Supplementary Information

Title: Mutations in *SNORD118* cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts

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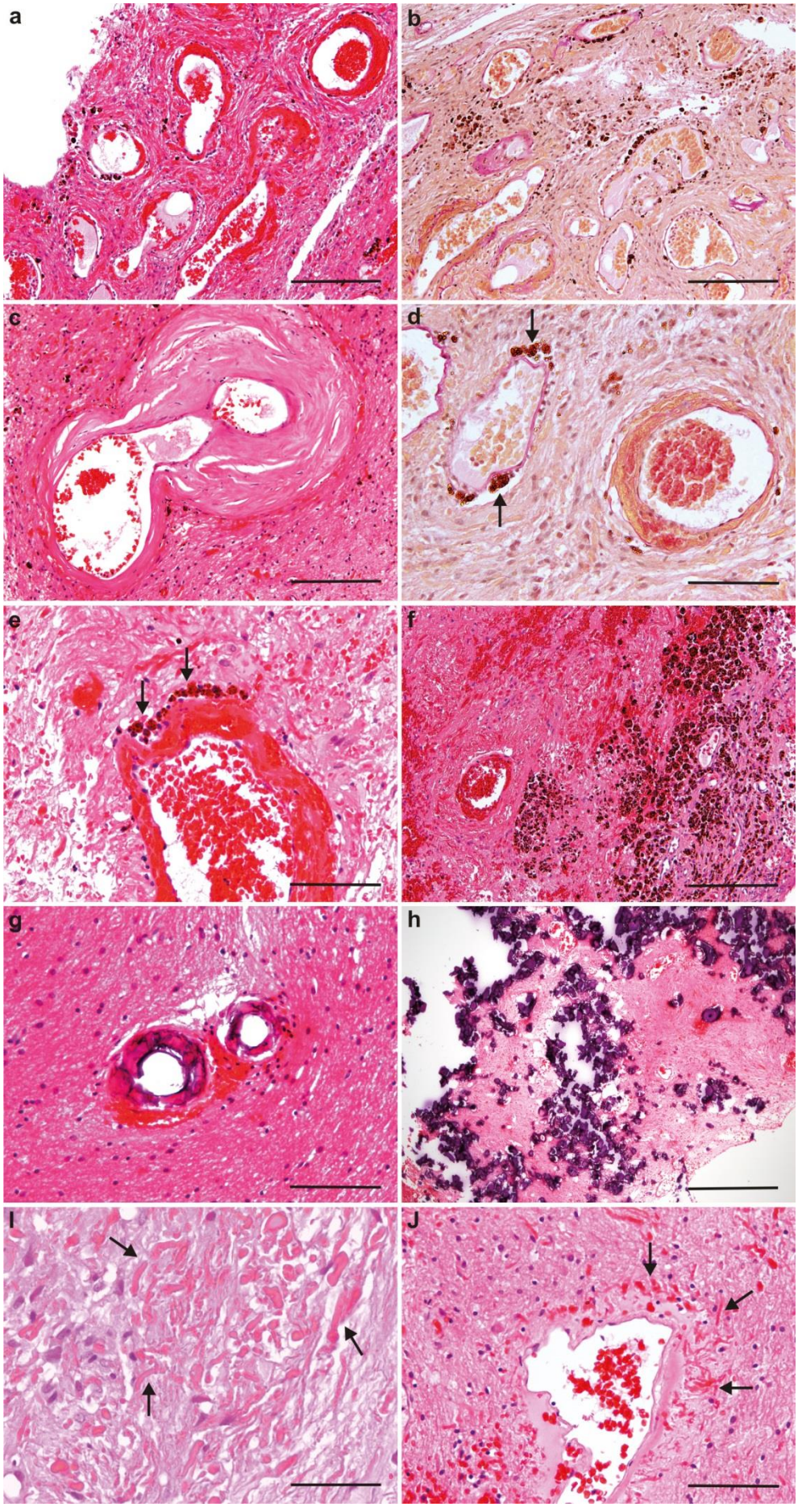
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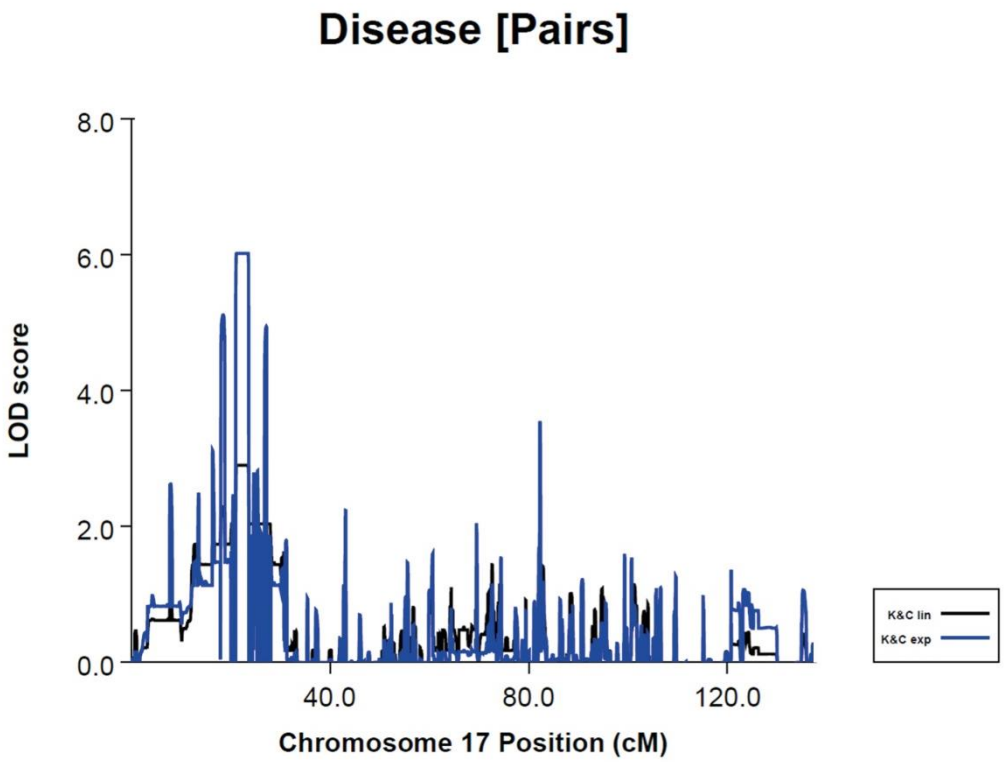
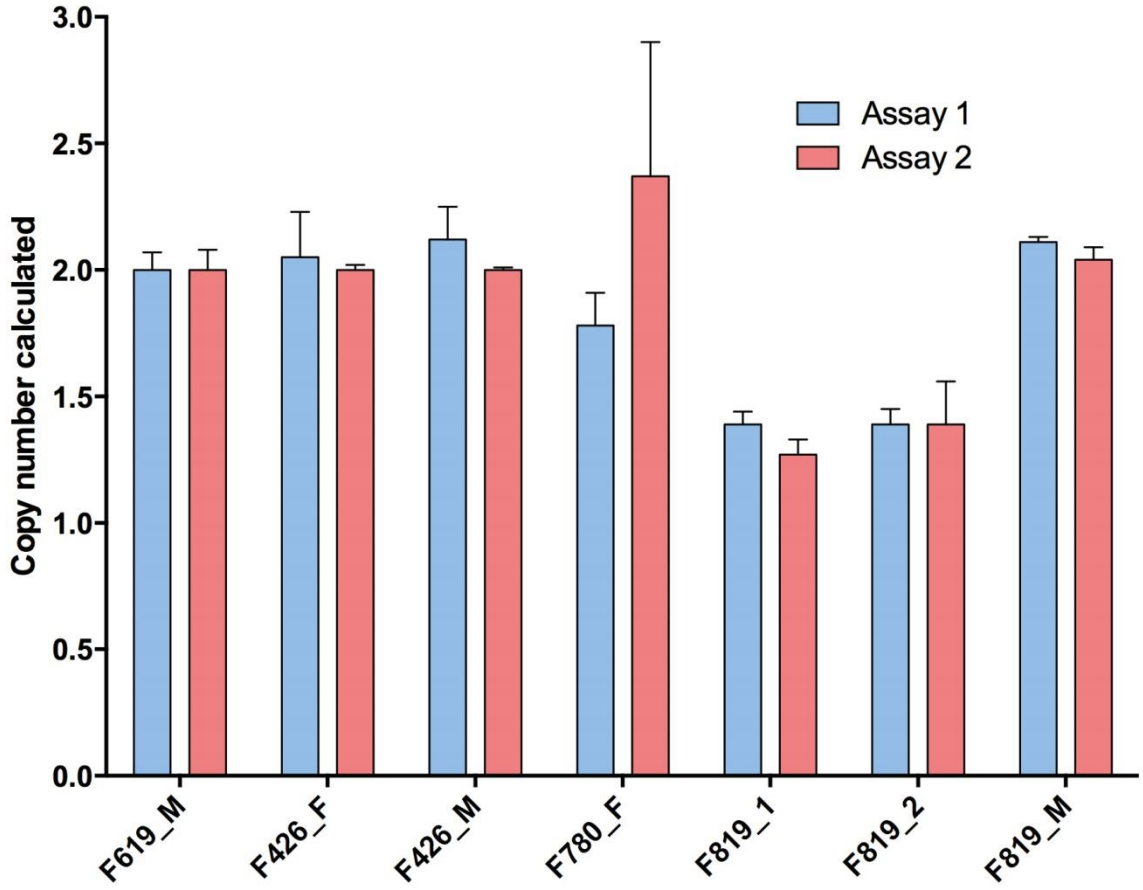
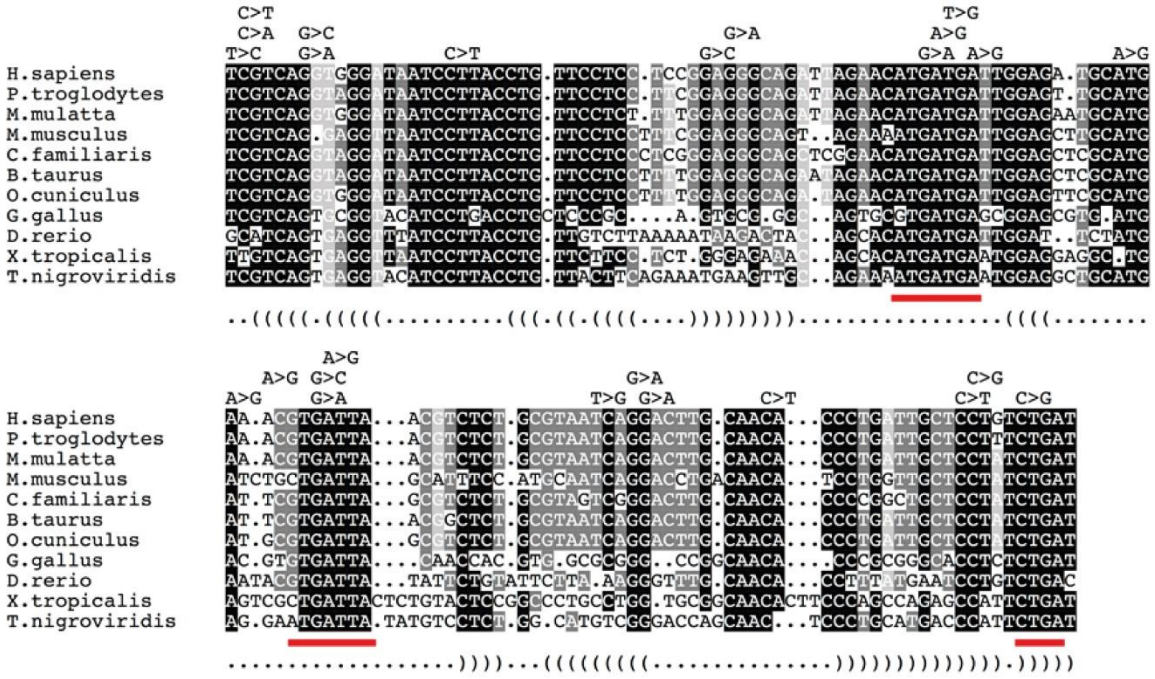
Supplementary Figure 1. **Histopathological characteristics of LCC**. Cerebellar brain biopsy taken from F1172 at the age of 50 years showing numerous blood vessels, with groups of vessels which resemble angioma **(a, b).** The vessels appear ectatic, partially thickened, hyalinized and demonstrate an irregular vessel wall **(c, d).** Inflammatory changes are not evident. Numerous macrophages with hemosiderin deposits around vessels **(d, e,** see arrows**)** and diffusely within the tissue **(f)** indicate old hemorrhage. Both vascular **(g)** and parenchymal **(h)** mineralization is seen. An extensive gliosis with strikingly high numbers of Rosenthal fibers are present in the parenchyma **(i,** some of which are indicated by arrows**)** and around vessels **(j,** marked with arrows**).** Stainings: Hematoxylin and eosin: a, c, e - j; Elastica van Gieson: b, d. Scale bars: a - c, f: 200 µm; d, e, g, j: 100 µm; h: 500 µm; i: 50 µm.



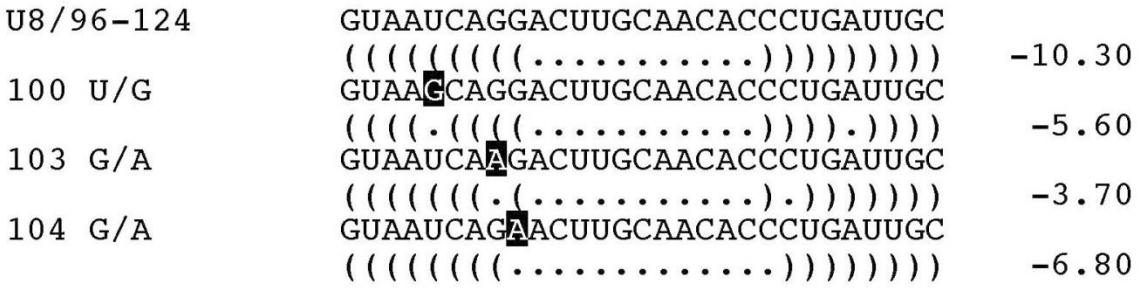
Supplementary Figure 2. **Linkage analysis in seven families**. Nonparametric linkage analysis was performed using the Merlin package in five pairs of affected siblings (F331, F426, F454, F521, F780) born to unrelated parents, and two singletons (F344 and F446) who were the product of independent consanguineous unions. K&C lin = Kong and Cox linear model; K&C exp = Kong and Cox exponential model.



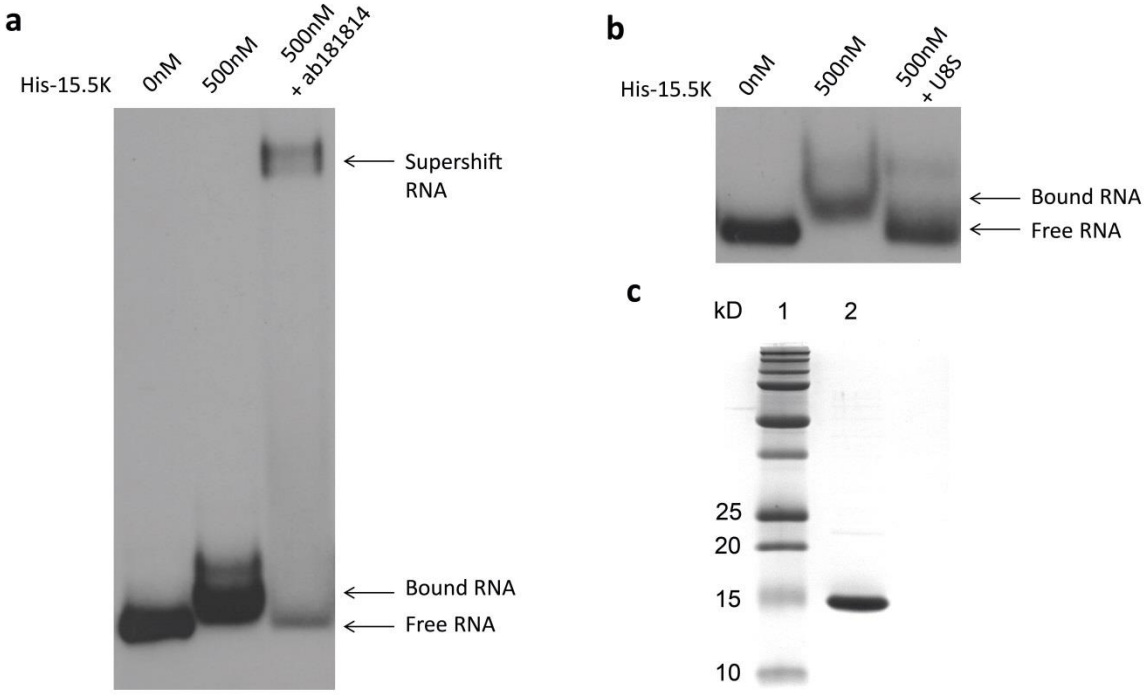
Supplementary Figure 3. ***SNORD118*** **copy number analysis in F819**. Copy number analysis was assessed in F819 using DNA from the two affected individuals (F819_1, F819_2) and their mother (F819_M: paternal DNA not available). These data indicate a loss of the paternally-derived allele in the affected individuals. The parents from 3 other LCC families were used as comparators, with F619_M chosen as the calibrator sample.



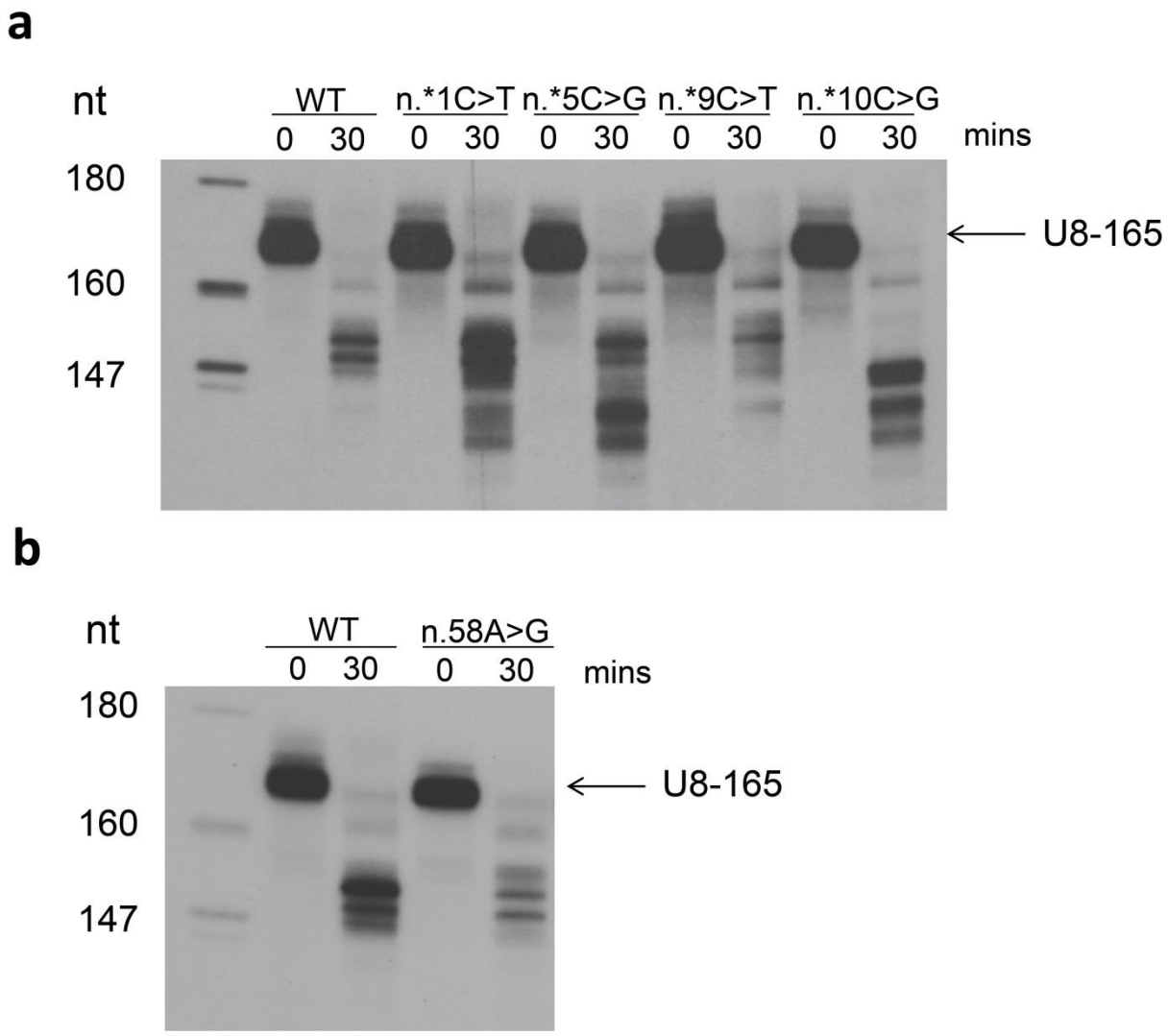
Supplementary Figure 4. Multiple sequence alignment of *SNORD118* sequences. *SNORD118* homologs were identified using Ensembl and Rfam, aligned using CLUSTALW, and the alignment manually refined using RALEE. Nucleotide alterations (not including deletions/insertions/duplications) identified in patients with LCC are annotated above the sequence. From 5' to 3', the C box, LsM binding sites and D box are highlighted by red lines. Aligned columns are coloured according to their sequence conservation: black (>80% identity), dark gray (>60% identity), and light gray (greater than 40% identity). A possible base-paired secondary structure, based on the consensus U8 structure in the Rfam database and analysis with RNAalifold, is shown in dot-bracket notation below the alignment. Homo sapiens (ENST00000363593); P.troglodytes, Pan troglodytes (ENSPTRT00000052278); M.mulatta, Macaca mulatta (ENSMMUT00000034372); B.taurus, Bos taurus (ENSBTAT00000060500); C.familiaris, Canis familiaris (ENSCAFT00000034685); M.musculus, Mus musculus (ENSMUST00000082965); O.cuniculus, Oryctolagus cuniculus (ENSOCUT00000018667); G.gallus, Gallus gallus (ENSGALT00000043652); X.tropicalis, Xenopus tropicalis (ENSXETT00000065858); T.nigroviridis, Tetraodon nigroviridis (ENSTNIT00000023953); D.rerio, Danio rerio (ENSDART00000115749).



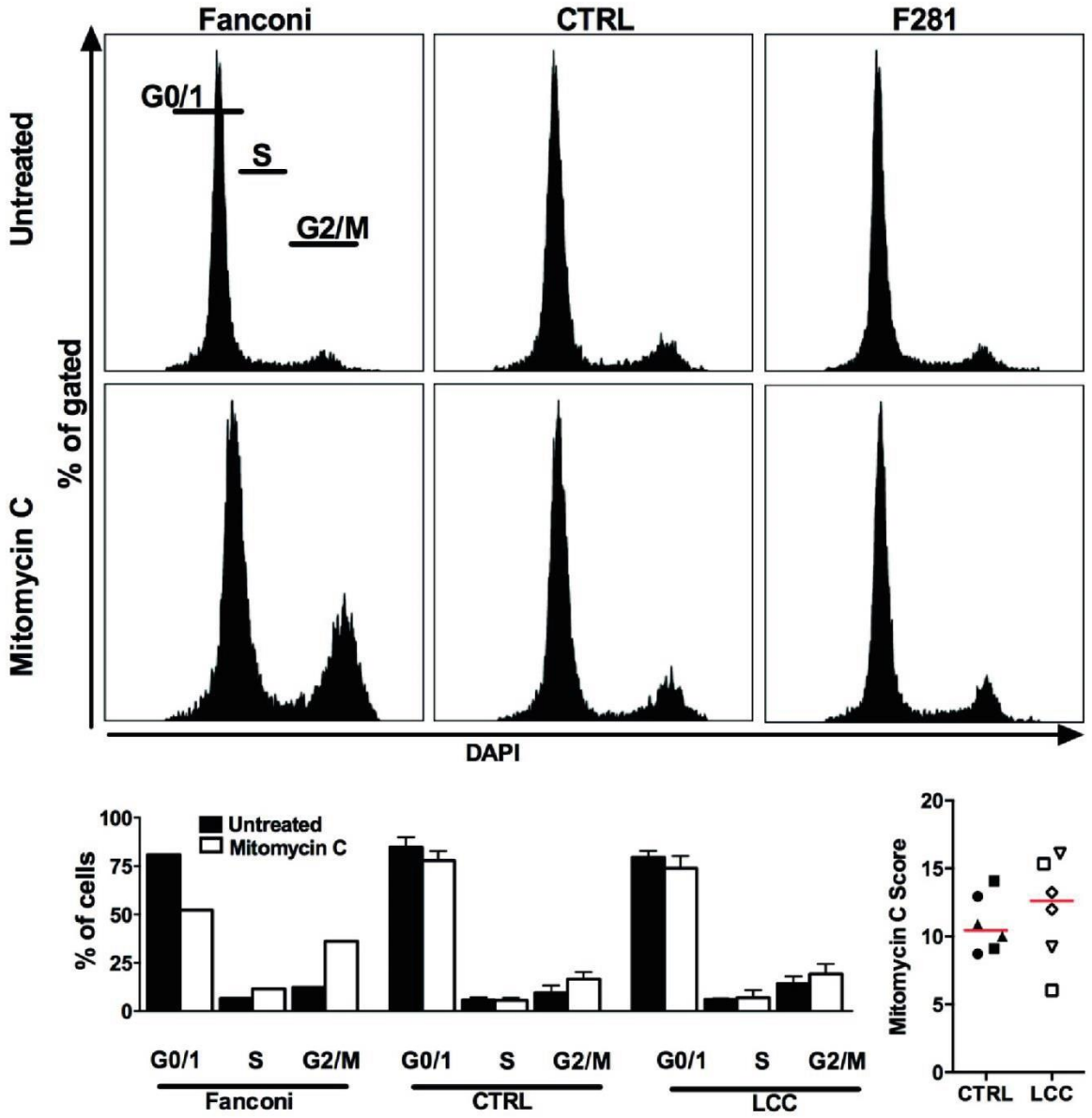
Supplementary Figure 5. *In silico* analysis of LCC patient variants. *In silico* analysis of variants located in the stem of a highly conserved hairpin loop from the predicted structure of U8. Bases 96-124 of the wildtype sequence of U8 are shown with patient variants underneath. The predicted base-paired secondary structure of each sequence is shown in dot-bracket notation, together with the minimum folding free energy (kcal/mol). Each of the three variants detected in LCC patients is predicted to decrease the stability of the hairpin.



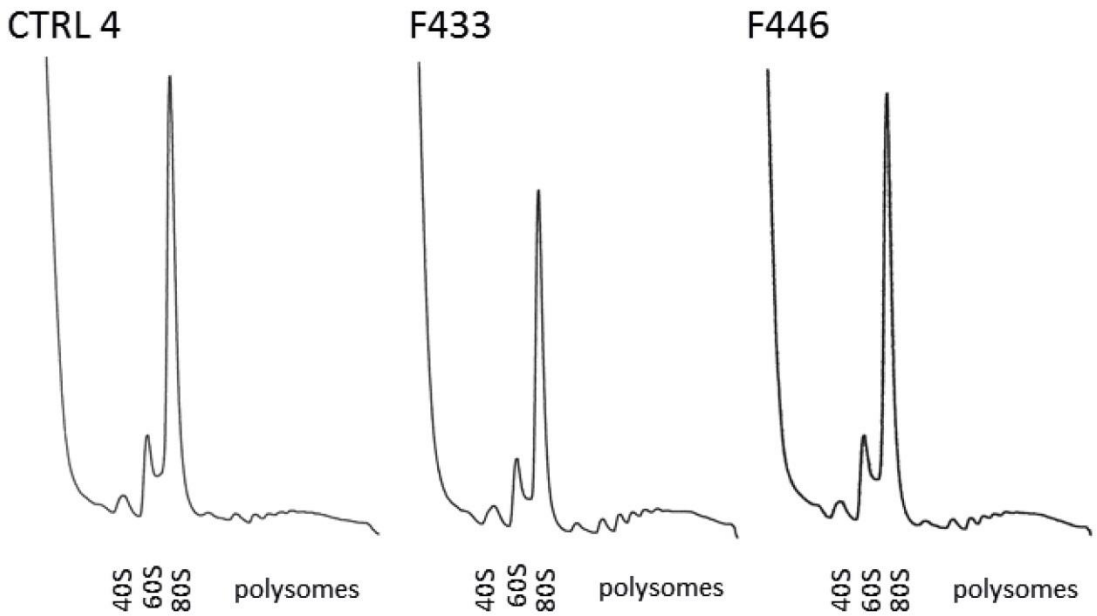
Supplementary Figure 6. 15.5K-U8 snoRNA EMSA control experiments. (a) Addition of a 6XHis antibody (ab18184) causes a super-shift demonstrating that the observed shift in U8 RNA is a result of binding to His-15.5K. **(b)** A competition assay to demonstrate binding specificity. An excess of unlabeled *in vitro* transcribed WT U8 RNA (2.5ug) is sufficient to out-compete 5' end-labeled *in vitro* transcribed U8 RNA and eliminate the band shift. **(c)** Coomasie stained gel showing purified His-15.5K protein. Lane 1 = Precision plus protein dual colour standard (Biorad), lane 2 = purified His-15.5K protein.



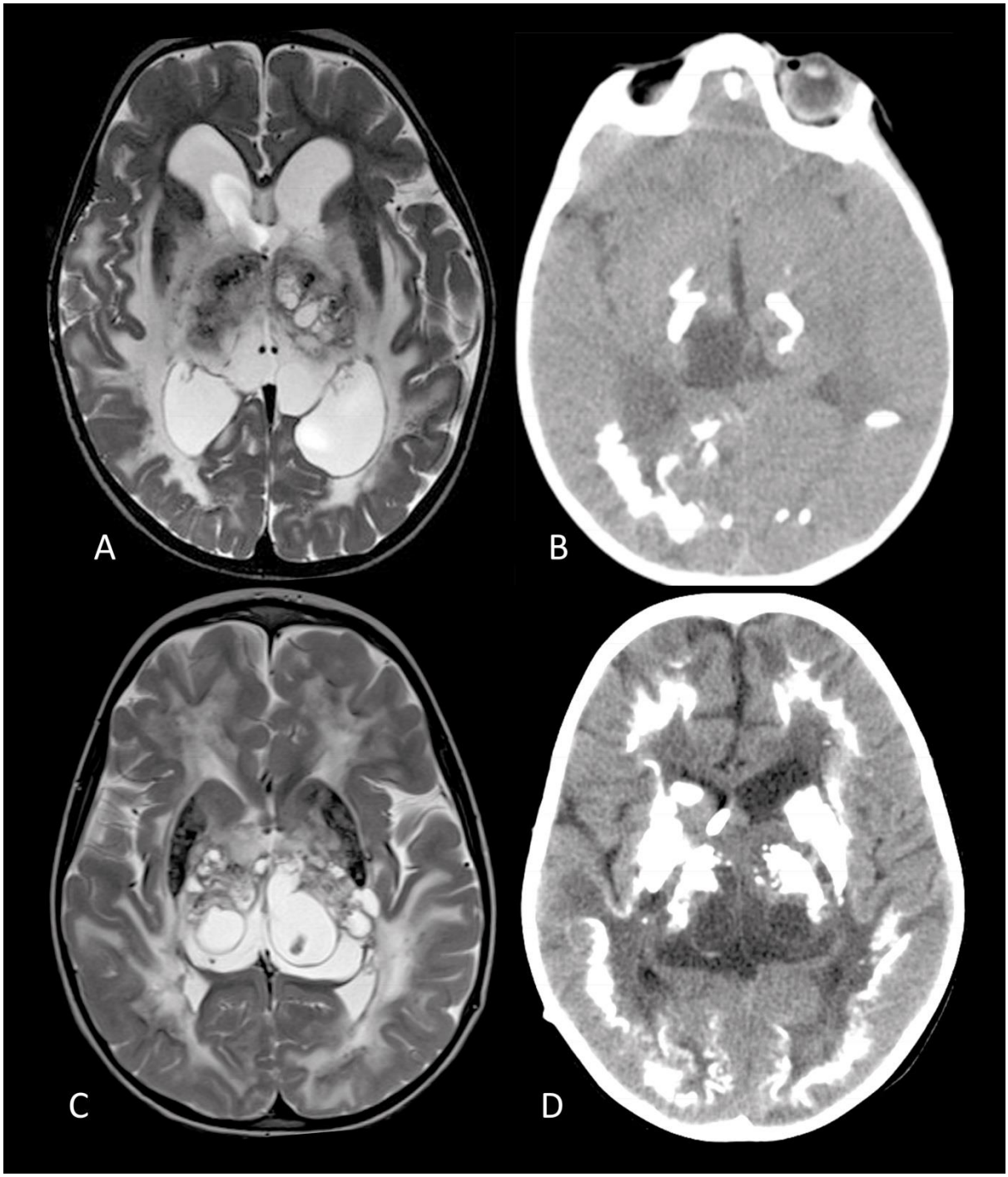
Supplementary Figure 7. U8 snoRNA precursor processing control experiments. (a) 3' end precursor processing of precursor U8 variants in the absence of RNasin. Removal of commercially available RNase inhibitors (RNasin, Promega) does not alter the *in vitro* 3' end processing of 5' end labeled precursor U8 snoRNA (U8-165) in HeLa nuclear extracts. **(b)** 3' end precursor processing of 5' end labeled precursor U8 variant n.58A>G. At 30 minutes the pattern of processing intermediates is the same as WT RNA.



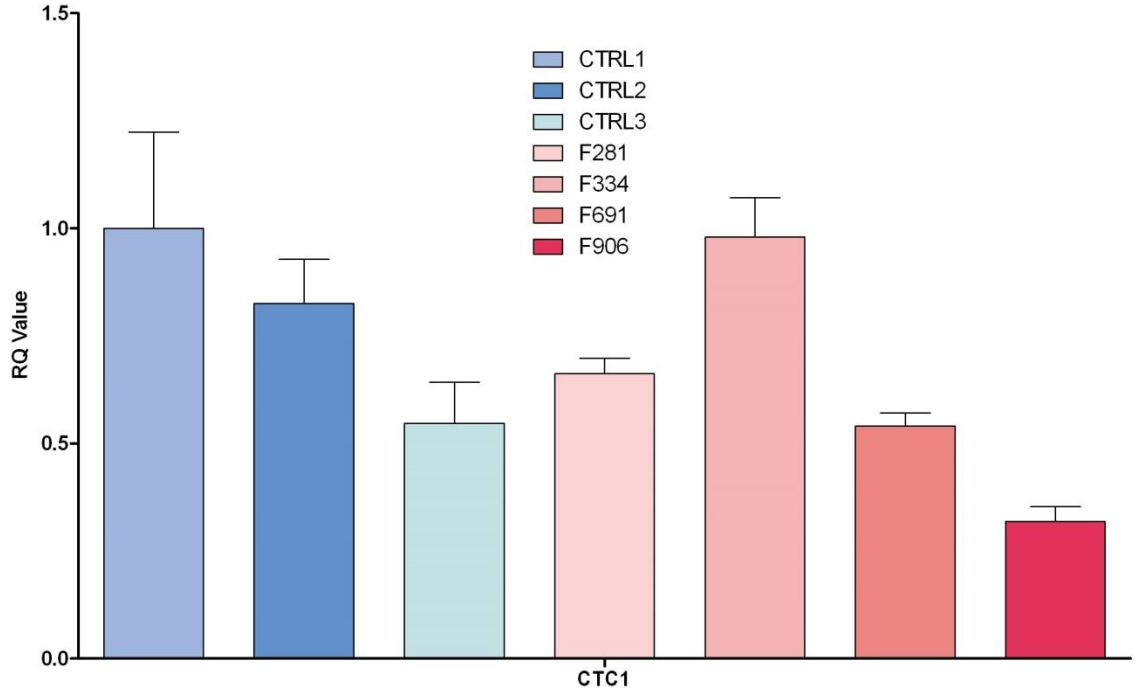
Supplementary Figure 8. Cell cycle analysis. Comparison of the effect of mitomycin C treatment on cell cycling in primary fibroblasts from a patient with Fanconi anemia (n = 1) (positive control), LCC patients (n = 3) and healthy controls (n = 3). Upper panel: representative histogram of DNA content in untreated and mitomycin C treated cells. Lower left panel: Bar graph representation of the percentage of treated or untreated cells in G0/1, S or G2M phase. Data shown are mean +/- SEM. Lower right panel: In order to be able to compare the effect of mitomycin C on cell cycling between controls and LCC patients, compared to cells from a patient with Fanconi anemia, we calculate a mitomycin score with the following formula: (% of increase of S + G2M phase fraction after treatment / % of increase of S + G2M phase fraction of Fanconi cells after treatment) X 100. No significant difference by Mann Whitney U testing; n = 2 experiments.



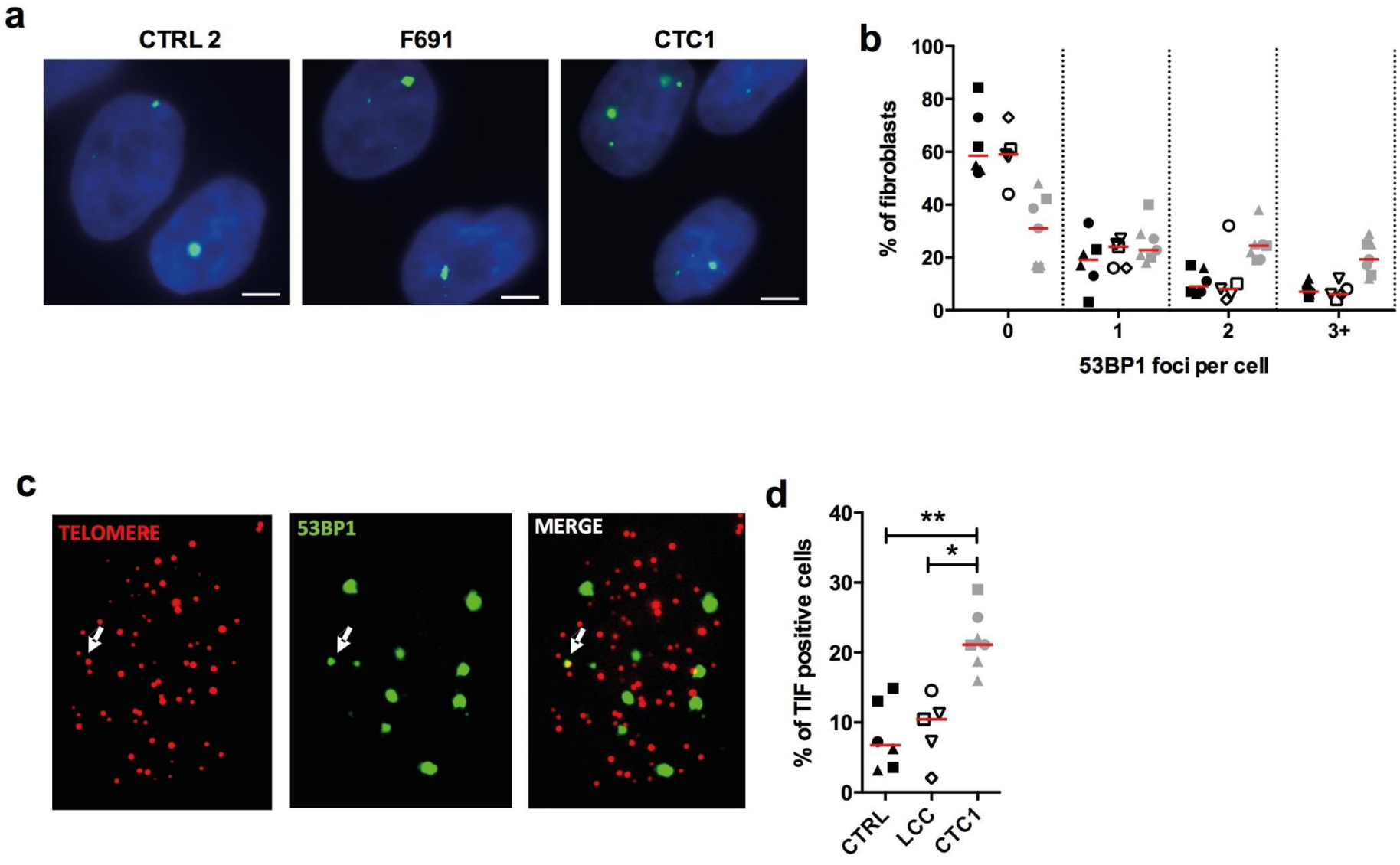
Supplementary Figure 9. Polysome analysis in lymphoblast cell lines (LCLs)**.** Polysome profiles in extracts of Epstein Barr virus (EBV) transformed LCLs. Extracts from two patient lines were compared to a healthy control and did not demonstrate consistent abnormalities in translation efficiency.



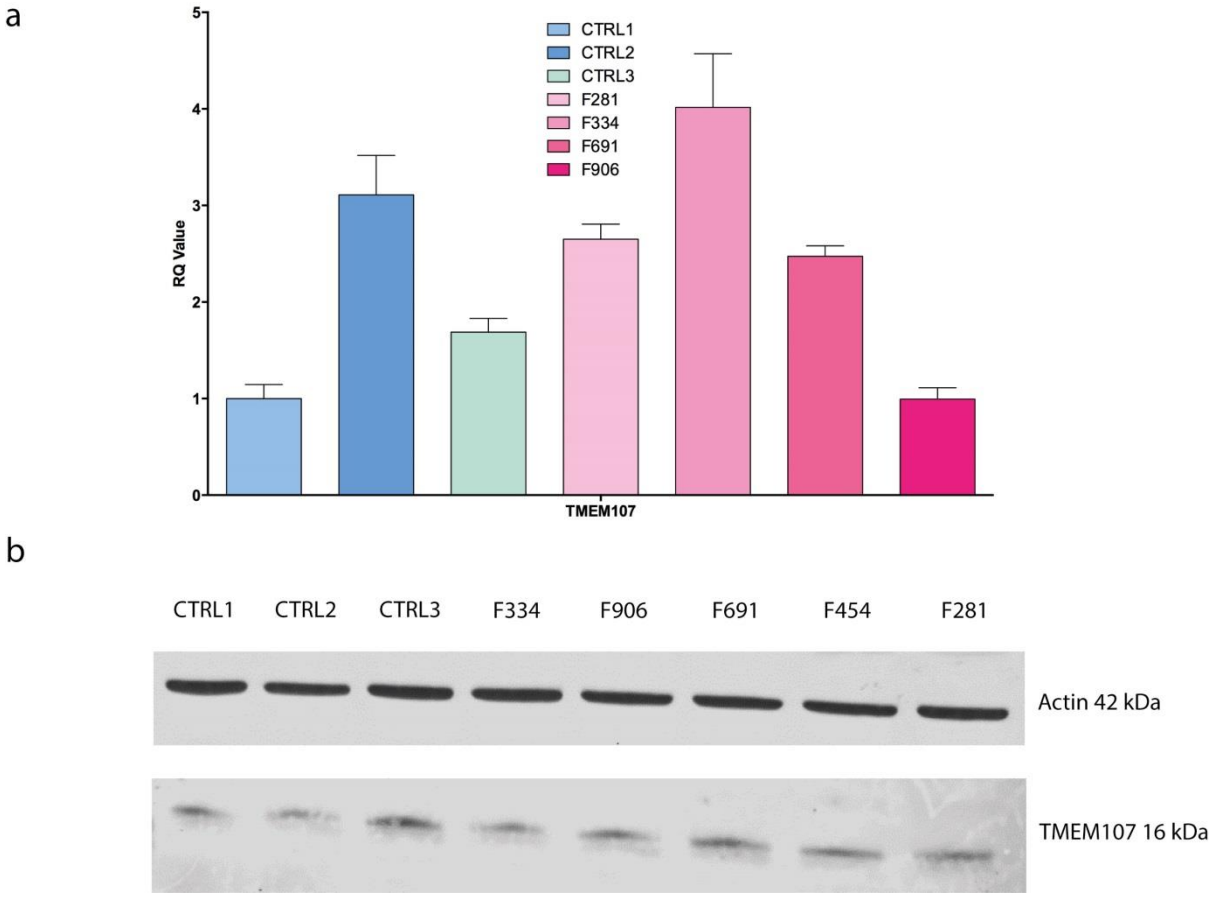
Supplementary Figure 10. **Comparison of neuroimaging in patients with CP due to *CTC1* mutations (A and B) and LCC due to mutations in *SNORD118* (C and D; F172)**. Axial T2 MR of patient with CP (A) and LCC (C) demonstrating a similar appearance with leukoencephalopathy, calcification and cysts. CT (B and D) images are also largely similar with dense thalamic and deep cortical calcification. There is more extensive calcification in the patient with LCC (D).



Supplementary Figure 11. ***CTC1* expression in LCC patients and controls**. Quantitative reverse transcription PCR (qPCR) of *CTC1* expression in three control and four LCC patient primary fibroblast cell lines, normalized to two housekeeping genes, *HPRT1* and *18S*. RQ is equal to $2^{-\Delta\Delta Ct}$ i.e. the normalized fold change relative to a control.


a
CTRL 2
F691
CTC1
b
% of fibroblasts
100
80
60
40
20
0
0
1
2
3+
53BP1 foci per cell
c
TELOMERE
53BP1
MERGE
d
% of TIF positive cells
40
30
20
10
0
**
*
CTRL
LCC
CTC1

Supplementary Figure 12. 53BP1 and telomere dysfunction-induced foci (TIF). **(a).** Representative images of 53BP1 staining of control, LCC and CTC1 primary fibroblasts. Scale bar represents 2.5 µM. **(b).** Comparison of the number of 53BP1 foci in primary fibroblasts from healthy controls (n = 3), LCC patients (n = 4) and CTC1 patients (n = 3). Red bar represents median value for each group. n = 2 independent experiments. **(c).** Representative images of a TIF are displayed for a control, LCC and CTC1 cell line. Scale bar represents 2.5 µM. **(d).** Comparison of the number of TIF in primary fibroblasts from CTC1 patients (n = 3), LCC patients (n = 4) and healthy controls (n = 2). Red bar represents the median value for each group. Data derived from n = 3 independent experiments and is grouped. Kruskal-Wallis with Dunn's multiple comparison test *p<0.05; ** p<0.01. No significant difference between LCC patients and controls. ●CTRL1, ■CTRL2, ▲CTRL3, ◇F281, ○F334, □F691, ▽F906, ▲F385, ●F1314_1, ■F1314_2.



Supplementary Figure 13. ***TMEM107* / TMEM107 expression (RNA / protein)**. **(a).** Quantitative reverse transcription PCR (qPCR) of *TMEM107* expression in three control and four LCC patient primary fibroblast cell lines, normalized to two housekeeping genes, *HPRT1* and *18S*. RQ is equal to $2^{-\Delta\Delta Ct}$ i.e. the normalized fold change relative to a control. **(b).** Western blot of TMEM107 in primary fibroblasts from three control and five LCC patient cell lines. Whole cell lysates were derived from $5x10^6$ cells per sample and 30 μg total protein loaded per lane. Immunoblotting of actin (42kDa) was used as a loading control.

Patient	Sex	Ethnicity	Parental consanguinity	Family history	Age at presentation	Presenting feature	Current age / age at death	Current status if alive
F172	M	White European (Swedish)	No	No	8 weeks	Epileptic seizures	Alive at age 11 years	Severe developmental delay
F278	M	White European (North American)	No	No	1 year	Significant developmental delay and seizures	Died at age 16 years	Progressive neurological decline
F281	M	White European (Estonian)	No	No	4 years	Abnormal head posture	Alive at age 11 years	Unilateral pyramidal signs
F285	M	White European (British)	No	No	12 years	Focal epileptic seizures	Died at age 32 years	Increasing spasticity; seizures; emotional lability
F309	F	White European (North American)	No	No	2 years	Failure to achieve motor milestones	Alive at age 22 years	Progressive spasticity and dystonia with complete loss of speech
F330	M	White European (British)	No	No	3 years	Unilateral tremor	Alive at age 18 years	4 limb dystonia and severe cognitive impairment
F331_1	F	White European (German)	No	1 of 2 affected siblings	2 years	Prolonged febrile seizures	Alive at age 19 years	Progressive gait disturbance, ataxia, dysarthria, cognitive impairment
F331_2	F	White European (German)	No	1 of 2 affected siblings	5 months	Identified as a neonate to have intracranial calcification. Presented age 5 months with focal epileptic seizures	Died at age 15 years	Progressive dystonia, ataxia, spasticity, severe mental retardation
F334	F	White	No	No	> 6 years	Progressive	Alive at	Progressive motor

		European (British)				problems with schooling	age 25 years	disorder with psychiatric features
F337	M	White European (Italian)	No	No	18 months	Focal epileptic seizures	Alive at age 20 years	Severe developmental delay
F343	M	White European (Dutch)	No	No	9 years	Abnormal gait	Alive at age 34 years	Can walk with support; demonstrates extrapyramidal, spastic and ataxic signs
F344	M	East African (Somali)	Yes	No	7 weeks	Focal epileptic seizures	Alive at age 10 years	Progressive neurological decline
F362_1	F	White European (British)	No	1 of 3 affected siblings	< 6 months	Developmental delay	Alive at age 10 years	Moderate developmental delay
F362_2	F	White European (British)	No	1 of 3 affected siblings	< 18 months	Developmental delay	Alive at age 8 years	Mild developmental delay
F362_3	M	White European (British)	No	1 of 3 affected siblings	< 6 months	Developmental delay	Alive at age 4 years	Mild developmental delay
F414	M	White European (Finnish)	No	No	25 years	Headaches and memory loss	Alive at age 36 years	Progressive spasticity requiring wheelchair use
F426_1	M	White European (North American)	No	1 of 2 affected siblings	< 6 months	Developmental delay	Alive at age 20 years	Severe developmental delay with dystonic spastic disorder
F426_2	M	White European (North American)	No	1 of 2 affected siblings	< 6 months	Developmental delay	Alive at age 19 years	Some intellectual delay with dystonia and spasticity although can walk with aids and

								works semi-independently
F433	M	White European (British)	No	No	54 years	Progressive hemiparesis	Died at age 58 years	Progressive neurological decline in adulthood
F445	F	White European (British)	No	No	< 6 months	Seizures	Alive at age 6 years	Asymmetrical dystonia with some learning difficulties
F446	M	White European (British)	Yes	No	10 months	Focal epileptic seizures	Died at age 13 years	Progressive neurological decline
F454_1	F	White European (Canadian)	No	1 of 2 affected siblings	Scan at age 5 years	Scan undertaken in absence of symptoms	Alive at age 11 years	Minor learning problems and some subtle focal motor signs on examination
F454_2	F	White European (Canadian)	No	1 of 2 affected siblings	7 months	Epileptic seizures	Alive at age 7 years	Moderate developmental delay with focal neurological signs
F465	M	Mixed white European	No	No	15 months	Epileptic seizures	Alive at age 10 years	Some intellectual delay and dyskinesia
F521_1	F	White European (North American)	No	1 of 2 affected siblings	< 12 months	Subtle delays in development	Alive at age 13 years	Some behavioral issues, but otherwise intellectually and physically intact
F521_2	M	White European (North American)	No	1 of 2 affected siblings	< 6 months	Developmental delay	Alive at age 9 years	Severe psychomotor delay
F551	F	White European (Belgium)	No	No	Infancy	Dystonic quadriplegia obvious by age 3 years	Died at age 28 years	Progressive neurological decline in adulthood
F564	M	White	No	No	9 months	Developmental	Alive at	Unable to walk

		European (Belgium)				delay	age 8 years	due to spasticity. Dysarthria. Uses sign language
F691	M	White European (British)	No	No	< 4 months	Developmental delay	Alive at age 4 years	Severe developmental delay
F730	F	White European (Australian)	No	No	2 months	Epileptic seizures	Alive at age 6 years	Severe developmental delay
F766	F	White European (British)	No	No	12 years	Motor deterioration with previous diagnosis of mild cerebral palsy	Alive at age 16 years	Progressive motor deterioration with dysarthria
F780_1	F	White European (North American)	No	1 of 2 affected siblings	7 years	Attention deficit on background of prematurity	Alive at age 13 years	Cognitive slowing, tremor, ataxia and epilepsy
F780_2	F	White European (North American)	No	1 of 2 affected siblings	6 years	Minor developmental problems (scanned in view of her sister's diagnosis)	Alive at age 7 years	Stable with minimal features
F819_1	M	White European (British)	No	1 of 2 affected siblings	Teens	Epileptic seizures	Alive at age 35 years	Some intellectual delay with hemiparesis
F819_2	F	White European (British)		1 of 2 affected siblings	Teens	Epileptic seizures	Alive at age 32 years	No major deficits
F906	M	White European (Italian)	No	No	18 months	Developmental delay and monoparesis	Alive at age 5 years	Mild hemiplegia
F1127	M	White European (French)	No	No	< 6 months	Developmental delay	Alive at age 2 years	Moderate developmental delay
F1172	F	White European (German)	No	No	50 years	Ataxia	Alive at age 54 years	Minor degree of ataxia and dysarthria but no

								major functional deficit
F1288	F	White European (North American)	No	No	3 years	Gait problems	Alive at age 17 years	Mainly unilateral dystonia / spasticity
F1424	F	Mixed White European (German) / North African	No	No	6 months	Epileptic seizures	Alive at age 9 years	Progressive motor disorder with psychiatric features
F1445	F	Mixed White European (British) / Asian	No	No	10 years	Gait problems	Alive at age 10 years	Probably slowly progressive motor deterioration with learning difficulties

Supplementary Table 1. Clinical table

Genomic coordinates†	rs number	*SNORD118* nomenclature ^	ExAC total allele count	Hom*	Het**	Calculated ExAC frequency	Highest population frequency on ExAC‡	Families harboring each variant
g.8076761C>A	rs116395281	n.*10G>T	112348	1	231	0.002056	African 0.01891 (1)	F172, F331, F334, F730
g.8076762G>A	rs201787275	n.*9C>T	112400	1	227	0.00202	European 0.00303 (1)	F551, F691, F819, F1127, F1172, F1288
g.8076766G>C	rs75008470	n.*5C>G	112440	0	65	0.0005781	Other 0.00119 (0)	F285, F343, F362, F426, F433, F445, F446, F454
g.8076770G>A	rs117595965	n.*1C>T	112476	4	532	0.00473	European 0.00708 (3)	F414, F564, F780, F819
g.8076776G>C		n.131C>G	112572	0	0	Novel	Novel	F309, F521, F780, F1172
g.8076777A>G		n.130T>C	112568	0	0	Novel	Novel	F1424
g.8076780G>C		n.127C>G	112750	0	6	0.00005322	East Asian 0.00024 (0)	F445, F551
g.8076781G>A	rs144429028	n.126C>T	112748	0	11	0.00009756	European 0.00013 (0)	F564
g.8076794G>A		n.113C>T	112774	0	2	0.00001773	European 0.000033 (0)	F344#
g.8076803C>T	rs201686383	n.104G>A	112774	0	55	0.0004877	European (Finnish) 0.00107 (0)	F521
g.8076804C>T		n.103G>A	112776	0	2	0.00001773	East Asian 0.00012 (0)	F906
g.8076807A>C		n.100T>G	112782	0	0	Novel	Novel	F1127
g.8076825T>C		n.82A>G	112786	0	8	0.00007093	East Asian 0.00012 (0)	F330, F334, F465
g.8076826C>G		n.81G>C	112788	0	0	Novel	Novel	F281
g.8076826C>T		n.81G>A	112788	0	4	0.00003546	East Asian 0.00012 (0)	F426, F730, F1445
g.8076832T>C		n.75A>G	112788	0	0	Novel	Novel	F278
g.8076835T>C	rs201558321	n.72A>G	112794	0	8	0.00007093	South Asian 0.00018 (0)	F331
g.8076846T>C		n.61A>G	112788	0	9	0.0000798	European 0.00011 (0)	F414
g.8076846_8076847insA		n.60_61insT	112788	0	2	0.00001773	African 0.00024 (0)	F465
g.8076848A>C		n.59T>G	112780	0	0	Novel	Novel	F1288
g.8076849T>C		n.58A>G	112788	0	3	0.0000266	South Asian 0.00012	F691

							(0)	
g.8076849dup		n.58dup	112788	0	0	Novel	Novel	F337
g.8076850C>T		n.57G>A	112784	0	0	Novel	Novel	F285
g.8076851dup		n.56dup	112774	0	0	Novel	Novel	F172
g.8076865C>T	rs148909909	n.42G>A	112762	0	115	0.00102	African 0.00343 (0)	F766
g.8076868C>G	rs200458465	n.39G>C	112734	0	16	0.0001419	Other 0.0012 (0)	F906
g.8076887G>A		n.20C>T	112754	0	2	0.00001774	East Asian 0.00012 (0)	F362, F433
g.8076899C>G		n.8G>C	112740	0	1	0.00000887	African 0.00012 (0)	F278, F344#
g.8076899C>T	rs201266955	n.8G>A	112740	3	316	0.002803	European 0.0161 (2)	F330
g.8076904G>A	rs117735243	n.3C>T	112682	2	166	0.001473	European (Finnish) 0.00562 (0)	F281, F309, F1445
g.8076904G>T	rs117735243	n.3C>A	112682	0	1	0.000008875	European 0.000016 (0)	F766
g.8076905A>G		n.2T>C	112676	0	4	0.0000355	South Asian 0.000062 (0)	F337
g.8076912C>T	rs200531412	n.-6G>A	112690	0	108	0.0009584	East Asian 0.00183 (0)	F1424
g.8076885_8076913dup		n.-7_22dup	112752	0	0	Novel	Novel	F343
g.8076955_8076960del		n.-54_-49del	111546	0	0	Novel	Novel	F454
g.8076696_8076977del§						Novel	Novel	F819

Supplementary Table 2. **List of *SNORD118* variants identified in patients with LCC**. Characteristics of variants identified and their frequency on ExAC are given by family number.

Hom = homozygous; Het = heterozygous; ExAC = Exome Aggregate consortium
†All genomic coordinates should be preceded by Chr17(GRCh37):
^ *SNORD118* NR_033294.1
TMEM107 NM_032354.3
***** Number of homozygote alleles recorded in ExAC for each variant
****** Number of heterozygote alleles recorded in ExAC for each variant
‡ Number in brackets is the number of homozygote alleles recorded in the population with the highest frequency on ExAC
§ Deletion extends beyond these boundaries, but boundaries have not been fully defined

In F344 both of these rare variants were seen in the homozygous state; however, n.8G>C was also seen in F278, suggesting that this is the likely pathogenic variant

Marker	F906 proband		F906 father		F906 mother	
	Allele 1	Allele 2	Allele 1	Allele 2	Allele 1	Allele 2
AMEL	X	Y	X	Y	X	X
CSF1PO	11	11	11	12	10	11
D13S317	11	12	8	12	11	12
D16S539	9	10	9	11	10	11
D18S51	11	15	14	15	11	21
D21S11	29	30	29	29	28	30
D3S1358	14	15	15	15	14	17
D5S818	10	12	12	12	10	12
D7S820	8	8	8	11	8	10
D8S1179	12	16	12	13	12	16
FGA	19	23	19	23	23	26
Penta_D	11	12	12	12	11	13
Penta_E	13	15	12	13	15	16
TH01	6	7	6	7	6	7
TPOX	8	12	8	12	8	8
vWA	15	17	15	18	17	17

Supplementary Table 3. **Microsatellite analysis undertaken in F906**. Polymorphic microsatellite markers were genotyped using DNA from the affected child and his parents to confirm maternity and paternity indicating the *de novo* occurrence of an n.103G>A nucleotide alteration.

	Total	Total WT (only variants >0.5%)	Total carrying 1 rare variant (<0.5%)	Total with 2 or more rare variants (<0.5%)	Total with 2 rare variants on different alleles (<0.5%)	Total with a novel variant (not found on ExAC)
Controls	677	587	84	6	4†	4
LCC probands	33	0	0	33	20*	11

Supplementary Table 4. **Panel of 413 European control DNA samples sequenced for variants in *SNORD118* showing the number of individuals carrying rare variants in comparison to patients**.

WT = wild-type
*20 families where parental inheritance could be determined (i.e. 18 probands with available parental samples plus two probands homozygous for a putative mutation in *SNORD118* but where parental DNA was not available: F278, F281, F331, F337, F362, F426, F454, F465, F521, F691, F766, F780, F819, F906, F1127, F1288, F1424, F1445, F344, F446)
Chi squared test for number with 2 rare variants $p<0.000005$
†Variants identified in an additional control sample not cloned, therefore assumed to be on separate alleles

Genomic coordinates†	rs number	*SNORD118* nomenclature^	Seen in LCC cohort?	ExAc allele count (hom/het/total)	Calculated ExAc frequency	Variants on same allele or different allele?
g.8076843C>T	rs372252345	n.64G>A	No	0/6/112786	0.0000532	Variants on same
g.8076883G>A	rs368022715	n.24C>T	No	0/34/112758	0.000302	allele
g.8076751T>C	rs143573551	n.*20A>G	No	0/93/112218	0.000829	Variants on different
g.8076912C>A	rs200531412	n.-6G>T	No	6/372/112690	0.003301	alleles
g.8076676G>A	rs78425352	n.*95C>T	No		0.005 (1000G)	Variants on same
g.8076757T>C	rs115989975	n.*14A>G	No	0/57/112288	0.000508	allele
g.8076874G>A	rs116658491	n.33C>T	No	18/1092/112760	0.009684	Variants on different
g.8076918G>A	rs201296288	n.-12C>T	No	2/405/112316	0.003606	alleles
g.8076827A>C	rs374183932	n.80T>G	No	0/6/112788	0.0000532	Variants on different
g.8076722T>C	rs73975808	n.*49A>G	No	0/37/111778	0.000331	alleles
g.8076761C>A	rs116395281	n.*10G>T	Yes	1/231/112348	0.002056	Variants on different
g.8076791G>A	rs181334320	n.116C>T	No	2/443/112746	0.003929	alleles*

Supplementary Table 5. **Cloning of six control DNA samples found to carry two rare variants in *SNORD118* to determine bi- or monoallelic status**.

Hom, homozygous; het, heterozygous
†All genomic coordinates should be preceded by Chr17(GRCh37):
1000G variant only identified on 1000 genomes
^ *SNORD118* NR_033294.1.
TMEM107 NM_032354.3
*DNA not cloned therefore variants assumed to be on separate alleles

'First' variant	ExAC frequency	Family	'Second' variant	ExAC frequency
n.*10G>T	0.002056	F172	n.56dup	Novel
		F331	n.72A>G	0.00007093
		F334	n.82A>G	0.00007093
		F730	n.81G>A	0.00003546
n.*9C>T	0.00202	F551	n.127C>G	0.00005322
		F691	n.58A>G	0.0000266
		F819	g.8076696_8076977del	Novel
		F1127	n.100T>G	Novel
		F1172	n.131C>G	Novel
		F1288	c.59T>G	Novel
n.*1C>T	0.00473	F414	n.61A>G	0.000079809
		F564	n.126C>T	0.00009756
		F780	n.131C>G	Novel
		F819	g.8076696_8076977del	Novel
n.42G>A	0.00102	F766	n.3C>A	0.000008875
n.8G>A	0.002803	F330	n.82A>G	0.00007093
n.3C>T	0.001473	F281	n.81G>C	Novel
		F309	n.131C>G	Novel
		F1445	n.81G>A	0.00003546

Supplementary Table 6. Allelic combinations seen in each family harboring one of the six putative mutant alleles in *SNORD118* with an allele frequency on the Exome Aggregation Consortium (ExAC) database of between 0.001 and 0.005.

	Single recorded allele on ExAC	Number of variants on ExAC with an allele frequency of <0.005 (excluding those seen only once)	Number of variants on ExAC with an allele frequency of >0.005
3'UTR (n.*1 to n.*49)	27	75	2
Coding (n.1 to n.136)	74	199	9
Promoter (n.-50 to n.-1)	15	36	5
Total	116	310	16
Percentage	26.2	70.1	3.6

Supplementary Table 7. Sequence variants across *SNORD118* recorded on the Exome Aggregation Consortium (ExAC) database.

Amplicon	Primer name	Sequence
Primers for patient and control sequencing	U8 F	ACTGCCTAAATTCCAGAAAGCA
	U8 R	TGATCGGAGCATTCTGGGAA
Primers to make templates for *in vitro* transcription	Long pGEM F	TGGTTACTACGGTAGGTGCC
	Long pGEM R	AGACAAACAGCAAGGTTATCCC
Primers for construct for luciferase cloning	Short pGEM F	TGGTTACTACGGTAGGTGCC
	Short pGEM R	ACGATACAGACAAACAGCCG
Primers for subcloning into pGL3	*Kpn*I forward	AGTGAGGTACCTGGTTACTACGGTAGGTGCC
	*Kpn*I reverse	AGTGAAAGCTTACGATACAGACAAACAGCCG
Primers for site directed mutagenesis	PSEDel F	CGCGTTATGAACTCACCCGTAACGGAATCTTTTTCA
	PSEDel R	TGAAAAAGATTCCGTTACGGGTGAGTTCATAACGCG
	n.58A>G F	GCAGATTAGAACATGGTGATTGGAGATGCAT
	n.58A>G R	ATGCATCTCCAATCACCATGTTCTAATCTGC
	n.61A>G F	GATTAGAACATGATGGTTGGAGATGCATGAA
	n.61A>G F	TTCATGCATCTCCAACCATCATGTTCTAATC
Transcription template primers	U8 F Trx	GGTAATACGACTCACTATAGGGATCGTCAGGTGGGATAATCC
	U8 R Trx	AATCAGACAGGAGCAATCAGGG
	U8 longR Trx	TAACACAAATGTAAGTGATCGTCAGAAAG
	U8 n.*5C>G R Trx	TAACACAAATGTAAGTGATCGTCACAAAGAATCAGACAGG
	U8 n.*1C>T R Trx	TAACACAAATGTAAGTGATCGTCAGAAAAAATCAGACAGG
	U8 n.*9C>T R Trx	TAACACAAATGTAAGTGATCATCAGAAAGAATCAGACAGG
	U8 n.*10C>G R Trx	TAACACAAATGTAAGTGATAGTCAGAAAGAATCAGACAGG
15.5K cloning primers	15.5KF2 Nde TEV	CATATGGAAAACCTGTATTTTCAGGGCATGACTGAGGCTGATGTGAATCC
	15.5KB Xho	CTCGAGTTAGACTAAGAGCCTTTCAATGG

Supplementary Table 8. Primers used to amplify human *SNORD118* and surrounding region.