Figure 1

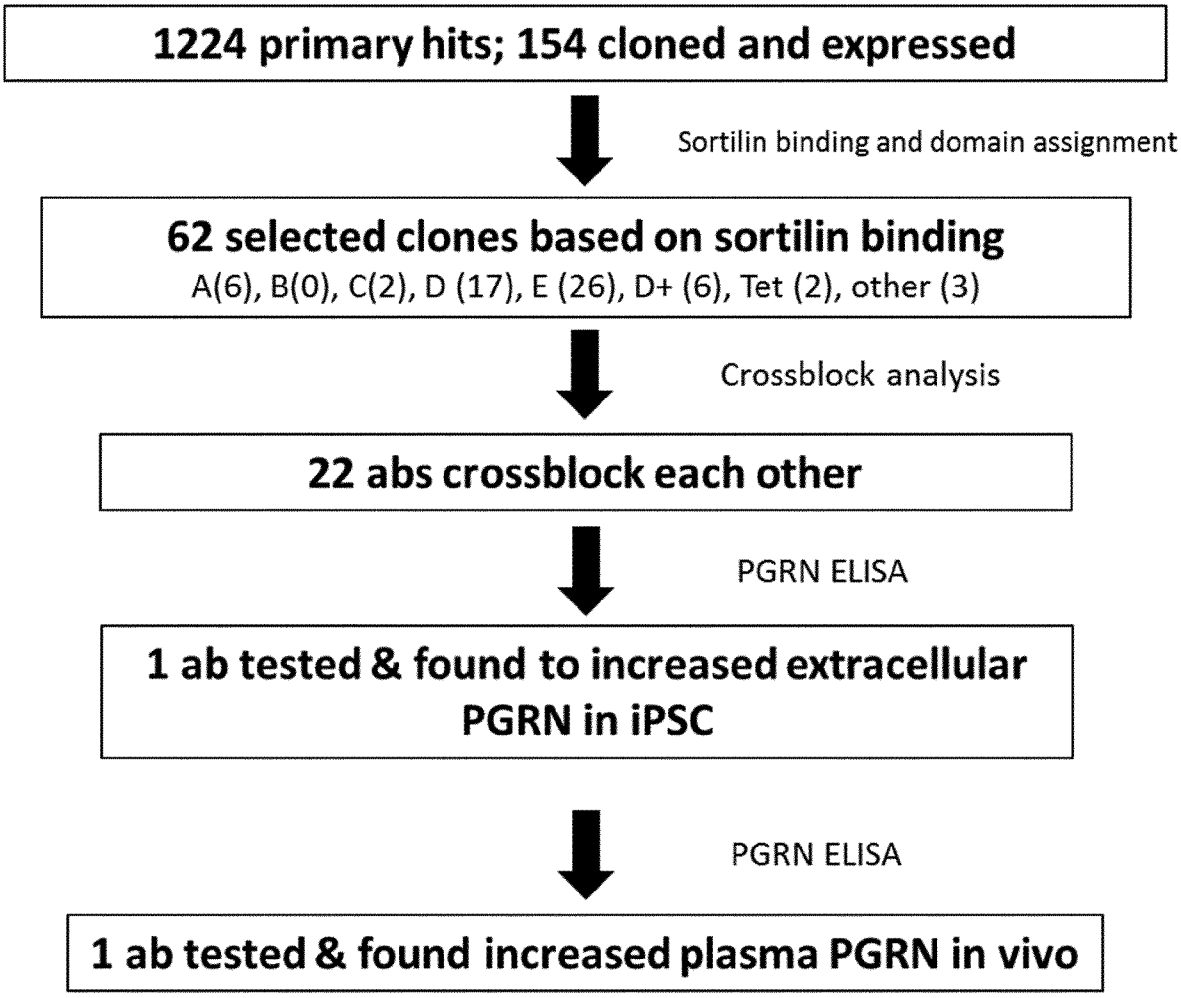

1224 primary hits; 154 cloned and expressed
Sortilin binding and domain assignment
62 selected clones based on sortilin binding
A(6), B(0), C(2), D (17), E (26), D+ (6), Tet (2), other (3)
Crossblock analysis
22 abs crossblock each other
PGRN ELISA
1 ab tested & found to increased extracellular PGRN in iPSC
PGRN ELISA
1 ab tested & found increased plasma PGRN in vivo

Figure 2A

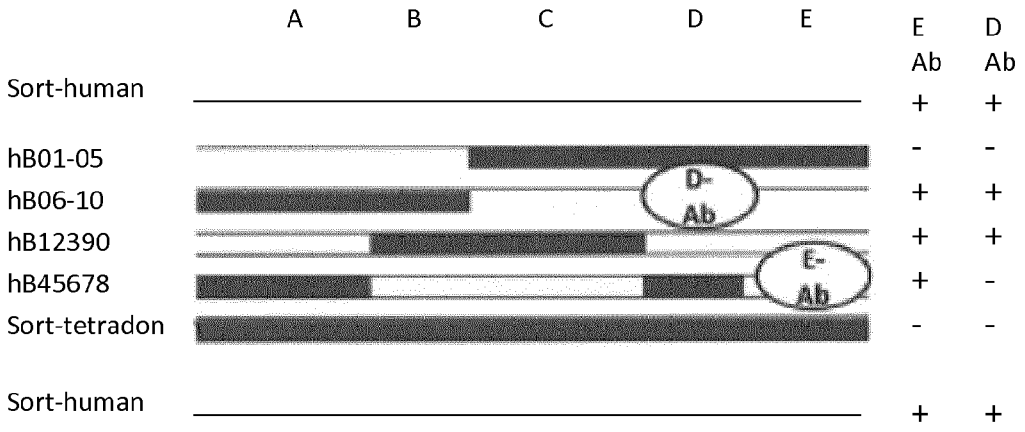


Figure 2B

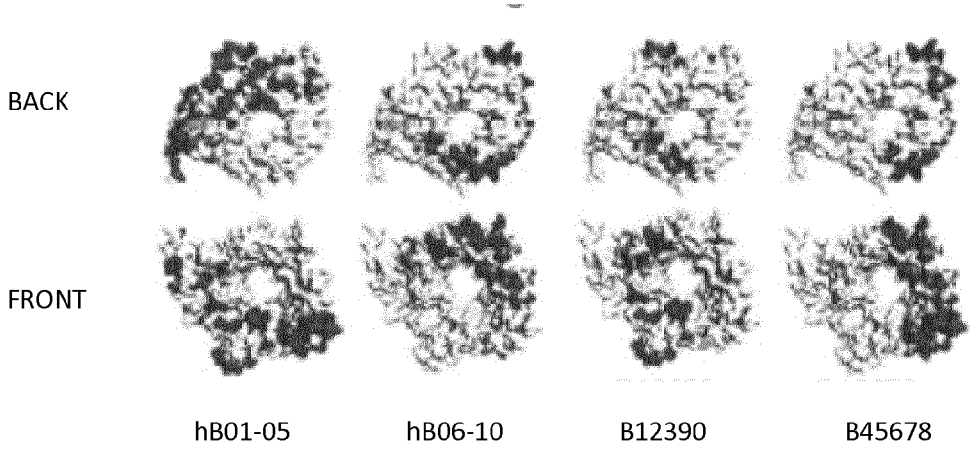


Figure 2C

mAbs	Domain	hSort	hB01-05	hB06-10	B12390	B45678	Tet
6	A	+	+	-	+	-	-
0	B	+	+	-	-	+	-
2	C	+	-	+	-	+	-
17	D	+	-	+	+	-	-
26	E	+	-	+	+	+	-
6	D+	+	-	-	+	-	-
2	Tet	+	+	+	+	+	+
3	Other	+	+/-	+/-	+/-	+	-

Figure 3

Antibody	Sort WT	hB01-05	hB06-10	hB12390	hB45678	hBack	hRim	Tetra
IgG1-6003-030	0.89	NB	0.74	0.82	0.85	0.85	0.86	NB
IgG1-6003-010	2.45	NB	2.29	3.00	4.39	2.85	3.77	NB
IgG1-6003-028	1.75	NB	1.56	1.86	1.96	1.87	2.04	NB
IgG1-6003-056	1.26	NB	0.97	1.42	1.10	1.14	1.24	NB
IgG1-6003-072	2.03	NB	1.96	6.29	4.41	2.63	4.93	NB
IgG1-6003-083	0.77	NB	0.76	0.86	0.92	1.34	0.99	NB
IgG1-6003-1277	3.03	NB	2.62	3.63	4.30	4.07	4.34	NB
IgG1-6003-1286	1.02	NB	0.87	0.86	1.02	1.02	1.05	NB
IgG1-6003-1342	1.79	NB	1.49	2.08	2.51	1.84	2.44	NB
IgG1-6003-381	1.82	NB	1.34	1.93	2.00	1.60	2.28	NB
IgG1-6003-408	1.93	NB	1.68	2.21	2.58	2.37	2.78	NB
IgG1-6003-423	3.47	NB	2.96	3.55	4.45	4.00	4.24	NB
IgG1-6003-471	2.63	NB	2.06	3.16	2.93	2.54	3.65	NB
IgG1-6003-530	4.77	NB	5.77	8.37	14.89	8.01	11.99	NB
IgG1-6003-532	1.30	NB	1.01	1.23	1.35	1.25	1.42	NB

Figure 3 (continued)

IgG1-6003-784	2.14	NB	2.33	4.27	6.50	3.25	5.86	NB
IgG1-6003-799	3.49	NB	2.63	3.36	4.16	3.20	5.02	NB
IgG1-6003-822	1.97	NB	1.49	1.89	2.08	2.59	2.31	NB
IgG1-6003-826	6.54	NB	6.95	15.40	18.06	9.36	18.27	NB
IgG1-6003-886	3.40	NB	2.44	3.36	3.45	2.72	4.42	NB
IgG1-6003-899	3.06	NB	2.32	17.70	5.55	4.54	5.35	NB
IgG1-6003-900	1.06	NB	0.91	1.06	1.19	1.16	1.26	NB
IgG1-6003-910	1.34	NB	1.16	1.84	2.23	1.54	2.59	NB
IgG1-6003-936	2.18	NB	1.85	11.40	2.86	2.62	3.20	NB
IgG1-6003-995	2.03	NB	1.42	10.21	2.99	2.03	3.31	NB
IgG1-6003-972	1.35	NB	1.12	2.36	2.57	1.49	3.08	NB

Figure 3 (continued)

Homogenous binding legend	
+	EC50 0.1-10 ng/ml
+	EC50 >10 ng/ml
NB	no binding

Figure 4

		E	E	E	E	E	E	E	E	E	E	E	E
	Antibody	530	784	010	471	532	910	072	972	826.0	028	030	056	083
Domain														
E	530	0.00	0.00	-0.01	-0.01	-0.01	0.00	0.00	-0.01	0.01	-0.04	-0.04	-0.04	-0.03
E	784	-0.01	-0.01	0.00	-0.01	0.00	0.00	-0.01	0.00	0.00	-0.01	-0.01	-0.03	-0.01
E	010	0.00	0.01	0.01	0.02	0.01	0.03	0.00	0.02	0.03	0.02	0.01	0.00	0.01
E	471	0.01	0.02	0.00	0.01	0.02	0.02	0.01	0.02	0.02	0.01	0.01	0.01	0.02
E	532	0.01	0.01	0.00	0.02	0.01	0.03	0.01	0.01	0.03	0.00	0.01	0.01	0.01
E	910	0.02	0.03	0.01	0.02	0.03	0.04	0.02	0.04	0.05	0.01	0.02	0.00	0.02
E	072	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.01	0.01	-0.01	0.00	0.00	0.00
E	972	x	x	0.01	0.10	x	x	0.06	x	x	0.00	0.00	0.06	0.06
E	826	0.00	0.00	0.00	-0.01	-0.01	0.00	0.00	0.00	0.01	-0.03	-0.03	-0.05	-0.03
E	028	0.03	0.04	0.00	0.02	0.04	0.07	0.01	0.04	0.06	0.00	0.00	0.01	0.02
E	030	0.03	0.03	0.00	0.02	0.04	0.06	0.01	0.05	0.06	0.00	0.01	0.01	0.02
E	056	0.01	0.01	0.01	0.00	0.01	0.02	-0.07	0.01	0.02	0.01	0.01	0.00	0.01
E	083	0.02	0.02	0.00	0.02	0.02	0.03	0.02	0.03	0.05	0.00	0.01	0.01	0.02

Figure 4 - continued

E	**381**	0.01	0.02	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.00	0.01	0.00	0.01	0.01	0.00	0.01	0.01
E	**408**	0.01	0.02	0.00	0.01	0.02	0.05	0.00	0.03	0.04	0.01	0.01	0.00	0.01	0.01	0.00	0.01	0.01
E	**423**	0.01	0.02	0.01	0.01	0.01	0.03	0.01	0.02	0.04	-0.01	-0.01	-0.02	-0.01	-0.01	-0.02	0.00	0.00
E	**799**	0.02	0.01	0.01	0.01	0.01	0.05	0.00	0.02	0.03	0.00	0.05	0.00	0.01	0.01	0.00	0.01	0.01
E	**822**	0.00	0.01	0.01	0.01	0.00	0.01	0.00	0.01	0.01	0.00	0.02	0.00	0.01	0.01	0.00	0.01	0.01
E	**1286**	0.04	0.04	0.00	0.05	0.04	0.05	0.03	0.04	0.07	0.01	0.01	0.03	0.01	0.01	0.01	0.01	0.04
E	**1342**	0.01	0.02	0.02	0.00	0.03	0.03	0.02	0.03	0.07	0.01	-0.04	-0.01	0.01	0.01	0.01	0.01	0.01
E	**900**	0.02	0.03	0.00	0.02	0.02	0.05	0.01	0.03	0.04	-0.01	-0.02	-0.01	0.01	0.01	0.01	0.01	0.00
E	**1277**	0.02	0.01	0.00	0.08	0.02	0.04	0.01	0.02	0.04	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02
E	**899***	b	b	b	b	b	B	x	ND	x	x	x	x	x	x	x	x	x
E	**995**	b	b	0.21	b	b	b	x	x	x	-0.03	-0.03	x	x	x	x	x	x
E	**936**	b	b	0.71	0.33	b	b	x	x	x	-0.22	-0.20	-0.07	x	x	x	x	x
E	**886**	0.34	0.39	0.37	0.57	0.58	0.37	0.02	0.02	0.02	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01

Figure 4 - continued

		E	E	E	E	E	E	E	E	E	E	E	E
Domain	Antibody	381	408	423	799	822	1286	1342	900	1277	899	995	936	886
E	530	-0.01	-0.02	-0.01	0.00	0.00	-0.03	-0.01	-0.03	-0.01	b	b	b	b
E	784	-0.01	0.00	0.00	0.00	0.00	-0.02	-0.01	-0.01	-0.01	b	b	b	b
E	010	0.00	0.01	0.01	0.02	0.03	0.01	0.03	0.02	0.01	0.52	0.60	0.53	0.44
E	471	0.01	0.02	0.01	0.02	0.01	0.01	0.02	0.02	0.01	0.54	0.62	0.58	0.54
E	532	0.01	0.01	0.01	0.02	0.03	0.02	0.03	0.01	0.01	0.64	0.71	0.64	0.51
E	910	0.01	0.02	0.04	0.03	0.03	0.02	0.04	0.03	0.02	0.23	0.31	0.35	0.51
E	072	0.00	0.00	0.00	0.01	0.01	0.00	0.02	0.00	0.00	0.01	0.02	0.01	0.05
E	972	x	x	0.10	x	x	x	x	x	x	ND	ND	ND	x
E	826	0.00	-0.01	0.00	0.00	0.00	-0.03	0.00	-0.03	-0.01	-0.02	-0.02	-0.03	0.00
E	028	0.02	0.02	0.03	0.05	0.07	0.04	0.07	0.04	0.04	0.02	0.02	-0.11	0.04
E	030	0.02	0.03	0.03	0.04	0.05	0.03	0.05	0.04	0.03	0.01	0.01	-0.10	0.03
E	056	0.00	0.01	0.01	0.01	0.01	0.01	0.03	0.01	0.01	0.01	0.00	-0.04	0.01
E	083	0.01	0.02	0.02	0.02	0.04	0.02	0.03	0.02	0.02	0.01	-0.02	-0.07	0.02

Figure 4 - continued

E	**381**	0.01	0.01	0.02	0.02	0.02	0.01	0.03	0.02	0.01	0.01	0.01	-0.07	0.01
E	**408**	0.00	0.01	0.02	0.02	0.06	0.02	0.03	0.02	0.02	0.02	0.05	0.02	0.01
E	**423**	0.00	0.01	0.00	0.02	0.02	0.00	0.03	0.01	0.01	0.01	0.00	-0.03	0.01
E	**799**	0.01	0.01	0.01	0.01	0.03	0.02	0.03	0.01	0.02	0.01	0.02	-0.09	0.02
E	**822**	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.01	0.00	-0.03	0.00
E	**1286**	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.03	-0.01	0.04
E	**1342**	0.00	0.02	0.01	0.03	0.01	0.01	0.03	0.02	0.01	0.00	-0.03	-0.09	0.01
E	**900**	0.01	0.01	0.01	0.03	0.03	0.02	0.05	0.02	0.04	0.03	0.04	0.03	0.02
E	**1277**	0.01	0.02	0.01	0.02	0.03	0.02	0.04	0.02	0.02	0.02	0.03	0.02	0.02
E	**899***	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	**995**	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	**936**	x	x	x	x	x	x	x	x	x	ND	ND	ND	x
E	**886**	0.01	0.01	0.01	0.02	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.01

0	**response <0.1**	**b = binding - no cross block**	ND= not done
0.2	**response >0.1**	**x = no binding - cross block**	

Figure 5

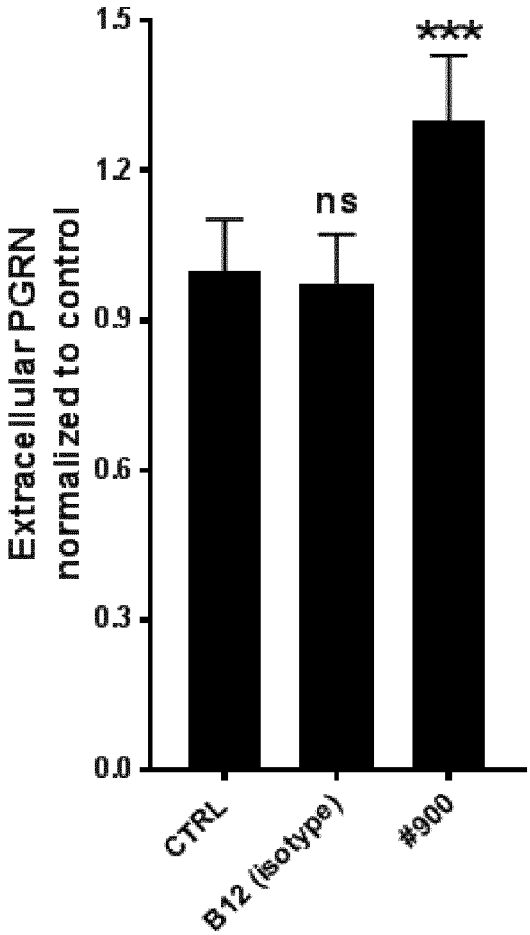

Extracellular PGRN
normalized to control
1.5
1.2
0.9
0.6
0.3
0.0
***
ns
CTRL
B12 (isotype)
#900

Figure 6

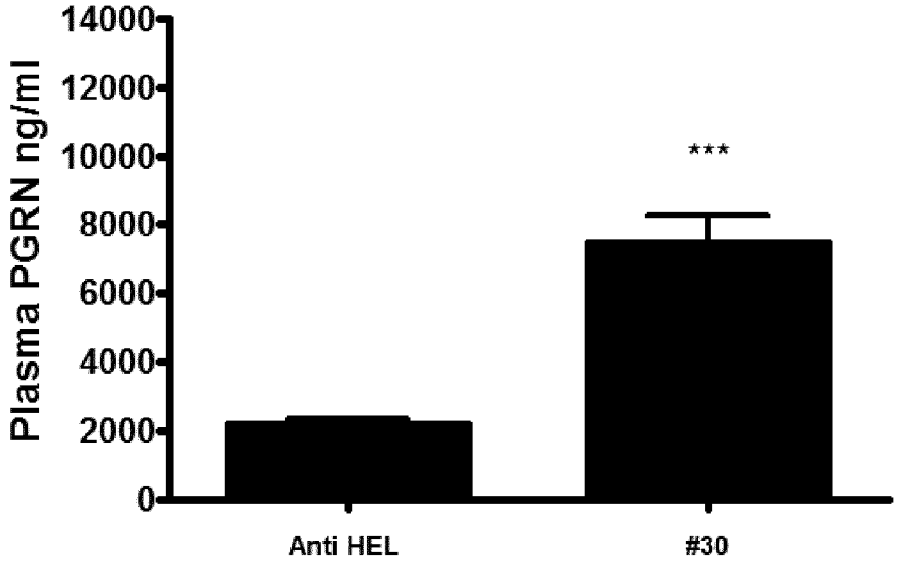

Plasma PGRN ng/ml
14000
12000
10000
8000
6000
4000
2000
0
***
Anti HEL
#30

Fig 7 A

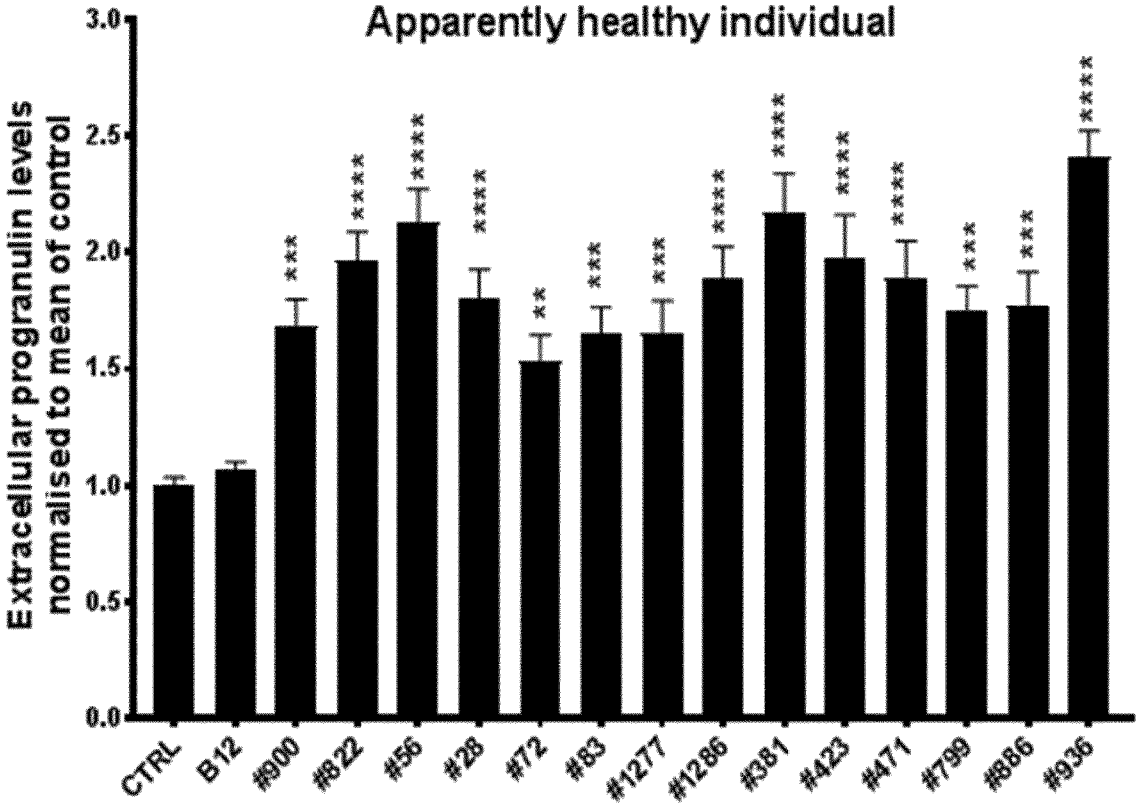

Apparently healthy individual
Extracellular progranulin levels normalised to mean of control
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CTRL
B12
#900
#822
#56
#28
#72
#83
#1277
#1286
#381
#423
#471
#799
#886
#936

Fig 7 B

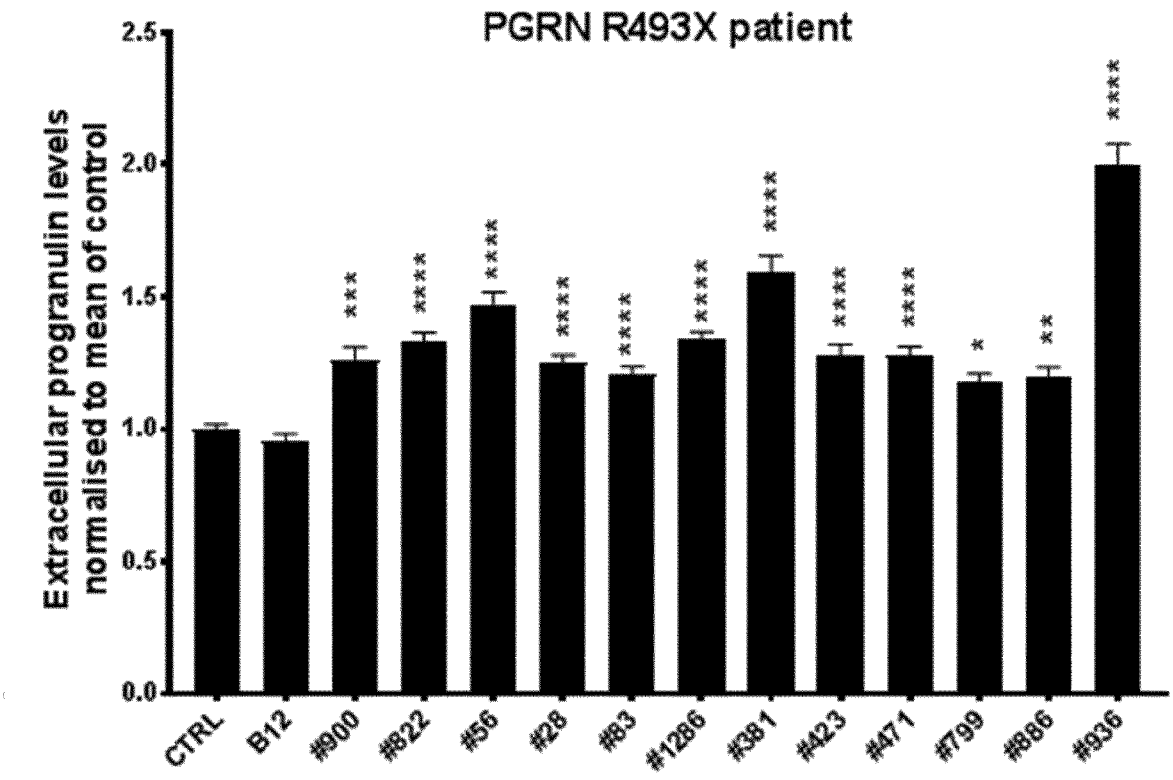

PGRN R493X patient
Extracellular progranulin levels normalised to mean of control
2.5
2.0
1.5
1.0
0.5
0.0
***
****
****
****
****
****
****
****
*
**
****
CTRL
B12
#900
#822
#56
#28
#83
#1286
#381
#423
#471
#799
#886
#936

Figure 8 A

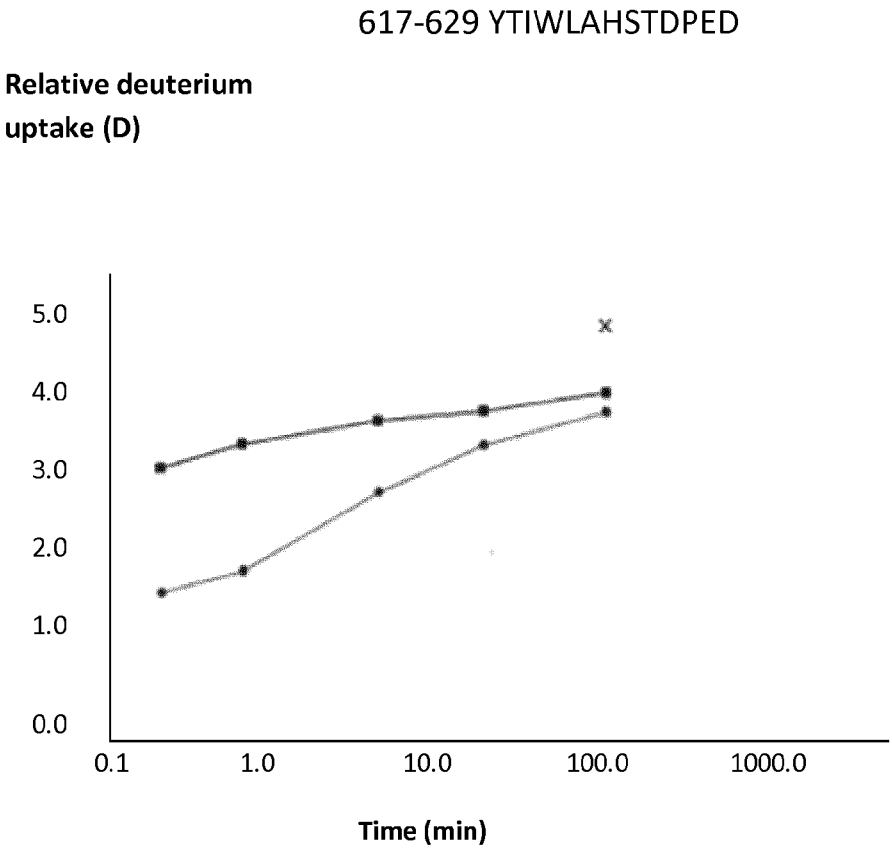

617-629 YTIWLAHSTDPED
Relative deuterium uptake (D)
5.0
4.0
3.0
2.0
1.0
0.0
0.1
1.0
10.0
100.0
1000.0
Time (min)
Sortilin
Sortilin + mAb30

Figure 8 B

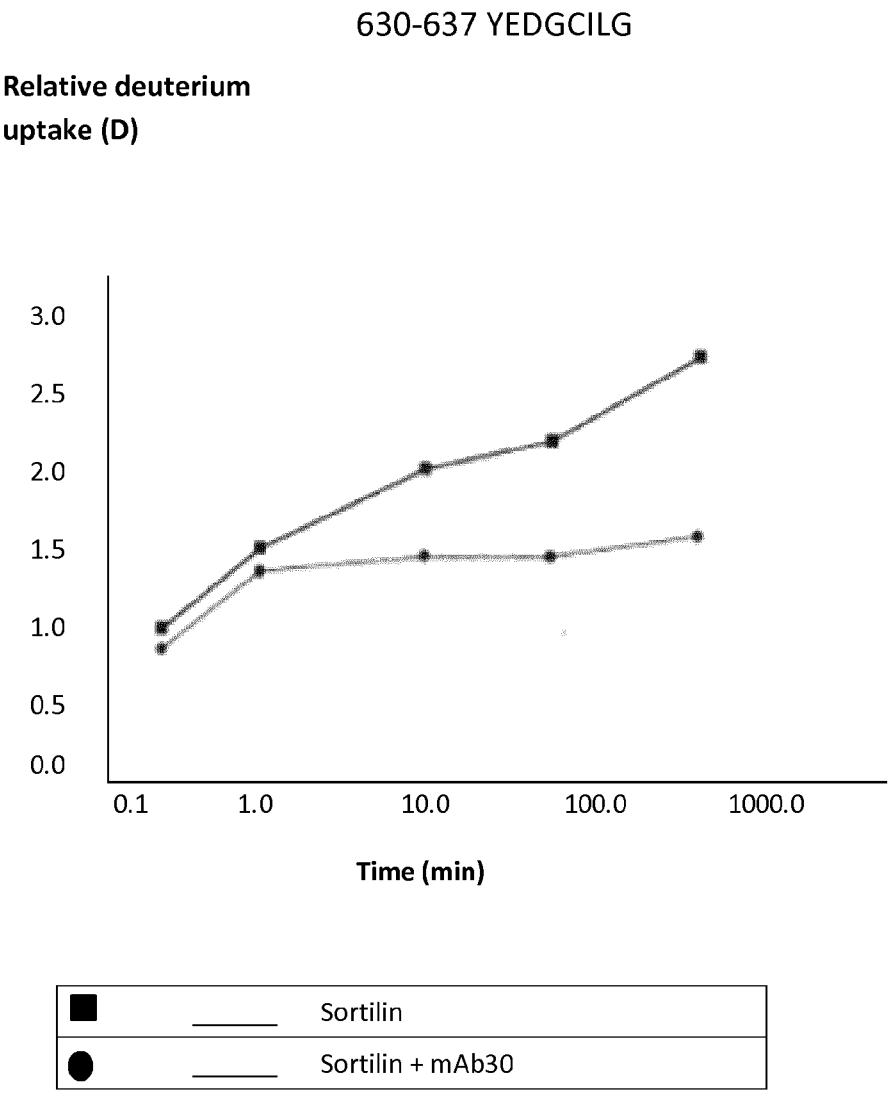

630-637 YEDGCILG
Relative deuterium uptake (D)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.1
1.0
10.0
100.0
1000.0
Time (min)
Sortilin
Sortilin + mAb30

Figure 8 C

637-642 GYKEQF

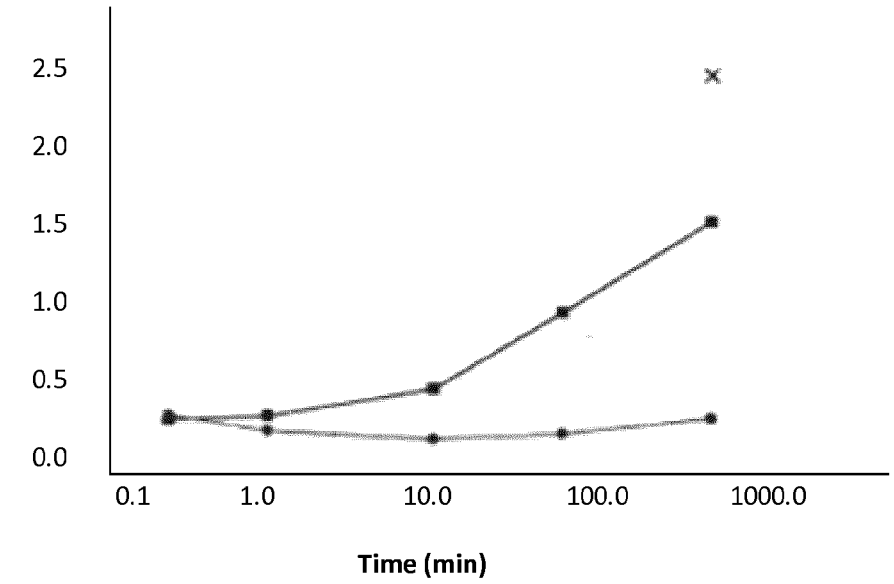


Figure 8 D

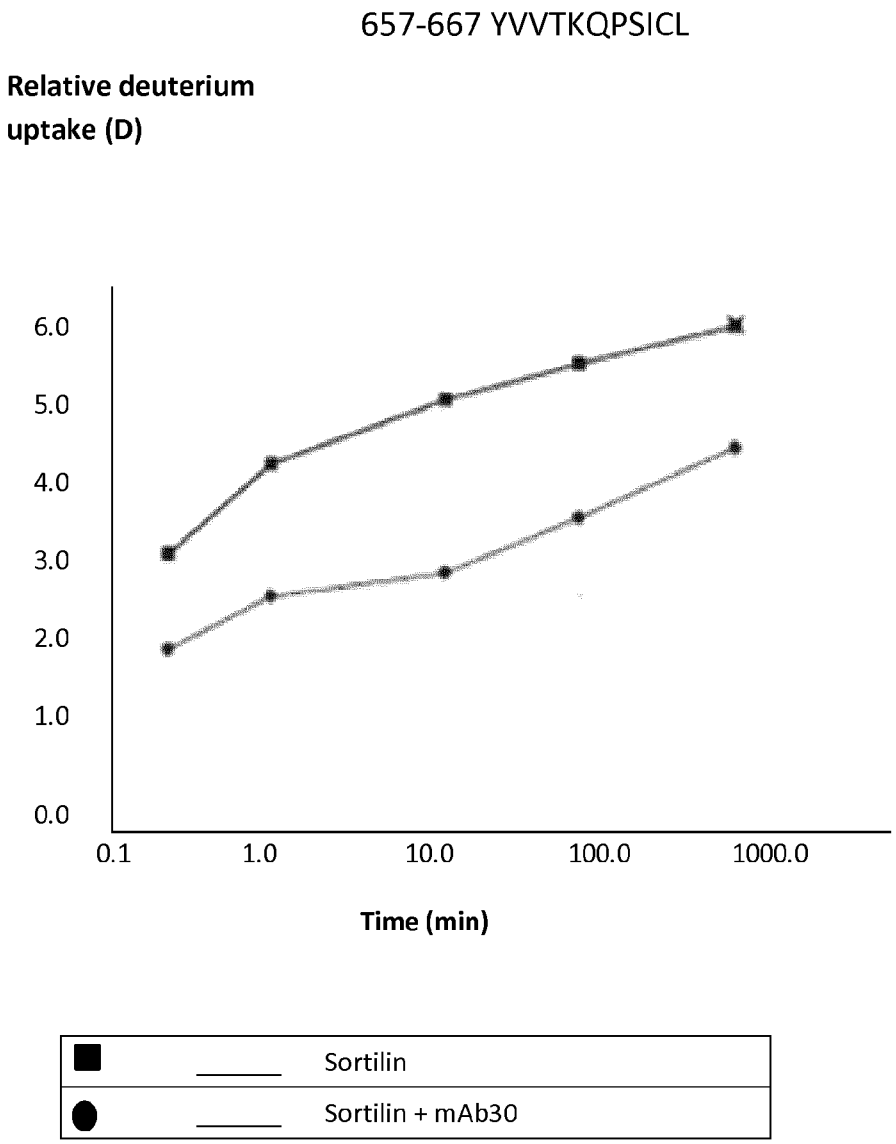

657-667 YVVTKQPSICL
Relative deuterium uptake (D)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.1
1.0
10.0
100.0
1000.0
Time (min)
Sortilin
Sortilin + mAb30

Figure 8 E

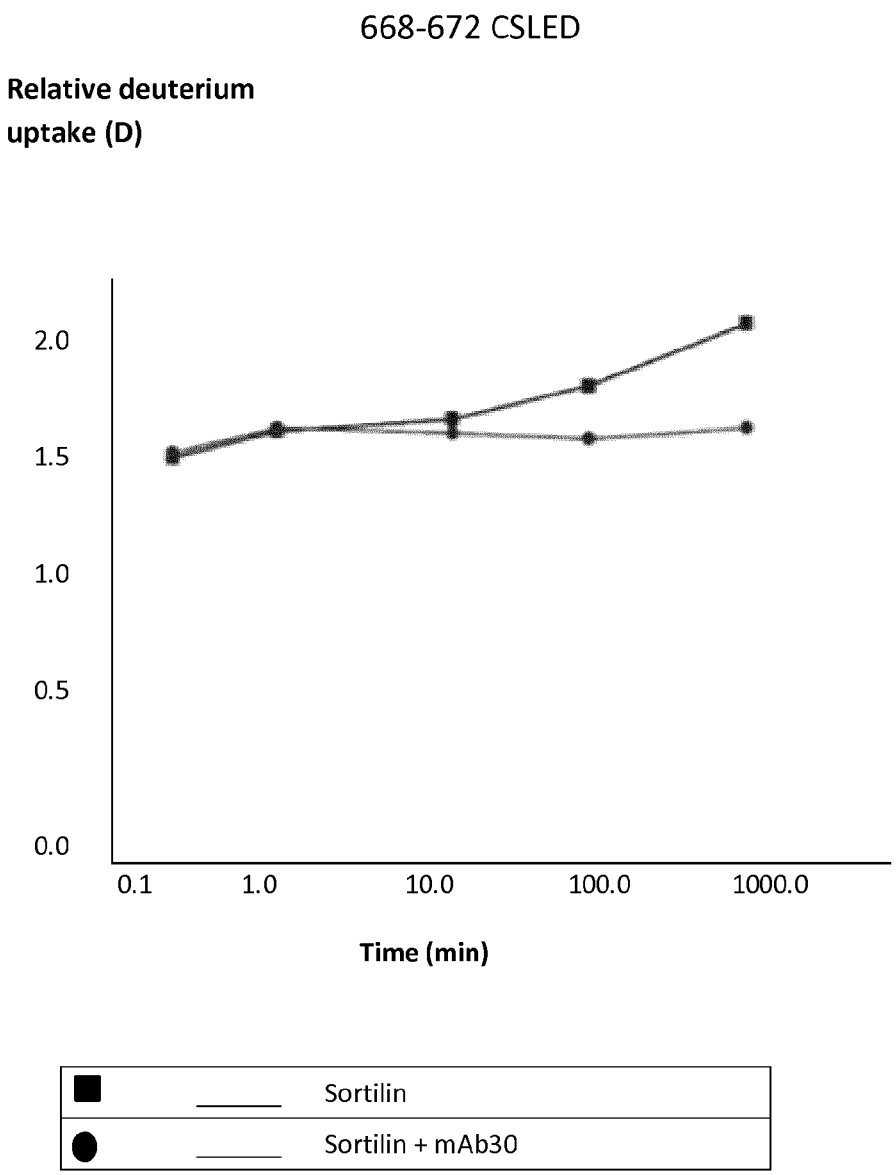
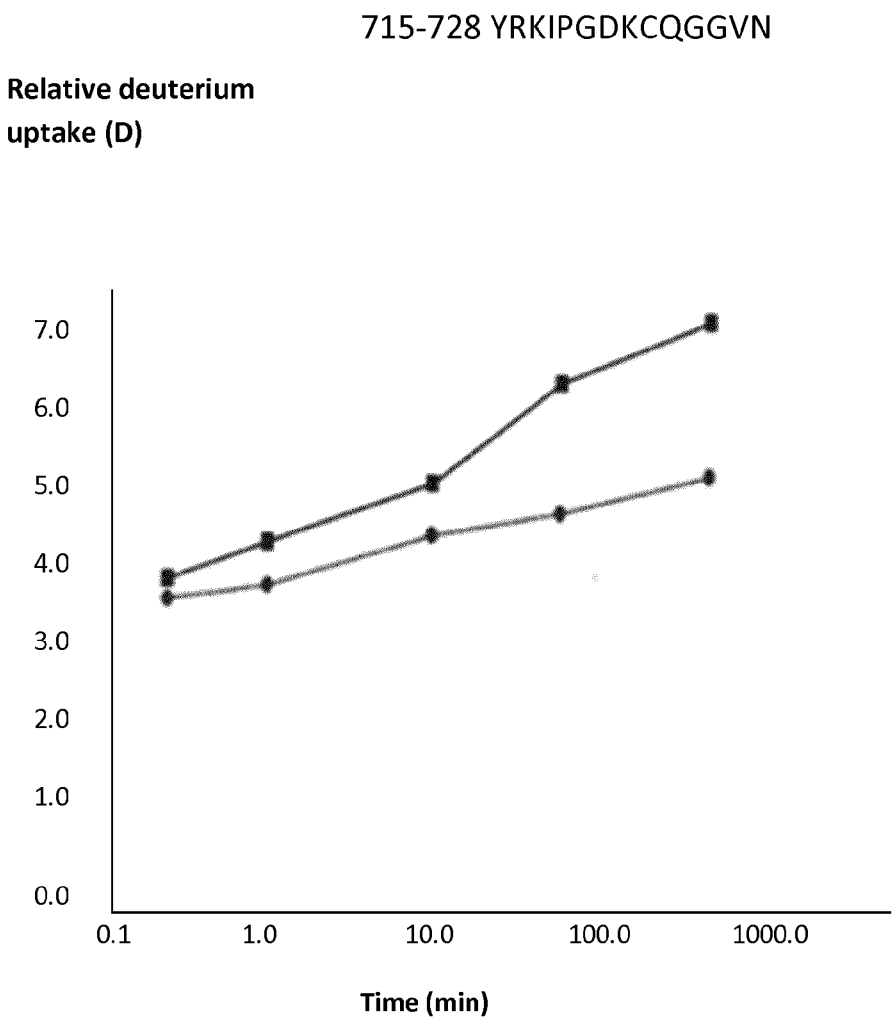

668-672 CSLED
Relative deuterium uptake (D)
2.0
1.5
1.0
0.5
0.0
0.1
1.0
10.0
100.0
1000.0
Time (min)
Sortilin
Sortilin + mAb30

Figure 8 F


715-728 YRKIPGDKCQGGVN
Relative deuterium uptake (D)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0.1
1.0
10.0
100.0
1000.0
Time (min)
Sortilin
Sortilin + mAb30