**Figure S1: Generation of an isogenic model of chronic STAG2 loss.**

1. Sanger sequencing chromatograms from OCI-AML3 cells in which the single copy of *STAG2* (X chromosome) was targeted for editing with CRISPR/Cas9 (ΔSTAG2 cells) creating a deletion in exon 20, generating a premature stop codon. Chromatogram from unedited STAG2-WT cells is shown for comparison.
2. Normalized RNA-seq gene count levels highlighting the significant reduction in *STAG2* mRNA expression (gene counts include all known STAG2 isoforms) in ΔSTAG2 cells compared to STAG2-WT cells.
3. Normalized RNA-seq gene count levels highlighting the mRNA expression levels of members of the cohesin complex in STAG2-WT cells and ΔSTAG2 cells.
4. Representative Western Blots demonstrating expression of cohesin complex members in STAG2-WT cells and ΔSTAG2 cells.

**Figure S2: STAG1 compensates for loss of stag2 chromatin binding**

Venn diagram of STAG1 binding peaks in STAG2-WT and ΔSTAG2 cells with 14,375 peaks present in both STAG2-WT and ΔSTAG2 cells, but significantly more STAG1 binding peaks in ΔSTAG2 cells compared to STAG2-WT cells.

**Figure S3: Further examples of altered 3D structure within the Δ STAG2 genome.**

1. HiChIP Contact matrixes displaying interactions over a 1 Mb region 29.2 Mb into chromosome 8 (this region encompasses the DUSP4 gene).
2. Virtual 4C plot displaying interactions over a 1 Mb region depicted above.
3. HiChIP Contact matrixes displaying interactions over a 2 Mb region 60 Mb into chromosome 18 (this region encompasses the BCL2 gene).
4. Virtual 4C plot displaying interactions over a 2 Mb region depicted above.

**Figure S4: Haematological developmental processes are deregulated with chronic loss of STAG2**

Deregulated Haematological developmental processes gene network identified through Ingenuity Pathway Analysis (IPA) as altered in ΔSTAG2 cells compared to STAG2-WT cells. Genes whose expression was increased or decreased in Δ STAG2 cells are highlighted in red and green respectively.

**Figure S5: Altered chromatin structure surrounding MAPK signaling related genes leads to sensitivity to MEK inhibition.**

1. Virtual 4C plot displaying interactions over a 1.2 Mb region of chromosome encompassing the DUSP4 gene. The V4c plot is anchored upstream of the DUSP4 gene.
2. Virtual 4C plot displaying interactions over a 1Mb region of chromosome encompassing the MMP9 gene. The V4c plot is anchored upstream of the TSS for MMP9.

C-E)Densitometry based quantification of pERK (C), Cleaved PARP (D) and Cleaved Caspase 3 (E), from the Representative Western Blot shown in figure 6G.

**Figure S6: Altered gene expression in an AML patient cohort**

1. Box and whisker plots of gene expression levels (log2) of STAG2 and genes in the HOXA locus between STAG2 mutant patients (n=6) relative to STAG2 wild-type (n=177) AML patients (GSE68833)

**Figure S7: Altered gene expression in an MDS patient cohort**

1. Box and whisker plots of gene expression levels (log2) of STAG2 and genes in the HOXA locus between STAG2 mutant patients (n=6) relative to STAG2 wild-type (n=83) MDS patients (GSE58831)

**Figure S8: Analysis of DUSP4 expression**

1. Box and whisker plots of gene expression levels (log2) of DUSP4 between STAG2 mutant patients (n=6) relative to STAG2 wild-type (n=177) AML patients (GSE68833)
2. Box and whisker plots of gene expression levels (log2) of DUSP4 between STAG2 mutant patients (n=6) relative to STAG2 wild-type (n=83) MDS patients (GSE58831)