

Fig. 1D. NCL Mature Cathepsin D/ Loading Control (norm. CTSD wt), SH5-S5Y5 CTSD KO cells

Number of families	1					
Number of comparisons per family	45					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
mock vs. wt	-0,999	-1,743 to -0,2548	Yes	**	0,0028	A-B
mock vs. A58V	-0,8626	-1,607 to -0,1184	Yes	*	0,0137	A-C
mock vs. S100F	-1,222	-2,026 to -0,4178	Yes	***	0,0006	A-D
mock vs. G149V	-0,00114	-0,7454 to 0,7431	No	ns	>0,9999	A-E
mock vs. F229I	-0,1575	-0,9017 to 0,5868	No	ns	0,9991	A-F
mock vs. Y255X	-0,01097	-0,7552 to 0,7333	No	ns	>0,9999	A-G
mock vs. W383C	-0,001438	-0,7457 to 0,7428	No	ns	>0,9999	A-H
mock vs. R399H	-0,0004265	-0,7447 to 0,7438	No	ns	>0,9999	A-I
mock vs. D97S	-1,726	-2,530 to -0,9221	Yes	****	<0,0001	A-J
wt vs. A58V	0,1364	-0,6078 to 0,8807	No	ns	0,9997	B-C
wt vs. S100F	-0,2227	-1,027 to 0,5812	No	ns	0,9929	B-D
wt vs. G149V	0,9979	0,2537 to 1,742	Yes	**	0,0028	B-E
wt vs. F229I	0,8416	0,09733 to 1,586	Yes	*	0,0174	B-F
wt vs. Y255X	0,9881	0,2438 to 1,732	Yes	**	0,0032	B-G
wt vs. W383C	0,9976	0,2534 to 1,742	Yes	**	0,0028	B-H
wt vs. R399H	0,9986	0,2544 to 1,743	Yes	**	0,0028	B-I
wt vs. D97S	-0,7269	-1,531 to 0,07698	No	ns	0,102	B-J
A58V vs. S100F	-0,3591	-1,163 to 0,4448	No	ns	0,8678	C-D
A58V vs. G149V	0,8615	0,1172 to 1,606	Yes	*	0,0139	C-E
A58V vs. F229I	0,7051	-0,03912 to 1,449	No	ns	0,0745	C-F
A58V vs. Y255X	0,8516	0,1074 to 1,596	Yes	*	0,0155	C-G
A58V vs. W383C	0,8612	0,1169 to 1,605	Yes	*	0,014	C-H
A58V vs. R399H	0,8622	0,1179 to 1,606	Yes	*	0,0138	C-I
A58V vs. D97S	-0,8633	-1,667 to -0,05947	Yes	*	0,0278	C-J
S100F vs. G149V	1,221	0,4167 to 2,024	Yes	***	0,0006	D-E
S100F vs. F229I	1,064	0,2604 to 1,868	Yes	**	0,0033	D-F
S100F vs. Y255X	1,211	0,4069 to 2,015	Yes	***	0,0006	D-G
S100F vs. W383C	1,22	0,4164 to 2,024	Yes	***	0,0006	D-H
S100F vs. R399H	1,221	0,4174 to 2,025	Yes	***	0,0006	D-I
S100F vs. D97S	-0,5042	-1,364 to 0,3551	No	ns	0,5981	D-J
G149V vs. F229I	-0,1563	-0,9006 to 0,5879	No	ns	0,9991	E-F
G149V vs. Y255X	-0,009828	-0,7541 to 0,7344	No	ns	>0,9999	E-G
G149V vs. W383C	-0,0002984	-0,7445 to 0,7439	No	ns	>0,9999	E-H
G149V vs. R399H	0,000713	-0,7435 to 0,7450	No	ns	>0,9999	E-I
G149V vs. D97S	-1,725	-2,529 to -0,9209	Yes	****	<0,0001	E-J
F229I vs. Y255X	0,1465	-0,5977 to 0,8907	No	ns	0,9995	F-G
F229I vs. W383C	0,156	-0,5882 to 0,9003	No	ns	0,9991	F-H
F229I vs. R399H	0,1571	-0,5872 to 0,9013	No	ns	0,9991	F-I
F229I vs. D97S	-1,568	-2,372 to -0,7646	Yes	****	<0,0001	F-J
Y255X vs. W383C	0,009529	-0,7347 to 0,7538	No	ns	>0,9999	G-H
Y255X vs. R399H	0,01054	-0,7337 to 0,7548	No	ns	>0,9999	G-I
Y255X vs. D97S	-1,715	-2,519 to -0,9111	Yes	****	<0,0001	G-J
W383C vs. R399H	0,001011	-0,7432 to 0,7452	No	ns	>0,9999	H-I
W383C vs. D97S	-1,725	-2,528 to -0,9206	Yes	****	<0,0001	H-J
R399H vs. D97S	-1,726	-2,529 to -0,9216	Yes	****	<0,0001	I-J

Fig. 1E. NCL CTSD Activity (norm. to CTSD wt), SH5-S5Y5 CTSD KO cells

Number of families	1					
Number of comparisons per family	45					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
mock vs. wt	-0,9819	-1,351 to -0,6128	Yes	****	<0,0001	A-B
mock vs. A58V	-0,778	-1,147 to -0,4089	Yes	****	<0,0001	A-C
mock vs. S100F	0,00504	-0,3936 to 0,4037	No	ns	>0,9999	A-D
mock vs. G149V	0,007849	-0,3612 to 0,3769	No	ns	>0,9999	A-E
mock vs. F229I	-0,3254	-0,6944 to 0,04369	No	ns	0,1201	A-F
mock vs. Y255X	-0,09271	-0,4618 to 0,2764	No	ns	0,9966	A-G
mock vs. W383C	-0,004512	-0,3736 to 0,3646	No	ns	>0,9999	A-H
mock vs. R399H	-0,0289	-0,3980 to 0,3402	No	ns	>0,9999	A-I
mock vs. D97S	0,02077	-0,3483 to 0,3898	No	ns	>0,9999	A-J
wt vs. A58V	0,2039	-0,1651 to 0,5730	No	ns	0,6754	B-C

wt vs. S100F	0,9869	0,5883 to 1,386	Yes	****	<0,0001	B-D
wt vs. G149V	0,9898	0,6207 to 1,359	Yes	****	<0,0001	B-E
wt vs. F229I	0,6565	0,2875 to 1,026	Yes	****	<0,0001	B-F
wt vs. Y255X	0,8892	0,5201 to 1,258	Yes	****	<0,0001	B-G
wt vs. W383C	0,9774	0,6083 to 1,346	Yes	****	<0,0001	B-H
wt vs. R399H	0,953	0,5839 to 1,322	Yes	****	<0,0001	B-I
wt vs. D97S	1,003	0,6336 to 1,372	Yes	****	<0,0001	B-J
A58V vs. S100F	0,783	0,3844 to 1,182	Yes	****	<0,0001	C-D
A58V vs. G149V	0,7858	0,4168 to 1,155	Yes	****	<0,0001	C-E
A58V vs. F229I	0,4526	0,08352 to 0,8217	Yes	**	0,0076	C-F
A58V vs. Y255X	0,6853	0,3162 to 1,054	Yes	****	<0,0001	C-G
A58V vs. W383C	0,7735	0,4044 to 1,143	Yes	****	<0,0001	C-H
A58V vs. R399H	0,7491	0,3800 to 1,118	Yes	****	<0,0001	C-I
A58V vs. D97S	0,7987	0,4297 to 1,168	Yes	****	<0,0001	C-J
S100F vs. G149V	0,002809	-0,3958 to 0,4014	No	ns	>0,9999	D-E
S100F vs. F229I	-0,3304	-0,7291 to 0,06822	No	ns	0,1715	D-F
S100F vs. Y255X	-0,09776	-0,4964 to 0,3009	No	ns	0,9972	D-G
S100F vs. W383C	-0,009552	-0,4082 to 0,3891	No	ns	>0,9999	D-H
S100F vs. R399H	-0,03394	-0,4326 to 0,3647	No	ns	>0,9999	D-I
S100F vs. D97S	0,01573	-0,3829 to 0,4144	No	ns	>0,9999	D-J
G149V vs. F229I	-0,3332	-0,7023 to 0,03584	No	ns	0,1034	E-F
G149V vs. Y255X	-0,1006	-0,4696 to 0,2685	No	ns	0,9939	E-G
G149V vs. W383C	-0,01236	-0,3814 to 0,3567	No	ns	>0,9999	E-H
G149V vs. R399H	-0,03675	-0,4058 to 0,3323	No	ns	>0,9999	E-I
G149V vs. D97S	0,01292	-0,3561 to 0,3820	No	ns	>0,9999	E-J
F229I vs. Y255X	0,2327	-0,1364 to 0,6017	No	ns	0,5063	F-G
F229I vs. W383C	0,3209	-0,04820 to 0,6899	No	ns	0,1307	F-H
F229I vs. R399H	0,2965	-0,07259 to 0,6655	No	ns	0,202	F-I
F229I vs. D97S	0,3462	-0,02291 to 0,7152	No	ns	0,0801	F-J
Y255X vs. W383C	0,0882	-0,2809 to 0,4573	No	ns	0,9977	G-H
Y255X vs. R399H	0,06381	-0,3053 to 0,4329	No	ns	0,9998	G-I
Y255X vs. D97S	0,1135	-0,2556 to 0,4826	No	ns	0,9858	G-J
W383C vs. R399H	-0,02439	-0,3935 to 0,3447	No	ns	>0,9999	H-I
W383C vs. D97S	0,02529	-0,3438 to 0,3944	No	ns	>0,9999	H-J
R399H vs. D97S	0,04967	-0,3194 to 0,4187	No	ns	>0,9999	I-J

Fig. 2D. PD Mature Cathepsin D/ Loading Control (norm. to CTSD wt), SH-S5Y5 CTSD KO cells

Number of families	1
Number of comparisons per family	21
Alpha	0,05

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
mock vs. wt	-0,9978	-2,623 to 0,6272	No	ns	0,4455	A-B
mock vs. V95I	-0,9943	-2,619 to 0,6306	No	ns	0,4494	A-C
mock vs. G145V	-1,234	-2,859 to 0,3908	No	ns	0,2203	A-D
mock vs. A239V	-0,4386	-2,064 to 1,186	No	ns	0,9722	A-E
mock vs. R266H	-1,212	-2,837 to 0,4127	No	ns	0,2369	A-F
mock vs. D97S	-1,524	-3,149 to 0,1008	No	ns	0,0754	A-G
wt vs. V95I	0,003464	-1,621 to 1,628	No	ns	>0,9999	B-C
wt vs. G145V	-0,2363	-1,861 to 1,389	No	ns	0,999	B-D
wt vs. A239V	0,5592	-1,066 to 2,184	No	ns	0,9152	B-E
wt vs. R266H	-0,2145	-1,839 to 1,410	No	ns	0,9994	B-F
wt vs. D97S	-0,5263	-2,151 to 1,099	No	ns	0,9349	B-G
V95I vs. G145V	-0,2398	-1,865 to 1,385	No	ns	0,9989	C-D
V95I vs. A239V	0,5557	-1,069 to 2,181	No	ns	0,9174	C-E
V95I vs. R266H	-0,218	-1,843 to 1,407	No	ns	0,9993	C-F
V95I vs. D97S	-0,5298	-2,155 to 1,095	No	ns	0,933	C-G
G145V vs. A239V	0,7955	-0,8294 to 2,420	No	ns	0,6888	D-E
G145V vs. R266H	0,02184	-1,603 to 1,647	No	ns	>0,9999	D-F
G145V vs. D97S	-0,29	-1,915 to 1,335	No	ns	0,9968	D-G
A239V vs. R266H	-0,7737	-2,399 to 0,8513	No	ns	0,7145	E-F
A239V vs. D97S	-1,086	-2,710 to 0,5394	No	ns	0,3506	E-G
R266H vs. D97S	-0,3118	-1,937 to 1,313	No	ns	0,9952	F-G

Fig. 2E. PD CTSD Activity/ Expression Level (norm. to CTSD wt), SH-S5Y5 CTSD KO cells

Number of families	1
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Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	-0,008479	-0,9233 to 0,9064	No	ns	>0,9999	A-B
wt vs. G145V	0,2387	-0,6762 to 1,154	No	ns	0,9683	A-C
wt vs. A239V	-1,476	-2,391 to -0,5616	Yes	***	0,0003	A-D
wt vs. R266H	0,4011	-0,5137 to 1,316	No	ns	0,7727	A-E
wt vs. D97S	0,9844	0,06960 to 1,899	Yes	*	0,0287	A-F
V95I vs. G145V	0,2472	-0,6677 to 1,162	No	ns	0,9633	B-C
V95I vs. A239V	-1,468	-2,383 to -0,5531	Yes	***	0,0003	B-D
V95I vs. R266H	0,4096	-0,5052 to 1,324	No	ns	0,7572	B-E
V95I vs. D97S	0,9929	0,07807 to 1,908	Yes	*	0,0268	B-F
G145V vs. A239V	-1,715	-2,630 to -0,8003	Yes	****	<0,0001	C-D
G145V vs. R266H	0,1624	-0,7524 to 1,077	No	ns	0,9944	C-E
G145V vs. D97S	0,7457	-0,1691 to 1,661	No	ns	0,1658	C-F
A239V vs. R266H	1,878	0,9627 to 2,792	Yes	****	<0,0001	D-E
A239V vs. D97S	2,461	1,546 to 3,376	Yes	****	<0,0001	D-F
R266H vs. D97S	0,5833	-0,3315 to 1,498	No	ns	0,408	E-F

Fig. 3B. PD Mature Cathepsin D/ Loading Control (norm. to CTSD wt), H4 CTSD KO cells

Number of families	1					
Number of comparisons per family	21					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
mock vs. wt	-0,8906	-1,460 to -0,3207	Yes	***	0,0008	A-B
mock vs. V95I	-0,8619	-1,432 to -0,2920	Yes	**	0,0012	A-C
mock vs. G145V	-0,6532	-1,223 to -0,08336	Yes	*	0,018	A-D
mock vs. A239V	-0,2351	-0,8049 to 0,3347	No	ns	0,8252	A-E
mock vs. R266H	-0,6207	-1,191 to -0,05085	Yes	*	0,027	A-F
mock vs. D97S	-1,007	-1,577 to -0,4372	Yes	***	0,0002	A-G
wt vs. V95I	0,02869	-0,5411 to 0,5985	No	ns	>0,9999	B-C
wt vs. G145V	0,2373	-0,3325 to 0,8072	No	ns	0,8189	B-D
wt vs. A239V	0,6555	0,08562 to 1,225	Yes	*	0,0175	B-E
wt vs. R266H	0,2699	-0,3000 to 0,8397	No	ns	0,7193	B-F
wt vs. D97S	-0,1165	-0,6863 to 0,4534	No	ns	0,9933	B-G
V95I vs. G145V	0,2087	-0,3612 to 0,7785	No	ns	0,8901	C-D
V95I vs. A239V	0,6268	0,05693 to 1,197	Yes	*	0,0251	C-E
V95I vs. R266H	0,2412	-0,3287 to 0,8110	No	ns	0,8081	C-F
V95I vs. D97S	-0,1452	-0,7150 to 0,4247	No	ns	0,9791	C-G
G145V vs. A239V	0,4181	-0,1517 to 0,9880	No	ns	0,2529	D-E
G145V vs. R266H	0,03251	-0,5373 to 0,6024	No	ns	>0,9999	D-F
G145V vs. D97S	-0,3538	-0,9237 to 0,2160	No	ns	0,4328	D-G
A239V vs. R266H	-0,3856	-0,9554 to 0,1842	No	ns	0,3366	E-F
A239V vs. D97S	-0,7719	-1,342 to -0,2021	Yes	**	0,0039	E-G
R266H vs. D97S	-0,3863	-0,9562 to 0,1835	No	ns	0,3345	F-G

Fig. 3C. PD CTSD Activity/ Expression Level (norm. to CTSD wt), H4 CTSD KO cells

Number of families	1					
Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	0,1824	-0,09142 to 0,4562	No	ns	0,3223	A-B
wt vs. G145V	0,3987	0,1249 to 0,6726	Yes	**	0,0024	A-C
wt vs. A239V	-0,9775	-1,251 to -0,7037	Yes	****	<0,0001	A-D
wt vs. R266H	0,3916	0,1178 to 0,6654	Yes	**	0,0029	A-E
wt vs. D97S	0,8943	0,6205 to 1,168	Yes	****	<0,0001	A-F
V95I vs. G145V	0,2164	-0,05746 to 0,4902	No	ns	0,1725	B-C
V95I vs. A239V	-1,16	-1,434 to -0,8861	Yes	****	<0,0001	B-D
V95I vs. R266H	0,2092	-0,06458 to 0,4830	No	ns	0,1983	B-E
V95I vs. D97S	0,7119	0,4381 to 0,9857	Yes	****	<0,0001	B-F
G145V vs. A239V	-1,376	-1,650 to -1,102	Yes	****	<0,0001	C-D
G145V vs. R266H	-0,007125	-0,2809 to 0,2667	No	ns	>0,9999	C-E
G145V vs. D97S	0,4956	0,2218 to 0,7694	Yes	***	0,0002	C-F

A239V vs. R266H	1,369	1,095 to 1,643	Yes	****	<0,0001	D-E
A239V vs. D97S	1,872	1,598 to 2,146	Yes	****	<0,0001	D-F
R266H vs. D97S	0,5027	0,2289 to 0,7765	Yes	***	0,0002	E-F

Fig. 3D. PD CTSB Activity (norm to. CTSD wt), H4 CTSD KO cells

Number of families	1					
Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	0,155	-0,1565 to 0,4666	No	ns	0,5726	A-B
wt vs. G145V	0,08848	-0,2231 to 0,4000	No	ns	0,924	A-C
wt vs. A239V	0,1543	-0,1572 to 0,4659	No	ns	0,5767	A-D
wt vs. R266H	0,2251	-0,08642 to 0,5367	No	ns	0,221	A-E
wt vs. D97S	0,3256	0,01404 to 0,6372	Yes	*	0,0388	A-F
V95I vs. G145V	-0,06654	-0,3781 to 0,2450	No	ns	0,976	B-C
V95I vs. A239V	-0,000674	-0,3122 to 0,3109	No	ns	>0,9999	B-D
V95I vs. R266H	0,07012	-0,2414 to 0,3817	No	ns	0,97	B-E
V95I vs. D97S	0,1706	-0,1410 to 0,4821	No	ns	0,4788	B-F
G145V vs. A239V	0,06586	-0,2457 to 0,3774	No	ns	0,977	C-D
G145V vs. R266H	0,1367	-0,1749 to 0,4482	No	ns	0,6859	C-E
G145V vs. D97S	0,2371	-0,07444 to 0,5487	No	ns	0,1823	C-F
A239V vs. R266H	0,0708	-0,2408 to 0,3824	No	ns	0,9688	D-E
A239V vs. D97S	0,1713	-0,1403 to 0,4828	No	ns	0,4749	D-F
R266H vs. D97S	0,1005	-0,2111 to 0,4120	No	ns	0,879	E-F

Fig. 3E. PD Gcase Activity (norm to. CTSD wt), H4 CTSD KO cells

Number of families	1					
Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	-0,1742	-0,7916 to 0,4431	No	ns	0,9257	A-B
wt vs. G145V	-0,05684	-0,6742 to 0,5605	No	ns	0,9995	A-C
wt vs. A239V	-0,1606	-0,7779 to 0,4568	No	ns	0,9459	A-D
wt vs. R266H	-0,05835	-0,6757 to 0,5590	No	ns	0,9994	A-E
wt vs. D97S	-0,01041	-0,6277 to 0,6069	No	ns	>0,9999	A-F
V95I vs. G145V	0,1174	-0,4999 to 0,7347	No	ns	0,9855	B-C
V95I vs. A239V	0,01368	-0,6037 to 0,6310	No	ns	>0,9999	B-D
V95I vs. R266H	0,1159	-0,5015 to 0,7332	No	ns	0,9863	B-E
V95I vs. D97S	0,1638	-0,4535 to 0,7812	No	ns	0,9415	B-F
G145V vs. A239V	-0,1037	-0,7210 to 0,5136	No	ns	0,9917	C-D
G145V vs. R266H	-0,001508	-0,6188 to 0,6158	No	ns	>0,9999	C-E
G145V vs. D97S	0,04643	-0,5709 to 0,6638	No	ns	0,9998	C-F
A239V vs. R266H	0,1022	-0,5151 to 0,7195	No	ns	0,9922	D-E
A239V vs. D97S	0,1501	-0,4672 to 0,7675	No	ns	0,9587	D-F
R266H vs. D97S	0,04794	-0,5694 to 0,6653	No	ns	0,9998	E-F

Fig. 3F. Dextran Blue/Celltag700 (Fold Change)

Number of families	1					
Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	0,1101	-0,2714 to 0,4917	No	ns	0,9455	A-B
wt vs. R266H	0,21	-0,1715 to 0,5916	No	ns	0,5466	A-C
wt vs. G145V	-0,05714	-0,4387 to 0,3244	No	ns	0,9971	A-D
wt vs. A234V	-0,1767	-0,5582 to 0,2049	No	ns	0,7111	A-E
wt vs. D97S	-0,1867	-0,5683 to 0,1949	No	ns	0,6626	A-F
V95I vs. R266H	0,0999	-0,2986 to 0,4984	No	ns	0,9697	B-C
V95I vs. G145V	-0,1673	-0,5658 to 0,2313	No	ns	0,7857	B-D
V95I vs. A234V	-0,2868	-0,6853 to 0,1117	No	ns	0,2651	B-E
V95I vs. D97S	-0,2968	-0,6954 to 0,1017	No	ns	0,2331	B-F
R266H vs. G145V	-0,2672	-0,6657 to 0,1314	No	ns	0,3361	C-D
R266H vs. A234V	-0,3867	-0,7852 to 0,01185	No	ns	0,0609	C-E
R266H vs. D97S	-0,3967	-0,7953 to 0,001804	No	ns	0,0515	C-F

G145V vs. A234V	-0,1195	-0,5180 to 0,2790	No	ns	0,9365	D-E
G145V vs. D97S	-0,1296	-0,5281 to 0,2690	No	ns	0,913	D-F
A234V vs. D97S	-0,01004	-0,4086 to 0,3885	No	ns	>0,9999	E-F

Fig. 4B. PD α -Synuclein Homeostasis/ Loading Control (norm. to CTSD wt). SH-SY5Y CTSD KO cells

Number of families	1					
Number of comparisons per family	5					
Alpha	0,05					
Dunnett's multiple comparisons test	Mean Diff,	95% CI of diff,	Significant?	Summary		A-?
wt vs. V95I	-0,043	-0,3302 to 0,2442	No	ns		B
wt vs. G145V	-0,1163	-0,4250 to 0,1925	No	ns		C
wt vs. A239V	0,3053	0,008627 to 0,6019	Yes	*		D
wt vs. R266H	-0,05248	-0,3491 to 0,2442	No	ns		E
wt vs. D97S	-0,1487	-0,4965 to 0,1992	No	ns		F

Fig. S1C. CTSD Signal Intensity (arbitrary numbers) SH-SY5Y cells

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
SH-SY5Y KO vs. SH-SY5Y wt	-0,7686	-0,8816 to -0,6555	Yes	****	<0,0001	A-B
SH-SY5Y KO vs. SH-SY5Y KO + CTSD wt	-0,4754	-0,5719 to -0,3789	Yes	****	<0,0001	A-C
SH-SY5Y wt vs. SH-SY5Y KO + CTSD wt	0,2932	0,1856 to 0,4008	Yes	****	<0,0001	B-C

Fig. S3A. NCL Pearson's Correlation Coefficient, SH-SY5Y CTSD KO cells

Number of families	1					
Number of comparisons per family	36					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. A58V	0,1082	-0,05227 to 0,2688	No	ns	0,4561	A-B
wt vs. S100F	0,01288	-0,1539 to 0,1797	No	ns	>0,9999	A-C
wt vs. G149V	0,5162	0,3494 to 0,6830	Yes	****	<0,0001	A-D
wt vs. F229I	0,1667	0,008805 to 0,3246	Yes	*	0,0302	A-E
wt vs. Y255X	0,5461	0,3856 to 0,7066	Yes	****	<0,0001	A-F
wt vs. W383C	0,5504	0,3899 to 0,7109	Yes	****	<0,0001	A-G
wt vs. R399H	0,544	0,3834 to 0,7045	Yes	****	<0,0001	A-H
wt vs. D97S	0,003566	-0,1672 to 0,1743	No	ns	>0,9999	A-I
A58V vs. S100F	-0,09536	-0,2593 to 0,06858	No	ns	0,6552	B-C
A58V vs. G149V	0,408	0,2440 to 0,5719	Yes	****	<0,0001	B-D
A58V vs. F229I	0,05848	-0,09639 to 0,2133	No	ns	0,956	B-E
A58V vs. Y255X	0,4379	0,2803 to 0,5954	Yes	****	<0,0001	B-F
A58V vs. W383C	0,4421	0,2846 to 0,5997	Yes	****	<0,0001	B-G
A58V vs. R399H	0,4357	0,2782 to 0,5932	Yes	****	<0,0001	B-H
A58V vs. D97S	-0,1047	-0,2726 to 0,06323	No	ns	0,5654	B-I
S100F vs. G149V	0,5033	0,3332 to 0,6735	Yes	****	<0,0001	C-D
S100F vs. F229I	0,1538	-0,007566 to 0,3152	No	ns	0,0745	C-E
S100F vs. Y255X	0,5332	0,3693 to 0,6972	Yes	****	<0,0001	C-F
S100F vs. W383C	0,5375	0,3736 to 0,7014	Yes	****	<0,0001	C-G
S100F vs. R399H	0,5311	0,3671 to 0,6950	Yes	****	<0,0001	C-H
S100F vs. D97S	-0,009318	-0,1833 to 0,1646	No	ns	>0,9999	C-I
G149V vs. F229I	-0,3495	-0,5109 to -0,1881	Yes	****	<0,0001	D-E
G149V vs. Y255X	0,02988	-0,1341 to 0,1938	No	ns	0,9997	D-F
G149V vs. W383C	0,03417	-0,1298 to 0,1981	No	ns	0,9992	D-G
G149V vs. R399H	0,02774	-0,1362 to 0,1917	No	ns	0,9998	D-H
G149V vs. D97S	-0,5127	-0,6866 to -0,3387	Yes	****	<0,0001	D-I
F229I vs. Y255X	0,3794	0,2245 to 0,5342	Yes	****	<0,0001	E-F
F229I vs. W383C	0,3837	0,2288 to 0,5385	Yes	****	<0,0001	E-G
F229I vs. R399H	0,3772	0,2224 to 0,5321	Yes	****	<0,0001	E-H
F229I vs. D97S	-0,1632	-0,3286 to 0,002273	No	ns	0,0563	E-I
Y255X vs. W383C	0,004286	-0,1532 to 0,1618	No	ns	>0,9999	F-G
Y255X vs. R399H	-0,002143	-0,1597 to 0,1554	No	ns	>0,9999	F-H
Y255X vs. D97S	-0,5425	-0,7104 to -0,3746	Yes	****	<0,0001	F-I
W383C vs. R399H	-0,006429	-0,1639 to 0,1511	No	ns	>0,9999	G-H
W383C vs. D97S	-0,5468	-0,7147 to -0,3789	Yes	****	<0,0001	G-I

R399H vs. D97S	-0,5404 -0,7083 to -0,3725	Yes	****	<0,0001	H-I
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Fig. S3B NCL Vesicles per Cell, SH-S5Y5 CTSD KO cells

Number of families	1				
Number of comparisons per family	45				
Alpha	0,05				
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
mock vs. wt	0,5294	-3,689 to 4,748	No	ns	>0,9999 A-B
mock vs. A58V	-3,108	-7,268 to 1,052	No	ns	0,334 A-C
mock vs. S100F	-7,941	-12,38 to -3,502	Yes	****	<0,0001 A-D
mock vs. G149V	-3,254	-7,538 to 1,031	No	ns	0,311 A-E
mock vs. F229I	0,3529	-3,866 to 4,572	No	ns	>0,9999 A-F
mock vs. Y255X	-0,6555	-5,095 to 3,784	No	ns	>0,9999 A-G
mock vs. W383C	-0,5728	-4,679 to 3,534	No	ns	>0,9999 A-H
mock vs. R399H	-1,066	-5,350 to 3,218	No	ns	0,9985 A-I
mock vs. D97S	-1,235	-5,454 to 2,983	No	ns	0,9949 A-J
wt vs. A58V	-3,637	-7,797 to 0,5225	No	ns	0,1433 B-C
wt vs. S100F	-8,471	-12,91 to -4,032	Yes	****	<0,0001 B-D
wt vs. G149V	-3,783	-8,067 to 0,5011	No	ns	0,1341 B-E
wt vs. F229I	-0,1765	-4,395 to 4,042	No	ns	>0,9999 B-F
wt vs. Y255X	-1,185	-5,624 to 3,254	No	ns	0,9974 B-G
wt vs. W383C	-1,102	-5,208 to 3,004	No	ns	0,9973 B-H
wt vs. R399H	-1,596	-5,880 to 2,689	No	ns	0,9721 B-I
wt vs. D97S	-1,765	-5,983 to 2,454	No	ns	0,9419 B-J
A58V vs. S100F	-4,833	-9,216 to -0,4503	Yes	*	0,0184 C-D
A58V vs. G149V	-0,1458	-4,372 to 4,080	No	ns	>0,9999 C-E
A58V vs. F229I	3,461	-0,6990 to 7,621	No	ns	0,195 C-F
A58V vs. Y255X	2,452	-1,931 to 6,835	No	ns	0,7366 C-G
A58V vs. W383C	2,535	-1,511 to 6,581	No	ns	0,5922 C-H
A58V vs. R399H	2,042	-2,184 to 6,268	No	ns	0,869 C-I
A58V vs. D97S	1,873	-2,287 to 6,032	No	ns	0,9108 C-J
S100F vs. G149V	4,688	0,1862 to 9,189	Yes	*	0,0339 D-E
S100F vs. F229I	8,294	3,855 to 12,73	Yes	****	<0,0001 D-F
S100F vs. Y255X	7,286	2,637 to 11,93	Yes	****	<0,0001 D-G
S100F vs. W383C	7,368	3,036 to 11,70	Yes	****	<0,0001 D-H
S100F vs. R399H	6,875	2,374 to 11,38	Yes	***	0,0001 D-I
S100F vs. D97S	6,706	2,267 to 11,14	Yes	***	0,0001 D-J
G149V vs. F229I	3,607	-0,6776 to 7,891	No	ns	0,1819 E-F
G149V vs. Y255X	2,598	-1,903 to 7,099	No	ns	0,7002 E-G
G149V vs. W383C	2,681	-1,493 to 6,854	No	ns	0,5568 E-H
G149V vs. R399H	2,188	-2,161 to 6,536	No	ns	0,839 E-I
G149V vs. D97S	2,018	-2,266 to 6,303	No	ns	0,8853 E-J
F229I vs. Y255X	-1,008	-5,447 to 3,431	No	ns	0,9993 F-G
F229I vs. W383C	-0,9257	-5,032 to 3,181	No	ns	0,9993 F-H
F229I vs. R399H	-1,419	-5,703 to 2,865	No	ns	0,9874 F-I
F229I vs. D97S	-1,588	-5,807 to 2,631	No	ns	0,97 F-J
Y255X vs. W383C	0,08271	-4,250 to 4,415	No	ns	>0,9999 G-H
Y255X vs. R399H	-0,4107	-4,912 to 4,091	No	ns	>0,9999 G-I
Y255X vs. D97S	-0,5798	-5,019 to 3,859	No	ns	>0,9999 G-J
W383C vs. R399H	-0,4934	-4,667 to 3,680	No	ns	>0,9999 H-I
W383C vs. D97S	-0,6625	-4,769 to 3,444	No	ns	>0,9999 H-J
R399H vs. D97S	-0,1691	-4,453 to 4,115	No	ns	>0,9999 I-J

Fig. S3C. NCL Average Vesicle Size per Cell, SH-S5Y5 CTSD KO cells

Number of families	1
Number of comparisons per family	45
Alpha	0,05

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
mock vs. wt	0,7563	0,4430 to 1,070	Yes	****	<0,0001 A-B
mock vs. A58V	0,7662	0,4573 to 1,075	Yes	****	<0,0001 A-C
mock vs. S100F	0,7077	0,3780 to 1,037	Yes	****	<0,0001 A-D
mock vs. G149V	0,4637	0,1455 to 0,7819	Yes	***	0,0003 A-E
mock vs. F229I	0,2642	-0,04918 to 0,5775	No	ns	0,1804 A-F
mock vs. Y255X	0,2975	-0,03224 to 0,6272	No	ns	0,1155 A-G
mock vs. W383C	0,1694	-0,1356 to 0,4744	No	ns	0,7447 A-H

mock vs. R399H	0,4202	0,1020 to 0,7384	Yes	**	0,0015	A-I
mock vs. D97S	0,7422	0,4288 to 1,056	Yes	****	<0,0001	A-J
wt vs. A58V	0,009877	-0,2991 to 0,3188	No	ns	>0,9999	B-C
wt vs. S100F	-0,04862	-0,3783 to 0,2811	No	ns	>0,9999	B-D
wt vs. G149V	-0,2926	-0,6108 to 0,02558	No	ns	0,1004	B-E
wt vs. F229I	-0,4922	-0,8055 to -0,1788	Yes	****	<0,0001	B-F
wt vs. Y255X	-0,4589	-0,7886 to -0,1292	Yes	***	0,0006	B-G
wt vs. W383C	-0,5869	-0,8919 to -0,2820	Yes	****	<0,0001	B-H
wt vs. R399H	-0,3362	-0,6544 to -0,01795	Yes	*	0,0293	B-I
wt vs. D97S	-0,01416	-0,3275 to 0,2992	No	ns	>0,9999	B-J
A58V vs. S100F	-0,0585	-0,3840 to 0,2670	No	ns	0,9999	C-D
A58V vs. G149V	-0,3025	-0,6164 to 0,01139	No	ns	0,0692	C-E
A58V vs. F229I	-0,5021	-0,8110 to -0,1931	Yes	****	<0,0001	C-F
A58V vs. Y255X	-0,4688	-0,7943 to -0,1432	Yes	***	0,0003	C-G
A58V vs. W383C	-0,5968	-0,8973 to -0,2963	Yes	****	<0,0001	C-H
A58V vs. R399H	-0,346	-0,6599 to -0,03214	Yes	*	0,0184	C-I
A58V vs. D97S	-0,02404	-0,3330 to 0,2849	No	ns	>0,9999	C-J
S100F vs. G149V	-0,244	-0,5783 to 0,09032	No	ns	0,3678	D-E
S100F vs. F229I	-0,4436	-0,7733 to -0,1139	Yes	**	0,0011	D-F
S100F vs. Y255X	-0,4103	-0,7556 to -0,06498	Yes	**	0,0073	D-G
S100F vs. W383C	-0,5383	-0,8601 to -0,2165	Yes	****	<0,0001	D-H
S100F vs. R399H	-0,2875	-0,6219 to 0,04679	No	ns	0,1595	D-I
S100F vs. D97S	0,03446	-0,2952 to 0,3642	No	ns	>0,9999	D-J
G149V vs. F229I	-0,1996	-0,5178 to 0,1186	No	ns	0,591	E-F
G149V vs. Y255X	-0,1663	-0,5006 to 0,1681	No	ns	0,848	E-G
G149V vs. W383C	-0,2943	-0,6043 to 0,01566	No	ns	0,0782	E-H
G149V vs. R399H	-0,04353	-0,3665 to 0,2795	No	ns	>0,9999	E-I
G149V vs. D97S	0,2785	-0,03974 to 0,5967	No	ns	0,1425	E-J
F229I vs. Y255X	0,03329	-0,2964 to 0,3630	No	ns	>0,9999	F-G
F229I vs. W383C	-0,09476	-0,3997 to 0,2102	No	ns	0,992	F-H
F229I vs. R399H	0,156	-0,1622 to 0,4742	No	ns	0,8585	F-I
F229I vs. D97S	0,478	0,1647 to 0,7914	Yes	***	0,0001	F-J
Y255X vs. W383C	-0,1281	-0,4498 to 0,1937	No	ns	0,9572	G-H
Y255X vs. R399H	0,1227	-0,2116 to 0,4571	No	ns	0,9746	G-I
Y255X vs. D97S	0,4447	0,1150 to 0,7744	Yes	**	0,0011	G-J
W383C vs. R399H	0,2508	-0,05918 to 0,5608	No	ns	0,2279	H-I
W383C vs. D97S	0,5728	0,2678 to 0,8778	Yes	****	<0,0001	H-J
R399H vs. D97S	0,322	0,003789 to 0,6402	Yes	*	0,0448	I-J

Fig. S5A. PD Pearson's Correlation Coefficient, SH-S5Y5 CTSD KO cells

Number of families	1				
Number of comparisons per family	15				
Alpha	0,05				
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
wt vs. V95I	0,05523	-0,09947 to 0,2099	No	ns	0,9001 A-B
wt vs. G145V	-0,0015	-0,1450 to 0,1420	No	ns	>0,9999 A-C
wt vs. A239V	-0,02536	-0,1711 to 0,1204	No	ns	0,9956 A-D
wt vs. R266H	-0,01295	-0,1676 to 0,1417	No	ns	0,9999 A-E
wt vs. D97S	-0,04114	-0,1958 to 0,1136	No	ns	0,97 A-F
V95I vs. G145V	-0,05673	-0,2038 to 0,09038	No	ns	0,8668 B-C
V95I vs. A239V	-0,08058	-0,2299 to 0,06873	No	ns	0,6126 B-D
V95I vs. R266H	-0,06818	-0,2262 to 0,08984	No	ns	0,8026 B-E
V95I vs. D97S	-0,09636	-0,2544 to 0,06166	No	ns	0,48 B-F
G145V vs. A239V	-0,02386	-0,1616 to 0,1139	No	ns	0,9957 C-D
G145V vs. R266H	-0,01145	-0,1586 to 0,1357	No	ns	>0,9999 C-E
G145V vs. D97S	-0,03964	-0,1867 to 0,1075	No	ns	0,9683 C-F
A239V vs. R266H	0,0124	-0,1369 to 0,1617	No	ns	0,9999 D-E
A239V vs. D97S	-0,01578	-0,1651 to 0,1335	No	ns	0,9996 D-F
R266H vs. D97S	-0,02818	-0,1862 to 0,1298	No	ns	0,9951 E-F

Fig. S5B. PD Vesicles per Cell, SH-S5Y5 CTSD KO cells

Number of families	1
Number of comparisons per family	21
Alpha	0,05

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
mock vs. wt	-0,1891	-6,034 to 5,656	No	ns	>0,9999 A-B
mock vs. V97S	-2,546	-8,391 to 3,299	No	ns	0,8449 A-C
mock vs. G145V	-3,93	-9,571 to 1,711	No	ns	0,3623 A-D
mock vs. A239V	-4,851	-10,59 to 0,8862	No	ns	0,1548 A-E
mock vs. R266H	-4,572	-10,84 to 1,695	No	ns	0,3069 A-F
mock vs. D97S	-1,765	-7,320 to 3,790	No	ns	0,9619 A-G
wt vs. V97S	-2,357	-8,478 to 3,764	No	ns	0,9074 B-C
wt vs. G145V	-3,741	-9,668 to 2,186	No	ns	0,4849 B-D
wt vs. A239V	-4,662	-10,68 to 1,357	No	ns	0,2395 B-E
wt vs. R266H	-4,383	-10,91 to 2,142	No	ns	0,4074 B-F
wt vs. D97S	-1,576	-7,421 to 4,269	No	ns	0,9833 B-G
V97S vs. G145V	-1,384	-7,311 to 4,543	No	ns	0,9921 C-D
V97S vs. A239V	-2,305	-8,323 to 3,714	No	ns	0,9096 C-E
V97S vs. R266H	-2,026	-8,551 to 4,499	No	ns	0,9659 C-F
V97S vs. D97S	0,7815	-5,064 to 6,627	No	ns	0,9997 C-G
G145V vs. A239V	-0,9208	-6,741 to 4,900	No	ns	0,9991 D-E
G145V vs. R266H	-0,642	-6,985 to 5,701	No	ns	>0,9999 D-F
G145V vs. D97S	2,165	-3,476 to 7,807	No	ns	0,9086 D-G
A239V vs. R266H	0,2788	-6,150 to 6,708	No	ns	>0,9999 E-F
A239V vs. D97S	3,086	-2,651 to 8,823	No	ns	0,67 E-G
R266H vs. D97S	2,807	-3,459 to 9,074	No	ns	0,8269 F-G

Fig. S5C. PD Average Vesicle Size per Cell, SH-S5Y5 CTSD KO cells

Number of families	1
Number of comparisons per family	21
Alpha	0,05

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
mock vs. wt	0,3033	0,1336 to 0,4729	Yes	****	<0,0001 A-B
mock vs. V97S	0,2862	0,1166 to 0,4558	Yes	****	<0,0001 A-C
mock vs. G145V	0,3271	0,1634 to 0,4908	Yes	****	<0,0001 A-D
mock vs. A239V	0,299	0,1325 to 0,4655	Yes	****	<0,0001 A-E
mock vs. R266H	0,3743	0,1925 to 0,5562	Yes	****	<0,0001 A-F
mock vs. D97S	0,2965	0,1353 to 0,4577	Yes	****	<0,0001 A-G
wt vs. V97S	-0,01706	-0,1947 to 0,1606	No	ns	>0,9999 B-C
wt vs. G145V	0,02381	-0,1482 to 0,1958	No	ns	0,9996 B-D
wt vs. A239V	-0,004274	-0,1789 to 0,1704	No	ns	>0,9999 B-E
wt vs. R266H	0,07107	-0,1183 to 0,2604	No	ns	0,9173 B-F
wt vs. D97S	-0,006765	-0,1764 to 0,1629	No	ns	>0,9999 B-G
V97S vs. G145V	0,04087	-0,1311 to 0,2129	No	ns	0,9914 C-D
V97S vs. A239V	0,01279	-0,1619 to 0,1874	No	ns	>0,9999 C-E
V97S vs. R266H	0,08813	-0,1012 to 0,2775	No	ns	0,7998 C-F
V97S vs. D97S	0,01029	-0,1593 to 0,1799	No	ns	>0,9999 C-G
G145V vs. A239V	-0,02809	-0,1970 to 0,1408	No	ns	0,9988 D-E
G145V vs. R266H	0,04726	-0,1368 to 0,2313	No	ns	0,987 D-F
G145V vs. D97S	-0,03058	-0,1943 to 0,1331	No	ns	0,9977 D-G
A239V vs. R266H	0,07534	-0,1112 to 0,2619	No	ns	0,8863 E-F
A239V vs. D97S	-0,002492	-0,1690 to 0,1640	No	ns	>0,9999 E-G
R266H vs. D97S	-0,07783	-0,2597 to 0,1040	No	ns	0,8555 F-G

Fig. S5D. Mature Cathepsin D/ Immature Cathepsin D (norm. to CTSD wt), SH-S5Y5 CTSD KO cells

Number of families	1
Number of comparisons per family	15
Alpha	0,05

Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value
wt vs. V95I	0,3254	-0,8597 to 1,510	No	ns	0,9622 B-C
wt vs. G145V	-0,3004	-1,485 to 0,8847	No	ns	0,9732 B-D
wt vs. A239V	-0,448	-1,633 to 0,7370	No	ns	0,8667 B-E
wt vs. R266H	-0,2634	-1,449 to 0,9216	No	ns	0,985 B-F
wt vs. D97S	-1,093	-2,278 to 0,09242	No	ns	0,0859 B-G
V95I vs. G145V	-0,6258	-1,811 to 0,5593	No	ns	0,6181 C-D
V95I vs. A239V	-0,7734	-1,959 to 0,4116	No	ns	0,3884 C-E
V95I vs. R266H	-0,5888	-1,774 to 0,5962	No	ns	0,6765 C-F
V95I vs. D97S	-1,418	-2,603 to -0,2330	Yes	*	0,0109 C-G
G145V vs. A239V	-0,1477	-1,333 to 1,037	No	ns	0,999 D-E

G145V vs. R266H	0,03695	-1,148 to 1,222	No	ns	>0,9999	D-F
G145V vs. D97S	-0,7923	-1,977 to 0,3928	No	ns	0,3618	D-G
A239V vs. R266H	0,1846	-1,000 to 1,370	No	ns	0,9971	E-F
A239V vs. D97S	-0,6446	-1,830 to 0,5405	No	ns	0,588	E-G
R266H vs. D97S	-0,8292	-2,014 to 0,3559	No	ns	0,3126	F-G

Fig. S5E. Mature Cathepsin D/ Immature Cathepsin D (norm. to CTSD wt), H4 CTSD KO cells

Number of families	1					
Number of comparisons per family	15					
Alpha	0,05					
Tukey's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	
wt vs. V95I	-0,4564	-1,727 to 0,8138	No	ns	0,8539	A-B
wt vs. G145V	-0,9487	-2,219 to 0,3215	No	ns	0,2142	A-C
wt vs. A239V	-0,8643	-2,236 to 0,5076	No	ns	0,374	A-D
wt vs. R266H	-0,3723	-1,643 to 0,8978	No	ns	0,9309	A-E
wt vs. D97S	-1,693	-2,963 to -0,4225	Yes	**	0,0058	A-F
V95I vs. G145V	-0,4923	-1,763 to 0,7779	No	ns	0,8117	B-C
V95I vs. A239V	-0,4079	-1,780 to 0,9640	No	ns	0,927	B-D
V95I vs. R266H	0,08406	-1,186 to 1,354	No	ns	>0,9999	B-E
V95I vs. D97S	-1,236	-2,506 to 0,03395	No	ns	0,059	B-F
G145V vs. A239V	0,08438	-1,288 to 1,456	No	ns	>0,9999	C-D
G145V vs. R266H	0,5764	-0,6938 to 1,847	No	ns	0,6972	C-E
G145V vs. D97S	-0,7439	-2,014 to 0,5263	No	ns	0,4495	C-F
A239V vs. R266H	0,492	-0,8800 to 1,864	No	ns	0,8549	D-E
A239V vs. D97S	-0,8283	-2,200 to 0,5437	No	ns	0,4179	D-F
R266H vs. D97S	-1,32	-2,590 to -0,05011	Yes	*	0,0391	E-F

Fig. S6B. a-Synuclein Signal Western Blot (norm. to mock)

Dunnett's multiple comparisons test	Mean Diff,	95,00% CI of diff,	Significant?	Summary	Adjusted P Value	A-?
mock vs. BafA1	-1,165	-2,089 to -0,2399	Yes	*	0,0216	B
mock vs. PepA	-1,518	-2,443 to -0,5937	Yes	**	0,0074	C