

Supplementary Table 1. Baseline characteristics.

	Classic males	Classic females	Later-Onset males	Later-Onset females
	N=21	N=36	N=5	N=4
<i>Clinical and biochemical characteristics</i>				
Serum Lyso-Gb3 (ng/ml), median (range)	52 (25–118)	10 (5.2–27)	7.5 (2.0 –17)	3.3 (0.8–5.2)
Age (years), median (range)	50 (22–73)	44 (23–74)	53 (47–74)	49 (39–79)
On ERT, n (%)	21 (100)	24 (67)	4 (80) ¹	1 (25)
Mutation Type:				
Missense, n (%)	13 (61)	21 (58)	5 (100)	4 (100)
Deletions, n (%)	5 (24)	6 (16)	0 (0)	0 (0)
Nonsense, n (%)	0 (0)	2 (6)	0 (0)	0 (0)
Duplication, n (%)	1 (5)	5 (14)	0 (0)	0 (0)
Splicing mutation, n (%)	2 (10)	2 (6)	0 (0)	0 (0)

Early-onset signs and symptoms				
Neuropathic pain, n (%)	20 (95)	25 (69)	0 (0)	0 (0)
Hypohidrosis, n (%)	21 (100)	10 (28)	0 (0)	0 (0)
Angiokeratoma, n (%)	17 (81)	9 (25)	0 (0)	0 (0)
Cornea verticillata, n (%)	18 (86)	27 (75)	0 (0)	0 (0)
Later-onset disease complications				
Kidney				
Serum creatinine (μmol/l), median (range)	150 (69–1181)	68 (43–97)	98 (90–233)	64 (55–110)
Urine protein/creatinine ratio ² (mg/mmol), median (range)	28 (7–256)	9 (bld–256)	48 (7–178)	5 (bld–57)
On RRT ³ , n (%)	7 (33)	0 (0)	0 (0)	0 (0)
Heart				

LVMMI (g/m2), median (range)	105 (49–299)	73 (42–199)	105 (49–186)	64 (39–114)
Brain				
History of stroke, n (%)	3 (14)	6 (17)	1 (20)	0 (0)

¹ One patient was untreated due to malcompliance.

² Patients on renal replacement were excluded from this analysis

³ Chronic dialysis: n=2; kidney transplant: n=5

Abbreviations: bld, below limit of detection; LVMMI, left ventricular myocardial mass index; NT-proBNP, N-terminal pro brain natriuretic peptide; RRT, renal replacement therapy.

Supplementary Table 2. Detailed baseline demographical and biochemical characteristics.

A. Classic Males

Age	GLA Mutation	Predicted Enzyme Protein Change	Serum Lyso-Gb3 Level (ng/ml)
56	Deletion exon 2 (g2962, g5871)		115.0
29	c.125T>C	p.M42T	39.0
41	c.125T>C	p.M42T	35.3
42	c.370-2A>G (<u>IVS2-2A>G</u>)	Functional null allele due to splice site mutation	36.8
50	c.370-2A>G (<u>IVS2-2A>G</u>)	Functional null allele due to splice site mutation	57.6
60	c.581C>T	p.T194I	41.0
73	c.581C>T	p.T194I	46.1
57	c.581C>T	p.T194I	40.0
42	c.581C>T	p.T194I	40.4

34	c.679C>T	p.R227X	57.5
22	c.744_745delTA	p.F248LfsX7	95.5
50	c.744_745delTA	p.F248LfsX8	92.2
54	c.744_745delTA	p.F248LfsX8	74.8
45	c.827G>A	p.S276N	45.6
61	c.899T>A	p.L300H	83.0
59	c.899T>A	p.L300H	40.1
45	c.1033T>C	p.S345P	24.7
65	c.1033T>C	p.S345P	52.3
60	c.1033T>C	p.S345P	55.2
35	c.1055_1057dupCTA	p.A352_M353insT	71.7
33	c.1147_1149delTTC	p.F383del	118.0

B. Classic Females

Age	GLA Mutation	Predicted Enzyme Protein Change	Serum Lyso-Gb3 Level (ng/ml)
54	c.72G>A	p.W24X	13.5
44	c.125T>C	p.M42T	7.3
35	c.125T>C	p.M42T	7.5
31	c.125T>C	p.M42T	8.6
37	c.125T>C	p.M42T	8.0

42	c.154T>C	p.C52R	5.9
54	c.365delA	p.N122IfsX8	23.1
71	c.370-2A>G (<u>IVS2-2A>G</u>)	Functional null allele due to splice site mutation	14.4
69	c.514T>C	p.C172R	9.3
74	c.581C>T	p.T194I	26.8
40	c.581C>T	p.T194I	8.3
71	c.581C>T	p.T194I	17.8
38	c.581C>T	p.T194I	6.1
45	c.581C>T	p.T194I	10.1
69	c.581C>T	p.T194I	12.0
43	c.581C>T	p.T194I	9.7
47	c.640-3C>G (<u>IVS4-3C>G</u>)	Functional null allele due to splice site mutation	10.0
35	c.704C>A	p.S235Y	8.2
26	c.744_745delTA	p.F248LfsX7	7.9
45	c.744_745delTA	p.F248LfsX7	5.2

70	c.744_745delTA	p.F248LfsX7	8.6
62	c.796G>T	p.D266T	8.9
61	c.796G>T	p.D266T	15.9
42	c.901C>T	p.R301X	10.7
48	c.1033T>C	p.S345P	7.8
57	c.1033T>C	p.S345P	16.5
34	c.1033T>C	p.S345P	13.6
29	c.1033T>C	p.S345P	7.0
31	c.1055_1057dupCTA	p.A352_M353insT	10.6
31	c.1147_1149delTTC	p.F383del	7.2
41	c.1167dupT	p.V390CfsX9	23.6
57	c.1167dupT	p.V390CfsX9	9.9
23	c.1167dupT	p.V390CfsX9	10.1
74	c.1167dupT	p.V390CfsX9	16.1
30	c.1167dupT	p.V390CfsX9	7.6
36	c.1235_1236delCT	p.N122IfsX8	12.6

C. Later-Onset Males

Age	GLA Mutation	Predicted Enzyme Protein Change	Serum Lyso-Gb3 Level (ng/ml)
53	c.613C>T	p.P205S	17.2

69	c.644A>G	p.N215S	5.3
51	c.902G>A	p.R301Q	7.5
74	c.902G>A	p.R301Q	11.5
47	c.1196G>C	p.W399S	2.0

D. Later-Onset Females

Age	GLA Mutation	Predicted Enzyme Protein Change	Serum Lyso-Gb3 Level (ng/ml)
39	c.337T>C	p.F113L	1.6
54	c.870G>C	p.M290I	0.8
43	c.902G>A	p.R301Q	5.2
79	c.902G>A	p.R301Q	4.9

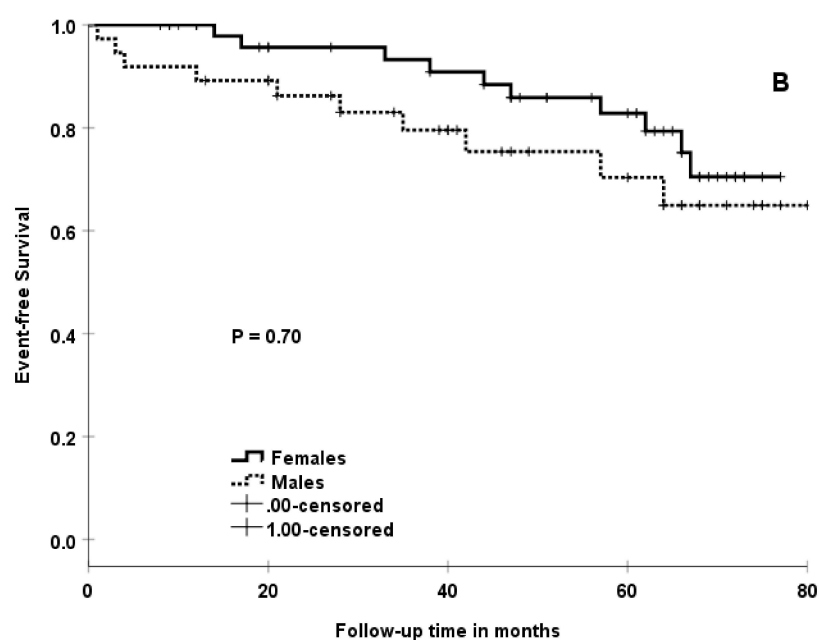
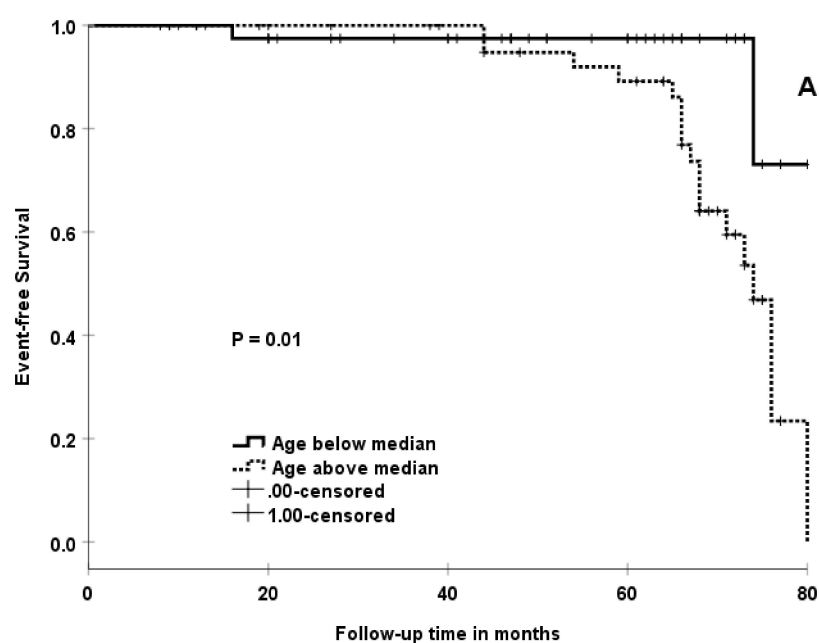
Supplementary Table 3. Detailed summary of clinical events occurred during the observational period.

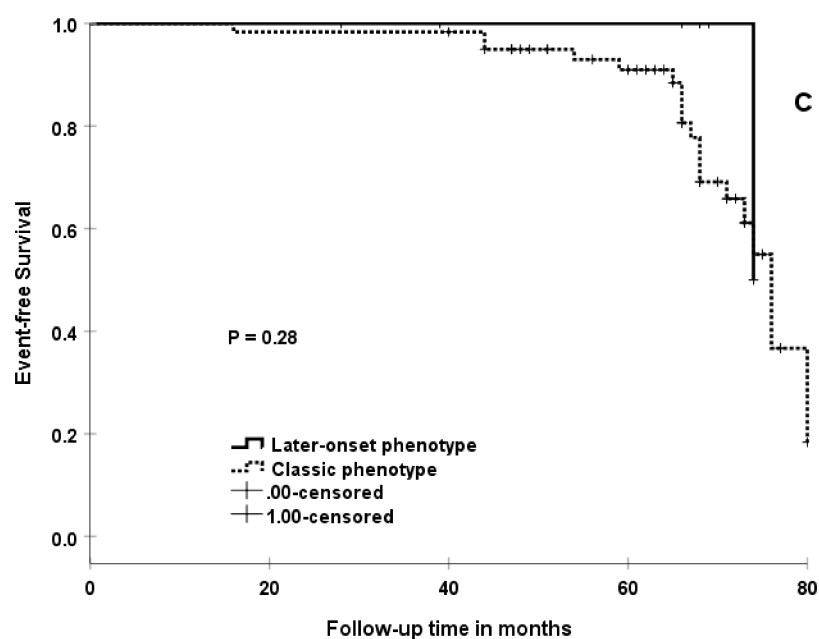
Event	Number of patients suffering the first event	Number of events
Pacemaker and/or ICD implantation*	7	7
New-onset of Atrial fibrillation	3	3
kidney transplantation	1	1
chronic dialysis requirement	1	1
stroke	1	3
myocardial infarction	1	1
death	5	5
	Total 19	Total 21

* Due to:

- high-degree atrioventricular block: n=3
- primary prophylaxis in high-degree myocardial hypertrophy and fibrosis: n=4

Supplementary Figure 1. Time to first complication in Fabry patients according to age (A), sex (B) and phenotype (C).*





*The diagram shows the results of Kaplan-Meier analysis and log-rank test of survival distributions equality.