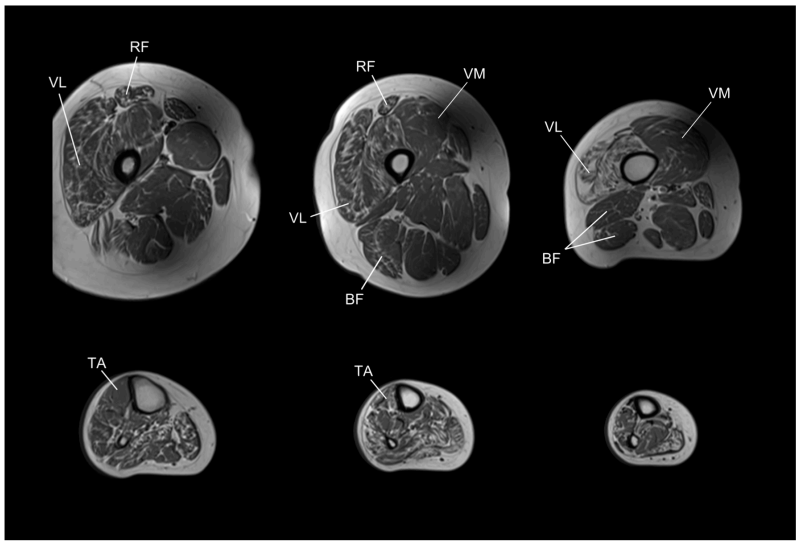

Figure S1: MRI from proband of UK1 family. Upper panel: Axial T1-weighted images of the proximal, mid- and distal right thigh demonstrating moderate fatty replacement of vastus lateralis (VL), especially the distal portion. Rectus femoris (RF) and biceps femoris (BF) are mildly affected, whilst vastus medialis is relatively spared. Lower panel: Axial T1-weighted images of the proximal, mid- and distal right calf demonstrating mild-to-moderate streaky fatty replacement of all muscles with relative preservation of the tibialis anterior (TA) proximally.

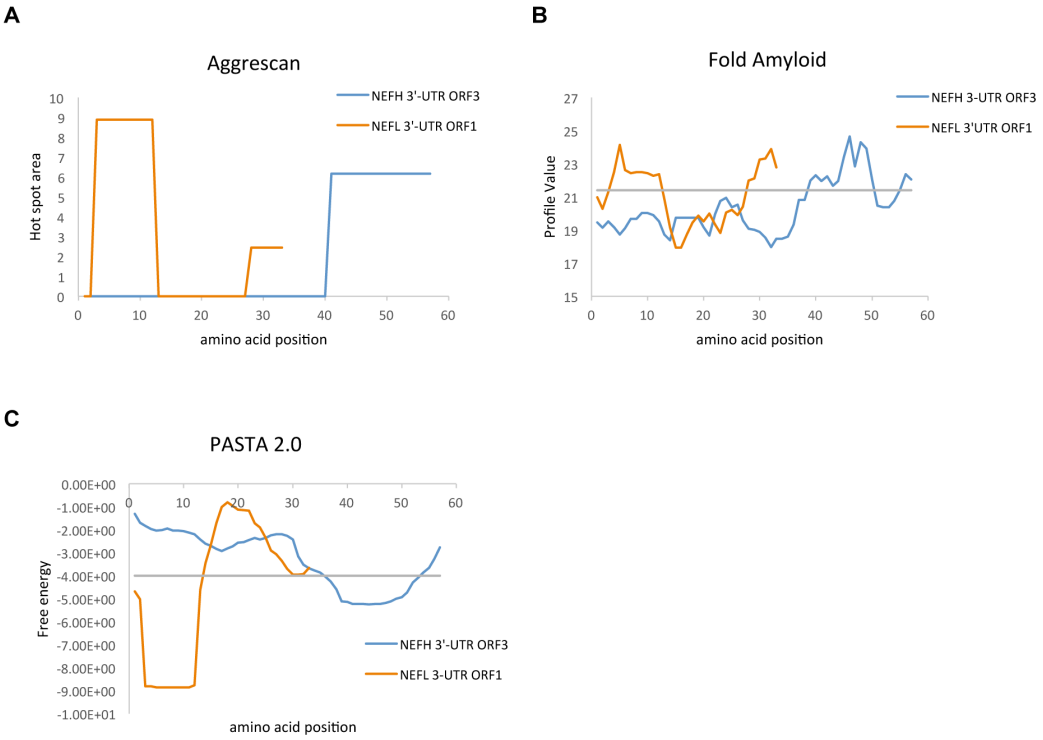

Figure S2. Aggregation scores for NEFH-3'-UTR ORF3 and NEFL-3'-UTR ORF1 using different prediction tools: (A) Aggrescan, **(B)** Fold Amyloid and **(C)** PASTA 2.0.

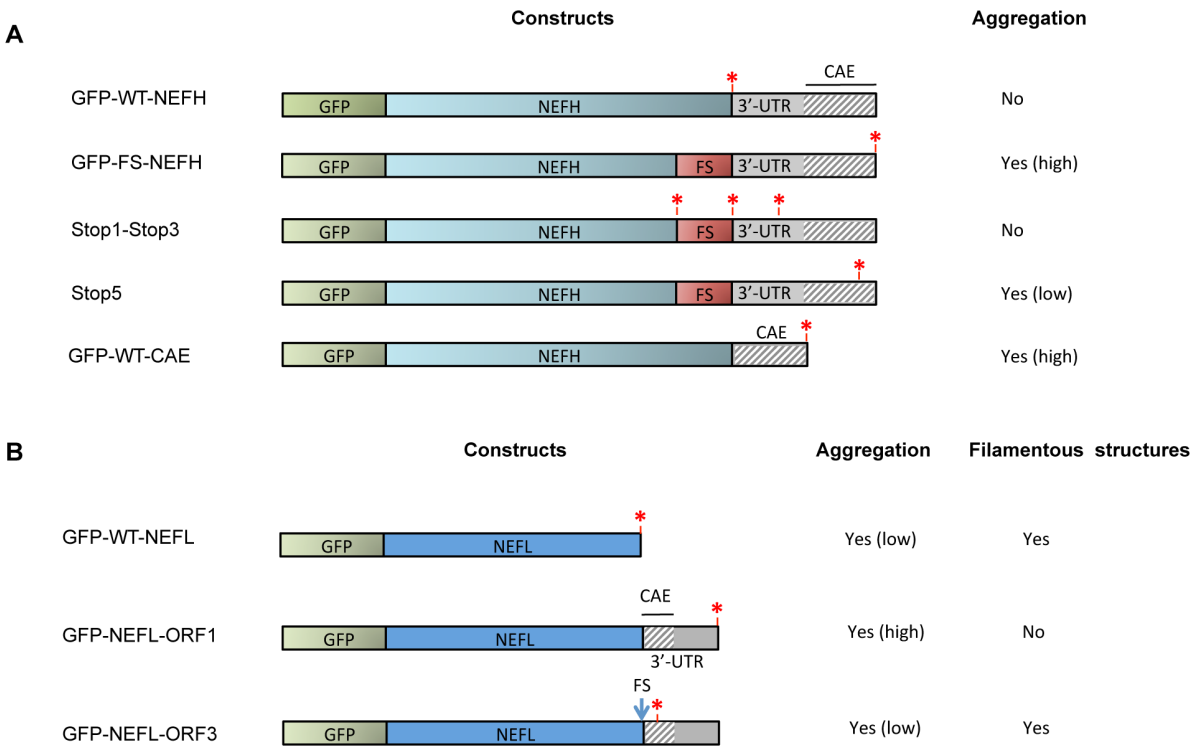

Figure S3. Evaluation of aggregation in cells expressing different size length of the NEFH mutant extension. Diagram illustrates constructs and aggregation results in transfected cells. Red asterisk indicates stop codon. Predicted cryptic amyloidogenic element (CAE) is indicated by grey striped pattern. **(A)** GFP-WT-NEFH construct shows full-length NEFH gene with original stop codon upstream the 3'-UTR. GFP-FS-NEFH showing frameshift (FS) and translation of the 3'-UTR. Stop1-Stop4: Series of truncated GFP-FS-NEFH constructs with stop codons at 4 different positions throughout the NEFH mutant amino acids extension resulted in no aggregation. Stop4 resulted in few cells with aggregates. GFP-WT-NEFH depicts wild-type NEFH without the original stop-codon fused to CAE resulted in high levels of aggregates. **(B)** GFP-WT-NEFL construct and NEFL constructs encoding 3'-UTR ORF1 and ORF2.

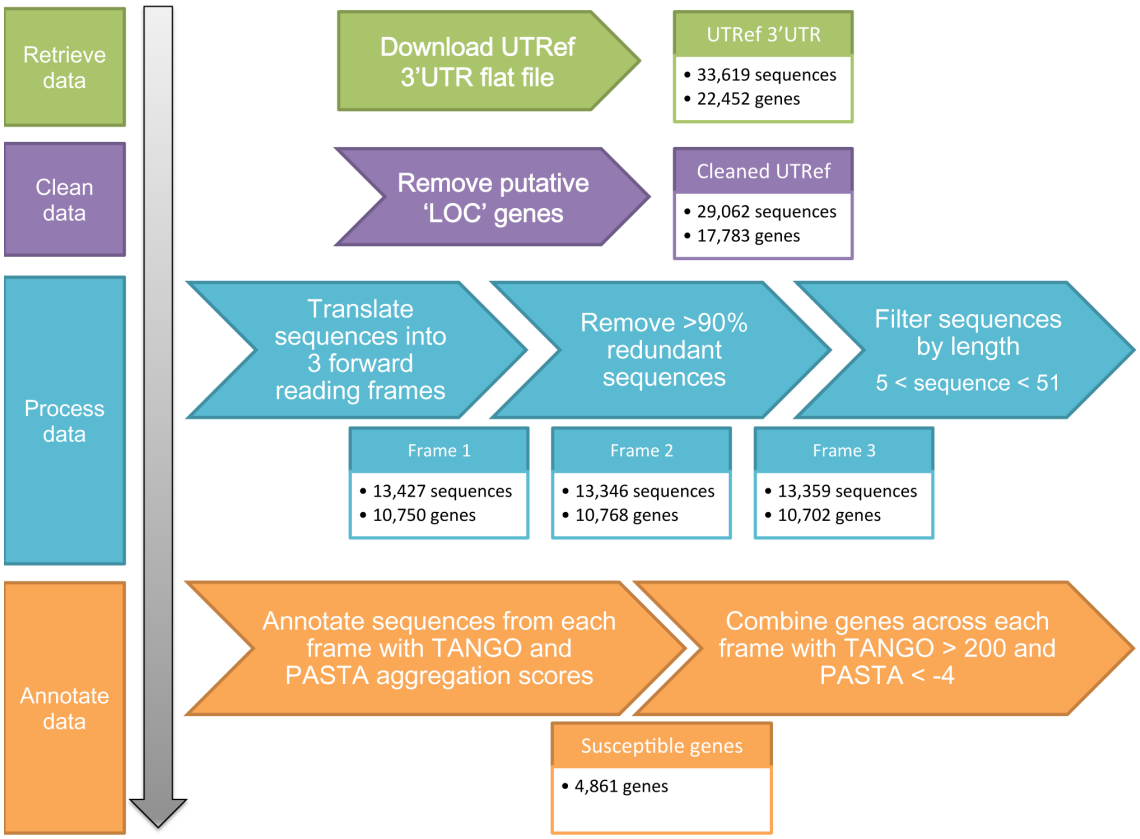

Figure S4. Bioinformatics aggregation prediction analysis of the human 3'-UTRef. Open-reading frames of human 3'-UTRefs were filtered for TANGO score > 200 and PASTA 2.O free energy score > -4.

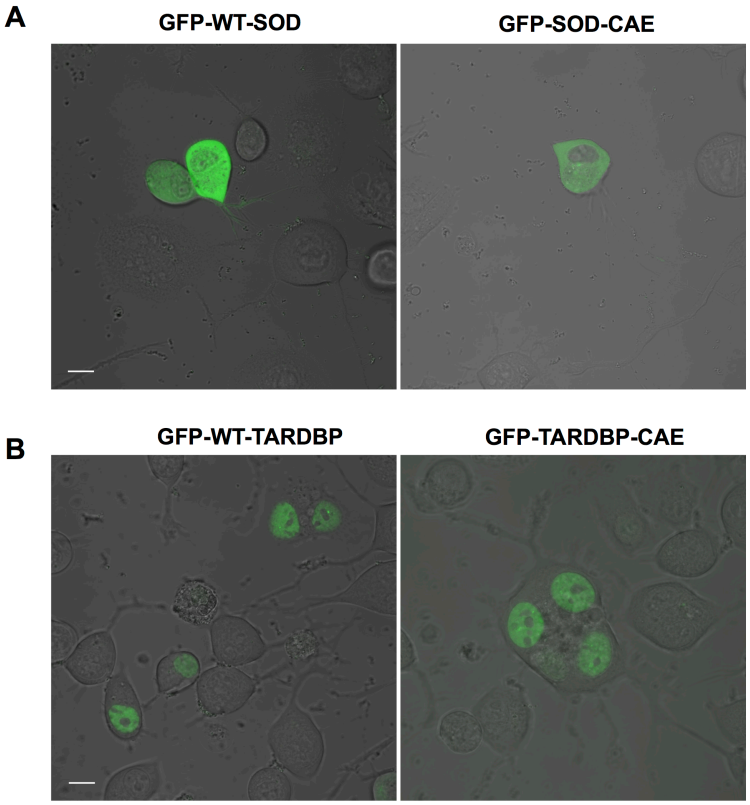

Figure S5: Expression of SOD1 and TARDBP fused to their predicted 3-UTR CAE do not cause aggregation. **(A)** SOD is diffusely expressed in both wild-type and SOD encoding the 3'-UTR-CAE. **(B)** TARDBP is localized to the nucleus in both wild-type (GFP-WT-TARDBP) and TARDBP encoding the 3-UTR-CAE.

Table S1. List of candidate genes from UK1 family's exome data

seattleseq_gene	MIM	pos	Ref	genotype	protein_notation	polyphen	gerp_score
NEFH	162230	29886637	AAG/AAG	AAG/A	p.Asp1004fs*56		
DNAH17	610063	76440872	G/G	G/A	p.S3781L	0.679	5.12
LYST	606897	235944236	C/C	C/T	p.E1715K	0.856	5.05
MED20	612915	41877152	A/A	A/G	p.V93A	0.309	5.91
PFKFB3	605319	6258150	T/T	T/C	p.I101T	0.995	5.11
SPAG5	615562	26905701	C/C	C/T	p.G1063S	1	3.49
TRAF4	602464	27076455	G/G	G/A	p.G425S	0.025	6.11

Table S2. List of aggregation disease genes predicted to contain a 3'-UTR CAE.

				Frame 1		Frame 2		Frame 3	
Gene	Gene MIM Number	Disease	Phenotype MIM	TANGO	PASTA	TANGO	PASTA	TANGO	PASTA
APOA2	107670	Apolipoprotein A-II deficiency	143890	182.8	no	0.0	no	0.0	no
ATXN2	601517	Spinocerebellar ataxia 2	183090	989.1	-7.9	76.5	no	853.0	-7.7
B2M	109700	Amyloidosis	105200	no	no	2265.7	-17.6	181.1	no
FGB	134830	Hypofibrinogenemia, congenital	202400	358.3	-3.5	998.2	-13.9	no	no
FUS	137070	Amyotrophic lateral sclerosis (ALS)	608030	1323.0	no	no	no	48.4	no
IAPP	147940	Type II diabetes	125853	no	no	541.1	-10.9	no	no
LYZ	153450	Amyloidosis	105200	183.1	no	962.9	-6.5	160.7	-5.7
NOTCH3	600276	Cerebral arteriopathy	125310	no	no	no	no	566.0	-5.1
PRNP	176640	Prion disease	606688	0.0	no	896.1	-10.3	no	no
RHO	180380	Retinitis pigmentosa	613731	697.1	-7.0	no	no	no	no
SAA1	104750	Amyloidosis	105210	no	no	no	no	326.2	-4.1
SNCA	163890	Parkinson's disease	168601	no	no	4.4	no	1442.5	-9.0
SOD1	147450	Amyotrophic lateral sclerosis (ALS)	105400	no	no	568.1	-7.0	6.7	no
TARDBP	605078	Amyotrophic lateral sclerosis (ALS)	612069	714.6	-5.8	no	no	464.4	-10.0
NEFL	162280	Charcot-marie tooth	607734	445.6	-8.7	no	no	5.5	-2.9
BSCL2	606158	Neuropathy, distal hereditary motor	600794	126.7	no	0.6	no	1.2	no
MAPT	157140	Parkinson disease	168600	no	no	156.6	no	6.7	no
TTR	176300	Amyloidosis	105210	0.0	no	0.0	no	112.3	no