

arrangements might also differ in their gene dosage, as is the case for several truncated but expressed copies of the gene *NSF* in the region under study. Individuals with different karyotypes have different numbers of copies and so differ in their expression levels.

But the most notable result is that, in the Icelandic population, carriers of the H2 haplotype are more fertile, having 3.2% more children per generation than noncarriers. Taking this into account, the action of selection becomes a sensible explanation for the high frequency of the H2 lineage among individuals of European ancestry. Moreover, a low level of genetic variability in chromosomes carrying the H2 lineage is consistent with a recent, selection-driven increase in frequency of H2 chromosomes. Although the data pointing at the action of selection are quite convincing, causal relationships have not yet been established, which makes it difficult to determine what kind of selection is acting on this region. The simplest scenario would be a recent episode of positive selection favoring H2 individuals. But the extensive divergence of the H1 and H2 lineages suggests that they separated ~3 million years ago. As it is very unlikely that the H2 haplotype could be maintained at its current low worldwide frequency for such a long time, more complex scenarios need to be considered. Stefansson *et al.*¹ suggest that the H2 lineage could have been introgressed from archaic humans before the worldwide expansion of modern humanity, but that hypothesis is contradicted by evidence from other regions of the genome⁹. Given what we know about inversions, the most convincing picture is that of an ancient inversion polymorphism under balancing selection. A long segregating time

would have allowed for the development of coadapted allele complexes whose equilibrium frequency would have changed with mutational input and environmental conditions.

This whole story illustrates a final point: rearrangement polymorphisms can be maintained for a very long time, maybe even across speciation events. Alternative structural forms can become associated with variants that are differentially selected in different places. These variants may evolve into coadapted allele sets or even coadapted gene complexes, if gene content varies between arrangements. In turn, coadaptation further decreases gene flow and increases the differentiation of alternative chromosomal forms. This sheds new light on the recent burst of research about chromosomal speciation¹⁰, showing that rearrangements found in primates may meet the requirements of some models of chromosomal speciation.

No doubt the findings of Stefansson *et al.*¹ will generate a rush to study this particular region, presenting as they do one of the best examples of the action of selection in human populations and the revitalization of some classical issues about genome dynamics. But is this such an exceptional case? To date, only a handful of human polymorphic inversions have been detected, most of them only after the painstaking dissection of disease-associated regions. Then again, the few available studies show that rearrangements can reach fairly high frequencies¹¹. Moreover, analysis of the human genome sequence has shown that it is extremely rich in segmental duplications¹² that can sponsor rearrangements by nonhomologous allelic recombination¹¹. It is, therefore, compelling to speculate that many small inversions are cur-

rently segregating at high frequencies in human populations. These hidden structural polymorphisms may contain many undiscovered targets of selection in human populations, could help to explain the considerable variability of LD patterns in the genome¹³ and across populations¹⁴ and, finally, might contribute to the increasingly apparent geographical structure of the genetic architecture of complex disease¹⁵.

It is fitting that modern genomics, which has managed to reach the tiniest nucleotide variants, can still draw valuable information from the very same larger-scale genetic changes that, ninety years ago, allowed us to look at genome diversity for the first time.

1. Stefansson, H. *et al.* *Nat. Genet.* **37**, 129–137 (2005).
2. Krimbas, C.B. & Powell, J.R. *Drosophila inversion polymorphism* (CRC, Boca Raton, 1992).
3. Hoffmann, A.A., Sgro, C.M. & Weeks, A.R. *Trends Ecol. Evol.* **19**, 482–488 (2004).
4. Navarro, A., Betran, E., Barbadilla, A. & Ruiz, A. *Genetics* **146**, 695–709 (1997).
5. Andolfatto, P., Depaulis, F. & Navarro, A. *Genet. Res.* **77**, 1–8 (2001).
6. Schultz, J. & Redfield, H. *Cold Spring Harbor Symp. Quant. Biol.* **16**, 175–197 (1951).
7. Lucchesi, J.C. & Suzuki, D.T. *Annu. Rev. Genet.* **2**, 53–86 (1968).
8. Marques-Bonet, T. *et al.* *Trends Genet.* **20**, 524–529 (2004).
9. Jobling, M.A., Hurles, M.E. & Tyler-Smith, C. *Human Evolutionary Genetics: Origins, Peoples and Disease* (Garland Science, New York, 2004).
10. Navarro, A. & Barton, N.H. *Science* **300**, 321–324 (2003).
11. Giglio, S. *et al.* *Am. J. Hum. Genet.* **68**, 874–833 (2001).
12. She, X. *et al.* *Nature* **431**, 927–930 (2004).
13. Wall, J.D. & Pritchard, J.K. *Nat. Rev. Genet.* **4**, 587–597 (2003).
14. Gonzalez-Neira, A. *et al.* *Hum. Genomics* **1**, 399–409 (2004).
15. Tishkoff, S.A. & Kidd, K.K. *Nat. Genet.* **36**, S21–S27 (2004).

Telomere-binding factors and general DNA repair

Woodring E Wright & Jerry W Shay

Telomeres cap the ends of linear chromosomes and prevent them from being recognized as double-strand breaks needing repair. How they go about hiding the ends from the DNA-repair apparatus is becoming a broader question, as a new study identifies an increasingly incestuous relationship between DNA-repair factors and telomere-binding proteins.

The ends of linear chromosomes pose a variety of special problems for eukaryotic cells. The lagging-strand mechanism of

DNA replication cannot copy all the way to the end of a linear molecule, and the consequent shortening (combined with processing events at leading and lagging daughter ends) is used as a counting mechanism that causes replicative aging and limits the proliferative capacity of normal human cells. Cells stop dividing when one or a few telomeres become so short that they generate a DNA damage signal that initiates cell-cycle arrest.

A related and important feature of telomeres is that they mask the ends of linear chromosomes from being treated as double-strand breaks needing repair. A partial explanation for how this end-masking is accomplished came with the discovery that telomeres can form structures called T loops. Human telomeres end with a 3' single-stranded overhang ~100 nucleotides long, which loops back and becomes inserted into the double-stranded

Woodring E. Wright and Jerry W. Shay are at the University of Texas Southwestern Medical Center at Dallas, Department of Cell Biology, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9039, USA. e-mail: Jerry.Shay@UTSouthwestern.edu or Woodring.Wright@UTSouthwestern.edu

region. This insertion is still an abnormal DNA structure but no longer appears as a double-strand break.

Human telomeres are composed of several kilobases of the repetitive hexamer TTAGGG and are bound by a large number of telomere-binding proteins. Many DNA-repair factors, such as Ku, DNA PKcs, ERCC1/XPC, Wrn, and the Mre11 complex, have been found at telomeres (Fig. 1). This has led some to believe that telomeres are recognized by these factors as damaged or abnormal DNA, but that telomere-specific proteins somehow organize or modify them so that the net result is a complex that protects the end from degradation and from eliciting a DNA damage response. But the idea that telomere-specific proteins have co-opted the function of DNA-repair factors is being turned on its head by some very exciting observations by Bradshaw *et al.*¹, as reported on page 193 of this issue. Their work suggests that telomere-binding factors may all be ancient and general DNA-repair factors that have been exploited by the cell to protect telomeres².

Targeting TRF2 to breaks

TRF2 (telomere repeat factor 2) is a sequence-specific DNA-binding protein that recognizes double-stranded TTAGGG repeats and is important in forming and maintaining T loops^{3,4}. Bradshaw *et al.* now show that TRF2 localizes to laser-induced double-strand DNA breaks within 2 s of irradiation, faster than ATM (4–6 s), Nbs1 or phosphorylated H2AX. This rapid recruitment occurs in mutants lacking the known early-response repair/signaling factors and is transient, peaking ~100 s after lesion induction and then declining with biphasic kinetics (an initial rapid phase that occurs within minutes followed by a second phase with a half-life of ~1 h).

Notably, the laser-induced stripe of damage across the nucleus does not contain telomeric repeats, and TRF2 localizes to the damaged ends even if it lacks its known DNA-binding myb domain. Therefore, TRF2 either is recognizing a damaged DNA structure or is being brought there in a complex with unidentified factors. Its very rapid localization tells us that, rather than being fundamentally a telomere-binding factor, TRF2 is probably an ancient and general DNA-repair factor that has developed some telomere-specific functions. The concept of telomere factors being fundamentally DNA-repair factors that have been adapted for telomeric protection can explain why a factor such as Rif1, discovered for its telomeric effects in yeast⁵, turns out not to be telomeric but a general DNA-repair protein in mammals^{6,7}.

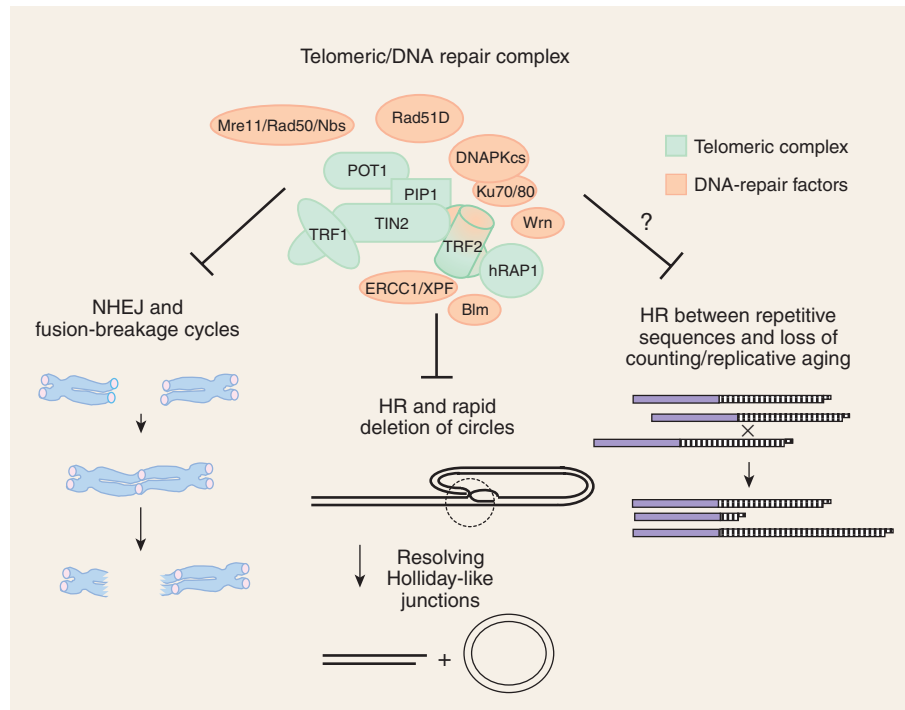


Figure 1 Telomere-binding factors (green) and the DNA-repair factors they recruit to telomeres (red) function to inhibit rather than promote a variety of repair processes. TRF2 is shown in both colors, because it localizes to sites of nontelomeric double-strand breaks. HR, homologous recombination.

Clues from telomeres

What could TRF2 be doing at general double-strand breaks? Some clues come from examining the functions of TRF2 and other factors at telomeres. Of the three general types of DNA masking that occur at telomeres, the most prominent is to prevent nonhomologous end joining (NHEJ) from ligating different chromosome ends together, which results in breakage-fusion cycles when cells attempt to divide (Fig. 1). The function of TRF2 is crucial for this process, as dominant-negative TRF2 mutants produce telomeric end-fusions⁸. Another DNA-repair blocking activity of TRF2 is to prevent the T-loop insertion site from being treated as a Holliday junction, an intermediate stage in homologous recombination (Fig. 1). The N-terminal basic domain of TRF2 is important for this function, as the XRCC3 resolvase activity converts T loops into shortened telomeres plus telomeric circles when a mutant lacking this domain is expressed⁹. A third presumed repair- and recombination-blocking function of telomeres is to prevent homologous recombination between telomeres (Fig. 1). Without a blocking mechanism, human telomeres should be hugely recombinogenic, because there are ~10 kb of repetitive hexamers at each of the 92 telomeres in a human cell. Recombination would

substantially and randomly alter telomeric length and would destroy the ability to use telomere shortening as a mechanism for replicative aging. Mammalian cells normally use CpG methylation to inhibit recombination among repetitive sequences, but there are no CpG sites in the TTAGGG telomeric sequence. Therefore, either some chromatin state or unusual base-modification^{10,11} probably substitutes for cytidine methylation to inhibit recombination at telomeres.

Because TRF2 is involved in inhibiting NHEJ and homologous recombination at telomeres, it probably has similar functions at nontelomeric double-strand breaks. TRF2 may transiently inhibit repair during assembly of the multimolecular repair complex, preventing the premature action of various helicases or nucleases. Because cells can repair double-strand breaks by either NHEJ or homologous recombination, and because NHEJ factors such as DNA-PKcs and Ku are recruited much more rapidly to breaks than are factors involved in homologous recombination, TRF2 may function to block NHEJ until the cell has time to assess which of these two pathways will be used. This idea is consistent with the very rapid appearance, but transient presence, of TRF2 at the breaks. Both Bradshaw *et al.*¹ and Karlseder *et al.*¹² found that TRF2 inhibits the ability of ATM

to phosphorylate itself and its downstream targets, and this could be part of its mechanism for inhibiting the activation of DNA-repair complexes both at telomeres and at double-strand breaks. The demonstration by Bradshaw *et al.* that TRF2 is rapidly recruited to generic double-strand breaks will initiate a mutually productive period of interaction between the fields of DNA repair and telomere biology, as the roles for telomeric fac-

tors in the choreography of repair come into the spotlight.

- Bradshaw, P.S., Stavropoulos, D.J. & Meyn, M.S. *Nat. Genet.* **37**, 193–197 (2005).
- de Lange, T. *Nat. Rev. Mol. Cell. Biol.* **5**, 323–329 (2004).
- Griffith, J.D. *et al. Cell* **97**, 503–514 (1999).
- Stansel, R.M., de Lange, T. & Griffith, J.D. *EMBO J.* **20**, 5532–5540 (2001).
- Hardy, C.F., Sussel, L. & Shore, D. *Genes Dev.* **6**, 801–814 (1992).
- Silverman, J., Takai, H., Buonomo, S.B., Eisenhaber,

F. & de Lange, T. *Genes Dev.* **18**, 2108–2119 (2004).

- Xu, L. & Blackburn, E.H. *J. Cell. Biol.* **167**, 819–830 (2004).
- van Steensel, B., Smogorzewska, A. & de Lange, T. *Cell* **92**, 401–413 (1998).
- Wang, R.C., Smogorzewska, A. & de Lange, T. *Cell* **119**, 355–368 (2004).
- Gommers-Ampt, J., Lutgerink, J. & Borst, P. *Nucleic Acids Res.* **19**, 1745–1751 (1991).
- Steinert, S., Shay, J.W. & Wright, W.E. *Mol. Cell. Biol.* **24**, 4571–4580 (2004).
- Karlseder, J. *et al. PLoS Biol.* **2**, E240 (2004)

© 2005 Nature Publishing Group <http://www.nature.com/naturegenetics>

The beauty of admixture

Ariel Darvasi & Sagiv Shifman

Admixture mapping is an old concept that has only now been applied with markers across the entire genome. Such a study scanning an African American population identified two chromosomal regions affecting susceptibility to hypertension.

Anecdotally, children of parents of mixed ethnicities are exotically beautiful. More scientifically established is the merit of admixed populations for gene mapping purposes. The potential value of admixed populations was suggested more than half a century ago¹. Substantial theoretical and practical aspects have been developed since then (reviewed by McKeigue²). A genome scan to identify genes affecting a complex trait is now presented for the first time to our knowledge by Xiaofeng Zhu and colleagues on page 177 of this issue³.

In a human admixed population, these ideal conditions will never be met, resulting in decreased power for mapping purposes. Except for gene effect, which has a strong

influence on power, the parameter that mostly affects power, specifically in admixture mapping, is the extent of difference in allele frequency between the ancestral populations⁵.



The admixed population

The concept behind admixture mapping is simple (Fig. 1). In essence, admixture mapping is most similar to linkage analysis in experimental crosses with inbred strains, with specific similarity to advanced intercross lines⁴. An advanced intercross line is a population derived from two inbred strains that were randomly intercrossed for several generations. An advanced intercross line constitutes the ideal admixed population: all variations can be identified in one of the two progenitors, the mean ancestral composition is 50% for each progenitor, allele frequencies in the progenitor populations are either 1 or 0, and random mating is followed after a single generation of intercrossing the progeni-

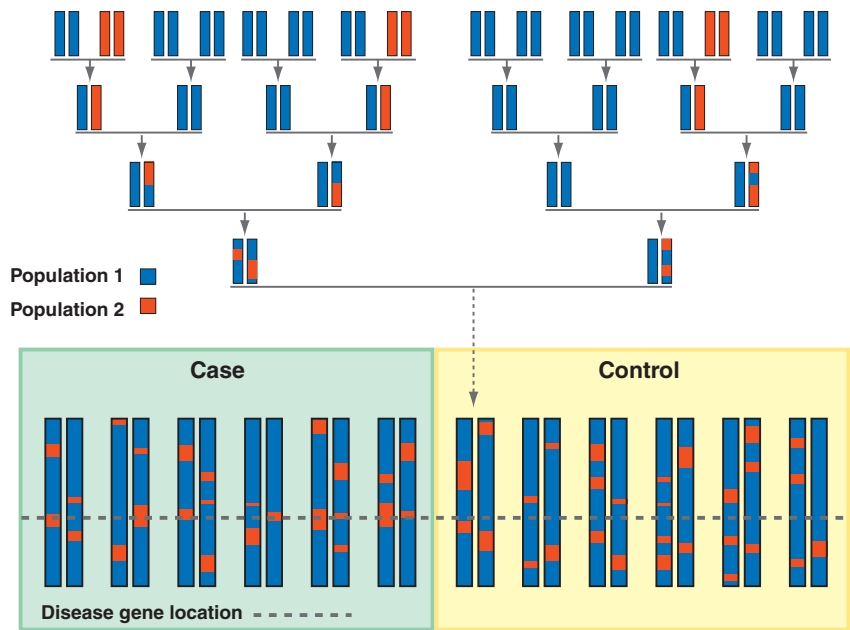


Figure 1 Schematic of one chromosome pair from each of several individuals in an admixed population. A group of cases (for a given disease) and a group of controls are separately presented at the bottom left and the bottom right, respectively. For one of the control individuals (arrow), a schematic presentation of all its ancestors in the last four generations is shown in the upper part of the figure. Admixture mapping can be ideally applied if population 1 (blue) and population 2 (red) carry a different allele at the disease locus (dashed line). Whole-genome scanning under the admixture mapping strategy consists of scanning the genome and identifying the regions with an excess of 'red' ancestry in the cases versus the controls, assuming that the 'red' population carries the predisposition allele. The size of the blocks from different ancestors will depend on the number of generations since the populations were mixed.

Ariel Darvasi is in The Life Sciences Institute, The Hebrew University, Jerusalem 91904, Israel. Sagiv Shifman is in the Wellcome Trust Centre for Human Genetics, Oxford OX3 7BN, UK. e-mail: arield@cc.huji.ac.il, sagiv@well.ox.ac.uk