

SUPPLEMENTARY MATHERIAL

Supplementary Table 1. Overall statistical power of the study for each analysed *IRAK1/MECP2* genetic variant at the 5% significance level accordingly with global disease, diffuse cutaneous systemic sclerosis and pulmonary fibrosis.

<i>Global SSc</i>					
SNP	OR=1.1	OR=1.2	OR=1.3	OR=1.4	OR=1.5
rs1059702	0.55	0.97	1.00	1.00	1.00
rs3027935	0.19	0.55	0.86	0.97	1.00
rs17435	0.61	0.98	1.00	1.00	1.00
rs5987201	0.19	0.55	0.86	0.97	1.00
rs5945175	0.26	0.71	0.95	0.99	1.00
<i>dcSSc</i>					
SNP	OR=1.1	OR=1.2	OR=1.3	OR=1.4	OR=1.5
rs1059702	0.25	0.69	0.94	0.99	1.00
rs3027935	0.10	0.27	0.51	0.74	0.89
rs17435	0.32	0.81	0.98	1.00	1.00
rs5987201	0.10	0.27	0.51	0.74	0.89
rs5945175	0.13	0.38	0.68	0.88	0.96
<i>PF</i>					
SNP	OR=1.1	OR=1.2	OR=1.3	OR=1.4	OR=1.5
rs1059702	0.16	0.48	0.81	0.95	0.99
rs3027935	0.08	0.17	0.32	0.50	0.68
rs17435	0.21	0.60	0.89	0.98	1.00
rs5987201	0.08	0.17	0.32	0.50	0.68
rs5945175	0.09	0.24	0.45	0.67	0.84

SSc, systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; PF, pulmonary fibrosis; SNP, single-nucleotide polymorphism; OR, odds ratio.

Supplementary Table 2. Hardy-Weinberg *P*-values of the analysed polymorphisms in the control cohorts included in the study.

SNP	Spain	USA	Germany	The Netherlands	UK
rs1059702	0.090	0.012	0.420	0.223	0.697
rs3027935	0.001	0.642	0.604	1.000	1.000
rs17435	0.185	0.138	0.144	0.838	0.583
rs5987201	0.394	0.189	1.000	1.000	0.130
rs5945175	0.529	1.000	1.000	0.187	1.000

SNP, single-nucleotide polymorphism.

Supplementary Table 3. Genotype and minor allele frequencies (MAF) of Xq28 genetic variants in Caucasian systemic sclerosis patients and unaffected controls from Spain.

Locus	rs#	Gene	1/2	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test		
					1/1	1/2	2/2		P-value*	P _{FDR} **	OR [CI 95%]***
ChrX: 152937386	rs1059702	IRAK1	A/G	Controls (n=1449)	39 (2.69)	344 (23.74)	1066 (73.57)	14.56			
				SSc (n=997)	37 (3.71)	254 (25.48)	706 (70.81)	16.45	0.072	0.096	1.16 [0.99-1.35]
				lcSSc (n=691)	24 (3.47)	166 (24.02)	501 (72.50)	15.48	0.427	0.427	1.08 [0.90-1.29]
				dcSSc (n=306)	13 (4.25)	88 (28.76)	205 (66.99)	18.63	0.011	0.028	1.34 [1.07-1.69]
				ACA+ (n=470)	11 (2.34)	113 (24.04)	346 (73.62)	14.36	0.880	0.880	0.98 [0.80-1.21]
				ATA+ (n=220)	8 (3.64)	61 (27.73)	151 (68.64)	17.50	0.107	0.399	1.25 [0.95-1.63]
				PF+ (n=216)	11 (5.09)	59 (27.31)	146 (67.59)	18.75	0.023	0.058	1.35 [1.04-1.76]
ChrX: 152957662	rs3027935	MECP2	T/C	Controls (n=1471)	10 (0.68)	111 (7.55)	1350 (91.77)	4.45			
				SSc (n=1005)	4 (0.40)	95 (9.45)	906 (90.15)	5.12	0.274	0.274	1.16 [0.89-1.51]
				lcSSc (n=701)	2 (0.29)	70 (9.99)	629 (89.73)	5.28	0.230	0.288	1.20 [0.89-1.60]
				dcSSc (n=304)	2 (0.66)	25 (8.22)	277 (91.12)	4.77	0.732	0.732	1.08 [0.71-1.62]
				ACA+ (n=470)	1 (0.21)	51 (10.85)	418 (88.94)	5.64	0.136	0.227	1.28 [0.92-1.78]
				ATA+ (n=220)	1 (0.45)	13 (5.91)	206 (93.64)	3.41	0.315	0.525	0.76 [0.44-1.31]
				PF+ (n=220)	2 (0.91)	19 (8.64)	199 (90.45)	5.23	0.467	0.584	1.18 [0.75-1.87]
ChrX: 152965174	rs17435	MECP2	T/A	Controls (n=1423)	56 (3.94)	412 (28.95)	955 (67.11)	18.41			
				SSc (n=1003)	56 (5.58)	327 (32.60)	620 (61.81)	21.88	2.82E-03	0.014	1.24 [1.08-1.43]
				lcSSc (n=699)	36 (5.15)	223 (31.90)	440 (62.95)	21.10	0.037	0.111	1.19 [1.01-1.39]
				dcSSc (n=304)	20 (6.58)	104 (34.21)	180 (59.21)	23.68	2.81E-03	0.014	1.38 [1.12-1.70]
				ACA+ (n=469)	19 (4.05)	146 (31.13)	304 (64.82)	19.62	0.412	0.515	1.08 [0.90-1.30]
				ATA+ (n=219)	11 (5.02)	71 (32.42)	137 (62.56)	21.23	0.159	0.399	1.20 [0.93-1.53]
				PF+ (n=220)	17 (7.73)	70 (31.82)	133 (60.45)	23.64	9.49E-03	0.047	1.37 [1.08-1.74]
ChrX: 152983236	rs5987201	MECP2	T/C	Controls (n=1355)	2 (0.15)	82 (6.05)	1271 (93.80)	3.17			
				SSc (n=1002)	2 (0.20)	79 (7.88)	921 (91.92)	4.14	0.077	0.096	1.32 [0.97-1.79]
				lcSSc (n=702)	2 (0.28)	55 (7.83)	645 (91.88)	4.20	0.090	0.150	1.34 [0.95-1.88]
				dcSSc (n=300)	0 (0.00)	24 (8.00)	276 (92.00)	4.00	0.307	0.383	1.27 [0.80-2.02]
				ACA+ (n=471)	1 (0.21)	42 (8.92)	428 (90.87)	4.67	0.033	0.132	1.50 [1.03-2.17]
				ATA+ (n=216)	1 (0.46)	11 (5.09)	204 (94.44)	3.01	0.856	0.856	0.95 [0.52-1.71]
				PF+ (n=215)	0 (0.00)	15 (6.98)	200 (93.02)	3.49	0.731	0.731	1.10 [0.63-1.93]
ChrX: 153011951	rs5945175	MECP2	C/T	Controls (n=1456)	1 (0.07)	64 (4.40)	1391 (95.54)	2.27			
				SSc (n=999)	1 (0.10)	65 (6.51)	933 (93.39)	3.35	0.021	0.053	1.50 [1.06-2.11]
				lcSSc (n=695)	0 (0.00)	46 (6.62)	649 (93.38)	3.31	0.045	0.111	1.48 [1.01-2.16]
				dcSSc (n=304)	1 (0.33)	19 (6.25)	284 (93.42)	3.45	0.086	0.144	1.54 [0.94-2.54]
				ACA+ (n=469)	0 (0.00)	32 (6.82)	437 (93.18)	3.41	0.053	0.132	1.52 [0.99-2.34]
				ATA+ (n=218)	0 (0.00)	12 (5.50)	206 (94.50)	2.75	0.531	0.663	1.22 [0.65-2.28]
				PF+ (n=217)	1 (0.46)	14 (6.45)	202 (93.09)	3.69	0.074	0.124	1.65 [0.95-2.88]

*All P-values have been calculated for the allelic model. **Benjamini & Hochberg (1995) step-up FDR control correction. ***Odds ratio for the minor allele. SSc, systemic sclerosis; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anti-centromere antibodies; ATA, anti-topoisomerase antibodies; M-H, Mantel-Haenszel test under fixed effect.

Supplementary Table 4. Genotype and minor allele frequencies (MAF) of Xq28 genetic variants in Caucasian systemic sclerosis patients and unaffected controls from United States of America.

Locus	rs#	Gene	1/2	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test		
					1/1	1/2	2/2		P-value*	P _{FDR} **	OR [CI 95%]***
ChrX: 152937386	rs1059702	IRAK1	A/G	Controls (n=487)	19 (3.90)	110 (22.59)	358 (73.51)	15.20			
				SSc (n=938)	29 (3.09)	245 (26.12)	664 (70.79)	16.15	0.507	0.634	1.08 [0.87-1.33]
				lcSSc (n=618)	21 (3.40)	158 (25.57)	439 (71.04)	16.18	0.527	0.659	1.08 [0.85-1.36]
				dcSSc (n=320)	8 (2.50)	87 (27.19)	225 (70.31)	16.09	0.626	0.783	1.07 [0.81-1.41]
				ACA+ (n=308)	6 (1.95)	79 (25.65)	223 (72.40)	14.77	0.818	0.818	0.97 [0.73-1.28]
				ATA+ (n=172)	4 (2.33)	50 (29.07)	118 (68.60)	16.86	0.465	0.774	1.13 [0.81-1.58]
				PF+ (n=82)	3 (3.66)	25 (30.49)	54 (65.85)	18.90	0.228	0.610	1.30 [0.85-2.00]
ChrX: 152957662	rs3027935	MECP2	T/C	Controls (n=479)	2 (0.42)	48 (10.02)	429 (89.56)	5.43			
				SSc (n=962)	2 (0.21)	114 (11.85)	846 (87.94)	6.13	0.449	0.634	1.14 [0.81-1.59]
				lcSSc (n=632)	1 (0.16)	75 (11.87)	556 (87.97)	6.09	0.508	0.659	1.13 [0.79-1.62]
				dcSSc (n=330)	1 (0.30)	39 (11.82)	290 (87.88)	6.21	0.505	0.783	1.15 [0.76-1.76]
				ACA+ (n=316)	0 (0.00)	38 (12.03)	278 (87.97)	6.01	0.622	0.818	1.12 [0.72-1.72]
				ATA+ (n=174)	1 (0.57)	15 (8.62)	158 (90.80)	4.89	0.698	0.873	0.89 [0.51-1.57]
				PF+ (n=85)	0 (0.00)	10 (11.76)	75 (88.24)	5.88	0.811	0.811	1.09 [0.54-2.19]
ChrX: 152965174	rs17435	MECP2	T/A	Controls (n=473)	22 (4.65)	136 (28.75)	315 (66.60)	19.03			
				SSc (n=957)	43 (4.49)	317 (33.12)	597 (62.38)	21.06	0.205	0.634	1.14 [0.93-1.38]
				lcSSc (n=629)	28 (4.45)	207 (32.91)	394 (62.64)	20.91	0.276	0.659	1.13 [0.91-1.39]
				dcSSc (n=328)	15 (4.57)	110 (33.54)	203 (61.89)	21.34	0.255	0.783	1.16 [0.90-1.48]
				ACA+ (n=316)	10 (3.16)	106 (33.54)	200 (63.29)	19.94	0.654	0.818	1.06 [0.82-1.37]
				ATA+ (n=172)	8 (4.65)	50 (29.07)	114 (66.28)	19.19	0.949	0.949	1.01 [0.74-1.38]
				PF+ (n=84)	4 (4.76)	29 (34.52)	51 (60.71)	22.02	0.366	0.610	1.20 [0.81-1.79]
ChrX: 152983236	rs5987201	MECP2	T/C	Controls (n=486)	2 (0.41)	36 (7.41)	448 (92.18)	4.12			
				SSc (n=965)	1 (0.10)	82 (8.50)	882 (91.40)	4.35	0.766	0.766	1.06 [0.72-1.56]
				lcSSc (n=634)	1 (0.16)	54 (8.52)	579 (91.32)	4.42	0.727	0.727	1.08 [0.71-1.63]
				dcSSc (n=331)	0 (0.00)	28 (8.46)	303 (91.54)	4.23	0.910	0.910	1.03 [0.63-1.69]
				ACA+ (n=317)	0 (0.00)	30 (9.46)	287 (90.54)	4.73	0.554	0.818	1.16 [0.71-1.88]
				ATA+ (n=174)	0 (0.00)	10 (5.75)	164 (94.25)	2.87	0.298	0.774	0.69 [0.34-1.39]
				PF+ (n=85)	0 (0.00)	8 (9.41)	77 (90.59)	4.71	0.723	0.811	1.15 [0.53-2.50]
ChrX: 153011951	rs5945175	MECP2	C/T	Controls (n=488)	0 (0.00)	41 (8.40)	447 (91.60)	4.20			
				SSc (n=965)	2 (0.21)	93 (9.64)	870 (90.16)	5.03	0.323	0.634	1.21 [0.83-1.75]
				lcSSc (n=634)	2 (0.32)	60 (9.46)	572 (90.22)	5.05	0.347	0.659	1.21 [0.81-1.81]
				dcSSc (n=331)	0 (0.00)	33 (9.97)	298 (90.03)	4.99	0.453	0.783	1.20 [0.75-1.91]
				ACA+ (n=317)	1 (0.32)	33 (10.41)	283 (89.27)	5.52	0.223	0.818	1.33 [0.84-2.12]
				ATA+ (n=174)	0 (0.00)	11 (6.32)	163 (93.68)	3.16	0.391	0.774	0.74 [0.38-1.47]
				PF+ (n=85)	0 (0.00)	10 (11.76)	75 (88.24)	5.88	0.327	0.610	1.43 [0.70-2.90]

*All P-values have been calculated for the allelic model. **Benjamini & Hochberg (1995) step-up FDR control correction. ***Odds ratio for the minor allele. SSc, systemic sclerosis; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anti-centromere antibodies; ATA, anti-topoisomerase antibodies; M-H, Mantel-Haenszel test under fixed effect.

Supplementary Table 5. Genotype and minor allele frequencies (MAF) of Xq28 genetic variants in Caucasian systemic sclerosis patients and unaffected controls from Germany.

Locus	rs#	Gene	1/2	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test		
					1/1	1/2	2/2		P-value*	P _{FDR} **	OR [CI 95%]***
ChrX: 152937386	rs1059702	IRAK1	A/G	Controls (n=169)	3 (1.78)	51 (30.18)	115 (68.05)	16.86			
				SSc (n=475)	26 (5.47)	124 (26.11)	325 (68.42)	18.53	0.495	0.642	1.12 [0.81-1.56]
				lcSSc (n=301)	13 (4.32)	78 (25.91)	210 (69.77)	17.28	0.872	0.872	1.03 [0.72-1.47]
				dcSSc (n=174)	13 (7.47)	46 (26.44)	115 (66.09)	20.69	0.200	0.333	1.29 [0.88-1.89]
				ACA+ (n=190)	6 (3.16)	44 (23.16)	140 (73.68)	14.74	0.435	0.452	0.85 [0.57-1.27]
				ATA+ (n=129)	9 (6.98)	33 (25.58)	87 (67.44)	19.77	0.362	0.603	1.22 [0.80-1.85]
				PF+ (n=121)	10 (8.26)	30 (24.79)	81 (66.94)	20.66	0.245	0.318	1.28 [0.84-1.96]
ChrX: 152957662	rs3027935	MECP2	T/C	Controls (n=172)	0 (0.00)	25 (14.53)	147 (85.47)	7.27			
				SSc (n=465)	3 (0.65)	44 (9.46)	418 (89.89)	5.38	0.203	0.507	0.73 [0.44-1.19]
				lcSSc (n=299)	3 (1.00)	30 (10.03)	266 (88.96)	6.02	0.454	0.754	0.82 [0.48-1.39]
				dcSSc (n=166)	0 (0.00)	14 (8.43)	152 (91.57)	4.22	0.089	0.223	0.56 [0.29-1.10]
				ACA+ (n=191)	0 (0.00)	20 (10.47)	171 (89.53)	5.24	0.257	0.445	0.71 [0.38-1.29]
				ATA+ (n=124)	2 (1.61)	9 (7.26)	113 (91.13)	5.24	0.321	0.603	0.71 [0.35-1.41]
				PF+ (n=122)	0 (0.00)	11 (9.02)	111 (90.98)	4.51	0.169	0.318	0.60 [0.29-1.25]
ChrX: 152965174	rs17435	MECP2	T/A	Controls (n=177)	6 (3.39)	72 (40.68)	99 (55.93)	23.73			
				SSc (n=461)	34 (7.38)	137 (29.72)	290 (62.91)	22.23	0.568	0.642	0.92 [0.69-1.23]
				lcSSc (n=292)	23 (7.88)	84 (28.77)	185 (63.36)	22.26	0.603	0.754	0.92 [0.67-1.26]
				dcSSc (n=169)	11 (6.51)	53 (31.36)	105 (62.13)	22.19	0.630	0.651	0.92 [0.64-1.31]
				ACA+ (n=187)	11 (5.88)	54 (28.88)	122 (65.24)	20.32	0.267	0.445	0.82 [0.58-1.17]
				ATA+ (n=126)	10 (7.94)	38 (30.16)	78 (61.90)	23.02	0.838	0.838	0.96 [0.66-1.41]
				PF+ (n=117)	8 (6.84)	37 (31.62)	72 (61.54)	22.65	0.762	0.762	0.94 [0.64-1.39]
ChrX: 152983236	rs5987201	MECP2	T/C	Controls (n=175)	0 (0.00)	23 (13.14)	152 (86.86)	6.57			
				SSc (n=471)	2 (0.42)	30 (6.37)	439 (93.21)	3.61	0.021	0.106	0.53 [0.31-0.92]
				lcSSc (n=300)	2 (0.67)	19 (6.33)	279 (93.00)	3.83	0.058	0.290	0.57 [0.31-1.03]
				dcSSc (n=171)	0 (0.00)	11 (6.43)	160 (93.57)	3.22	0.041	0.206	0.47 [0.23-0.98]
				ACA+ (n=194)	0 (0.00)	14 (7.22)	180 (92.78)	3.61	0.065	0.327	0.53 [0.27-1.05]
				ATA+ (n=126)	1 (0.79)	6 (4.76)	119 (94.44)	3.18	0.063	0.314	0.47 [0.21-1.06]
				PF+ (n=122)	0 (0.00)	7 (5.74)	115 (94.26)	2.87	0.043	0.213	0.42 [0.18-0.99]
ChrX: 153011951	rs5945175	MECP2	C/T	Controls (n=176)	0 (0.00)	17 (9.66)	159 (90.34)	4.83			
				SSc (n=456)	4 (0.88)	42 (9.21)	410 (89.91)	5.48	0.642	0.642	1.14 [0.65-2.01]
				lcSSc (n=286)	3 (1.05)	30 (10.49)	253 (88.46)	6.29	0.353	0.754	1.32 [0.73-2.39]
				dcSSc (n=170)	1 (0.59)	12 (7.06)	157 (92.35)	4.12	0.651	0.651	0.85 [0.41-1.75]
				ACA+ (n=180)	2 (1.11)	18 (10.00)	160 (88.89)	6.11	0.452	0.452	1.28 [0.67-2.46]
				ATA+ (n=130)	1 (0.77)	8 (6.15)	121 (93.08)	3.85	0.558	0.698	0.79 [0.35-1.75]
				PF+ (n=119)	0 (0.00)	7 (5.88)	112 (94.12)	2.94	0.255	0.318	0.60 [0.24-1.46]

*All P-values have been calculated for the allelic model. **Benjamini & Hochberg (1995) step-up FDR control correction. ***Odds ratio for the minor allele. SSc, systemic sclerosis; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anti-centromere antibodies; ATA, anti-topoisomerase antibodies; M-H, Mantel-Haenszel test under fixed effect.

Supplementary Table 6. Genotype and minor allele frequencies (MAF) of Xq28 genetic variants in Caucasian systemic sclerosis patients and unaffected controls from The Netherlands.

Locus	rs#	Gene	1/2	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test		
					1/1	1/2	2/2		P-value*	P _{FDR} **	OR [CI 95%]***
ChrX: 152937386	rs1059702	IRAK1	A/G	Controls (n=263)	8 (3.04)	61 (23.19)	194 (73.76)	14.64			
				SSc (n=209)	9 (4.31)	49 (23.44)	151 (72.25)	16.03	0.555	0.555	1.11 [0.78-1.59]
				lcSSc (n=151)	7 (4.64)	34 (22.52)	110 (72.85)	15.89	0.627	0.684	1.10 [0.74-1.63]
				dcSSc (n=58)	2 (3.45)	15 (25.86)	41 (70.69)	16.38	0.634	0.634	1.14 [0.66-1.98]
				ACA+ (n=57)	1 (1.75)	18 (31.58)	38 (66.67)	17.54	0.433	0.715	1.24 [0.72-2.13]
				ATA+ (n=51)	3 (5.88)	14 (27.45)	34 (66.67)	19.61	0.204	0.255	1.42 [0.82-2.45]
				PF+ (n=76)	3 (3.95)	20 (26.32)	53 (69.74)	17.11	0.456	0.550	1.20 [0.74-1.96]
ChrX: 152957662	rs3027935	MECP2	T/C	Controls (n=257)	0 (0.00)	21 (8.17)	236 (91.83)	4.09			
				SSc (n=224)	2 (0.89)	31 (13.84)	191 (85.27)	7.81	0.014	0.052	1.99 [1.14-3.47]
				lcSSc (n=162)	0 (0.00)	21 (12.96)	141 (87.04)	6.48	0.122	0.304	1.63 [0.87-3.03]
				dcSSc (n=62)	2 (3.23)	10 (16.13)	50 (80.65)	11.29	1.56E-03	3.91E-03	2.99 [1.47-6.06]
				ACA+ (n=60)	0 (0.00)	8 (13.33)	52 (86.67)	6.67	0.223	0.558	1.68 [0.72-3.88]
				ATA+ (n=53)	0 (0.00)	10 (18.87)	43 (81.13)	9.43	0.021	0.049	2.45 [1.12-5.36]
				PF+ (n=82)	1 (1.22)	14 (17.07)	67 (81.71)	9.76	5.38E-03	0.027	2.54 [1.29-4.99]
ChrX: 152965174	rs17435	MECP2	T/A	Controls (n=276)	9 (3.26)	80 (28.99)	187 (67.75)	17.75			
				SSc (n=226)	19 (8.41)	69 (30.53)	138 (61.06)	23.67	0.021	0.052	1.44 [1.06-1.96]
				lcSSc (n=162)	13 (8.02)	46 (28.40)	103 (63.58)	22.22	0.106	0.304	1.32 [0.94-1.86]
				dcSSc (n=64)	6 (9.38)	23 (35.94)	35 (54.69)	27.34	0.014	0.023	1.74 [1.12-2.72]
				ACA+ (n=63)	7 (11.11)	17 (26.98)	39 (61.90)	24.60	0.077	0.386	1.51 [0.95-2.40]
				ATA+ (n=57)	6 (10.53)	23 (40.35)	28 (49.12)	30.70	1.64E-03	8.21E-03	2.05 [1.30-3.23]
				PF+ (n=80)	6 (7.50)	26 (32.50)	48 (60.00)	23.75	0.089	0.149	1.44 [0.94-2.21]
ChrX: 152983236	rs5987201	MECP2	T/C	Controls (n=271)	0 (0.00)	18 (6.64)	253 (93.36)	3.32			
				SSc (n=213)	2 (0.94)	21 (9.86)	190 (89.20)	5.87	0.056	0.094	1.82 [0.98-3.37]
				lcSSc (n=148)	0 (0.00)	12 (8.11)	136 (91.89)	4.05	0.585	0.684	1.23 [0.58-2.59]
				dcSSc (n=65)	2 (3.08)	9 (13.85)	54 (83.08)	10.00	1.11E-03	3.91E-03	3.24 [1.54-6.79]
				ACA+ (n=60)	0 (0.00)	5 (8.33)	55 (91.67)	4.17	0.647	0.715	1.27 [0.46-3.48]
				ATA+ (n=50)	0 (0.00)	8 (16.00)	42 (84.00)	8.00	0.029	0.049	2.53 [1.07-5.99]
				PF+ (n=76)	1 (1.32)	9 (11.84)	66 (86.84)	7.24	0.033	0.082	2.27 [1.05-4.92]
ChrX: 153011951	rs5945175	MECP2	C/T	Controls (n=272)	2 (0.74)	26 (9.56)	244 (89.71)	5.52			
				SSc (n=229)	0 (0.00)	20 (8.73)	209 (91.27)	4.37	0.406	0.507	0.78 [0.44-1.40]
				lcSSc (n=164)	0 (0.00)	16 (9.76)	148 (90.24)	4.88	0.684	0.684	0.88 [0.47-1.64]
				dcSSc (n=65)	0 (0.00)	4 (6.15)	61 (93.85)	3.08	0.254	0.317	0.54 [0.19-1.57]
				ACA+ (n=63)	0 (0.00)	8 (12.70)	55 (87.30)	6.35	0.715	0.715	1.16 [0.52-2.60]
				ATA+ (n=53)	0 (0.00)	5 (9.43)	48 (90.57)	4.72	0.739	0.739	0.85 [0.32-2.24]
				PF+ (n=81)	0 (0.00)	7 (8.64)	74 (91.36)	4.32	0.550	0.550	0.77 [0.33-1.80]

*All P-values have been calculated for the allelic model. **Benjamini & Hochberg (1995) step-up FDR control correction. ***Odds ratio for the minor allele. SSc, systemic sclerosis; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anti-centromere antibodies; ATA, anti-topoisomerase antibodies; M-H, Mantel-Haenszel test under fixed effect.

Supplementary Table 7. Genotype and minor allele frequencies (MAF) of Xq28 genetic variants in Caucasian systemic sclerosis patients and unaffected controls from United Kingdom.

Locus	rs#	Gene	1/2	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test		
					1/1	1/2	2/2		P-value*	P _{FDR} **	OR [CI 95%]***
ChrX: 152937386	rs1059702	IRAK1	A/G	Controls (n=162)	1 (0.62)	33 (20.37)	128 (79.01)	10.80			
				SSc (n=271)	6 (2.21)	57 (21.03)	208 (76.75)	12.73	0.398	0.498	1.21 [0.78-1.86]
				lcSSc (n=208)	2 (0.96)	40 (19.23)	166 (79.81)	10.58	0.922	0.922	0.98 [0.61-1.56]
				dcSSc (n=63)	4 (6.35)	17 (26.98)	42 (66.67)	19.84	0.011	0.028	2.04 [1.17-3.58]
				ACA+ (n=120)	0 (0.00)	25 (20.83)	95 (79.17)	10.42	0.883	0.883	0.96 [0.56-1.65]
				ATA+ (n=38)	0 (0.00)	11 (28.95)	27 (71.05)	14.47	0.367	0.611	1.40 [0.67-2.90]
				PF+ (n=48)	0 (0.00)	12 (25.00)	36 (75.00)	12.50	0.643	0.929	1.18 [0.59-2.37]
ChrX: 152957662	rs3027935	MECP2	T/C	Controls (n=160)	1 (0.63)	24 (15.00)	135 (84.38)	8.13			
				SSc (n=347)	1 (0.29)	38 (10.95)	308 (88.76)	5.76	0.157	0.498	0.69 [0.41-1.16]
				lcSSc (n=262)	1 (0.38)	31 (11.83)	230 (87.79)	6.30	0.313	0.781	0.76 [0.45-1.30]
				dcSSc (n=85)	0 (0.00)	7 (8.24)	78 (91.76)	4.12	0.092	0.153	0.49 [0.21-1.14]
				ACA+ (n=141)	0 (0.00)	17 (12.06)	124 (87.94)	6.03	0.319	0.847	0.73 [0.39-1.37]
				ATA+ (n=54)	0 (0.00)	5 (9.26)	49 (90.74)	4.63	0.226	0.611	0.55 [0.21-1.47]
				PF+ (n=66)	0 (0.00)	8 (12.12)	58 (87.88)	6.06	0.449	0.929	0.73 [0.32-1.66]
ChrX: 152965174	rs17435	MECP2	T/A	Controls (n=159)	6 (3.77)	44 (27.67)	109 (68.55)	17.61			
				SSc (n=343)	18 (5.25)	102 (29.74)	223 (65.01)	20.12	0.349	0.498	1.18 [0.84-1.66]
				lcSSc (n=262)	6 (2.29)	78 (29.77)	178 (67.94)	17.18	0.872	0.922	0.97 [0.67-1.40]
				dcSSc (n=81)	12 (14.81)	24 (29.63)	45 (55.56)	29.63	2.51E-03	0.013	1.97 [1.26-3.07]
				ACA+ (n=141)	1 (0.71)	45 (31.91)	95 (67.38)	16.67	0.760	0.883	0.94 [0.61-1.43]
				ATA+ (n=52)	3 (5.77)	17 (32.69)	32 (61.54)	22.12	0.307	0.611	1.33 [0.77-2.29]
				PF+ (n=64)	2 (3.13)	19 (29.69)	43 (67.19)	17.97	0.929	0.929	1.03 [0.60-1.75]
ChrX: 152983236	rs5987201	MECP2	T/C	Controls (n=162)	2 (1.23)	17 (10.49)	143 (88.27)	6.48			
				SSc (n=334)	1 (0.30)	29 (8.68)	304 (91.02)	4.64	0.223	0.498	0.70 [0.40-1.24]
				lcSSc (n=252)	1 (0.40)	22 (8.73)	229 (90.87)	4.76	0.287	0.781	0.72 [0.39-1.32]
				dcSSc (n=82)	0 (0.00)	7 (8.54)	75 (91.46)	4.27	0.321	0.321	0.64 [0.27-1.55]
				ACA+ (n=139)	0 (0.00)	13 (9.35)	126 (90.65)	4.68	0.339	0.847	0.71 [0.35-1.44]
				ATA+ (n=53)	0 (0.00)	5 (9.43)	48 (90.57)	4.72	0.508	0.635	0.71 [0.26-1.94]
				PF+ (n=59)	0 (0.00)	4 (6.78)	55 (93.22)	3.39	0.213	0.929	0.51 [0.17-1.51]
ChrX: 153011951	rs5945175	MECP2	C/T	Controls (n=158)	0 (0.00)	9 (5.70)	149 (94.30)	2.85			
				SSc (n=342)	0 (0.00)	22 (6.43)	320 (93.57)	3.22	0.755	0.755	1.13 [0.52-2.49]
				lcSSc (n=259)	0 (0.00)	14 (5.41)	245 (94.59)	2.70	0.901	0.922	0.95 [0.41-2.22]
				dcSSc (n=83)	0 (0.00)	8 (9.64)	75 (90.36)	4.82	0.265	0.321	1.73 [0.65-4.56]
				ACA+ (n=138)	0 (0.00)	6 (4.35)	132 (95.65)	2.17	0.603	0.883	0.76 [0.27-2.16]
				ATA+ (n=53)	0 (0.00)	3 (5.66)	50 (94.34)	2.83	0.992	0.992	0.99 [0.26-3.74]
				PF+ (n=61)	0 (0.00)	4 (6.56)	57 (93.44)	3.28	0.812	0.929	1.16 [0.35-3.83]

*All P-values have been calculated for the allelic model. **Benjamini & Hochberg (1995) step-up FDR control correction. ***Odds ratio for the minor allele. SSc, systemic sclerosis; lcSSc, limited cutaneous SSc; dcSSc, diffuse cutaneous SSc; ACA, anti-centromere antibodies; ATA, anti-topoisomerase antibodies; M-H, Mantel-Haenszel test under fixed effect.

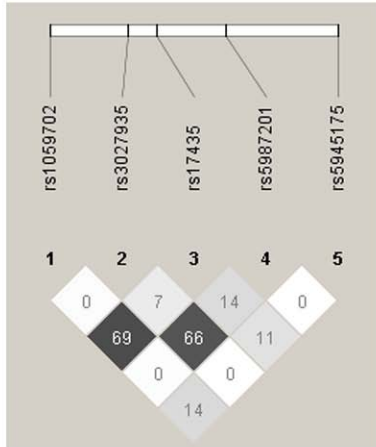
Supplementary Table 8. Pooled-analysis of rs1059702-rs17435 allelic combinations in the global disease, diffuse cutaneous systemic sclerosis and pulmonary fibrosis data. Only haplotypes with frequency > 5% were analysed.

Allelic combination	SSc vs controls					dcSSc vs controls					PF vs controls**				
	% cases	% control	P_{MH}	OR [95% CI]	P_{BD}	% cases	% control	P_{MH}	OR [95% CI]	P_{BD}	% cases	% control	P_{MH}	OR [95% CI]	P_{BD}
GA	77.8	80.7	4.00E-04	0.84 [0.76-0.93]	0.28	75.8	80.8	8.52E-05	0.77 [0.67-0.88]	0.08	74.7	80.9	0.018	0.81 [0.68-0.96]	0.47
AT	16.0	14.1	6.45E-03	1.16 [1.04-1.30]	0.97	17.5	14.1	8.76E-04	1.29 [1.11-1.49]	0.46	18.5	13.9	4.80E-03	1.32 [1.09-1.60]	0.85
GT	5.7	4.7	0.385*	1.14 [0.84-1.55]	0.02	6.0	4.7	0.251*	1.27 [0.85-1.90]	0.02	6.2	4.7	0.873	0.96 [0.70-1.33]	0.30

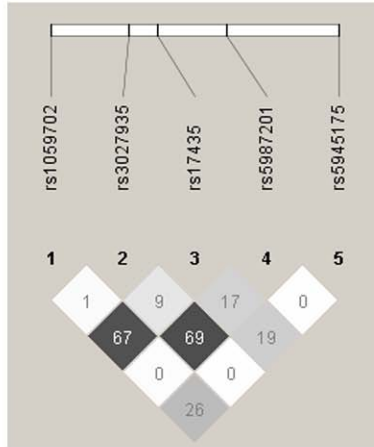
Order of the SNPs: rs1059702-rs17435; P_{MH} , allelic Mantel-Haenszel fixed effects model P -value.; P_{BD} , Breslow-Day P -value; *DerSimonian-Laird random effects model P -value.

Supplementary Figure 1. Linkage disequilibrium plot of the Xq28 genetic variants analysed in this study (r^2 values are shown).

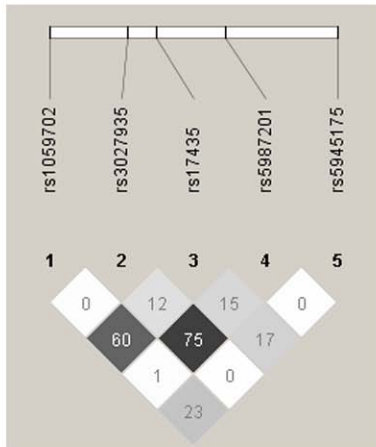
Spain



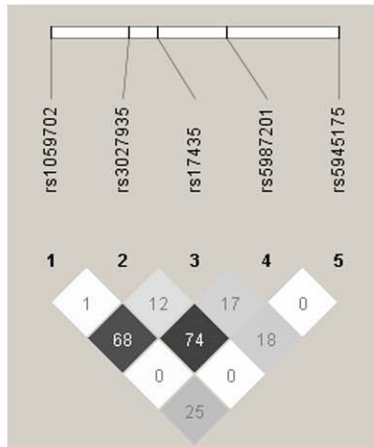
USA



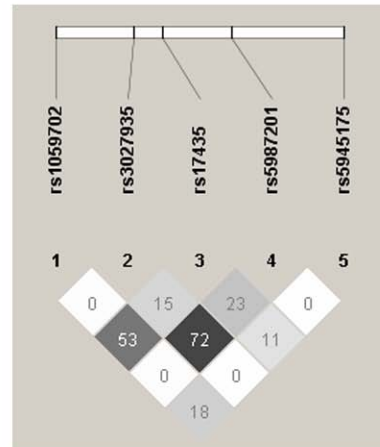
Germany



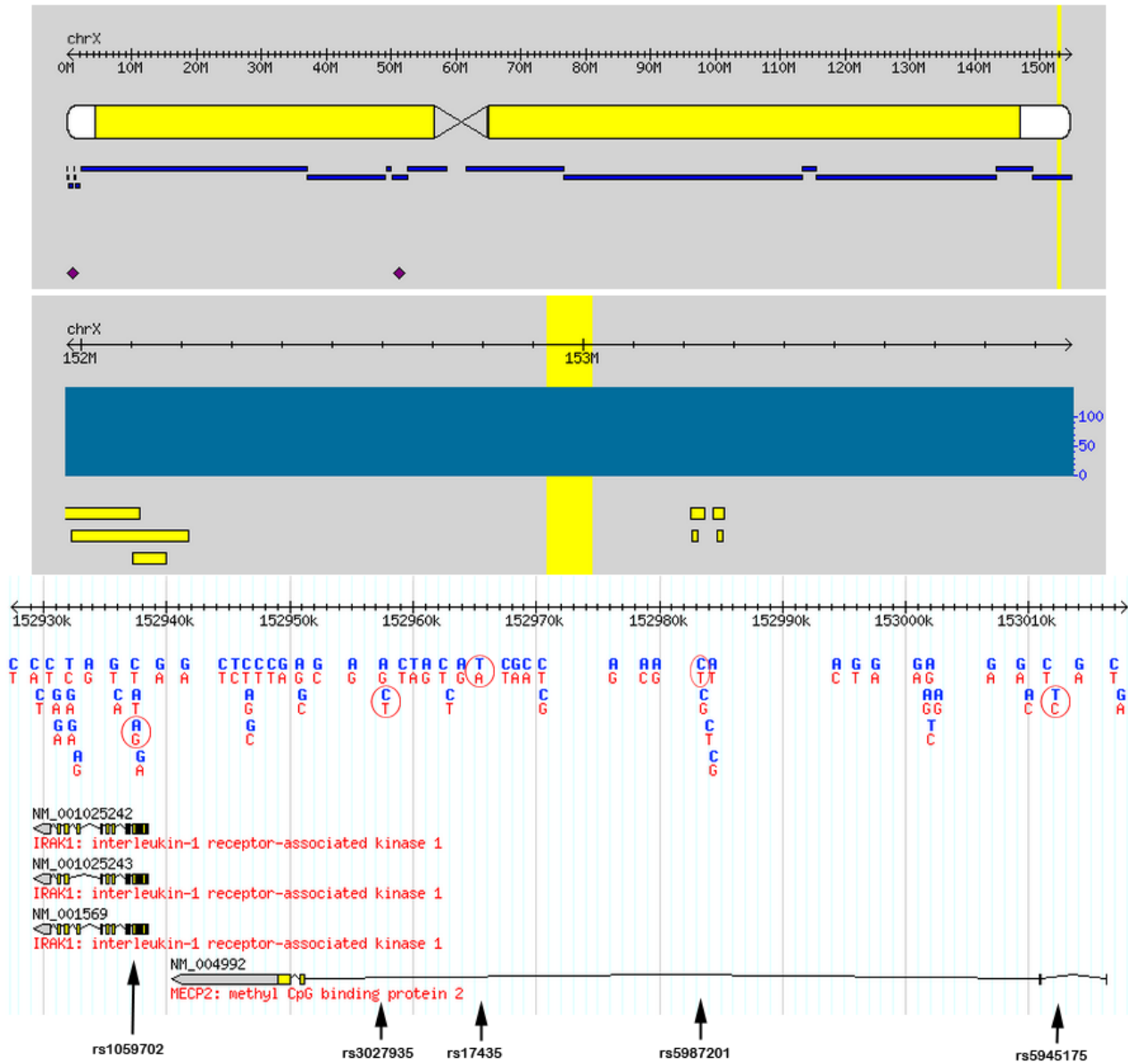
The Netherlands



UK



Supplementary Figure 2. Genomic position of the five polymorphisms included in this study. Nucleotide changes are surrounded by red circles. The image has been downloaded from the HapMap website (<http://hapmap.ncbi.nlm.nih.gov/>).



Supplementary Note.

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