Supporting Information

Schoeftner et al. 10.1073/pnas.0909265106

SI Materials and Methods

Expression microarray background subtraction were carried out using normexp correction. Quantiles method was performed for normalization. Differentially expressed genes were obtained by using R limma package from the Bioconductor Project (http://www.bioconductor.org/) (1). The estimated significance level (*P* value) was corrected to account for multiple hypotheses testing using Benjamini and Hochberg false discovery rate (FDR) adjustment. Genes showing FDR <0.05 were selected as differentially expressed among classes. Annotations, including chromosome locations for every gene in the array, were retrieved from Ensembl v.50. A Welch 2-sample *t* test was used to calculate significance values for global transcriptome changes in pairwise comparisons. Gene set enrichment analyses: Gene set enrichment analyses (GSEA) were applied using annotations from Biocarta and GenMAPP pathway databases. Thus, genes were ranked based on limma moderated *t* statistic. After Kolmogorov–Smirnov testing, those gene sets showing FDR <0.25, a well-established cutoff for the identification of biologically relevant gene sets, were considered enriched between classes under comparison (2). Freely distributed R software was used for these calculations. The FatiGO server was used for analysis for overrepresentation of biological processes (3). The tool applies a Fisher's exact test to obtain significant overrepresentation of GO terms (biological processes) and KEGG pathways. Terms with FDR <0.05 were considered as significantly overrepresented.

1. Smyth GK, Michaud J, Scott HS (2005) Use of within-array replicate spots for assessing differential expression in microarray experiments. *Bioinformatics* 21:2067–2075.
2. Subramanian A, et al. (2005) Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA* 102:15545–15550.
3. Al-Shahrour F, et al. (2007) FatiGO +: A functional profiling tool for genomic data. Integration of functional annotation, regulatory motifs and interaction data with microarray experiments. *Nucleic Acids Res* 35:W91–W96.
4. Niedernhofer LJ, et al. (2006) A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature* 444:1038–1043.
5. Oberdoerffer P, et al. (2008) SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. *Cell* 135:907–918.

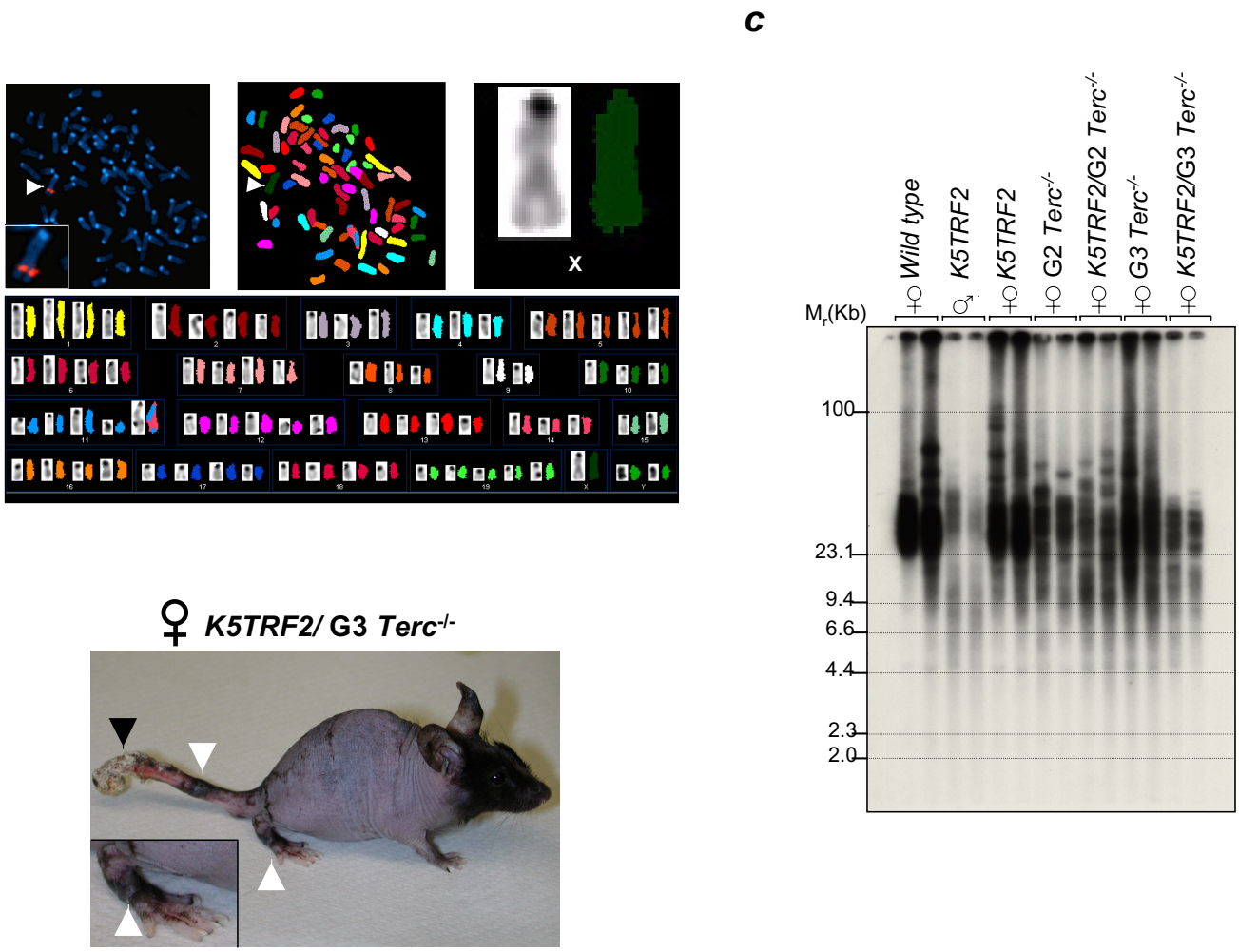


Fig. S1. Severe skin phenotypes in female *G3 Terc*$^{-/-}$ mice carrying an X-linked *K5TRF2* transgene. (*A*) SKY DNA FISH analysis combined with TRF2 DNA FISH mapped the integration site of the *K5TRF2* transgene to the X chromosome in male PM *K5TRF2* mice. (*B*) Female PM *K5TRF2/G3 Terc*$^{-/-}$ mice display skin hyperpigmentation (white arrows), hair loss, and severe skin necrosis (black arrows). (*C*) TRF analysis of experimental mice. Telomere length was determined by TRF analysis using primary keratinocytes prepared from back skin. Terminal telomeric fragments were detected using a telomere-specific ^{32}P-labeled probe. Telomerase deficiency in female PM *K5TRF2/G1–G3 Terc*$^{-/-}$ mice results in an accelerated telomere shortening compared with single-mutant *Terc*$^{-/-}$ controls.

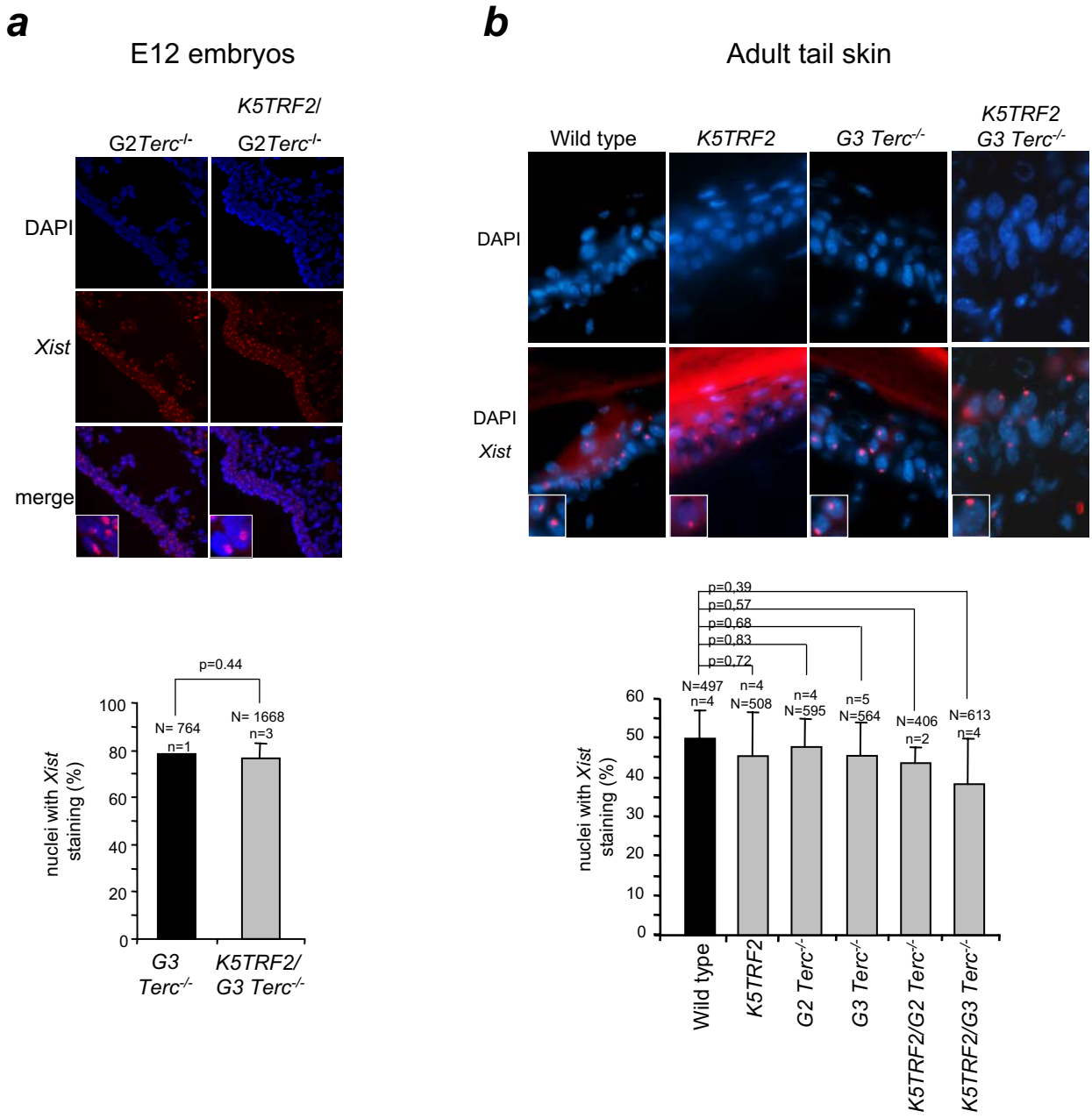


Fig. S2. Initiation of X chromosome inactivation and association of *Xist* RNA with chromatin is unaffected by telomere shortening. (*A*) *Xist* RNA was detected by RNA FISH on frozen tissue sections obtained from day E12 embryos. N, number of nuclei analyzed; n, number of animals; standard error and statistical significance values (Student's *t* test) are shown. (*B*) *Xist* RNA FISH on adult tail-skin sections. Genomic DNA was labeled using DAPI. (*C*) Determination of TelRNA/TERRA levels by Northern blotting. pMEFs were exposed to 3 Gy of ionizing radiation; total RNA was prepared at the indicated time points, and TelRNA/TERRA levels were determined by Northern blotting. A probe, specific for the 18S ribosomal subunit, was used as a loading control. Experiment was repeated 4 times. (*D*) Quantification of Northern blot described in (*C*). TelRNA/TERRA levels were normalized against the 18S ribosomal subunit. Ionizing radiation does not have a significant influence on telomeric transcription in the experimental time-window. n, number of experiments carried out; error bars indicate standard error. An unpaired Student's *t* test was used to calculate statistical significance. (*E*) Quantification of TelRNA foci in nuclei of female pMEFs after γ irradiation (see Fig. S3*B*). Ionizing radiation slightly increases the number of TelRNA foci per nucleus 3 h postirradiation. (*F*) Quantification of Tac frequency in irradiated pMEFs (see Fig. S3*B*). Ionizing radiation slightly decreases the number of TelRNA foci per nucleus 3 h postirradiation. (*G*) Determination of area of TelRNA signals in experimental cells. γ irradiation does not significantly areas of TelRNA stainings indicating that ionizing radiation does not affect TelRNA levels in the tested time interval. In Fig. S2 *E–G*, N denotes the number of mice, and n the total number of nuclei analyzed. Error bars indicate standard error. An unpaired Student's *t* test was used to calculate statistical significance. Note: in (*G*), n refers to the total number of TelRNA signals analyzed.

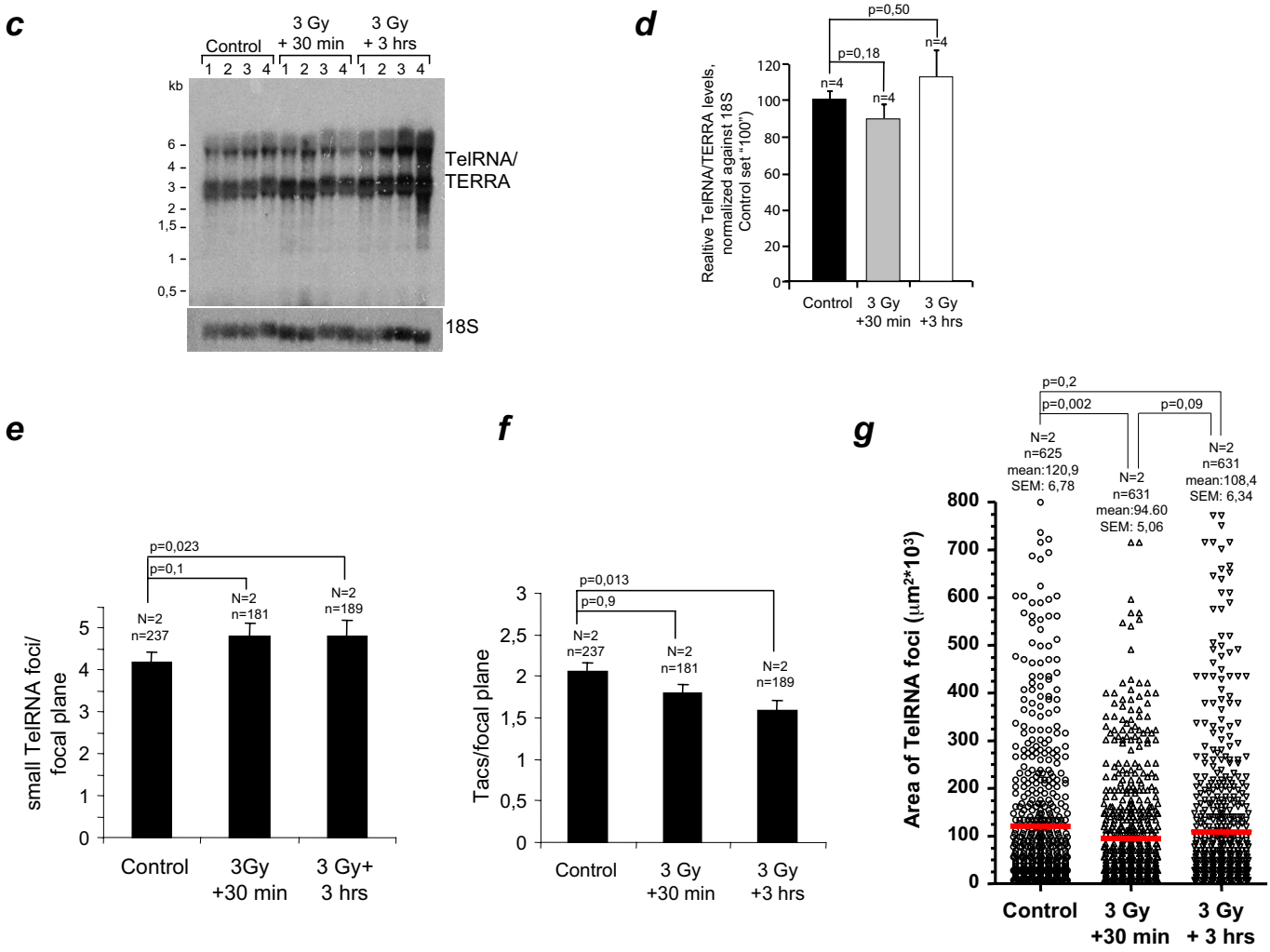


Fig. S2 (continued).

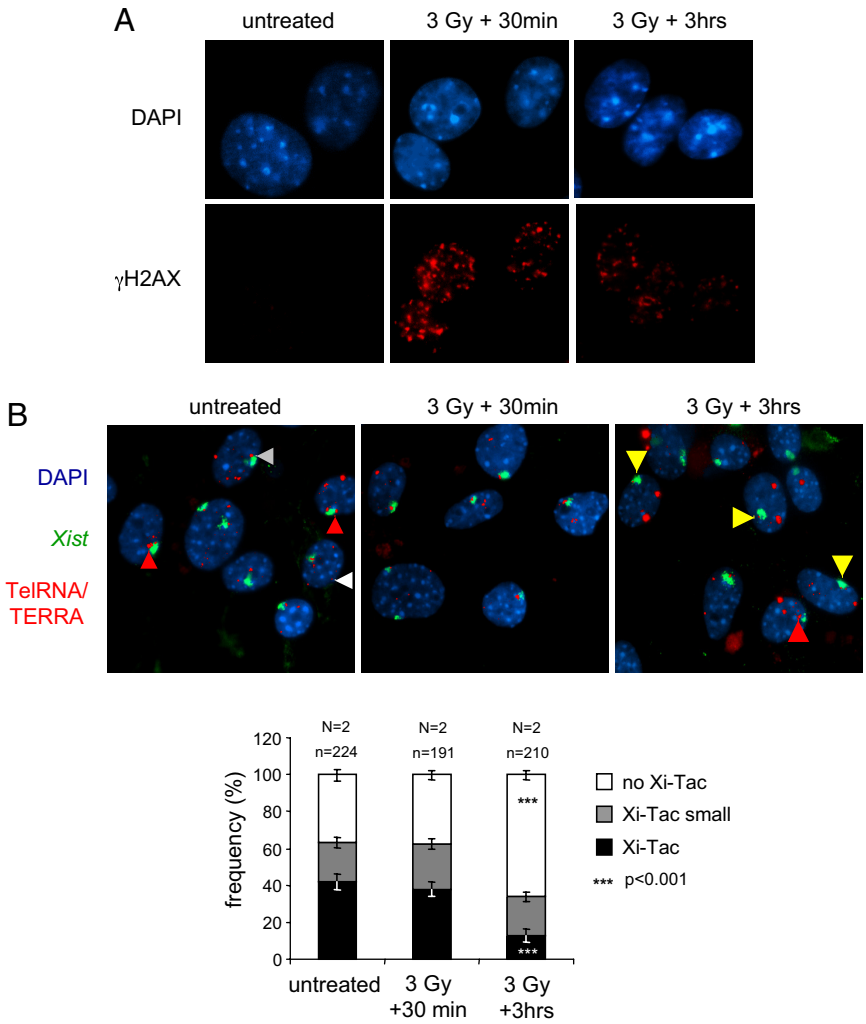


Fig. S3. Ionizing radiation results in a loss of *Xist*-Tacs association. (*A*) Visualization of sites of DNA damage by immunostaining for γH2AX after exposing pMEFs to 3 Gy of γ irradiation. (*B*) Combined *Xist*–TelRNA/TERRA RNA FISH. White arrowheads, telomere-associated focal TelRNA/TERRA staining; red arrowheads, full-size Tac; gray arrowheads, smaller Tacs in the vicinity of the Xi; yellow arrowheads, Xi-Tac dissociation. N, independent cell lines tested; n, nuclei analyzed. ***, $P < 0.001$.

a

	K5TRF2 vs. Wild type	G2 Terc$^{-/-}$ vs. Wild type	K5TRF2/G2 Terc$^{-/-}$ vs. Wild type	K5TRF2/G3 Terc$^{-/-}$ vs. Wild type	K5TRF2/G3 Terc$^{-/-}$ vs. K5TRF2/G2 Terc$^{-/-}$	K5TRF2/G3 Terc$^{-/-}$ vs. G2 Terc$^{-/-}$
K5TRF2 vs. Wild type		0,16	0,11	1,87E-06	1,90E-04	7,19E-06
G2 Terc$^{-/-}$ vs. Wild type	0,16		0,83	1,67E-04	8,29E-03	5,27E-04
K5TRF2/G2 Terc$^{-/-}$ vs. Wild type	0,11	0,83		3,25E-04	6,87E-04	9,84E-04
K5TRF2/G3 Terc$^{-/-}$ vs. Wild type	1,87E-06	1,67E-04	3,25E-04		0,23	0,76
K5TRF2/G3 Terc$^{-/-}$ vs. K5TRF2/G2 Terc$^{-/-}$	1,90E-04	8,29E-03	6,87E-04	0,23		3,79E-02
K5TRF2/G3 Terc$^{-/-}$ vs. G2 Terc$^{-/-}$	7,19E-06	5,27E-04	9,84E-04	0,76	3,79E-02	

b

	K5TRF2 vs. Wild type female				G2 Terc$^{-/-}$ vs. Wild type female			K5TRF2/G2 Terc$^{-/-}$ vs. Wild type female			K5TRF2/G3 Terc$^{-/-}$ vs. Wild type female			K5TRF2/G3 Terc$^{-/-}$ vs. K5TRF2/G2 Terc$^{-/-}$ female			K5TRF2/G3 Terc$^{-/-}$ vs. G2 Terc$^{-/-}$ female			K5TRF2 vs. Wild type male		
FDR	total	total	up	down	total	up	down	total	up	down	total	up	down	total	up	down	total	up	down	total	up	down
< 0.05	**0**	**213**	183	20	**1181**	679	502	**2757**	1247	1510	**1941**	718	1223	**2191**	860	1331	**2112**	890	1222
< 0.01	**0**	**0**	0	0	**50**	39	11	**2291**	981	1310	**1236**	417	819	**1477**	575	902	**969**	364	605
< 0.001	**0**	**0**	0	0	**0**	0	0	**1455**	571	884	**610**	184	426	**741**	261	480	**102**	27	75

Fig. S4. Deregulation of the mouse transcriptome is linked to progressive telomere shortening. (*A*) Tabular representation of statistical significance values for global transcriptome changes between the indicated pairwise microarray comparisons. Red and yellow, highly significant global gene expression changes. Red, expression changes in *K5TRF2/G3 Terc*$^{-/-}$ cells are highly significant in all comparisons with wild-type cells. A Welch 2-sample *t* test was used to calculate statistical significance. (*B*) Tabular representation of number of genes displaying significant altered transcript levels in pairwise comparisons. Up, up-regulated; down, down-regulated; FDR, false detection rate. An FDR <0.05 is regarded as statistically significant.

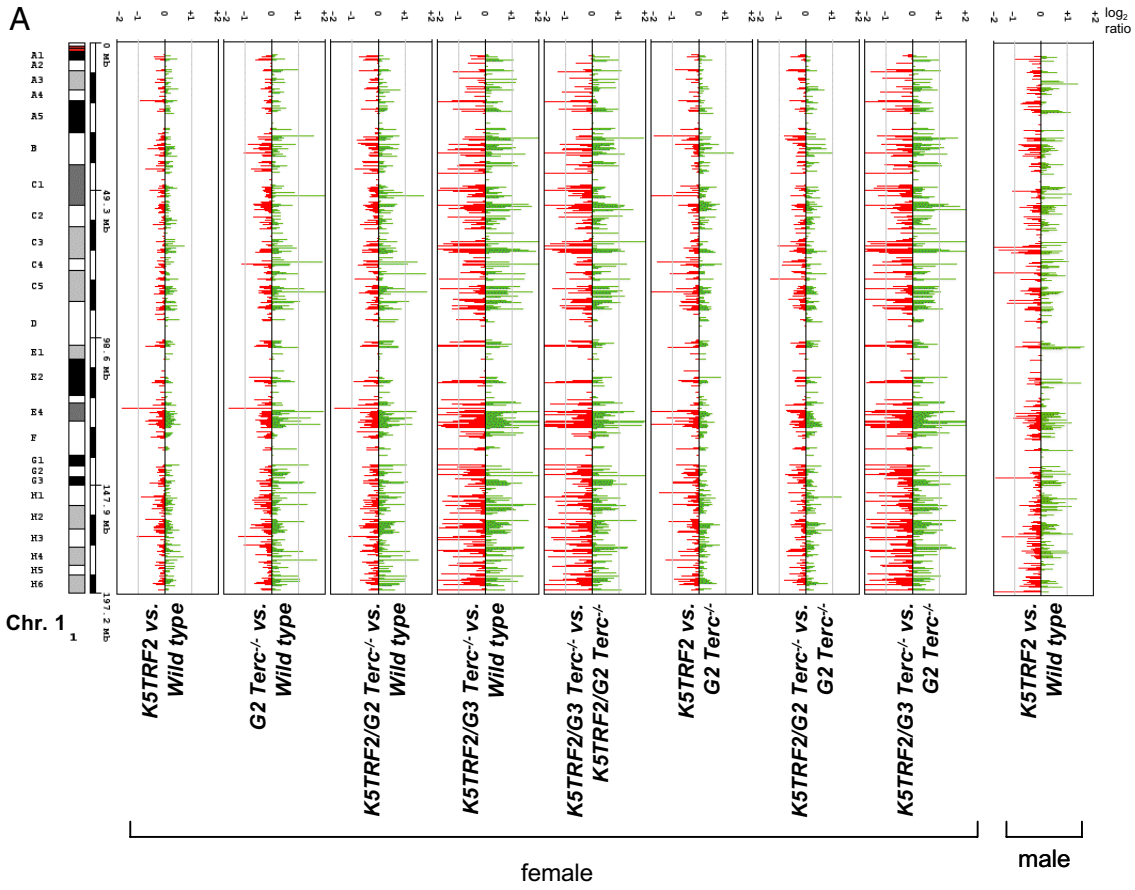


Fig. S5. (*A–J*) Comparative transcriptome analyses. Total RNA was prepared from tail keratinocytes derived from female PM wild-type ($n = 4$), *K5TRF2* ($n = 4$), *G2 Terc*$^{-/-}$ ($n = 2$), *K5TRF2/G2 Terc*$^{-/-}$, ($n = 3$), and *K5TRF2/G3 Terc*$^{-/-}$ ($n = 3$) mice, as well as from male wild-type ($n = 4$) and PM *K5TRF2* transgenic ($n = 4$) mice. RNA was one-color labeled and hybridized to Agilent 4 × 44K mouse genomic arrays. Intensity ratios of corresponding gene probes where calculated and blotted along the chromosomal maps of all mouse chromosomes. Critical telomere shortening in keratinocytes from *K5TRF2/G3 Terc*$^{-/-}$ mice is associated with genome-wide alterations in gene transcription. Transcriptional changes are expressed as ($\log_2$) ratios. Red bars, down-regulated genes; green bars, up-regulated genes.

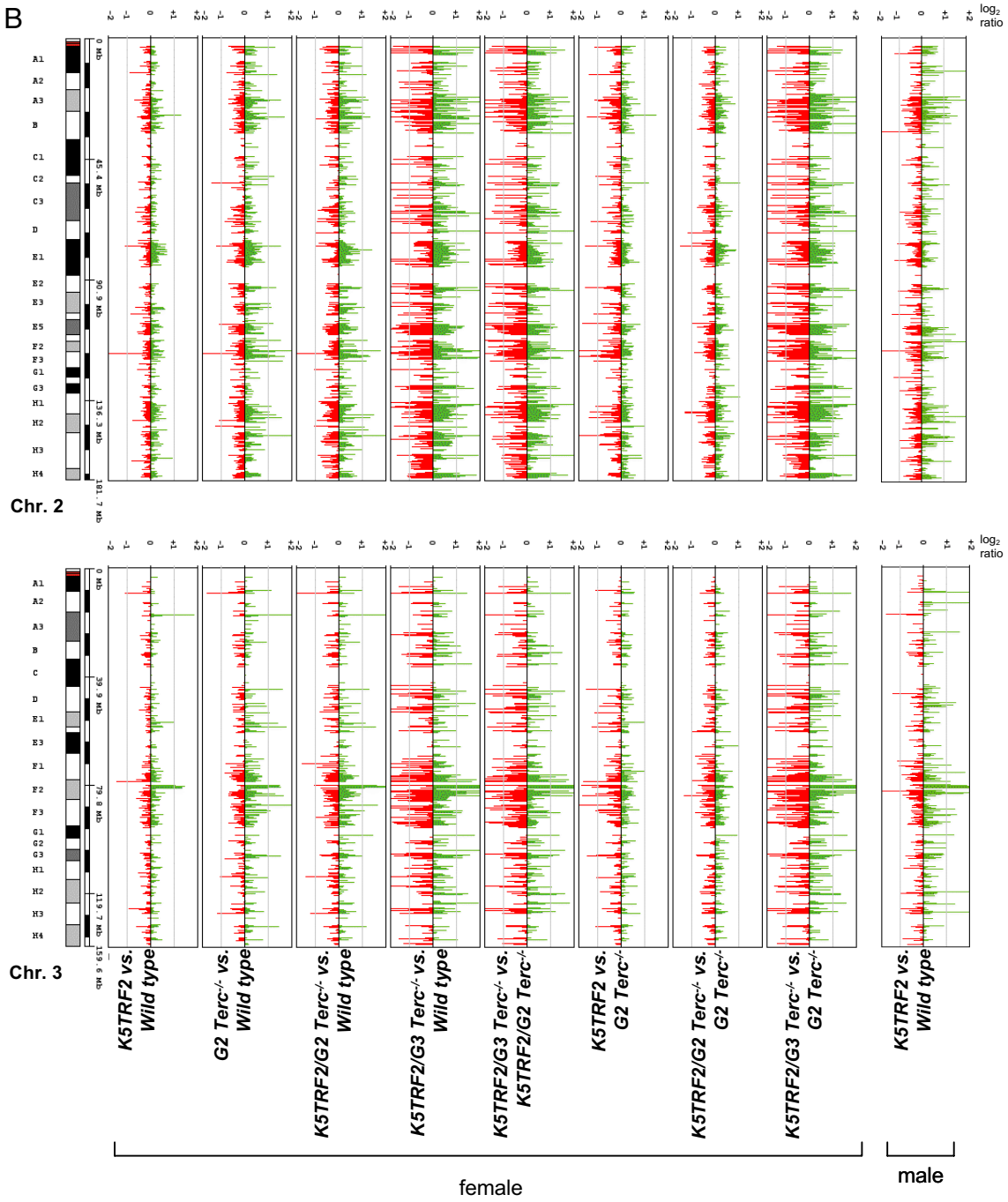
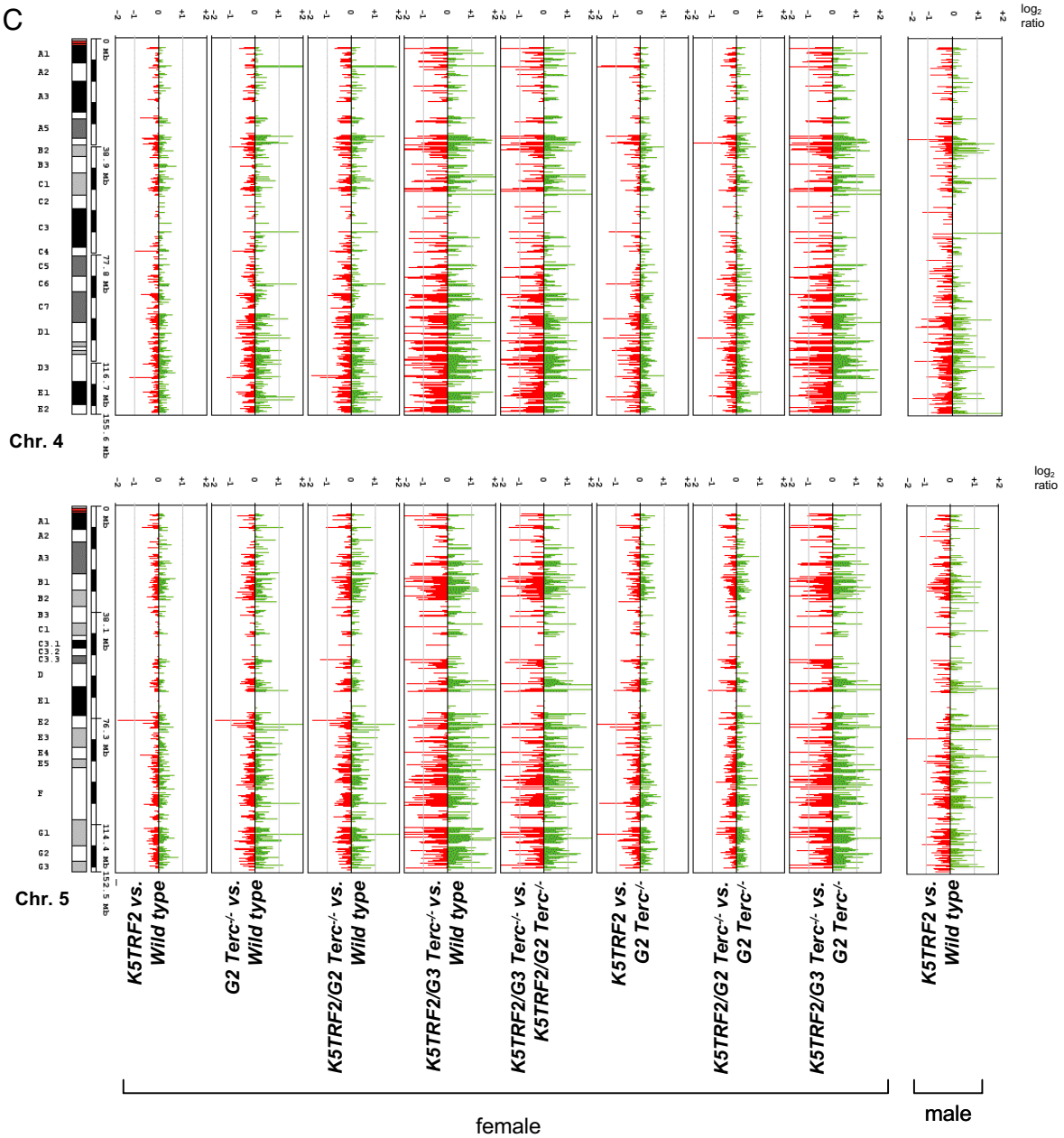


Fig. S5 (continued).



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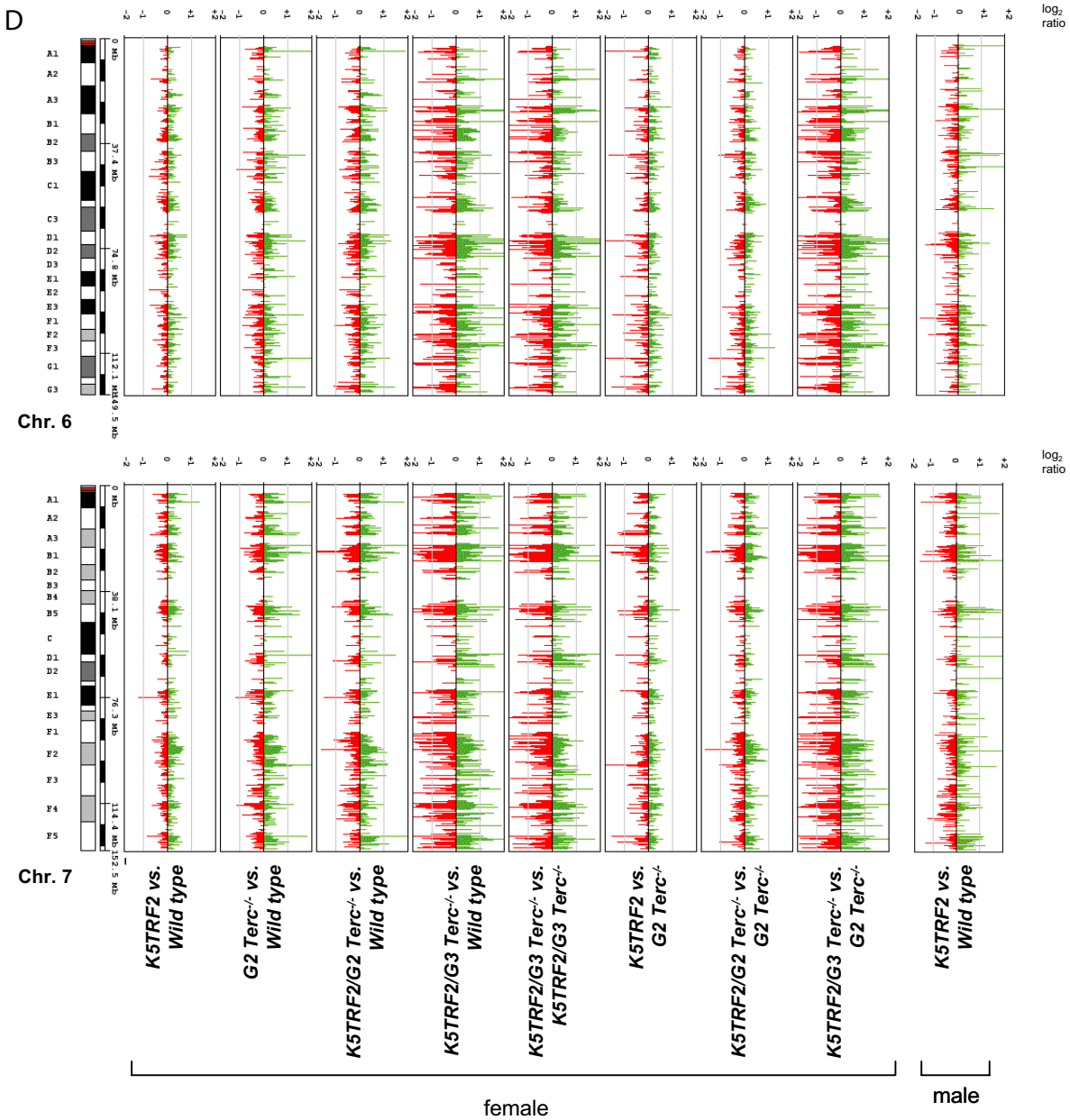


Fig. S5 (continued).

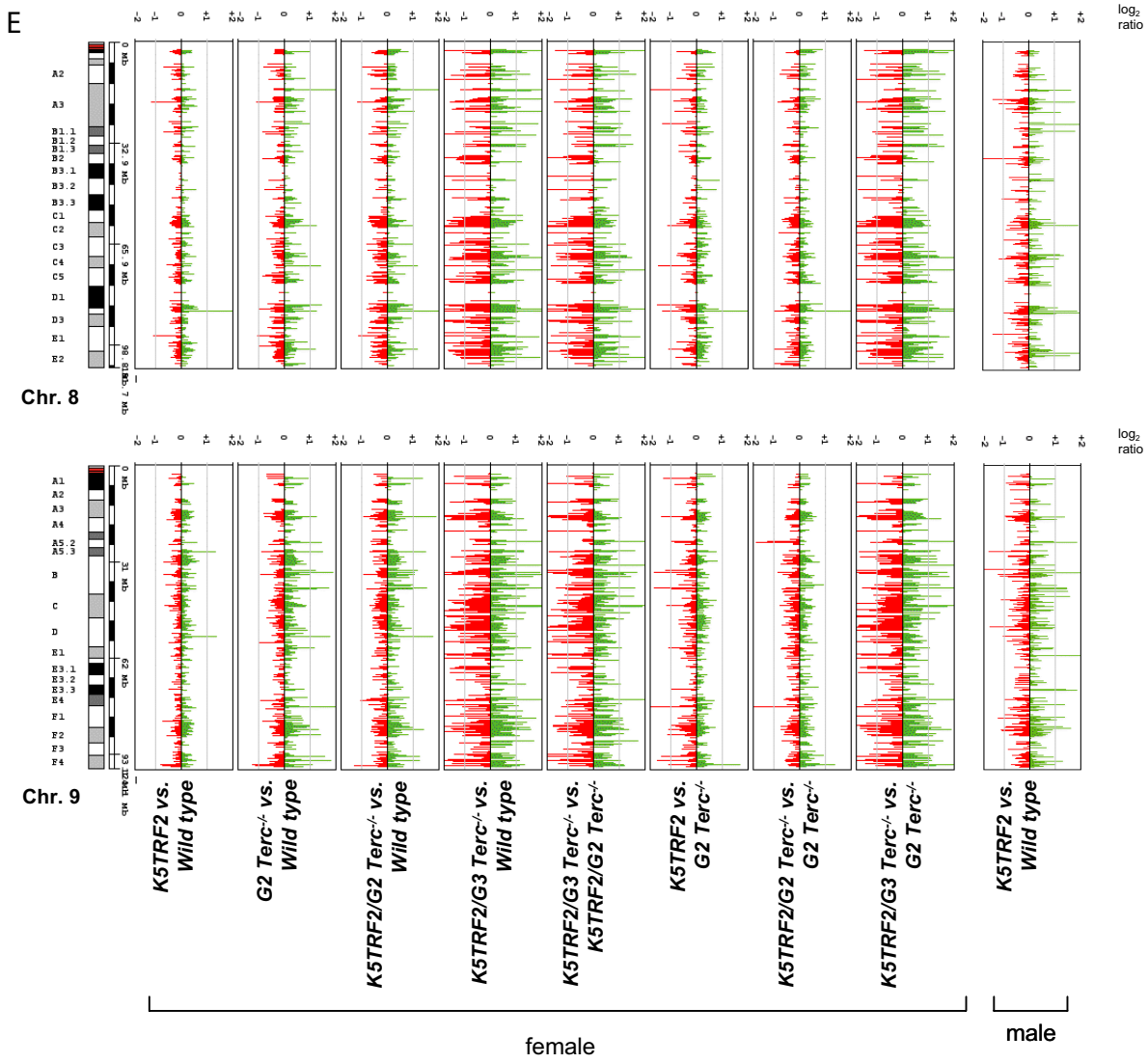


Fig. S5 (continued).

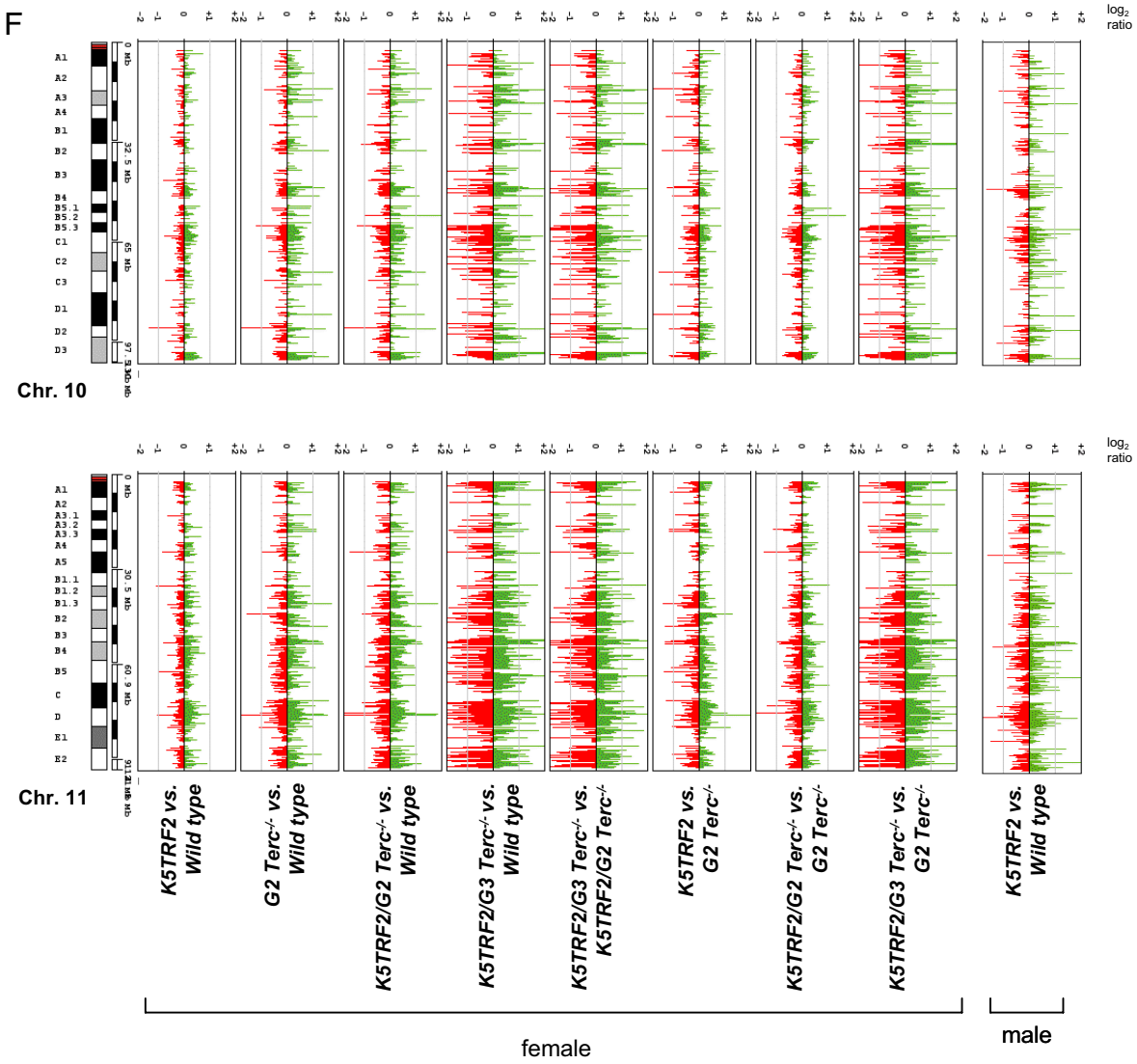
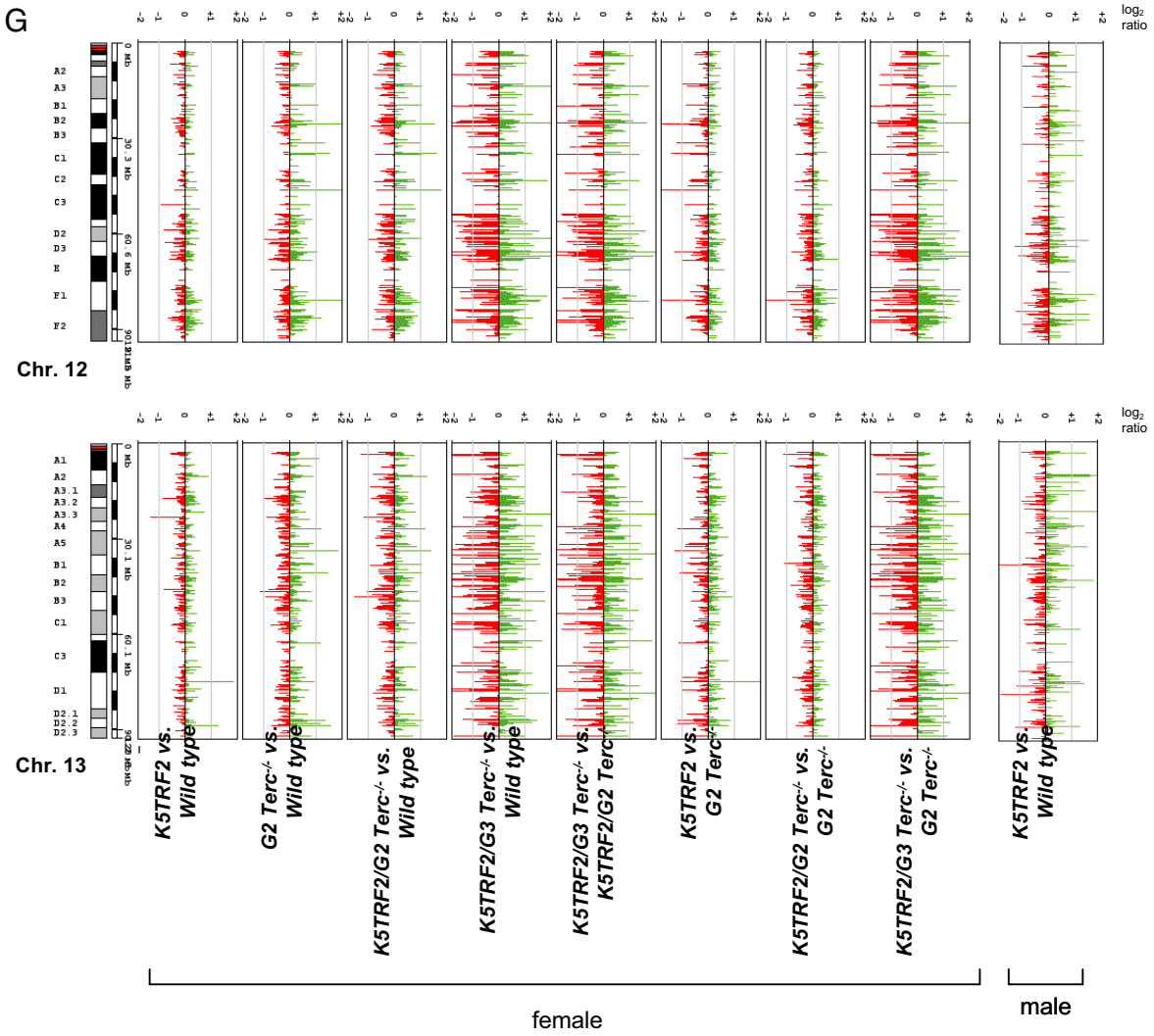


Fig. S5 (continued).



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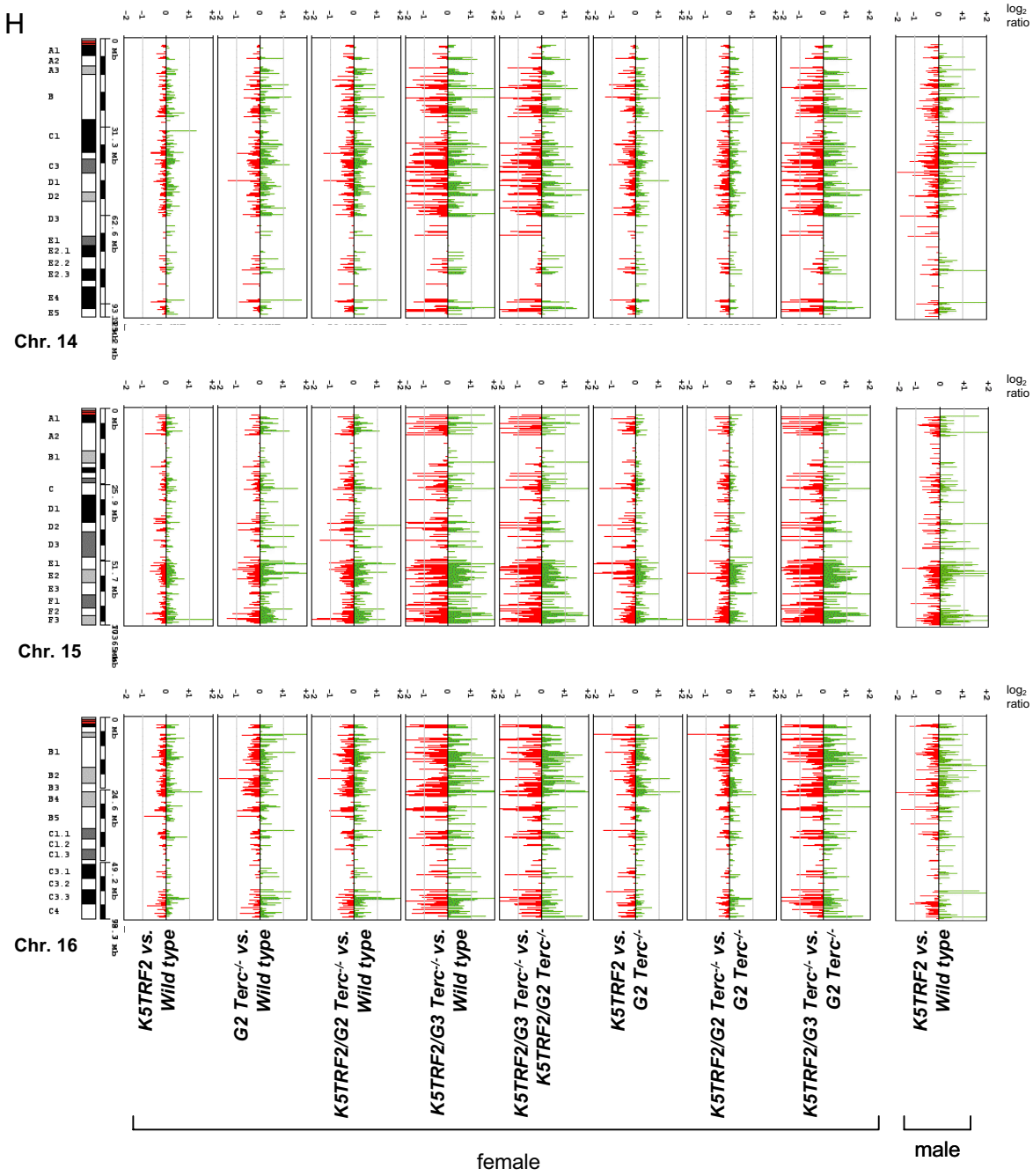

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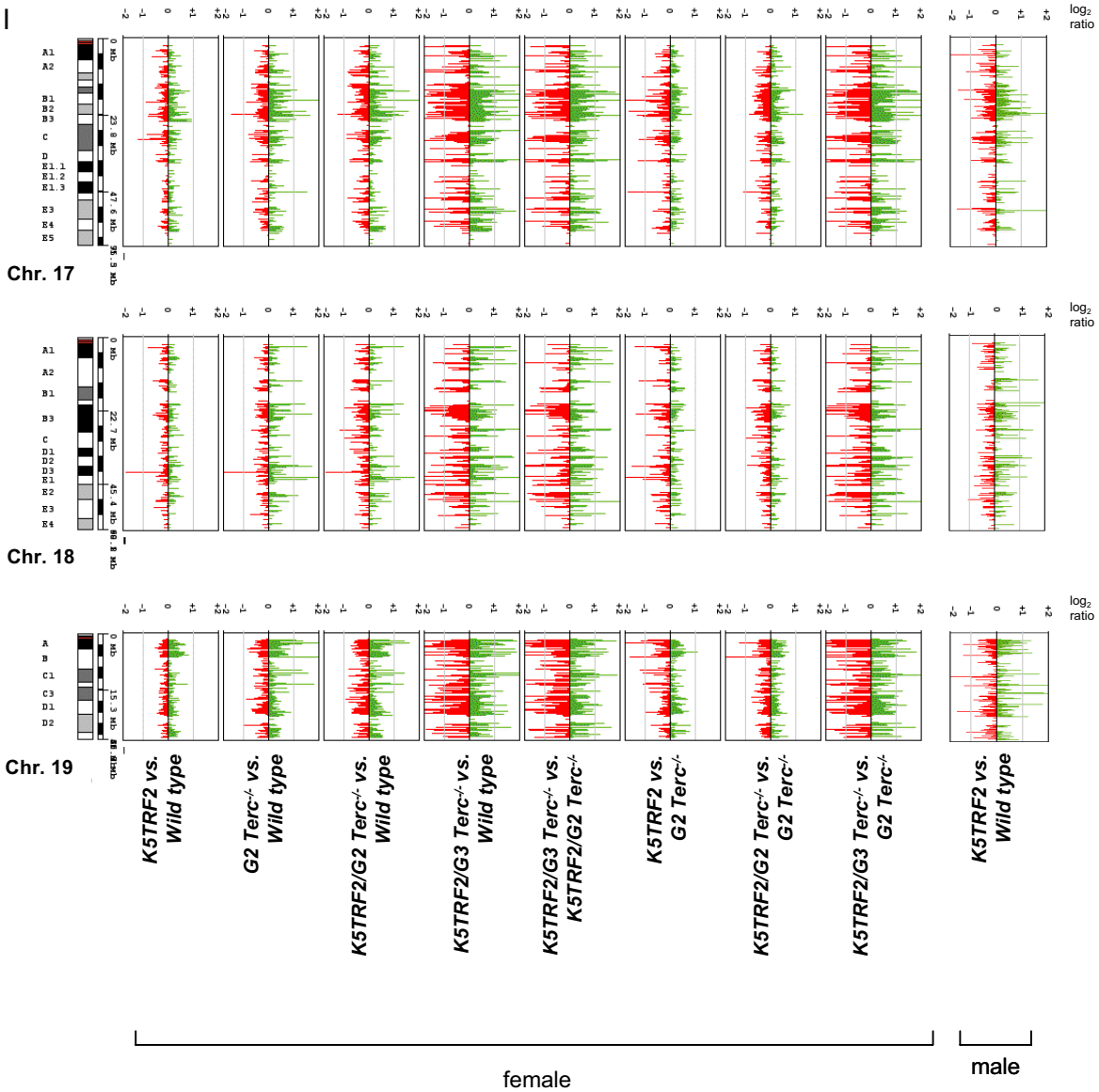

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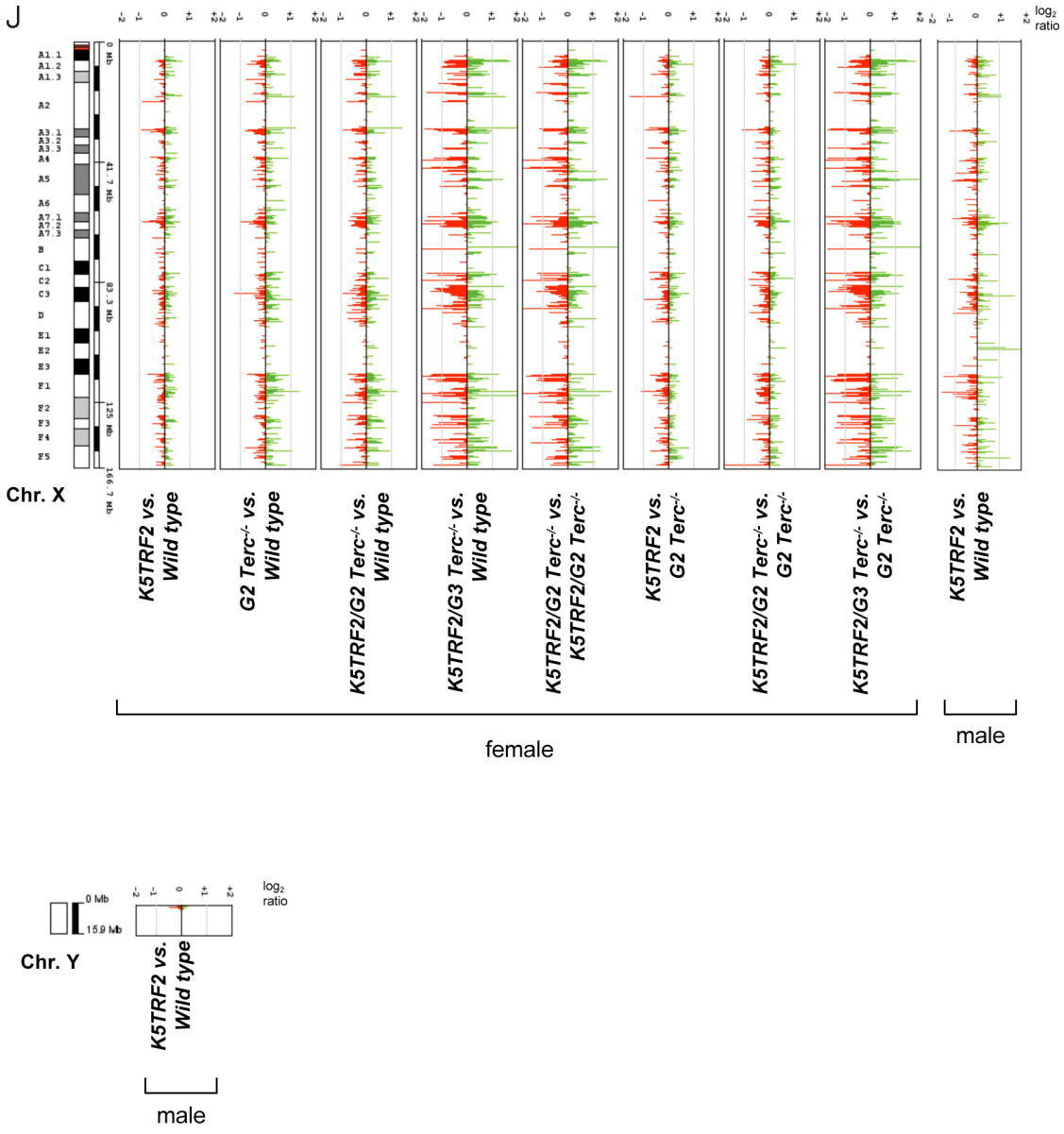

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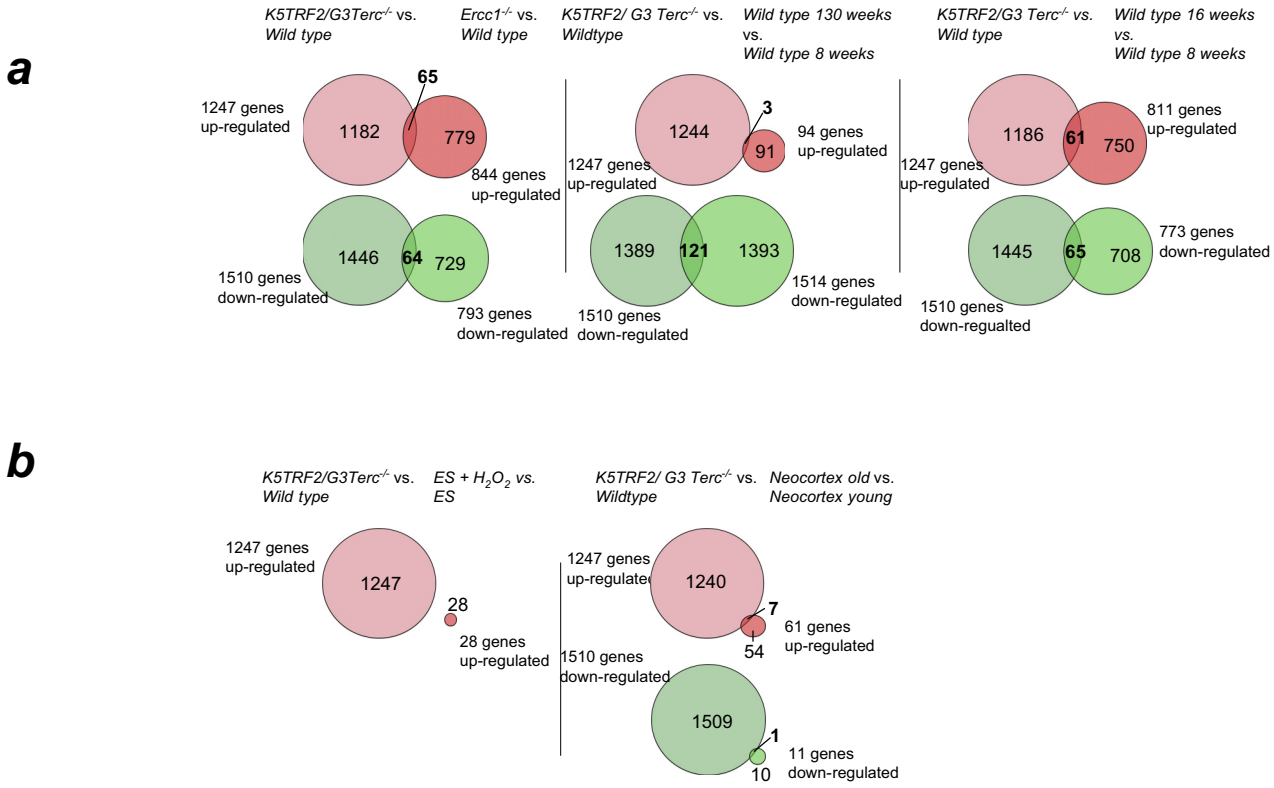

Fig. S6. Overlapping gene expression pattern in aging mice. Genes, displaying significant expression changes in aging mice (liver and neocortex) (13, 14), premature aging *Ercc1*$^{-/-}$ mice (4), and an in vitro model for DNA damage [H_2O_2-treated ES cells (5)] were compared with gene changes in *K5TRF2/G3 Terc*$^{-/-}$ keratinocytes (FDR <0.05). Venn diagrams showing overlapping gene expression patterns between the indicated comparisons of transcriptomes. Red circles, up-regulated genes; green circles, down-regulated genes.

Table S1. Frequency of altered genes per chromosome

	K5TRF2 vs.		*G2 Terc*$^{-/-}$ vs.		*K5TRF2/G2 Terc*$^{-/-}$vs.		*K5TRF2/G3 Terc*$^{-/-}$ vs.		*K5TRF2/G3 Terc*$^{-/-}$ vs.		*K5TRF2/G3 Terc*$^{-/-}$ vs.		*Wild type* vs.	
	Wild type								K5TRF2/ G2 Terc$^{-/-}$		G2 Terc$^{-/-}$		K5TRF2	
	Female												Male	
Chr.	%Up	%Down	%Up	%Down	%Up	%Down	%Up	%Down	%Up	%Down	%Up	%Down	%Up	%Down
1	0	0	1.7	0.1	4.2	2.6	6.9	10.4	3.7	8.2	4.5	8.2	6.4	10.8
2	0	0	1	0.1	4.5	2.8	7.4	6.5	3.7	6	4.5	6.5	5.2	10.5
3	0	0	1	0.2	5.2	3.3	8	11	5.8	8.2	6.1	9.6	6.4	15.2
4	0	0	1	0.1	3.6	2	6.5	9.6	3.3	7.3	4.2	8.3	8.7	8.2
5	0	0	1.4	0	3.6	2.9	6	7.2	3.9	5.8	4.3	6.3	7.5	11.2
6	0	0	0.8	0.1	3.8	2.8	6.1	7.1	3.8	6.5	5	6.6	5.0	7.9
7	0	0	1.2	0.1	3.7	2.5	6	6.8	3.5	6.2	4.3	6.1	4.3	9.6
8	0	0	1	0.7	3	3.3	5.9	10.6	4.3	7.9	4.4	8.5	6.0	9.4
9	0	0	1	0.4	3.3	2.1	5.3	7.1	3.3	6.3	3.6	6.5	6.8	9.6
10	0	0	1.2	0.2	4.1	2.6	7.9	7.6	4	6.4	5.2	6.7	5.1	11.0
11	0	0	0.9	0.1	3	2.5	7.4	8.4	3.8	6.9	5.2	7	6.6	9.1
12	0	0	1.6	0.4	5.1	3.1	9.5	10.3	5.3	7.9	6.4	8.8	4.6	10.3
13	0	0	0.9	0.1	2.5	3.7	5.7	9.7	4	6.6	3.9	7.6	6.1	10.5
14	0	0	0.6	0.3	3.2	2.7	6.5	8.9	3.2	6.4	4.6	7.8	7.3	9.9
15	0	0	1.1	0.3	4.2	3.8	8.4	10.5	5.3	8.4	5.8	9.4	7.3	14.4
16	0	0	1.1	0.4	2.7	3.3	7.8	8.8	4.2	7.1	4.7	7.7	6.0	11.5
17	0	0	0.6	0.1	3.1	2.8	5.6	6.9	3.3	4.6	3.9	6.1	6.3	7.4
18	0	0	1.9	0	4.3	2.9	7.4	7.2	5	6.9	4.5	7.9	3.6	18.2
19	0	0	0.6	0.2	3.7	2.6	5.6	6.9	2.7	6.2	2.9	7.2	5.1	10.4
X	0	0	0.3	0	2.3	2.4	4.5	6.6	2.6	5.1	2.7	6.5	6.2	6.3
Average	0	0	1.1	0.2	3.7	2.8	6.7	8.4	3.9	6.8	4.5	7.5	6.0	10.6

Percentage of significantly altered probe sets (FDR < 0.05) per individual chromosome in the indicated transcriptome comparisons. Percentage increases with progressive telomere shortening. Changes on autosomes and the X chromosome accumulate in a similar way. %Up, percentage of up-regulated genes; %Down, percentage of down-regulated genes. Average frequency per chromosome is indicated.

Table S2. Top 50 upregulated genes in *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type transcriptome comparisons

	K5TRF2/G3 Terc$^{-/-}$ vs. *Wild type*		*K5TRF2/G3 Terc*$^{-/-}$ vs. *G2 Terc*$^{-/-}$		*K5TRF2/G3 Terc*$^{-/-}$ vs. *K5TRF2/G2 Terc*$^{-/-}$		*K5TRF2/G2 Terc*$^{-/-}$ vs. *Wild type*	
Gene symbol	logFC	FDR	logFC	FDR	logFC	FDR	logFC	FDR
Fkbp5	3.34	*3.18E-09*	2.78	3.81E-07	2.98	5.26E-08	0.36	1.29E-01
Fkbp5	4.04	*3.18E-09*	3.40	3.81E-07	4.03	2.94E-08	0.01	9.64E-01
Slc38a2	2.77	*9.38E-09*	1.73	1.06E-05	1.46	1.70E-05	1.30	3.89E-03
2310002A05Rik	6.52	*1.08E-08*	5.10	1.88E-06	4.34	2.53E-06	2.17	7.90E-03
5430432H19Rik	3.02	*1.90E-08*	2.47	1.88E-06	2.27	1.28E-06	0.76	1.97E-02
9630055N22Rik	2.79	*1.90E-08*	2.08	4.10E-06	1.84	4.50E-06	0.95	9.13E-03
Gpsm1	2.83	*2.51E-08*	2.44	1.88E-06	1.82	9.61E-06	1.01	9.13E-03
2810003C17Rik	4.29	*2.51E-08*	3.82	1.57E-06	3.33	1.46E-06	0.96	3.14E-02
Ifngr1	2.84	*2.51E-08*	2.31	3.21E-06	2.54	5.28E-07	0.29	2.45E-01
NA	3.96	*3.10E-08*	3.75	1.39E-06	3.39	8.67E-07	0.57	1.24E-01
2810457I06Rik	3.04	*3.45E-08*	2.96	1.39E-06	2.74	6.07E-07	0.30	2.84E-01
NA	2.59	*4.14E-08*	1.80	1.95E-05	1.70	1.21E-05	0.89	1.14E-02
BC011467	4.10	*4.16E-08*	4.06	1.39E-06	3.55	9.39E-07	0.56	1.56E-01
Lnx1	2.67	*4.55E-08*	2.27	3.96E-06	2.34	9.39E-07	0.33	2.05E-01
App	3.32	*4.55E-08*	2.21	3.41E-05	2.11	1.97E-05	1.21	1.08E-02
Slc6a6	3.29	*4.55E-08*	2.29	2.24E-05	2.62	2.53E-06	0.67	5.23E-02
Fkbp5	4.91	*6.74E-08*	2.72	1.97E-04	2.67	9.98E-05	2.24	6.00E-03
Blcap	2.75	*8.88E-08*	2.20	1.16E-05	1.85	1.97E-05	0.90	1.76E-02
Sdcbp2	3.12	*8.91E-08*	2.51	1.13E-05	2.38	7.24E-06	0.74	3.89E-02
Lnx1	2.67	*9.20E-08*	2.24	8.18E-06	2.31	2.15E-06	0.36	1.88E-01
Ctdsp2	2.38	*1.02E-07*	1.88	1.50E-05	1.54	3.38E-05	0.84	1.43E-02
NA	2.78	*1.33E-07*	2.37	9.41E-06	2.11	9.83E-06	0.67	4.15E-02
Wdfy1	2.33	*1.35E-07*	1.63	4.98E-05	1.26	1.80E-04	1.06	7.32E-03
Klhl24	2.08	*1.49E-07*	1.84	7.36E-06	1.37	3.87E-05	0.71	1.76E-02
Tnnt2	2.60	*1.49E-07*	2.38	5.41E-06	1.83	2.08E-05	0.77	2.46E-02
Shd	2.81	*1.53E-07*	3.13	1.39E-06	2.64	1.46E-06	0.17	5.79E-01
Ctdsp2	2.42	*1.68E-07*	2.29	4.30E-06	1.91	9.44E-06	0.52	6.42E-02
Cecr2	3.39	*1.73E-07*	2.40	5.51E-05	2.42	2.06E-05	0.97	2.76E-02
1810015C04Rik	2.39	*1.74E-07*	2.02	1.28E-05	2.07	3.75E-06	0.32	2.17E-01
Cpa4	4.15	*1.89E-07*	3.32	2.20E-05	3.04	1.90E-05	1.11	3.47E-02
NA	2.21	*1.89E-07*	2.48	1.47E-06	1.91	3.93E-06	0.30	2.24E-01
Tead4	2.50	*2.05E-07*	1.85	4.55E-05	1.62	5.70E-05	0.88	1.76E-02
Ramp3	2.40	*2.38E-07*	2.14	1.12E-05	1.71	2.84E-05	0.69	3.04E-02
4933429H19Rik	2.15	*2.86E-07*	2.17	4.01E-06	1.63	1.97E-05	0.52	5.18E-02
Nfe2l2	3.06	*2.91E-07*	3.15	3.74E-06	2.91	2.53E-06	0.15	6.86E-01
Lypd5	2.10	*3.06E-07*	1.89	1.28E-05	1.77	9.31E-06	0.33	1.73E-01
Sprrl1	5.12	*3.08E-07*	3.73	7.55E-05	3.37	7.60E-05	1.75	1.97E-02
2310033K02Rik	2.71	*3.17E-07*	2.69	5.26E-06	2.23	1.11E-05	0.49	1.31E-01
Otud7a	2.88	*3.19E-07*	3.47	1.39E-06	3.05	9.43E-07	−0.17	6.18E-01
Lonrf3	2.21	*3.62E-07*	1.02	2.83E-03	0.81	7.31E-03	1.40	4.17E-03
Plcxd1	2.86	*3.70E-07*	2.15	6.73E-05	2.14	2.77E-05	0.71	5.31E-02
Flg2	3.81	*4.33E-07*	2.80	9.43E-05	2.74	4.80E-05	1.08	3.73E-02
NA	2.56	*4.42E-07*	1.97	6.16E-05	1.84	4.80E-05	0.72	3.78E-02
NA	3.47	*4.62E-07*	3.00	2.47E-05	2.58	3.70E-05	0.89	5.23E-02
Sprrl1	5.19	*4.97E-07*	3.67	1.48E-04	3.21	1.82E-04	1.97	1.76E-02
Ablim3	2.06	*5.18E-07*	1.72	3.63E-05	1.36	1.10E-04	0.70	2.39E-02
Sigirr	2.36	*5.23E-07*	2.28	1.11E-05	1.75	4.15E-05	0.60	5.48E-02
1700080G18Rik	1.94	*6.32E-07*	2.12	4.01E-06	1.65	1.49E-05	0.29	2.34E-01
Baalc	2.50	*6.75E-07*	2.77	4.00E-06	2.67	1.81E-06	−0.17	5.88E-01
Tfdp2	2.08	*7.13E-07*	1.97	1.60E-05	1.46	9.20E-05	0.62	3.70E-02

Probe sets with most robust up-regulation obtained by *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type comparisons were ranked based on the false detection rate (FDR). *K5TRF2/G3 Terc*$^{-/-}$ probe sets show persistent up-regulation when compared to *K5TRF2/G2 Terc*$^{-/-}$, and *G2 Terc*$^{-/-}$ keratinocytes. Genes up-regulated in *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type comparisons are also found to be up-regulated in *K5TRF2/G2 Terc*$^{-/-}$ versus wild-type comparisons, albeit in some cases at a FDR $>$ 1.00E-1. Also see Figure 5*B*.

Table S3. Top 50 downregulated genes in *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type transcriptome comparisons

	K5TRF2/G3 Terc$^{-/-}$ vs. *Wild type*		*K5TRF2/G3 Terc*$^{-/-}$ vs. *G2 Terc*$^{-/-}$		*K5TRF2/G3 Terc*$^{-/-}$ vs. *K5TRF2/G2 Terc*$^{-/-}$		*K5TRF2/G2 Terc*$^{-/-}$ vs. *Wild type*	
Gene symbol	logFC	FDR	logFC	FDR	logFC	FDR	logFC	FDR
Slc27a3	−3.38	*3.18E-09*	−3.43	6.01E-08	−3.00	4.43E-08	−0.38	1.02E-01
Tnc	−4.15	*6.17E-09*	−4.15	2.08E-07	−3.76	8.56E-08	−0.39	2.05E-01
Scd2	−2.92	*6.29E-09*	−2.24	1.57E-06	−2.22	5.28E-07	−0.70	1.76E-02
Aldh18a1	−3.15	*1.08E-08*	−3.07	3.81E-07	−2.36	8.67E-07	−0.79	1.76E-02
Fcgr3	−3.16	*1.99E-08*	−2.65	1.88E-06	−2.77	4.94E-07	−0.39	1.54E-01
4732466D17Rik	−2.70	*1.99E-08*	−2.70	4.43E-07	−2.16	8.86E-07	−0.54	3.97E-02
Parp1	−2.40	*1.99E-08*	−2.45	3.81E-07	−1.81	1.46E-06	−0.59	2.20E-02
Edg8	−2.85	*2.51E-08*	−2.45	1.93E-06	−2.38	8.67E-07	−0.47	7.99E-02
1810011O10Rik	−2.99	*2.67E-08*	−2.71	1.57E-06	−2.67	5.35E-07	−0.33	2.27E-01
Fstl1	−3.09	*2.67E-08*	−2.62	2.44E-06	−2.62	8.67E-07	−0.47	1.02E-01
Npl	−3.35	*3.34E-08*	−3.92	3.16E-07	−3.16	4.94E-07	−0.18	5.58E-01
2810055F11Rik	−3.15	*4.16E-08*	−2.95	1.66E-06	−2.63	1.33E-06	−0.52	9.13E-02
Rerg	−2.97	*4.27E-08*	−2.59	3.12E-06	−2.46	1.46E-06	−0.51	8.37E-02
Slc16a9	−3.26	*4.55E-08*	−3.16	1.57E-06	−2.77	1.31E-06	−0.49	1.26E-01
BC029169	−2.71	*6.86E-08*	−2.41	3.84E-06	−2.49	8.86E-07	−0.22	4.04E-01
Galnt14	−2.59	*7.64E-08*	−2.06	1.13E-05	−1.77	1.63E-05	−0.83	1.76E-02
S100a4	−2.28	*7.64E-08*	−1.98	4.77E-06	−2.35	4.94E-07	0.07	7.76E-01
A730090H04Rik	−2.47	*8.51E-08*	−2.26	3.53E-06	−1.66	1.91E-05	−0.81	1.76E-02
Dmpk	−2.83	*8.76E-08*	−2.64	3.14E-06	−2.47	1.70E-06	−0.36	2.15E-01
Pla2 g4f	−2.82	*8.89E-08*	−2.14	1.87E-05	−2.13	8.05E-06	−0.69	3.54E-02
Fndc1	−3.30	*9.19E-08*	−3.26	1.93E-06	−3.70	2.98E-07	0.40	2.40E-01
Ccdc80	−3.15	*1.05E-07*	−2.89	4.01E-06	−2.57	4.03E-06	−0.58	9.10E-02
Eppb9	−2.89	*1.35E-07*	−2.89	2.43E-06	−2.89	8.67E-07	0.00	9.93E-01
Sulf2	−2.13	*1.86E-07*	−1.80	1.32E-05	−1.50	2.46E-05	−0.63	2.58E-02
Fmo5	−2.35	*2.05E-07*	−2.00	1.34E-05	−1.77	1.63E-05	−0.58	4.38E-02
Ptn	−2.32	*2.15E-07*	−3.11	3.81E-07	−2.84	2.98E-07	0.52	6.11E-02
Pdlim3	−3.19	*2.36E-07*	−3.58	1.57E-06	−3.29	9.28E-07	0.10	7.97E-01
Hoxd4	−3.41	*2.38E-07*	−2.68	3.16E-05	−2.54	1.93E-05	−0.87	4.15E-02
Igfbp5	−3.03	*2.38E-07*	−3.79	7.25E-07	−3.48	4.94E-07	0.45	1.84E-01
Myom2	−4.41	*2.42E-07*	−3.82	1.40E-05	−4.18	2.15E-06	−0.23	6.59E-01
Col4a5	−2.72	*2.45E-07*	−2.99	1.88E-06	−2.49	3.02E-06	−0.23	4.56E-01
2210016F16Rik	−2.33	*2.64E-07*	−2.18	7.82E-06	−1.84	1.32E-05	−0.49	7.71E-02
Ankrd23	−2.78	*2.81E-07*	−2.50	1.16E-05	−2.14	1.73E-05	−0.64	5.94E-02
Rdhe2	−2.74	*2.81E-07*	−2.70	4.82E-06	−2.31	8.46E-06	−0.44	1.70E-01
Plxna3	−2.36	*2.98E-07*	−1.71	7.92E-05	−1.92	1.15E-05	−0.45	1.13E-01
Marveld1	−2.49	*3.17E-07*	−2.95	1.47E-06	−2.70	8.67E-07	0.21	4.73E-01
Frem2	−2.49	*3.29E-07*	−2.74	2.42E-06	−2.22	5.30E-06	−0.27	3.47E-01
Srd5a1	−2.17	*3.30E-07*	−1.72	3.81E-05	−1.83	9.56E-06	−0.34	1.86E-01
Alox12	−2.53	*3.30E-07*	−2.41	8.25E-06	−2.08	1.15E-05	−0.45	1.36E-01
4632428N05Rik	−2.27	*3.36E-07*	−2.12	1.07E-05	−2.07	4.44E-06	−0.20	4.50E-01
NA	−1.73	*3.81E-07*	−1.37	4.49E-05	−0.95	3.95E-04	−0.78	1.08E-02
Tdh	−3.39	*4.09E-07*	−2.04	4.39E-04	−2.10	1.51E-04	−1.29	1.76E-02
NA	−2.35	*4.15E-07*	−2.49	3.96E-06	−2.79	5.35E-07	0.44	1.29E-01
NA	−1.99	*4.23E-07*	−1.59	4.49E-05	−1.53	2.45E-05	−0.46	6.77E-02
Spon2	−2.58	*4.33E-07*	−2.80	3.51E-06	−2.44	3.89E-06	−0.14	6.72E-01
Cyr61	−2.21	*4.76E-07*	−2.28	5.09E-06	−1.84	1.36E-05	−0.36	1.77E-01
Slc35f1	−2.91	*4.80E-07*	−2.66	1.59E-05	−2.51	1.02E-05	−0.40	2.59E-01
B3 gnt8	−2.91	*4.80E-07*	−1.93	2.34E-04	−2.12	4.66E-05	−0.79	4.37E-02
Ehd2	−2.16	*4.97E-07*	−2.57	1.88E-06	−2.07	4.01E-06	−0.10	7.27E-01
4930583H14Rik	−2.16	*5.68E-07*	−1.99	1.69E-05	−1.91	9.61E-06	−0.24	3.57E-01

Probe sets with most robust down-regulation obtained by *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type comparisons were ranked based on the false detection rate (FDR). *K5TRF2/G3 Terc*$^{-/-}$ probe sets show persistent down-regulation when compared to *K5TRF2/G2 Terc*$^{-/-}$, and *G2 Terc*$^{-/-}$ keratinocytes. Genes down-regulated in by *K5TRF2/G3 Terc*$^{-/-}$ versus wild-type comparisons are also found to be down-regulated in *K5TRF2/G2 Terc*$^{-/-}$ versus wild-type comparisons; albeit in some cased at a FDR $>$ 1.00E-1. Also see Figure 5*B*.

Table S4. a: Genes with most robust regulation in male PM *K5TRF2* versus male wild type transcriptome comparisons

	male K5TRF2 vs. male Wild type	
Gene symbol	logFC	FDR
Terf2	8.41	5.90E-10
Terf2	5.63	8.82E-07
Hbb-bh1	3.55	2.55E-06
Ptgds	3.76	9.55E-06
Terf2	5.54	1.04E-05
Tyrp1	3.39	1.84E-05
Slc45a2	2.68	2.42E-05
Mcam	3.28	2.63E-05
3110007F17Rik	2.36	3.19E-05
Cpt1c	2.02	6.76E-05
Trpm1	3.48	7.75E-05
Dct	2.86	7.75E-05
Nrg1	2.37	8.06E-05
Nrg1	2.35	8.06E-05
Loxl2	2.33	8.06E-05
Mrpplf4	2.26	9.73E-05
Vim	2.39	1.03E-04
Si	2.87	1.13E-04
Mrpplf4	2.18	1.13E-04
Mlana	2.69	1.26E-04
Dct	2.73	1.33E-04
A830073O21Rik	1.99	1.43E-04
Emp3	1.93	1.50E-04
Lgals1	2.02	1.72E-04
Syt4	2.00	1.78E-04
Syt4	1.94	1.78E-04
Plod2	1.84	2.07E-04
Adamts1	2.35	2.14E-04
Ednrb	2.14	2.14E-04
Plat	1.76	2.14E-04
Mamdc2	1.67	2.14E-04
Mc1r	2.09	2.35E-04
Phlda1	1.79	2.35E-04
Gapdhs	2.65	2.58E-04
Slc24a5	2.26	2.58E-04
Plf2	2.08	2.72E-04
Enpp2	1.96	2.88E-04
Syngr1	1.79	3.03E-04
Syngr1	1.81	3.11E-04
Scrn1	1.86	3.11E-04
C2	1.77	3.11E-04
Bace2	2.22	3.15E-04
C2	2.60	3.17E-04
Adamts1	2.30	3.17E-04
Sprr1b	1.79	3.17E-04
Mcam	1.42	3.17E-04
Mcoln3	1.98	3.28E-04
Plat	1.82	3.28E-04
Sprr1a	1.88	3.53E-04
Polk	1.33	3.56E-04

Table S4. b

	male K5TRF2 vs. male Wild type	
Gene symbol	logFC	FDR
Pgm5	−3.02	1.84E-05
Cd34	−1.84	9.29E-05
Fndc1	−2.25	1.47E-04
Irs1	−2.10	1.72E-04
Fras1	−2.29	2.07E-04
Igfbp5	−1.92	2.14E-04
1190002H23Rik	−1.59	2.72E-04
Grik4	−1.92	2.99E-04
BC029169	−1.47	2.99E-04
Ccl27	−2.31	3.17E-04
Spock2	−1.63	3.18E-04
Ccdc80	−1.53	3.56E-04
Tmem35	−1.50	3.68E-04
Rgs7	−1.49	4.37E-04
1600015H20Rik	−1.74	4.51E-04
Ogn	−2.11	5.67E-04
Tns1	−1.58	5.82E-04
Vit	−1.50	5.82E-04
Foxp1	−1.33	5.82E-04
Cmkor1	−1.18	5.82E-04
Selenbp1	−1.76	5.89E-04
Cdh4	−1.29	6.25E-04
Nfib	−1.26	6.63E-04
2310067E19Rik	−1.12	7.77E-04
Arhgap25	−1.37	9.00E-04
BC029169	−1.34	9.62E-04
Prrg3	−1.10	9.70E-04
Fgf18	−1.60	9.94E-04
Dapk2	−1.54	1.00E-03
Echdc3	−1.19	1.00E-03
Chst12	−1.16	1.03E-03
Gpha2	−1.25	1.10E-03
Avpr1a	−1.24	1.10E-03
Tulp2	−1.02	1.10E-03
Lhx2	−2.06	1.12E-03
Hrbl	−1.18	1.13E-03
Mrc2	−1.20	1.15E-03
Glul	−1.19	1.15E-03
Tsc22d3	−1.58	1.23E-03
Slc2a5	−1.57	1.29E-03
Tsc22d3	−1.56	1.33E-03
Tbx3	−1.18	1.34E-03
Dtx4	−1.25	1.36E-03
Defb2	−1.38	1.37E-03
Kif21a	−1.09	1.37E-03
Mrc2	−1.19	1.38E-03
Ngfr	−1.21	1.58E-03
Gucy1b3	−1.09	1.70E-03
Ramp1	−1.25	1.72E-03
Phf21a	−1.10	1.76E-03

a. Top 50 upregulated probe sets in PM *K5TRF2* keratinocytes, ranked by increasing FDR. b. Top 50 downregulated probe sets in PM *K5TRF2* keratinocytes, ranked by increasing FDR.

Table S5. a: Overrepresented in *K5TRF2/G2 Terc*$^{-/-}$ and *K5TRF2/G3 Terc*$^{-/-}$ females compared to female *Wild type*

Source	Pathway	Biological functions	*K5TRF2/G3 Terc*$^{-/-}$ FDR	*K5TRF2/G2 Terc*$^{-/-}$ FDR
Biocarta	mTOR	mammalian target of rapamycin (mTOR) senses mitogenic factors and nutrients, including ATP, and induces cell proliferation	0.116	n.a.
Biocarta	Akt	second messenger PIP3 promotes cell survival by activating the anti-apoptotic kinase AKT	0.143	n.a.
Biocarta	eIF4	the eIF-4F complex recognizes 5′ mRNA caps, recruits RNA helicases, and maintains mRNA-ribosome bridging.	0.181	n.a.
Biocarta	Ecm	extracellular matrix induces integrin-mediated FAK phosphorylation in epithelial cells, leading to PI3 and MAP kinase activation and actin reorganization	0.197	n.a.
Reactome	ERK/MAPK targets	ERK/MAPK kinases have a number of targets within the nucleus, usually transcription factors or other kinases	0.246	0.236
Reactome	FGFR ligand binding and activation	a series of signals generated as a consequence of a fibroblast growth factor receptor binding to one of its physiological ligands	0.107	n.s.
Reactome	FGFR4 ligand binding and activation	a series of signals generated as a consequence of a fibroblast growth factor receptor binding to one of its physiological ligands	0.114	n.s. (0.254)
Reactome	FGFR1 ligand binding and activation	a series of signals generated as a consequence of a fibroblast growth factor receptor binding to one of its physiological ligands	0.127	n.s.
Reactome	FGFR2 ligand binding and activation	a series of signals generated as a consequence of a fibroblast growth factor receptor binding to one of its physiological ligands	0.128	n.s.
Reactome	FGFR2C lignad binding and activation	a series of signals generated as a consequence of a fibroblast growth factor receptor binding to one of its physiological ligands	0.146	n.s.

Table S5. b: Overrepresented in Wild type females compared to *K5TRF2/G2 Terc*$^{-/-}$ and *K5TRF2/G3 Terc*$^{-/-}$ females

Source	Pathway	Biological function	*K5TRF2/G3 Terc*$^{-/-}$ FDR	*K5TRF2/G2 Terc*$^{-/-}$ FDR
Reactome	DNA repair	Restoring DNA after damage	0.069	n.s. (0.275)
Reactome	base excision repair	Removal of altered base by hydrolytic removal	0.033	n.s. (0.262)
KEGG	base excision repair	Removal of altered base by hydrolytic removal	0.004	0.202
KEGG	nucleotide excision repair	Removal of region around DNA damage and subsequent gap filling	0.155	n.s.
Reactome	nucleotide excision repair	Removal of region around DNA damage and subsequent gap filling	0.195	n.s.
Reactome	gap-filling DNA repair synthesis and ligation in GG-NER	DNA gap filling after removal of pyrimidine dimers during globlal genomic nuclear excision repair	0.138	n.s.
Reactome	gap-filling DNA repair synthesis and ligation in TC-NER	DNA gap filling after removal of pyrimidine dimers during transcription coupled nuclear excision repair	0.141	n.s.
KEGG	missmatch repair	corrects DNA mismatches generated during DNA replication	0.086	n.s.
Reactome	Telomere maintenance	telomere elongation	0.101	n.s.
Reactome	cell cycle, mitotic	mitotic cell cycle regulation	<0.001	n.s. (0.264)
Reactome	G1 phase	mitotic cell cycle regulation, G1 phase	0.185	n.s. (0.258)
Reactome	G1/S transition	mitotic cell cycle regulation, G1/S transition	0.006	n.s.
Reactome	lagging strand synthesis	mitotic cell cycle regualtion, S Phase	0.164	n.s.
Reactome	G2/M transition	mitotic cell cycle regulatio, G2/M transition	0.018	n.s. (0.258)
Reactome	mitotic prometaphase	mitotic cell cycle regulation, M phase	<0.001	n.s.
Reactome	M/G1 transition	mitotic cell cycle regualtion, M/G1 transition	0.134	0.204
Reactome	cell cycle checkpoints	Cell cycle checkpoints	0.006	0.249
Reactome	DNA replication	DNA replication	0.036	n.s. (0.265)
KEGG	p53 signaling	activation by stress signals, including DNA damage, oxidative stress and activated oncogenes. activation of p53-regulated genes results in cell cycle arrest, cellular senescence or apoptosis.	0.158	n.s.

Table S5. c: Overrepresented in Wild type males compared to *K5TRF2* males

Source	Pathway	Description	FDR q-value
KEGG	mismatch repair	corrects DNA mismatches generated during DNA replication	0.008
KEGG	base excision repair	removal of altered base by hydrolytic removal	0.115
KEGG	nucleotide excision repair	removal of region around DNA damage and subsequent gap filling	0.116
Reactome	gap-filling DNA repair synthesis and ligation in GG NER	DNA gap filling after removal of pyrimidine dimers during globlal genomic nuclear excision repair	0.142
GeneMAPP	DNA replication reactome	network of interacting proteins and enzymes required for DNA replication	0.220
Reactome	DNA strand elongation	cell cycle, mitotic	0.253
KEGG	DNA replication	network of interacting proteins and enzymes required for DNA replication	0.014

Table S5. d: Overrepresented in *K5TRF2* males compared to Wild type males

Source	Pathway	Description	FDR q-value
KEGG	Toll-like receptor signaling	activation of innate immunity; inducing production of proinflammatory cytokines and costimulatory molecules	0.004
KEGG	ErbB signaling	ErbB family of receptor tyrosine kinases; regulating diverse biologic responses, including proliferation, differentiation, cell motility, and survival;MAPK pathway is a common target downstream of all ErbB receptors	0.091
BioCarta	Jak-Stat signaling	Transduction of signals for development and homeostasis; also mediate the recruitment of other molecules such as the MAP kinases	0.186
KEGG	p53 signaling	activation by stress signals, including DNA damage, oxidative stress and activated oncogenes. activation of p53-regulated genes results in cell cycle arrest, cellular senescence or apoptosis.	0.183
KEGG	apoptosis	controlled mechanisms of cell death involved in the regulation of tissue homeostasis	0.191
GeneMAPP	apoptosis	controlled mechanisms of cell death involved in the regulation of tissue homeostasis	0.196
KEGG	mTOR signaling	Mammalian target of rapamycin (mTOR) senses mitogenic factors and nutrients, including ATP, and induces cell proliferation	0.262
KEGG	NTHI		0.116

Pathway analysis based on female PM *K5TRF2/G2-G3 Terc*$^{-/-}$ versus female wild type transcriptome comparisons and on male wild-type versus male PM *K5TRF2* transcriptome comparisons.

a. Pathways enriched in *K5TRF2/G3 Terc*$^{-/-}$ (FDR < 0.25) are listed. Over-representation of genes involved in the mTOR, eIF4a and Akt pathways suggests the activation of a cell survival program to escape cellular senescence induced by critically short telomeres. In addition ERK/MAPK targets and FGF signalling were found to be augmented in *K5TRF2/G3 Terc*$^{-/-}$ cells. n.a., not analyzed b. Pathways enriched in wild-type cells (FDR < 0.25) are listed. Over-representation of genes involved in various aspects of DNA damage repair as well as p53 signalling. Activation of a series of mitotic cell cycle regulation pathways reflects an increased proliferative activity of wild type cells compared to *K5TRF2/G2-3 Terc*$^{-/-}$ keratinocytes. Pathway activation is reduced when compared with *K5TRF2/G2 Terc*$^{-/-}$ keratinocytes with higher telomere reserve. c. Pathways enriched in wild-type cells (FDR < 0.25) are listed. Over-representation of genes involved in various aspects of DNA damage repair and mitotic cell cycle regulation pathways. d. Pathways enriched in male *K5TRF2* keratinocytes (FDR < 0.25) are listed. Over-representation of genes involved in the mTOR and ErbB signalling suggests the activation of a cell survival program responding to the activation of apoptosis pathways induced by critically short telomeres and p53 signalling pathways

Table S6. a: Overview on over-lapping gene expression changes in *Ercc1*$^{-/-}$ mice (4) vs *K5TRF2/G3 Terc*$^{-/-}$ primary keratinocytes and ageing mice (4) vs *K5TRF2/G3 Terc*$^{-/-}$ primary keratinocytes

Ercc1$^{-/-}$ vs. Wild type	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
up-regulated	$\log_2$ ratio
Srpk2	1.26
Sfrs8	1.38
Mta3	0.59
Mdm2	0.67
Lgals7	1.09
Aox1	1.59
Slc6a6	3.29
Cxadr	1.62
Malat1	1.59
Eif5	1.15
Prss8	1.71
Ccng1	0.87
Slc15a4	0.92
Plekhb2	1.06
Prune	0.62
Wbscr27	0.67
Ssh1	0.57
Cdc42bpg	1.39
Rhoc	0.80
Cpm	4.07
Gtf2ird1	1.66
Krt18	2.04
Ubd	1.62
Ak2	0.67
Anxa3	1.72
F11r	0.97
Cldn1	0.96
Jarid1a	0.63
Slc20a1	0.84
Csnk1d	0.98
Cyp2d9	0.93
Slpi	2.80
Txnip	2.13
Aatf	0.67
Sox4	1.94
Arhgef7	0.87
Dusp7	0.92
Krt23	2.80
Pde4b	0.95
Hist1 h1c	0.77
Nfe2l2	1.81
Rhod	1.01
Sbsn	1.39
Lhx6	0.88
Ocln	0.92
Tnfaip2	1.03
Litaf	0.92
Ipmk	1.53
Slk	1.35
Gnb2l1	0.72
Cdkn1c	0.94
Tmcc3	0.92
Gmeb1	0.66
Klk1	0.97
Rnf24	1.23
Foxk1	0.67
Cxcl16	1.52
C1qtnf4	0.78
Pcolce2	1.04
Chka	1.71
Ptpre	1.86
Marcks	0.67
Id4	1.01
Arhgef2	0.91
Alcam	1.16

Table S6. b

Ercc1$^{-/-}$ vs. Wild type	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
up-regulated	$\log_{(2)}$ ratio
Srpk2	1.26
Sfrs8	1.38
Mta3	0.59
Mdm2	0.67
Lgals7	1.09
Aox1	1.59
Slc6a6	3.29
Cxadr	1.62
Malat1	1.59
Eif5	1.15
Prss8	1.71
Ccng1	0.87
Slc15a4	0.92
Plekhb2	1.06
Prune	0.62
Wbscr27	0.67
Ssh1	0.57
Cdc42bpg	1.39
Rhoc	0.80
Cpm	4.07
Gtf2ird1	1.66
Krt18	2.04
Ubd	1.62
Ak2	0.67
Anxa3	1.72
F11r	0.97
Cldn1	0.96
Jarid1a	0.63
Slc20a1	0.84
Csnk1d	0.98
Cyp2d9	0.93
Slpi	2.80
Txnip	2.13
Aatf	0.67
Sox4	1.94
Arhgef7	0.87
Dusp7	0.92
Krt23	2.80
Pde4b	0.95
Hist1 h1c	0.77
Nfe2l2	1.81
Rhod	1.01
Sbsn	1.39
Lhx6	0.88
Ocln	0.92
Tnfaip2	1.03
Litaf	0.92
Ipmk	1.53
Slk	1.35
Gnb2l1	0.72
Cdkn1c	0.94
Tmcc3	0.92
Gmeb1	0.66
Klk1	0.97
Rnf24	1.23
Foxk1	0.67
Cxcl16	1.52
C1qtnf4	0.78
Pcolce2	1.04
Chka	1.71
Ptpre	1.86
Marcks	0.67
Id4	1.01
Arhgef2	0.91
Alcam	1.16

Table S6. c

Wild type 130 weeks vs. Wild type 8 weeks	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
up-regulated	$\log_2$ ratio
Hist1 h1c	0.77
Tacstd2	0.82
Cd36	0.87

Table S6. d

Wild type 130 weeks vs. Wild type 8 weeks	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
down-regulated	$\log_2$ ratio
Hunk	−2.09
Rapgef3	−1.23
Pias2	−0.74
Commd5	−0.92
Calm1	−0.58
Ddit4l	−0.62
Sc5d	−0.71
Hsd3b2	−1.47
Gspt1	−2.13
Nnt	−1.24
Hps4	−1.32
Srd5a1	−2.17
Asb3	−0.95
Polr3k	−0.91
Egfr	−2.04
Vcl	−0.78
Rasl11b	−1.70
Gtf3c3	−1.26
Acat2	−0.83
Nfic	−0.93
Crot	−1.14
Pigq	−1.22
Disp1	−1.49
Mrpl15	−0.57
Mmab	−1.75
Akr1c19	−1.32
Cog8	−0.61
Wdr59	−1.36
Usp40	−1.01
Nsdhl	−1.58
Ikbkg	−1.26
Mcm10	−0.96
Tial1	−1.23
Zfp524	−0.76
Dnajc11	−1.36
Gtf3c1	−0.95
Edaradd	−1.99
Lactb2	−1.86
Thtpa	−1.44
Slc18a1	−1.10
Fzd6	−0.93
Grb14	−1.51
Yme1l1	−0.89
Parp1	−2.40
Dot1l	−0.48
Senp7	−1.17
Clspn	−1.37
Nudcd1	−1.52
Zfp386	−1.20
Pdcl	−0.54
Bbs7	−1.13
Rab7l1	−2.43
Ttc19	−1.01
Nup37	−2.11
Vegfa	−0.94
Dpp4	−2.19
Spsb4	−2.13
Acsl1	−1.27
Capns2	−1.33
Nr2c1	−0.78
Selenbp1	−1.94
Hsdl2	−1.49
Marveld2	−0.70
Spnb3	−0.83
Nupl2	−0.90
Alas2	−1.32
Rtn4rl1	−1.52
Armc8	−0.97
Ralgps2	−1.04
Mmp15	−1.56
Sdha	−0.82
Akr1c13	−0.89
Higd1a	−0.69
P2ry5	−1.82
Hsd17b7	−0.68
Ccbl1	−1.94
Mrp63	−0.76
Map3k12	−1.00
Pdxk	−0.72
Ppp1r3c	−1.98
Trim37	−1.33
B3 galnt2	−0.68
Idh1	−0.54
Hspa4	−1.93
Zfp294	−0.59
Gldc	−1.62
Fbxo25	−1.06
Hexim1	−0.84
Mrpl44	−0.67
Hsd3b6	−0.90
Sox6	−1.30
Pes1	−0.95
As3mt	−1.13
Trip4	−1.56
Akap1	−0.85
Mtap	−1.42
Ttc14	−0.72
Lmbr1	−0.77
Mkks	−1.78
Itpr2	−0.76
Sh2d4a	−0.71
Btrc	−0.76
Bri3bp	−1.59
Znrf1	−0.99
Tacr3	−0.55
Oxa1l	−1.29
Lig3	−1.81
Det1	−1.25
Psip1	−1.58
Usp10	−0.87
Rabif	−0.63
Cpt2	−1.18
Aasdhppt	−0.98
Ngfr	−1.76
Mrpl36	−1.65
Gcsh	−1.31
Fusip1	−0.99
Oma1	−1.05
Manea	−0.78
Brwd2	−0.93
Ephx2	−1.50

Table S6. e

Wild type 16 weeks vs. Wild type 8 weeks	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
up-regulated	log(2) ratio
Kif1c	1.12
Tsc1	0.81
Ugcg	1.20
Srpk2	1.26
Htatsf1	0.80
Cct2	0.83
Tiam1	1.10
Rb1cc1	0.84
Vapb	1.30
Ppih	1.00
Krtap6–3	1.50
Cry2	1.51
Arl5b	0.76
Atp1b1	1.41
Slc15a4	0.92
Centa2	0.58
Gpd2	0.60
Gltscr2	0.67
Tfdp2	2.08
Ssh1	0.57
Glrx	0.67
Sh3bp2	1.30
Ankrd17	1.22
Lmo7	0.85
Eef2	1.00
Cdc42bpg	1.39
Oraov1	0.72
Hlf	1.08
Eif4e2	0.55
Por	1.31
Pdpk1	1.34
Rab22a	0.87
Kif13a	1.03
Riok3	0.84
Arhgef10	0.82
Jarid1a	0.63
Pik3cb	1.06
Zfp91	1.81
Gabarapl1	1.68
Ube2e2	1.09
Ipo7	1.04
Eif2c2	0.60
Clk4	0.82
Prodh2	0.53
Tcf12	1.36
Siah1a	0.92
Leng1	0.57
Nat13	1.02
Tollip	1.36
Cyp51	0.76
Cpsf6	1.16
Ccnt2	1.31
Eif2 s3x	1.11
Fbxo30	0.89
Ndel1	0.89
Bach1	0.96
Il6 st	1.18
Per2	0.75
Il18	2.20
Ddx3x	0.85
Hipk1	1.30

Table S6. f

Wild type 16 weeks vs. Wild type 8 weeks	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
down-regulated	log(2) ratio
Hsdl2	−1.49
Selenbp1	−1.94
Rtn4rl1	−1.52
	−0.58
Neu3	−0.96
Nrp1	−0.86
Iars	−0.81
Lap3	−1.01
Hsd3b2	−1.47
Galc	−0.84
Sdha	−0.82
Spon2	−2.58
Irf2bp2	−1.07
P2ry5	−1.82
Tmem38a	−0.60
Myom2	−4.41
Ccbl1	−1.94
Zfand5	−0.62
Hps4	−1.32
Mrp63	−0.76
Arhgef19	−1.81
Srd5a1	−2.17
Gnai2	−0.83
Mef2c	−1.01
Sparc	−1.51
Ppp1r3c	−1.98
Gtpbp3	−0.82
Epb4.1l1	−0.80
Nav1	−2.02
Igfbp2	−1.25
Gldc	−1.62
Crot	−1.14
Sulf1	−0.95
Pigq	−1.22
Hsd3b6	−0.90
Col4a1	−0.81
Olah	−1.64
Ttc14	−0.72
Spag5	−1.08
Ikbkg	−1.26
Btg2	−1.21
Aldh18a1	−3.15
Gatm	−1.07
Gtf3c1	−0.95
Itpr2	−0.76
Edaradd	−1.99
Pja1	−1.29
Cd44	−1.37
Tor3a	−1.14
Grb14	−1.51
Sipa1l1	−1.24
Prkcz	−0.71
Ubap2l	−1.30
Prelp	−0.98
Mocos	−0.60
Aasdhppt	−0.98
Nudcd1	−1.52
Mrpl36	−1.65
Pdcl	−0.54
Serpinh1	−1.71
Brwd2	−0.93
Dpp4	−2.19

Wild type 16 weeks vs. Wild type 8 weeks	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
Bcl11a	−1.54
Immp2l	−0.91
Acsl1	−1.27

a. Summary of genes up-regulated in both mouse ageing models. b. Summary of genes up-regulated in both mouse ageing models. Log_2 ratios in *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type transcriptome comparisons are indicated. c. Summary of genes up-regulated in both mouse models. d. Summary of genes down-regulated in both mouse ageing models. Log_2 ratios in *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type transcriptome comparisons are indicated. e. Summary of genes up-regulated in both mouse models. f. Summary of genes down-regulated in both mouse ageing models. Log_2 ratios in *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type transcriptome comparisons are indicated.

Table S7. a: Overview on over-lapping gene expression changes in ageing mouse neocortex (5) and *K5TRF2/G3 Terc*$^{-/-}$ primary keratinocytes

Neocortex old vs. Neocortex young	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
up-regualted	(log_2) ratio
Srrm1	1.08
Ppp1r12b	0.87
Rab14	1.07
Tmem87a	0.64
5830417C01Rik	1.09
4930504E06Rik	0.84

Table S7. b

Neocortex old vs. Neocortex young	*K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type
down-regualted	(log_2) ratio
Atp8b3	−0.95
Pisd	−0.93

a. Summary of genes up-regulated in both mouse models. b. Summary of genes down-regulated in both mouse ageing models. Log_2 ratios in *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type transcriptome comparisons are indicated.

Table S8. a: Biological themes in transcriptome intersections of ageing models and *K5TRF2/G3 Terc*$^{-/-}$ keratinocytes

Intersection *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type with *Ercc1*$^{-/-}$ vs. Wild type

down-regulated	FDR	Process number	Term of database
Cellular metabolic process	0.029	GO:0044237	GO level 3
up-regulated	FDR	Process number	Term of database
No significant terms	-	-	-

Table S8. b

Intersection *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type with Wild type 130 weeks vs. Wild type 8 weeks

down-regulated	FDR	Process number	Term of database
Cellular metabolic process	0.005	GO:0044237	GO level 3
Steroid biosynthetic process	0.022	GO:0006694	GO level 7
up-regulated	FDR	Process number	Term of database
No significant terms	-	-	-

Table S8. c

Intersection *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type with Wild type 16 weeks vs. Wild type 8 weeks

Down-regulated	FDR	Process number	Term of database
Biosynthetic process	0.010	GO:0009058	GO level 3
Cellular biosynthetic process	0.046	GO:0044249	GO level 4
up-regulated	FDR	Process number	Term of database
mTOR signaling pathway	0.043	mm04150	KEGG

Transcriptome intersections shown in Supplementary Figure 5a,b were analysed for the presence of over-represented biological pathways. a. Intersection of *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type with *Ercc1*$^{-/-}$ vs. Wild type (4) and b. Intersections of *K5TRF2/G3 Terc*$^{-/-}$ *vs.* Wild type with Wild type 130 weeks vs. Wild type 8 weeks (4) transcriptomes do not show up-regulation of a relevant biological process. c. Intersections of *K5TRF2/G3 Terc*$^{-/-}$ vs. Wild type with Wild type 16 weeks vs. Wild type 8 weeks (4) indicate an up-regulation of the mTOR pathway. mTOR pathway members Eif4e2, Pdpk1 and Tsc1 are up-regulated in *K5TRF2/G3 Terc*$^{-/-}$ keratinocytes.