

**Supplementary Table 1.** Demographic and immunologic characterization of the individuals in the score development cohort.

Variable	SSc (n)	%	Controls (n)	%
Male	49	14.71	113	21.56
Female	284	85.29	411	78.44
lcSSc	95	58.28	NA	NA
dcSSc	68	41.72	NA	NA
ACA+	79	48.47	NA	NA
ATA+	84	51.53	NA	NA
Lung fibrosis +	68	39.53	NA	NA
Variable	SSc (mean)	(25%,75% quantiles)	Controls (mean)	(25%,75% quantiles)
Age	57.88	(49, 68)	46.88	(37, 57)
Naive B cells*	0.02937864	(0.009201649, 0.042028323)	0.0324531	(0.01569948, 0.04688772)
Memory B cells*	0.007477577	(0, 0.01147687)	0.01267188	(0, 0.02003717)
Plasma cells*	0.001304802	(0, 0.001690348)	0.0007381787	(0, 0)
CD8 T cells*	0.06729529	(0.02860479, 0.09334222)	0.09727865	(0.06345768, 0.12997611)
Naive CD4 T cells*	0.07571614	(0.03575162, 0.10886041)	0.09255342	(0.05763792, 0.12319734)
Resting memory CD4 T cells*	0.1031702	(0.07320252, 0.13462763)	0.1156484	(0.08355767, 0.14185179)
Activated memory CD4 T cells*	0.00921801	(0.003980152, 0.013659997)	0.007856805	(0.0004000, 0.0122865)
Regulatory T cells (Tregs)*	0.002029284	(0, 7x10 <sup>-4</sup> )	0.001453498	(0, 5x10 <sup>-4</sup> )
Resting NK cells*	0.07648648	(0.05496048, 0.09279007)	0.09156808	(0.06775202, 0.11000317)
Activated NK cells*	0.0004892726	(0, 0)	0.000282294	(0, 0)
Monocytes*	0.1898639	(0.1448186, 0.2321907)	0.1606817	(0.1273005, 0.1977857)
M0 Macrophages*	0.002192233	(0, 0)	0.0005343795	(0, 0)
M1 Macrophages*	1.334093x10 <sup>-5</sup>	(0, 0)	1.335878x10 <sup>-6</sup>	(0, 0)
M2 Macrophages*	0.001202121	(0, 0)	0.001627978	(0, 0.001358678)
Resting dendritic cells*	8.208706x10 <sup>-6</sup>	(0, 0)	0	(0, 0)
Activated dendritic cells*	0.001821882	(0, 0.002755573)	0.0009882329	(0, 0.000425)

Resting mast cells*	0.02028563	(0.01480146, 0.02540636)	0.0188888	(0.01431149, 0.02370527)
Eosinophils*	0.000163299	(0, 0)	0.0001154277	(0, 0)
Neutrophils*	0.4118842	(0.3205400, 0.4936094)	0.3646565	(0.2928160, 0.4338762)

% is calculated over the total of individuals with available data

\*Mean (25% , 75% quantiles)

Immune cell type data correspond to fractions of cells in each subtype as defined in Jamin, C. et al. 2016

**Supplementary Table 2.** Effect of the independent addition of each demographic and immunological parameter to the GRS model (LRT p-value < 0.05).

	(SSc status ~ GRS+Sex vs SSc status ~ GRS+Sex+Variable)
Variable	LRT p-value
(Intercept)	NA
GRS	NA
Sex	NA
Age	3.47x10 <sup>-20</sup>
Naive B cells	0.28
Memory B cells	1.16x10 <sup>-5</sup>
Plasma cells	4.59x10 <sup>-2</sup>
CD8 T cells	2.86x10 <sup>-12</sup>
Naive CD4 T cells	8.70x10 <sup>-6</sup>
Resting memory CD4 T cells	5.62x10 <sup>-3</sup>
Activated memory CD4 T cells	8.23x10 <sup>-3</sup>
Regulatory T cells (Tregs)	0.74
Resting NK cells	1.99x10 <sup>-6</sup>
Activated NK cells	0.26
Monocytes	4.62x10 <sup>-8</sup>
M0 Macrophages	6.32x10 <sup>-5</sup>
M1 Macrophages	0.43
M2 Macrophages	0.29
Resting dendritic cells	0.33
Activated dendritic cells	2.82x10 <sup>-5</sup>
Resting mast cells	1.23x10 <sup>-2</sup>
Eosinophils	0.43
Neutrophils	<b>1.14x10<sup>-5</sup></b>

**Supplementary Table 3.** Comparison between the full GLM including all informative covariates and the multivariate GLM comprising only independently associated covariates (SSc status ~ GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells).

	Full GLM*				Multivariate GLM**			
Variable	Estimate	SE	Z value	Pr(> z )	Estimate	SE	Z value	Pr(> z )
(Intercept)	-1.14	4.84	-0.24	0.81	-1.60	0.51	-3.13	<b>1.75x10-3</b>
GRS	73.60	11.88	6.20	<b>5.75x10-10</b>	71.98	11.11	6.48	<b>9.08x10-11</b>
Sex	-0.51	0.32	-1.62	0.10	NA	NA	NA	NA
Age	0.05	9.35x10-3	5.82	<b>5.79x10-9</b>	6.50x10-2	8.45x10-3	7.70	<b>1.38x10-14</b>
Memory B cells	-17.96	8.80	-2.04	<b>4.12x10-2</b>	-23.40	8.06	-2.90	<b>3.71x10-3</b>
Plasma cells	-48.61	55.69	-0.87	0.38	NA	NA	NA	NA
CD8 T cells	-6.51	6.11	-1.07	0.29	NA	NA	NA	NA
Naive CD4 T cells	-6.57	5.95	-1.10	0.27	NA	NA	NA	NA
Resting memory CD4 T cells	-2.74	5.48	-0.50	0.62	NA	NA	NA	NA
Activated memory CD4 T cells	5.74	17.57	0.33	0.74	NA	NA	NA	NA
Resting NK cells	-19.97	6.54	-3.05	<b>2.26x10-3</b>	-19.66	3.82	-5.14	<b>2.69x10-7</b>
Monocytes	9.37	5.42	1.73	0.08	NA	NA	NA	NA
M0 Macrophages	67.55	28.42	2.38	<b>1.75x10-2</b>	68.30	28.44	2.40	<b>1.63x10-2</b>
Activated dendritic cells	186.47	53.64	3.48	<b>5.08x10-4</b>	158.93	49.68	3.20	<b>1.38x10-3</b>
Resting mast cells	8.19	17.63	0.46	0.64	NA	NA	NA	NA
Neutrophils	-0.72	4.94	-0.14	0.88	NA	NA	NA	NA

\*Full model: GLM (SSc status ~ GRS+Sex+Age+Memory B cells+Plasma cells+CD8 T cells+Naive CD4 T cells+resting memory CD4 T cells+Activated memory CD4 T cells+Resting NK cells+Monocytes+M0 Macrophages+Activated dendritic cells+Resting mast cells+Neutrophils)

\*\*Multivariate model: GLM (SSc status ~ GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells)

**Supplementary Table 4.** Comparison between the multivariate GLM (SSc status ~ GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells) and all the models built by dropping one covariate at a time.

	<b>Multivariate GLM (SSc status ~ GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells)</b>
<b>Null GLM</b>	<b>LRT p-value</b>
SSc status ~ Age+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells	2.59x10 <sup>-12</sup>
SSc status ~ GRS+Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells	1.73x10 <sup>-17</sup>
SSc status ~ GRS+Age	1.26x10 <sup>-12</sup>
SSc status ~ Memory B cells+Resting NK cells+M0 Macrophages+Activated dendritic cells	1.31x10 <sup>-27</sup>
SSc status ~ GRS+Age+Resting NK cells+M0 Macrophages+Activated dendritic cells	4.42x10 <sup>-3</sup>
SSc status ~ GRS+Age+Memory B cells+M0 Macrophages+Activated dendritic cells	1.00x10 <sup>-8</sup>
SSc status ~ GRS+Age+Memory B cells+Resting NK cells+Activated dendritic cells	6.71x10 <sup>-3</sup>
SSc status ~ GRS+Age+Memory B cells+Resting NK cells+M0 Macrophages	6.63x10 <sup>-4</sup>

**Supplementary Table 5.** List of the 33 variants selected to generate the SSc GRS. The columns show (left to right): SNP name (chromosome:base pair:alternative allele), chromosome, base pair position (GRCh37, hg19), allelic effect, GWAS p-value and rs identifier.

SNP	CHR	BP	P	OR	rs#
1:67814440:T	1	67,814,440	3.84x10 <sup>-10</sup>	1.1645	rs3790566
1:167420425:G	1	167,420,425	1.31x10 <sup>-11</sup>	0.8088	rs2056626
1:173243581:C	1	173,243,581	5.05x10 <sup>-08</sup>	1.1889	rs844663
1:173332629:A	1	173,332,629	5.02x10 <sup>-09</sup>	0.8698	rs1857066
2:191534372:C	2	191,534,372	5.20x10 <sup>-09</sup>	1.1815	rs16832798
2:191902758:A	2	191,902,758	1.94x10 <sup>-23</sup>	1.3129	rs3821236
2:191940451:G	2	191,940,451	4.72x10 <sup>-11</sup>	0.8132	rs7601754
3:58131515:T	3	58,131,515	1.24x10 <sup>-08</sup>	1.144	rs7355798
3:58375286:G	3	58,375,286	1.04x10 <sup>-10</sup>	1.1629	rs4076852
3:119116150:A	3	119,116,150	1.89x10 <sup>-10</sup>	0.8347	rs9884090
3:159733527:T	3	159,733,527	1.95x10 <sup>-10</sup>	0.8591	rs589446
4:965779:A	4	965,779	5.31x10 <sup>-11</sup>	1.1672	rs11724804
4:103449041:T	4	103,449,041	5.38x10 <sup>-09</sup>	1.1512	rs230534
5:150455732:G	5	150,455,732	2.42x10 <sup>-12</sup>	1.2042	rs3792783
6:32663851:C	6	32,663,851	3.25x10 <sup>-43</sup>	0.7431	rs6457617
6:106734040:T	6	106,734,040	2.84x10 <sup>-09</sup>	1.1321	rs633724
6:106734189:T	6	106,734,189	8.56x10 <sup>-09</sup>	0.8387	rs9486314
7:128568960:C	7	128,568,960	1.41x10 <sup>-09</sup>	0.8574	rs729302
7:128651522:T	7	128,651,522	3.10x10 <sup>-21</sup>	1.4031	rs36073657
7:128658739:G	7	128,658,739	2.87x10 <sup>-13</sup>	0.8493	rs12155080
7:135736414:C	7	135,736,414	2.21x10 <sup>-07</sup>	1.3346	rs322213
8:8123607:G	8	8,123,607	7.67x10 <sup>-08</sup>	1.1449	rs951702
8:11343973:T	8	11,343,973	3.33x10 <sup>-21</sup>	1.242	rs2736340

<b>8:61564964:T</b>	8	61,564,964	3.82x10-08	0.868	rs685985
<b>11:618172:A</b>	11	618,172	1.97x10-08	0.8021	rs6598008
<b>11:2348619:T</b>	11	2,348,619	2.54x10-10	0.8164	rs2651804
<b>11:118639353:A</b>	11	118,639,353	2.08x10-11	0.8414	rs11217020
<b>15:75077367:C</b>	15	75,077,367	1.84x10-14	1.1789	rs1378942
<b>15:75385990:A</b>	15	75,385,990	4.83x10-11	0.8615	rs6495151
<b>16:85971922:C</b>	16	85,971,922	3.82x10-15	0.8056	rs11117420
<b>17:38063381:T</b>	17	38,063,381	4.79x10-09	1.1254	rs883770
<b>17:73224639:G</b>	17	73,224,639	1.87x10-08	0.853	rs1005714
<b>19:18193191:A</b>	19	18,193,191	4.64x10-10	0.8293	rs2305743