Supplementary Information

Insights into the dynamics of lyso-Gb1 accumulation in untreated patients with Gaucher disease type 1 in LYSO-PROOF study

A comprehensive list of all detected *GBA1* variants in the LYSO-PROOF study is provided in Table S1.

Table S1. Individual variants/alleles

No.	cDNA	allele	n	frequency in %
1	c.1226A>G	p.(Asn409Ser)	175	54.7
2	c.1448T>C	p.(Leu483Pro)	21	6.6
3	c.1603C>T	p.(Arg535Cys)	10	3.1
4	c.1342G>C	p.(Asp448His)	8	2.5
5	c.259C>T	p.(Arg87Trp)	8	2.5
6	c.1171G>A	p.(Val391Met)	8	2.5
7	c.1184C>T	p.(Ser395Phe)	8	2.5
8	c.1060G>A	p.(Asp354Asn)	6	1.9
9	c.479T>C	p.(Val160Ala)	6	1.9
10	c.667T>C	p.(Trp223Arg)	5	1.6
11	c.1177C>G	p.(Leu393Val)	4	1.3
12	c.1297G>T	p.(Val433Leu)	4	1.3
13	c.352A>G	p.(Lys118Glu)	4	1.3
14	c.84dupG	p.(Leu29Alafs*18)	4	1.3
15	c.1193G>A	p.(Arg398Gln)	3	0.9
16	c.371T>C	p.(Met124Thr)	3	0.9
17	c.1111C>A	p.(Pro371Thr)	2	0.6
18	c.1304A>C	p.(Asn435Thr)	2	0.6
19	c.475C>T	p.(Arg159Trp)	2	0.6
20	c.1296G>T	p.(Trp432Cys)	2	0.6
21	c.1300C>T	p.(Arg434Cys)	2	0.6
22	c.1316G>C	p.(Ser439Thr)	2	0.6
23	c.1331A>T	p.(Asp444Val)	2	0.6
24	c.1224G>A	p.((=))	2	0.6
25	c.1574G>A	p.(Gly525Asp)	2	0.6
26	c.1604G>A	p.(Arg535His)	2	0.6
27	c.253G>A	p.(Gly85Arg)	2	0.6
28	c.252_257dup	p.(Gly85_Arg86dup)	2	0.6
29	c.43_66del24bp	p.(Leu15_Ala22del)	2	0.6
30	c.786C>G	p.(Phe266Leu)	2	0.6
31	c.847T>C	p.(Tyr283His)	2	0.6
32	c.470_482delinsA	p.(Ile157_Pro161delinsAsn)	1	0.3
33	c.485T>C	p.(Met162Thr)	1	0.3
34	c.496G>T	p.(Asp166Tyr)	1	0.3
35	c.721G>A	p.(Gly241Arg)	1	0.3
36	c.849C>A	p.(Tyr283*)	1	0.3
37	c.544C>T	p.(Gln182*)	1	0.3

38	c.971G>A	p.(Arg324His)	1	0.3
39	c.222_224del	p.(Thr75del)	1	0.3
40	c.254G>A	p.(Gly85Glu)	1	0.3
41	c.653G>A	p.(Trp218*)	1	0.3
42	c.990G>A	p.(Trp330*)	1	0.3
43	c.492C>G	p.(Ser164Arg)	1	0.3
44	c.680A>G	p.(Asn227Ser)	1	0.3
total			320	100

A comprehensive list of all *GBA1* genotypes identified in the LYSO-PROOF study is provided in Table S2 including references for classification.

Table S2. Genotypes (at cDNA and protein level)

No.	genotype	n	frequency in %	classification and reference
1	c.1226A>G p.(Asn409Ser) homozygous	66	41.2	1 [1,2]
2	c.1226A>G p.(Asn409Ser) / c.1448T>C p.(Leu483Pro)	13	8.1	1 [1,2]
3	c.1226A>G p.(Asn409Ser) / c.1342G>C p.(Asp448His)	6	3.8	1 [1,2]
4	c.1603C>T p.(Arg535Cys) homozygous	5	3.1	-
5	c.1171G>A p.(Val391Met) homozygous	4	2.5	-
6	c.1226A>G p.(Asn409Ser) / c.1297G>T p.(Val433Leu)	4	2.5	1 [1,2]
7	c.1226A>G p.(Asn409Ser) / c.667T>C p.(Trp223Arg)	4	2.5	1 [1,2]
8	c.1060G>A p.(Asp354Asn) homozygous	3	1.9	-
9	c.1184C>T p.(Ser395Phe) homozygous	3	1.9	-
10	c.1226A>G p.(Asn409Ser) / c.84dupG p.(Leu29Alafs*18)	3	1.9	1 [1,2]
11	c.1448T>C p.(Leu483Pro) / c.259C>T p.(Arg87Trp)	3	1.9	-
12	c.479T>C p.(Val160Ala) homozygous	3	1.9	-
13	c.1177C>G p.(Leu393Val) homozygous	2	1.3	1 ClinVar
14	c.1226A>G p.(Asn409Ser) / c.1304A>C p.(Asn435Thr)	2	1.3	1 [1,2]
15	c.1226A>G p.(Asn409Ser) / c.475C>T p.(Arg159Trp)	2	1.3	1 [1,2]
16	c.1300C>T p.(Arg434Cys) / c.1342G>C p.(Asp448His)	2	1.3	-
17	c.1448T>C p.(Leu483Pro) / c.1224G>A p.((=))	2	1.3	-
18	c.259C>T p.(Arg87Trp) homozygous	2	1.3	1 ClinVar
19	c.352A>G p.(Lys118Glu) homozygous	2	1.3	-
20	c.1111C>A p.(Pro371Thr) homozygous	1	0.3	-
21	c.1184C>T p.(Ser395Phe) / c.1226A>G p.(Asn409Ser)	1	0.3	1 [1,2]
22	c.1184C>T p.(Ser395Phe) / c.1448T>C p.(Leu483Pro)	1	0.3	-
23	c.1193G>A p.(Arg398Gln) homozygous	1	0.3	1 [3]
24	c.1193G>A p.(Arg398Gln) / c.1448T>C p.(Leu483Pro)	1	0.3	-
25	c.1226A>G p.(Asn409Ser) / c.371T>C p.(Met124Thr)	1	0.3	1 [1,2]
26	c.1226A>G p.(Asn409Ser) / c.470_482delinsA p.(Ile157_Pro161delinsAsn)	1	0.3	1 [1,2]
27	c.1226A>G p.(Asn409Ser) / c.485T>C p.(Met162Thr)	1	0.3	1 [1,2]
28	c.1226A>G p.(Asn409Ser) / c.496G>T p.(Asp166Tyr)	1	0.3	1 [1,2]

29	c.1226A>G p.(Asn409Ser) / c.721G>A p.(Gly241Arg)	1	0.3	1 [1,2]
30	c.1226A>G p.(Asn409Ser) / c.849C>A p.(Tyr283*)	1	0.3	1 [1,2]
31	c.1226A>G p.(Asn409Ser) / c.544C>T p.(Gln182*)	1	0.3	1 [1,2]
32	c.1226A>G p.(Asn409Ser) / c.971G>A p.(Arg324His)	1	0.3	1 [1,2]
33	c.1296G>T p.(Trp432Cys) homozygous	1	0.3	-
34	c.1316G>C p.(Ser439Thr) homozygous	1	0.3	-
35	c.1331A>T p.(Asp444Val) homozygous	1	0.3	-
36	c.1448T>C p.(Leu483Pro) / c.222_224del p.(Thr75del)	1	0.3	-
37	c.1574G>A p.(Gly525Asp) homozygous	1	0.3	-
38	c.1604G>A p.(Arg535His) / c.84dupG p.(Leu29Alafs*18)	1	0.3	-
39	c.1604G>A p.(Arg535His) / c.990G>A p.(Trp330*)	1	0.3	-
40	c.252_257dup p.(Gly85_Arg86dup) homozygous	1	0.3	-
41	c.253G>A p.(Gly85Arg) homozygous	1	0.3	-
42	c.254G>A p.(Gly85Glu) / c.492C>G p.(Ser164Arg)	1	0.3	-
43	c.259C>T p.(Arg87Trp) / c.653G>A p.(Trp218*)	1	0.3	-
44	c.371T>C p.(Met124Thr) homozygous	1	0.3	-
45	c.43_66del24bp p.(Leu15_Ala22del) homozygous	1	0.3	-
46	c.667T>C p.(Trp223Arg) / c.680A>G p.(Asn227Ser)	1	0.3	-
47	c.786C>G p.(Phe266Leu) homozygous	1	0.3	-
48	c.847T>C p.(Tyr283His) homozygous	1	0.3	-
total		160	100	

References:

1. Grabowski GA, Zimran A, Ida H. Gaucher disease types 1 and 3: Phenotypic characterization of large populations from the ICGG Gaucher Registry. *Am J Hematol* 2015;90 Suppl 1:S12-8. doi: 10.1002/ajh.24063 [published Online First: 2015/06/23]
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3. Mozafari H, Tghikhani M, Rahimi Z, et al. Analysis of glucocerebrosidase (GBA) gene mutations in Iranian patients with Gaucher disease. *Iran J Child Neurol* 2021;15(3):139-66. doi: 10.22037/ijcn.v15i4.23834 [published Online First: 2021/07/21]

A comprehensive list regarding the frequency of the indicated clinical symptoms for all, type 1, mild type 1, severe type 1, and not classified patients in the LYSO-PROOF study is provided in Table S3.

Table S3. Frequency of presence of indicated clinical symptoms

	Condition present				
Clinical symptoms	**All patients N = 160**	**Type 1 N = 114**	**Mild type 1 N = 66**	**Severe Type 1 N = 48**	**Not classified N = 46**
	(%) N present/N total	(%) N present/N total	(%) N present/N total	(%) N present/N total	(%) N present/N total
Splenomegaly	(75.0) 117/156	(68.8) 77/112	(54.5) 36/66	(62.1) 41/46	(90.9) 40/44
Thrombocytopenia	(74.4) 116/156	(74.1) 83/112	(68.2) 45/66	(82.6) 38/46	(75.0) 33/44
Hepatomegaly	(62.4) 98/157	(53.6) 60/112	(39.4) 26/66	(73.9) 34/46	(84.4) 38/45

Anemia	(56.3) 89/158	(53.1) 60/113	(39.4) 26/66	(72.3) 34/47	(64.4) 29/45
Gaucher cells in Bone Marrow	(75.8) 75/99	(71.4) 45/63	(59.4) 19/32	(83.9) 26/31	(83.3) 30/36
Erlenmeyer flask' deformity of femur	(28.7) 43/150	(32.4) 34/105	(21.5) 14/65	(50.0) 20/40	(20.0) 9/45
Bone pain	(24.7) 39/158	(29.2) 33/113	(25.8) 17/66	(34.0) 16/47	(13.3) 6/45
Pancytopenia	(20.5) 32/156	(18.8) 21/112	(16.7) 11/66	(21.7) 10/46	(25.0) 11/44
Dyspnea	(6.9) 11/158	(5.3) 6/113	(4.5) 3/66	(6.4) 3/47	(11.1) 5/45
Osteonecrosis	(10.8) 16/148	(15.2) 16/105	(9.2) 6/65	(25.0) 10/40	(0.0) 0/43
Bone crises	(8.4) 13/154	(9.1) 10/110	(4.6) 3/65	(15.6) 7/45	(6.8) 3/44
Osteolytic lesions	(6.1) 9/147	(7.7) 8/104	(7.8) 5/64	(7.5) 3/40	(2.3) 1/43
Avascular necrosis of femoral head	(6.5) 10/153	(8.3) 9/109	(3.1) 2/65	(15.9) 7/44	(2.3) 1/44
Pathologic fractures	(5.8) 9/156	(7.2) 8/111	(9.2) 6/65	(4.3) 2/46	(2.2) 1/45
Seizures	(1.9) 3/157	(0.0) 0/112	(0.0) 0/66	(0.0) 0/46	(6.7) 3/45
Vertebral compression	(2.7) 4/148	(3.8) 4/104	(1.6) 1/64	(7.5) 3/40	(0.0) 0/44
Interstitial lung disease	(0.7) 1/152	(0.0) 0/110	(0.0) 0/64	(0.0) 0/46	(2.4) 1/42
Monoclonal gammopathy	(1.3) 2/149	(1.9) 2/105	(1.5) 1/65	(2.4) 1/41	(0.0) 0/44
Pulmonary hypertension	0.7) 1/148	(1.0) 1/105	(1.5) 1/65	(0.0) 0/41	(0.0) 0/43
Corneal pathology	(1.4) 2/144	(1.0) 1/101	(0.0) 0/63	(2.6) 1/38	(2.3) 1/43
Multiple myeloma	(0.0) 0/157	(0.0) 0/113	(0.0) 0/66	(0.0) 0/47	(0.0) 0/44

The following collaborators contributed with the participants recruitment and data collection to the LYSO-PROOF study (Table S4). Only collaborators that are not listed as co-authors are listed in Table S4.

Table S4: LYSO-PROOF Study Group

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