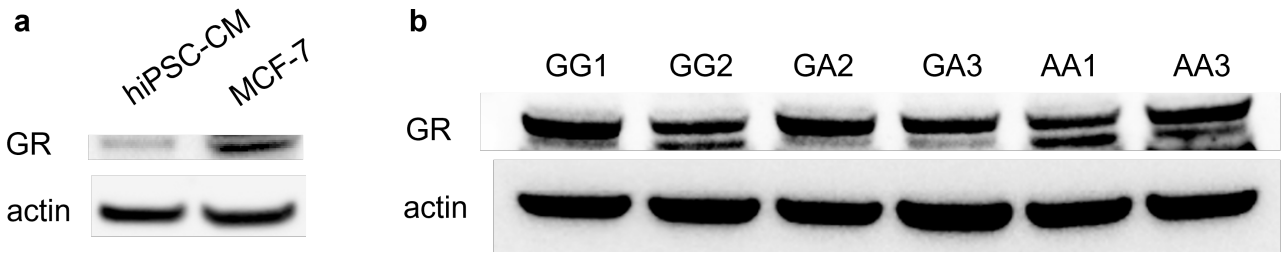
**Supplementary Information**




**Supplementary Figure 1. Glucocorticoid receptor (GR) expression levels in hiPSC-CMs and MCF-7 breast cancer cells. a-b,** GR expression levels were analyzed by western blotting using whole cell lysate from hiPSC-CMs of different *rs28714259* genotypes and MCF-7 breast cancer cells. At least three independent experiments were repeated with similar results. Source data for suppl. fig 3a-b are provided as a Source Data file.

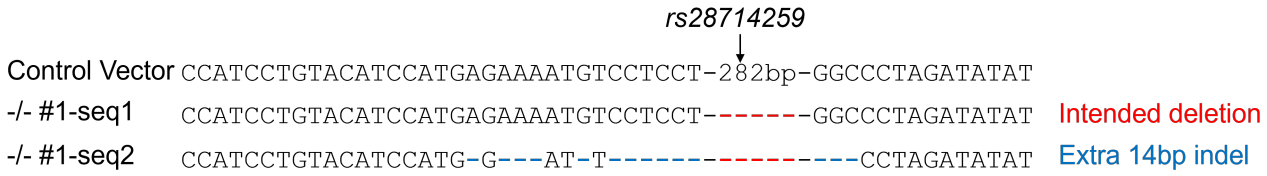
Major (G) AGAAACA TGTTTTG
1 2 3 4 5 6 7 5 6 7 8 9 10 11

| | | |
|---|---|---|
| Dissimilarity | 3.76% | 3.76% |
| RE equality | 0.01501 | 0.01501 |
| RE query | 0.06477 | 0.06477 |

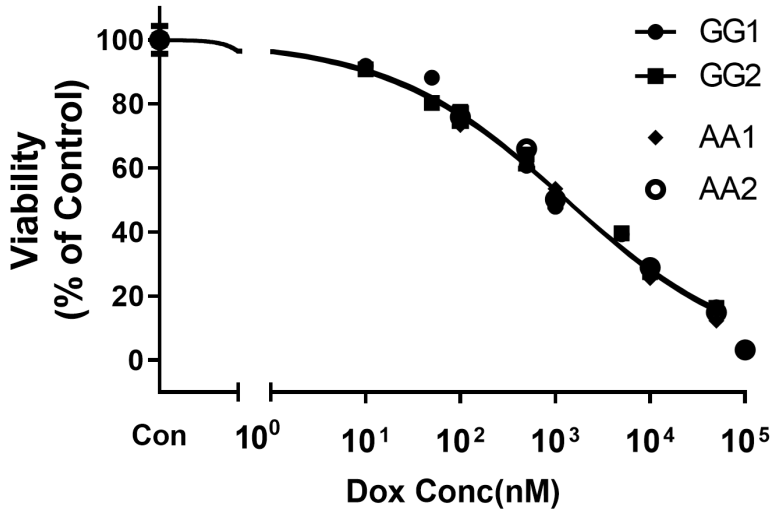
Minor (A) AGAAACA TGTTTTA
1 2 3 4 5 6 7 5 6 7 8 9 10 11

| | | |
|---|---|---|
| Dissimilarity | 3.76% | N/A |
| RE equality | 0.01501 | N/A |
| RE query | 0.06477 | N/A |

**Supplementary Figure 2. PROMO *in silico* prediction of GR binding at *rs28714259* region.** Two overlapping GR binding half sites are predicted by PROMO 3.0.2. *rs28714259 (position 11)* and are highlighted in yellow. Dissimilarities to canonical GRE are shown for major and minor allele genotypes.




**Supplementary Figure 3. Deep sequencing of Crispr-Cas9 mediated genomic deletion of rs28714259 region in hiPSC-CMs.** 500bp amplicon surrounding rs28714259 deletion site was sequenced via Amplicon-EZ by Azenta. One homozygous deletion clone has the intended deletion in one copy (seq1) and an extra 14bp indel in the other copy (seq2). The 14bp indel does not contain any known GRE or SNPs in LD with *rs28714259*.




**Supplementary Figure 4. Characterization of doxorubicin-induced cell death in hiPSC-CMs.** Cell viability of hiPSC-CMs was assessed by measurement of ATP levels using CellTiter-Glo® after 24 h of doxorubicin treatment. Source data are provided as a Source Data file.

**Supplementary Table 1 (A-B). Genes and pathways differentially regulated by doxorubicin treatment over vehicle control in cardiomyocytes. (A)** Expression fold change of known doxorubicin response genes in cardiomyocytes. Tests for differential expression with an FDR < 0.05 (Benjamini-Hochberg corrected) were considered statistically significant. **(B)** Top pathways differentially regulated by doxorubicin treatment identified by Ingenuity Pathway Analysis. Benjamini-Hochberg (B-H) adjusted p-values were calculated to account for multiple comparisons, and the B-H adjusted p-value < 0.05 was considered as statistically significant. Dox, doxorubicin.

*Supplementary Table 1A*

| Dox Target Genes | log2FC | FDR |
|---|---|---|
| TNFRSF10A | 4.95 | 6.52E-49 |
| TNFRSF10B | 2.43 | 6.60E-39 |
| TNFRSF10D | 3.91 | 1.78E-34 |
| TNFRSF10C | 3.53 | 1.71E-19 |
| FAS | 3.06 | 1.21E-16 |

*Supplementary Table 1B*

| Top Pathways | # Genes | *P*-value | Adjusted *p*-value |
|---|---|---|---|
| p53 Signaling | 36 | 3.98E-07 | 2.04E-04 |
| Role of BRCA1 in DNA Damage Response | 31 | 6.48E-07 | 2.04E-04 |
| Kinetochore Metaphase Signaling Pathway | 35 | 2.75E-06 | 5.76E-04 |
| Molecular Mechanisms of Cancer | 96 | 1.35E-05 | 1.78E-03 |
| Adipogenesis pathway | 41 | 1.41E-05 | 1.78E-03 |

**Supplementary Table 2 (A-B). Top genes and pathways differentially regulated between doxorubicin-only (DOX) and dexamethasone/doxorubicin combination (DD) treatment.** Tests for differential expression with an FDR < 0.05 (Benjamini-Hochberg corrected) were considered statistically significant. For IPA analysis, Benjamini-Hochberg (B-H) adjusted p-values were calculated to account for multiple comparisons, and the B-H adjusted p-value < 0.05 was considered as statistically significant.

*Supplementary Table 2A*

| Gene | ΔLog2FC | *P*-value (Dox) | FDR (Dox) | *P*-value (DD) | FDR (DD) |
|---|---|---|---|---|---|
| GJA4 | 4.17 | 2.02E-15 | 7.18E-14 | 1.62E-08 | 1.88E-07 |
| DAND5 | -3.36 | 1.06E-05 | 5.96E-05 | 2.71E-13 | 8.17E-12 |
| BEND5 | 3.15 | 1.71E-07 | 1.43E-06 | 6.56E-04 | 2.45E-03 |
| MIR145 | 3.09 | 2.98E-13 | 7.45E-12 | 6.60E-08 | 6.71E-07 |
| SPC25 | -3.04 | 4.48E-02 | 9.14E-02 | 6.85E-06 | 4.32E-05 |

*Supplementary Table 2B*

| Top Pathways | # Genes | *P*-value | Adjusted *p*- value |
|---|---|---|---|
| Breast Cancer Regulation by Stathmin1 | 57 | 3.93E-05 | 1.27E-02 |
| CREB Signaling in Neurons | 57 | 5.20E-05 | 1.27E-02 |
| Kinetochore Metaphase Signaling Pathway | 16 | 1.43E-04 | 2.33E-02 |
| cAMP-mediated signaling | 26 | 4.66E-04 | 5.70E-02 |
| G-Protein Coupled Receptor Signaling | 29 | 7.22E-04 | 7.07E-02 |

**Supplementary Table 3. Genes identified by Ingenuity Pathway Analysis in the GPCR/cAMP pathway differentially regulated between doxorubicin-only and dexamethasone/doxorubicin combination treatment.** Genes were ranked by their differences in expression fold change between combination and doxorubicin-only treatment groups (∆log2FC). Role of each gene as "activator" or "repressor" of the GPCR/cAMP pathway was based on the IPA analysis. Tests for differential expression or interaction with an FDR < 0.05 (Benjamini-Hochberg corrected) were considered statistically significant.

| Gene | ∆log2FC | *p*-value (Dox) | FDR (Dox) | *p*-value (DD) | FDR (DD) | Role | Impact on GPCR/cAMP |
|---|---|---|---|---|---|---|---|
| CHRM1 | 2.43 | 3.15E-05 | 1.58E-04 | 1.55E-03 | 5.19E-03 | activator | enhance |
| TBXA2R | 1.35 | 6.89E-03 | 1.85E-02 | 1.42E-02 | 3.49E-02 | activator | enhance |
| AVPR1B | 1.05 | 3.09E-03 | 9.16E-03 | 9.44E-05 | 4.45E-04 | activator | enhance |
| PDE1A | 0.79 | 9.64E-04 | 3.30E-03 | 1.59E-02 | 3.85E-02 | repressor | decrease |
| HTR2A | 0.78 | 1.62E-02 | 3.84E-02 | 2.13E-02 | 4.94E-02 | activator | enhance |
| PRKCG | 0.63 | 6.94E-08 | 6.37E-07 | 7.42E-09 | 9.21E-08 | activator | enhance |
| GRM6 | 0.5 | 3.18E-04 | 1.24E-03 | 1.39E-03 | 4.72E-03 | activator | enhance |
| RGS4 | 0.45 | 6.61E-07 | 4.90E-06 | 2.37E-06 | 1.67E-05 | repressor | decrease |
| PLCB2 | 0.43 | 5.63E-03 | 1.55E-02 | 1.66E-02 | 3.99E-02 | activator | enhance |
| ADRA1B | 0.39 | 3.21E-04 | 1.25E-03 | 3.13E-02 | 6.83E-02 | activator | enhance |
| ADCY8 | 0.38 | 1.13E-07 | 9.87E-07 | 2.09E-09 | 2.90E-08 | activator | enhance |
| PDE7B | 0.36 | 3.12E-04 | 1.22E-03 | 2.11E-02 | 4.90E-02 | activator | enhance |
| MAP2K1 | 0.32 | 1.21E-03 | 4.01E-03 | 6.12E-04 | 2.31E-03 | activator | enhance |
| ADRA2B | 0.31 | 3.92E-02 | 8.17E-02 | 1.64E-02 | 3.96E-02 | activator | enhance |
| RAPGEF4 | -0.34 | 2.30E-02 | 5.18E-02 | 9.46E-04 | 3.36E-03 | repressor | enhance |
| PDE9A | -0.35 | 7.23E-03 | 1.92E-02 | 3.43E-05 | 1.81E-04 | repressor | enhance |
| CNR2 | -0.35 | 1.36E-02 | 3.31E-02 | 1.71E-02 | 4.11E-02 | repressor | enhance |
| APLNR | -0.35 | 1.56E-03 | 5.02E-03 | 4.94E-03 | 1.41E-02 | repressor | enhance |
| AVPR1A | -0.37 | 1.26E-13 | 3.34E-12 | 5.17E-11 | 9.78E-10 | repressor | enhance |
| GRM8 | -0.37 | 1.21E-10 | 1.92E-09 | 1.96E-07 | 1.79E-06 | repressor | enhance |
| S1PR1 | -0.38 | 1.09E-12 | 2.50E-11 | 1.03E-18 | 7.99E-17 | repressor | enhance |
| ADORA1 | -0.39 | 1.81E-02 | 4.23E-02 | 3.80E-03 | 1.12E-02 | repressor | enhance |
| PDE3B | -0.41 | 8.02E-04 | 2.81E-03 | 4.59E-02 | 9.36E-02 | repressor | enhance |
| OPRD1 | -0.49 | 1.46E-15 | 5.37E-14 | 1.82E-14 | 6.67E-13 | repressor | enhance |
| DUSP9 | -0.64 | 9.78E-03 | 2.48E-02 | 1.32E-02 | 3.30E-02 | activator | decrease |
| RAPGEF3 | -0.66 | 1.33E-02 | 3.23E-02 | 6.57E-04 | 2.46E-03 | repressor | enhance |
| HTR6 | -0.87 | 1.80E-02 | 4.20E-02 | 1.21E-02 | 3.05E-02 | activator | decrease |
| SSTR3 | -1.29 | 2.76E-02 | 6.08E-02 | 9.45E-03 | 2.46E-02 | repressor | enhance |
| P2RY14 | -1.32 | 2.01E-03 | 6.26E-03 | 3.26E-05 | 1.74E-04 | repressor | enhance |

**Supplementary Table 4 (A-B). Top pathways differentially regulated by the *rs28714259* risk allele following (A) doxorubicin and (B) dexamethasone/doxorubicin combination treatment identified by IPA.** Benjamini-Hochberg (B-H) adjusted p-values were calculated in IPA to account for multiple comparisons, and the B-H adjusted p-value < 0.05 was considered statistically significant.

*Supplementary Table 4A*

| Top Pathways | # Genes | *P*-value | Adjusted *p*-value |
|---|---|---|---|
| Mitochondrial Dysfunction | 31 | 7.17E-17 | 1.62E-14 |
| Glucose metabolism | 6 | 6.27E-05 | 5.68E-03 |
| HER-2 Signaling in Breast Cancer | 15 | 3.43E-04 | 2.22E-02 |
| Sirtuin Signaling Pathway | 19 | 5.15E-04 | 2.92E-02 |

*Supplementary Table 4B*

| Top Pathways | # Genes | *P*-value | Adjusted *p*-value |
|---|---|---|---|
| Mitochondrial Dysfunction | 33 | 1.33E-16 | 3.22E-14 |
| Sirtuin Signaling Pathway | 26 | 3.86E-06 | 6.24E-04 |
| Huntington's Disease Signaling | 21 | 4.12E-05 | 5.00E-03 |
| Cardiac Hypertrophy Signaling | 32 | 2.27E-04 | 2.20E-02 |
| Glioblastoma Multiforme | 15 | 3.47E-04 | 2.40E-02 |

**Supplementary Table 5. Top genes differentially regulated by the *rs28714259* risk allele following dexamethasone/doxorubicin combination treatment**. Tx = Treatment. Tests for interaction with an FDR < 0.05 (Benjamini-Hochberg corrected) were considered statistically significant.

| Gene | Tx Log2FC | Interaction Log2FC | FDR |
|---|---|---|---|
| ASAP1 | 0.93 | -0.55 | 0.03383 |
| SLFNL1-AS1 | 3.46 | -2.05 | 0.03383 |
| HDAC4 | 1.46 | -0.84 | 0.03383 |
| HECTD4 | 1.31 | -0.60 | 0.04880 |

**Supplementary Table 6 (A-B). Genes in the cardiac hypertrophy signaling pathway differentially regulated by the *rs28714259* risk allele following dexamethasone/doxorubicin combination treatment identified by Ingenuity Pathway Analysis.** (**A**) Effect of the risk allele on gene expression and expected outcome on hypertrophy signaling. Role of each gene as pro- or anti-hypertrophic was based on the IPA analysis. Tests for interaction with an FDR < 0.05 (Benjamini-Hochberg corrected) were considered statistically significant. **(B)** Identified genes with intersection in canonical pathways regulating cardiomyocyte pathophysiology.

*Supplementary Table 6A*

| Gene | Treatment Log2FC (DD) | Interaction Log2FC | Interaction *P*-value | Interaction FDR | Pro-/Anti-hypertrophic | Variant impact on hypertrophy signaling |
|---|---|---|---|---|---|---|
| HDAC4 | 1.46 | -0.84 | 8.77E-06 | 2.60E-02 | Pro | Decrease |
| PLD6 | 3.88 | -1.89 | 4.30E-04 | 1.98E-01 | Pro | Decrease |
| IGF1R | 0.67 | -0.5 | 4.96E-04 | 1.98E-01 | Pro | Decrease |
| PDE10A | 0.63 | -0.57 | 1.36E-03 | 3.21E-01 | Pro | Decrease |
| EIF4EBP1 | -1.82 | 0.76 | 1.77E-03 | 3.23E-01 | Anti | Decrease |
| DIAPH2 | 0.2 | -0.67 | 2.53E-03 | 3.62E-01 | Pro | Decrease |
| PRKAR2B | -1.53 | 0.63 | 2.81E-03 | 3.70E-01 | Anti | Decrease |
| TG | 4.9 | -1.7 | 3.12E-03 | 3.76E-01 | Pro | Decrease |
| ITPR1 | 1.83 | -0.8 | 3.47E-03 | 3.84E-01 | Pro | Decrease |
| NFAT5 | 0.64 | -0.5 | 4.30E-03 | 4.18E-01 | Pro | Decrease |
| HDAC7 | 0.89 | -0.7 | 5.40E-03 | 4.41E-01 | Pro | Decrease |
| WNT10B | 3.98 | -2.14 | 8.88E-03 | 4.88E-01 | Pro | Decrease |
| WNT7B | 9.54 | -2.48 | 9.80E-03 | 5.03E-01 | Pro | Decrease |
| GNG7 | -0.8 | 0.63 | 1.28E-02 | 5.30E-01 | Anti | Decrease |
| HSPB1 | -0.5 | 0.84 | 1.29E-02 | 5.33E-01 | Anti | Decrease |
| RCAN1 | 1.64 | -1.2 | 1.45E-02 | 5.48E-01 | Pro | Decrease |
| ADCY7 | 0.75 | -0.62 | 1.51E-02 | 5.48E-01 | Pro | Decrease |
| RPS6KA5 | 2.66 | -0.52 | 1.69E-02 | 5.53E-01 | Pro | Decrease |
| WNT2B | 1.99 | -0.81 | 1.80E-02 | 5.53E-01 | Pro | Decrease |
| MAP2K6 | -2.99 | 0.7 | 1.94E-02 | 5.53E-01 | Anti | Decrease |
| ATP2A2 | -1 | 0.52 | 2.63E-02 | 5.86E-01 | Anti | Decrease |
| GNB3 | -0.08 | -0.75 | 3.03E-02 | 6.16E-01 | Pro | Decrease |
| FZD9 | 3.68 | -0.72 | 3.22E-02 | 6.25E-01 | Pro | Decrease |
| PRKCG | 5.58 | -1.66 | 3.27E-02 | 6.31E-01 | Pro | Decrease |
| NFATC1 | 0.08 | -0.56 | 3.59E-02 | 6.40E-01 | Pro | Decrease |
| NOTUM | 0.64 | 2.04 | 3.74E-02 | 6.46E-01 | Pro | Increase |
| FGFR2 | 2.12 | -0.53 | 3.86E-02 | 6.51E-01 | Pro | Decrease |
| RAP1B | 0.54 | -0.51 | 4.26E-02 | 6.63E-01 | Pro | Decrease |
| LIF | 2.93 | -0.73 | 4.71E-02 | 6.76E-01 | Pro | Decrease |
| MAPK3 | -1.29 | 0.57 | 4.84E-02 | 6.79E-01 | Anti | Decrease |
| TNFSF13B | 2.47 | -1.07 | 4.91E-02 | 6.82E-01 | Pro | Decrease |

*Supplementary Table 6B*

| Gene | Intersected pathway | Reference |
|---|---|---|
| HDAC4 | MAPK/ERK5 | Choi et al., Mol Cell 2012 |
| IGF1R | MAPK/ERK1/2/ERK5 | Nguyen et al., Reproduction 2007; Benito-Jardón, Cancer Research 2019 |
| PDE10A | GPCR/cAMP | Spiwoks-Becker et al, Neuroendocrinology 2011 |
| EIF4EBP1 | MAPK/ERK1/2 | Qin et al., Cell Cycle 2016 |
| DIAPH2 | GPCR | Lartey et al., Reproduction 2009 |
| PRKAR2B | GPCR/cAMP | Weise et al., Molecular Neurobiology 2019 |