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Supplemental Data

Mutation in *TECPR2* Reveals a Role for Autophagy in Hereditary Spastic Paraparesis

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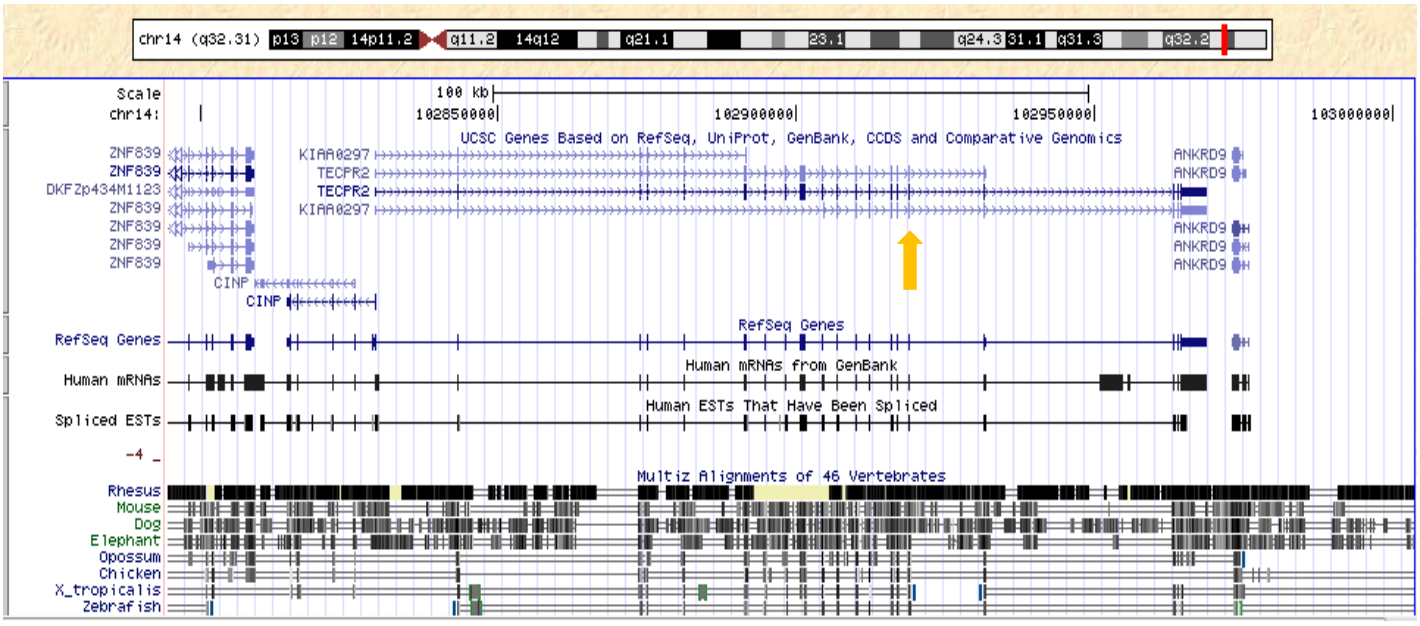


Figure S1. Location and Conservation of the Deletion in *TECPR2*

Adapted from the UCSC Genome Browser (GRCh37/hg19). The region shown is chr14: 211,818,201-211,081,201which encompasses *TECPR2* (transcript uc001ylw.1 [ENST00000359520]). The frameshift mutation is located in exon 16 (orange arrow), highly conserved among vertebrates (multiz alignment of 46 vertebrates). The protein is encoded on the plus DNA strand, thus the 5' end and the N-terminus are displayed on the left.

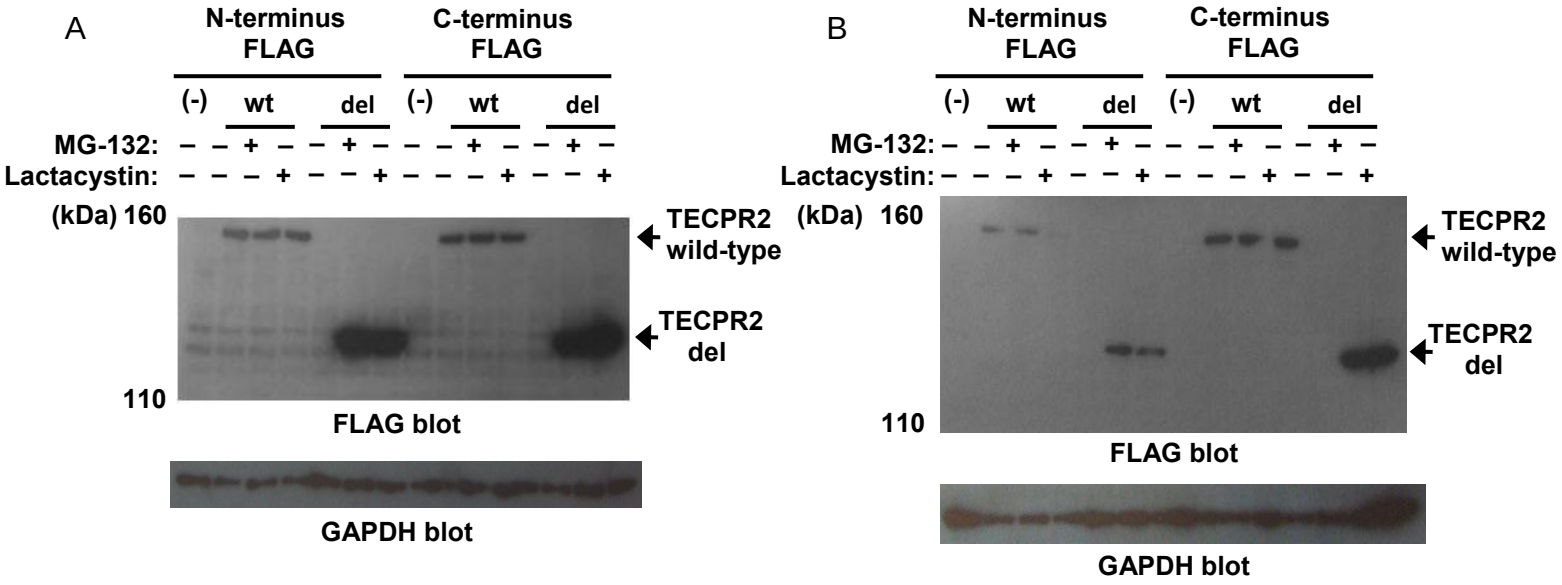


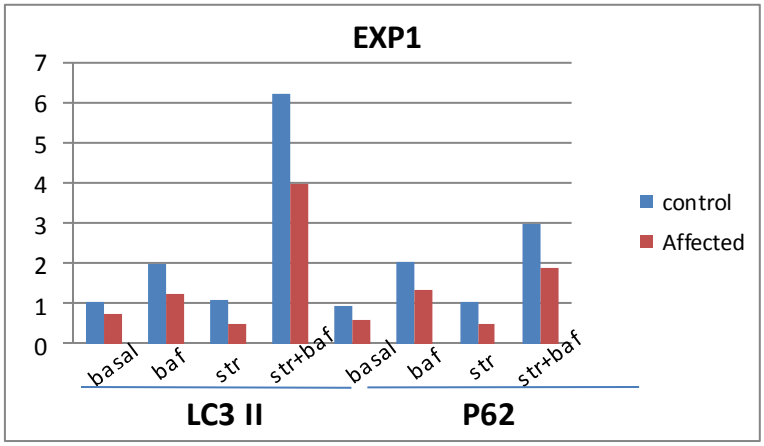
Figure S2. Effect of FLAG-Tagged TECPR2 on the Mutation

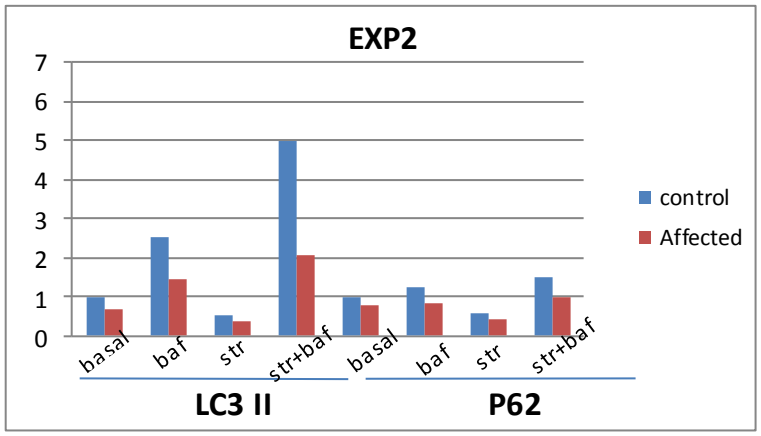
Expressions of each alleles of N-terminus or C-terminus FLAG tagged TECPR2 and their effects of proteasome inhibition with MG132 and Lactacystin. (A) Immunoblotting with anti-FLAG monoclonal antibody for HEK293 transfectants of N-terminus or C-terminus FLAG tagged TECPR2. (-),empty vector; GAPDH, loading control. (B) Immunoblotting with anti-FLAG monoclonal antibody for HeLa transfectants of N-terminus or C-terminus FLAG tagged TECPR2. Data supports the results in Figure 3D,E with the same notations.

Plasmid preparation: First half and second half of cDNAs encoding human TECPR2 were amplified from the human kidney cell line HEK-293 with RNeasy plus (QIAGEN, Santa Clarita, CA), High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster city, CA), PfuUltra II Fusion HS DNA Polymerase (Agilent Technologies, Palo Alto, CA), with primer sets shown in Table S3. cDNAs were subcloned into the pCR-Blunt II-TOPO vector (Invitrogen-Life Technologies, Carlsbad, CA, USA) and subjected to sequence analysis. Using pCR-Blunt II-TECPR2-2nd-3416T, 3416delT of TECPR2 was made by PCR-directed mutagenesis using Phusion HF DNA polymerase and specific T4-phosphorylated primer set, and amplicon was self-ligated using T4 DNA ligase (Promega, Madison, WI), and subjected to sequence analysis. Using pCR-blunt II-TECPR2-1st, N-terminus FLAG was made by two-step PCR-directed mutagenesis using Phusion HF DNA polymerase and specific T4-phosphorylated primer sets, self-ligated using T4 DNA ligase, and subjected to sequence analysis. Using pCR-Blunt II-TECPR2-2nd-3416T or pCR-Blunt II-TECPR2-2nd-3416delT, C-terminus FLAG was made by the same way. cDNA encoding 1st half of human TECPR2 which was subcloned into pCR-blunt II vectors that included the second half of TECPR2, using the Sal I sites from pCR-blunt II vectors which include first half of TECPR2. cDNAs encoding full length N-terminus or C-terminus FLAG-tagged human TECPR2 which contain each of the alleles were subcloned into pcDNA3.1(+) vector (Invitrogen-Life Technologies) using the KpnI and XhoI sites and subjected to sequence analysis.

Inhibiting the proteasome pathway: Empty pcDNA3.1 (+) vector, pcDNA3.1(+)-TECPR2-3416T-N-FLAG, pcDNA3.1(+)-TECPR2-3416delT-N-FLAG, pcDNA3.1(+)-TECPR2-3416T-C-FLAG or pcDNA3.1(+)-TECPR2-3416delT-C-FLAG were transfected into monkey kidney cell line COS-7, human kidney cell line HEK-293 and human epithelial cell line HeLa by lipofection using Lipofectamine 2000 (Invitrogen-Life Technologies). After 32h, transfectants were incubated with

20μM of MG132 (Sigma Aldrich) and 20μM of Lactacystin (Sigma Aldrich). After 48h of transfection, the cells were lysed with Nupage LDS sample buffer (Invitrogen) with DL-Dithiothreitol (Sigma Aldrich) and the lysates were subjected to SDS–PAGE gel and transferred to a polyvinylidene difluoride membrane (Millipore, Billerica, MA).





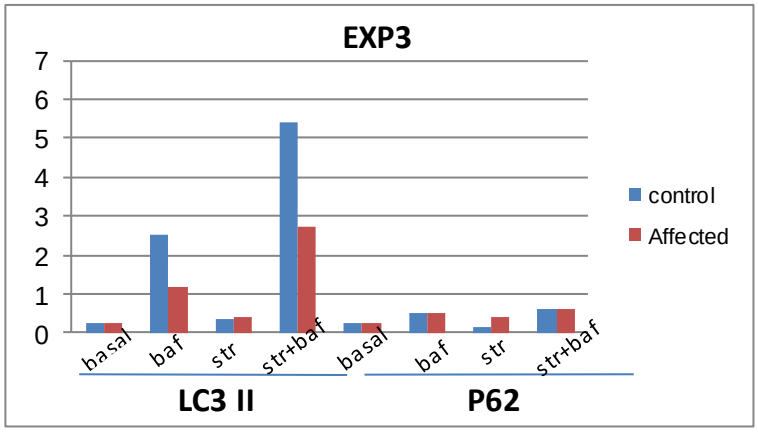


Figure S3. Effect of Mutation on Autophagy Markers in Skin Fibroblasts

Full data supporting the results of the three biological replicates in Figure 4B with the same notations, using immunoblot scan quantitation and normalization by GAPDH (Exp1 and 2) or Actin (Exp 3) control.

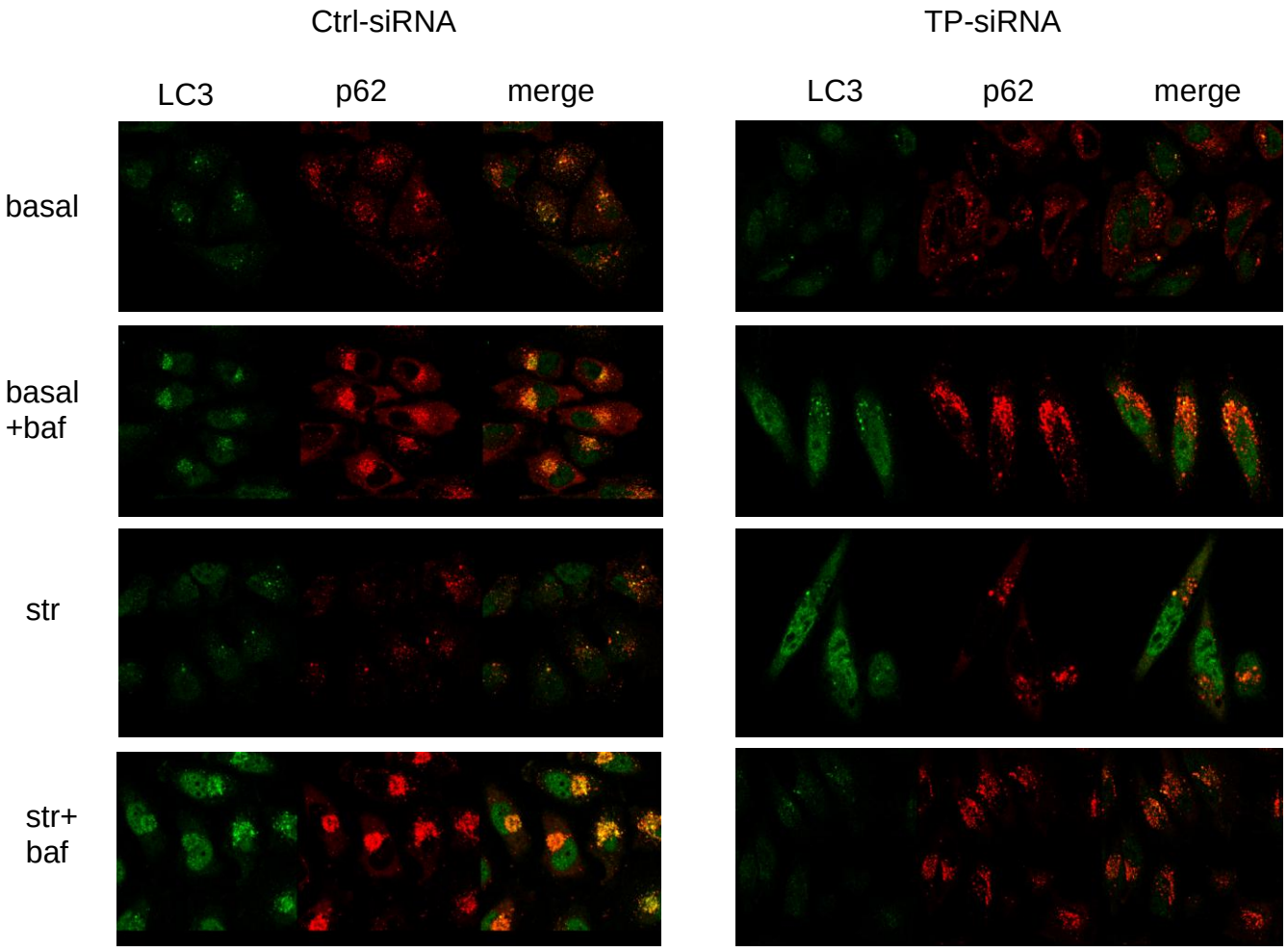


Figure S4. Confocal Immunofluorescence Assays in HeLa Cells

Full data supporting the results in Figure 5C and D with the same notations.

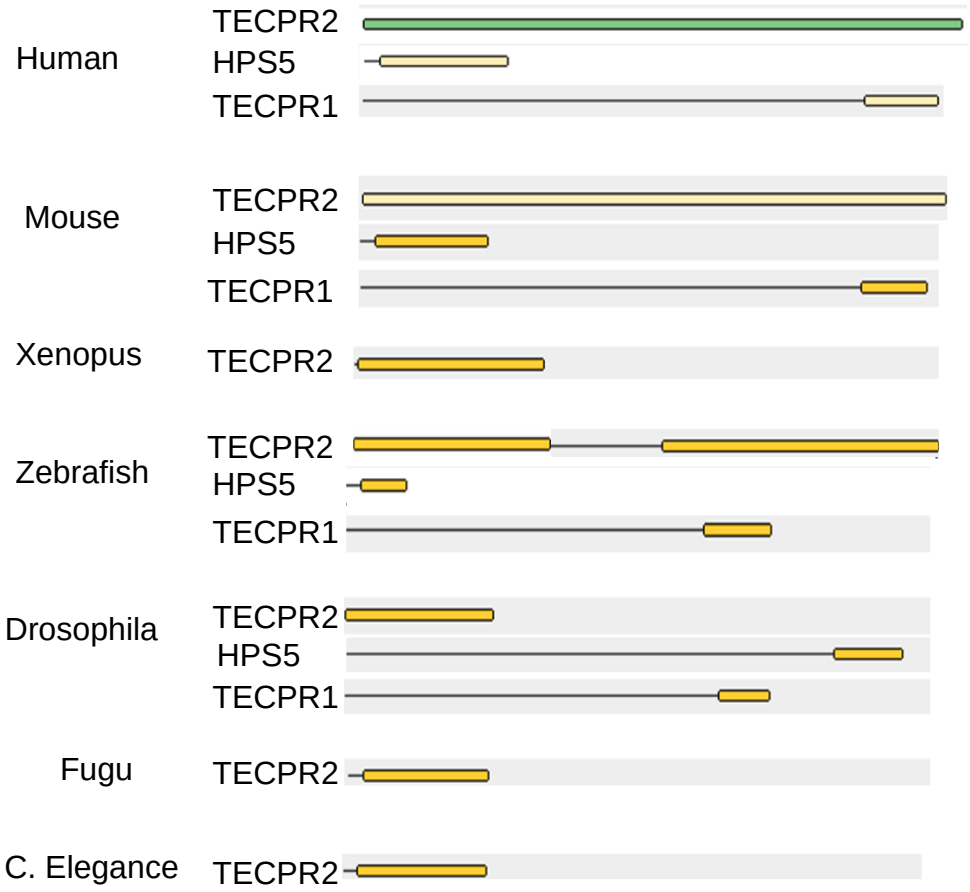


Figure S5. Similarity Search of the TECPR2 Protein

Paralogs and Orthologs of TECPR2. Similarity searches by PairsDB show sequence similarity regions in color. Shown are two different paralogs as well as orthologs in several species.

Table S1. Known Loci and Genes for Hereditary Spastic Paraparesis

Locus	Gene	Chromosome	Inheritance	Form	Other Names	Reference
SPG1	*L1CAM*	X	X-linked	Complicated	MASA	1
SPG2	*PLP1*	X	X-linked	Pure		2
SPG3	*ATL1*	14	Dominant	complicated	Strumpell-Lorrain syndrome	3
SPG4	*SPAST*	2	Dominant	Pure		4
SPG5	*CYP7B1*	8	Recessive	Pure		5
SPG6	*NIPA1*	15	Dominant	Pure		6
SPG7	*SPG7*	16	Recessive	Complicated		7
SPG8	*KIAA0196*	8	Dominant	Pure		8
SPG9		10	Dominant	Complicated		9
SPG10	*KIF5A*	12	Dominant	Pure		10
SPG11	*SPG11*	15	Recessive	Complicated		11
SPG12	*RTN2*	19	Dominant	Pure		12
SPG13	*HSPD1*	2	Dominant	Pure		13
SPG14		3	Recessive	Complicated		14
SPG15	*ZFYVE26*	14	Recessive	Complicated		15
SPG16		X	X-linked	Complicated		16
SPG17	*BSCL2*	11	Dominant	Pure	Silver Syndrome	17
SPG18	*ERLIN2*	8	Recessive	Complicated		18
SPG19		9	Dominant	Pure		19
SPG20	*SPG20* (spartin)	13	Recessive	Complicated	Troyer Syndrome	20
SPG21	*SPG21*	15	Recessive	Complicated	Mast Syndrome	21
SPG22		X	X-linked	Complicated	Allan-Herndon Syndrome	22
SPG23	*SPG23*	1	Recessive	Complicated	Vitiligo Spasticity	23
SPG24		13	Recessive	Pure		24
SPG25		6	Recessive	Complicated		25
SPG26		12	Recessive	Complicated		26
SPG27		10	Recessive	Pure		27
SPG28		14	Recessive	Pure		28
SPG29		1	Dominant	Complicated		29
SPG30	*KIF1A* and *SPG30*	2	Recessive	SPG30- Comp KIF1A- Pure		30
SPG31	*REEP1*	2	Dominant	Pure		31
SPG32		14	Recessive	Complicated		32
SPG33	*ZFYVE27*	10	Dominant	Pure		33
SPG34		X	X-linked	Pure		34
SPG35	*FA2H*	16	Recessive	Complicated		35

SPG36		12	Dominant	Complicated		[36]
SPG37		8	Dominant	Pure		[37]
SPG38		4	Dominant	Complicated	Similar to Silver	[38]
SPG39	*PNPLA6*	19	Recessive	Complicated		[39]
SPG40		14	Dominant	Pure		[40]
SPG41		11	Dominant	Pure		[41]
SPG42	*SLC33A1*	3	Dominant	Pure		[42]
SPG43		19	Recessive	Complicated		[43]
SPG44	*GJC2*	1	Recessive	Complicated		[44]
SPG45		10	Recessive	Complicated		[45]
SPG46		9	Recessive	Complicated		[46]
SPG47		1	Recessive	Complicated		[47]
SPG48	*KIAA0415*	7	Recessive	Complicated		[48]
SPG49	*TECPR2*	14	Recessive	Complicated		

48 different types of Hereditary Spastic Paraparesis in several mode of inheritance for which 27 genes have been identified. The presently reported disease is proposed to be SPG49.

Table S2. Sequence Variants Identified in Exome Sequencing of Four Affected Individuals with SPG49

Filter	Variants
Total shared variants	3413
Total shared homozygous variants	426
Total Functional (Nonsynonymous, Stop, Frameshift, Splice site	93
Absent in dbSNP132 and 1000 genomes	8
Absent in 909 exome/genome sequenced in- house controls	1

Table S3. Primers Used in This Study

(A) **Genotyping Primers**

Primer Name	**Primer Sense**	**Primer Sequence (5' – 3')**
3416delT (1,098 controls)	**Forward**	CATGACCCCTTTCTGCAGGAA
	Reverse	GCTGCACAGGTCCTTGCT
	Probe	CGAAGG[A/-]CACCGACAC
3416delT (150 controls)	**Forward**	CGTCTGCTGAAAGGC AAAG
	Reverse	CACAGGTCCTTGCTGCTC T

(B) Plasmids Primers

Primer Name	**Primer Sense**	**Primer Sequence (5' – 3')**
cDNA-first half	**Forward**	CCAGGTTTCCCTAGATGACA
	Reverse	TGCAAGTATAGGTCCCCACT
cDNA-second half	**Forward**	TTCTGAACGTGTCTTGGGGA
	Reverse	TCTGGACAAGTGTTGAGGCA
3416delT mutagenesis	**Forward**	GTGGCTGTGCCAGAGCA
	Reverse	GGAAGCTTCCTTCCTTCGT
C-terminus FLAG tag for 3416T-first step	**Forward**	GACAAGTGAAGGAGCCCTGGCCGAGT
	Reverse	GTAGTCGATGACCTCCCACTCGTCCT
C-terminus	**Forward**	GACGATGACAAGTGAAGGAGCCCTGG

FLAG tag for 3416T-second step	**Reverse**	GTCCTTGTAGTCGATGACCTCCCACT
C-terminus FLAG tag for 3416delT -first step	**Forward**	GACAAGTAGGAGCTGTAAAATTGACA
	Reverse	GTAGTCGCTGGGAGAGGTCCAGCCTG
C-terminus FLAG tag for 3416delT - second step	**Forward**	GACGATGACAAGTAGGAGCTGTAAAA
	Reverse	GTCCTTGTAGTCGCTGGGAGAGGTCC
N-terminus FLAG tag first step	**Forward**	GACAAGATGGCATCGATATCCGCGCCTGTTACA
	Reverse	GTAGTCCATGGCCAAGGTTTCCACAGAC
N-terminus FLAG tag second step	**Forward**	GACGATGACAAG ATGGCATCGATATCAGAG
	Reverse	GTCCTTGTAGTC CATGGCCAAGGTTTC

(C) Semi-quantitative RT-PCR Primers

Primer Name	Primer Sense	Primer Sequence (5' – 3')
TECPR2-RT-PCR	**Forward**	GCCCTTCTCTGGAAGATTGA
	Reverse	TGCAAGTATAGGTCCCCACT

(D) Quantitative Real-Time PCR Primers

Primer Name	Primer Sense	Primer Sequence (5' – 3')
TECPR2-EX 16-17	**Forward**	CAGCTAGGAGCTGTAAAATTGACAAG
	Reverse	CGGAAGTAAACTCCACCCCTG

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