Supplementary material

Supplementary Table 1: The Mainz Severity Score Index, a clinical scoring system used to determine the severity of the signs and symptoms of Fabry disease

General score			**Neurological score**		
Sign/symptom	**Rating**	**Score**	**Sign/symptom**	**Rating**	**Score**
Characteristic facial appearance	No	0	Tinnitus	No	0
	Yes	1		Mild	1
Angiokeratoma	None	0		Severe	2
	Some	1	Vertigo	No	0
	Extensive	2		Mild	1
Oedema	No	0		Severe	2
	Yes	1	Acroparaesthesia	No	0
Musculoskeletal	No	0		Occasional	3
	Yes	1		Chronic	6
Cornea verticillata	No	0	Fever pain crisis	No	0
	Yes	1		Yes	2
Diaphoresis	Normal	0	Cerebrovascular	No	0
	Hypo/hyper	1		Ischaemic lesions (in MRI/CT)	1
	Anhidrosis	2		TIA/migraine etc.	3
Abdominal pain	No	0		Stroke	5
	Yes	2	**Psychiatric/psychosocial**		
Diarrhoea/constipation	No	0	Depression	No	0
	Yes	1		Yes	1
Haemorrhoids	No	0	Fatigue	No	0
	Yes	1		Yes	1
Pulmonary	No	0	Reduced activity level	No	0
	Yes	2		Yes	1
New York Heart Association (NYHA) classification*	No	0			
	Class I	1			
	Class II	2			
	Class III	3			
	Class IV	4			
Maximum score		**18**	**Maximum score**		**20**
Cardiovascular score			**Renal score**		
Changes in cardiac muscle thickness	No	0	Evidence of renal dysfunction	No proteinuria	0
	Thickening of wall/septum	1		Proteinuria	4
	LVH seen on ECG	6		Tubular dysfunction/low	8

				GFR or creatinine clearance	
	Cardiomyopathy (< 15 mm)	8		End-stage renal failure (serum creatinine levels > 3.5 mg/dl)	12
	Severe cardiomyopathy (> 15 mm)	12		Dialysis	18
Valve insufficiency	No	0			
	Yes	1			
ECG abnormalities	No	0			
	Yes	2			
Pacemaker	No	0			
	Yes	4			
Hypertension	No	0			
	Yes	1			
Maximum score		**20**	**Maximum score**		**18**

*Limitation on physical activity: Class I, none. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain but shows heart involvement in the echocardiogram; Class II, slight. Comfortable at rest, but ordinary physical activity results in fatigue. Class III, marked. Comfortable at rest, but less than ordinary physical activity causes fatigue; Class IV, unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. Physical activity increases discomfort. MRI, magnetic resonance imaging; CT, computed tomography; TIA, transient ischemic attack; LVH, left ventricular hypertrophy; ECG, electrocardiography; GFR, glomerular filtration rate.

Supplementary Table 2: *GLA* gene pathogenic variants and α-galactosidase A enzyme activity at time of diagnosis in the National Danish Fabry Cohort

Amino acid change		Nucleotide change	Phenotype	n = 86
Missense				
p.Gly85Asp	G85D	c.254G>A	Classic	19 (22)
p.Arg112Cys	R112C	c.334C>T	Classic	13 (15)
p.Ala156Thr	A156T	c.466G>A	Classic	12 (14)
p.Asn34Ser	N34S	c.101A>G	Classic	8 (9)
p.Ile232Thr	I232T	c.695T>C	Likely classic	6 (7)
p.Gly271Ser	G271S	c.811G>A	Classic	4 (5)
p.Asn355Lys	N355K	c.1065C>A	Classic	2 (2)
p.Gly261Asp	G261D	c.782G>A	Classic	2 (2)
p.Ser297Phe	S297F	c.890C>T	Classic	2 (2)
p.Trp236Cys	W236C	c.708G>C	Classic	2 (2)
p.Gly171Ser	G171S	c.511G>A	Late-onset	2 (2)
p.Ile317Thr	I317T	c.950T>C	Classic	1 (1)
p.Ser276Asn	S276N	c.827G>A	Classic	1 (1)
Nonsense				
p.Arg342Ter	R342*	c.1024C>T	Classic	3 (3)
p.Arg227Ter	R227*	c.679C>T	Classic	2 (2)
p.Arg301Ter	R301*	c.901C>T	Classic	1 (1)
Other				
p.Phe295Leufs*22		c.885del	Not investigated[x]	3 (3)
Deletion-frameshift				
Deletion-insertion		c.369+3_c.547+954del4096insT	Classic	1 (1)
Large_del		c.999+1del	Not investigated[x]	1 (1)
Splice site deletion exon 6 skipping		c.195-? 801 + ?del	Not investigated[x]	1 (1)
α-galactosidase A (nmol/h/mg protein)[y]				
Female		11 [1.6 – 19]		
Male		1.7 [0.3 – 11]		

Frequency (%) or median [range].
n, number of patients; not investigated[x], no available data in the International Fabry Disease Genotype-Phenotype Database (dbFGP) (http://dbfgp.org/dbFgp/fabry/) nor in the http://fabry-database.org; [y], measured in leucocytes, reference range: 20-65 nmol/h/mg protein.

Supplementary table 3: A summary of cohort studies on pulmonary involvement in Fabry disease in chronological order

Authors, year of publ. and ref. no.	No. of patients	Methods	Control group	Follow-up	Outcome
Bartimmo et. al., 1972 (17)	3 males	Spirometry, Chest x-ray, smoking history (pack-years), biochemistry and pulmonary scintigraphy	No	No	No clinical or laboratory evidence of primary pulmonary dysfunction. No pulmonary dysfunction in 1 out of 3 patients. Pulmonary abnormalities present in 2 out of 3 patients were related to prior illnesses such as pectus excavatum and left ventricular failure.
Brown et. al., 1997 (18)	25 males	Spirometry, smoking history, biochemistry, chest x-ray, methacholine challenge testing, and radionuclide scan	No	No	36% had dyspnoea and 24% had cough and/or wheezing. 36% had airway obstruction primarily associated with age and dyspnoea or wheezing, weakly associated with smoking.
Rosenberg et. al., 2000 (15)	7 (6 males, 1 female)	Spirometry, chest x-ray, smoking history (pack-years), biochemistry, bronchoscopy and ventilation and perfusion scan	No	No	All patients had airway obstruction, worse in patients who smoked. Bronchoscopy showed that airway epithelial cells contained inclusion bodies.
Bierer et. al., 2005 (19)	39 (15 males, 24 females)	Spirometry, ECG, non-invasive cardiopulmonary exercise test and echocardiogram	Yes	No	18 out of 39 Fabry patients (46%) had significant decrease in diastolic blood pressure during exercise. None of the control patients had a significant decrease in diastolic

					blood pressure during exercise.
Bierer et. al., 2006 (20)	21 (6 in RCT)	Spirometry, ECG, cardiopulmonary exercise test and physical examination	6 patients were randomized 2:1 to receive either placebo or ERT	Cardiopulmonary exercise test every 3 months over a period of at least 18 months	3 patients had mild airway obstruction, 1 had severe airway obstruction, 2 had decreased FVC and 1 had restrictive ventilatory defect. None had a diffusion capacity less than 75%. Patients receiving ERT compared to placebo had increased exercise tolerance.
Aubert et. al., 2006 (21)	67 (from the Fabry Outcome Survey)	Spirometry and smoking history (active, past, or never smokers)	No	No	23 out of 67 patients (34%) had airway obstruction, exceeding the prevalence in the general adult population.
Magage et. al., 2007 (22)	50	Spirometry and bronchodilatory test.	Yes	39 were longitudinal follow-ups over a period of 24 months	61% of males and 26% of females had mild to severe airway obstruction. Significant age-dependent reduction in %FVC and $\%FEV_1$ in males. In both males and females $\%FEF_{25-75}$ decreased by similar degree.
Wang et. al., 2007 (23)	44 females	Spirometry, ECG, non-invasive exercise test, biochemistry, cerebral MRI and questionnaire on symptoms, pain, and quality of daily living	No	No	All patients had reduced quality of life. Cardiopulmonary, renal system and central/peripheral nervous manifestations for Fabry disease were present far above predicted for random X-inactivation of the normal allele.
Sorbello et.	2 males	Spirometry and 3-	No	Respectively at 52	Standard

al., 2008 (24)		lead ECG in connection with anaesthesia		months and 13 months	anaesthesiological protocol for kidney transplant was used. Both patients had uneventful awakening after uncomplicated surgery and restored renal function on day 2 and 3 posttransplant with no need for dialysis.
Havndrup et. al., 2010 (25)	3 probands	Spirometry, ECG, echocardiogram, and genetic analysis	No	No	Genetic testing is needed in females to diagnose Fabry disease, as they can have normal measured enzyme activity. Enzyme measurements in males are sufficient to diagnose Fabry disease, as they have severely reduced or almost absent enzyme activity.
Koskenvuo et. al., 2010 (26)	17 (6 males, 11 females)	Spirometry, ECG, bicycle stress test, pulmonary HRTC, cardiac MRI, and questionnaire on lifestyle and symptoms	No	No	LVH and reduced exercise capacity were the most apparent cardiac changes, with little association to cardiopulmonary symptoms. Spirometry showed small reduction in vital capacity and FEV_1. Slightly morphological pulmonary changes detected by HRTC, were not associated with changes in pulmonary function.
Duning et. al., 2013 (3)	23 (12 males, 11 females)	Echocardiogram, cerebral MRI, polysomnography, and electro-neurography	Yes	No	5 out of 23 patients had CSA-CSR. The severity of central sleep apnoea correlated with the severity of structural brainstem

					damage. Fabry disease patients had widespread structural changes compared to healthy controls.
Odler et. al., 2015 (27)	7 patients and 4 carriers	Pulmonary function test, ECG, biochemistry, smoking history, chest X-ray, physical examination, and questionnaire about respiratory symptoms	Yes	5 patients on ERT had an average longitudinal follow-up of 5 years	Mild symptoms related to non-reversible obstructive ventilatory lung disorder. Follow-up showed stabilization of airway obstruction using ERT in 4 out of 5 patients.
Franzen et. al., 2015 (5)	52 (17 males, 35 females)	Respiratory polygraphy, questionnaire about sleep propensity, echocardiogram, biochemistry, and PHQ-9	No	No	Sleep-disordered breathing, especially obstructive sleep apnoea, is highly prevalent in Fabry patients. Excessive daytime sleepiness is related with depression rather than sleep-disordered breathing in Fabry patients.
Franzen et. al., 2017 (28)	95	Pulmonary function test and smoking history (pack-years)	No	Yearly pulmonary function test from 1999 to 2015	46% had bronchial obstruction with age, smoking and male sex as significant predicters. FEV_1 declined significantly in males and patients receiving ERT.
Franzen et. al., 2018 (4)	53	Pulmonary function test, smoking history (pack-years), and biochemistry	No	Yearly pulmonary function test from 1999 to 2015	The greatest decrease of FEV_1/FVC z-score was observed in classic males compared with later-onset males and later-onset females. After initiation of ERT the FEV_1/FVC z-

		score decrease was significantly reduced. Late ERT initiation and smoking were independently associated with faster FEV_1 decline.

ECG, electrocardiogram; ERT, enzyme replacement therapy; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first-second; FEF_{25-75}, forced expiratory flow at 25 and 75% of the pulmonary volume; MRI, magnetic resonance imaging; HRCT, high-resolution CT; LVH, left ventricular hypertrophy; CSA-CSR, central sleep apnoea with Cheyne-Strokes respiration; PHQ-9, patient health questionnaire-9 for depression; FEV_1/FVC ratio, forced expiratory volume in the first-second divided by forced vital capacity.