

## Expanded View Figures

**Figure EV1. A synthetic viability screening identifies the SIR complex as the major driver of *tof1Δ* camptothecin hypersensitivity.**

- A Spontaneous suppressors of camptothecin sensitivity of *tof1Δ* cells.
- B Suppressor strains recovered from the *tof1Δ* synthetic viability screen are G418 resistant, suggesting presence of the *TOF1* deletion cassette.
- C Deletion of *IRC15* does not suppress *tof1Δ* camptothecin hypersensitivity.
- D Deletion of *IME2* does not suppress *tof1Δ* camptothecin hypersensitivity.
- E Deletion of *SIR2* and deletion of *TOP1* lead to similar levels of camptothecin resistance, and combining the two mutations does not further increase camptothecin resistance.
- F Deletion of *HML* does not alter the camptothecin hypersensitivity of *tof1Δ* cells.
- G *tof1Δ* cells and congeneric wild-type cells were pre-grown either in the absence or in the presence of sirtinol. They were subsequently synchronised in G1 and released into S phase in the presence of camptothecin, either with or without sirtinol. Cell cycle progression was monitored by FACS analysis.

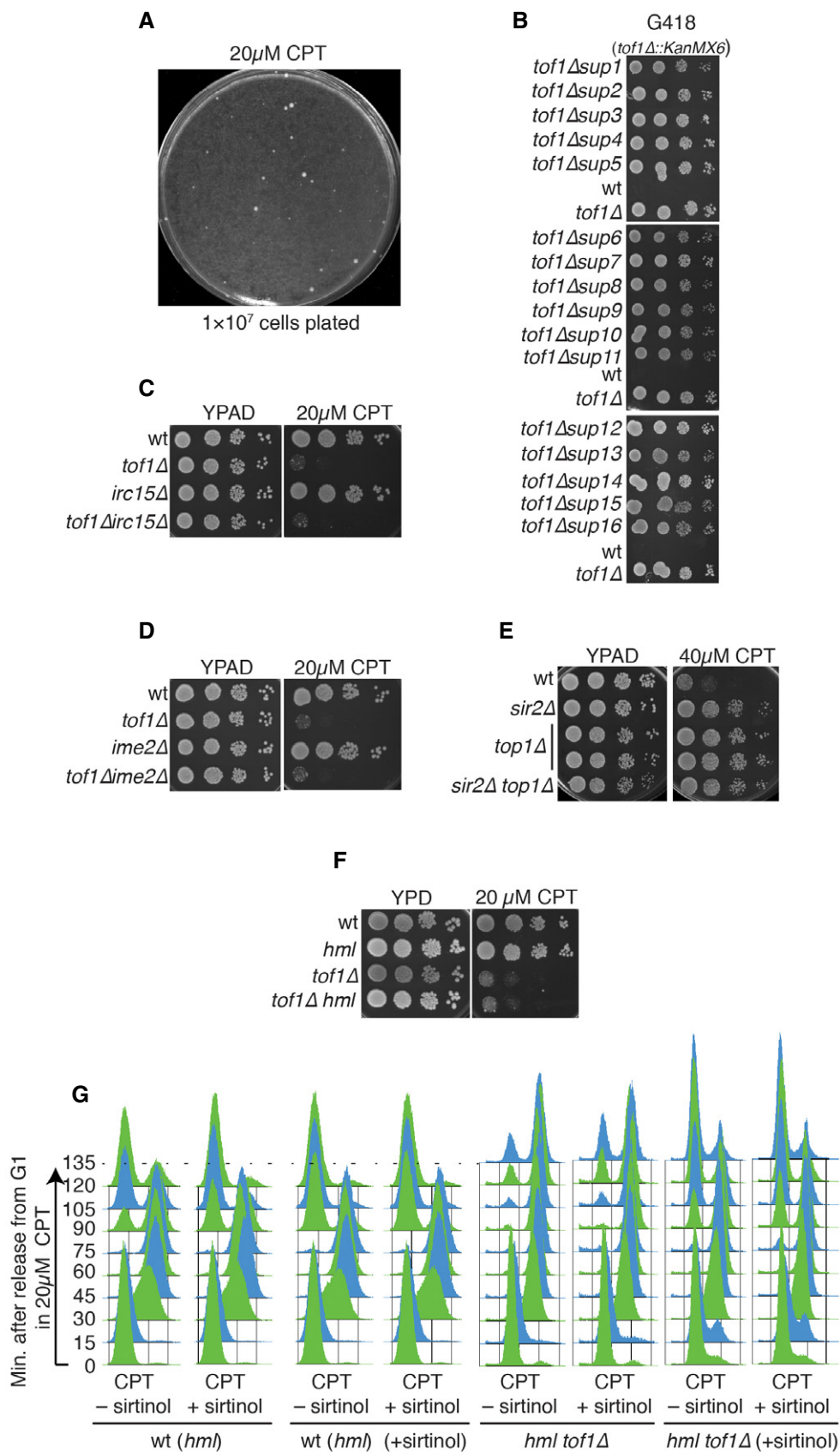


Figure EV1.

**Figure EV2. Binding of the SIR complex to highly expressed genomic loci mediates camptothecin sensitivity.**

- A Deletion of *SIR1* does not rescue camptothecin hypersensitivity in *rad51Δ* cells.
- B Deletion of *SIR1*, *SIR2*, *SIR3* or *SIR4* increases camptothecin resistance to a similar extent, both in a wild-type and in a *tof1Δ* background.
- C Analysis of ChIP-seq data for the indicated proteins: enrichment is plotted as a function of the genomic coordinate; in green is the protein/modification tested; in grey are controls. The position of each ORF is indicated at the bottom of the panel and by two vertical red lines. The horizontal red lines indicate the thresholds used in this work to determine enrichment (Sir2/Sir3/Sir4/GFP/H3) or loss (H4-K16) of ChIP signal.
- D The majority of SIR-positive ORFs are highly expressed genes, but high expression does not necessarily correlate with high SIR score. Vertical lines identify quartiles (I, II, III, IV) of the gene expression distribution.

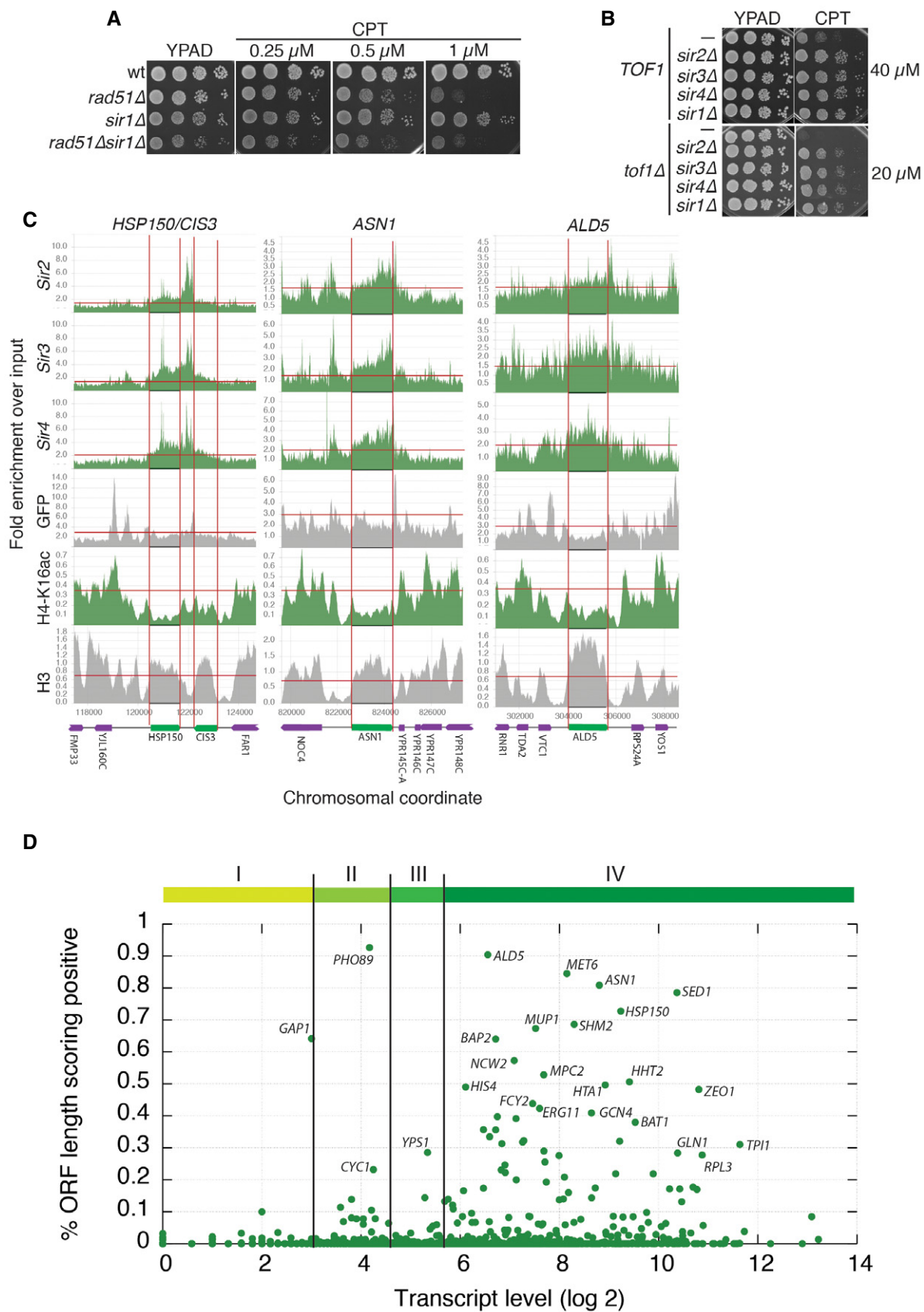


Figure EV2.