

Table s1. Population specific composition of the complete SSc set of patients for the analyzed features of the disease.

Population	lcSSc %	dcSSc %	ACA+ %	ATA+ %	Fib +%
Spain	67.95	32.05	45.54	22.82	25.25
Germany	57.14	42.86	40.00	30.20	34.90
The Netherlands	69.70	30.30	22.90	28.96	47.47
Italy	74.33	25.67	45.50	34.50	33.67
Sweden	76.70	23.30	27.84	17.05	52.27
The United Kingdom	69.27	30.73	36.07	19.79	39.32
Norway	65.45	34.55	53.64	14.55	39.09
Overall	68.34	31.66	40.01	25.21	35.02

lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ACA+: anti-centromere autoantibody positive patients; ATA+: anti-topoisomerase autoantibody positive patients.
NA: not available data.

Table s2. Genotype and allele distribution of *CD226* rs763361 (chr:18, 65,682,622bp) genetic variant in seven European cohorts.

CHR	Subgroup (N)	Genotype, N (%)			MAF (%)	Allele test	
		1/1	1/2	2/2		P-value	OR [CI 95%]
Spain	Controls (n=1342)	298 (22.21)	640 (47.69)	404 (30.10)	46.05		
	SSc (n=793)	181 (22.82)	380 (47.92)	232 (29.26)	46.78	0.64	1.03 [0.91-1.17]
	lcSSc (n=536)	125 (23.32)	262 (48.88)	149 (27.80)	47.76	0.34	1.07 [0.93-1.23]
	dcSSc (n=257)	56 (21.79)	118 (45.91)	83 (32.30)	44.75	0.59	0.95 [0.78-1.15]
	ACA+ (n=365)	81 (22.19)	183 (50.14)	101 (27.67)	47.26	0.56	1.05 [0.89-1.24]
	ATA+ (n=176)	40 (22.73)	80 (45.45)	56 (31.82)	45.45	0.83	0.98 [0.78-1.22]
	Fib+ (n=206)	47 (22.82)	100 (48.54)	59 (28.64)	47.09	0.69	1.04 [0.85-1.28]
Germany	Controls (n=271)	60 (22.14)	141 (52.03)	70 (25.83)	48.15		
	SSc (n=134)	32 (23.88)	53 (39.55)	49 (36.57)	43.66	0.23	0.83 [0.62-1.12]
	lcSSc (n=73)	19 (26.03)	26 (35.62)	28 (38.36)	43.84	0.35	0.84 [0.58-1.21]
	dcSSc (n=61)	13 (21.31)	27 (44.26)	21 (34.43)	43.44	0.35	0.83 [0.56-1.23]
	ACA+ (n=42)	10 (23.81)	19 (45.24)	13 (30.95)	46.43	0.77	0.93 [0.59-1.48]
	ATA+ (n=37)	9 (24.32)	17 (45.95)	11 (29.73)	47.3	0.89	0.97 [0.59-1.57]
	Fib+ (n=65)	14 (21.54)	24 (36.92)	27 (41.54)	40	0.09	0.72 [0.49-1.06]
The Netherlands	Controls (n=538)	127 (23.61)	269 (50.00)	142 (26.39)	48.61		
	SSc (n=272)	56 (20.59)	155 (56.99)	61 (22.43)	49.08	0.86	1.02 [0.83-1.25]
	lcSSc (n=190)	39 (20.53)	107 (56.32)	44 (23.16)	48.68	0.98	1.00 [0.79-1.27]
	dcSSc (n=82)	17 (20.73)	48 (58.54)	17 (20.73)	50	0.74	1.06 [0.76-1.47]
	ACA+ (n=60)	12 (20.00)	33 (55.00)	15 (25.00)	47.5	0.82	0.96 [0.66-1.40]
	ATA+ (n=79)	18 (22.78)	48 (60.76)	13 (16.46)	53.16	0.28	1.20 [0.86-1.68]
	Fib+ (n=127)	24 (18.90)	76 (59.84)	27 (21.26)	48.82	0.95	1.01 [0.77-1.33]
Italy	Controls (n=777)	201 (25.87)	356 (45.82)	220 (28.31)	48.78		
	SSc (n=306)	66 (21.57)	156 (50.98)	84 (27.45)	47.06	0.47	0.93 [0.77-1.13]
	lcSSc (n=223)	49 (21.97)	112 (50.22)	62 (27.80)	47.09	0.53	0.93 [0.76-1.15]

	dcSSc (n=83)	17 (20.48)	44 (53.01)	22 (26.51)	46.99	0.66	0.93 [0.68-1.28]
	ACA+ (n=132)	28 (21.21)	71 (53.79)	33 (25.00)	48.11	0.84	0.97 [0.75-1.26]
	ATA+ (n=133)	29 (21.80)	61 (45.86)	43 (32.33)	44.74	0.22	0.85 [0.65-1.10]
	Fib+ (n=108)	25 (23.15)	52 (48.15)	31 (28.70)	47.22	0.67	0.94 [0.71-1.25]
Sweden	Controls (n=265)	57 (21.51)	137 (51.70)	71 (26.79)	47.36		
	SSc (n=155)	32 (20.65)	83 (53.55)	40 (25.81)	47.42	0.99	1.00 [0.76-1.33]
	lcSSc (n=117)	26 (22.22)	59 (50.43)	32 (27.35)	47.44	0.98	1.00 [0.74-1.37]
	dcSSc (n=38)	6 (15.79)	24 (63.16)	8 (21.05)	47.37	1.00	1.00 [0.62-1.62]
	ACA+ (n=42)	10 (23.81)	17 (40.48)	15 (35.71)	44.05	0.57	0.88 [0.55-1.39]
	ATA+ (n=24)	3 (12.50)	14 (58.33)	7 (29.17)	41.67	0.45	0.79 [0.44-1.45]
	Fib+ (n=81)	18 (22.22)	43 (53.09)	20 (24.69)	48.77	0.75	1.06 [0.74-1.51]
The United Kingdom	Controls (n=366)	76 (20.77)	184 (50.27)	106 (28.96)	45.9		
	SSc (n=270)	72 (26.67)	125 (46.30)	73 (27.04)	49.81	0.17	1.17 [0.94-1.46]
	lcSSc (n=196)	47 (23.98)	88 (44.90)	61 (31.12)	46.43	0.87	1.02 [0.80-1.31]
	dcSSc (n=74)	25 (33.78)	37 (50.00)	12 (16.22)	58.78	4.23E-03	1.68 [1.18-2.41]
	ACA+ (n=105)	18 (17.14)	51 (48.57)	36 (34.29)	41.43	0.25	0.83 [0.61-1.14]
	ATA+ (n=42)	15 (35.71)	16 (38.10)	11 (26.19)	54.76	0.12	1.43 [0.91-2.25]
	Fib+ (n=103)	27 (26.21)	50 (48.54)	26 (25.24)	50.49	0.24	1.20 [0.88-1.64]
Norway	Controls (n=252)	68 (26.98)	114 (45.24)	70 (27.78)	49.6		
	SSc (n=93)	23 (24.73)	38 (40.86)	32 (34.41)	45.16	0.30	0.84 [0.60-1.17]
	lcSSc (n=62)	14 (22.58)	27 (43.55)	21 (33.87)	44.35	0.29	0.81 [0.55-1.20]
	dcSSc (n=31)	9 (29.03)	11 (35.48)	11 (35.48)	46.77	0.67	0.89 [0.53-1.52]
	ACA+ (n=51)	12 (23.53)	22 (43.14)	17 (33.33)	45.1	0.41	0.83 [0.54-1.28]
	ATA+ (n=12)	5 (41.67)	3 (25.00)	4 (33.33)	54.17	0.66	1.20 [0.53-2.73]
	Fib+ (n=39)	10 (25.64)	14 (35.90)	15 (38.46)	43.59	0.26	0.76 [0.47-1.23]

Controls are used as reference for all comparisons. MAF: minor allele frequency; *P*-value: allelic Chisq uncorrected *p*-value; SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ATA: anti-topoisomerase antibodies; Fib+: lung fibrosis positive SSc patients.

Table s3. Genotype and allele distribution of *CD226* rs34794968 (chr:18; 65,682,006bp) genetic variant in seven European cohorts.

CHR	Subgroup (N)	Genotype, N (%)		Allele test		MAF (%)	P-value	OR [CI 95%]
		1/1	1/2	2/2				
Spain	Controls (n=1377)	230 (16.70)	644 (46.77)	503 (36.53)	40.09			
	SSc (n=786)	138 (17.56)	356 (45.29)	292 (37.15)	40.2	0.94	1.01 [0.89-1.14]	
	lcSSc (n=531)	96 (18.08)	244 (45.95)	191 (35.97)	41.05	0.59	1.04 [0.90-1.20]	
	dcSSc (n=255)	42 (16.47)	112 (43.92)	101 (39.61)	38.43	0.48	0.93 [0.77-1.13]	
	ACA+ (n=363)	65 (17.91)	168 (46.28)	130 (35.81)	41.05	0.64	1.04 [0.88-1.23]	
	ATA+ (n=175)	28 (16.00)	80 (45.71)	67 (38.29)	38.86	0.66	0.95 [0.76-1.19]	
	Fib+ (n=205)	34 (16.59)	97 (47.32)	74 (36.10)	40.24	0.95	1.01 [0.81-1.24]	
Germany	Controls (n=277)	41 (14.80)	150 (54.15)	86 (31.05)	41.88			
	SSc (n=154)	23 (14.94)	68 (44.16)	63 (40.91)	37.01	0.16	0.82 [0.61-1.09]	
	lcSSc (n=82)	12 (14.63)	38 (46.34)	32 (39.02)	37.8	0.35	0.84 [0.59-1.21]	
	dcSSc (n=72)	11 (15.28)	30 (41.67)	31 (43.06)	36.11	0.21	0.78 [0.54-1.15]	
	ACA+ (n=50)	5 (10.00)	28 (56.00)	17 (34.00)	38	0.47	0.85 [0.55-1.32]	
	ATA+ (n=42)	8 (19.05)	18 (42.86)	16 (38.10)	40.48	0.81	0.94 [0.59-1.51]	
	Fib+ (n=80)	10 (12.50)	33 (41.25)	37 (46.25)	33.12	0.046	0.69 [0.47-1.00]	
The Netherlands	Controls (n=528)	100 (18.94)	251 (47.54)	177 (33.52)	42.71			
	SSc (n=273)	38 (13.92)	138 (50.55)	97 (35.53)	39.19	0.18	0.86 [0.70-1.07]	
	lcSSc (n=191)	24 (12.57)	102 (53.40)	65 (34.03)	39.27	0.24	0.87 [0.68-1.10]	
	dcSSc (n=82)	14 (17.07)	36 (43.90)	32 (39.02)	39.02	0.37	0.86 [0.61-1.20]	
	ACA+ (n=62)	6 (9.68)	30 (48.39)	26 (41.94)	33.87	0.06	0.69 [0.46-1.02]	
	ATA+ (n=82)	14 (17.07)	39 (47.56)	29 (35.37)	40.85	0.65	0.93 [0.66-1.29]	
	Fib+ (n=131)	14 (10.69)	73 (55.73)	44 (33.59)	38.55	0.22	0.84 [0.64-1.11]	
Italy	Controls (n=782)	162 (20.72)	371 (47.44)	249 (31.84)	44.44			
	SSc (n=320)	66 (20.63)	163 (50.94)	91 (28.44)	46.09	0.48	1.07 [0.89-1.29]	
	lcSSc (n=234)	50 (21.37)	115 (49.15)	69 (29.49)	45.94	0.57	1.06 [0.86-1.31]	

	dcSSc (n=86)	16 (18.60)	48 (55.81)	22 (25.58)	46.51	0.60	1.09 [0.79-1.49]
	ACA+ (n=139)	27 (19.42)	69 (49.64)	43 (30.94)	44.24	0.95	0.99 [0.77-1.28]
	ATA+ (n=136)	34 (25.00)	71 (52.21)	31 (22.79)	51.1	0.042	1.31 [1.01-1.69]
	Fib+ (n=116)	27 (23.28)	54 (46.55)	35 (30.17)	46.55	0.55	1.09 [0.83-1.44]
Sweden	Controls (n=271)	33 (12.18)	136 (50.18)	102 (37.64)	37.27		
	SSc (n=159)	20 (12.58)	81 (50.94)	58 (36.48)	38.05	0.82	1.03 [0.78-1.38]
	lcSSc (n=122)	15 (12.30)	63 (51.64)	44 (36.07)	38.11	0.82	1.04 [0.76-1.42]
	dcSSc (n=37)	5 (13.51)	18 (48.65)	14 (37.84)	37.84	0.92	1.03 [0.62-1.69]
	ACA+ (n=45)	5 (11.11)	21 (46.67)	19 (42.22)	34.44	0.61	0.88 [0.55-1.41]
	ATA+ (n=27)	2 (7.41)	16 (59.26)	9 (33.33)	37.04	0.97	0.99 [0.55-1.77]
	Fib+ (n=81)	12 (14.81)	39 (48.15)	30 (37.04)	38.89	0.71	1.07 [0.75-1.54]
The United Kingdom	Controls (n=362)	55 (15.19)	170 (46.96)	137 (37.85)	38.67		
	SSc (n=271)	47 (17.34)	132 (48.71)	92 (33.95)	41.7	0.28	1.13 [0.90-1.42]
	lcSSc (n=197)	28 (14.21)	93 (47.21)	76 (38.58)	37.82	0.78	0.96 [0.75-1.24]
	dcSSc (n=74)	19 (25.68)	39 (52.70)	16 (21.62)	52.03	2.61E-03	1.72 [1.21-2.45]
	ACA+ (n=105)	13 (12.38)	51 (48.57)	41 (39.05)	36.67	0.60	0.92 [0.67-1.26]
	ATA+ (n=42)	8 (19.05)	22 (52.38)	12 (28.57)	45.24	0.24	1.31 [0.83-2.07]
	Fib+ (n=103)	16 (15.53)	51 (49.51)	36 (34.95)	40.29	0.67	1.07 [0.78-1.47]
Norway	Controls (n=261)	48 (18.39)	120 (45.98)	93 (35.63)	41.38		
	SSc (n=97)	16 (16.49)	40 (41.24)	41 (42.27)	37.11	0.30	0.84 [0.60-1.17]
	lcSSc (n=65)	9 (13.85)	30 (46.15)	26 (40.00)	36.92	0.35	0.83 [0.56-1.23]
	dcSSc (n=32)	7 (21.88)	10 (31.25)	15 (46.88)	37.5	0.55	0.85 [0.50-1.45]
	ACA+ (n=52)	8 (15.38)	23 (44.23)	21 (40.38)	37.5	0.46	0.85 [0.55-1.31]
	ATA+ (n=14)	6 (42.86)	3 (21.43)	5 (35.71)	53.57	0.20	1.64 [0.76-3.51]
	Fib+ (n=39)	9 (23.08)	15 (38.46)	15 (38.46)	42.31	0.88	1.04 [0.64-1.68]

Controls are used as reference for all comparisons. MAF: minor allele frequency; *P*-value: allelic Chisq uncorrected *p*-value; SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ATA: anti-topoisomerase antibodies; Fib+: lung fibrosis positive SSc patients.

Table s4. Genotype and allele distribution of *CD226* rs727088 (chr:18, 65,681,419bp) genetic variant in seven European cohorts.

CHR	Subgroup (N)	Genotype, N (%)		Allele test		MAF (%)	P-value	OR [CI 95%]
		1/1	1/2	2/2				
Spain	Controls (n=1356)	301 (22.20)	661 (48.75)	394 (29.06)	46.57			
	SSc (n=784)	181 (23.09)	380 (48.47)	223 (28.44)	47.32	0.64	1.03 [0.91-1.17]	
	lcSSc (n=533)	128 (24.02)	263 (49.34)	142 (26.64)	48.69	0.24	1.09 [0.94-1.25]	
	dcSSc (n=251)	53 (21.12)	117 (21.12)	81 (46.61)	44.42	0.38	0.92 [0.76-1.11]	
	ACA+ (n=365)	84 (23.01)	184 (50.41)	97 (26.58)	48.22	0.43	1.07 [0.91-1.26]	
	ATA+ (n=178)	41 (23.03)	82 (46.07)	55 (30.90)	46.07	0.86	0.98 [0.79-1.22]	
	Fib+ (n=203)	48 (23.65)	96 (47.29)	59 (29.06)	47.29	0.79	1.03 [0.84-1.27]	
Germany	Controls (n=270)	63 (23.33)	141 (52.22)	66 (24.44)	49.44			
	SSc (n=149)	36 (24.16)	69 (46.31)	44 (29.53)	47.32	0.56	0.92 [0.69-1.22]	
	lcSSc (n=79)	17 (21.52)	36 (45.57)	26 (32.91)	44.3	0.26	0.81 [0.57-1.16]	
	dcSSc (n=70)	19 (27.14)	33 (27.14)	18 (47.14)	50.71	0.79	1.05 [0.73-1.53]	
	ACA+ (n=47)	8 (17.02)	26 (55.32)	13 (27.66)	44.68	0.39	0.83 [0.53-1.28]	
	ATA+ (n=42)	9 (21.43)	20 (47.62)	13 (30.95)	45.24	0.36	0.81 [0.51-1.28]	
	Fib+ (n=74)	19 (25.68)	32 (43.24)	23 (31.08)	47.3	0.64	0.92 [0.64-1.32]	
The Netherlands	Controls (n=535)	130 (24.30)	270 (50.47)	135 (25.23)	49.53			
	SSc (n=280)	57 (20.36)	159 (56.79)	64 (22.86)	48.75	0.76	0.97 [0.79-1.19]	
	lcSSc (n=195)	39 (20.00)	112 (57.44)	44 (22.56)	48.72	0.78	0.97 [0.77-1.22]	
	dcSSc (n=85)	18 (21.18)	47 (21.18)	20 (55.29)	48.82	0.86	0.97 [0.70-1.34]	
	ACA+ (n=63)	12 (19.05)	35 (55.56)	16 (25.40)	46.83	0.57	0.90 [0.62-1.30]	
	ATA+ (n=82)	16 (19.51)	51 (62.20)	15 (18.29)	50.61	0.80	1.04 [0.75-1.45]	
	Fib+ (n=133)	26 (19.55)	78 (58.65)	29 (21.80)	48.87	0.85	0.97 [0.74-1.27]	
Italy	Controls (n=764)	221 (28.93)	350 (45.81)	193 (25.26)	51.83			
	SSc (n=304)	85 (27.96)	157 (51.64)	62 (20.39)	53.78	0.42	1.08 [0.89-1.30]	
	lcSSc (n=220)	64 (29.09)	111 (50.45)	45 (20.45)	54.32	0.36	1.10 [0.89-1.37]	

	dcSSc (n=84)	21 (54.76)	46 (20.24)	17 (20.24)	52.38	0.89	1.02 [0.74-1.40]
	ACA+ (n=134)	35 (26.12)	72 (53.73)	27 (20.15)	52.99	0.73	1.05 [0.80-1.36]
	ATA+ (n=129)	42 (32.56)	61 (47.29)	26 (20.16)	56.2	0.19	1.19 [0.91-1.55]
	Fib+ (n=109)	34 (31.19)	52 (47.71)	23 (21.10)	55.05	0.37	1.14 [0.85-1.51]
Sweden	Controls (n=263)	53 (20.15)	143 (54.37)	67 (25.48)	47.34		
	SSc (n=155)	32 (20.65)	82 (52.90)	41 (26.45)	47.1	0.95	0.99 [0.75-1.31]
	lcSSc (n=119)	26 (21.85)	61 (51.26)	32 (26.89)	47.48	0.97	1.01 [0.74-1.37]
	dcSSc (n=36)	6 (16.67)	21 (16.67)	9 (58.33)	45.83	0.81	0.94 [0.57-1.54]
	ACA+ (n=45)	9 (20.00)	19 (42.22)	17 (37.78)	41.11	0.27	0.78 [0.49-1.22]
	ATA+ (n=27)	4 (14.81)	16 (59.26)	7 (25.93)	44.44	0.68	0.89 [0.51-1.56]
	Fib+ (n=80)	17 (21.25)	41 (51.25)	22 (27.50)	46.88	0.92	0.98 [0.69-1.40]
The United Kingdom	Controls (n=366)	80 (21.86)	183 (50.00)	103 (28.14)	46.86		
	SSc (n=273)	72 (26.37)	128 (46.89)	73 (26.74)	49.82	0.30	1.13 [0.90-1.41]
	lcSSc (n=197)	47 (23.86)	89 (45.18)	61 (30.96)	46.45	0.90	0.98 [0.77-1.26]
	dcSSc (n=76)	25 (32.89)	39 (32.89)	12 (51.32)	58.55	0.01	1.60 [1.13-2.28]
	ACA+ (n=107)	18 (16.82)	53 (49.53)	36 (33.64)	41.59	0.17	0.81 [0.59-1.10]
	ATA+ (n=43)	15 (34.88)	18 (41.86)	10 (23.26)	55.81	0.12	1.43 [0.91-2.25]
	Fib+ (n=103)	26 (25.24)	52 (50.49)	25 (24.27)	50.49	0.36	1.16 [0.85-1.58]
Norway	Controls (n=261)	69 (26.44)	121 (46.36)	71 (27.20)	49.62		
	SSc (n=97)	26 (26.80)	39 (40.21)	32 (32.99)	46.91	0.52	0.90 [0.64-1.25]
	lcSSc (n=66)	15 (22.73)	30 (45.45)	21 (31.82)	45.45	0.39	0.85 [0.58-1.24]
	dcSSc (n=31)	11 (35.48)	9 (35.48)	11 (29.03)	50	0.95	1.02 [0.60-1.72]
	ACA+ (n=53)	12 (22.64)	25 (47.17)	16 (30.19)	46.23	0.52	0.87 [0.57-1.33]
	ATA+ (n=13)	4 (30.77)	2 (15.38)	7 (53.85)	38.46	0.24	0.62 [0.27-1.38]
	Fib+ (n=37)	10 (27.03)	12 (32.43)	15 (40.54)	43.24	0.25	0.75 [0.46-1.23]

Controls are used as reference for all comparisons. MAF: minor allele frequency; *P*-value: allelic Chisq uncorrected *p*-value; SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ATA: anti-topoisomerase antibodies; Fib+: lung fibrosis positive SSc patients.