**High throughput functional genomics identifies modulators of TCE metabolite genotoxicity and candidate susceptibility genes**

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**SUPPLEMENTARY DATA**

**Figure S1.** Dose response of TCE metabolites DCVG and DCVC in yeast

**Figure S2.** DCVC dose response in translesion synthesis and HR/NER yeast deletion mutants.

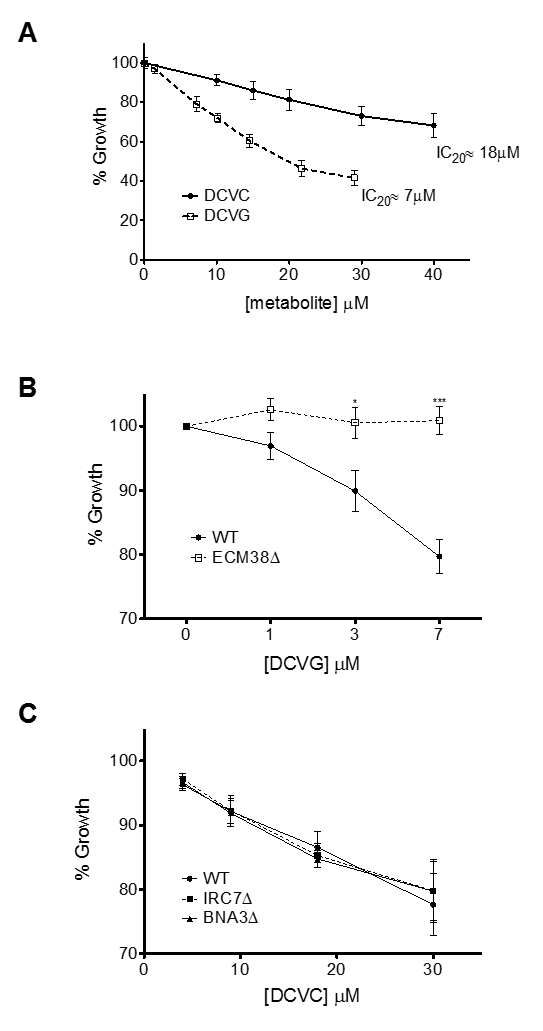
**Figure S3.** DT40 DNA repair mutant dose response curves for DCVC and Cisplatin

**Figure S4**. Sensitivity of ICL repair deficient lymphoblasts (PD20) and FANCD2 complemented (PD20D2) cells to DCVC at 24hrs and 72hrs

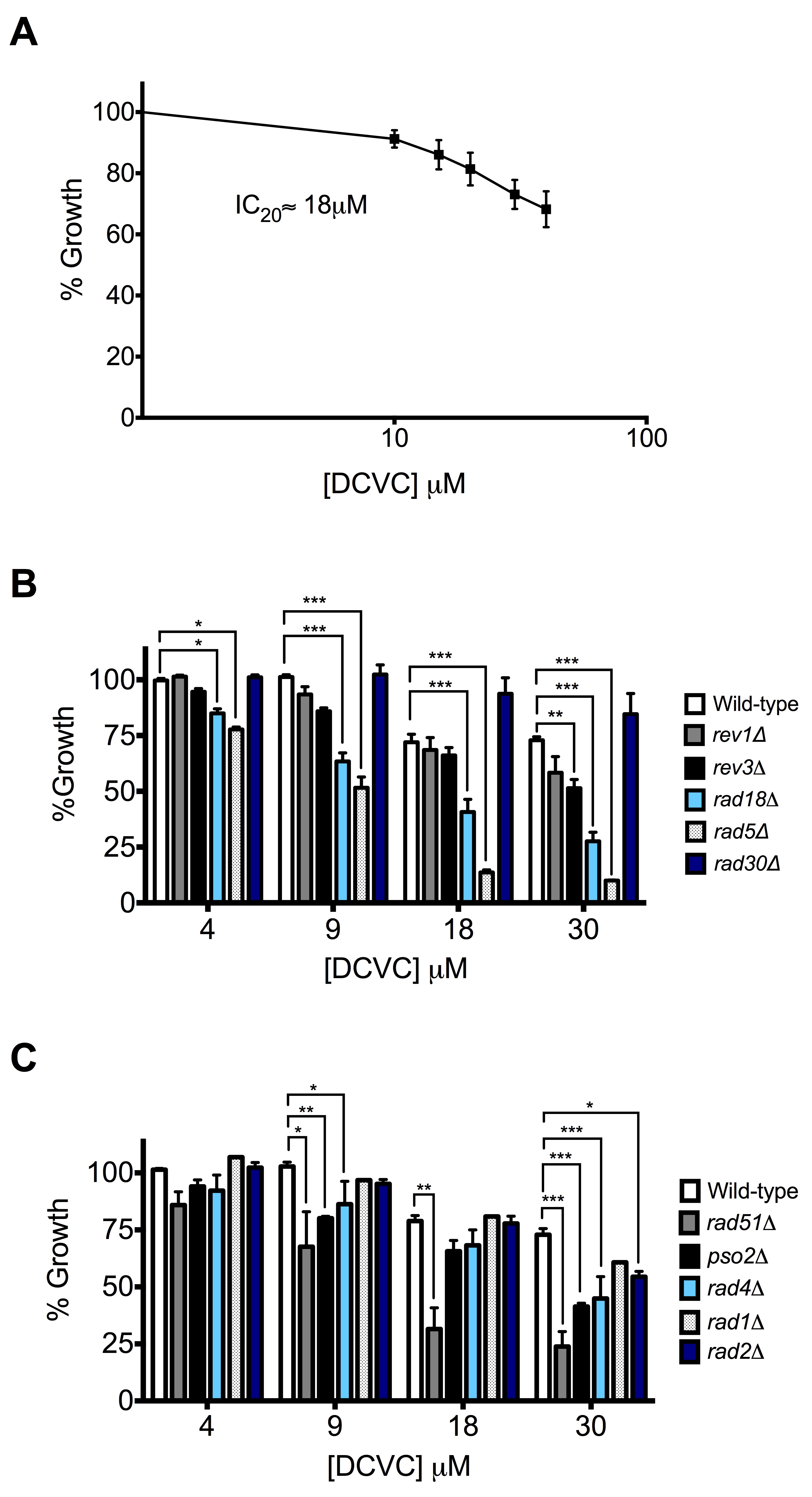
**Table S1.** Total genes from yeast profiling studies identified as sensitive or resistant to DCVC treatments by differential strain sensitivity analysis (DSSA).

**Table S2**. Mutation frequency of DCVC in human lymphoblast cells

**Table S3.** DT40 mutant cells used in this study

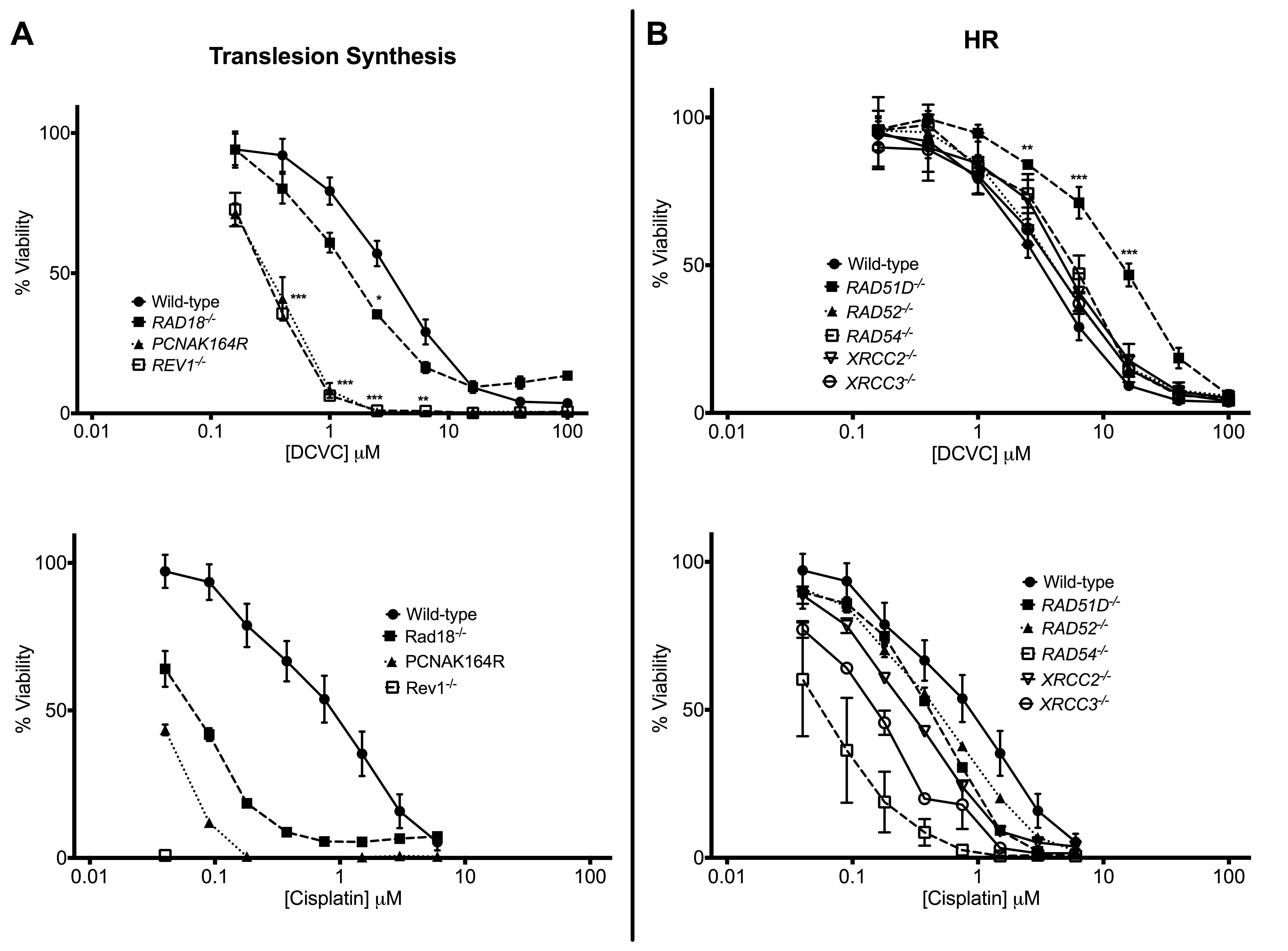


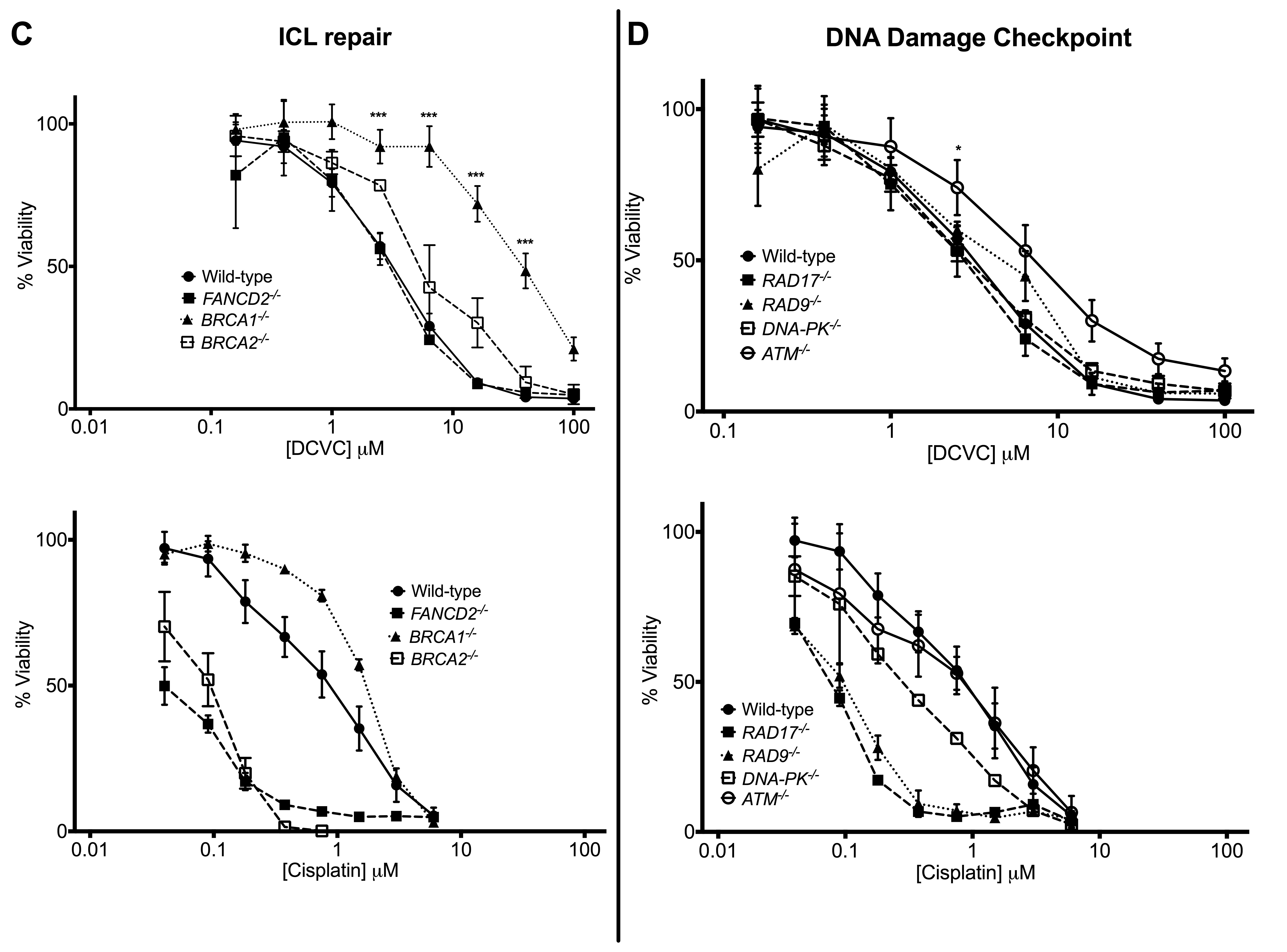
**Figure S1.** Dose response of TCE metabolites DCVG and DCVC in yeast. (A) The IC20 concentration was determined in wild-type yeast and used for functional profiling exposures. Dose response in gamma-glutamyl dipeptidase (B) and beta-lyase yeast deletion mutants Values are mean ± SE; n ≥ 3 for each measurement. Significance values were calculated by two-way ANOVA \*\*\*p < 0.001, \*\*p < 0.01, \*p < 0.05 *for treated mutant versus treated wild-type.*

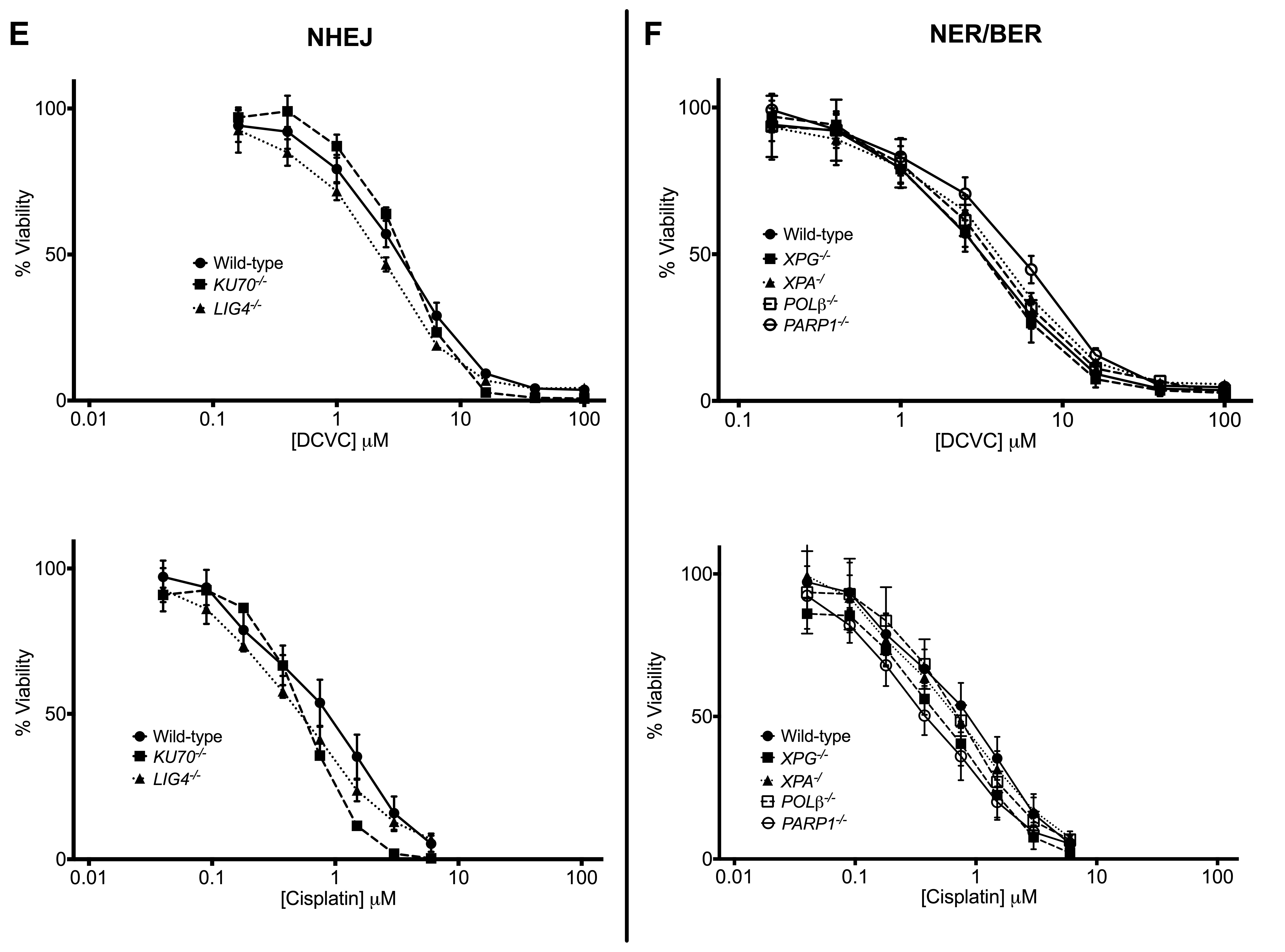
**A**

**B.**

**Figure S2.** DCVC dose response in (A) tranlesion synthesis and (B) HR/NER yeast deletion mutants. Values are mean ± SE; n ≥ 3 for each measurement. Significance values were calculated by two-way ANOVA \*\*\*p < 0.001, \*\*p < 0.01, \*p < 0.05 *for DCVC-treated mutant versus DCVC treated wild-type.*

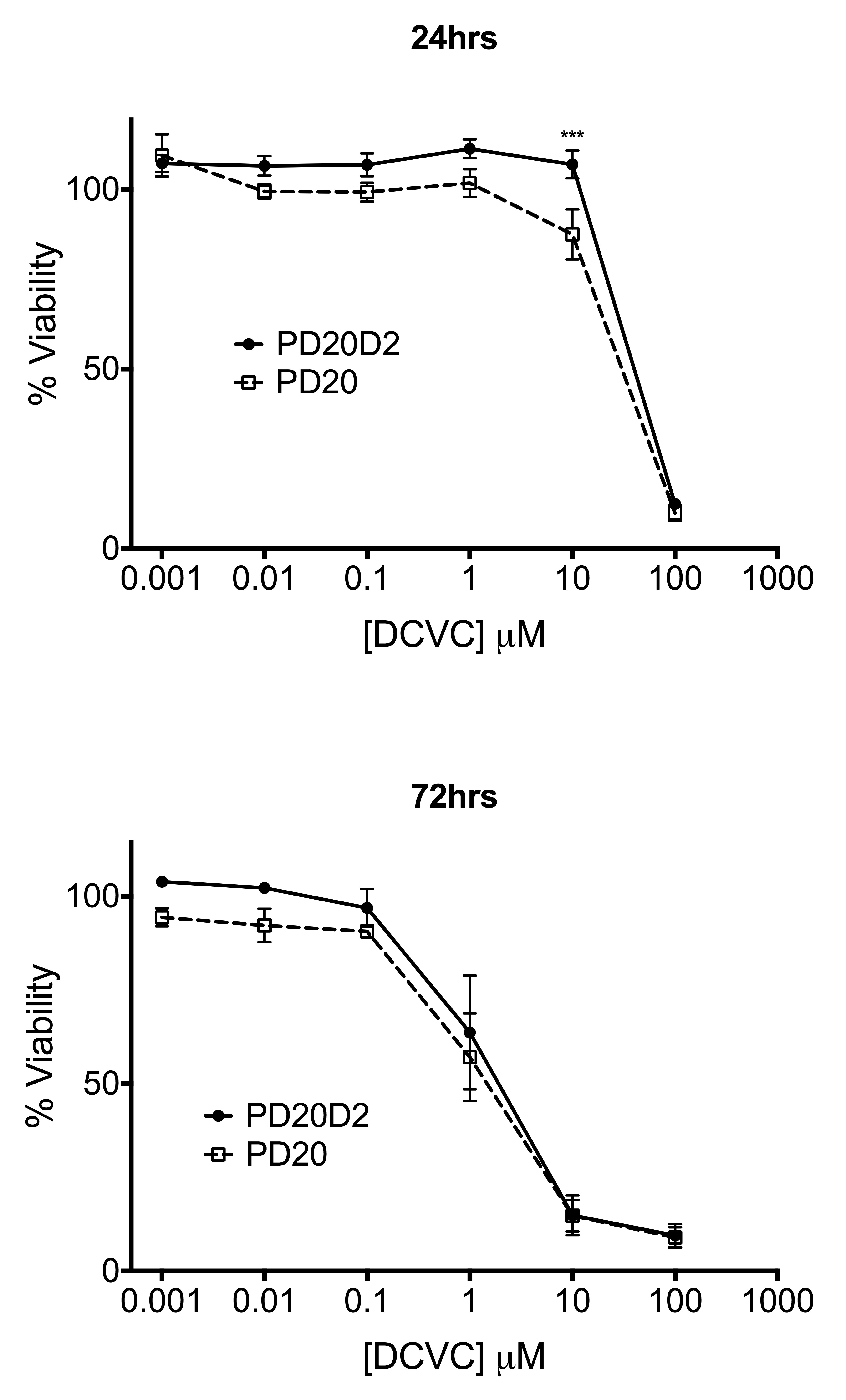








**Figure S3.** DT40 DNA repair mutant dose response curves for DCVC and Cisplatin. (A) Tranlesion synthesis mutants (B) HR mutants (C) ICL mutants (D) DNA damage checkpoint mutants (E) NHEJ mutants (F) NER/BER mutants (G) DNA helicase mutants. Sensitivity was assessed by XTT viability assays. Values are mean ± SE; n ≥ 3 for each measurement. Significant values were calculated by two-way ANOVA, where \*\*\*p < 0.001, \*\*p < 0.01, \*p < 0.05 *for DCVC-treated mutant versus DCVC treated wild-type.*



**Figure S4**. Sensitivity of ICL repair deficient lymphoblasts (PD20) and FANCD2 complemented (PD20D2) cells to DCVC at 24hrs and 72hrs. Values are mean ± SE; n = 3 for each measurement. Values are mean ± SE; n ≥ 3 for each measurement. Significance values were calculated by two-way ANOVA, where \*\*\*p < 0.001, \*\*p < 0.01, \*p < 0.05 *for DCVC-treated PD20 versus DCVC treated PD20*

**Table S1.** Total genes identified by differential strain sensitivity analysis (DSSA) from yeast profiling studies as sensitive or resistant to DCVC treatments.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ORF | Standard Name | 5 generations | | | Number of Significant |
| 25% IC20 | 50% IC20 | IC20 |
| 4.5 µM | 9 µM | 18 µM |
| *YIL162W* | *SUC2* | -4.2 | -4.1 | -4 | 3 |
| *YFR036W* | *CDC26* | -3.2 | -3.8 | -3.05 | 3 |
| *YDR112W* | *IRC2* | -2.7 | -4 | -2.95 | 3 |
| *YLR032W* | *RAD5* |  | -2.2 | -2.7 | 2 |
| *YCR066W* | *RAD18* |  | -2.1 | -2.4 | 2 |
| *YBR171W* | *SEC66* |  | -2 | -2.4 | 2 |
| *YAL002W* | *VPS8* |  | -1.8 | -2.3 | 2 |
| *YOR304C-A* |  | -2 | -2.5 | -2.2 | 3 |
| *YML097C* | *VPS9* |  | -2.3 | -2.2 | 2 |
| *YKL188C* | *PXA2* |  |  | -2 | 1 |
| *YMR141C* |  |  |  | -2 | 1 |
| *YOR089C* | *VPS21* |  | -1.9 | -1.95 | 2 |
| *YGL154C* | *LYS5* |  |  | -1.8 | 1 |
| *YDR338C* |  |  |  | -1.8 | 1 |
| *YKL199C* |  |  |  | -1.8 | 1 |
| *YML095C* | *RAD10* |  |  | -1.8 | 1 |
| *YMR137C* | *PSO2* |  | -1.8 | -1.75 | 2 |
| *YGL164C* | *YRB30* | -1.6 | -1.5 | -1.7 | 3 |
| *YAL024C* | *LTE1* |  |  | -1.7 | 1 |
| *YDR247W* | *VHS1* |  |  | -1.7 | 1 |
| *YER095W* | *RAD51* |  |  | -1.7 | 1 |
| *YPL022W* | *RAD1* |  |  | -1.65 | 1 |
| *YLR218C* |  |  | -1.5 | -1.6 | 2 |
| *YER162C* | *RAD4* |  |  | -1.6 | 1 |
| *YKR046C* | *PET10* | -1.4 |  | -1.5 | 2 |
| *YMR237W* | *BCH1* | -1.2 |  | -1.5 | 2 |
| *YGL166W* | *CUP2* |  |  | -1.4 | 1 |
| *YPL147W* | *PXA1* |  |  | -1.4 | 1 |
| *YIL146C* | *ECM37* |  |  | -1.4 | 1 |
| *YKL167C* | *MRP49* |  |  | -1.4 | 1 |
| *YGL253W* | *HXK2* |  |  | -1.4 | 1 |
| *YKL215C* |  | -1.3 | -1.1 | -1.3 | 3 |
| *YKL197C* | *PEX1* | -1.4 |  | -1.3 | 2 |
| *YER067W* |  | -1.3 |  | -1.3 | 2 |
| *YKR033C* |  | -1.3 |  | -1.3 | 2 |
| *YOR346W* | *REV1* |  |  | -1.3 | 1 |
| *YLR210W* | *CLB4* |  |  | -1.3 | 1 |
| *YOR017W* | *PET127* |  |  | -1.3 | 1 |
| *YHR110W* | *ERP5* |  |  | -1.3 | 1 |
| *YDR291W* | *HRQ1* |  |  | -1.3 | 1 |
| *YMR008C* | *PLB1* |  |  | -1.2 | 1 |
| *YML109W* | *ZDS2* |  |  | -1.2 | 1 |
| *YMR283C* | *RIT1* |  |  | -1.2 | 1 |
| *YKL100C* |  |  |  | -1.1 | 1 |
| *YDL034W* |  |  |  | 1.2 | 1 |
| *YJR154W* |  |  |  | 1.3 | 1 |
| *YDR463W* | *STP1* |  |  | 1.3 | 1 |
| *YCR082W* | *AHC2* |  | 1.5 | 1.4 | 2 |
| *YOR006C* |  |  |  | 1.4 | 1 |
| *YDR333C* |  |  |  | 1.4 | 1 |
| *YPL123C* | *RNY1* |  |  | 1.4 | 1 |
| *YCR001W* |  |  | 1.6 | 1.5 | 2 |
| *YJR051W* | *OSM1* |  | 1.6 | 1.5 | 2 |
| *YMR238W* | *DFG5* |  | 2.1 | 1.5 | 2 |
| *YMR124W* |  | 1.4 |  | 1.5 | 2 |
| *YGL198W* | *YIP4* | 1.4 |  | 1.5 | 2 |
| *YDR440W* | *DOT1* |  |  | 1.5 | 1 |
| *YML124C* | *TUB3* |  |  | 1.55 | 1 |
| *YCR060W* | *TAH1* | 1.2 | 1.4 | 1.6 | 3 |
| *YOR085W* | *OST3* |  | 1.5 | 1.6 | 2 |
| *YLR093C* | *NYV1* | 2.1 | 1.6 | 1.6 | 3 |
| *YBL107C* |  |  | 1.7 | 1.6 | 2 |
| *YPR201W* | *ARR3* |  | 1.7 | 1.6 | 2 |
| *YOR183W* | *FYV12* |  | 1.7 | 1.6 | 2 |
| *YOR137C* | *SIA1* | 1.7 | 1.8 | 1.6 | 3 |
| *YDR217C* | *RAD9* | 1.6 |  | 1.6 | 2 |
| *YLR023C* | *IZH3* |  |  | 1.6 | 1 |
| *YJL208C* | *NUC1* | 1.6 | 1.6 | 1.7 | 3 |
| *YPL197C* |  | 1.6 | 1.6 | 1.7 | 3 |
| *YGR192C* | *TDH3* | 1.7 | 1.9 | 1.7 | 3 |
| *YGR263C* | *SAY1* |  | 2.2 | 1.7 | 2 |
| *YDR441C* | *APT2* | 1.9 | 1.8 | 1.8 | 3 |
| *YLR202C* |  | 2 | 1.8 | 1.8 | 3 |
| *YML073C* | *RPL6A* |  | 1.8 | 1.8 | 2 |
| *YGL214W* |  |  | 1.8 | 1.8 | 2 |
| *YMR286W* | *MRPL33* | 1.9 | 2 | 1.8 | 3 |
| *YHR034C* | *PIH1* |  | 2 | 1.8 | 2 |
| *YKR035C* | *OPI8* |  | 2.4 | 1.8 | 2 |
| *YMR244C-A* |  |  | 2.8 | 1.8 | 2 |
| *YPL178W* | *CBC2* |  | 3 | 1.8 | 2 |
| *YCR011C* | *ADP1* |  | 1.8 | 1.9 | 2 |
| *YLR042C* |  | 2 | 1.9 | 1.9 | 3 |
| *YDR465C* | *RMT2* |  | 1.9 | 1.9 | 2 |
| *YEL068C* |  |  | 2 | 1.9 | 2 |
| *YMR294W-A* |  |  | 2.6 | 1.9 | 2 |
| *YGL252C* | *RTG2* |  |  | 1.9 | 1 |
| *YPL140C* | *MKK2* | 2.1 | 1.6 | 2 | 3 |
| *YLR057W* |  | 2.2 | 1.6 | 2 | 3 |
| *YMR272C* | *SCS7* | 2.3 | 1.9 | 2.1 | 3 |
| *YDR255C* | *RMD5* | 2.1 | 2.2 | 2.1 | 3 |
| *YJR130C* | *STR2* |  | 2.2 | 2.1 | 2 |
| *YOR021C* |  | 2.3 | 2.4 | 2.1 | 3 |
| *YFR018C* |  |  | 3.1 | 2.1 | 2 |
| *YFL021W* | *GAT1* |  |  | 2.1 | 1 |
| *YJL131C* |  |  |  | 2.1 | 1 |
| *YMR289W* | *ABZ2* | 2.5 | 2.4 | 2.15 | 3 |
| *YCL046W* |  | 1.9 | 1.9 | 2.2 | 3 |
| *YDR215C* |  | 1.8 | 2.1 | 2.2 | 3 |
| *YIL032C* |  |  | 2.1 | 2.2 | 2 |
| *YOR314W* |  | 2.5 | 2.3 | 2.2 | 3 |
| *YBR272C* | *HSM3* | 1.7 |  | 2.2 | 2 |
| *YFL025C* | *BST1* |  |  | 2.2 | 1 |
| *YIL090W* | *ICE2* | 2.1 | 2.6 | 2.3 | 3 |
| *YLR133W* | *CKI1* |  | 2.7 | 2.3 | 2 |
| *YHL039W* |  |  |  | 2.3 | 1 |
| *YML122C* |  |  | 2 | 2.4 | 2 |
| *YPR116W* |  | 2.8 | 2.2 | 2.4 | 3 |
| *YHR037W* | *PUT2* |  | 2.4 | 2.4 | 2 |
| *YOR133W* | *EFT1* |  | 3.1 | 2.4 | 2 |
| *YBR298C* | *MAL31* | 2.2 |  | 2.4 | 2 |
| *YDR389W* | *SAC7* |  |  | 2.4 | 1 |
| *YBR159W* | *IFA38* | 2.4 | 2 | 2.5 | 3 |
| *YLR262C* | *YPT6* | 2.5 | 2.1 | 2.5 | 3 |
| *YLR044C* | *PDC1* | 2.7 | 2.3 | 2.5 | 3 |
| *YMR166C* |  |  | 2.4 | 2.5 | 2 |
| *YBR113W* |  | 2.6 | 2.6 | 2.5 | 3 |
| *YER169W* | *RPH1* | 2.5 | 2.9 | 2.5 | 3 |
| *YDR153C* | *ENT5* |  | 3.1 | 2.5 | 2 |
| *YGR261C* | *APL6* |  | 3.7 | 2.5 | 2 |
| *YLR169W* |  | 2.6 | 2.3 | 2.6 | 3 |
| *YDR105C* | *TMS1* | 2.6 | 2.7 | 2.6 | 3 |
| *YGL229C* | *SAP4* | 2.5 | 2.4 | 2.7 | 3 |
| *YGL226C-A* | *OST5* | 2.5 | 2.5 | 2.7 | 3 |
| *YBR114W* | *RAD16* | 2.7 | 2.7 | 2.7 | 3 |
| *YCR006C* |  | 2.6 | 2.8 | 2.7 | 3 |
| *YGL138C* |  | 2.8 | 3 | 2.7 | 3 |
| *YBR175W* | *SWD3* |  | 3.9 | 2.7 | 2 |
| *YDL223C* | *HBT1* | 1.5 | 2.25 | 2.8 | 3 |
| *YDR175C* | *RSM24* | 2.8 | 2.3 | 2.8 | 3 |
| *YCR073W-A* | *SOL2* | 2.5 | 2.5 | 2.8 | 3 |
| *YHL011C* | *PRS3* | 3 | 2.6 | 2.8 | 3 |
| *YDR377W* | *ATP17* | 3.1 | 2.8 | 2.8 | 3 |
| *YDR456W* | *NHX1* | 3.5 | 2.9 | 2.8 | 3 |
| *YEL012W* | *UBC8* |  | 3.9 | 2.8 | 2 |
| *YJR044C* | *VPS55* | 2.8 | 2.8 | 2.9 | 3 |
| *YER066C-A* |  | 2.7 | 2.9 | 2.9 | 3 |
| *YLR450W* | *HMG2* | 3.3 | 2.8 | 3 | 3 |
| *YER002W* | *NOP16* | 3 | 3 | 3 | 3 |
| *YJR088C* |  | 3.2 | 3.1 | 3 | 3 |
| *YBR213W* | *MET8* | 3.1 | 3.1 | 3.1 | 3 |
| *YDR163W* | *CWC15* | 3 | 2.9 | 3.2 | 3 |
| *YPL157W* | *TGS1* |  | 3.8 | 3.2 | 2 |
| *YHR157W* | *REC104* | 3.2 | 3.1 | 3.3 | 3 |
| *YMR304W* | *UBP15* | 3.3 | 2.9 | 3.4 | 3 |
| *YMR261C* | *TPS3* | 3.3 | 2.9 | 3.5 | 3 |
| *YDR458C* | *HEH2* | 3.6 | 3.7 | 3.8 | 3 |
| *YBR187W* | *GDT1* | 4 | 4 | 4.3 | 3 |
| *YML079W* |  |  |  | 4.3 | 1 |
| *YEL056W* | *HAT2* | -3.5 | -3.1 |  | 2 |
| *YEL043W* |  | -3.3 | -2.8 |  | 2 |
| *YPL138C* | *SPP1* | -1.9 | -2.1 |  | 2 |
| *YPL167C* | *REV3* |  | -1.7 |  | 1 |
| *YKL097C* |  |  | -1.4 |  | 1 |
| *YOR253W* | *NAT5* |  | -1.3 |  | 1 |
| *YMR326C* |  |  | 1.1 |  | 1 |
| *YNL010W* |  | 1.4 | 1.2 |  | 2 |
| *YLR121C* | *YPS3* | 1.6 | 1.4 |  | 2 |
| *YLR098C* | *CHA4* |  | 1.6 |  | 1 |
| *YDR314C* | *RAD34* |  | 1.6 |  | 1 |
| *YDR283C* | *GCN2* |  | 1.6 |  | 1 |
| *YJL108C* | *PRM10* | 1.6 | 1.7 |  | 2 |
| *YDR251W* | *PAM1* | 1.7 | 1.7 |  | 2 |
| *YLR192C* | *HCR1* | 1.7 | 1.7 |  | 2 |
| *YBL008W* | *HIR1* |  | 1.7 |  | 1 |
| *YML048W-A* |  | 1.7 | 1.8 |  | 2 |
| *YHR046C* | *INM1* |  | 1.9 |  | 1 |
| *YFL013W-A* |  |  | 1.9 |  | 1 |
| *YDR285W* | *ZIP1* |  | 1.9 |  | 1 |
| *YHR160C* | *PEX18* |  | 1.9 |  | 1 |
| *YKL096W-A* | *CWP2* |  | 1.9 |  | 1 |
| *YGR041W* | *BUD9* |  | 2 |  | 1 |
| *YOR161C* | *PNS1* |  | 2 |  | 1 |
| *YOR364W* |  |  | 2 |  | 1 |
| *YPR044C* | *OPI11* |  | 2 |  | 1 |
| *YJR010C-A* | *SPC1* |  | 2 |  | 1 |
| *YBR037C* | *SCO1* |  | 2.1 |  | 1 |
| *YKL174C* | *TPO5* |  | 2.1 |  | 1 |
| *YMR280C* | *CAT8* |  | 2.2 |  | 1 |
| *YMR262W* |  |  | 2.2 |  | 1 |
| *YBL062W* |  |  | 2.4 |  | 1 |
| *YLR335W* | *NUP2* | 1.6 | 2.5 |  | 2 |
| *YFL032W* |  |  | 2.5 |  | 1 |
| *YPL035C* |  |  | 2.5 |  | 1 |
| *YGL118C* |  |  | 2.5 |  | 1 |
| *YNL101W* | *AVT4* |  | 2.5 |  | 1 |
| *YFL019C* |  |  | 2.7 |  | 1 |
| *YOR086C* | *TCB1* | 3 | 2.8 |  | 2 |
| *YGL071W* | *AFT1* | -2.5 |  |  | 1 |
| *YOR276W* | *CAF20* | -2.2 |  |  | 1 |
| *YFL003C* | *MSH4* | -1.9 |  |  | 1 |
| *YOR054C* | *VHS3* | -1.8 |  |  | 1 |
| *YIL089W* |  | -1.6 |  |  | 1 |
| *YDR057W* | *YOS9* | -1.4 |  |  | 1 |
| *YLR131C* | *ACE2* | 1.3 |  |  | 1 |
| *YNL058C* |  | 1.4 |  |  | 1 |
| *YLR099C* | *ICT1* | 1.4 |  |  | 1 |
| *YOR041C* |  | 1.4 |  |  | 1 |
| *YLR018C* | *POM34* | 1.4 |  |  | 1 |
| *YLR456W* |  | 1.5 |  |  | 1 |
| *YLR443W* | *ECM7* | 1.5 |  |  | 1 |
| *YLR053C* |  | 1.6 |  |  | 1 |
| *YLR049C* |  | 1.7 |  |  | 1 |
| *YGR183C* | *QCR9* | 1.7 |  |  | 1 |
| *YMR175W* | *SIP18* | 1.8 |  |  | 1 |
| *YLR270W* | *DCS1* | 1.8 |  |  | 1 |
| *YBR044C* | *TCM62* | 1.9 |  |  | 1 |
| *YLR257W* |  | 2 |  |  | 1 |
| *YOR199W* |  | 2 |  |  | 1 |
| *YIL139C* | *REV7* | 2.2 |  |  | 1 |
| *YOR201C* | *MRM1* | 2.2 |  |  | 1 |
| *YLL009C* | *COX17* | 2.8 |  |  | 1 |

**Table S2**. Mutation frequency (mean ± SE x 10-6 cells) of DCVC in human lymphoblast cellsa

|  |  |  |
| --- | --- | --- |
| DCVC (μM) | MF | Fold changeb |
| 0 | 5.8 ± 1.8 |  |
| 2 | 12.8 ± 1.5\*\* | 2.2 |
| 4 | 13.2 ± 1.6\* | 2.3 |
| 8 | 10.3 ± 4.0 | 1.8 |
| 15 | 11.6 ± 1.7 | 2.0 |

aMutagenesis at the TK locus was measured in human lymphoblasts after exposure to DCVC for 6 weeks. Mutation frequency is the number of mutation events per 1 million cells. Values are mean ± SE; n = 2 for each measurement. \*\*p < 0.01, \*p < 0.05 for DCVC-treated versus untreated

bFold increase compared to untreated control.

**Table S3.** DT40 mutant cells used in this study

|  |  |  |
| --- | --- | --- |
| Gene | Function | References |
| POLβ | Base excision repair | (Tano et al., 2007) |
| FEN1 | Base excision repair | (Matsuzaki et al., 2002) |
| PARP1 | Base excision repair | (Hochegger et al., 2006) |
| XPA | Nucleotide excision repair | (Okada et al., 2002) |
| XPG | Nucleotide excision repair | (Kikuchi et al., 2005) |
| WRN | DNA helicase | (Kawabe et al., 2006) |
| BLM | DNA helicase | (Wang et al., 2000) |
| FANCD2 | Fanconi anemia pathway | (Yamamoto et al., 2005) |
| BRCA1 | Fanconi anemia pathway | (Vandenberg et al., 2003) |
| BRCA2 | Fanconi anemia pathway | (Hatanaka et al., 2005) |
| XRCC2 | Homologous recombination | (Takata et al., 2001) |
| XRCC3 | Homologous recombination | (Takata et al., 2001) |
| RAD52 | Homologous recombination | (Yamaguchi-Iwai et al., 1998) |
| RAD51D | Homologous recombination | (Takata et al., 2001) |
| RAD54 | Homologous recombination | (Bezzubova et al., 1997) |
| KU70 | Non-homologous end joining | (Takata et al., 1998) |
| LIGIV | Non-homologous end joining | (Adachi et al., 2001) |
| DNA-PK | Non-homologous end joining | (Fukushima et al., 2001) |
| RAD9 | DNA damage checkpoint | (Kobayashi et al., 2004) |
| ATM | DNA damage checkpoint | (Takao et al., 1999) |
| RAD17 | DNA damage checkpoint | (Kobayashi et al., 2004) |
| REV1 | Translesion synthesis repair | (Simpson and Sale, 2003) |
| POLQ | Translesion synthesis repair | (Yoshimura et al., 2006) |
| PCNAK164R | Translesion synthesis repair | (Arakawa et al., 2006) |
| RAD18 | Translesion synthesis repair | (Yamashita et al., 2002) |

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