

Supplementary file

Supplementary Table S1. Samples description and number of reads.

SampleID	StudyID	Description	Subgroup	Reads	Included	Reason
<i>m107</i>	Ctrl1	Control	-	2808	Yes	-
<i>m108</i>	Ctrl2	Control	-	3003	Yes	-
<i>m173</i>	Ctrl3	Control	-	2263	Yes	-
<i>m174</i>	Ctrl4	Control	-	4903	Yes	-
<i>m175</i>	Ctrl5	Control	-	5744	Yes	-
<i>m179</i>	Ctrl6	Control	-	6048	Yes	-
<i>m180</i>	Ctrl7	Control	-	5689	Yes	-
<i>m181</i>	Ctrl8	Control	-	4425	Yes	-
<i>m318</i>	Ctrl9	Control	-	1186	Yes	-
<i>m416</i>	Ctrl10	Control	-	633	No	Low reads
<i>m417</i>	Ctrl11	Control	-	1848	Yes	-
<i>m418</i>	Ctrl12	Control	-	1850	Yes	-
<i>m419</i>	Ctrl13	Control	-	2731	Yes	-
<i>m420</i>	Ctrl14	Control	-	1903	Yes	-
<i>m449</i>	Ctrl15	Control	-	3206	Yes	-
<i>m450</i>	Ctrl16	Control	-	3860	Yes	-
<i>m451</i>	Ctrl17	Control	-	4256	Yes	-
<i>m452</i>	Ctrl18	Control	-	5494	Yes	-
<i>m425</i>	Ctrl19	Control	-	438	No	Low reads
<i>m415</i>	Unassigned	Control	-	-	No	Other
<i>m299</i>	SSc1	SSc	Early	887	Yes	-
<i>m300</i>	SSc2	SSc	Early	1929	Yes	-
<i>m301</i>	SSc3	SSc	Early	2955	Yes	-
<i>m302</i>	SSc4	SSc	Early	2156	Yes	-
<i>m303</i>	SSc5	SSc	Early	2002	Yes	-
<i>m304</i>	SSc6	SSc	Early	2744	Yes	-
<i>m305</i>	SSc7	SSc	Early	912	Yes	-
<i>m306</i>	SSc8	SSc	Early	1720	Yes	-
<i>m307</i>	SSc9	SSc	Early	2286	Yes	-
<i>m308</i>	SSc10	SSc	Early	2203	Yes	-
<i>m309</i>	SSc11	SSc	Early	6004	Yes	-
<i>m310</i>	SSc12	SSc	Early	1901	Yes	-
<i>m311</i>	SSc13	SSc	Overweight	897	Yes	-
<i>m312</i>	SSc14	SSc	Overweight	1567	Yes	-
<i>m313</i>	SSc15	SSc	Overweight	2310	Yes	-
<i>m314</i>	SSc16	SSc	Overweight	626	No	Low reads
<i>m315</i>	SSc17	SSc	Overweight	1469	Yes	-
<i>m316</i>	SSc18	SSc	Overweight	1907	Yes	-
<i>m317</i>	SSc19	SSc	Overweight	3255	Yes	-
<i>m319</i>	SSc20	SSc	Overweight	2989	Yes	-
<i>m320</i>	SSc21	SSc	Overweight	1538	Yes	-
<i>m321</i>	SSc22	SSc	Overweight	1200	Yes	-
<i>m322</i>	SSc23	SSc	Overweight	1150	Yes	-
<i>m323</i>	SSc24	SSc	Long-standing	2299	Yes	-
<i>m324</i>	SSc25	SSc	Underweight	1901	Yes	-
<i>m325</i>	SSc26	SSc	Underweight	2893	Yes	-
<i>m326</i>	SSc27	SSc	Long-standing	5571	Yes	-
<i>m328</i>	SSc28	SSc	Underweight	3096	Yes	-
<i>m329</i>	SSc29	SSc	Underweight	4724	Yes	-
<i>m330</i>	SSc30	SSc	Underweight	2009	Yes	-
<i>m331</i>	SSc31	SSc	Early	3778	Yes	-
<i>m332</i>	SSc32	SSc	Underweight	3191	Yes	-
<i>m333</i>	SSc33	SSc	Underweight	3777	Yes	-
<i>m334</i>	SSc34	SSc	Underweight	3215	Yes	-
<i>m335</i>	SSc35	SSc	Underweight	2871	Yes	-
<i>m336</i>	SSc36	SSc	Underweight	3797	Yes	-
<i>m401</i>	SSc37	SSc	Overweight	483	No	Low reads
<i>m402</i>	SSc38	SSc	Long-standing	831	Yes	-
<i>m403</i>	SSc39	SSc	Long-standing	862	Yes	-
<i>m404</i>	SSc40	SSc	Long-standing	749	Yes	-
<i>m405</i>	SSc41	SSc	Long-standing	790	Yes	-
<i>m406</i>	SSc42	SSc	Long-standing	919	Yes	-
<i>m407</i>	SSc43	SSc	Long-standing	3622	Yes	-
<i>m408</i>	SSc44	SSc	Overweight	603	No	Low reads
<i>m409</i>	SSc45	SSc	Long-standing	956	Yes	-
<i>m410</i>	SSc46	SSc	Underweight	340	No	Low reads
<i>m411</i>	SSc47	SSc	Early	330	No	Low reads
<i>m412</i>	SSc48	SSc	Long-standing	1415	Yes	-

SampleID	StudyID	Description	Subgroup	Reads	Included	Reason
m413	SSc49	SSc	Long-standing	764	Yes	-
m414	SSc50	SSc	Early	739	Yes	-
m421	SSc51	SSc	Early	3440	Yes	-
m422	SSc52	SSc	Long-standing	2657	Yes	-
m423	SSc53	SSc	Early	1959	Yes	-
m424	SSc54	SSc	Long-standing	1608	Yes	-
m426	SSc56	SSc	Underweight	1071	Yes	-
m427	SSc57	SSc	Long-standing	2155	Yes	-
m428	SSc58	SSc	Long-standing	3796	Yes	-
m429	SSc59	SSc	Early	1185	Yes	-
m430	SSc60	SSc	Long-standing	822	Yes	-
m431	SSc61	SSc	Long-standing	3254	Yes	-
m432	SSc62	SSc	Long-standing	4830	Yes	-
m433	SSc63	SSc	Long-standing	3122	Yes	-
m434	SSc64	SSc	Long-standing	4881	Yes	-
m453	SSc65	SSc	Underweight	1992	Yes	-
m454	SSc66	SSc	Early	6065	Yes	-
m455	SSc67	SSc	Underweight	6474	Yes	-
m456	SSc68	SSc	Early	2162	Yes	-
m457	SSc69	SSc	Overweight	7113	Yes	-

Supplementary Table S2. Summary of treatments and blood chemistry parameters in early and long-standing SSc.

	Early SSc n=19	Long-standing SSc n=20	<i>p</i>	All SSc (normal BMI) n=39
Proton Pump Inhibitor, n (%)	17 (89.5)	18 (90.0)	-	35 (89.7)
Prokinetic, n (%)	3 (15.8)	4 (20.0)	-	7 (17.9)
Hydroxychloroquine, n (%)	8 (42.1)	5 (25.0)	-	13 (33.3)
Methotrexate, n (%)	6 (31.6)	2 (10.0)	-	8 (20.5)
Azathioprine, n (%)	2 (10.5)	1 (5.0)	-	3 (7.7)
Mycophenolate, n (%)	0 (0)	3 (15.0)	-	3 (7.7)
Cyclophosphamide (ever), n (%)	5 (26.3)	6 (30.0)	-	11 (28.2)
Glucocorticoid, n (%)	7 (36.8)	9 (45.0)	-	16 (41.0)
Iloprost, n (%)	10 (52.6)	12 (60.0)	-	22 (56.4)
Calcium Channel Blocker, n (%)	12 (63.1)	14 (70.0)	-	26 (66.7)
Endothelin Receptor Antagonist, n (%)	4 (21.1)	5 (25.0)	-	9 (23.1)
Phosphodiesterase 5 inhibitor, n (%)	3 (15.8)	4 (20.0)	-	7 (17.9)
Haemoglobin, g/dl, mean±SD	12.1 ± 1.2	12.7 ± 1.1	NS	12.4 ± 1.2
Albumin, g/dl, mean±SD	3.7 ± 0.3	3.9 ± 0.3	NS	3.8 ± 0.3
Glucose, mg/dl, mean±SD	82.5 ± 7.2	86.8 ± 9.7	NS	84.7 ± 8.7
Total cholesterol, mg/dl,	164.0 ± 34.4	173.8 ± 30.0	NS	169.1 ± 32.1
HDL, mg/dl, mean±SD	51.1 ± 12.3	57.3 ± 14.8	NS	54.3 ± 12.6
Triglycerides, mg/dl, mean±SD	90.4 ± 34.2	88.6 ± 9.7	NS	88.5 ± 31.2
Ferritin, ng/ml, mean±SD	50.5 ± 42.5	36.8 ± 26.8	NS	43.5 ± 35.6
Folate, ng/ml, mean±SD	9.4 ± 4.8	8.8 ± 4.1	NS	9.1 ± 4.4
Vitamin B12, pg/ml, mean±SD	371.5 ± 150.0	403.5 ± 170.8	NS	387.9 ± 159.7
25-hydroxyvitamin D, ng/ml, mean±SD	20.8 ± 10.6	23.3 ± 8.2	NS	22.1 ± 9.4

SD: standard deviation; HDL: high-density lipoprotein.

Supplementary Table S3. Main characteristics of patients' subgroups according to BMI.

	Underweight SSc n=13	Overweight SSc n=11	<i>p</i>
Age, years, mean ± SD	57.2 ± 20.3	57.4 ± 10.0	NS
Female, n (%)	12 (92.3)	11 (100.0)	NS
Body mass index, kg/m ² , mean ± SD	18.3 ± 0.2	31.7 ± 5.2	<0.001
Disease duration, years from RP, mean ± SD	11.5 ± 6.6	14.9 ± 12.1	NS
Disease duration, years from first non-RP symptom, mean ± SD	9.7 ± 6.3	12.0 ± 9.2	NS
ATA / ACA / positivity to other antibodies, n (%)	6 (46.2) / 3 (23.1) / 4 (30.8)	4 (36.4) / 4 (36.4) / 3 (27.3)	NS / NS / NS
Diffuse cutaneous SSc, n (%)	7 (53.8)	6 (54.5)	NS
Modified Rodnan skin score, mean ± SD	13.8 ± 9.2	9.7 ± 6.1	NS
Digital ulcers (ever), n (%)	4 (30.8)	5 (45.4)	NS
Interstitial lung disease (HRCT), n (%)	7 (53.8)	6 (54.5)	NS
FVC, %, mean±SD	104.0 ± 32.8	82.9 ± 21.1	NS
DLCO, %, mean±SD	53.4 ± 22.3	43.4 ± 22.0	NS
Pulmonary arterial hypertension, n (%)	3 (23.1)	2 (18.2)	NS
PASP, mmHg, mean±SD	32.2 ± 11.9	32.2 ± 6.7	NS
UCLA SCTC GIT 2.0 Total score, mean ± SD	0.50 ± 0.42	0.35 ± 0.22	NS
UCLA SCTC GIT 2.0 Reflux, mean ± SD	0.59 ± 0.20	0.55 ± 0.44	NS
UCLA SCTC GIT 2.0 Bloating, mean ± SD	0.79 ± 0.56	0.82 ± 0.73	NS
UCLA SCTC GIT 2.0 Faecal soilage, mean ± SD	0.62 ± 0.77	0.18 ± 0.41	NS
UCLA SCTC GIT 2.0 Diarrhea, mean ± SD	0.31 ± 0.48	0.23 ± 0.26	NS
UCLA SCTC GIT 2.0 Social functioning, mean ± SD	0.36 ± 0.51	0.23 ± 0.29	NS
UCLA SCTC GIT 2.0 Emotional well-being, mean ± SD	0.35 ± 0.51	0.08 ± 0.12	NS
UCLA SCTC GIT 2.0 Constipation, mean ± SD	0.62 ± 0.53	0.41 ± 0.62	NS
Moderate/severe GI symptoms, n (%)	4 (30.8)	2 (18.2)	NS
Malnutrition universal screening tool, score ≥1 b, n (%)	13 (100.0)	1 (9.1)	<0.001
Proton pump inhibitor, n (%)	11 (84.6)	11 (100.0)	NS
Prokinetic, n (%)	1 (7.7)	0 (0.0)	NS
Haemoglobin, g/dl, mean ± SD	12.6 ± 1.6	12.5 ± 1.4	NS
Albumin, g/dl, mean ± SD	3.6 ± 0.4	4.0 ± 0.5	0.024
Glucose, mg/dl, mean ± SD	81.5 ± 8.0	92.1 ± 6.2	0.002
Total cholesterol, mg/dl,	149.9 ± 23.8	185.5 ± 46.6	0.038
HDL, mg/dl, mean ± SD	49.3 ± 10.0	53.7 ± 19.1	NS
Triglycerides, mg/dl, mean ± SD	86.0 ± 32.2	104.6 ± 42.5	NS
Ferritin, ng/ml, mean ± SD	31.9 ± 22.4	41.5 ± 40.9	NS
Folate, ng/ml, mean ± SD	10.0 ± 5.4	7.8 ± 3.0	NS
Vitamin B12, pg/ml, mean ± SD	384.5 ± 133.9	365.9 ± 120.4	NS
25-hydroxyvitamin D, ng/ml, mean ± SD	25.9 ± 16.1	31.4 ± 15.5	NS

SD: standard deviation; ATA: anti-topoisomerase I antibodies; ACA: anti-centromere antibodies; HRCT: high resolution computed tomography; HDL: high-density lipoprotein; according to UCLA SCTC GIT 2.0 Total Score [1]. cMUST score >1 is intrinsic for BMI ≤18.5 kg/m².

Supplementary Table S4. Summary of alpha and beta diversity comparisons between SSc patients with normal BMI and HCs.

	<i>Alpha diversity</i>				<i>Beta diversity</i>	
	Chao 1	Observed OTUs	Shannon	Simpson	Bray-Curtis	Weighted UniFrac
<i>HCS vs. early SSc</i>	<i>p</i> =.032	<i>p</i> =0.68	<i>p</i> =0.37	<i>p</i> =0.72	<i>p</i><0.001, R²=0.076	<i>p</i><0.001, R²=0.165
<i>HCS vs. long-standing SSc</i>	<i>p</i>=0.024	<i>p</i>=0.029	<i>p</i> =0.52	<i>p</i> =0.62	<i>p</i><0.001, R²=0.061	<i>p</i> =0.19, R ² =0.038

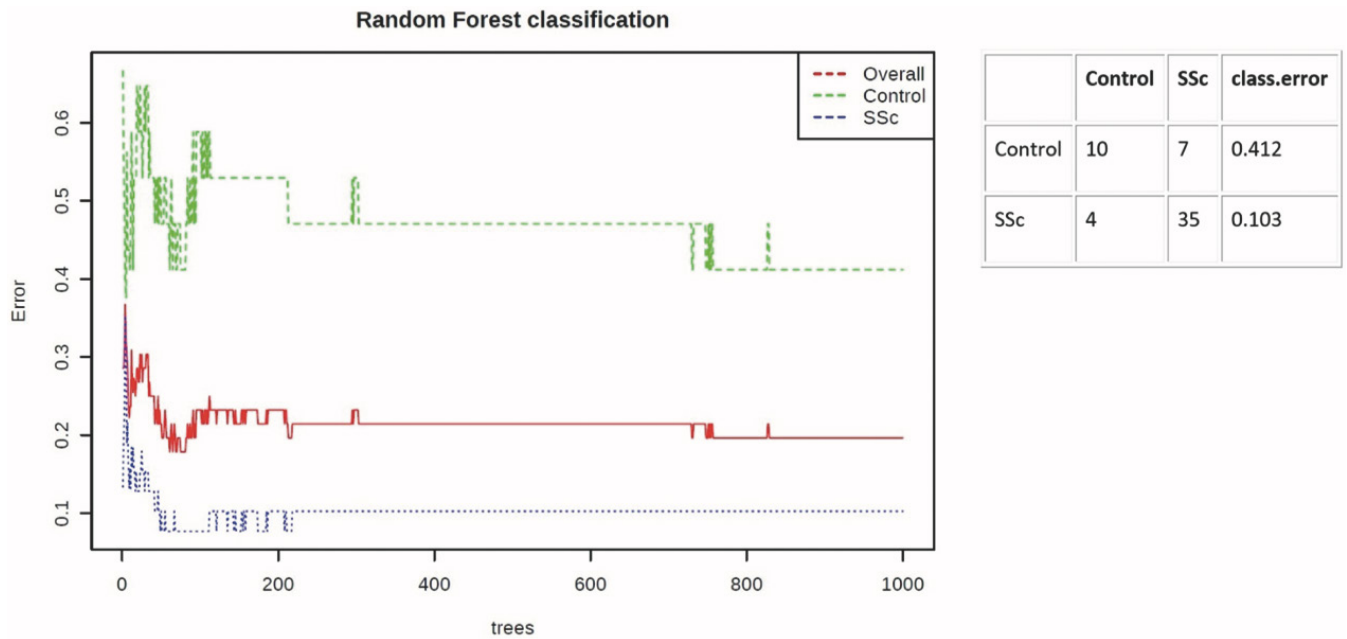
Supplementary Table S5. Main characteristics of patients' subgroups according to LeRoy classification.

	lcSSc n=18	dcSSc n=21	P
Age, years, mean $\pm$ SD	57.2 $\pm$ 14.0	48.5 $\pm$ 13.4	ns
Female, n (%)	15 (83.3)	18 (85.7)	ns
Body Mass Index, kg/m ² , mean $\pm$ SD	22.4 $\pm$ 1.6	22.5 $\pm$ 1.7	ns
Disease duration, years from RP, mean $\pm$ SD	7.7 $\pm$ 5.3	8.7 $\pm$ 7.6	ns
Disease duration, years from first non-RP symptom, mean $\pm$ SD	6.3 $\pm$ 5.5	6.9 $\pm$ 5.3	ns
ATA / ACA / positivity to other antibodies, n (%)	5 (27.8) / 8 (44.4) / 5 (27.8)	16 (76.2) / 0 (0.0) / 5 (23.8)	.004 / .001 / ns
Modified Rodnan Skin Score, mean $\pm$ SD	4.2 $\pm$ 2.5	14.6 $\pm$ 7.7	<.001
Digital ulcers (ever), n (%)	6 (33.3)	11 (52.4)	ns
Interstitial Lung Disease (HRCT), n (%)	7 (38.9)	12 (57.1)	ns
FVC, %, mean $\pm$ SD	100.5 $\pm$ 17.5	80.9 $\pm$ 23.5	.001
DLCO, %, mean $\pm$ SD	61.7 $\pm$ 18.5	55.0 $\pm$ 19.8	ns
Pulmonary Arterial Hypertension, n (%)	4 (22.2)	2 (9.5)	ns
PASP, mmHg, mean $\pm$ SD	31.3 $\pm$ 8.6	32.6 $\pm$ 7.0	ns
UCLA SCTC GIT 2.0 Total Score, mean $\pm$ SD	0.47 $\pm$ 0.30	0.34 $\pm$ 0.28	ns
UCLA SCTC GIT 2.0 Reflux, mean $\pm$ SD	0.57 $\pm$ 0.64	0.64 $\pm$ 0.59	ns
UCLA SCTC GIT 2.0 Bloating, mean $\pm$ SD	1.26 $\pm$ 0.85	0.52 $\pm$ 0.47	.002
UCLA SCTC GIT 2.0 Fecal soilage, mean $\pm$ SD	0.28 $\pm$ 0.57	0.19 $\pm$ 0.68	ns
UCLA SCTC GIT 2.0 Diarrhea, mean $\pm$ SD	0.14 $\pm$ 0.29	0.28 $\pm$ 0.46	ns
UCLA SCTC GIT 2.0 Social functioning, mean $\pm$ SD	0.30 $\pm$ 0.27	0.23 $\pm$ 0.30	ns
UCLA SCTC GIT 2.0 Emotional well-being, mean $\pm$ SD	0.28 $\pm$ 0.64	0.15 $\pm$ 0.20	ns
UCLA SCTC GIT 2.0 Constipation, mean $\pm$ SD	0.57 $\pm$ 0.67	0.45 $\pm$ 0.62	ns
Moderate/severe GI symptoms ^a , n (%)	5 (27.8)	3 (14.3)	ns
Malnutrition Universal Screening Tool, score ≥ 1 ^b , n (%)	2 (11.1)	4 (19.0)	ns

SD: standard deviation; ATA: anti-topoisomerase I antibodies; ACA: anti-centromere antibodies; HRCT: high resolution computed tomography; ^aaccording to UCLA SCTC GIT 2.0 Total Score [1]; ^bMUST score >1 is intrinsic for BMI ≤ 18.5 kg/m².

Supplementary Table S6. Summary of alpha and beta diversity comparisons between SSc patients with normal BMI grouped according to key features. The number of subjects for each group is shown in brackets.

	<i>Alpha diversity</i>				<i>Beta diversity</i>	
	Chao 1	Observed OTUs	Shannon	Simpson	Bray-Curtis	Weighted UniFrac
ATA (21) vs. ACA (8) vs. positivity to other antibodies (10)	<i>P</i> =.61	<i>P</i> =.29	<i>P</i> =.65	<i>P</i> =.81	<i>P</i> =.14 <i>R</i> ² =.066	<i>P</i> =.47 <i>R</i> ² =.052
None to mild GI symptoms (31) vs. moderate to severe GI symptoms (8)	<i>P</i> =.69	<i>P</i> =.70	<i>P</i> =.40	<i>P</i> =.13	<i>P</i> =.32 <i>R</i> ² =.028	<i>P</i> =.61 <i>R</i> ² =.021
MUST ≥ 1 (at risk of malnutrition) (6) vs MUST =0 (33)	<i>P</i>=.042	<i>P</i>=.035	<i>P</i> =.13	<i>P</i> =.37	<i>P</i> =.058 <i>R</i> ² =.036	<i>P</i> =.85 <i>R</i> ² =.014
SSc-ILD (19) vs. no SSc-ILD (20)	<i>P</i> =.98	<i>P</i> =.91	<i>P</i> =.73	<i>P</i> =.69	<i>P</i> =.16 <i>R</i> ² =.037	<i>P</i> =.37 <i>R</i> ² =.027
SSc-PAH (6) vs. no SSc-PAH (33)	<i>P</i> =.56	<i>P</i> =.91	<i>P</i> =.66	<i>P</i> =.58	<i>P</i> =.58 <i>R</i> ² =.025	<i>P</i> =.84 <i>R</i> ² =.015
SSc-ulcers (17) vs. no SSc-ulcers (22)	<i>P</i> =.92	<i>P</i> =.45	<i>P</i> =.31	<i>P</i> =.38	<i>P</i> =.16 <i>R</i> ² =.031	<i>P</i> =.35 <i>R</i> ² =.028



Supplementary Fig. S1. Cumulative error rates by random forests classification and random forests classification performance (table). The overall error rate is shown as the red line; the red and green lines represent the error rates for each class.

Reference

1. KHANNA D, HAYS RD, MARANIAN P *et al.*: Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. *Arthritis Rheum* 2009; 61: 1257-63.