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## Supplementary information

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# Site-saturation mutagenesis of 500 human protein domains

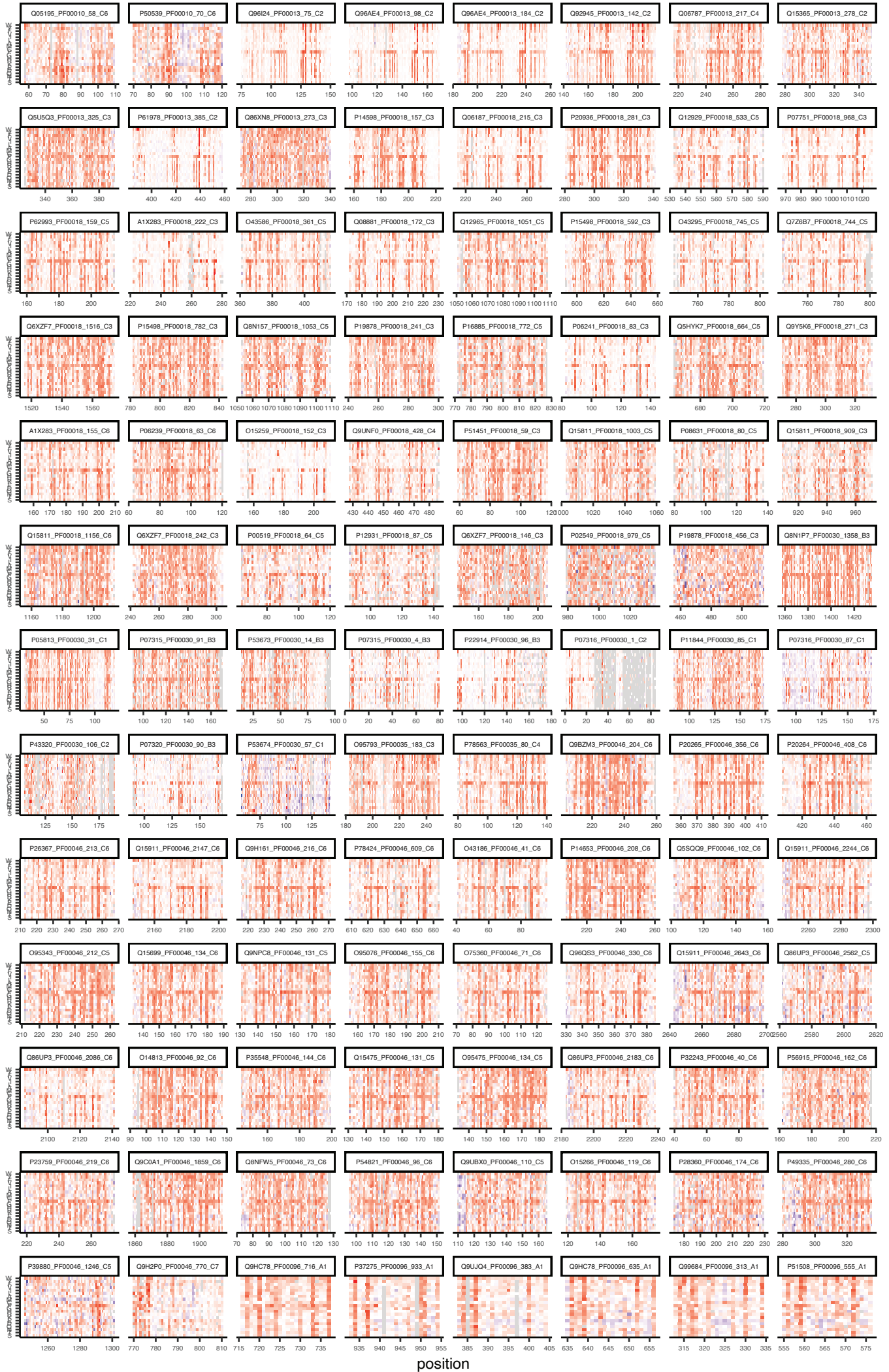
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In the format provided by the  
authors and unedited

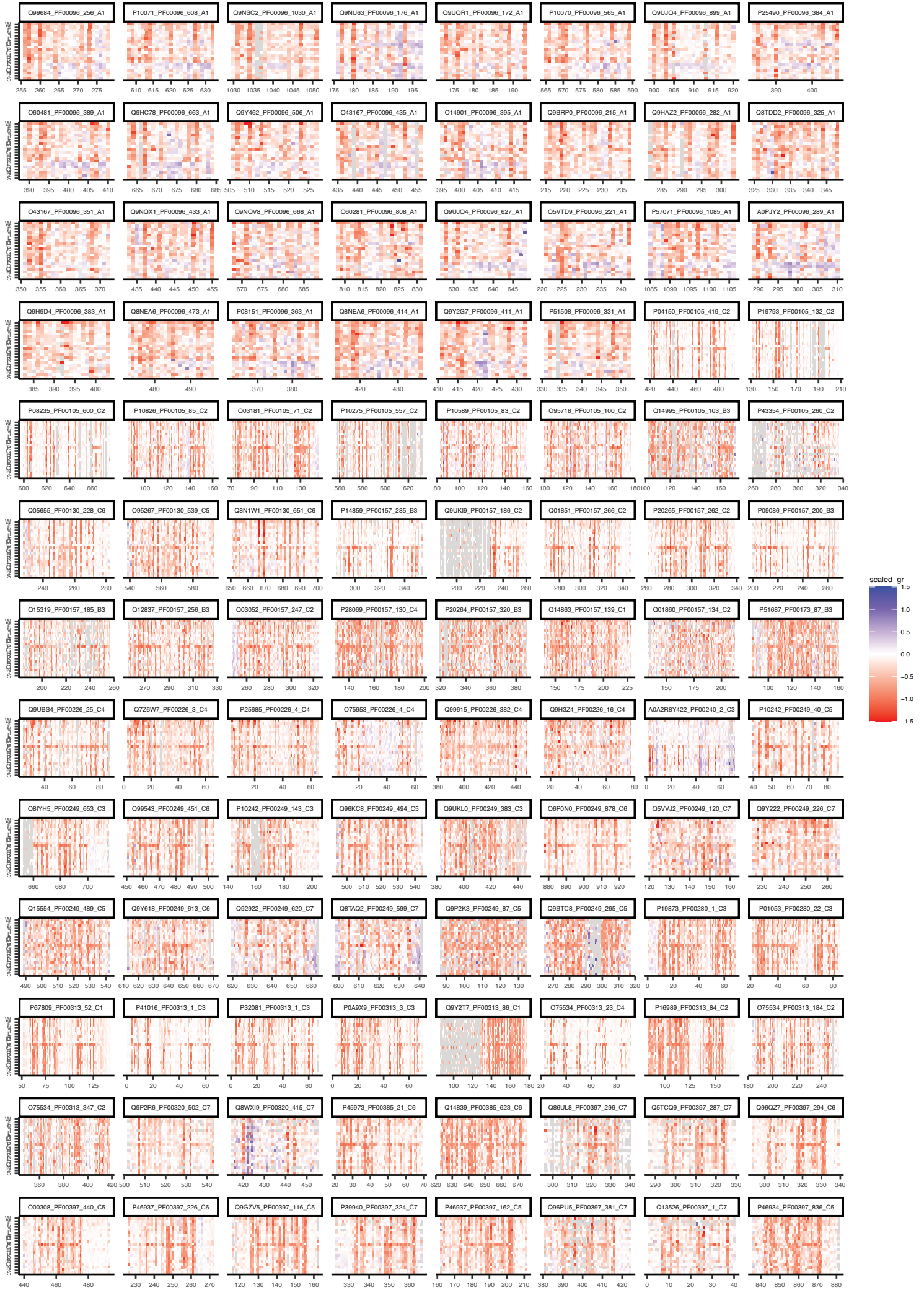
## Supplementary Figures

**Supplementary Figure 1: Deep mutational scans of protein abundance of 522 protein domains.** Domains are sorted by protein family and ranked by quality within families.

mutant aa



mutant aa



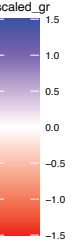
position

mutant aa

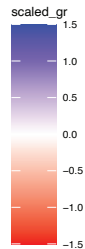


position

mutant aa



mutant aa



position



# Supplementary Tables

**Supplementary Table 1:** Library design: sequences, library statistics. Provided as an excel file.

**Supplementary Table 2:** Fitness scores and errors. Provided as an excel file.

**Supplementary Table 3:** Weighted mean residuals of abundance to evolutionary fitness predictions. Provided as an excel file.

**Supplementary Table 4:** Homolog-averaged  $\Delta\Delta G$  predictions across families mapped to homologous domains proteome-wide. Provided as an excel file.

**Supplementary Table 5:** aPCA fitness scores and variant effect predictor scores. Provided as an excel file.

**Supplementary Table 6:** Plasmids

|         |            |                                                                |
|---------|------------|----------------------------------------------------------------|
| pGJJ162 | aPCA empty | Available upon request (Material Transfer Agreement required). |
|---------|------------|----------------------------------------------------------------|

**Supplementary Table 7:** Oligonucleotides

|                            |                                                         |
|----------------------------|---------------------------------------------------------|
| qPCR quantification oligos |                                                         |
| oGJJ152                    | GCCTACATACCTCGCTCTGC                                    |
| oGJJ153                    | CAACCCGGTAAGACACGACT                                    |
| Frameshifting PCR1 oligos  |                                                         |
| oGJJ595                    | ACACTCTTCCCTACACGACGCTCTCCGATCTGCTGCTCTAGAATGGCTAGC     |
| oGJJ595_+1                 | ACACTCTTCCCTACACGACGCTCTCCGATCTNGCTGCTCTAGAATGGCTAGC    |
| oGJJ595_+2                 | ACACTCTTCCCTACACGACGCTCTCCGATCTNNGCTGCTCTAGAATGGCTAGC   |
| oGJJ595_+3                 | ACACTCTTCCCTACACGACGCTCTCCGATCTHWAGCTGCTCTAGAATGGCTAGC  |
| oGJJ595_+4                 | ACACTCTTCCCTACACGACGCTCTCCGATCTNHTAGCTGCTCTAGAATGGCTAGC |
| oGJJ595_+5                 | ACACTCTTCCCTACACGACGCTCTCCGATCTSSAAGCTGCTCTAGAATGGCTAGC |
| oGJJ748                    | GTGACTGGAGTTCAGACGTGTGCTCTCCGATCTCCCGCCACCGCCAAG        |
| oGJJ748_+1                 | GTGACTGGAGTTCAGACGTGTGCTCTCCGATCTNCCCGCCACCGCCAAG       |
| oGJJ748_+2                 | GTGACTGGAGTTCAGACGTGTGCTCTCCGATCTTNCCCGCCACCGCCAAG      |
| oGJJ748_+3                 | GTGACTGGAGTTCAGACGTGTGCTCTCCGATCTNTGCCCGCCACCGCCAAG     |
| oGJJ748_+4                 | GTGACTGGAGTTCAGACGTGTGCTCTCCGATCTGWWWCCCGCCACCGCCAAG    |



|            |                                                          |
|------------|----------------------------------------------------------|
| oGJJ748_+5 | GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTACTWWCCCGCCACCGCCAAG   |
| oGJJ748_+6 | GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTCATWWCCCGCCACCGCCAAG   |
| oGJJ748_+7 | GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTGTATADCCCGCCACCGCCAAG  |
| oGJJ748_+8 | GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTTGGGDWWCCCGCCACCGCCAAG |

### Supplementary Table 8: Sequences used in AF3 predictions

MECP2 MBD bound to methylated DNA;

- MECP2 MBD:  
RGPMYDDPTLPEGWTRKLKQRKSGRSAGKYDVYLINPQGKAFRSKVELIAYFEKVG  
DTSLDPNDFDFTVTGR
- DNA chain 1: TCTGGAA-5mC-GGAATTCTTCTA
- DNA chain 2: TAGAAGAATTC-5meC-GTTCCAGA

CRX homeodomain bound to DNA:

- CRX homeodomain:  
RERTTFTRSQLEELEALFAKTQYPDYAREEVALKINLPESRVQVWFKNRRRAKCRQ
- DNA chain 1: ACGTGTGCACGTGATTAGTGCCATGCAACA
- DNA chain 2: TGTTGCATGGCACTAATCACGTGCACACGT