

Table S1. Sample Demographic data for human biosamples used in manuscript. Related to Figure S1 and STAR Methods section “Human biofluid sample collection”.

	Non-GRN Clinically Normal (N=20)	Non-GRN FTD (N=26)	GRN+ Clinically Normal (N=2)	GRN+ FTD (N=16)
Source				
NCRAD	20 (100%)	6 (23.1%)	0 (0%)	9 (56.2%)
UCSF	0 (0%)	20 (76.9%)	2 (100%)	7 (43.8%)
AGE_AT_ONSET				
45-49	0 (0%)	1 (3.8%)	0 (0%)	1 (6.2%)
55-59	0 (0%)	4 (15.4%)	0 (0%)	0 (0%)
70-74	0 (0%)	1 (3.8%)	0 (0%)	0 (0%)
50-54	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)
60-64	0 (0%)	0 (0%)	0 (0%)	5 (31.2%)
65-69	0 (0%)	0 (0%)	0 (0%)	2 (12.5%)
Missing	20 (100%)	20 (76.9%)	2 (100%)	7 (43.8%)
AGE_AT_VISIT				
45-49	1 (5.0%)	0 (0%)	0 (0%)	1 (6.2%)
50-54	5 (25.0%)	0 (0%)	0 (0%)	0 (0%)
55-59	6 (30.0%)	3 (11.5%)	0 (0%)	1 (6.2%)
60-64	6 (30.0%)	2 (7.7%)	0 (0%)	2 (12.5%)
65-69	2 (10.0%)	0 (0%)	0 (0%)	4 (25.0%)
75-79	0 (0%)	1 (3.8%)	0 (0%)	0 (0%)
70-74	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)
Missing	0 (0%)	20 (76.9%)	2 (100%)	7 (43.8%)
RACE				
White	20 (100%)	25 (96.2%)	2 (100%)	14 (87.5%)
Native Hawaiian or Pacific Islander	0 (0%)	1 (3.8%)	0 (0%)	0 (0%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)
Multiracial	0 (0%)	0 (0%)	0 (0%)	1 (6.2%)
DIAGNOSIS				
Clinically Normal	20 (100%)	0 (0%)	2 (100%)	0 (0%)
FTD	0 (0%)	26 (100%)	0 (0%)	16 (100%)
PHENOTYPE				
Clinically Normal	20 (100%)	0 (0%)	2 (100%)	0 (0%)
FTD	0 (0%)	24 (92.3%)	0 (0%)	7 (43.8%)
AD	0 (0%)	1 (3.8%)	0 (0%)	3 (18.8%)
MCI	0 (0%)	0 (0%)	0 (0%)	5 (31.2%)
Corticobasal syndrome	0 (0%)	1 (3.8%)	0 (0%)	1 (6.2%)
FAMILY_GENE				
NONE	20 (100%)	25 (96.2%)	0 (0%)	0 (0%)
MAPT	0 (0%)	1 (3.8%)	0 (0%)	0 (0%)
GRN	0 (0%)	0 (0%)	2 (100%)	16 (100%)

Table S2. PTV:PGRN variant sequences. Related to STAR Methods section “Engineering PTV variants with improved stability”.

Variant	Peptide sequence	[M+2H] ²⁺	RT (min)	AUC	%
QLL (wt, Expi293)	DPALRQLL	463.277	22.4	4.55e8	94.6
	DPALRQL	406.735	16.3	7.12e6	1.5
	DPALRQ	350.193	10.4	1.65e7	3.4
	DPALR	286.164	9.05	2.20e6	0.5
PIL (CHO-K1)	DPALRPIL	447.775	22.63	3.84e9	90.9
	DPALRPI	391.233	17.56	3.63e8	8.6
	DPALRP	334.691	13.02	1.76e7	0.4
	DPALR	286.164	9.05	3.46e6	0.1

Table S3. Stability of PTV:PGRN variants with the three C-terminal amino acids of PGRN (QLL) replaced with the corresponding amino acids from orthologous proteins. Related to STAR Methods section “Engineering PTV variants with improved stability”.

C-terminal PGRN sequence	Sequence database	Identifier	Expression cell line	% intact C-terminus
QLL (Homo sapiens)	NCBI	NM_002087	Expi293	95%
QLL (Homo sapiens)	NCBI	NM_002087	CHO-K1	7%
PIL (Latimeria chalumnae)	UniProtKB/ TrEMBL	H3AMW7	CHO-K1	91%
PFL (Xenopus tropicalis)	NCBI	NM_001078701	CHO-K1	87%
QQL (Pteropus vampyrus)	NCBI	XM_023521549	CHO-K1	59%
VVL (Electrophorus electricus)	NCBI	XP_035379781	CHO-K1	39%
VTL (Oreochromis niloticus)	UniProtKB/ TrEMBL	I3JXP4	CHO-K1	29%
LLL (Chinchilla lanigera)	NCBI	XM_005394531	CHO-K1	<1%
PLL (Mus musculus)	NCBI	NM_008175	CHO-K1	<1%
PRL (Cavia porcellus)	NCBI	XM_013148159	CHO-K1	<1%

Table S6: LC-MS acquisition parameters for the GlcCer/GalCer/GlcSph/GalSph assay.

Related to STAR Methods section “Analysis of GlcCer, GalCer, GlcSph, and GalSph”.

Lipid	Internal Standard	Q1 (m/z)	Q3 (m/z)	DP (V)	CE (V)
GlcCer(d18:1/16:0)	GlcCer(d18:1/16:0(d3))	700.6	264.3	45	45
GlcCer(d18:1/18:0)	GlcCer(d18:1(d5)/18:0)	728.6	264.3	45	45
GlcCer(d18:2/18:0)	GlcCer(d18:1(d5)/18:0)	726.6	262.3	45	45
GlcCer(d18:1/20:0)	GlcCer(d18:1(d5)/18:0)	756.6	264.3	45	45
GlcCer(d18:2/20:0)	GlcCer(d18:1(d5)/18:0)	754.6	262.3	45	45
GlcCer(d18:1/22:0)	GlcCer(d18:1(d5)/18:0)	784.7	264.3	45	45
GlcCer(d18:1/22:1)	GlcCer(d18:1(d5)/18:0)	782.7	264.3	45	45
GlcCer(d18:2/22:0)	GlcCer(d18:1(d5)/18:0)	782.7	262.3	45	45
GlcCer(d18:1/24:1)	GlcCer(d18:1(d5)/18:0)	810.7	264.3	45	45
GlcCer(d18:1/24:0)	GlcCer(d18:1(d5)/18:0)	812.7	264.3	45	45
Glucosylsphingosine	Glucosylsphingosine(d5)	462.2	282.3	45	26
GlcCer(d18:1(d5)/18:0)	Internal Standard	733.6	269.3	45	45
GlcCer(d18:1/16:0(d3))	Internal Standard	703.6	264.3	45	45
GalCer(d18:1/15:0)	Internal Standard	686.3	264.3	45	45
Glucosylsphingosine(d5)	Internal Standard	467.2	287.3	30	26
GalCer(d18:1/16:0)	GalCer(d18:1/15:0)	700.6	264.3	45	45
GalCer(d18:1/18:0)	GalCer(d18:1/15:0)	728.6	264.3	45	45
GalCer(d18:2/18:0)	GalCer(d18:1/15:0)	726.6	262.3	45	45
GalCer(d18:1/20:0)	GalCer(d18:1/15:0)	756.6	264.3	45	45
GalCer(d18:2/20:0)	GalCer(d18:1/15:0)	754.6	262.3	45	45
GalCer(d18:1/22:0)	GalCer(d18:1/15:0)	784.7	264.3	45	45
GalCer(d18:1/22:1)	GalCer(d18:1/15:0)	782.7	264.3	45	45

GalCer(d18:2/22:0)	GalCer(d18:1/15:0)	782.7	262.3	45	45
GalCer(d18:1/24:1)	GalCer(d18:1/15:0)	810.7	264.3	45	45
GalCer(d18:1/24:0)	GalCer(d18:1/15:0)	812.7	264.3	45	45
Galactosylsphingosine	Glucosylsphingosine(d5)	462.2	282.3	45	16
alpha-GalCer(d18:1/16:0)	GalCer(d18:1/15:0)	700.6	264.3	45	45
alpha-GalCer(d18:1/18:0)	GalCer(d18:1/15:0)	728.6	264.3	45	45
alpha-GalCer(d18:2/18:0)	GalCer(d18:1/15:0)	726.6	262.3	45	45
alpha-GalCer(d18:1/20:0)	GalCer(d18:1/15:0)	756.6	264.3	45	45
alpha-GalCer(d18:2/20:0)	GalCer(d18:1/15:0)	754.6	262.3	45	45
alpha-GalCer(d18:1/22:0)	GalCer(d18:1/15:0)	784.7	264.3	45	45
alpha-GalCer(d18:1/22:1)	GalCer(d18:1/15:0)	782.7	264.3	45	45
alpha-GalCer(d18:2/22:0)	GalCer(d18:1/15:0)	782.7	262.3	45	45
alpha-GalCer(d18:1/24:1)	GalCer(d18:1/15:0)	810.7	264.3	45	45
alpha-GalCer(d18:1/24:0)	GalCer(d18:1/15:0)	812.7	264.3	45	45
Cholesteryl glucoside	GlcCer(d18:1(d5)/18:0)	566.6	369.3	80	17
Cholesteryl galactoside	GlcCer(d18:1(d5)/18:0)	566.6	369.3	80	17
Sitosteryl glucoside	GlcCer(d18:1(d5)/18:0)	594.6	397.4	80	17
Sitosteryl galactoside	GlcCer(d18:1(d5)/18:0)	594.6	397.4	80	17