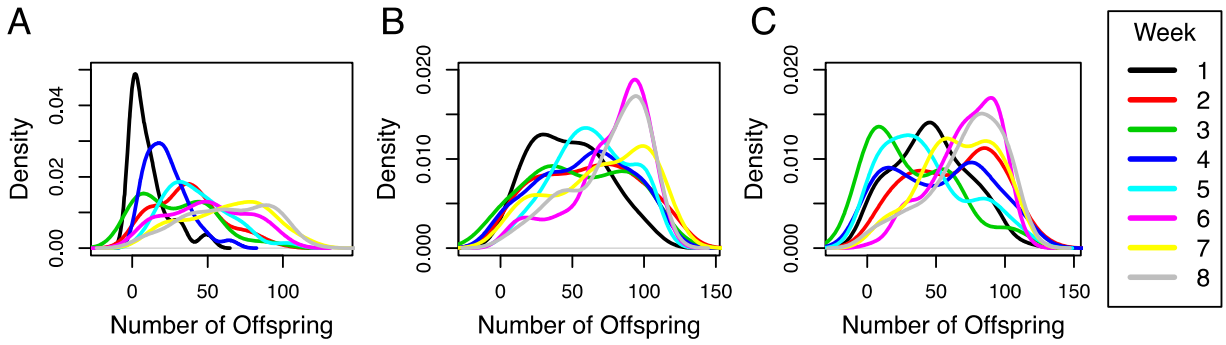
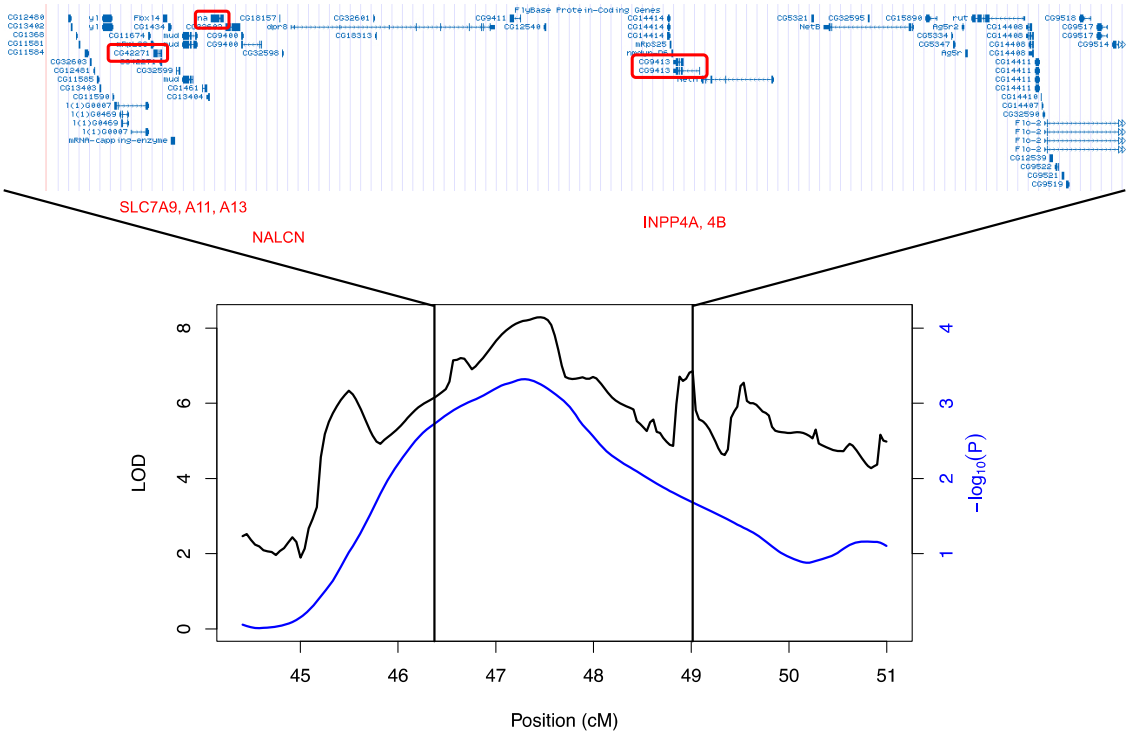
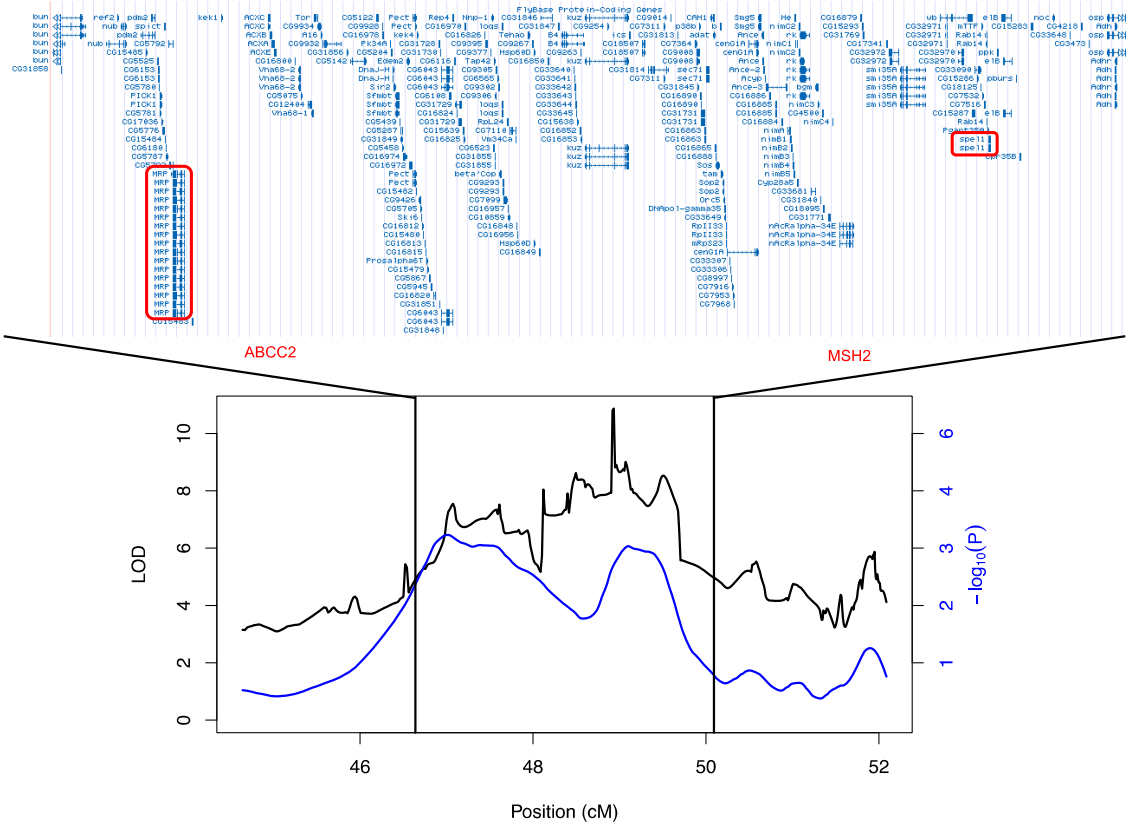


Figure S1 Density plots of the mean number of offspring produced by the three replicate females from each RIL cross for A) carboplatin, B) gemcitabine, and C) mitomycin C. Different colors correspond to different weeks (blocks) of the experiment. In all three drugs weeks 6,7, and 8 were dropped because of too low knockdown. In addition, for carboplatin, weeks 1,3, and 4 were dropped because of too high knockdown. For mitomycin C, week 3 was dropped because of too high knockdown.

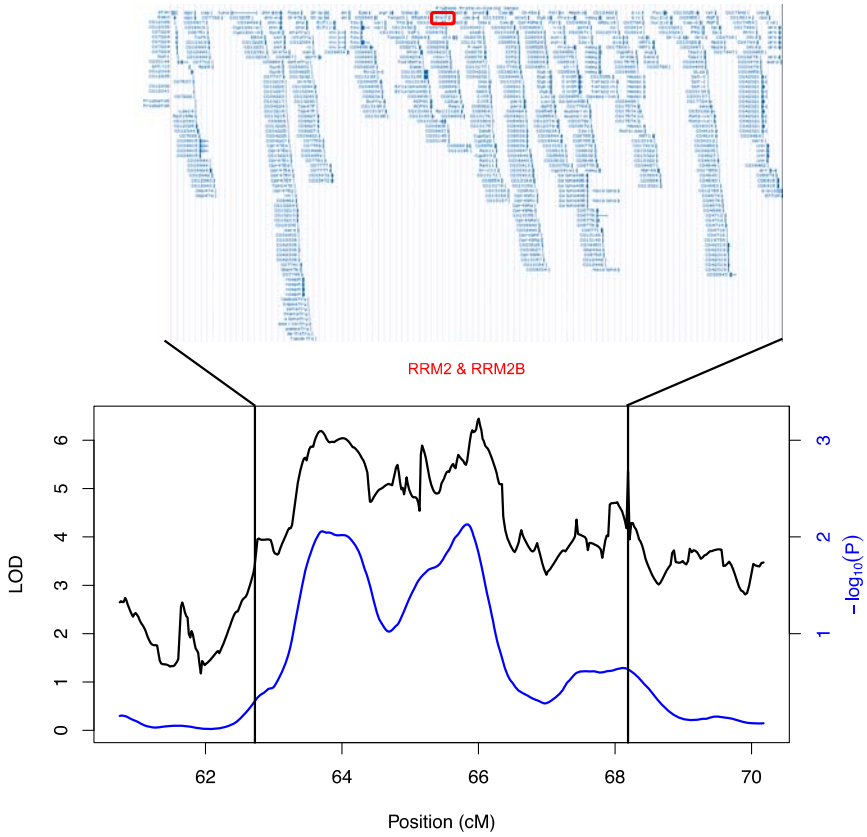
A


SLC7A9, A11, A13
NALCN
INPP4A, 4B
LOD
$-\log_{10}(P)$
Position (cM)
0
2
4
6
8
1
2
3
4
45
46
47
48
49
50
51

B


FlyBase Protein-Coding Genes
ABCC2
MSH2
LOD
$-\log_{10}(P)$
Position (cM)
0
2
4
6
8
10
1
2
3
4
6
46
48
50
52

C



D

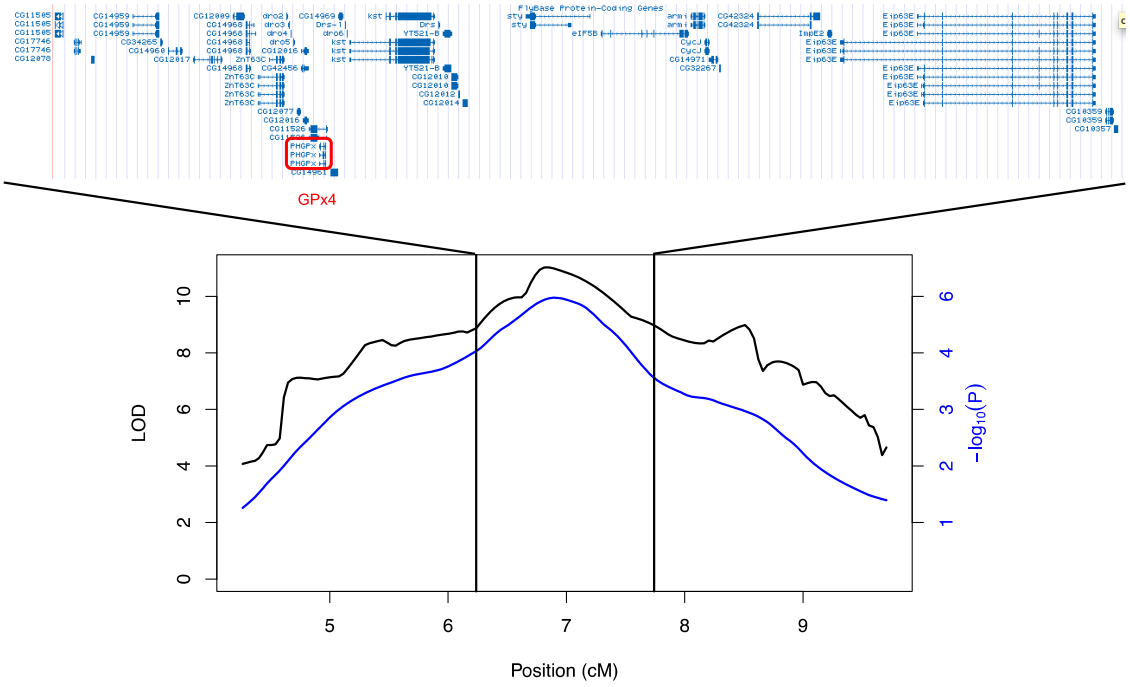


Figure S2 Santa Cruz Genome Browser for the widest combined confidence interval (Table1) for QTLs A) CA, B) CB, C) GA, and D) GB. The *Drosophila* orthologs of possible human candidate genes are circled in red with the associated human gene name also in red.

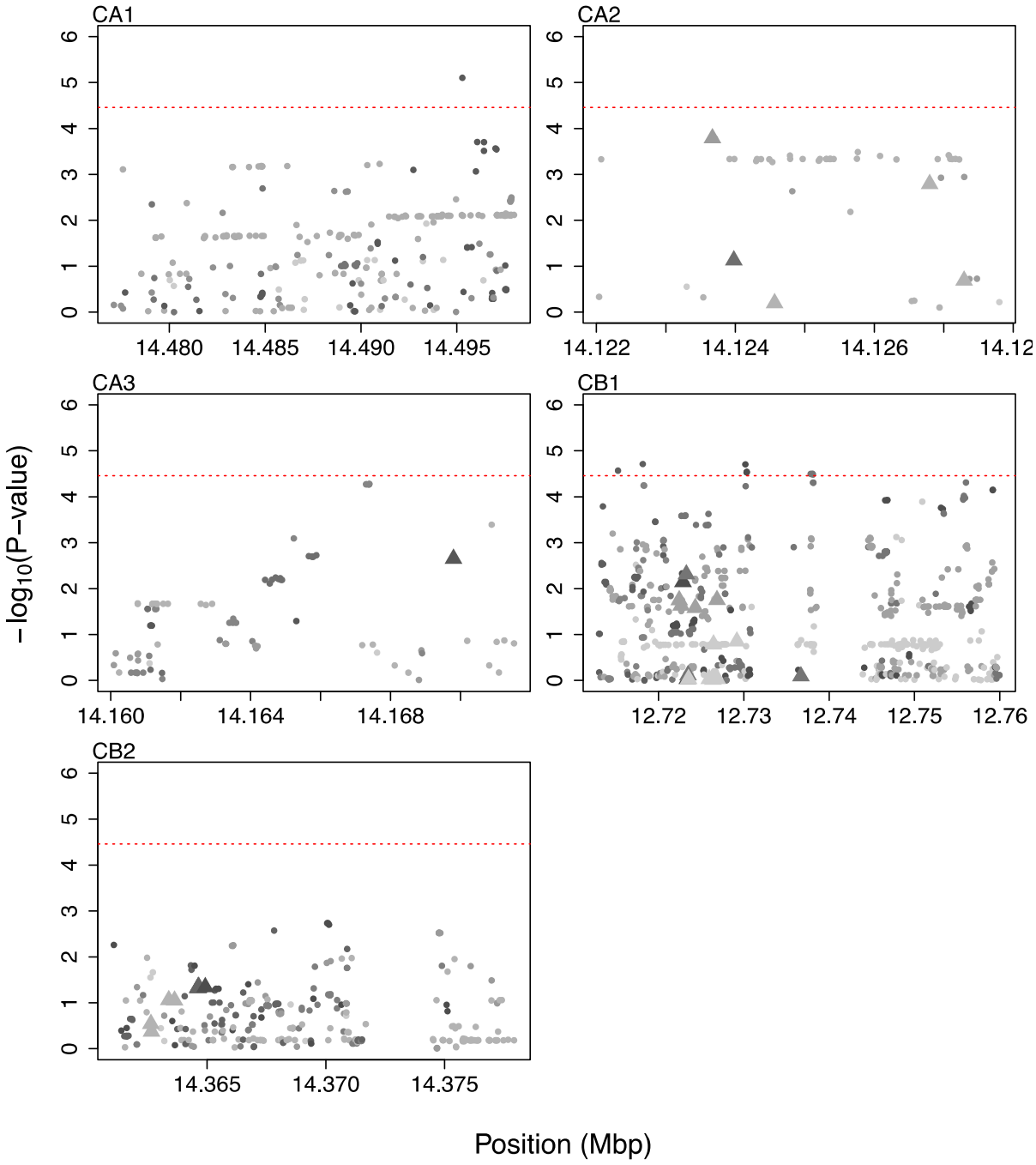


Figure S3 Association scans with carboplatin toxicity for all SNPs in candidate genes listed in Table S2. Red threshold is the Bonferroni over all candidate gene regions for carboplatin. Symbols are shaded by the minor allele frequency in the founders such that darker circles are more common SNPs. Triangles are nsSNPs.

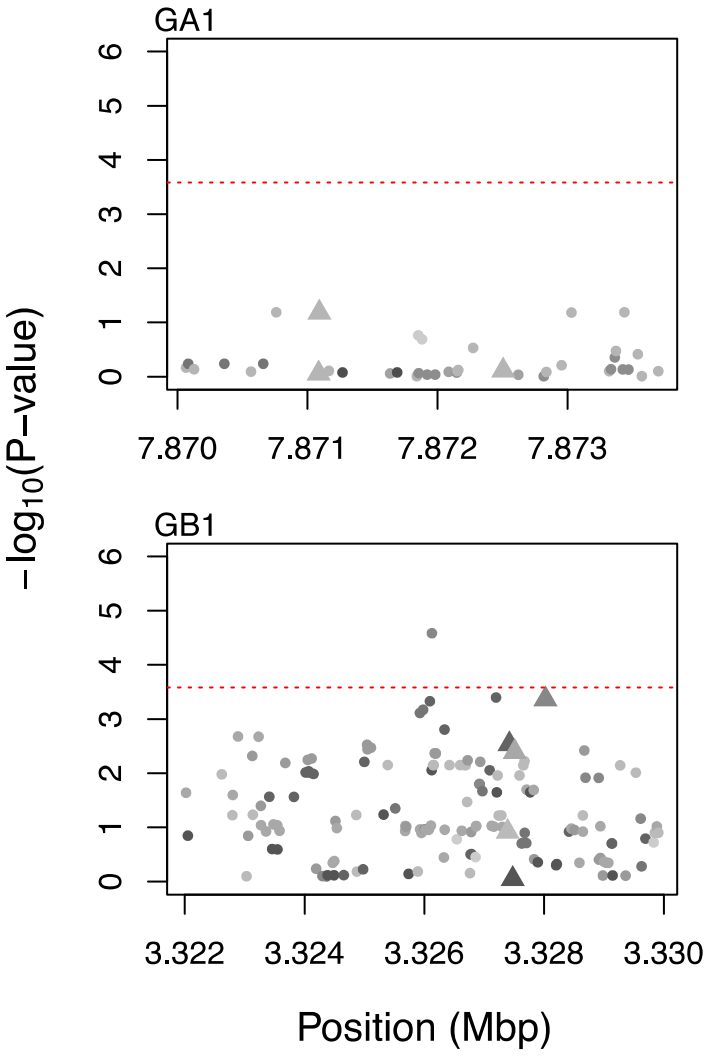


Figure S4 Association scans with gemcitabine toxicity for all SNPs in candidate genes listed in Table S2. Red threshold is the Bonferroni over all candidate gene regions for gemcitabine. Symbols are shaded by the minor allele frequency in the founders such that darker circles are more common SNPs. Triangles are nsSNPs.

Table S1 ***A priori*** **identified Candidate Genes**

Carboplatin

Human Gene	Polymorphism[1]	Ortholog Type[2]	Fly Gene(s)[2]	References
ALDH1A1	A1*2	1:Many	Aldh-III	Ekhart *et al.* 2008
ALDH3A1	A1*2	Possible	CG31075	Ekhart, *et al.* 2008
ERCC1	C8092A	1:1	Ercc1	Li *et al.* 2010
	T118C			Li *et al.* 2010; Steffensen *et al.* 2009
ERCC2	A35931C	1:1	Xpd	Li *et al.* 2010
GSTp1	A342G	No Ortholog		Sun *et al.* 2010
hMSH2	T6C	1:1	spel1	Cheng *et al.* 2010
hMLH1	T1151A	1:1	Mlh1	Cheng *et al.* 2010
MRP2	C24T	Possible	Dl	Sun *et al.* 2010
SLC31A1	Pathway	1:1	Ctr1A	Marsh *et al.* 2009
ABCG2	Pathway	Possible	bw	Marsh *et al.* 2009
		Possible	st	
		Possible	w	
ABCC2	Pathway	1:Many	MRP	Marsh *et al.* 2009
MT1A	Pathway	No Ortholog		Marsh *et al.* 2009
MPO	Pathway	Possible	Pxd	Marsh *et al.* 2009
		Possible	CG10211	
		Possible	Irc	
		Possible	CG4009	
		Possible	CG5873	
		Possible	CG6969	
		Possible	CG42331	
		Possible	Pxt	
GSPT1	Pathway	No Ortholog		Marsh *et al.* 2009
NQO1	Pathway	No Ortholog		Marsh *et al.* 2009
GSTT1	Pathway	Many:Many	CG1681	Marsh *et al.* 2009
		Many:Many	CG1702	
		Many:Many	CG30000	
		Many:Many	CG30005	
		Possible	CG16936	
		Possible	CG11784	
		Possible	CG4688	
		Possible	CG5224	
		Possible	CG17639	
		Possible	gfzf	
		Function	GstD1-10[3]	
		Function	GstE1-10[3]	
MT2A	Pathway	No Ortholog		Marsh *et al.* 2009
SOD1	Pathway	No Ortholog		Marsh *et al.* 2009
GSTM1	Pathway	No Ortholog		Marsh *et al.* 2009
ATP7A	Pathway	1:Many	ATP7	Marsh *et al.* 2009
ATP7B	Pathway	1:Many	ATP7	Marsh *et al.* 2009
HMGB1	Pathway	No Ortholog		Marsh *et al.* 2009
POLH	Pathway	1:1	DNApol-eta	Marsh *et al.* 2009
POLM	Pathway	No Ortholog		Marsh *et al.* 2009
POLB	Pathway	NoOrtholog		Marsh *et al.* 2009
REV3L	Pathway	1:Many	Mus205	Marsh *et al.* 2009
MSH2	Pathway	1:1	spel1	Marsh *et al.* 2009
MLH1	Pathway	1:1	Mlh1	Marsh *et al.* 2009
MSH6	Pathway	1:1	Msh6	Marsh *et al.* 2009
PMS2	Pathway	1:1	Pms2	Marsh *et al.* 2009
ERCC1	Pathway	1:1	Ercc1	Marsh *et al.* 2009
ERCC2	Pathway	1:1	Xpd	Marsh *et al.* 2009
ERCC3	Pathway	1:1	Hay	Marsh *et al.* 2009
ERCC4	Pathway	1:1	Mei-9	Marsh *et al.* 2009
ERCC6	Pathway	No Ortholog		Marsh *et al.* 2009
XRCC1	Pathway	1:Many	XRCC1	Marsh *et al.* 2009, Gurubhagavatula *et al.* 2004
XPA	Pathway	1:1	Xpac	Marsh *et al.* 2009
SNF	Pathway	1:1	CG8485	Marsh *et al.* 2009
SWI	Pathway	1:Many	Iswi	Marsh *et al.* 2009

Gemcitabine

Human Gene	Polymorphism[1]	Ortholog Type[2]	Fly Gene(s)[2]	References
CDA	A76C	1:Many	CG8353	Tanaka *et al.* 2010

			CG8349	
	A79C			Metharom *et al.* 2011; Maring *et al.* 2010 ; Xu *et al*. 2012
	G208A			Sugiyama *et al.* 2009; Yonemori *et al.* 2005; Ueno *et al.* 2009; Xu *et al.* 2012
dCK	C(-1205)T	1:Many	dnk	Tanaka *et al.* 2010
	A9846G			Si *et al.* 2011
hCNT1	G565A	Many:Many	CG8083 CNT1	Gusella *et al.* 2011
hENT1	A(-201)G	1:Many	Ent1	Tanaka *et al.* 2010
	C913T	Possible	Ent2	Tanaka *et al.* 2010
	G(-706)C			Gusella *et al.* 2010
MRP2	G40A	Possible	Dl	Tanaka *et al.* 2011
MTHFR	C677T	No Ortholog		Alberola *et al.* 2004; Hong 2013
RRM1	A33G	1:1	RnrL	Tanaka *et al.* 2010
SMYD3	Knock-down	1:Many	Bzd	Kalari *et al.* 2010
SLC29A1	Pathway	1:Many	Ent1	Whirl-Carrillo *et al.* 2012
		Possible	Ent2	
SLC28A1	Pathway	Many:Many	CG8083	Whirl-Carrillo *et al.* 2012
		Many:Many	CNT1	
SLC28A3	Pathway	Many:Many	CG8083	Whirl-Carrillo *et al.* 2012
		Many:Many	CNT1	
CDA	Pathway	1:Many	CG8353 CG8349	Whirl-Carrillo *et al.* 2012
dCK	Pathway	1:Many	dnk	Whirl-Carrillo *et al.* 2012
NT5C	Pathway	No Ortholog		Whirl-Carrillo *et al.* 2012
CMPK1	Pathway	1:1	Dak1	Whirl-Carrillo *et al.* 2012
RRM1	Pathway	1:1	RnrL	Whirl-Carrillo *et al.* 2012, Kwon *et al.* 2006
RRM2	Pathway	1:Many	RnrS	Whirl-Carrillo *et al.* 2012
RRM2B	Pathway	1:Many	RnrS	Whirl-Carrillo *et al.* 2012

Mitomycin C

Human Gene	**Polymorphism[1]**	**Ortholog Type[2]**	**Fly Gene(s)[2]**	**References**
FANCL	Pathway	1:1	Fancl	Zhang *et al.* 2006
FANCD2	Pathway	1:1	Fancd2	Roques *et al.* 2009, Ho *et al.* 2006
Rad51	Pathway	1:1	spn-A	Ko *et al.* 2011
Mre11A	Pathway	1:1	Mre11	Roques *et al.* 2009
Rad50	Pathway	1:1	rad50	Roques *et al.* 2009, Kim *et al.* 2002
Nibrin	Pathway	1:1	nbs	Roques *et al.* 2009
CHK1	Pathway	1:1	grp	Boamah *et al.* 2010

1. Polymorphism refers either to a SNP within a gene (SNP resulting in amino acid substitution given) or "pathway" indicates that the gene is in the drug's cellular pathway based on the literature (but that gene does not harbor a germ-line SNP impacting toxicity).

2. Ortholog types and gene names are represented as on the ensembl.org genome browser (Birney *et al.* 2004)

3. Gene family. The orthology prediction is based on both human and fly GST gene families having the same apparent biochemical function

Table S2 Candidate genes associated with QTL peaks of Figure XX and Table 1.

QTL	Gene Name	Chr	Left[1]	Right[1]	nsSNP[2]	SNPs[2]	TEs[2,3]
Carboplatin							
CA1	*CG9413*	X	14477	14498	0	280	1{A3}
CA2	*CG42271*	X	14122	14128	5	48	
CA3	*na*	X	14160	14172	1	94	1{B7}
CB1	*MRP*	2L	12713	12760	15	701	3{A6,B2,A3}
CB2	*spel1*	2L	14361	14378	11	315	1{A6}
Gemcitabine							
GA1	RnrS	2R	7870	7874	3	40	
GB1	*PHGPx*	3L	3322	3330	5	151	

1. Method for determining Left and Right limits of candidate genes defined in Materials and Methods. Coordinates are given in kilobases.

2. Number of non-synonymous SNPs, other SNPs in the gene region, and transposable elements.

3. All transposable elements were only present in a single founder. Founder line harboring TE in {}.

Table S3 Biallelic SNPs significant after Bonferroni correction from gene-centric association scans.

QTL	chr	base	$\%V_T$	P	$\%V_G$	MiAC	MaAC
CA1	*X*	14495288	10.3	7.9E-06	15.2	4	5
CB1	*2L*	12715263	9.1	2.7E-05	13.5	3	4
CB1	*2L*	12718169	9.5	1.9E-05	13.9	3	4
CB1	*2L*	12730194	9.5	2.0E-05	13.9	3	3
CB1	*2L*	12730331	9.1	2.9E-05	13.3	3	3
CB1	*2L*	12730336	9.1	2.9E-05	13.3	3	3
CB1	*2L*	12730358	9.1	2.9E-05	13.4	3	3
CB1	*2L*	12737838	9.0	3.2E-05	13.2	2	4
CB1	*2L*	12738050	9.0	3.1E-05	13.3	2	4
CB1	*2L*	12738104	9.0	3.3E-05	13.2	2	4
GB1	*3L*	3326126	4.3	2.6E-5	6.8	4	11

Note: QTL corresponds to QTL in Supplementary Table 2, chr=chromosome, base=base position in chromosome, $\%V_T$=percent of total variation explained by SNP, P=p-value, $\%V_G$=percent of genetic variation explained by SNP, MiAC= Minor Allele Count = Number of founder chromosomes having minor allele represented in panel at this position, MaAC=Major Allele Count.

Table S4 Biallelic SNPs with p-values less than 0.01 for both gemcitabine toxicity and methotrexate toxicity within the GB1 candidate gene region (see Table S2).

chr	base	GEM $\%V_T$	MTX $\%V_T$	GEM P	MTX P	GEM $\%V_G$	MTX $\%V_G$	GEM MAF	MTX MAF
3L	3325388	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326092	3.0	2.3	0.0005	0.008	4.7	3.6	40.0	57.1
3L	3326126	4.3	2.2	2.6E-05	0.01	6.8	3.4	26.7	28.5
3L	3326147	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326157	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326171	2.0	2.9	0.004	0.003	3.2	4.5	20.0	21.4
3L	3326188	2.0	2.9	0.004	0.003	3.2	4.5	20.0	21.4
3L	3326189	2.0	2.9	0.004	0.003	3.2	4.5	20.0	21.4
3L	3326419	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326597	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326672	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326690	1.8	2.3	0.007	0.008	2.8	3.5	6.7	7.1
3L	3326933	1.8	2.9	0.006	0.003	2.9	4.6	20.0	21.4
3L	3327091	1.7	2.5	0.009	0.006	2.7	3.8	40.0	50.0
3L	3329269	1.8	2.3	0.007	0.008	2.8	3.6	6.7	7.1
3L	3329532	1.6	2.3	0.010	0.008	2.6	3.6	6.7	7.1

Note: chr=chromosome, base=base position in chromosome, GEM = gemcitabine, MTX = methotrexate, $\%V_T$=percent of total variation explained by SNP, P=p-value, $\%V_G$=percent of genetic variation explained by SNP, MAF = minor allele frequency= number of founder chromosomes having minor allele represented at this position/total number of founder chromosomes. Shaded rows are SNPs with p-values less than 0.001 for gemcitabine toxicity.

References cited in Supporting Information

ALBEROLA, V., C. SARRIES, R. ROSELL, M. TARON, R. PENAS et al., 2004 Effect of the methylenetetrahydrofolate reductase C677T polymorphism on patients with cisplatin/gemcitabine-treated stage IV non-small-cell lung cancer. Clin Lung Cancer 5: 360-365.

BIRNEY, E., T. D. ANDREWS, P. BEVAN, M. CACCAMO, Y. CHEN et al., 2004 An overview of Ensembl. Genome Res 14: 925-928.

BOAMAH, E. K., A. BREKMAN, M. TOMASZ, N. MYEKU, M. FIGUEIREDO-PEREIRA et al., 2010 DNA adducts of decarbamoyl mitomycin C efficiently kill cells without wild-type p53 resulting from proteasome-mediated degradation of checkpoint protein 1. Chem Res Toxicol 23: 1151-1162.

EKHART, C., V. D. DOODEMAN, S. RODENHUIS, P. H. M. SMITS, J. H. BEIJNEN et al., 2008 Influence of polymorphisms of drug metabolizing enzymes (CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, GSTA1, GSTP1, ALDH1A1 and ALDH3A1) on the pharmacokinetics of cyclophosphamide and 4-hydroxycyclophosphamide. Pharmacogenet Genomics 18: 515-523.

GURUBHAGAVATULA, S., G. LIU, S. PARK, W. ZHOU, L. SU et al., 2004 XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. J Clin Oncol 22: 2594-2601.

GUSELLA, M., F. PASINI, C. BOLZONELLA, S. MENEGHETTI, C. BARILE et al., 2011 Equilibrative nucleoside transporter 1 genotype, cytidine deaminase activity and age predict gemcitabine plasma clearance in patients with solid tumours. Br J Clin Pharmacol 71: 437-444.

HO, G. P. H., S. MARGOSSIAN, T. TANIGUCHI and A. D. D'ANDREA, 2006 Phosphorylation of FANCD2 on two novel sites is required for mitomycin C resistance. Molecular and Cellular Biology 26: 7005-7015.

HONG, W., K. WANG, Y.-P. ZHANG, J.-Y. KOU, D. HONG et al., 2013 Methylenetetrahydrofolate reductase C677T polymorphism predicts response and time to progression to gemcitabine-based chemotherapy for advanced non-small cell lung cancer in a Chinese Han population. J Zhejiang Univ Sci B 14: 207-215.

KALARI, K. R., S. J. HEBBRING, H. S. CHAI, L. LI, J.-P. A. KOCHER et al., 2010 Copy number variation and cytidine analogue cytotoxicity: a genome-wide association approach. BMC Genomics 11: 357.

KIM, Y., J. KOH, B. SHIN, K. AHN, B. CHOI et al., 2002 An antisense construct of full-length human RAD50 cDNA confers sensitivity to ionizing radiation and alkylating agents on human cell lines. Radiat Res 157: 19-25.

KO, J.-C., M.-S. TSAI, S.-H. WENG, Y.-H. KUO, Y.-F. CHIU et al., 2011 Curcumin enhances the mitomycin C-induced cytotoxicity via downregulation of MKK1/2-ERK1/2-mediated Rad51 expression in non-small cell lung cancer cells. Toxicol Appl Pharmacol 255: 327-338.

KWON, W. S., S. Y. RHA, Y. H. CHOI, J. O. LEE, K. H. PARK et al., 2006 Ribonucleotide reductase M1 (RRM1) 2464G>A polymorphism shows an association with gemcitabine chemosensitivity in cancer cell lines. Pharmacogenet Genomics 16: 429-438.

LI, H., H. SHI, H. WANG, Z. ZHU, X. LI et al., 2010 Crystal structure of the two N-terminal RRM domains of Pub1 and the poly(U)-binding properties of Pub1. J Struct Biol 171: 291-297.

MARING, J. G., F. M. WACHTERS, M. SLIJFER, J. M. MAURER, H. M. BOEZEN et al., 2010 Pharmacokinetics of gemcitabine in non-small-cell lung cancer patients: impact of the 79A>C cytidine deaminase polymorphism. Eur J Clin Pharmacol 66: 611-617.

METHAROM, E., P. GALETTIS, S. MANNERS, M. JELINEK, W. LIAUW et al., 2011 The pharmacological advantage of prolonged dose rate gemcitabine is restricted to patients with variant alleles of cytidine deaminase c.79A>C. Asia Pac J Clin Oncol 7: 65-74.

ROQUES, C., Y. COULOMBE, M. DELANNOY, J. VIGNARD, S. GROSSI et al., 2009 MRE11-RAD50-NBS1 is a critical regulator of FANCD2 stability and function during DNA double-strand break repair. EMBO J 28: 2400-2413.

SI, S., Q. LIAO, Y. ZHAO, Y. HU, Q. ZHANG et al., 2011 Relationship between single nucleotide polymorphisms in the deoxycytidine kinase gene and chemosensitivity of gemcitabine in six pancreatic cancer cell lines. Chin Med J (Engl) 124: 419-422.

STEFFENSEN, K. D., M. WALDSTRØM and A. JAKOBSEN, 2009 The relationship of platinum resistance and ERCC1 protein expression in epithelial ovarian cancer. Int J Gynecol Cancer 19: 820-825.

SUGIYAMA, E., S.-J. LEE, S. S. LEE, W.-Y. KIM, S.-R. KIM et al., 2009 Ethnic differences of two non-synonymous single nucleotide polymorphisms in CDA gene. Drug Metab Pharmacokinet 24: 553-556.

SUN, L., S. WANG, C. HU and X. ZHANG, 2010 Regulation of cell proliferation and apoptosis through fibrocystin-prosaposin interaction. Arch Biochem Biophys 502: 130-136.

TANAKA, M., M. JAVLE, X. DONG, C. ENG, J. L. ABBRUZZESE et al., 2010 Gemcitabine metabolic and transporter gene polymorphisms are associated with drug toxicity and efficacy in patients with locally advanced pancreatic cancer. Cancer 116: 5325-5335.

TANAKA, M., T. OKAZAKI, H. SUZUKI, J. L. ABBRUZZESE and D. LI, 2011 Association of multi-drug resistance gene polymorphisms with pancreatic cancer outcome. Cancer 117: 744-751.

UENO, H., N. KANIWA, T. OKUSAKA, M. IKEDA, C. MORIZANE et al., 2009 Homozygous CDA*3 is a major cause of life-threatening toxicities in gemcitabine-treated Japanese cancer patients. Br J Cancer 100: 870-873.

XU, J., Y. ZHOU, J. ZHANG, Y. CHEN, R. ZHUANG et al., 2012 High incidence of severe neutropenia after gemcitabine-based chemotherapy in Chinese cancer patients with CDA 79A>C mutation. Clin Chim Acta 413: 1284-1287.

YONEMORI, K., H. UENO, T. OKUSAKA, N. YAMAMOTO, M. IKEDA et al., 2005 Severe drug toxicity associated with a single-nucleotide polymorphism of the cytidine deaminase gene in a Japanese cancer patient treated with gemcitabine plus cisplatin. Clin Cancer Res 11: 2620-2624.

ZHANG, J., X. WANG, C.-J. LIN, F. J. COUCH and P. FEI, 2006 Altered expression of FANCL confers mitomycin C sensitivity in Calu-6 lung cancer cells. Cancer Biol Ther 5: 1632-1636.