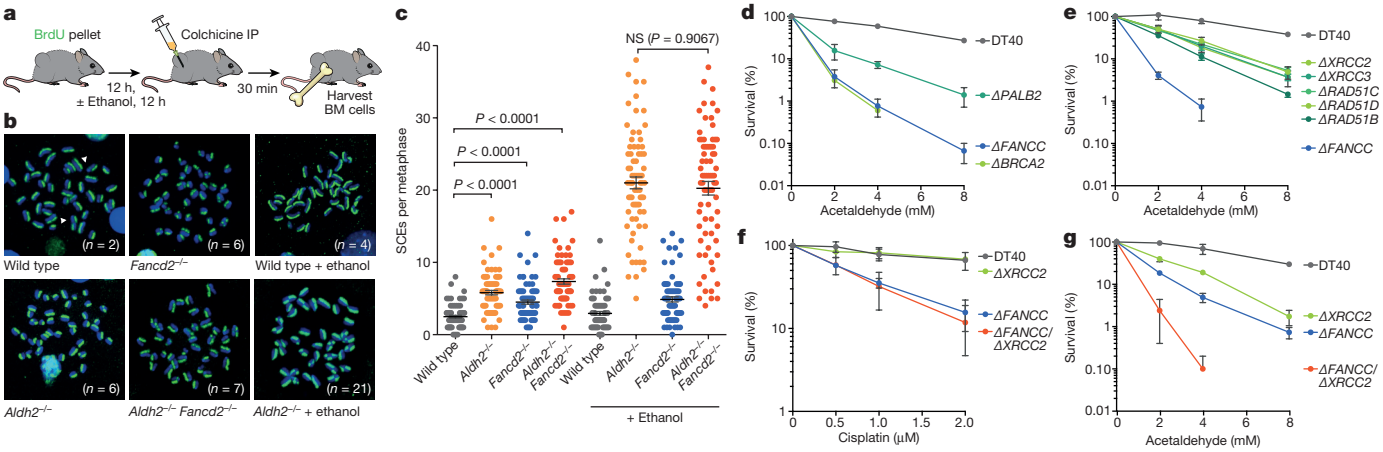

Figure 1 | Ethanol induces potent homologous recombination *in vivo*. **a**, Treatment of mice with BrdU for differential labelling of sister chromatids of bone marrow cells *in vivo*. Some mice were also treated with ethanol, a precursor of acetaldehyde. IP, intraperitoneal injection; BM, bone marrow. **b**, Representative images of bone-marrow metaphase spreads (*n*, number of SCEs per metaphase). **c**, Number of SCEs in the bone marrow of $Aldh2^{-/-}Fancd2^{-/-}$ and control mice (triplicate experiments, 25 metaphases per mouse, $n = 75$; *P* calculated by two-sided Mann–Whitney test; data shown as mean and s.e.m.). NS, not significant. **d**–**g**, Clonogenic survival of DT40 DNA-repair mutants (triplicate experiments; data shown as mean and s.e.m.).

DT40 cells carrying disruptions of key homologous recombination genes show hypersensitivity to acetaldehyde (Fig. 1d, e), in a similar way to cells lacking the Fanconi anaemia gene *FANCC*. To test the relationship between the Fanconi anaemia and homologous recombination pathways, we analysed the sensitivity of cells deficient in both *FANCC* and *XRCC2*. These cells showed the same sensitivity to cisplatin as the single knockout cells (Fig. 1f), but were much more sensitive to acetaldehyde (Fig. 1g), indicating that homologous recombination repair confers additional acetaldehyde resistance beyond that provided by Fanconi anaemia crosslink repair. In summary, detoxification provides the dominant protection mechanism against endogenous aldehydes; however, when aldehydes damage DNA, cells use both DNA-crosslink and homologous recombination repair.

FANCD2 prevents alcohol-induced genomic instability

The active DNA recombination in bone marrow cells indicates that even in the absence of FANCD2, there is an alternative repair response to both endogenous and ethanol-derived aldehydes. However, our previous work has shown that $Aldh2^{-/-}Fancd2^{-/-}$ mice lose the ability to maintain blood production[5,6]. To determine whether this is due to the accumulation of damaged DNA, we examined haematopoietic cells for evidence of broken chromosomes. One marker of genetic instability is the formation of micronuclei, which are formed from lagging or broken chromosomes. Micronuclei are easily quantified in normochromic erythrocytes (NCEs) *in vivo*, because they persist following enucleation (Fig. 2a, Extended Data Fig. 1c). There is a significant increase in the proportion of NCEs with micronuclei in

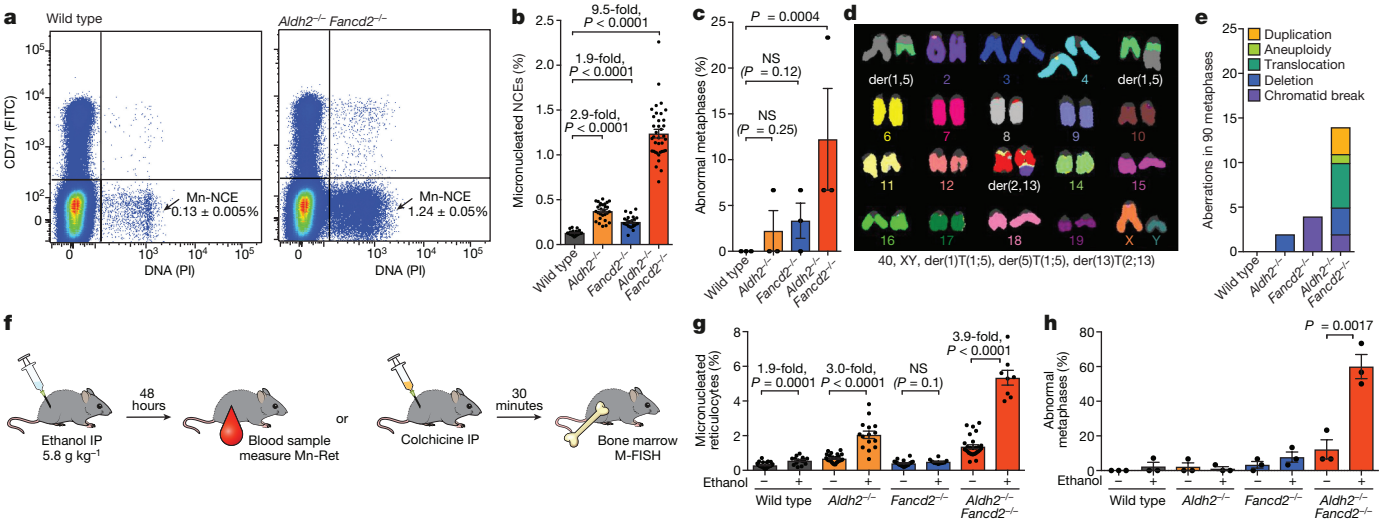

Figure 2 | Spontaneous and ethanol-induced genomic instability in $Aldh2^{-/-}Fancd2^{-/-}$ mice. **a**, Quantification of micronucleated normochromic erythrocytes (Mn-NCE, $CD71^{-}$ PI^{+}) by flow cytometry. **b**, Percentage of micronucleated normochromic erythrocytes (*P* calculated by two-sided Mann–Whitney test; data shown as mean and s.e.m.; $n = 28$, 28, 25 and 37 mice, left to right). **c**, Percentage of abnormal metaphases in bone marrow cells (*P* calculated by one-sided Fisher's exact test; data shown as mean and s.e.m.; three mice per genotype, 30 metaphases per mouse). **d**, A $Aldh2^{-/-}Fancd2^{-/-}$ metaphase, showing two translocations, see Extended Data Fig. 1f–i for the complete list of aberrations. **e**, Types of chromosomal aberrations (90 metaphases per genotype). **f**, Treatment of mice with ethanol to assess genomic instability with the micronucleus assay (**g**) or M-FISH karyotyping (**h**). **g**, Percentage of micronucleated reticulocytes (Mn-Ret, $CD71^{+}$ PI^{+}) after ethanol treatment. *P* calculated by two-sided Mann–Whitney test; data shown as mean and s.e.m.; $n = 29$, 15, 25, 15, 20, 10, 28 and 9 mice, left to right. **h**, Abnormal metaphases in bone marrow cells after ethanol treatment. *P* calculated by one-sided Fisher's exact test; data shown as mean and s.e.m.; 3 mice per genotype, 30 metaphases per mouse.