
Supplementary Materials

Genome-wide association study identifies candidate loci associated with opioid analgesic requirements in the treatment of cancer pain

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Supplementary Table S1. Estimated systemic dose equipotent to 90 mg oral morphine (mg).

| Analgesics | Dose |
|---------------------------------------|------|
| Morphine (oral) | 90 |
| Morphine (intravenous, subcutaneous) | 30 |
| Oxycodone (oral) | 60 |
| Oxycodone (intravenous, subcutaneous) | 45 |
| Fentanyl (intravenous) | 0.9 |
| Fentanyl (transdermal) | 3 |
| Tapentadol | 300 |
| Tramadol | 450 |
| Methadone (oral) | 18 |
| Hydromorphone (oral) | 18 |
| Hydromorphone (intravenous) | 3.6 |

Supplementary Table S2. Top 10 candidate gene sets selected from gene-set analysis.

Model, genetic model in which candidate gene sets were selected by analysis; nGenes, number of genes in the data that are in the gene set; Beta, regression coefficient of the gene set; SE, standard error of the regression coefficient; p^a , adjusted p value for multiple testing.

| Model | Rank | Gene set name | nGenes | Beta | SE | p | p^a |
|-----------|------|--|--------|---------|----------|-------------|-------------|
| Additive | 1 | go_arginine_binding | 7 | 1.5697 | 0.36089 | 0.106308293 | 0.106308293 |
| Additive | 2 | go_sleep | 31 | 0.61055 | 0.15283 | 0.50337243 | 0.50337243 |
| Additive | 3 | boyault_liver_cancer_subclass_g6_up | 66 | 0.43693 | 0.10985 | 0.541328616 | 0.541328616 |
| Additive | 4 | reactome_interleukin_37_signaling | 20 | 0.74948 | 0.19082 | 0.667012992 | 0.667012992 |
| Additive | 5 | go_negative_regulation_of_torc1_signaling | 14 | 0.95642 | 0.24846 | 0.920240064 | 0.920240064 |
| Additive | 6 | watanabe_ulcerative_colitis_with_cancer_dn | 15 | 0.78085 | 0.20622 | 1.187884602 | 1 |
| Additive | 7 | go_rrna_adenine_methyltransferase_activity | 8 | 0.91368 | 0.25542 | 2.69750634 | 1 |
| Additive | 8 | biocarta_fas_pathway | 30 | 0.54087 | 0.15477 | 3.68427426 | 1 |
| Additive | 9 | go_primitive_hemopoiesis | 8 | 1.0388 | 0.29812 | 3.8304621 | 1 |
| Additive | 10 | go_positive_regulation_of_extrinsic_apoptotic_signaling_pathway_via_death_domain_receptors | 17 | 0.66703 | 0.19962 | 6.4669536 | 1 |
| Dominant | 1 | go_phosphatidylglycerol_biosynthetic_process | 7 | 1.0318 | 0.27705 | 0.000098374 | 1 |
| Dominant | 2 | wong_embryonic_stem_cell_core | 322 | 0.15449 | 0.043806 | 0.00021101 | 1 |
| Dominant | 3 | gentile_uv_response_cluster_d9 | 26 | 0.61884 | 0.1782 | 0.00025822 | 1 |
| Dominant | 4 | go_membrane_hyperpolarization | 11 | 0.82733 | 0.25692 | 0.00064192 | 1 |
| Dominant | 5 | reactome_rrna_modification_in_the_mitochondrion | 6 | 0.93826 | 0.29291 | 0.00068067 | 1 |
| Dominant | 6 | go_axonal_transport_of_mitochondrion | 10 | 0.73055 | 0.22977 | 0.00073917 | 1 |
| Dominant | 7 | go_clathrin_sculpted_gamma_aminobutyric_acid_transport_vesicle_membrane | 8 | 0.89238 | 0.28304 | 0.00081001 | 1 |
| Dominant | 8 | cadwell_atg16l1_targets_up | 96 | 0.25946 | 0.082733 | 0.0008576 | 1 |
| Dominant | 9 | go_response_to_tumor_necrosis_factor | 288 | 0.1631 | 0.052997 | 0.0010456 | 1 |
| Dominant | 10 | go_negative_regulation_of_epithelial_cell_migration | 63 | 0.33269 | 0.10891 | 0.0011278 | 1 |
| Recessive | 1 | go_arginine_binding | 7 | 1.5647 | 0.36193 | 7.7371E-06 | 0.119793519 |
| Recessive | 2 | go_sleep | 31 | 0.65245 | 0.15327 | 0.000010422 | 0.161363826 |
| Recessive | 3 | reactome_cytosolic_iron_sulfur_cluster_assembly | 12 | 1.3065 | 0.31084 | 0.000013248 | 0.205118784 |
| Recessive | 4 | go_mmx_d_complex | 4 | 1.8154 | 0.43512 | 0.000015171 | 0.234892593 |
| Recessive | 5 | go_cia_complex | 5 | 1.6469 | 0.41628 | 0.000038244 | 0.592131852 |
| Recessive | 6 | boyault_liver_cancer_subclass_g6_up | 64 | 0.43122 | 0.11171 | 0.000056909 | 0.881122047 |
| Recessive | 7 | reactome_interleukin_37_signaling | 20 | 0.73232 | 0.19138 | 0.000065252 | 1 |
| Recessive | 8 | ingram_shh_targets_dn | 56 | 0.45578 | 0.11956 | 0.000069166 | 1 |
| Recessive | 9 | go_regulation_of_triglyceride_metabolic_process | 8 | 1.1279 | 0.30386 | 0.00010326 | 1 |
| Recessive | 10 | go_negative_regulation_of_torc1_signaling | 14 | 0.91368 | 0.24919 | 0.00012332 | 1 |

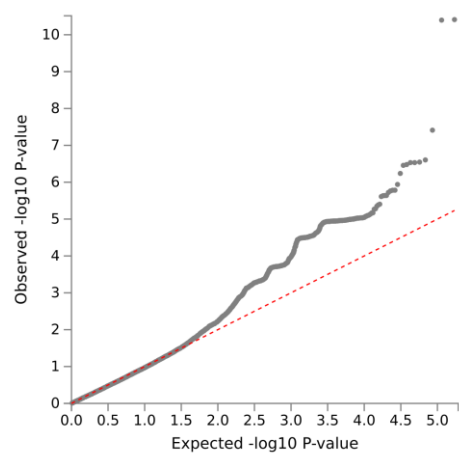
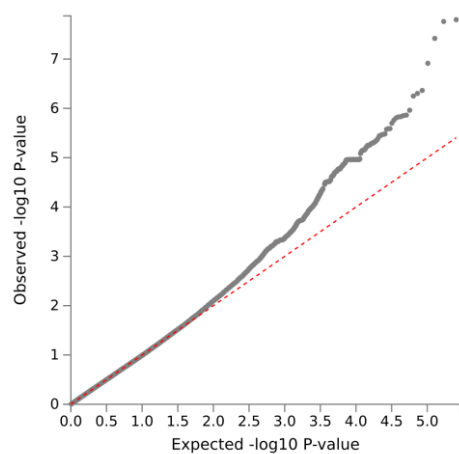
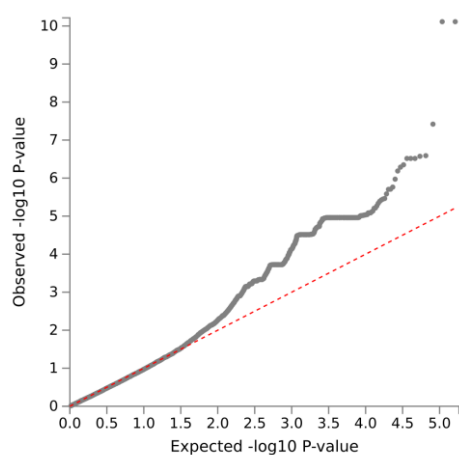
(a) Additive:**(b) Dominant:****(c) Recessive:**

Figure S1. Log quantile-quantile (QQ) p -value plot as a result of the GWAS for all patient samples. (a) Plot of the results from the additive model. (b) Plot of the results from the dominant model. (c) Plot of the results from the recessive model.

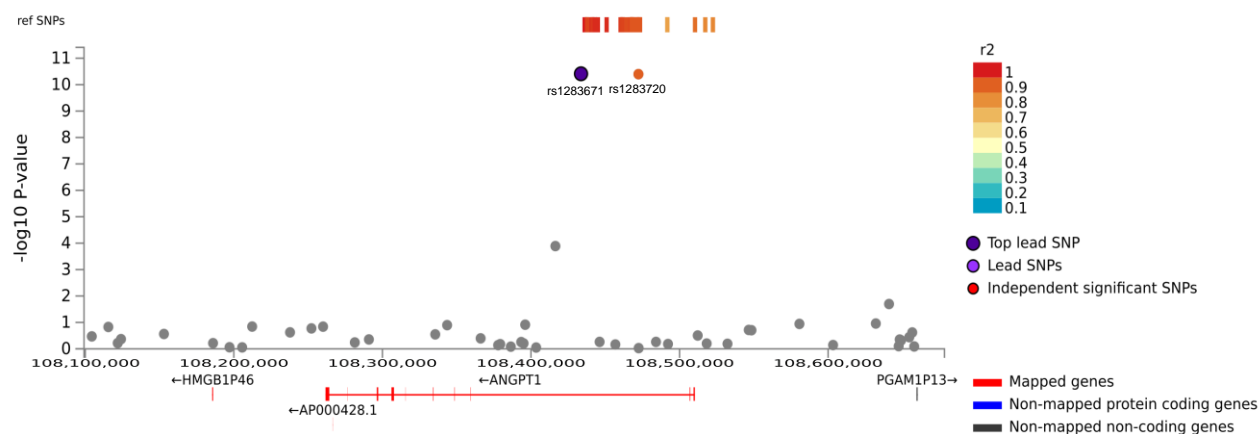
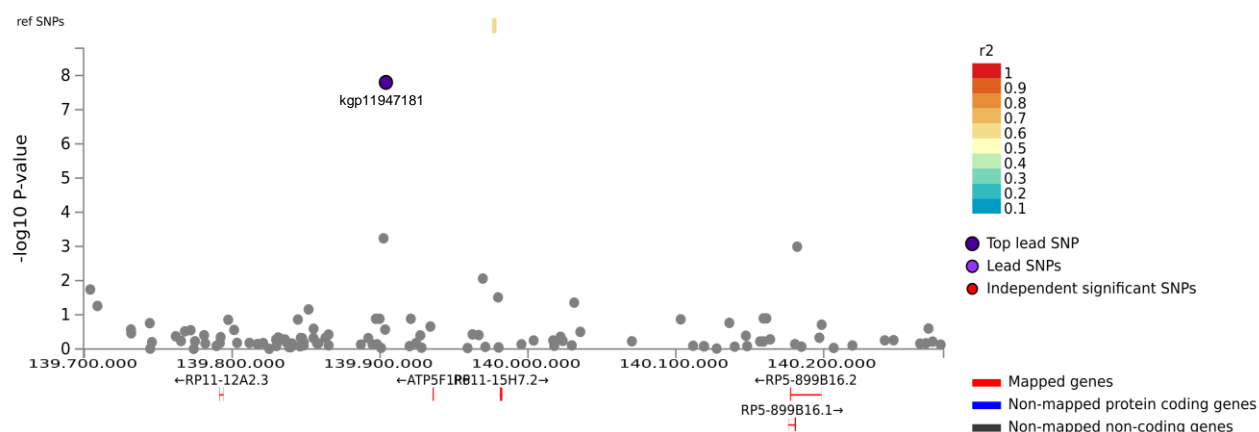
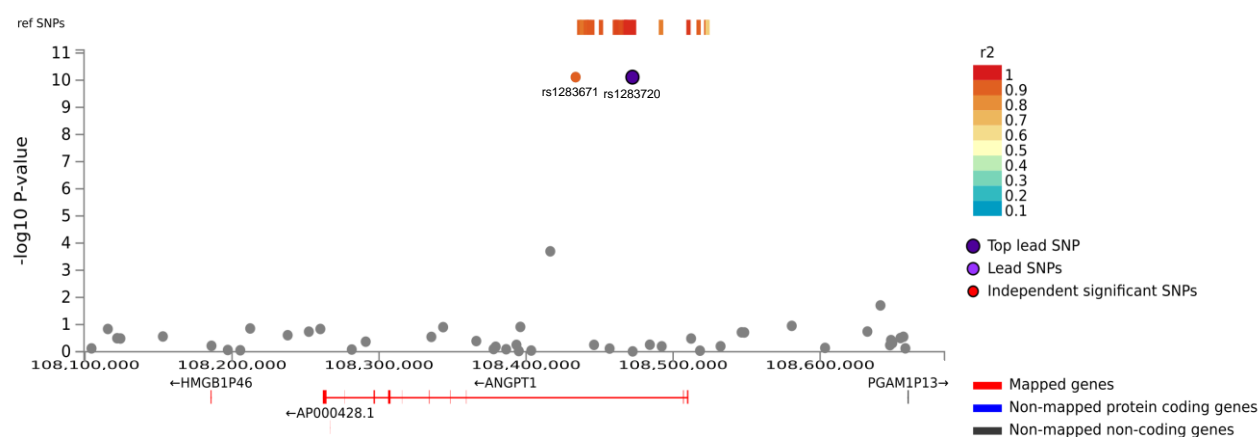
(a) Additive:**(b) Dominant:****(c) Recessive:**

Figure S2. Regional plots of potent loci that were associated with daily opioid requirements in cancer pain treatment. The results of the association analyses in each genetic model were plotted, with information on annotated genes, referenced SNPs in the database (ref SNPs), and the pairwise-calculated strength of linkage disequilibrium (LD; r^2 values) with the top lead SNP in these regions. (a) The genomic position from ~108 100 000 to ~108 670 000 on chromosome 8 (GRCh37) is illustrated with the results of the association analysis in the additive model. (b) The genomic position from ~139 700 000 to ~140 270 000 on chromosome 6 (GRCh37) is illustrated with the results of the association analysis in the dominant model. (c) The genomic position from ~108 100 000 to ~108 670 000 on chromosome 8 (GRCh37) is illustrated with the results of the association analysis in the recessive model.

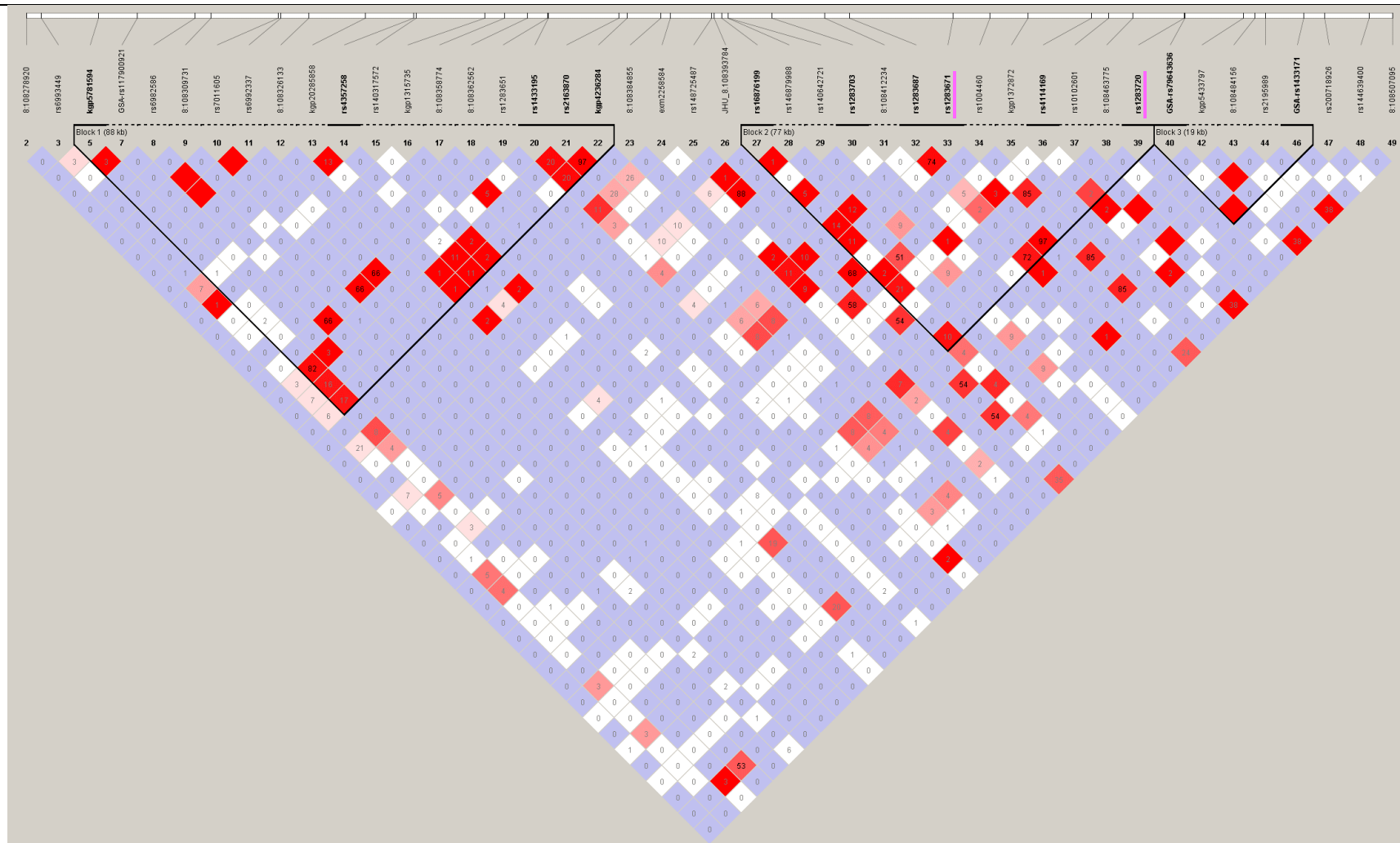


Figure S3. State of linkage disequilibrium (LD) between SNPs in the genomic region of the *ANGPT1* gene. The genotype data for the 428 patient subjects that passed the quality control criteria were used in the LD analysis, and SNPs with a minor allele frequency ≥ 0.05 were selected in the genomic position around the rs1283671 SNP and rs1283720 SNP, which spans from ~170 kbp upstream of the rs1283671 SNP to ~35 kbp downstream of the rs1283720 SNP. Numbers in squares in which two SNPs face each other represent the percentage of r^2 values that were calculated from genotype data of the SNPs. Blank squares represent $r^2 = 1$. The rs1283671 and rs1283720 SNPs are highlighted with pink lines.