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**Author Contributions** J.I.G., G.P.C. and K.J.P. conceived the study and wrote the manuscript. J.I.G. conducted the majority of the experiments and analysed the data. G.P.C. assisted in the characterization of genomic instability in *Aldh2*<sup>-/-</sup>*Fancd2*<sup>-/-</sup> mice and single HSC transplantation. F.L. analysed the survival of chicken DT40 cells, performed western blotting and assisted with the analysis of micronucleus samples. L.M. assisted with single cell transplantation and performed the BigBlue *in vivo* point-mutation analysis. S.L. and F.Y. performed the M-FISH karyotyping of mouse metaphases. N.P. performed validations of indels by targeted deep sequencing. G.G., S.R., S.N.-Z. and M.R.S. provided assistance with the analysis and interpretation of sequencing data.

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