Supplementary Table S1. Details of human fibroblasts used in this study.

Category	Identifier	Sex	Age	Genotype	Clinical features
Young	*GBA1*$^{wt/wt}_{55}$	Female	55	WT/WT	Apparently healthy
	GBA1$^{mut/mut\ GD}_{55}$	Male	55	N370S/ 1263del55	Type I Gaucher Disease
	GBA1$^{wt/mut\ PD}_{55}$	Female	55	WT/N370S	Parkinson Disease
	GBA1$^{wt/mut\ ASX}_{58}$	Male	58	WT/N370S	Non-manifesting carrier
	GBA1$^{wt/mut\ ASX}_{59}$	Female	59	WT/N370S	Non-manifesting carrier
Aged	*GBA1*$^{wt/wt}_{70}$	Female	70	WT/WT	Apparently healthy
	GBA1$^{wt/wt}_{78}$	Male	78	WT/WT	Apparently healthy
	GBA1$^{wt/mut\ PD}_{75}$	Female	75	WT/N370S	Parkinson Disease
	GBA1$^{wt/wt}_{82}$	Female	82	WT/WT	Apparently healthy
	GBA1$^{wt/mut\ ASX}_{80}$	Female	80	WT/N370S	Non-manifesting carrier

Fig. S1. Pathogenic *GBA1* disrupts ER and lysosomal Ca^{2+} content. Summary data quantifying area under the curve measurements in cells stimulated with thapsigargin (**A-B**) or GPN (**C**). **A**, Thapsigargin responses in fibroblasts upon *GBA1* mutation. Data are expressed as a percentage of the indicated age-matched control and correspond to experiments described in Figures 1-2. **B**, Thapsigargin responses upon β-glucocerebrosidase inhibition. Data from fibroblasts (left) or SHSY5Y cells (middle, right) are expressed as a percentage of control cells not treated with CBE or cells expressing scrambled shRNA ($GBA1^{+/+}$) and correspond to experiments described in Fig. 3. **C**, GPN responses in fibroblasts upon *GBA1* mutation or CBE treatment. Data are expressed as in B and correspond to experiments described in Fig. 5.

Fig. S2. Pathogenic *GBA1* disrupts lysosomal morphology. A-C, Representative confocal fluorescence images of LAMP2 staining (white) in $GBA1^{wt/wt}_{55}$, $GBA1^{mut/mut}_{55}{}^{GD}$ and $GBA1^{wt/mut}_{55}{}^{PD}$ cells. Nuclei were stained with DAPI (blue). Zoomed images are displayed in the right panels. Scale bars, 10 µm. **D-E**, Representative confocal fluorescence images of live $GBA1^{wt/wt}_{55}$ and $GBA1^{wt/mut}_{55}{}^{PD}$ cells labelled with Lysotracker red (100 nM, 15 min.). **F**, Summary data quantifying LAMP2 and Lysotracker intensity as a percentage of the control (48-130 cells). **G**, Western blot analysis using antibodies to LAMP1 (left) or LC3 (right) and homogenates prepared from $GBA1^{wt/wt}_{55}$, $GBA1^{mut/mut}_{55}{}^{GD}$ and $GBA1^{wt/mut}_{55}{}^{PD}$ cells (21 µg). Blots were stripped and re-probed using an antibody to actin (bottom panels). Migration of molecular mass markers (in kDa) is shown on the right of the panels. Migration of LC3II is highlighted. Blots are representative of those using 3 independent homogenate preparations.

Fig. S3. Effect of GPN on cytosolic Ca^{2+} and lysosome integrity. A, Cytosolic Ca^{2+} release from individual fibroblasts stimulated with GPN (200 µM) from a representative population of $GBA1^{wt/wt}_{55}$, $GBA1^{mut/mut}_{55}{}^{GD}$ and $GBA1^{wt/mut}_{55}{}^{PD}$ cells. **B,** Summary data quantifying percentage of cells that oscillated in response to GPN. Data are from 2 independent passages analysing 118-120 cells. **C**, Lysotracker red responses of fibroblasts (representative population average) stimulated with GPN (200 µM). **D**, Summary data quantifying the time taken to reach a half-maximal loss of Lysotracker red fluorescence (25-34 cells).

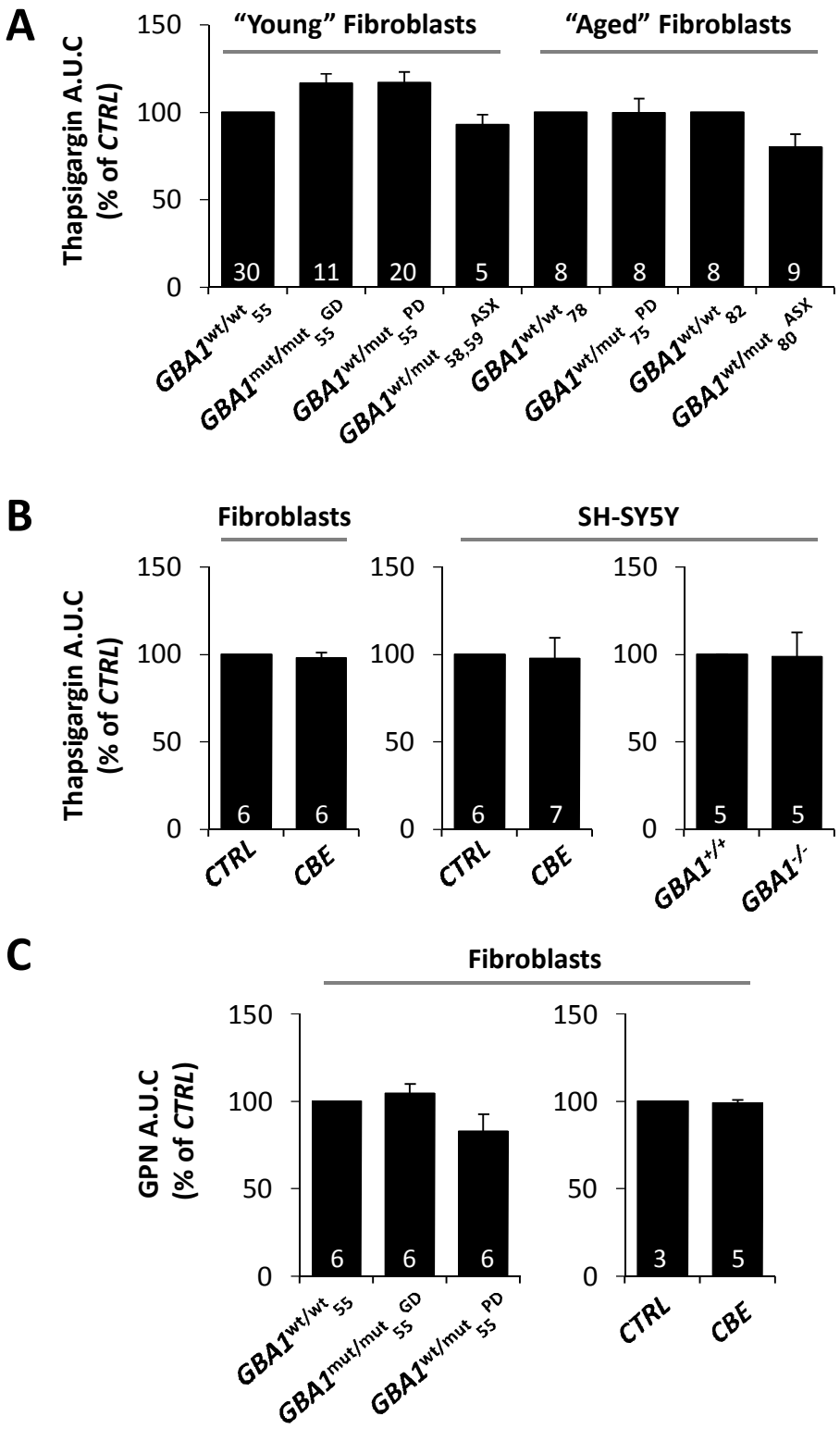
A
"Young" Fibroblasts
"Aged" Fibroblasts
Thapsigargin A.U.C
(% of CTRL)
150
100
50
0
30
11
20
5
8
8
8
9
GBA1wt/wt 55
GBA1mut/mut GD 55
GBA1wt/mut PD 55
GBA1wt/mut ASX 58,59
GBA1wt/wt 78
GBA1wt/mut PD 75
GBA1wt/wt 82
GBA1wt/mut ASX 80
B
Fibroblasts
SH-SY5Y
Thapsigargin A.U.C
(% of CTRL)
6
6
6
7
5
5
CTRL
CBE
CTRL
CBE
GBA1+/+
GBA1-/-
C
Fibroblasts
GPN A.U.C
(% of CTRL)
6
6
6
3
5
GBA1wt/wt 55
GBA1mut/mut GD 55
GBA1wt/mut PD 55
CTRL
CBE

Fig. S1.

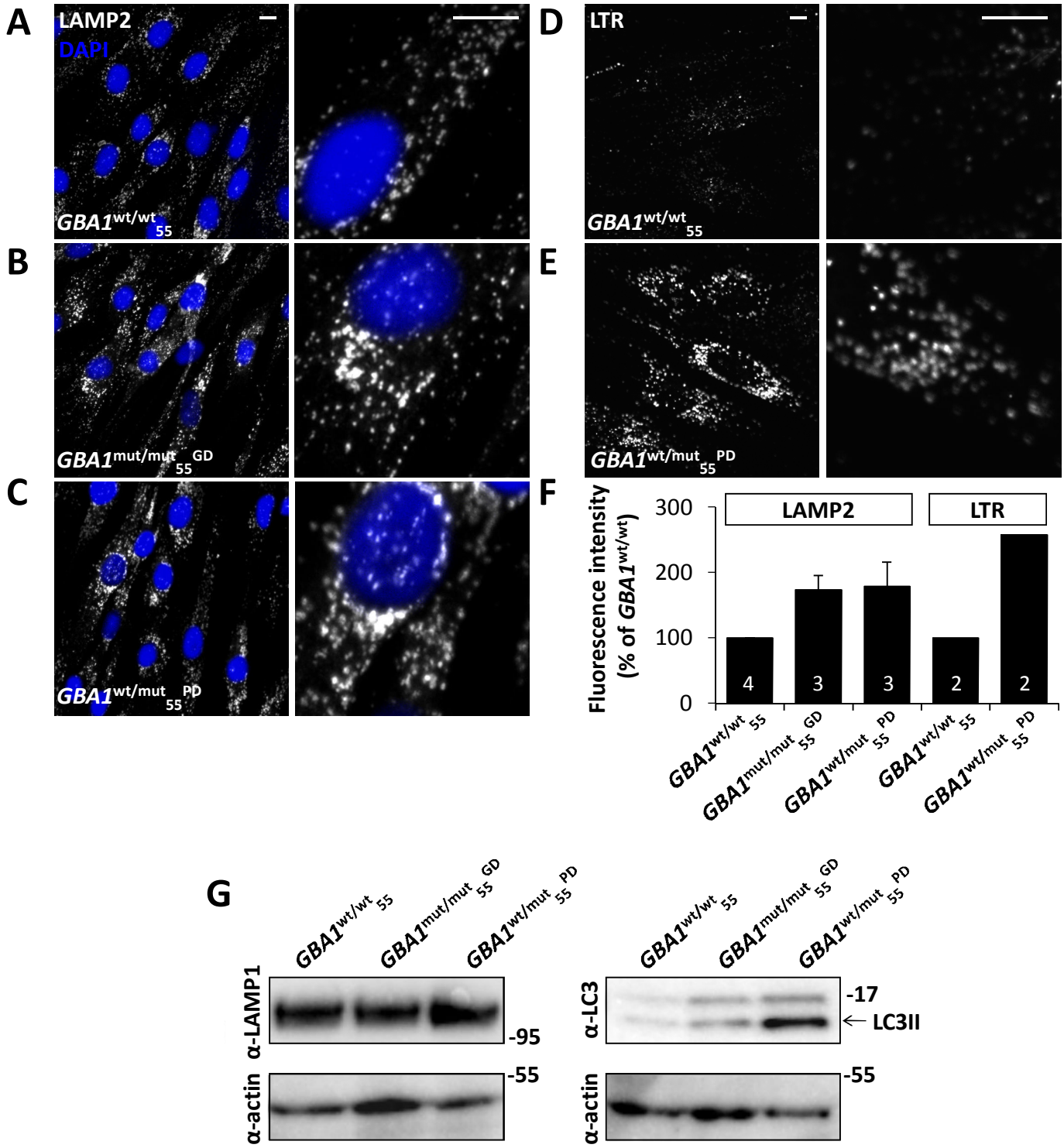
A
LAMP2
DAPI
GBA1wt/wt 55
B
GBA1mut/mut 55 GD
C
GBA1wt/mut 55 PD
D
LTR
GBA1wt/wt 55
E
GBA1wt/mut 55 PD
F
Fluorescence intensity (% of GBA1wt/wt)
300
200
100
0
LAMP2
LTR
4
3
3
2
2
GBA1wt/wt 55
GBA1mut/mut 55 GD
GBA1wt/mut 55 PD
GBA1wt/wt 55
GBA1wt/mut 55 PD
G
GBA1wt/wt 55
GBA1mut/mut 55 GD
GBA1wt/mut 55 PD
α-LAMP1
-95
α-actin
-55
GBA1wt/wt 55
GBA1mut/mut 55 GD
GBA1wt/mut 55 PD
α-LC3
-17
LC3II
α-actin
-55

Fig. S2.

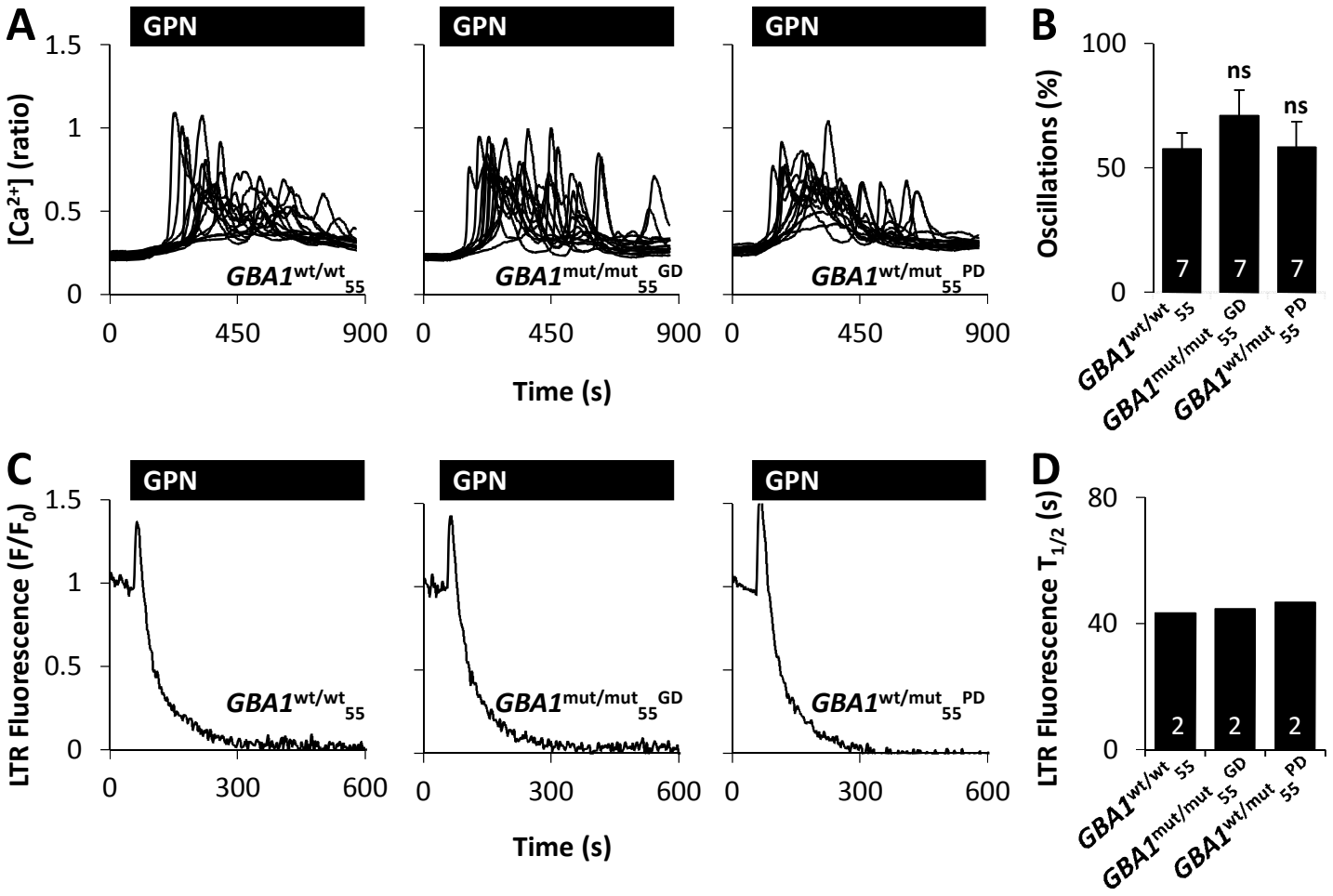
A
GPN
GPN
GPN
[Ca2+] (ratio)
1.5
1
0.5
0
0
450
900
GBA1wt/wt55
GBA1mut/mut55GD
GBA1wt/mut55PD
Time (s)
B
Oscillations (%)
100
50
0
ns
ns
7
7
7
GBA1wt/wt 55
GBA1mut/mut 55 GD
GBA1wt/mut 55 PD
C
GPN
GPN
GPN
LTR Fluorescence (F/F0)
1.5
1
0.5
0
0
300
600
GBA1wt/wt55
GBA1mut/mut55GD
GBA1wt/mut55PD
Time (s)
D
LTR Fluorescence T1/2 (s)
80
40
0
2
2
2
GBA1wt/wt 55
GBA1mut/mut 55 GD
GBA1wt/mut 55 PD

Fig. S3.