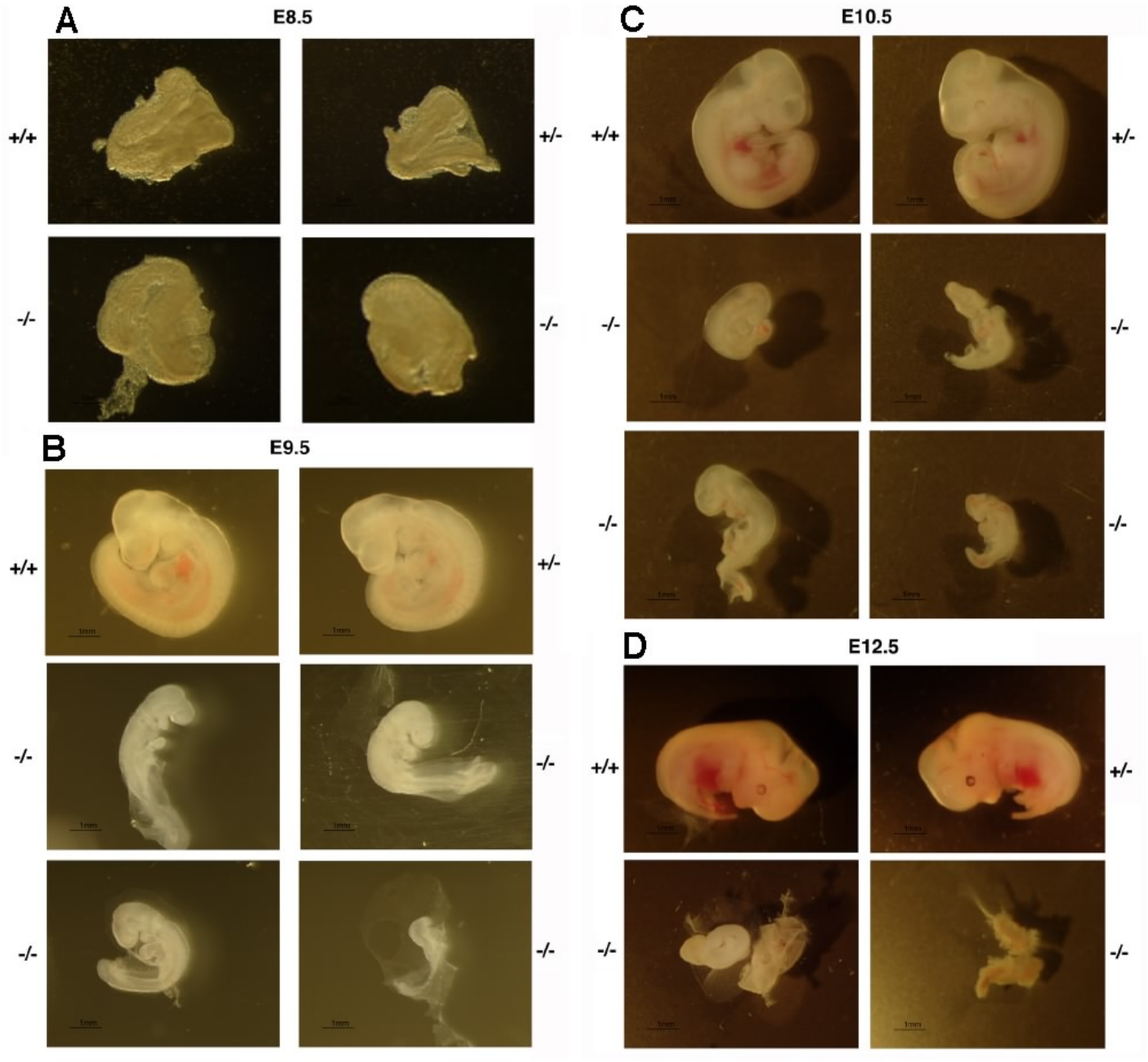
Table S1. Tumors developed in two independdent lines of PinX1+/- mice

Mouse ID	Tumor-Related Phenotypes
PinX1+/- A line (sex) (n=7)	
A165 (F)	Hepatocellular carcinoma
A951 (M)	Lung adenocarcinoma
A952 (M)	Lung adenocarcinoma
A954 (M)	Lung adenocarcinoma, chest leiomyosarcoma
A1014 (F)	Mammary adenocarcinoma
A1016 (F)	Mammary adenocarcinoma, lung metastasis
A1019 (M)	Hepatocellular carcinoma
PinX1+/- B line (sex) (n=45)	
B441 (M)	Histiocytic sarcoma in liver
B598 (F)	Lung adenocarcinoma, small intestine adenomucoitous polyps
B619 (F)	Hepatocellular carcinoma
B759 (F)	Mammary adenocarcinoma
B773 (F)	Lung adenocarcinoma
B777 (F)	Mammary adenocarcinoma, lung metastasis
B793 (F)	Lymphoma
B781 (F)	Lung adenocarcinoma
B816 (F)	Lung adenocarcinoma
B820 (F)	Lung adenocarcinoma, gastric squamous cell adenocarcinoma
B845 (F)	Mammary adenocarcinoma
B872 (F)	Skin hyperplasia
B916 (M)	Lung adenocarcinoma
B957 (M)	Lung adenoma, hepatoma
B960 (M)	No tumor
B963 (M)	Lymphoma in lymph node, liver, spleen, colon
B975 (F)	Lung adenocarcinoma, colon adenocarcinoma
B987 (F)	Eye Harderian gland adenomar
B993 (M)	Lung adenocarcinoma
B1032 (M)	Lung adenocarcinoma
B1066 (F)	Lung adenocarcinoma in both sides and lung metastasis in both sides
B1082 (F)	Lung adenocarcinoma
B1125 (F)	Hepatocellular carcinoma
B1128 (M)	No tumor
B1130 (M)	Lung adenocarcinoma
B1148 (F)	Lung adenocarcinoma
B1158 (F)	Hepatocellular carcinoma
B1159 (F)	Lung adenocarcinoma, mammary adenocarcinoma
B1316 (M)	Undifferentiated sarcoma
B1318 (M)	Lung adenocarcinoma, hepatocellular carcinoma, liver angiosarcoma
B1324 (F)	Histiocytic sarcoma in liver, colon and thymus
B1344 (F)	Lung adenocarcinoma, hepatocellular carcinoma, mammary adenocarcinoma
B1354 (M)	Lung adenocarcinoma
B1511 (M)	Hepatocellular carcinoma
B1525 (F)	Skin hyperplasia
B1603 (M)	Rectal tumor
B1606 (F)	Lymphoma
B1631 (F)	Lymphoma
B1675 (F)	Colon polyps
B1766 (M)	Small intestine adenomucoitous polyps
B1808 (M)	Hepatocellular carcinoma
B1900 (F)	Lung adenoma, hepatocellular carcinoma, eye Harderian gland adenoma
B1964 (F)	No tumor
B2037 (F)	Mammary adenocarcinoma
B2106 (F)	Lung adenocarcinoma, hibernoma in leg derived from brown adipose tissue

PinX1+/+ A+B line (sex) (n=15)

A950 (M)	No tumor	B1498 (M)	No tumor
B819 (F)	No tumor	B1530 (F)	No tumor
B822 (F)	No tumor	B1610 (F)	No tumor
B844 (F)	No tumor	B1612 (M)	Hepatocellular carcinoma
B846 (F)	No tumor		
B916 (M)	No tumor		
B924 (F)	No tumor		
B962 (F)	No tumor		
B998 (M)	No tumor		
B1042 (F)	No tumor		
B1044 (M)	No tumor		

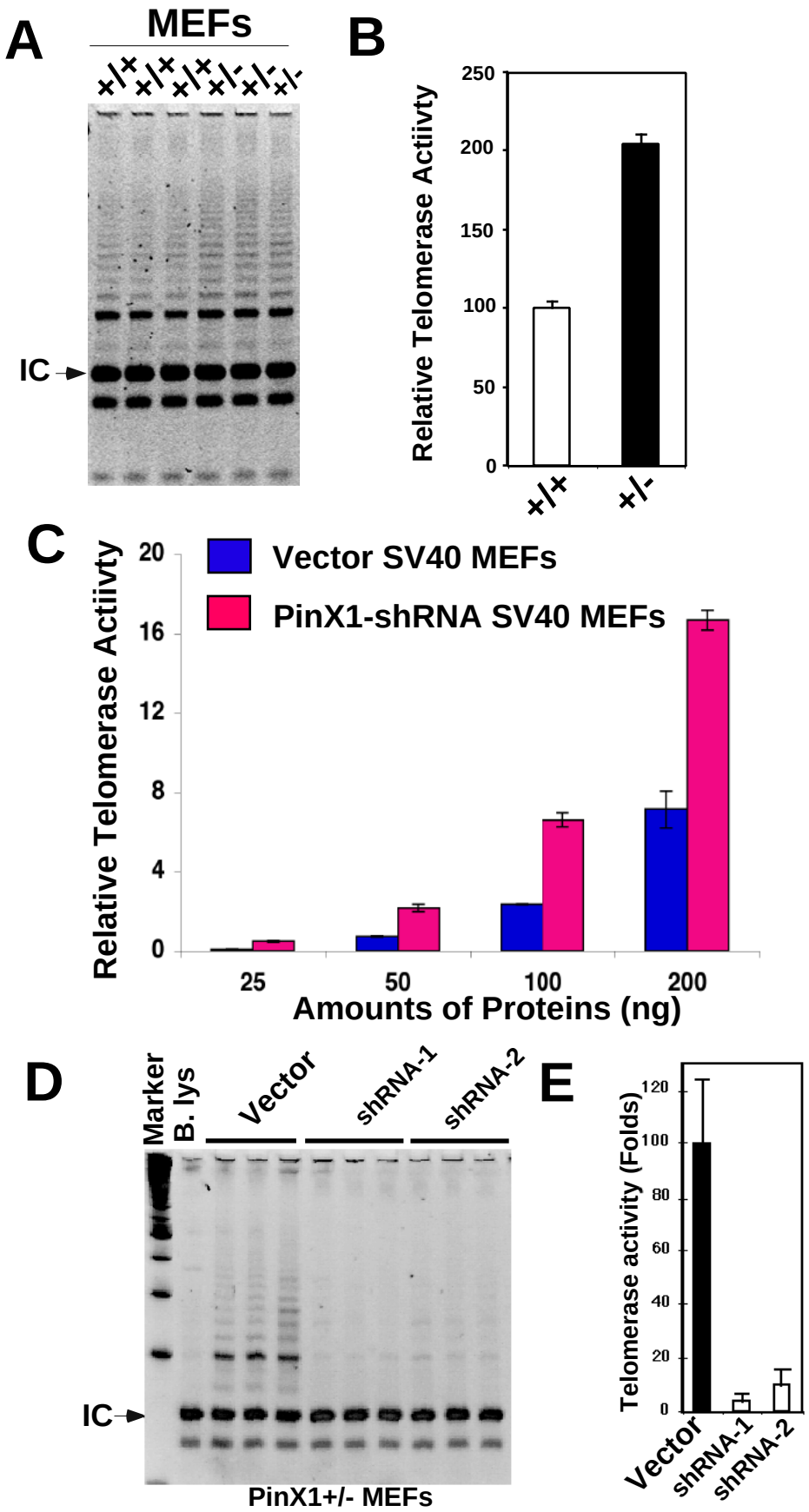


E **Genotypes of offspring from PinX1+/- intercrosses**

	Number of animals with genotypes				
Stage	**Total**	**+/+**	**+/-**	**-/-**	**ND**
Postnatal	**114**	**55**	**59**	**0**	
E 12.5	**20**	**6**	**9**	**0 (5*)**	
E 11.5	**49**	**16**	**21**	**0 (7*)**	**5**
E 10.5	**62**	**17**	**25**	**4 (12*)**	**4**
E 9.5	**46**	**15**	**19**	**6 (6*)**	
E 8.5	**17**	**5**	**8**	**4**	

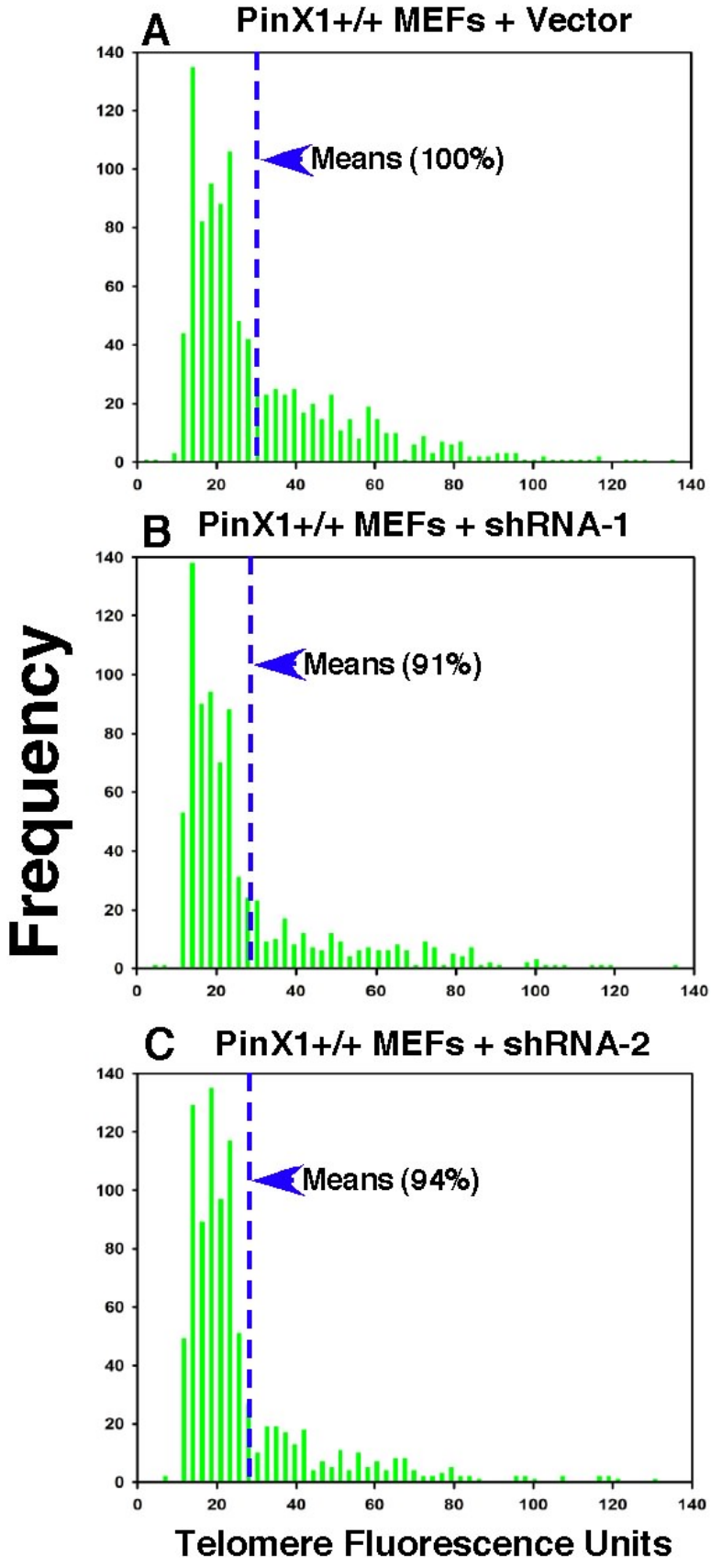
Asterisks indicate partially observed embryos. ND, not determined

Zhou et al., Fig. S1. PinX1-null mice are embryonic lethal.
(A-D) Representative morphologies of PinX1+/+, PinX1+/- and PinX1-/- embryos at 8.5 (A), 9.5 (B), 10.5 (C) and 12.5 (D) days post-conception produced from intercrosses of PinX1+/- mice. (E) Summary of genotypes of offspring from PinX1+/- intercrosses. The PinX1+/+ and PinX1+/- mouse ratio at F1 and F2 generations was approximately 1:1.1 (48% and 52%). Alive embryos were assayed by the presence of heartbeat.

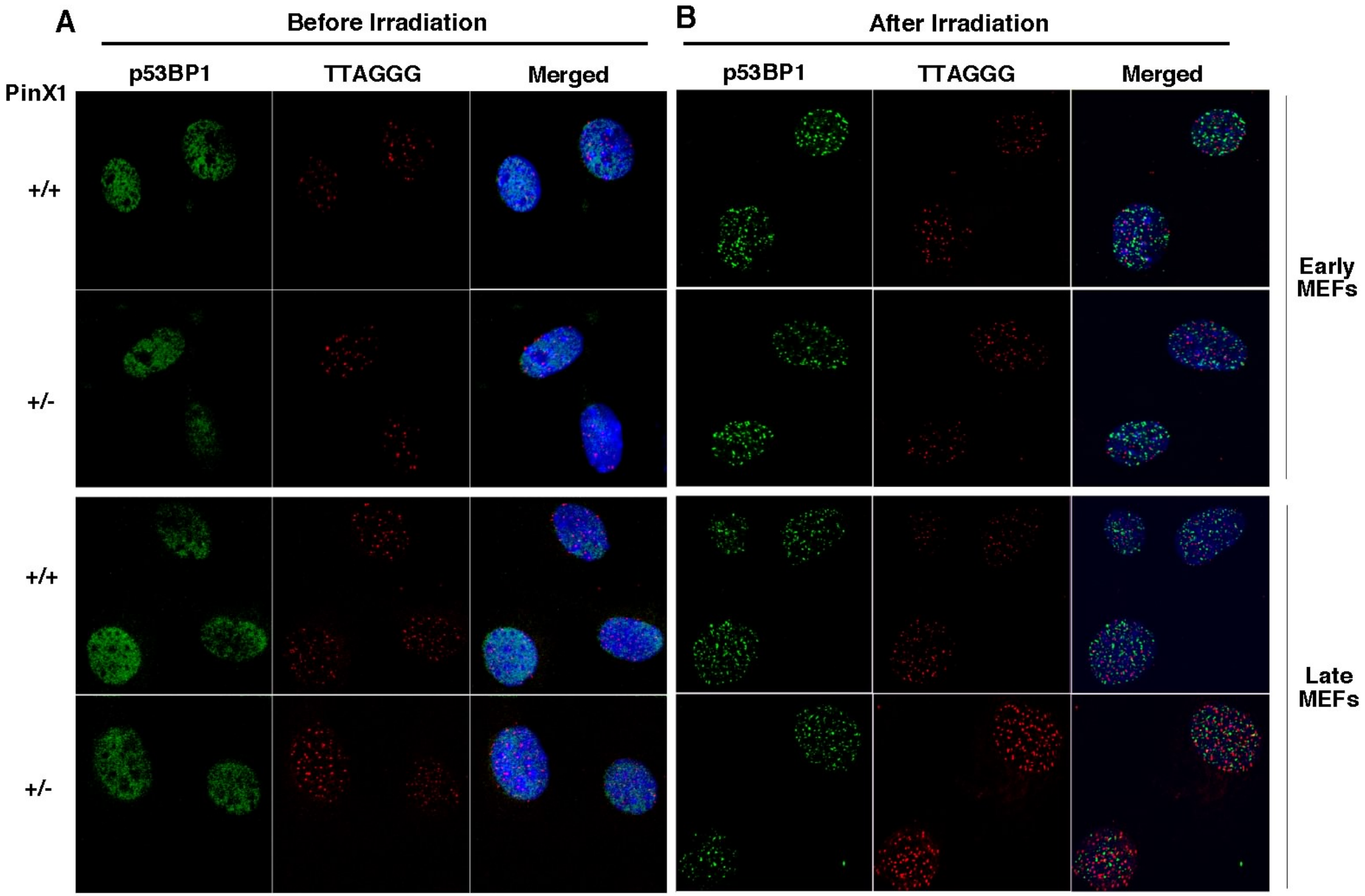


Zhou et al., Fig. S2. PinX1 heterozygous knockout or knockdown activates telomerase and TERT knockdown inhibits telomerase activation in PinX1+/- MEFs

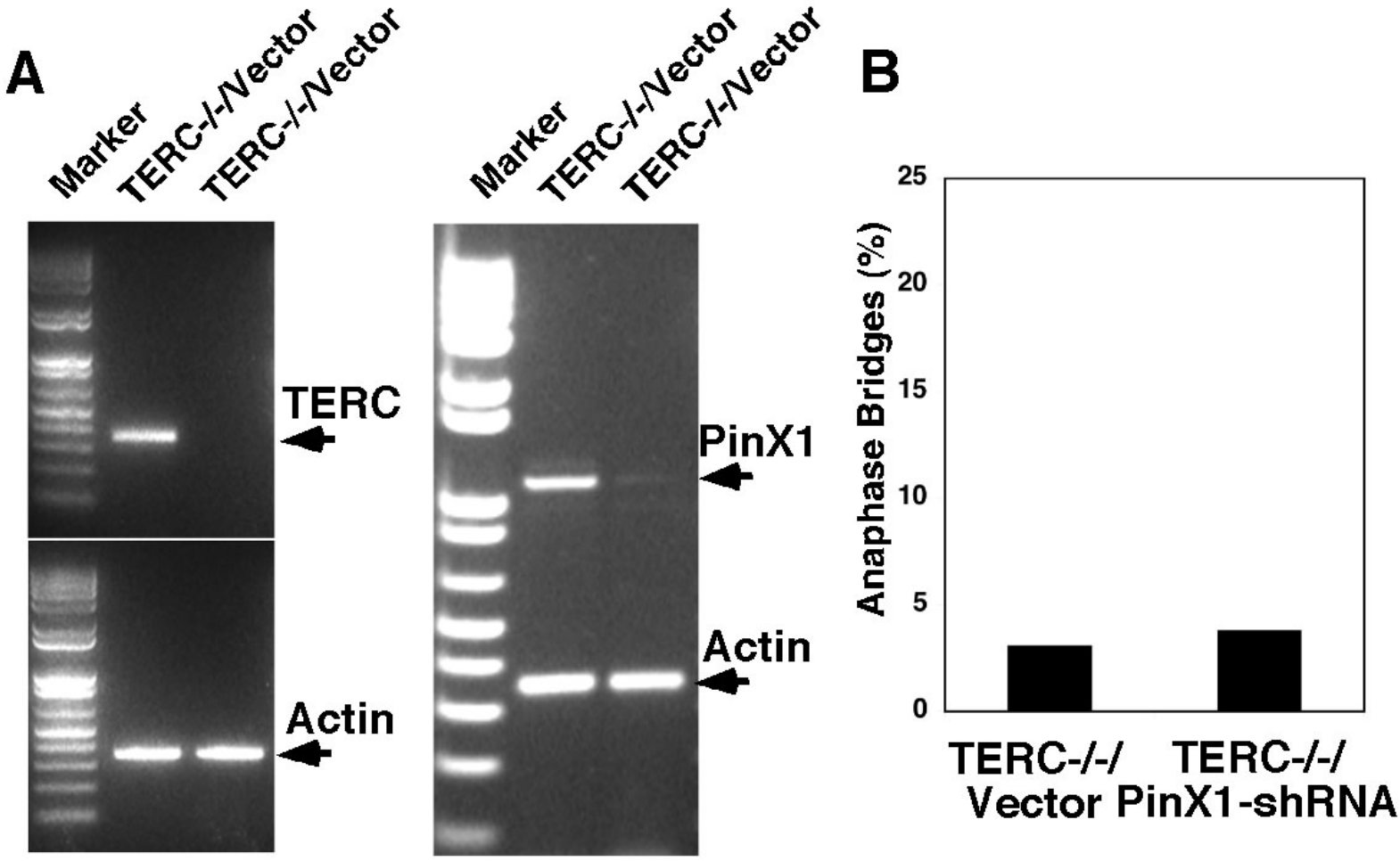
(A, B) PinX1 heterozygous knockout activates telomerase in MEFs. Telomerase activity in three independent PinX1+/+ and PinX1+/- MEF lines were assayed by TRAP assay (**A**), followed by semi-quantification with the vector being set at 100% (**B**). (**C**) PinX1 knockdown activates telomerase in SV40-immortalized MEFs. SV40 immortalized MEFs stably expressing PinX1-shRNA or vector control were subjected to TRAP assay (**Fig. 4E**), followed by semi-quantification, with the ratios between telomerase products and the internal control (IC) being shown. (**D**) TERT knockdown inhibits telomerase activation in PinX1+/- MEFs. PinX1+/- MEF pools stably expressing two different TERT-shRNA constructs or vector control were subjected to TRAP assay, followed by semi-quantification, with the vector being set at 100% (**E**).



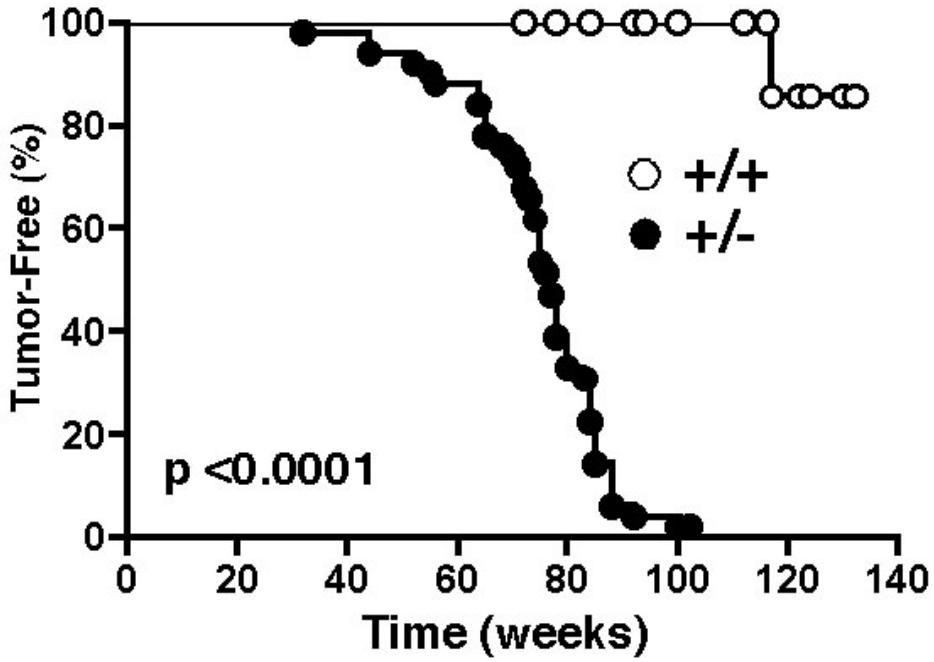
Zhou et al., Fig. S3. TERT kncockdown does not affect telomere length in PinX1+/+ MEFs. PinX1+/+ MEFs at passage 3 were infected with two different TERT-shRNA lentiviruses (-1 or -2) (**B, C**) or vector control viruses (**A**), followed by selection for stable cell pools. After 20 passage, cells were fixed and subjected to qFISH analysis. There was not obvious difference in telomere lengths between TERT-shRNA-1 or -2 cells and control cells.



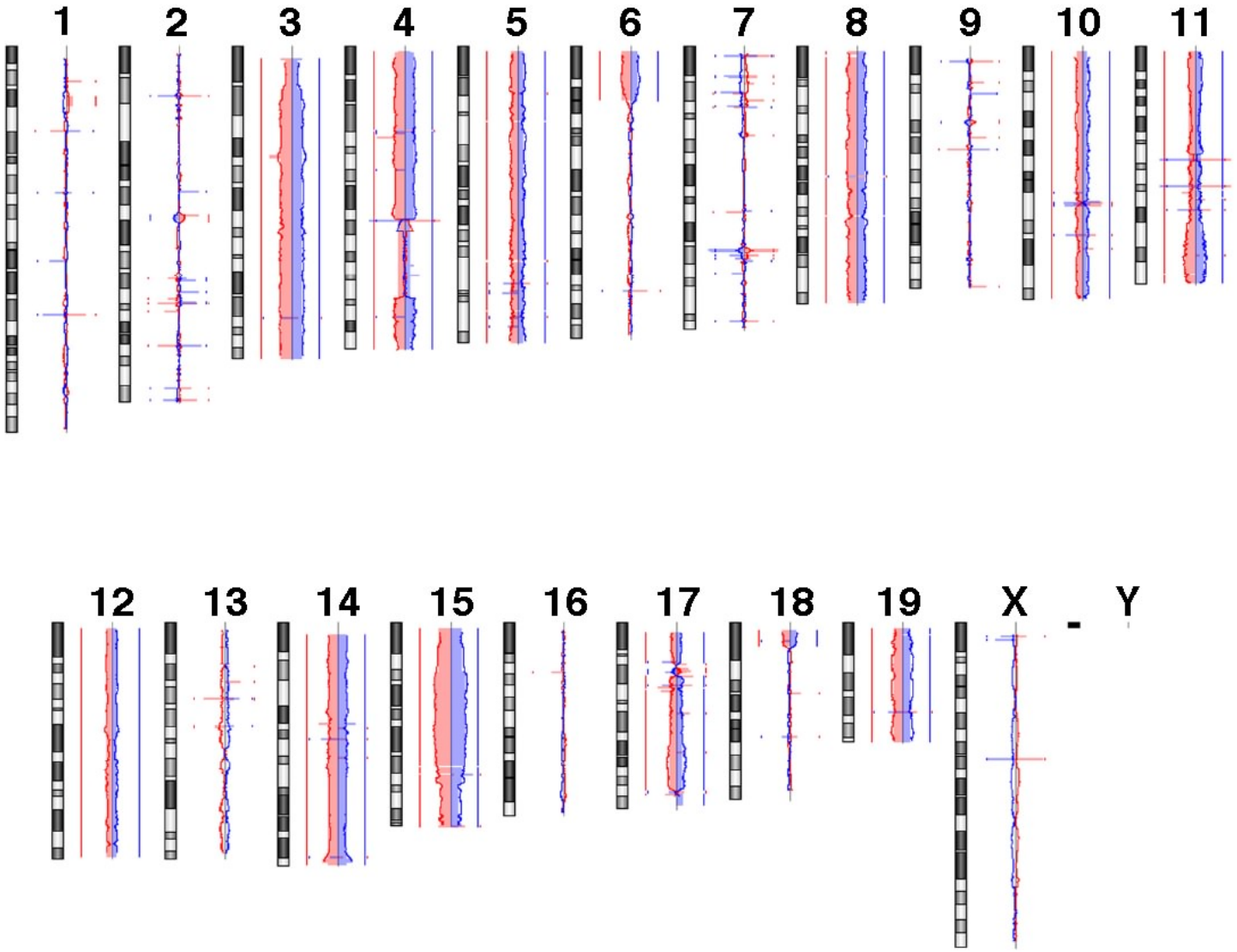
Zhou et al., Fig. S4. PinX1 heterozygous knockout does not induce obvious telomere-mediated DNA damage. PinX1+/- MEFs before (A) and after (B) γ-radiation were subjected to p53BP1 immunostaining (green) and telomere FISH (red) as well as DNA staining (blue) before confocal microscopy.



Zhou et al., Fig. S5. PinX1 knockdown does not induce anaphase bridges and/or lagging chromosomes in TERC-/- MEFs.
MEFs derived from G1 TERC-/- mice were stably infected with PinX1-shRNA or vector control lentiviruses, followed by RT-PCR analysis to confirm TERC knockout and PinX1 knockdown (A) as well as scoring for anaphase bridges and/or lagging chromosomes after continuous cell culture in vitro (B).



Zhou et al., Fig. S6. Most PinX1 knockout mice develop tumors. PinX1+/- animals were intercrossed to obtain the experimental cohorts that were followed for the development of tumors (Table S1) and subjected to Kaplan-Meier analysis. The data were plotted as the percent tumor-free of PinX1+/+ (n = 15) and PinX1+/- (n = 52) cohort mice versus age in weeks. The tumor differences between PinX1+/+ and PinX1+/- mice were highly significant ($p < 0.0001$).



Zhou et al., Fig. S7. PinX1+/- tumors show widespread chromosomal imbalances, as shown by genome-wide aCGH analysis.