Supplementary Information

Changes in gene expression predictably shift and switch genetic interactions

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Supplementary Figure 1. Experimental pipeline.



Supplementary Figure 2. Reproducibility of mutational effects between biological replicates.

(a) Correlation of target gene expression estimated by deep sequencing, with target gene expression individually quantified for a second validation dataset of 9 single and double mutants at low and high expression levels together with wild type. Error bars denote standard error of the mean from three biological replicates.

(b) Violin plots of the standard error for enrichment scores from sequencing data for the analysed datasets (n=1182), reference dataset as shown in Figure 1d (n=22, excluding wild type variant) and the independent validation dataset as shown in the panel (a) (n=9). Groups compared using Kruskal-Wallis test with post hoc Dunn's test.

(c and d) Spearman correlations of mutational effects among three biological replicates for low (c) and high (d) CI expression. (e) Comparisons of mutational effects between low and high expression level for 22 individually retested single and double mutants together with wild type. Error bars denote standard error of the mean.

(f) Density plots of GFP expression for the 22 individually re-tested single and double mutants at the two expression levels of CI.



Supplementary Figure 3. Mutational effects depend on both the chemical features of amino acid substitutions and the tertiary structural positions.

(a) Structure of CI dimer bound to an operator (PDB 3bdn). One monomer is shown as a ribbon and the other one with all its atoms shown as spheres. Only the mutagenized HTH domain is shown. Left panel is the structural classification of the residues. Middle and right panels show the positional median z-scores of GFP expression levels after subtracting wild type z-scores at the two expression levels of CI. Z-scores rather than absolute GFP expression levels are shown here to compare positional sensitivity to mutations at two expressions of CI. (b) Heatmaps of mean GFP expression for single mutations at the two expression levels. Amino acids are ordered based on their similarities, from top to bottom: hydrophobic aromatic (F,W,Y), hydrophobic nonpolar aliphatic (P,M,I,L,V,A,G), hydrophilic polar uncharged (C,S,T,N,Q), hydrophilic negatively charged (D,E) and hydrophilic positively charged (H,K,R). Wild type amino acids are shown as letters inside the heatmap. (c and d) Target GFP expression compared to the binned FoldX-predicted changes in the folding energy of the protein (e) and protein-DNA binding (f) at the two expression levels. Bin1 corresponds to $\Delta\Delta G \le 0$; Bin2: $0<\Delta\Delta G \le 2.5$; Bin3 : $2.5<\Delta\Delta G \le 5$; and Bin4: $\Delta\Delta G>5$. (g and h) Target gene expression compared to the changes in the hydrophobicity at low (g) and high (h) expression of CI. (i and j) Target gene expression compared to changes in the side chain charges at low (i) and high (j) expression of CI. Classes compared using Kruskal-Wallis test with post hoc Dunn's test. All P-values were Bonferroni adjusted.



Supplementary Figure 4. Epistasis versus GFP expression levels for observed data.



Supplementary Figure 5. Mathematical models.

(a) Eight configuration states (CS) of the PR promoter. (b) Obtaining functional protein concentration (panels b1,b4), fraction of folded protein (panels b2,b3), and change in folding energy (panels b2,b3) from GFP expression levels of a mutation at low expression of the protein. (c) Scheme for predicting double mutants' GFP expression levels from single mutants' GFP expression levels based on different models. (d) Folding-only model. (e) Regulation-only model.



Supplementary Figure 6. Predictions of double mutants based on folding-only or regulation-only model.

(a and b) Observed versus predicted GFP expression levels for the folding-only (a) and regulation-only (b) models. RMSD: rootmean-square-deviation from the predicted to the observed data. (c - f) Binned median target gene expression levels (c, e) and epistasis scores (d, f) for the folding-only (c, d) and regulation-only (e, f) models. Mutations were sorted into 5 equally populated bins by their single mutant phenotypes as in Figure 3j,k.



Supplementary Figure 7. Epistasis pattern predicted from different models.

(a – c) Epistasis versus GFP expression levels predicted from full model (a), folding-only model (b) and regulation-only model (c). (d – f) Epistasis scores at the two expression levels of CI protein for full model (d), folding-only model (e) and regulation-only model (f). Two-sample Kolmogorov–Smirnov test was performed for cumulative distributions of epistasis scores at the two expression levels of CI protein.



Supplementary Figure 8. Observed versus predicted expression level-dependent changes in epistasis.

(a) Histogram of the model-predicted epistasis score distributions at the two expression levels of the protein. The grey dotted lines mark the centre bin with the epistasis score thresholds of -0.25 and 0.25; and the black dotted lines mark the centre three bins with the epistasis score thresholds of -0.75 and 0.75. (b and c) Distribution of the observed epistasis scores grouped by the model-predicted classes of epistasis scores, with classification threshold of -0.25 and 0.25. (d and e) Distribution of the observed epistasis scores grouped by the model-predicted classes of epistasis scores, with classification threshold of -0.25 and 0.25. (d and e) Distribution of the observed epistasis scores grouped by the model-predicted classes of epistasis scores, with two additional classification thresholds, between -0.75 and 0.75 (d) and between -0.1 and 0.1 (e). "L" - low expression and "H" - high expression. The one-sample Wilcoxon signed rank test was performed to test whether average epistasis scores are significantly different from 0. P-values are adjusted with Bonferroni multiple test correction method.



Supplementary Figure 9. Concentration-dependent genetic interactions in the yeast fitness landscape.

(a - c) Concentration-dependent mutation effects and epistasis in a "decreasing" expression-fitness function54. (d - I) Concentration-dependent epistasis for three common expression-fitness functions with stable, marginally stable and unstable proteins.



Supplementary Figure 10. Unpredictable double mutant phenotypes.

(a) A measured fitness effect can be caused by two different changes in protein concentration in a 'peaked' fitness landscape when the WT protein is expressed at the fitness optimum. (b) Only very small changes in fitness can be mapped to either increased or decreased fraction of folded protein, due to the limit of fraction of folded protein (maximum equals to 1). For example, a mutant with the fitness effect of -0.02 (ω A) can be caused by two different mutations (A1 and A2) that cause changes in the free energy of protein folding ($\Delta\Delta$ GF,A1 or $\Delta\Delta$ GF,A2) and so two different changes in protein concentration. In contrast, larger fitness changes can only be caused by one change in free energy of folding. For example, a mutant with a fitness effect of -0.05 (ω B) can be caused by either a 5-fold increase or decrease in the functional protein concentration. However, a 5-fold increase in concentration cannot be achieved by a change in folding because it would require more than 100% of the protein to be folded. Therefore, a mutant with a fitness effect of -0.05 can only be caused by a decrease in protein stability (mutant B1). (c) Combining two mutations of known fitness can lead to two possible double mutant outcomes and either positive or negative epistasis. For the case of A2 + B1, mutant A2 is detrimental in the wild type background (ω A2=-0.02), but beneficial at the mutant B1 background (ω A2B1- ω B1= -0.02 –(-0.05)= 0.03). The interaction between mutant A2 and B1 is. Therefore an example of sign epistasis. The possible outcomes are up to 4 if the fitness landscape is not symmetrical.



Supplementary Figure 11. Fluorescence-activated cell sorting (FACS).

(a and b) An example (High expression, replicate 3) of the gating strategy for FACS. Gate P2 and P6 correspond to Output 1 and Ouptut2 in Figure 1c respectively. (c) FACS recordings from each biological replicate performed on different days. GFP_index is used to quantify variation in fluorescence readings between batches.



Supplementary Figure 12. Protein quantification.

(a) Distribution of fluorescence signal of cells expressing C-terminal GFP-tagged CI at high and low expression levels.
(b) Fluorescence linearly correlates with the number of molecules of equivalent soluble fluorochrome (MESF) from GFP beads.
(c) Relative fold-change of soluble CI protein concentrations at high versus low expression levels. Error bars denote standard error of the mean.



Supplementary Figure 13. Filtering of sequencing data.

(a and b) Sequencing data was filtered to only retain genotypes with at least 100 read counts (red line) in all three biological replicates for both low (a) and high (b) expression datasets. Each smooth scatter panel shows the relationship between enrichment scores (Sv,o1 for Output1 and Sv,o2 for Output2) and input read counts for each replicate. The top density plot shows the input count distribution for each replicate. (c and d) Only variants with propagated mean enrichment score standard errors smaller than 1 (red line) were retained.



Supplementary Figure 14. Converting enrichment scores to GFP expression.

(a – c) Relationship between GFP signals either with Output1 enrichment scores (a), with Output2 enrichment scores (b), or with transformed Output2 enrichment scores (c) for the individually tested variants (n=23). (d and e) Relationship between Output1 and Output2 enrichment scores (d) or transformed Output2 enrichment scores (e) for all single nucleotide variants (n=531). (f and g) Comparisons of individually tested mean GFP signals with the predicted mean GFP signals from Output1 and Output2 enrichment scores (f) or with Output1 and transformed Output2 enrichment scores (g) (n=23). All error bars denote standard error of the mean. RMSD: root-mean-square-deviation between the predicted and observed data, after averaging the replicates.



Supplementary Figure 15. Correcting for technical biases.

(a) Relationship between predicted GFP expression for biological replicates for all single nucleotide variants (n=531) before (grey) and after (blue or red) transforming the replicate 1 and 3 data to the reference replicate 2 (see Methods). (b and c) Density plot of GFP expression before (b) and after (c) correcting for technical biases by transforming replicates 1 and 3 to the reference replicate 2 for all single nucleotide variants (n=531). (d) Smooth scatter showing the relationship between the mean GFP signal of all amino acid genotypes (n=888) before and after scaling to the detection range (see Supplementary Methods).



Supplementary Figure 16. Mathematical modelling.

(a) Relationship between free CI dimer concentration and total CI concentration in the cell in Ackers' model. (b - d) Parameter search for the line intercept that best describes the relationship of GFP at low and high expression for the folding-only model. Dashed lines in (b) and (d) mark equal GFP level at the two expression levels. Solid lines in (b) mark the range of the intercepts searched for the best fit. Red dashed line in (c) shows the best fit (the smallest SSDC). (e) Projection of individual data points from observed GFP expression levels at low and high CI expression to the model-predicted curve.

Supplementary Table 1. PCR primers F: Forward; R: Reverse, 5' to 3'

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d CI H8.6 C CONCOLOGICAL CONCOLUCIÓN CONCO	d_Cl_Fs_6	CGTACCTTGCTTGAGGACGCACGTC	Output1 &2 rep3 barcoded
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CASEMUL: F. TRATECATTANTANAGGE CASEMUL: Z.R. TRATECATTANTANGGE G124A,C125G CASEMUL: F. TRATECATTANTANGGE G124A,C125A CASEMUL: F. TRATECATTANTANGGE G70A,G71C CASEMUL: F. CARACTICITECE G49A CASEMUL: F. CARACTICITECACOTACTICITECE G49A CASEMUL: F. CARACTICICACOTACTICICA A27T CASEMUL: F. CARACTICICACOTACTICICA A27T CASEMUL: F. CARACTICICACOTACTICICA A27T <t< td=""><td>Q5SDM1_F O5SDM1.1_B</td><td></td><td>G124T,C125G</td></t<>	Q5SDM1_F O5SDM1.1_B		G124T,C125G
SSEMI-2, R TOATTAATATTATAAGCOODATTG G124A,C125G OSSEMI-3, R TOATTAATAGCOODATTG G124A,C125A OSSEMI-4, R GOADAGATTGGTGGGAT G70A,G71C OSSEMIA, R GOADAGATTGGTGGGATG G70A,G71C OSSEMIA, R GOADAGATTGGTGGGATAGATGGGA ABOC (synonymous) OSSEMIA, R COCADAGATTGGTGGGATAGATTGGC G78A (synonymous) OSSEMIA, R CACAACATTGGGATAGATTGGCAGATTGCC G78A (synonymous) OSSEMIA, R CACAACATTGGGATGGACAATTGCC G78A (synonymous) OSSEMIA, R CACAACATTGGGATGGCCAGATTGCC G48A OSSEMIA, R CACAACATTGGGATGGCCAGAATTGCC G48A OSSEMIA, R CACAACATTGGGATGGCCAGAATTGCC G48A OSSEMIA, R CACAACTTGGGATGGCCAGAATTGCC G48A OSSEMIA, R CACAATTGGAAAAAAAAAAAAGAAGAGA G48A OSSEMIA, R CACAATTGGGATGGCCAGAATTGCC G24A OSSEMIA, R CACAATTGGAATGGACCAATTGCC G24A OSSEMIA, R CACAATTGGAATGGACCAATTGCC G26G OSSEMIA, R CACAATTGGAATGAACTTGCC G26G OSSEMIA, R CACAATTGGAATTAATGGAAGAAGAAG	Q5SDM1 F	TTGATGCCATTAAATAAAGCAC	
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CSSDM6, R AAGCCAAGTTCATTTTTTTTTTTTTTTTTTTTTTTTTTT	Q5SDM6_F	GCAATTTATGAAAAAAAAAAAAAAAAAAGAACTTGGCTT	
CBSDM7_F CITEGAAAATTEGTAACTTGAACATTGACC C156G(synonymous) CBSDM8_F CATACAACTTGGACATTGACCAGGAATTGGCC T41G (nonsense) CBSDM9_F CITATCCCAGAAATTGGCCAGCAATTGGC G49A CBSDM10_F CCAACTTGGTATTTTTTTTTTCCAAGCCAGGAATTGGCC G24A CBSDM11_F TGCCACACAAAAAAAAAAAAAAAAGCTGGCCA T68A CBSDM11_F TGCCACACAAAAAAGGAGGAATGGGCG ACTT CBSDM12_R CATAATTGCTTAAGGCCA ACTT CBSDM13_R TAAATTGCTTAAGGCGA ACTT CBSDM14_R CGCAACTTGGCTATGGCTAT CBSDM12_R CBSDM13_R TAAATTGCTTAAGGCGA A25G CBSDM14_R CGAAACTTGGCTAAGCGTGAACTGGC A25G CBSDM14_R GCAAGCATGCGGGGGTA A157C CBSDM14_R GCAAGCATGCGGGGGTA C95G CBSDM16_R TGACCACATGCGGGGGGTA G95G CBSDM16_R GGCGCAGTGGGGGGCTA G95G CBSDM16_R GGCGCAGTGAGGGGGGGGG G85A CBSDM18_R GGCCAGCGCGCGCGGGG G106T CBSDM18_R GGCCAGCGTGCGGGGGGGGGGGGGGGGGGGGGGGGGGGG	Q5SDM6_R	AAGCCAAGTTCATTTTTTTTTTTTTCATAAATTGC	GY 6A (Synonymous)
USSIMIN_F GENARTICITAGES (CARACTERCE) OSSDM8_R CGRACKATTECTGGGATCAGECAASTCATT T41G (nonsense) OSSDM9_R CCRACTCATTTTTCTTTTTTC G49A OSSDM10_R ACCARTCATTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	Q5SDM7_F	CTTGCAAAAATTCTgAAAGTTAGCGTTGAAGAATTTAGC	C156G(synonymous)
Desching_r characterization of the second	Q5SDM7_R		
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CSSDM9_R CCAAGTCATTITICTTITIC CHSA CSSDM10_R AAGCCAAGTCATTITITITITIC G24A CSSDM11_R CTGCCAACCAGACTCAATTITITITITITITICATAAATTGC G24A CSSDM11_R CTGCCCACTCCCCTTIGTCTGCGA T68A CSSDM12_R CATAATTGCTTAGGCGAC A27T CSSDM13_R TAAATAGCTTAGGCGAC A25G CSSDM13_R TAAATAGCTTAGGCGAC A157C CSSDM13_R GCAAGCATCCCCCTCTGCCTGC C95G CSSDM14_F AAAATTGCTTAGGCGAC C95G CSSDM15_R TGAATAGCTTAGGCGACGC C95G CSSDM16_R ATCCCCACTCCCCAT C95G CSSDM16_R ATCCCCACTCTGGTGGTTATATAGGC G85A CSSDM15_R TGACCCCATCTGCTGGGGCATTA G85A CSSDM16_R ATCCCCATCTGGTGGGGCATTA G85A CSSDM17_R GCGGCCTTATAGG G106T CSSDM19_R CTGCCAACCCCTGACTCG G106T CSSDM19_R CTGCCAACCCCTGACTCGC G106T CSSDM19_R CTGCCAACCCCTGACTCGC G106T CSSDM19_R CTGCTATCCGAGGATTAAGC T68G CSSDM2_R ACCCATCTTGTTGCGGCAGGG T82A CSSDM2_R CCCCTGTGGTGATAACCC T68G CSSDM2_R CCCCTGTGGTAAAACGCATAACCCC T105A CSSDM2_R CCCCTGT	Q5SDM9_F	CTTATCCCAGaAATCTGTCGC	6404
CSSDM10_F GCATTIATRAAAMAAAAAAATGAACTIGGCTT G24A CSSDM11_F CGCCAACAAGTGCATTITITITITITITAAATGCC G24A CSSDM11_F TCCCAACAAGAAGGGGATGGGGCAG G68A CSSDM12_F AAAAAAGAAAAATGAACTIGGCTTATC A27T CSSDM13_R CATAATIGCTTAAGGCGCAC A25G CSSDM14_R GCAAGCAATGCGTTAAGCCTTAAGACATTGG A25G CSSDM14_R GCAAGCAATGCGGGCGTA A157C CSSDM15_R TGAACTGCGCCCCCCAT C95G CSSDM15_R GGGCGTGGGGGTTAAGCGGTGAGGAG G85A CSSDM16_R GGGCGCGCCAAGCGTTGGGCGCATA G85A CSSDM16_R GGGCGCGTCAAGCGTTGGGCGAGG G85A CSSDM17_F GGGGCGGCTAAGGGTTGGGCGCAGT G106T CSSDM18_R CTACGCGCGCTGCGCGC G106T CSSDM19_R CGCAGCTAAGGGCTGGCGGCAGTC A73T CSSDM19_R CTGCCGACAGCGGGGGGGGGG G106T CSSDM19_R CTGCCGCAAGGGCGGGGGGGGG G106T CSSDM19_R CTGCCGCAGCGGGCGGGGGGGGG G106T CSSDM19_R GCACGCAAGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	Q5SDM9_R	CCAAGTTCATTTTTCTTTTTTC	649A
USSDM10_H AAGEDAAGITGGATTATICATAATIGE USSDM11_R CTGCCCCATCCCCTTGTGTGCGACAG T68A OSSDM12_R CATAATIGGTTAAGGCATGGGGACGAG A27T OSSDM13_R TGAAATAGGAAAGAGGGACTGGGCAC A25G OSSDM14_R CATAATIGGTTAAGGCGAC A25G OSSDM13_R TGAAATGGTTAAGGCGAC A157C OSSDM14_F AAAATGGTTAAGGCGTGAGGAC C95G OSSDM15_F GGCGTGGGGCTTA G85A OSSDM15_R TGAATGGCCCACTCCCCAT C95G OSSDM15_R TGAATGGCCCACTCCCCAT G85A OSSDM15_R GGCGGTGAGGCTGTGGTGG G85A OSSDM15_R GCGCGGTTAAGCATTAATGGCTATAGGCATTAAGGCTTAAGCATGAGGCGCAGGC G106T OSSDM17_R GCGCGGTTATAGCATTAAGCATTAAGCGTTAAGCGCT A73T OSSDM18_R GCACAAGGGGGGAGGGGGGGGGGGGGGGGGGGGGGGGG	Q5SDM10_F	GCAATTTATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	G24A
CSSDM11_R CTGCCCATCCCCTCTTGTCTGCGA T68A CSSDM12_F AAAAAAGAAAATGAACTTGCTATC A27T CSSDM13_R CTAATTGCTTAAGGCGA A25G CSSDM13_F TAATTGCTTAAGGCGAC A157C CSSDM14_F AAAAATGCGTAAGGCTTGAGGAC A157C CSSDM14_R GCAAGCAATGCCGCGTA A157C CSSDM14_R GCAAGCATGCGGCGTA C95G CSSDM15_R TGACTGCCCATCCCCAT C95G CSSDM16_R ATCCCCATCTGTGTGGTAG G85A CSSDM17_R GCGGCGTTAAGGCGTTGATAGC G106T CSSDM18_R TTGTGTGCAGAGATTGCGGGCAGTC A73T CSSDM19_R CGGCCATTACGGGGGGCATC A73T CSSDM19_R CGGCAGATAGGGGTGGGGGCATC G5SDM12_R CSSDM20_R AGTCATTTTGCTTACGGGGGAGATC GCSSDM20_R CSSDM20_R AGTCATTTTTTTATTGCTC C46G CSSDM21_R GCACGACGGGGGATAGC T68G CSSDM22_R CCCACTTGTCGCGAGAA T05A CSSDM23_R AAGGCATTGTGCAAGGGATTGGGTTAAGGGTTGC T05A CSSDM24_R CCCACTTGTCGCGAGAGGGGTTGG T05A CSSDM25_R AGGCAGAGGAGGGGTGGC T06A CSSDM24_R CACCAACGCCTAACTGCC T05A CSSDM25_R TTATTTACGCTTAAGGGATTGGCTTAACGC T105A CSSDM25	Q5SDM10_R O5SDM11_F		
CSSDM12_FAAAAAASAMAATGAACTTGGCTTATCA27TQSSDM12_RCATAATTGCTTTAAGGCGA25GQSSDM13_RTAAATTGCTTTAAGGCGAA157CQSSDM14_RGCAAGCAATGCGGGCGTTAC95GQSSDM15_RTGAAAAAAGGAATGACTTGGC95GQSSDM15_RGCAGCCAATGCCGCCCCCCCCATC95GQSSDM15_RGGGGGAGTGAGCCGTTGGTGGG85AQSSDM17_FATTGCTTGCGACAGCG106TQSSDM17_FATTGCTTGCGACAGCCCTATCGGG106TQSSDM19_RCCACCAAGGCGTGATCGGG106TQSSDM19_RCCACCAAGGCGTGGTGGGA73TQSSDM19_RCCGGGACATTCGTGGC46GQSSDM21_RGCACCACAGGGGATAGGGGT68GQSSDM21_FGATGGGCAGTCGGGGGAGGGGGT68GQSSDM22_RCCCACTCTGGTGCCCCTGGGCTAAGGCCTTACGGCT105AQSSDM23_RAAGGCAGTGGGCGCAGTCGGGT105AQSSDM24_RCCCACTCTGGGCATAAGCCCTTGGT105AQSSDM24_RCCCACTCTGGGCTAAGCCGTGGGCTGGT105AQSSDM24_RCCCACTGTGGTGCCGCTGT105AQSSDM24_RCCCACTGTGGTGCGCTGCTGT105AQSSDM24_RCCCATCTGTGCGCATTAAGCCTTACAGGCTTATCA14GQSSDM24_RCCCATCTGTGCGCATTAAGCCTTACGGTTATCGGCTTATCG133AQSSDM25_RTTTATTACGCGCGATTGCAGGCG169AQSSDM26_RCTTACTTTAGGATTTGCAGGCG169AQSSDM27_RCTTATTTAGCGTTGAAGACTTGGCAGGGG169AQSSDM27_RCTTATTTAGCGCTTGCAGGCG169AQSSDM27_RTTAGGCGTGGTCGTCT175CQSSDM27_RCTTATTTAGGCGTTGAAGAGCTTGGCGGGG169AQSSDM28_R <td>Q5SDM11_I</td> <td>CTGCCCCATCCCCtTCTTGTCTGCGA</td> <td>T68A</td>	Q5SDM11_I	CTGCCCCATCCCCtTCTTGTCTGCGA	T68A
CSSDM12_R CATAANTGCTTAAGGCG A251 CSSDM13_F TAAATGCTTAGGCAAGAATGAGCTIGG A25G CSSDM14_F AAAATGCTTCCAAGTTAGCGTGAAGAATTAGC A157C CSSDM14_R GCAGCAAGCAGCGCGCTTA C95G CSSDM15_F GGCGTTGGTGTTATTAAGCGC C95G CSSDM16_F GGGGGGGGCGTTGGTGC G85A CSSDM16_R ATCCCCATCTTGTCTGCGCACAG G85A CSSDM17_R GCGGCGTTAGTGAGTTAAGCTTAAGGCT G106T CSSDM18_F TTTATTATGCATTGAGGACAGC G106T CSSDM19_F CAAGATGGGGGGGGGGGGGGGG A73T CSSDM19_R TCTCCCACAGCATCTGG G46G CSSDM20_F TGGCTTACCGAGGGGGGGGGGGGGG T68G CSSDM21_F GATGGGGCAGGACAGGGGGTGGGGGGGGGG T82A CSSDM22_F GATGGGGCAGGCAGGACGGGGTGG T82A CSSDM21_F GACGGCGGCGCTCAGCAGGCGTGGGGGGGGGGGGGGGGG	Q5SDM12_F	AAAAAAAGAAtAATGAACTTGGCTTATC	۸ 07 Τ
CSSDM13_FTGAMAMAGGAAATGAGCTIGGA25GCSSDM14_FAMAATGCTTAGGCGTGATTAGCGTTGAGAGAATTAGCA157CCSSDM14_RGCAAGCAATGCGGCGTTAC95GCSSDM15_FGCGCGTGGTGGTTATTTTATGGCC95GCSSDM16_RTGCCCCATCTGCGTGTGCG85ACSSDM17_FATGCTTGCGAGAAGTTAATGCTAAATGCTATAACGCCG106TCSSDM18_FTTTATTATGCAGGAGAATTCGCAAGGCGG106TCSSDM19_RCAGCCAACGCCTAATGCATTAATGCTATAACGCCG106TCSSDM19_RTCTGCGACAGATTCGTGGA73TCSSDM19_RTCTGCGACAGATTCGTGGC46GCSSDM20_RAGTTCATTTTGTGGGACAAGCT68GCSSDM21_FGCAGGCGGCGTGGGGGGGGGGGGGGGT68GCSSDM21_FGCAGGACAGAGGGGGGGGGGGGGGGGGGGGGGGGGGGG	Q5SDM12_R	CATAAATTGCTTTAAGGCG	RZ/1
USSDMI14_F AMAATTOTCOLONGTIGAGGATATOGC A157C OSSDM14_F GAAGAATCCOGGGTTA C95G OSSDM15_R GGGCAGTCAGCGTGAGAGATTAGGC C95G OSSDM16_R ATGCCCCATCTTGTGTGCGCAG G85A OSSDM17_F ATGCTTGCGACAG G85A OSSDM17_R GGGGCAGTCAGCGTTATAGGATTAGG A148G OSSDM17_R GCGGCGTTATAGGCATTAATG G106T OSSDM18_R GTTATTAGCGATTAATGCTTATAGGC G106T OSSDM19_R CTGCGGACGATCCACATGCATGC A73T OSSDM20_F TGGCTTATCGGAGGGATCGTGC A73T OSSDM20_F TGGCTTATCGGAGGGATCGGG T68G OSSDM21_R GATGGGGGAGGGGGG T68G OSSDM22_F GATGGGGCAGGCAGGCAGGCAGGGGGGGG T82A OSSDM23_R AAGCAATTGCTGGGACAGG T105A OSSDM24_F CTTATTAGGCGCTCCT A14G OSSDM24_F CTTATTAGGCCACTAATGCATTAATGCTTATAAGG T105A OSSDM24_F CTTATTAGGCCACTAATGCATTAATGCTTATAAGG G133A OSSDM24_F CTTATTAGGCCATTAATGCATTAAGGCTGCTC G133A OSSDM24_F CTTATTAGGCGATTAGCCTGC G133A OSSDM25_F TGGCTATAGCCATAAT	Q5SDM13_F	TGAAAAAAAGGAAAATGAACTTGG	A25G
AISTONIAL R GCAGCAAGACATGCCGCGGTTA GSSDM15_F GCGCTTGGTGGTGTTTATTAATGC GSSDM16_F GGGCAGTCAAGCCTTGGTGC GSSDM16_F GGGCAGTCAAGCCTTGGTGC GSSDM17_F GGGCCATCCAGCCGTGGTGC GSSDM17_F GCGCGCTTATAGCCATTAGCATTAATGC GSSDM17_F GCGCGCTTATAGCGCTTGATGCG GSSDM17_F GCGCGCGTGATAGCATTTAATGCTTAATGCTTATACGCC GSSDM18_F GCACCAACGCCGGGGCAGTC GSSDM19_F CCAGAGTGGGGGGGGGCAGTC GSSDM19_F CCAGAGTGGGGCAGTCC GSSDM20_F GGSCTTATCCGAGGAATCGTG GSSDM20_F GGCGTTATCCGAGGAATCGTG GSSDM21_F GCAGACAAGGGGGTGGGG GSSDM21_F GCAGACAAGGGGGTGGGG GSSDM22_F GCAGACAAGGGGGTGGGGCAGTC GSSDM22_F GCAGACAAGGGGGTGGGGCAGTC GSSDM22_F GCCAGCTGGGCCAGC GSSDM22_F GCCAGCTGGGCCAGC GSSDM22_F GCCAGCCGGGCTGCT GSSDM23_R AAGCCACGCGGGGCTGC GSSDM24_F CCTTTATTAGGCGCGAAGAGGGGCTTGA GSSDM24_F CCTTTATTAGGCGCGATAGGCA GSSDM24_F CCTTTATTAGGCGCGCTTGC GSSDM24_F CGTTTATAGCGCGCTTGACTC GSSDM24_F CGTTTATAGCCGGCTTAAGGCTTAAATGCTTTATCC GSSDM24_F CGTTTATAGCCGCGATTGGCTC GSSDM24_F CGTTTATAGCGCGCTTGACTCG GSSDM24_F CGTTTATAGCGCGTTTGCTGCGCAG GSSDM24_F CGTTTATAGCCGGCTTGACTCC GSSDM25_F TGCTTTATAGCCGCATTGGCTCC GSSDM26_F CGTTGAGAACTTGCGCCTCC GSSDM26_F CGTTGAGGACTTGCCTCC CGSDM26_R CGTTGAGGACTTGGCGCTTGC GSSDM27_F AGTAGCGCGTTGGTTGCGCC CGSDM26_R CGTTGAGGACTTGCTGCA CGSDM27_F TTGAGAATTTGCCAGGCTTGACTGC CGSDM28_R AGCATTTATGCCGGGTTGGTCC CGSDM28_R AGCATTTATGCCTGGGTGGGGG CTC GSSDM28_F TTTACCCGGGTTGGTTGC CGSDM28_R AGCATTTATGCCTGGGTGGGGG CTC CGSDM28_F CGGCAAGACGCGTTGGTTGC CGSDM28_R AGCATTTATGCCGGGTGGGGG CTC CGSDM28_R AGCATTTATGCCGGGTGGGGG CTC CGSDM28_R CGCAAGACGCGTGGTGCCTC CTC CGSDM28_R CGCAAGACGCGGGTTGGCTCC CTC CGSDM28_R CGCAAGACGCGGTTGCTCC CTC CGSDM28_R CGCAAGACGCGGGTGGGTCCC CTC CGSDM28_R CGCAAGACGCGGTTGCTCC CTC CTC CGSDM28_R CGCAAGACGCGGCTGCTCC CTC CTC CTC CTC CTC CTC CTC	Q55DM13_R O5SDM14_F		
QSSDM15_FGGCGTTGGTGgTTATTTATGGCC95GQSSDM15_RTGACTGCCCATCCCCATG85AQSSDM16_FATCCCCATCTTGTCTGCGACAGG85AQSSDM17_FATTGCTTGCAGAAGCATTAGTGGA148GQSSDM17_RGCGCGGTTATAAGCATTATATGA148GQSSDM17_RGCGCGGTTATAAGCATTATATGG106TQSSDM19_FTTTATTATGTGGGCACAGTCA73TQSSDM19_RTCTGCGACAGGCTGGGGCAGTCA73TQSSDM20_FTGGCTATCGAGGATCGGGCG6GQSSDM21_FGCACAACAGGGGGAGGGGT68GQSSDM22_RGATCATTTGTGGGACAGGT82AQSSDM22_FCACGAGCTGCGCT82AQSSDM22_RCCCATCTTGTCTGCGCACAGT105AQSSDM23_RAAGCGACGTGCGCT105AQSSDM24_FCTTTATTAAGGCAGAATAGCCTTGCT105AQSSDM24_RCACCAACGCTGACTGCT105AQSSDM24_RCACCACGCCTGACTGCT175CQSSDM25_FTGCTTATACGCGGATTAGTGAT175CQSSDM26_FCGTTGAAGAACTTAGCCATTAATAGCT175CQSSDM27_FAGTGAGTTAAGCAGTTAGACTTGCG169AQSSDM27_FAGTGAGTTAAGAATTAGCAGCC137AQSSDM28_RAGCATTAATGCATTGAAGCC137AQSSDM28_RAGCAGTTGGGGATTGGGG169AQSSDM28_RAGCAGTTGGGGATTGGGC137AQSSDM28_RAGCAGTTGATGCATTGCAC137AQSSDM28_RAGCAGTTGATGCATGCAGGGGC137AQSSDM29_RGCAGAACAAGGGGATGGGGC137AQSSDM29_RGCAGAATAGCGGGATTGGGGCC137AQSSDM29_RGCAGAACAAGGGGATGGGGC137AQSSDM29_RGC	Q5SDM14_I	GCAAGCAATGCGGCGTTA	A157C
OSSDM15_RTGACTGCCCCATCCCCATOSSCIQSSDM16_FGGGGCAGTCAGGCGTTGGTGGCG85AQSSDM16_RATCCCCATCTTGTGTGCGACAGA148GQSSDM17_FATTGCTTGCAGAAATTTCAAAGTTTAATGA148GQSSDM18_FTTATTAATGCATCAATGCATTAATGCTTATAACGCCG106TQSSDM19_RGCACCAACGCCTGACTGCA73TQSSDM19_RTCGCGACAGACTCCTGGC46GQSSDM2_FTGGCTTATCCGAGGAATCCTGCC46GQSSDM2_RAGTCATTTTCTTTTTTCATAATTGC46GQSSDM2_RGCAGACAAGgGGGGATGGGGT82AQSSDM2_RGACAAAGGGGCGTGCGACGT82AQSSDM2_RCCCATCTTGCGCGACAAGT82AQSSDM2_RCCCATCTGCGCGACAGT05AQSSDM2_FTGTTATAGCGGTCCCT05AQSSDM2_RCCCATCTTGCGCACAGT105AQSSDM2_RCCCATCTTGCTGCGCACAG133AQSSDM2_RCTTTATTAGCGCGCATTGATGGT175CQSSDM2_RCGCCACTTGCTGCGACAGCCG169AQSSDM2_RCTTATTTAGCGTTAAGGCTTGCAC137AQSSDM2_RCTTACTTGAGGGAATTGCTGCAC137AQSSDM2_RCTTACTTGAGGGTGGGGGT68CQSSDM2_RCTTACTTGAGGATTGCAGCC137AQSSDM2_RAGCATTAGCGTGAAGGGT68CQSSDM2_RGCAGACAGGGGGATGGGT68CQSSDM2_RGCAGACAGGGGGATGGGT68CQSSDM2_RGCAGACAGGGGGATGGGGT68CQSSDM2_RGCAGACAGGGGGATGGGT68CQSSDM2_RGCAGACAGAGGGGATGGGT68CQSSDM2_RGCAGACAGAGGGGATGGGT68CQSSDM2_RGCAGACAGAGGGGATGGGG <td< td=""><td>Q5SDM15_F</td><td>GGCGTTGGTGgTTTATTTAATGGC</td><td>C05G</td></td<>	Q5SDM15_F	GGCGTTGGTGgTTTATTTAATGGC	C05G
QSSDM16_FGGGGCAGTCAAGCGTTGGTGCG85AQSSDM17_FATGCTCATGTGGCGACAGA148GQSSDM17_FGCGCGGTTATAAGCATTTAATGA148GQSSDM18_FTITATTATAGCACAATGCATTAATGCTTATAGCCCG106TQSSDM18_FCACCAAGCGCTGACTGCA73TQSSDM19_FCAAGATGGGGITGGGGCAGTCA73TQSSDM20_FTGGCTTATCCGAGGAATCGTGCC46GQSSDM20_RAGTCATTTTTTTTTTTTTTTTTTATAGCGCCT68GQSSDM21_FGCAGACAAAGAGGGGATGGGGT68GQSSDM22_FGAGGGCGAGCAGCAGCGCTGGT82AQSSDM22_FGAGGGCGAGCAGCAGCGGGTGGGT82AQSSDM23_FAAGCGACTTGCGGCAAGAT105AQSSDM24_FCTTATTATAGCGCTGACTGCTT105AQSSDM25_FTGCTTATACCCGCATGCTGCT175CQSSDM25_FTGTTGAGAAATTGCTTAAAGGT175CQSSDM26_FCGTTGAAGAACTTGCCTTCT175CQSSDM26_FCGTTGAAGAACTTGCCTTCT175CQSSDM27_FAGTGGGGAGAGTGGTGCGG169AQSSDM27_FTTAATGCGTGAAGAATTAGCTTAAAGGG169AQSSDM28_FTTAAGCGTAAAGACTAGCC137AQSSDM28_FTAAACGCGGAATTGCTTGCAC137AQSSDM28_FTAAGCGTTAAAGCAGGGGGGGGT68CQSSDM29_FGCAGAACAAGAGGGGATGGGGG68CQSSDM29_FGCAGACAAGAGGGGGGGGGGG68CQSSDM29_FGCAGACAAGAGGGGATGGGGG169AQSSDM29_FGCAGACAAGAAGGGGGATGGGGG168CQSSDM29_FGCAGACAAGAAGGGGGGGGGGG168CQSSDM29_FGCAGACAAGAAGGGGGATGGGGG205DM29_FQSSDM29_FGCAGACAAGAAGGGGGA	Q5SDM15_R	TGACTGCCCCATCCCCAT	0350
USSDM15_F AltGCTGCAGAATTCTGAAGTTAG QSSDM17_F GCGGCGTTATAAGCATTTAATG QSSDM18_F TTTATTTATGCATCAATGCATTGAATGCTTATAACGCC QSSDM18_R GCACCAACGCCTGAATGCATTGAATGCTTATAACGCC QSSDM19_F CAAGATGGGGTGGGGCAGTC QSSDM20_F TGGCTTATCCGAGGAATCTGTC QSSDM20_R AGTCATTTTICTTTTTTTTTATTGATTAATTG QSSDM20_R AGTCATTTTICTTTTTTTTTTTTATAATTG QSSDM21_F GCAGAACAGGGGATAGGGG QSSDM22_F GATGGGGCAGCAGGGGGTGGG QSSDM22_R CCCACTTGTGTGCGCACAG QSSDM22_R CCCACTTGTGTGCGCACAG QSSDM23_F AAGGCAATTTGTGAAAAAAGAAAAATGAACTTGGCTTATC QSSDM24_F CTTTATTAAGGCCACAGTGCGTCC QSSDM25_R TGTTATACAGCCGCATTGCTGC QSSDM25_R TGTTATAACGCCGCATTGCTGC QSSDM25_R TGTTATAACGCCGCATTGCTGC QSSDM25_R TGTTATAACGCCGCATTGCTGC QSSDM25_R TGTATAACGCCGCATTGCTTC QSSDM25_R TGTATAACGCCGCATTGCTGC QSSDM25_R TGTATAACGCCGCATTGCTGC QSSDM25_R TGTATAACGCCGCATTGCTTGC QSSDM25_R TGTAAGCGTAAAGAATTTAGC QSSDM25_R TGAAGCGCGATTGCTGCATTAATAAAG <t< td=""><td>Q5SDM16_F</td><td>GGGGCAGTCAaGCGTTGGTGC</td><td>G85A</td></t<>	Q5SDM16_F	GGGGCAGTCAaGCGTTGGTGC	G85A
CostA148GQSSDM12_FGCGCGCTTATAAGCATTAATGQSSDM18_FTITATTAATGCATCAATGCATTAATGCATTAAATGCCTQSSDM19_FCAAGATGGGGTGGGGCAGTCQSSDM19_RTCTGCGACAGATTCCTGGQSSDM20_FTGGCTTATCCGAGGAATCGTGCQSSDM20_FTGGCTTATCCGAGGAATCGTGCQSSDM21_FGCACACAGAGGGGGATGGGGQSSDM21_FGCACACAGGGGGATGGGGQSSDM22_FGACAGATTCCTGGGATAAGCCQSSDM22_FGATGGGGCAGGCGTTGGQSSDM22_RACCACTTTGTCGCGACAGQSSDM23_FAAAGCAATTCTGGCACAGQSSDM24_FCTTTATTTAAGGCATCAATGCATTAAATGCTTATAACGQSSDM25_FTGGCTATACACCGCATGCTGCQSSDM24_FCTTTATTTAAGGCATCATGCATTAAATGCTTATAACGQSSDM25_FTGCTATAACCCGCATGCTGCQSSDM25_FTGCTATAACCCGCATTGCTGQSSDM25_RTTAATGCATTGATGCCTTCQSSDM26_FCGTGGAAGACTTAGCCTTCQSSDM26_FCGTGAAGAACTTAGCCTTCQSSDM27_FAGTGGCGAACTTAGCCTTCQSSDM26_FCGTGAAGAACTTAGCCTTCQSSDM27_FAGTTATACACTGATGCATTACGQSSDM27_FTTGAGAATTTTGCAGQSSDM27_FTTGAGAATTTGGCAGCQSSDM28_FTATAACGCCGGATTGCTGCQSSDM28_FTATAACGCCGGATTGCTGCACQSSDM29_RGCAGACAGGGGGATGGCGQSSDM29_RGCAGACAGGGGGATGGCGQSSDM29_RGCAGACAGGGGGATGGCGCQSSDM29_RGCAGACAGGGGGATGGCGC	Q5SDM16_R O5SDM17_F		
QSSDM18_FTTTATTTAATIGCATCAATGCATTAAATGCTTATAACGCCG106TQSSDM18_RGCACCAACGCCTGACTGCA73TQSSDM19_FCAAGATGGGGITGGGGCAGTCA73TQSSDM20_FTGGCTTATCCGAGGAATCCTGGC46GQSSDM20_RAGTTCATTTTTCTTTTTTCATAAATTGC46GQSSDM21_FGCAGACAAGAGGGGGATAGGCT68GQSSDM22_FGATGGGGCAGGACAGGCGTTGGT82AQSSDM22_FGATGGGCAGGACAGGCGTTGGT82AQSSDM23_FAAAGCCAATGCTGGCATGAAAAAAGAAAATGAACTTGGCTTATCA14GQSSDM24_FCTTTATTTGAAAAAAGGAAAATGAACTTGGCTTATCACGT105AQSSDM25_FTGCTTATACGACGCGTGCGTCCT105AQSSDM25_FTGCTTATAACGCCGCATTGCTTGG133AQSSDM26_RCAACTTGGGACAGCCTTCT175CQSSDM26_FCGTTGAAGAACTTAGCCTTCT175CQSSDM27_FAGTAGCGTAAAGATTTTGCAAGG169AQSSDM27_FTTGAAGCTAAGAATTTAGCCTTCC137AQSSDM28_RACACTTTAGCGTTGACGC137AQSSDM28_RACACTTTATGCGGGGGT68CQSSDM29_RGCAGACAAGGGGATAGTGCGCC137A	Q5SDM17_R	GCGGCGTTATAAGCATTTAATG	A148G
QSSDM18_RGCACCAACGCCTGACTGCCHOTQSSDM19_FCAAGATGGGGTGGGGCAGTCA73TQSSDM20_FTGGCTTATCCGAGATTCTGGC46GQSSDM20_RAGTTCATTTTTCTTTTTTCATAAATTGC46GQSSDM21_FGCACACAAGAGGGGATGGGGT68GQSSDM22_RGACAGATCCTGGGATAAGCCT82AQSSDM22_RCCCACTTGTCGCGACAGT82AQSSDM23_FAAGGCAGTGCGGCCTGGT82AQSSDM24_FCTTATTTAAGGCGCGACTGAGCGCTTGGT05AQSSDM25_FTGGCTGACAGCGCGTCGCT05AQSSDM25_RCACCACGCCGACTGCCCQSSDM25_RTTTATTAAGGCCGATTGATGCCTTAAATGCTTAAAGGT175CQSSDM25_RTTTAATGCATTGAGAATTTAGCCG169AQSSDM27_RTGGAGATTAGCCCTTCC137AQSSDM27_RTTGAGATTTTTGCAAGCC137AQSSDM28_RACCATTAATCGGGATAGTGCC137AQSSDM28_RGCACATTAATGCGGGGGGT68CQSSDM29_RGCACAAGACGGGGGGGGGGT68C	Q5SDM18_F	TTTATTTAATtGCATCAATGCATTAAATGCTTATAACGCC	G106T
Q5SDM19_FCAAGATGGGGTGGGGCAGTCA73TQ5SDM20_FTGGCGTAACCAGATTCCTGGC46GQ5SDM20_FTGGCTTATCCGAGGAATCTGTCC46GQ5SDM21_FGCAGACAAGAgGGGGATGGGGT68GQ5SDM22_FGATGGGCAGGCAGGCAGGCGGTGGT82AQ5SDM22_FGATGGGCAGGCAGGCAGGCGGTGGT82AQ5SDM23_FAAGCAATTCTGTGGAAAAAAGAAAAAGAAAATGAACTTGGCTTATCA14GQ5SDM23_FAAGCCGCGGCGGCGCTCT105AQ5SDM24_FCTITTATTAAGGCATGACTTGATTAAATGCTTATAACGT105AQ5SDM25_FTGCCTATGACGCCGCG133AQ5SDM25_FCGCATGGCAATTGCTGT175CQ5SDM25_RTTTAATGCATTGACGCATTAAATGACTG169AQ5SDM27_FCGTGGAGAATTTTGCAAGG169AQ5SDM27_RTTGAGAATTTTGCAAGCC137AQ5SDM28_FTATAACGCCGGATGCTGCAAC137AQ5SDM28_RAGCATTTATGCATGATGCG169AQ5SDM28_RAGCATTTATGCATGGATGGCGG169AQ5SDM28_RAGCATTTATGCATGGATGGCGG169AQ5SDM28_RAGCATTTATGCATGGATGGCGG169AQ5SDM28_RAGCATTTATGCATGGATGGCGG169AQ5SDM28_RAGCATTTATGCATGGATGGCGG169AQ5SDM28_RAGCATTTATGCATGGATGGGGT68CQ5SDM29_RGCAGAAAGAGGGGATGGGGT68C	Q5SDM18_R	GCACCAACGCCTGACTGC	
QSSDM19_HTOTOGACAGATTCOTGGQSSDM20_FTGGCTTATCCGAGGAATCTGTCC46GQSSDM21_FGCAGACAAGAgGGGGATGGGGT68GQSSDM22_FGACAGATTCCTGGGGATAAGCCT82AQSSDM22_FCATGGGCAGAGCAGGGTTGGT82AQSSDM23_FAAGCCATTTGTGCACAGT44GQSSDM23_RAAGCCAGTTGGCTCCC45DQSSDM24_FCTTTATTTAAGGCGTCCTCT105AQSSDM25_FTGCTTATACACCGCATGCCG133AQSSDM25_FTGCTTATACACCGCATTGCTGCT175CQSSDM26_FCGTTGAAGAAATTTGGCCGTCCTCT175CQSSDM26_FCGTGAGAGAATTTAGCCGTTCT175CQSSDM26_FCGTGAAGAAATTTGCCATTAAATAAGG169AQSSDM27_FAGTACGCGGAATTGCTGCAC137AQSSDM28_FTATACGCCGAATTGCTGCAATTGATGCATTAATGCGCG169AQSSDM28_FTATACGCCGAATTGCTGCAATTGCAGGGGATTGCTGCAATTAATGCAGGGGGATGGCGGGGGGGG	Q5SDM19_F		A73T
GSDIMEQ_FNatrial cartra ca	Q55DM19_R		
Q5SDM21_FGCAGACAAGAgGGGGATGGGGT68GQ5SDM21_RGACAGATTCCTGGGATAAGCCT82AQ5SDM22_FGATGGGCAGACAGGGTTGGT82AQ5SDM23_FAAAGCAATTTGTGCACAGA14GQ5SDM23_RAAGCAGTGCGTCCTCCQ5SDM24_FCTTTATTTAAGGCATGACTGCATGACTT105AQ5SDM25_FTGCTATAACCCGATGCTGCG133AQ5SDM26_FTGCTTATAACCCGCATTGCTGG133AQ5SDM26_FCGTTGAAGAAATTTGGATGCCTTCT175CQ5SDM26_RCTACTTTAAGCATTAGATGCCTTCT175CQ5SDM27_FAGTTAGCGTTGAAGAATTTAGCGG169AQ5SDM27_RTTGAGGATTTATGCAGCQ5SDM28_FTATAACGCCGAATTGCTGCAC137AQ5SDM28_RAGCATTATAGCATGATGCG58DM28_RQ5SDM28_RAGCATTATAGCATGAGCG58DM28_RQ5SDM29_RGCAGACAAGACGGGGATGGCGT68CQ5SDM29_RGACAGATTCCTGGGATAAGCCG169A	Q5SDM20_I	AGTTCATTTTTCTTTTTTCATAAATTG	C46G
QSSDM21_RGACAGATTCCTGGGATAAGCCTBGGQSSDM22_FGATGGGCAGaCAGGGGTTGGT82AQSSDM22_RCCCATCTTGTCTGCGACAGA14GQSSDM23_FAAAGCAATTTgTGAAAAAAGAAAAGGAACTTGGCTTATCA14GQSSDM24_FCTITATTTAAGGCATCAATGCATTGAATGCATTAAATGCTTATAACGT105AQSSDM24_RCACCAACGCCTGACTGCCG133AQSSDM25_FTGCTTATAACGCCGATTGCTGG133AQSSDM26_FCGTTGAAGAACTTAGCCGTTCT175CQSSDM26_RCTACTTTGAGAATTTGCAGG169AQSSDM27_FAGTTAGCGTTGAAGCC137AQSSDM28_FTATAACGCCGAATTGCTGCAC137AQSSDM28_RAGCATTATAATGCATTGATGCG68CQSSDM29_RGACAGATTCTGGGATAGCCT68C	Q5SDM21_F	GCAGACAAGAgGGGGATGGGG	TepC
Q5SDM22_FGATGGGCAGaCAGGCGTTGGT82AQ5SDM22_RCCCATCTTGTCTGCGACAGA14GQ5SDM23_FAAAGCAATTTGTGAAAAAAGAAAAGGAACTTGGCTTATCA14GQ5SDM23_RAAGCCGTGCGTCCTCT105AQ5SDM24_FCTTTATTTAAGGCATCAATGCATTAAATGCTTATAACGT105AQ5SDM25_FTGCTTATAACGCCGCATTGCTGG133AQ5SDM26_FCGTTGAAGAACTTAGCCCTTCT175CQ5SDM26_RCTTAACTTGAGCCCTTCT175CQ5SDM27_FAGTTAGCGTTAAAGAATTTAGCAG169AQ5SDM27_RTTGAGGAATTTGCTGCAC137AQ5SDM28_FTATAACGCCGAATTGCTGCAC137AQ5SDM28_RAGCATTATATCGATGCATGCAG52DM28_RQ5SDM29_FGCAGACAAGACGGGATGGCGT68CQ5SDM29_RGACGATTACTCTGGGATAAGCCG169A	Q5SDM21_R	GACAGATTCCTGGGATAAGCC	1000
QSSDM22_R CCCATCHIGE/GEGACAG QSSDM23_F AAAGCAATTIGTGAAAAAAGAAAAGGAAAATGAACTIGGCTTATC A14G QSSDM23_R AAGCCAATTIGTGAAAAAAGAAAAGGAAAATGAACTIGGCTTATC A14G QSSDM24_F CTITATTIAAGGCGTCAATGCATTGAATGCATTAAATGCTTATAACG T105A QSSDM25_F TGCTTATAACGCCGCATTGCTTG G133A QSSDM26_F CGTTGAAGAACTTAGCCCTTC T175C QSSDM26_R CTAACTITGAGAACTTAGCCCTTC T175C QSSDM26_R CTAACTITGAGAATTTIGCAAG G169A QSSDM27_F AGTTAGCGTTAAAGACC G169A QSSDM28_F TATAACGCCGGAATTGCTTGCA C137A QSSDM28_R AGCATTATAGCATTGATGC G137A QSSDM29_F GCAGACAAGACGGGGATGGCG T68C QSSDM29_R GACAGATTCCTGGGATAGCC T68C	Q5SDM22_F	GATGGGGCAGaCAGGCGTTGG	T82A
GSSDM23_R AAGCCAATTIGTGAAAAAAGAAAAATGAAAATGAAATGAA	Q5SDM22_R O5SDM23_E		A1//G
QSSDM24_F CTITATITAA3GGCATCAATGCATTAAATGCTTATAACG T105A QSSDM24_R CACCAACGCCTGACTGCC G133A QSSDM25_F TGCTTATAACaCCGCATTGCTTG G133A QSSDM25_R TITAATGCATTGATGCCATTAAATAAG T175C QSSDM26_R CTAACTTTGAGAACTTAGCCGTC T175C QSSDM27_F AGTTAGCGTTAAAGAATTTAGCA G169A QSSDM27_R TTGAGAATTTTGCAAGC C137A QSSDM28_R AGCATTATAGCATGATGC C137A QSSDM29_F GCAGACAAGACGGGGATGGGGG T68C QSSDM29_R GACGACTTCCTGGGATAGCC C137A	Q5SDM23 R		Alta
Q5SDM24_RcaccaacgcctgactgccQ5SDM25_FtgcttataacgccgattgcttgG133AQ5SDM25_RtttatgcattgatgccattaataaagT175CQ5SDM26_RcttaacttagcgattgatgccattgcttgT175CQ5SDM26_RcttaactttagcgattgatgccattgctgG169AQ5SDM27_FagttagcgttaaagaatttagccattgctgcaG169AQ5SDM28_FtatacgccggattgcttgcagC137AQ5SDM28_RagcatttagcattgatgcC137AQ5SDM29_FgcagattgcattgatgcT68CQ5SDM29_RgacagttgcattgatgcT68C	Q5SDM24_F	CTTTATTTAAaGGCATCAATGCATTAAATGCTTATAACG	T105A
Q5SDM25_F TGCTTATAACaCCGCATTGCTTG G133A Q5SDM25_R TTTAATGCATTGATGCCATTAAATAAAG TTAATGCATTGATGCCATTAAATAAAG Q5SDM26_F CGTTGAAGAACTTAGCCCTTC T175C Q5SDM26_R CTAACTTTGAGAATTTAGCAAG G169A Q5SDM27_F AGTTAGCGTTAAAGAATTTAGCA G169A Q5SDM28_F TATAACGCCGAATTGCTTGCA C137A Q5SDM28_R AGCATTAATGCATTGATGC C137A Q5SDM29_F GAGACAAGACGGGATGGGGG T68C Q5SDM29_R GACAGATTCCTGGGATAAGCC T68C	Q5SDM24_R	CACCAACGCCTGACTGCC	
Q5SDM25_H TITAATGCATTGGTCGCATTAAATAAAG Q5SDM26_F CGTTGAAGAACTTAGCCCTTC T175C Q5SDM26_R CTAACTTGAGGAATTTAGCATG G169A Q5SDM27_F AGTTAACGTTAAAGAATTTAGC G169A Q5SDM27_R TTGAGAATTTTGCAAGC C137A Q5SDM28_F TATAACGCGGAATTGCTTGCA C137A Q5SDM29_F GCAGACAAGACGGGATGGCG T68C Q5SDM29_R GACAGATTCTGCGGATAAGCC G169A	Q5SDM25_F	TGCTTATAACaCCGCATTGCTTG	G133A
Q5SDM26_R CTAACTITGAGAATTITIGCAAG TT/30 Q5SDM27_F AGTIAGCGTTAAAGAATTITAGCA G169A Q5SDM27_R TTGAGAATTITTGCAAGC C137A Q5SDM28_F TATAACGCCGaATTGCTTGCA C137A Q5SDM29_F GCAGACAAGACGGGGATGGCG T68C Q5SDM29_R GACAGATTCCTGGGATAAGCC G62	USSUM25_K	TTTAATGCATTGATGCCATTAAATAAAG	T175C
Q5SDM27_F AGTTAGCGTTAAAGAATTTAGC G169A Q5SDM27_R TTGAGAATTTTTGCAAGC G169A Q5SDM28_F TATAACGCCGaATTGCTTGCA C137A Q5SDM28_R AGCATTTAATGCATTGATGC G5SDM29_F G5SDM29_F GCAGACAAGACGGGATGGGG T68C Q5SDM29_R GACAGATTCCTGGGATAAGCC G6C	Q5SDM26 R	CTAACTTGAGAACTTAGCCCTTC	
Q5SDM27_RTTGAGAATTTTTGCAAGCQ5SDM28_FTATAACGCCGBATTGCTTGCAC137AQ5SDM28_RAGCATTTAATGCATTGATGCQ5SDM29_FGCAGACAAGACGGGGATGGGGT68CQ5SDM29_RGACAGATTCCTGGGATAAGCC	Q5SDM27_F	AGTTAGCGTTaAAGAATTTAGC	G169A
Q5SDM28_FTATAACGCCGBATTGCTTGCAC137AQ5SDM28_RAGCATTTAATGCATTGATGCQ5SDM29_FGCAGACAAGACGGGGATGGGGQ5SDM29_RGACAGATTCCTGGGATAAGCC	Q5SDM27_R	TTGAGAATTTTTGCAAGC	
QSSDIVIZ6_H AGCATTTAATGCATTGATGC QSSDM29_F GCAGACAAGAcGGGGATGGGG T68C QSSDM29_R GACAGATTCCTGGGATAAGCC T68C	Q5SDM28_F	TATAACGCCGaATTGCTTGCA	C137A
Q5SDM29_R GACAGATTCCTGGGATAAGCC	QSSDIVIZU_K QSSDM29 F	AGCATTTAATGCATTGATGC	T68C
	Q5SDM29_R	GACAGATTCCTGGGATAAGCC	

Lower case letter sin the primer sequences indicate the targeted mutation to incorporate.

Supplementary Table 2. Reference set

ID	category	WT	Substitution	Position
G24A	missense	G	А	24
A25G	missense	А	G	25
A27T	missense	А	Т	27
T41G	nonsense	Т	G	41
C46G	missense	С	G	46
G49A	missense	G	Α	49
A60C	synonymous	А	С	60
T68G	missense	Т	G	68
A73T	missense	А	Т	73
G78A	synonymous	G	А	78
T68A	missense	Т	А	78
T82A	missense	Т	A	82
G85A	missense	G	A	85
C95G	missense	С	G	95
G106T	missense	G	Т	106
A148G	missense	А	G	148
C156G	synonymous	С	G	156
A157C	missense	А	С	157
G70A,G71C	missense	G,G	A,C	70,71
G124T,C125G	missense	G,C	T,G	124,125
G124A,C125G	missense	G,C	A,G	124,125
G124A,C125A	missense	G.C	A,A	124,125

Supplementary Table 3. Validation set

ID	category	WT	Substitution	Position
A14G	missense	А	G	14
T68C	missense	Т	С	68
T105A	missense	Т	А	105
G133A	missense	G	А	133
C137A	missense	С	А	137
G169A	missense	G	А	169
T175C	missense	Т	С	175
A25G,G133A	missense	A,G	G,A	25,133
G133A,T175C	missense	G,T	A,C	133,175

Supplementar	y Table 4. Coefficie	nts for linear mod	dels to predict GFP si	gnals from enri	ichment scores
Expression	Intercent	Sv 01	Sv og trans	adi- B2	n-value

Expression	Intercept	Sv,01	Sv,o2_trans	adj- R2	p-value	
	α	β	γ			
Low	7.23***	-0.51***	0.52***	0.96	5.1e-15	_
High	4.56***	-2.23***	-1.64	0.84	3.6e-9	
A						_

Significance code P<1e-4 ***

CI fraction folded

Supplementary Table 5. Covariance of Enrichment scores Sv,o1 and Sv,o2, trans				
Expression level	Rep1	Rep2	Rep3	
Low	-1.48	-1.95	-1.85	
High	-0.16	-0.22	-0.12	

Supplementary Table 6. Coefficients to map replicates 1 and 3 to replicate2

	α1	β1	α3	β3	
Low	1.5±0.02	0.9±0.02	1.3±0.02	0.9±0.002	
High	1.7±0.03	0.8±0.03	0.7±0.04	1.1±0.05	

Supplementary	Table 7	Configuration	states and the	onoray torma	from Ackoro	model
Supplemental	y lable 1.	Connyuration	states and the	energy terms	S IIUIII ACKEIS	mouer

CSi	Occupied OR	CI dimer (N <i>i</i>)	Downstream gene	Total energy (ΔG_{CS})
1	_	0	ON	0
2	OR3	1	ON	ΔG_3
3	OR2	1	OFF	ΔG_2
4	OR1	1	OFF	ΔG_1
5	OR2, OR3	2	OFF	$\Delta G_2 + \Delta G_3 + \Delta G_{co}$
6	OR1, OR2	2	OFF	$\Delta G_1 + \Delta G_2 + \Delta G_{co}$
7	OR1, OR3	2	OFF	$\Delta G_1 + \Delta G_3$
8	OR1, OR2, OR3	3	OFF	$\Delta G_1 + \Delta G_2 + \Delta G_3 + \Delta G_{co}$

Supplementary Table 8. Pa	rameters for CI model, from the literature	
K _a	5×10^{7}	Ackers, 1982
[OR]	10 ⁻⁹ mole	Ackers, 1982
ΔG_1	-11.7 kcal	Ackers, 1982
ΔG_2	-10.1 kcal	Ackers, 1982
ΔG_3	-10.1 kcal	Ackers, 1982
ΔG_{co}	-2 kcal	Ackers, 1982

0.993

Huang, 1995

Supplementary Table 9. Parameters estimated for modeling regulatory interaction		
[CI _{E,low}]	$5.5 \times 10^{-8} M$	Calculated based on GFP _{wt,low}
[CI _{E,high}]	$8.4 \times 10^{-7} M$	Calculated based on GFP _{wt,high}