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1. The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* **474**, 609–615 (2011).
2. Farmer, H. *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* **434**, 917–921 (2005).
3. Bryant, H. E. *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* **434**, 913–917 (2005).
4. Kennedy, R. D. & D'Andrea, A. D. DNA repair pathways in clinical practice: lessons from pediatric cancer susceptibility syndromes. *J. Clin. Oncol.* **24**, 3799–3808 (2006).
5. Bast, R. C. Jr, Hennessey, B. & Mills, G. B. The biology of ovarian cancer: new opportunities for translation. *Nature Rev. Cancer* **9**, 415–428 (2009).
6. Yousefzadeh, M. J. & Wood, R. D. DNA polymerase POLQ and cellular defense against DNA damage. *DNA Repair* **12**, 1–9 (2013).
7. Shima, N., Munroe, R. J. & Schimenti, J. C. The mouse genomic instability mutation *chaos1* is an allele of *Polq* that exhibits genetic interaction with *Atm*. *Mol. Cell. Biol.* **24**, 10381–10389 (2004).
8. Yoshimura, M. *et al.* Vertebrate POLQ and POL β cooperate in base excision repair of oxidative DNA damage. *Mol. Cell* **24**, 115–125 (2006).
9. Muzzini, D. M., Plevani, P., Boulton, S. J., Cassata, G. & Marini, F. *Caenorhabditis elegans* POLQ-1 and HEL-308 function in two distinct DNA interstrand cross-link repair pathways. *DNA Repair* **7**, 941–950 (2008).
10. McVey, M. & Lee, S. E. MMEJ repair of double-strand breaks (director's cut): deleted sequences and alternative endings. *Trends in Genet.* **24**, 529–538 (2008).
11. Chan, S. H., Yu, A. M. & McVey, M. Dual roles for DNA polymerase theta in alternative end-joining repair of double-strand breaks in *Drosophila*. *PLoS Genet.* **6**, e1001005 (2010).
12. Yu, A. M. & McVey, M. Synthesis-dependent microhomology-mediated end joining accounts for multiple types of repair junctions. *Nucleic Acids Res.* **38**, 5706–5717 (2010).
13. Koole, W. *et al.* A polymerase theta-dependent repair pathway suppresses extensive genomic instability at endogenous G4 DNA sites. *Nat. Commun.* **5**, 3216 (2014).
14. Nakanishi, K. *et al.* Human Fanconi anemia monoubiquitination pathway promotes homologous DNA repair. *Proc. Natl Acad. Sci. USA* **102**, 1110–1115 (2005).
15. Moldovan, G. L. *et al.* Inhibition of homologous recombination by the PCNA-interacting protein PARI. *Mol. Cell* **45**, 75–86 (2012).
16. Ira, G., Malkova, A., Liberi, G., Foiani, M. & Haber, J. E. Srs2 and Sgs1-Top3 suppress crossovers during double-strand break repair in yeast. *Cell* **115**, 401–411 (2003).
17. Ward, J. D. *et al.* Overlapping mechanisms promote postsynaptic RAD-51 filament disassembly during meiotic double-strand break repair. *Mol. Cell* **37**, 259–272 (2010).
18. Seki, M., Marini, F. & Wood, R. D. POLQ (Pol theta), a DNA polymerase and DNA-dependent ATPase in human cells. *Nucleic Acids Res.* **31**, 6117–6126 (2003).
19. Jackson, D. A. & Pombo, A. Replicon clusters are stable units of chromosome structure: evidence that nuclear organization contributes to the efficient activation and propagation of S phase in human cells. *J. Cell Biol.* **140**, 1285–1295 (1998).
20. The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature* **497**, 67–73 (2013).
21. Morrison, C. *et al.* The controlling role of ATM in homologous recombinational repair of DNA damage. *EMBO J.* **19**, 463–471 (2000).
22. Parmar, K. *et al.* Hematopoietic stem cell defects in mice with deficiency of Fancd2 or Usp1. *Stem Cells* **28**, 1186–1195 (2010).
23. Hu, Y. *et al.* PARP1-driven poly-ADP-ribosylation regulates BRCA1 function in homologous recombination mediated DNA repair. *Cancer Discov.* **4**, 1430–1447 (2014).
24. Yang, D. *et al.* Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. *J. Am. Med. Assoc.* **306**, 1557–1565 (2011).
25. Seki, M. *et al.* High-efficiency bypass of DNA damage by human DNA polymerase θ . *EMBO J.* **23**, 4484–4494 (2004).
26. Seki, M. & Wood, R. D. DNA polymerase theta (POLQ) can extend from mismatches and from bases opposite a (6–4) photoproduct. *DNA Repair* **7**, 119–127 (2008).
27. Zhang, Y. & Jasin, M. An essential role for CtIP in chromosomal translocation formation through an alternative end-joining pathway. *Nature Struct. Mol. Biol.* **18**, 80–84 (2011).
28. Chiruvella, K. K., Liang, Z. & Wilson, T. E. Repair of double-strand breaks by end joining. *Cold Spring Harb. Perspect. Biol.* **5**, a012757 (2013).
29. Alexandrov, L. B. *et al.* Signatures of mutational processes in human cancer. *Nature* **500**, 415–421 (2013).
30. Lemée, F. *et al.* DNA polymerase theta up-regulation is associated with poor survival in breast cancer, perturbs DNA replication, and promotes genetic instability. *Proc. Natl Acad. Sci. USA* **107**, 13390–13395 (2010).

Supplementary Information is available in the online version of the paper.

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Author Contributions R.C. conceived the study, performed experiments, and wrote the manuscript. J.C.L. and T.Y. purified Pol θ fragments from insect cells and performed ATPase and gel shift assays. R.A. performed D-loop formation assays. I.H. and S.J.E. performed the DNA fibres assay. B.P. performed mice work and analysed *in vivo* data. M.I.R.P. and S.J.B. performed the Pol θ peptide array and the RAD51–ssDNA filament assembly and release assays. K.W.O. scored RAD51 foci. P.A.K. curated TCGA datasets for Figure 3a and Extended Data Figures 5h and 9e and provided clinical perspectives. A.D.D. conceived the study and wrote the manuscript. All authors approved the final version of the manuscript.

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