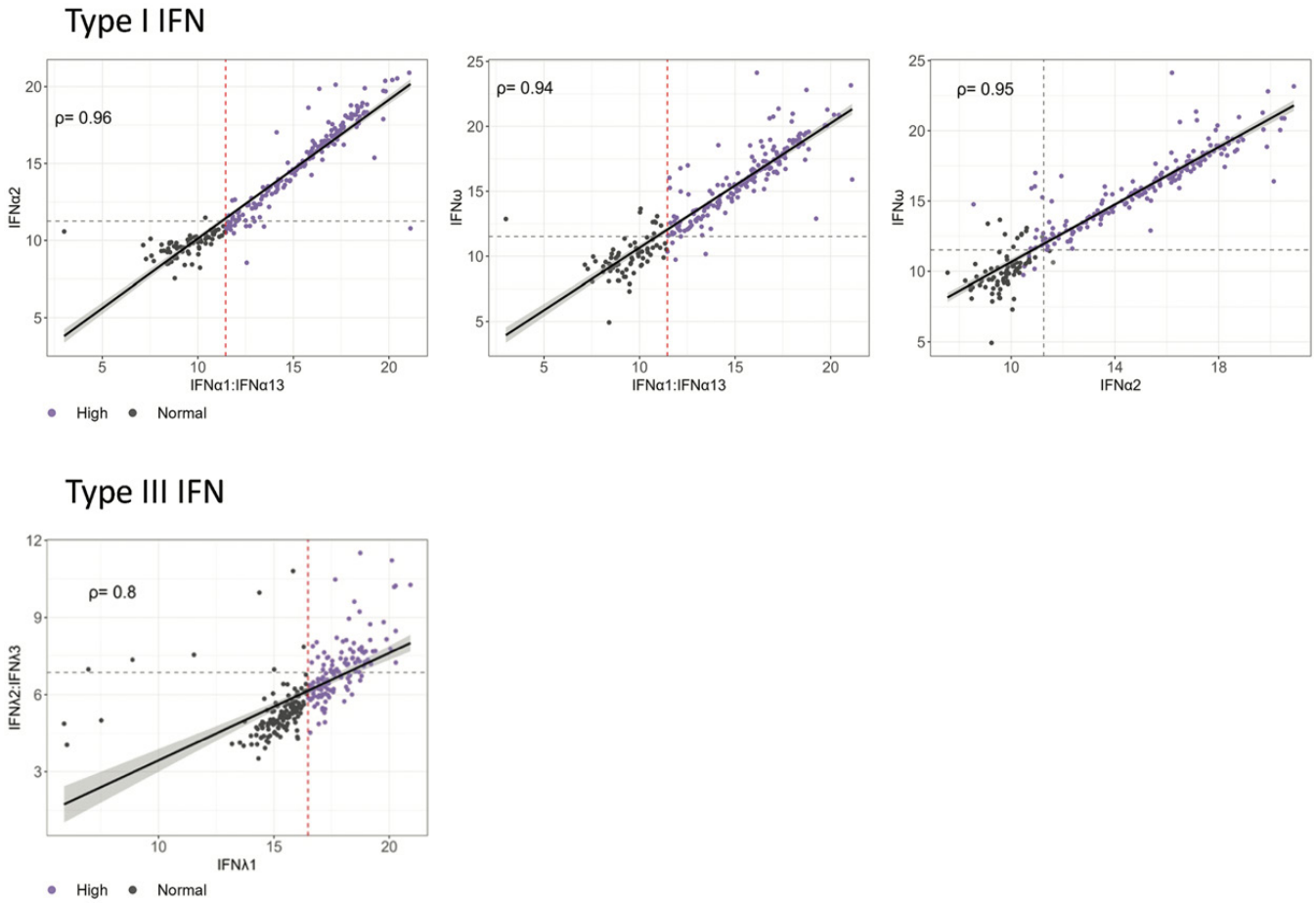
Supplementary Fig. S3. Correlations of circulating IFN proteins with other proteins in NULISA inflammatory panel. 22 proteins with greater than 0.5 correlation with at least one IFN protein shown. Circles contain Spearman correlation coefficients; all were significant $p<0.001$.



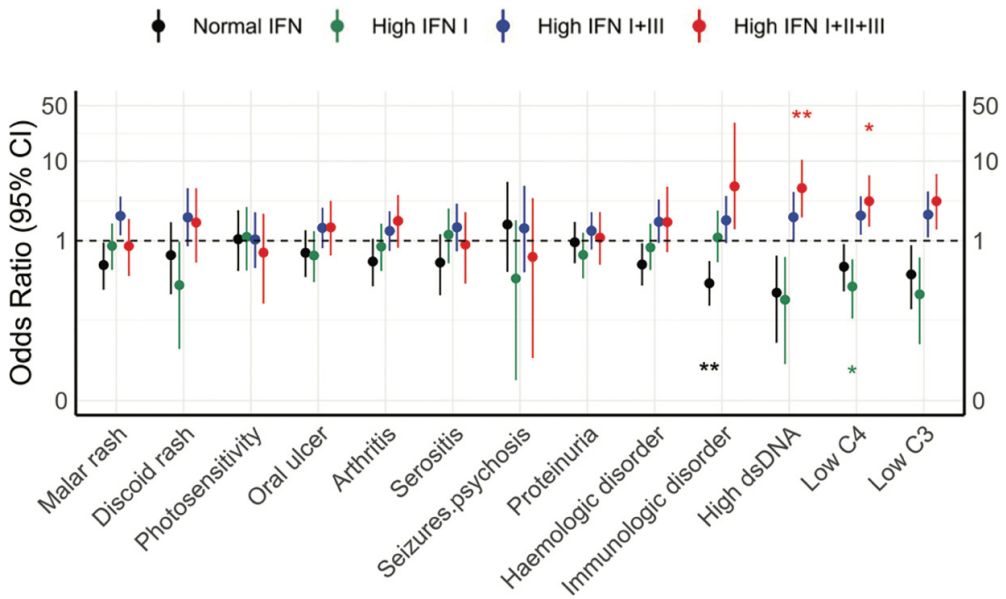
Supplementary Fig. S4. Type I and Type III but not Type II IFN protein levels are associated with increasing disease activity. Linear ordinal model analysing association of protein abundance with disease activity. Disease activity groups ordered as: DORIS (n=129); LLDAS (n=38); MDA (n=88); HDA (n=11). -log10 (Adjusted *p*-value) = $-\log_{10}$ Benjamini-Hochberg adjusted *p*-value. Yellow highlights IFN proteins with significant (P_{adj} <0.05) positive association with disease activity. Red and blue indicate proteins that with significant (P_{adj} <0.05) positive and negative association with disease activity, respectively. Linear gradient represents the estimate coefficient of the ordinal regression model, *i.e.* the change in log-odds for being in a particular category or below, given a one-unit change in protein abundance.

Supplementary Fig. S5. IFN protein levels in patients with extractable nuclear antigen antibodies.
A: Patients grouped by anti-Smith positive or negative antibody status.
B: Patients grouped by status positive for anti-Ro52 and/or anti-Ro60 antibody or negative for both.
C: Patients grouped by status positive for anti-RNP68 and/or anti-RNPA antibody or negative for both.
NPQ: NULISA Protein Quantification.
Significant differences assessed by Mann-Whitney test:
**p*<0.05; ***p*<0.01; ****p*<0.001; *****p*<0.0001.
Boxplots represent median and IQR.





Supplementary Fig. S6. Correlation between the measured type I IFN proteins (upper panel) and type III proteins (lower panel). Measurements are annotated as either high (purple) or normal (grey) based on an upper limit cut off threshold (red dashed line) of 11.45 for IFNα1:IFNα1 and 16.49 for IFNλ1. Thresholds derived from other IFN proteins, not used for analysis, are represented by grey dashed lines. See also main figure 6. Line with shading represents linear regression with 95% confidence interval. ρ = Spearman correlation coefficient.



Supplementary Fig. S7. Relationship between clinical manifestations at any time in disease history and the four most frequent IFN profiles. High type I and III (35%, n=93, blue); normal levels of all IFN proteins (25%, n=67, black); high type I only (21%, n=56, green); and high type I and II and III (13%, n=34, red). Odds ratio with 95% confidence interval (CI) using these four groups together with adjusted *p*-values are shown.