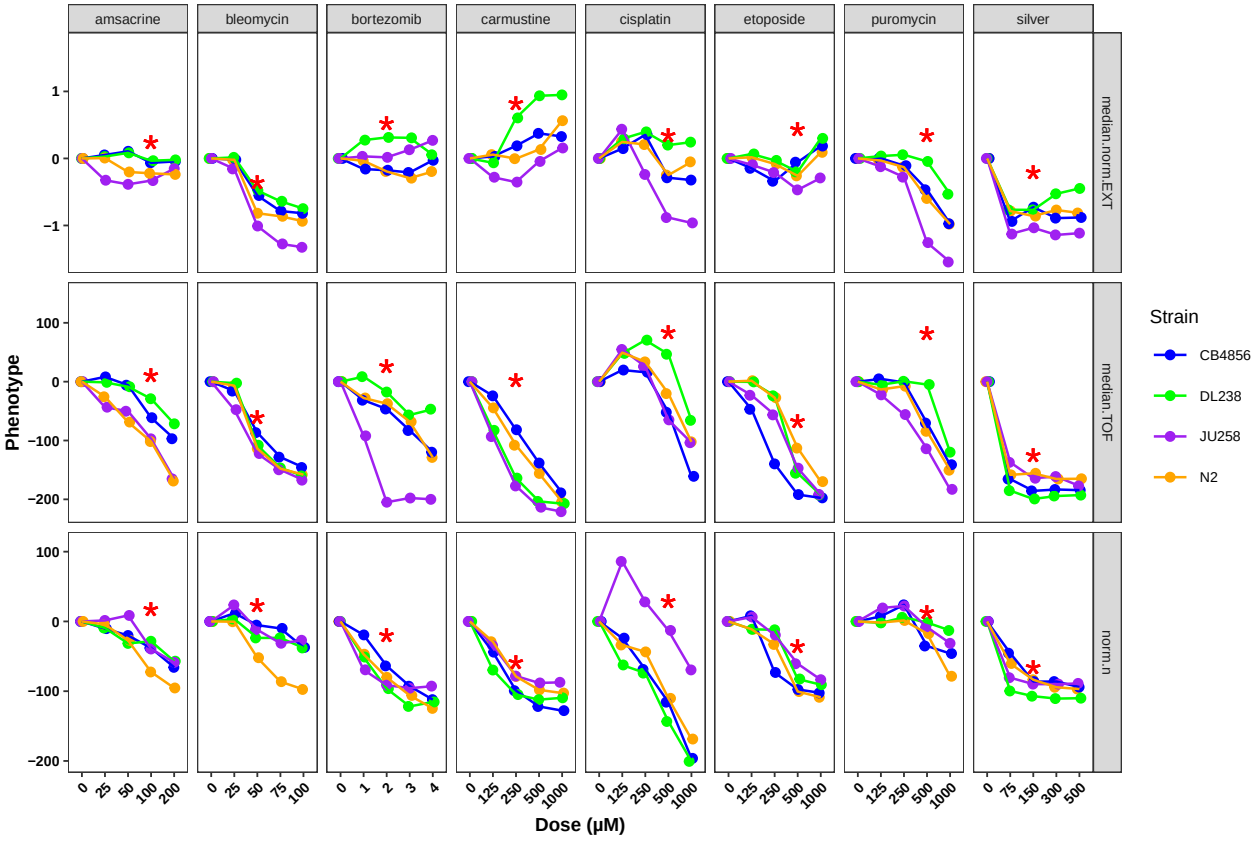
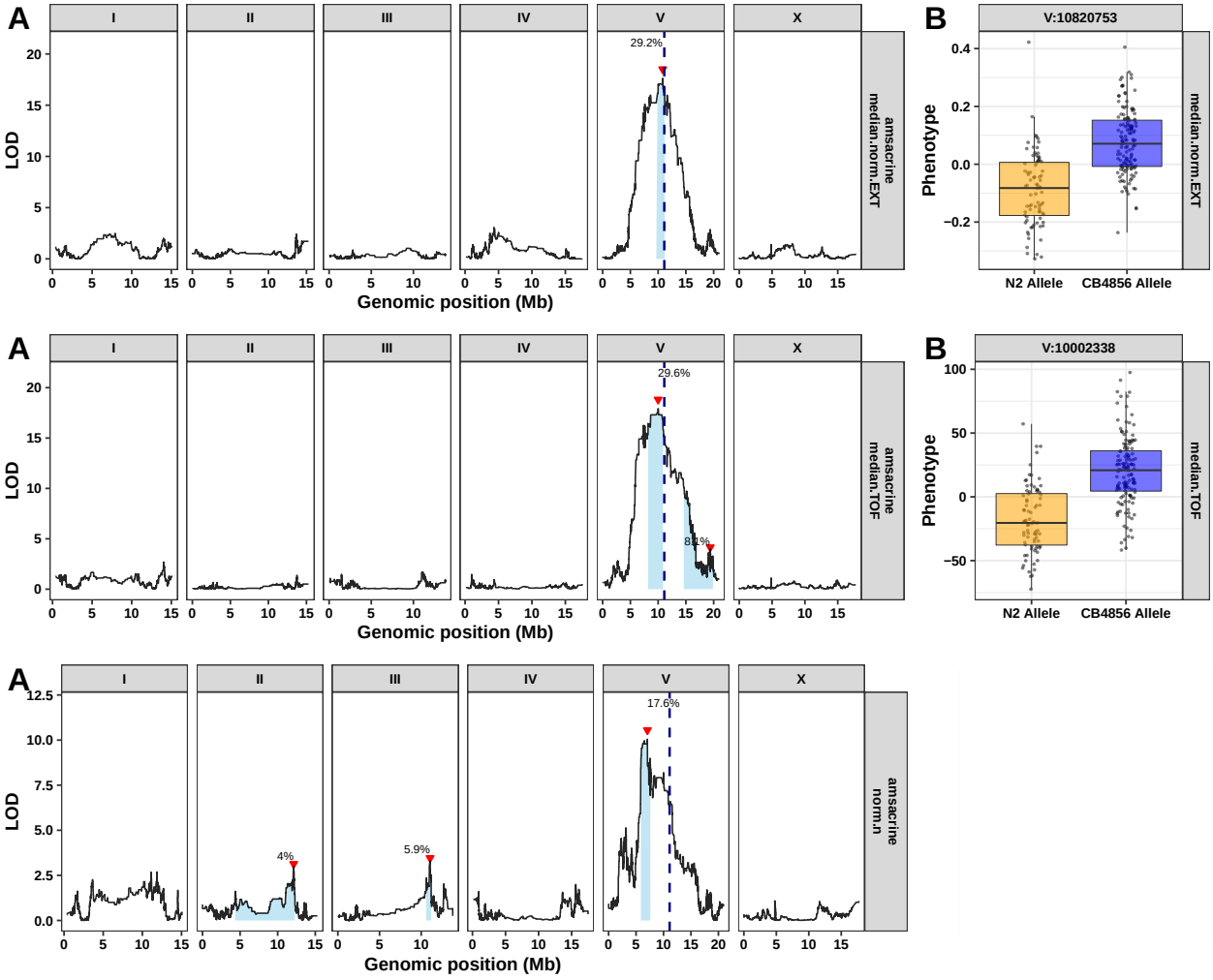
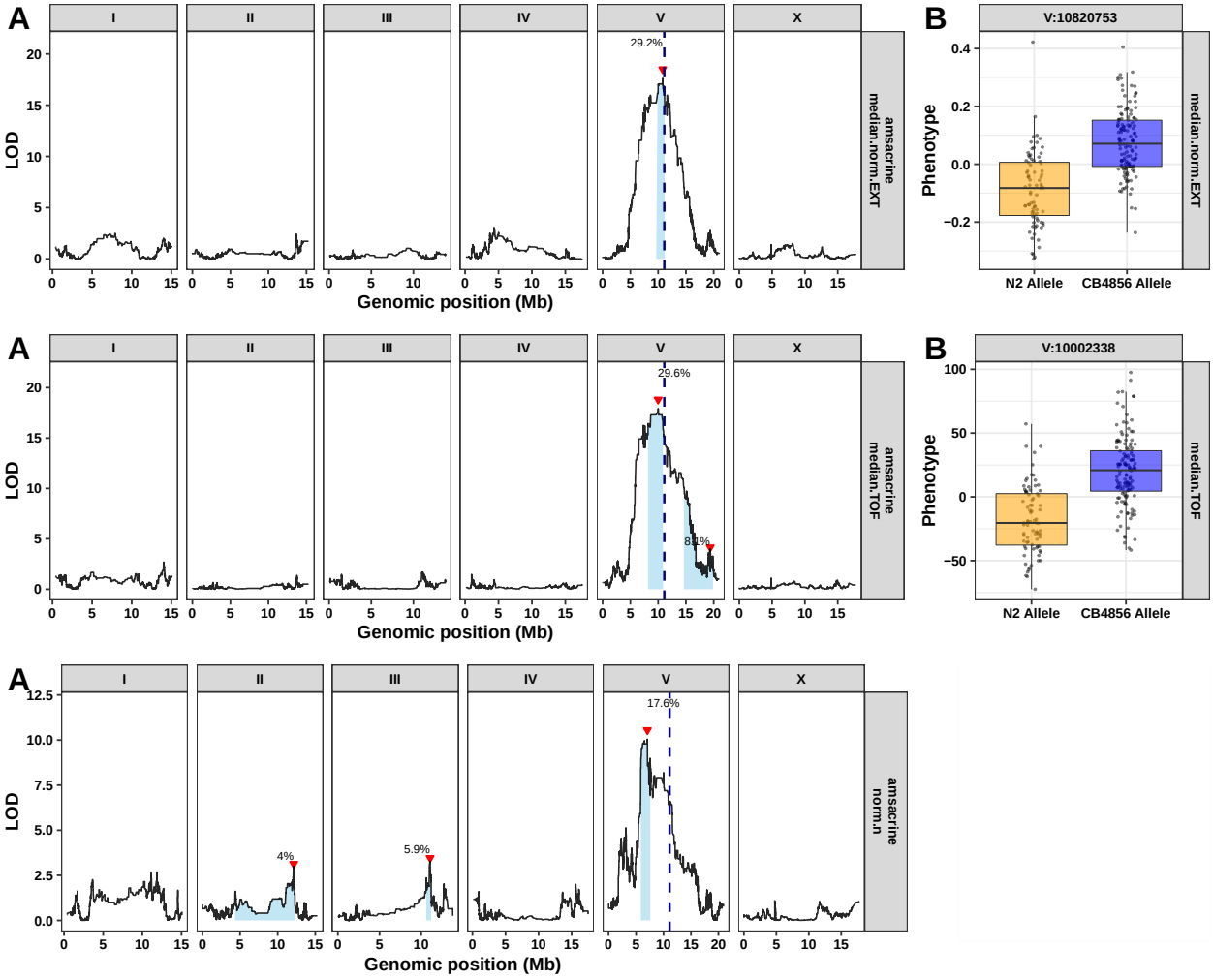


Figure S1 Dose response with four divergent wild isolates. Results from dose response HTA for all eight chemotherapeutics (x-axis) for each trait (y-axis). For each drug-response trait, drug concentration (µM) (x-axis) is plotted against phenotype subtracted from control (y-axis), colored by strain (CB4856: blue, DL238: green, JU258: purple, N2: orange). A red asterisk indicates the dose selected for linkage mapping analysis.


A
I
II
III
IV
V
X
29.2%
LOD
Genomic position (Mb)
amsacrine
median.norm.EXT
B
V:10820753
Phenotype
N2 Allele
CB4856 Allele
median.norm.EXT
A
29.6%
81%
amsacrine
median.TOF
B
V:10002338
median.TOF
4%
5.9%
17.6%
amsacrine
norm.n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V
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LOD
Genomic position (Mb)
amsacrine
median.norm.EXT
B
V:10820753
Phenotype
N2 Allele
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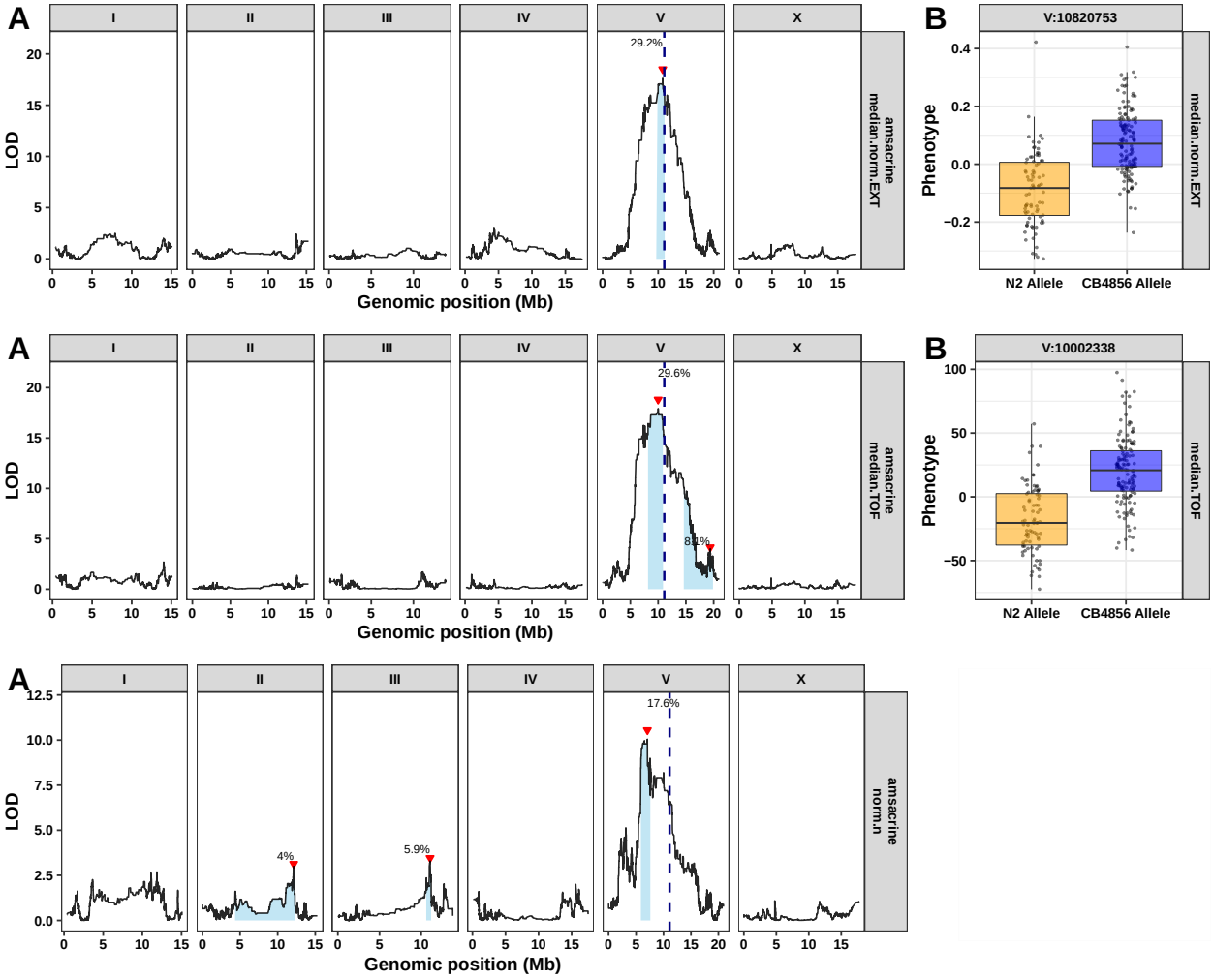
median.norm.EXT
A
29.6%
81%
amsacrine
median.TOF
B
V:10002338
median.TOF
4%
5.9%
17.6%
amsacrine
norm.n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B
V:10820753
Phenotype
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CB4856 Allele
median.norm.EXT
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amsacrine
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V:10002338
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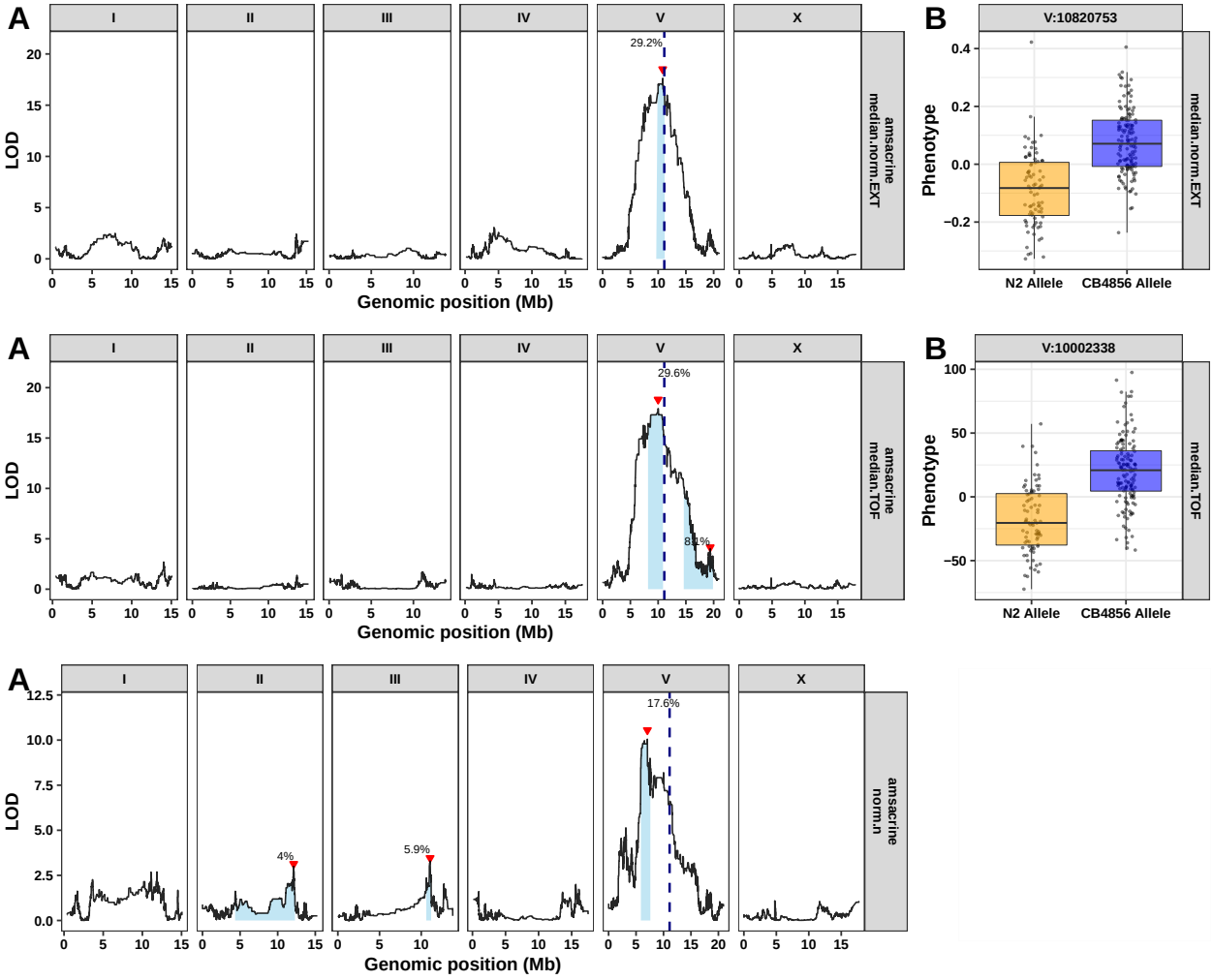
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median.TOF
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5.9%
17.6%
amsacrine
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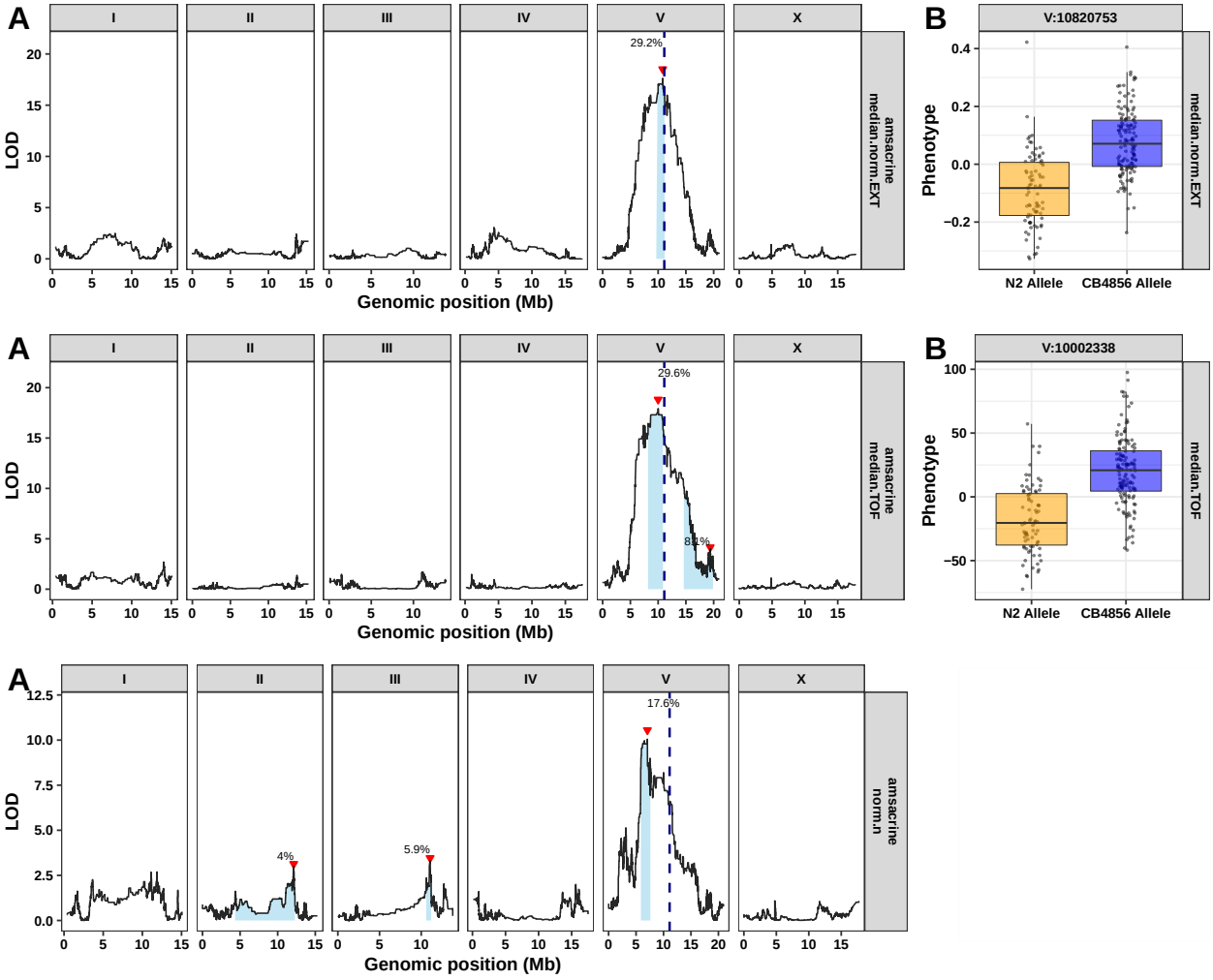
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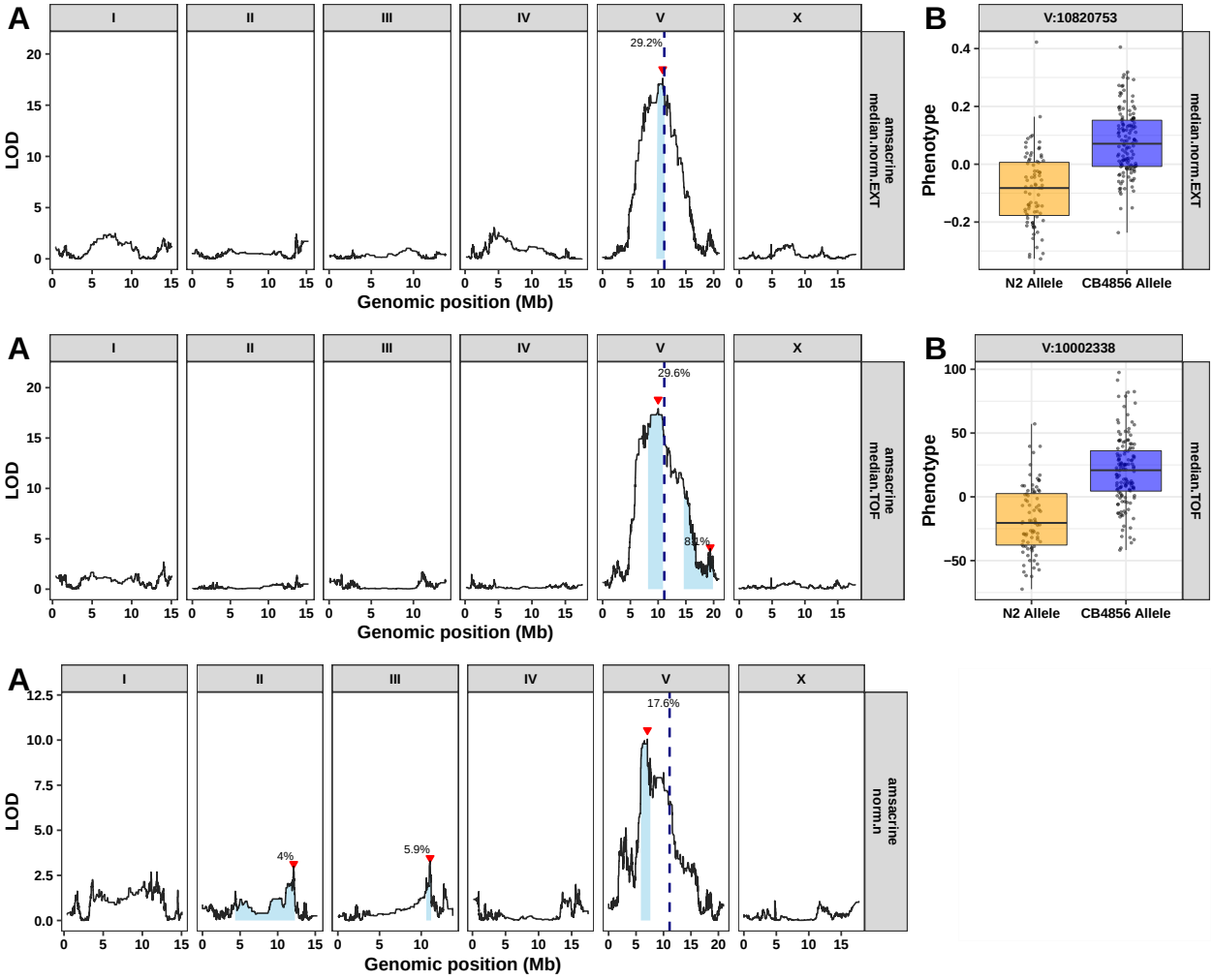
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median.TOF
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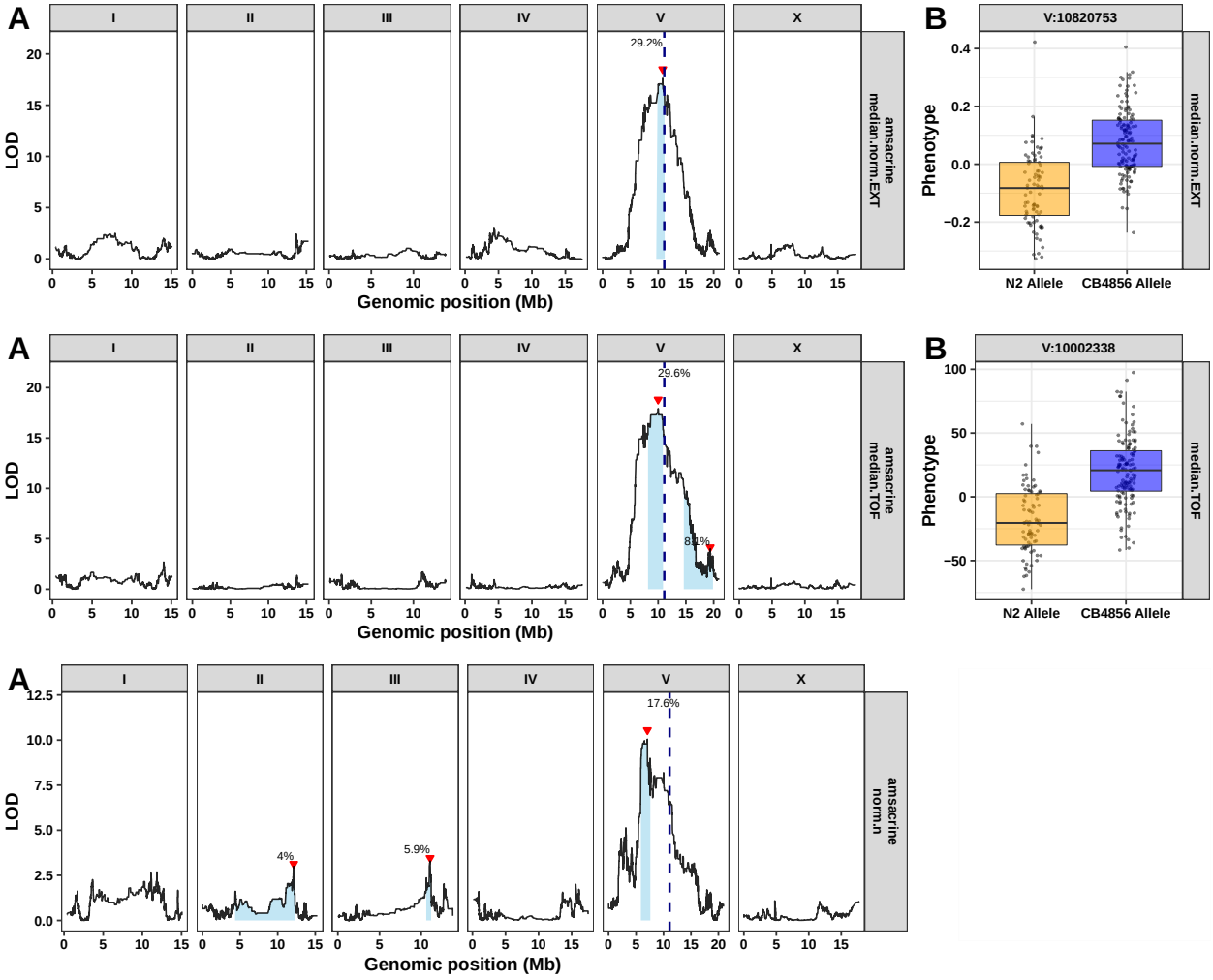
17.6%
amsacrine
norm.n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Genomic position (Mb)
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median.norm.EXT
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V:10820753
Phenotype
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amsacrine
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5.9%
17.6%
amsacrine
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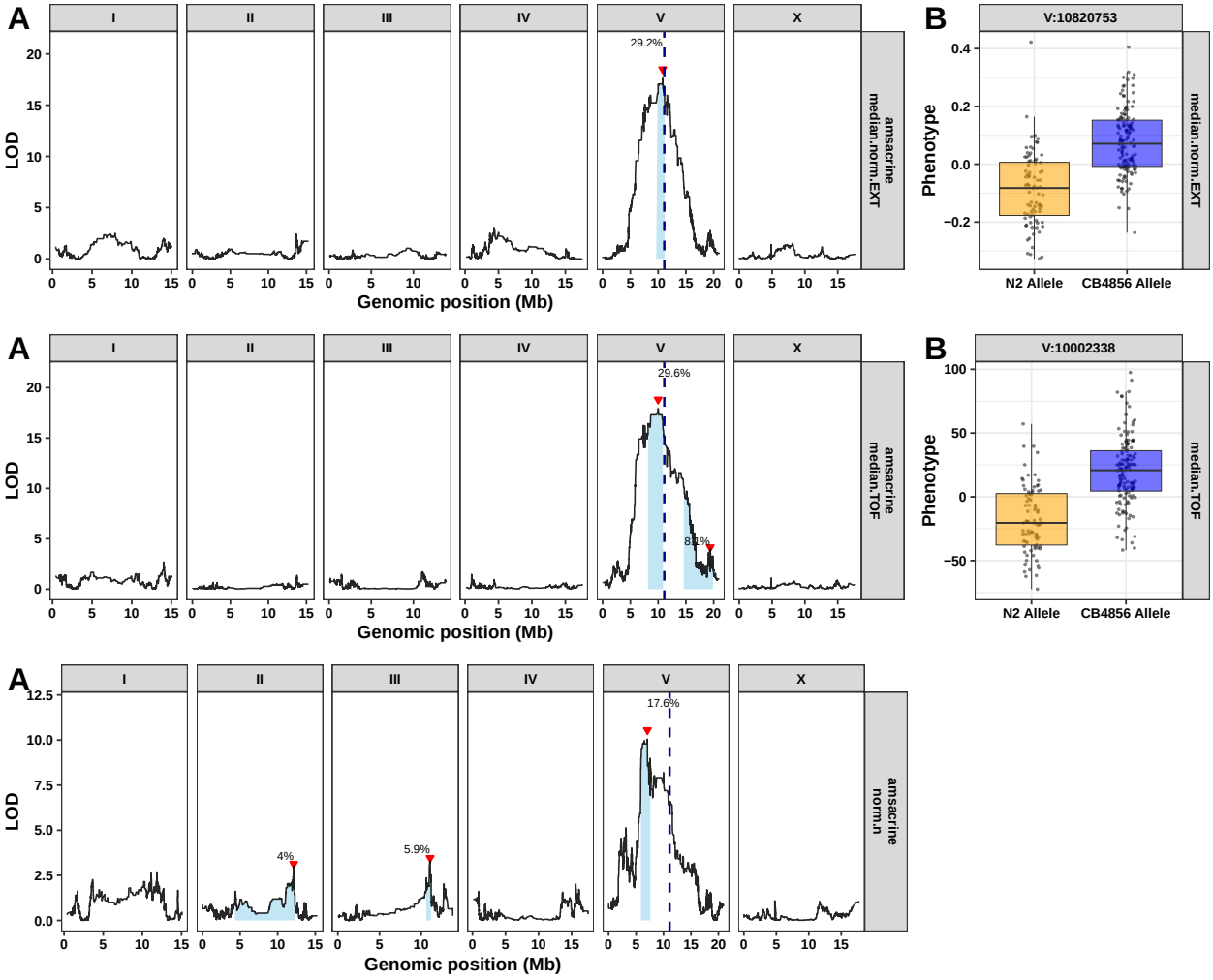
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CB4856 Allele
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81%
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V:10002338
median.TOF
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17.6%
amsacrine
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Figure S2 Linkage mapping analysis for all drug-response traits. For each drug-response trait, (A) genomic position (x-axis) is plotted against the logarithm of the odds (LOD) score (y-axis) for 13,003 genomic markers. Each significant QTL is indicated by a red triangle at the peak marker, and a blue rectangle shows the 95% confidence interval around the peak marker. The percentage of the total variance in the RIAIL population that can be explained by each QTL is shown above the QTL. The dotted vertical line represents the genomic position of *scb-1*. (B) For each QTL on chromosome V plotted in A, the residual phenotypes (y-axis) of RIAILs split by genotype at the marker with the maximum LOD score (x-axis) are plotted as Tukey box plots. Each point corresponds to a unique recombinant strain. Strains with the N2 allele are colored orange and strains with the CB4856 allele are colored blue.

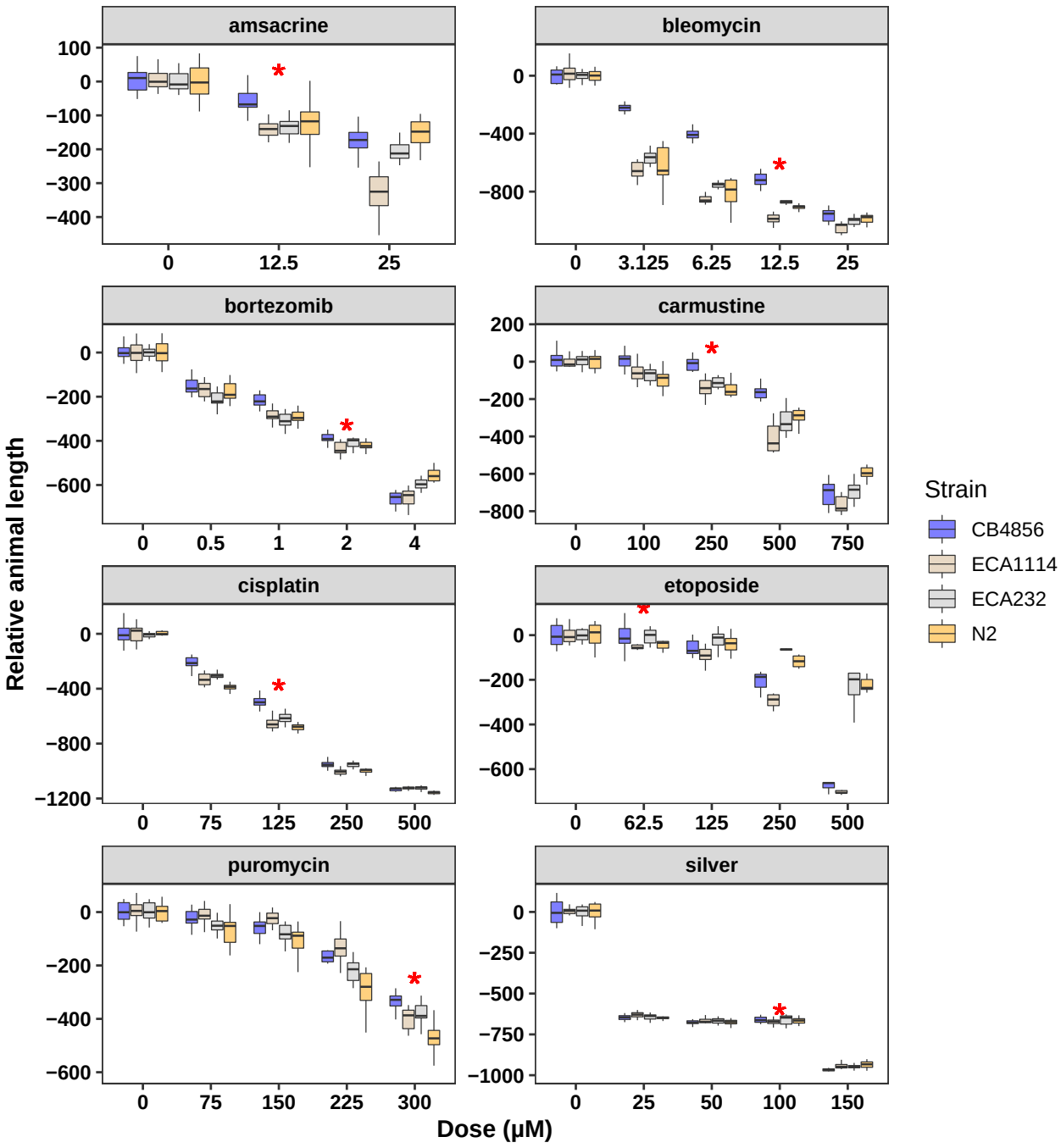

Figure S3 Dose responses for NILs and parents with modified HTA. Relative animal length (median.EXT, y-axis) measured for each strain, colored by genotype, across five drug concentrations (µM, x-axis). For each strain, phenotype is subtracted from the control. A red asterisk indicates the dose selected for further experiments.

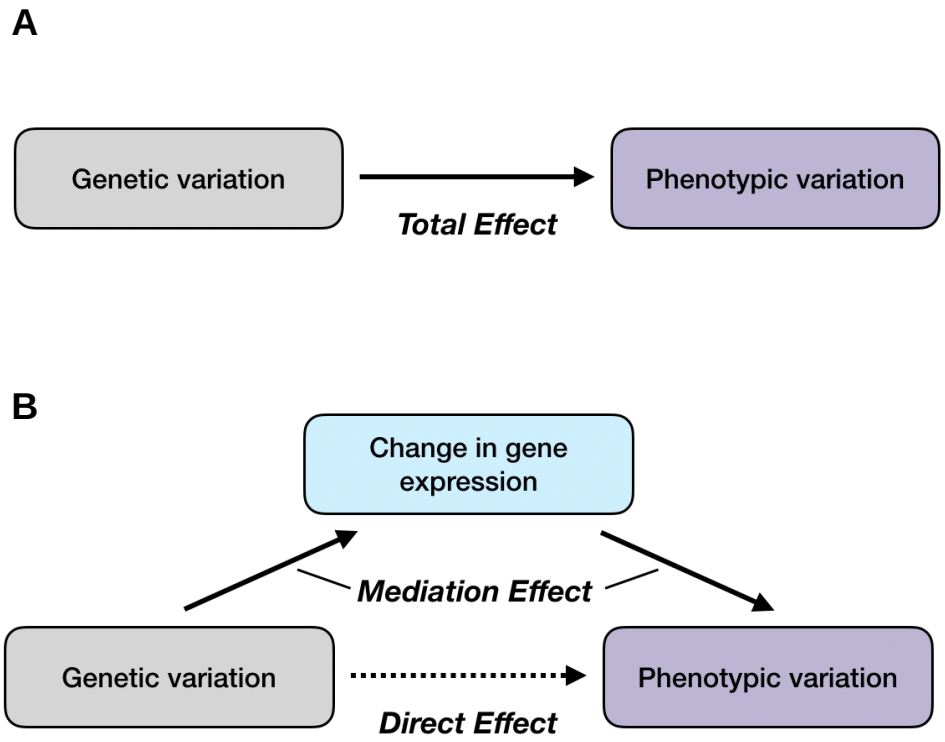

Figure S4 Model for gene expression as a mediator of a drug-response QTL. (A) The effect size of a QTL is calculated as the total effect a genetic variant has on the phenotypic variation of the population, regardless of the causal association of the genetic variant. (B) Mediation analysis tests the hypothesis that a genetic variant does not directly lead to phenotypic variation but rather causes a change in gene expression that further drives the change in phenotype observed. The "Direct Effect" can be calculated by including gene expression as a cofactor in the linear model between genotype and phenotype and extracting the partial coefficient of the effect of genotype on phenotype. The "Mediation Effect" can be calculated by subtracting the "Total Effect" - "Direct Effect". Mediation estimates are then calculated as the proportion of the "Total Effect" that can be explained by the "Mediation Effect" ("Mediation Effect" / "Total Effect")

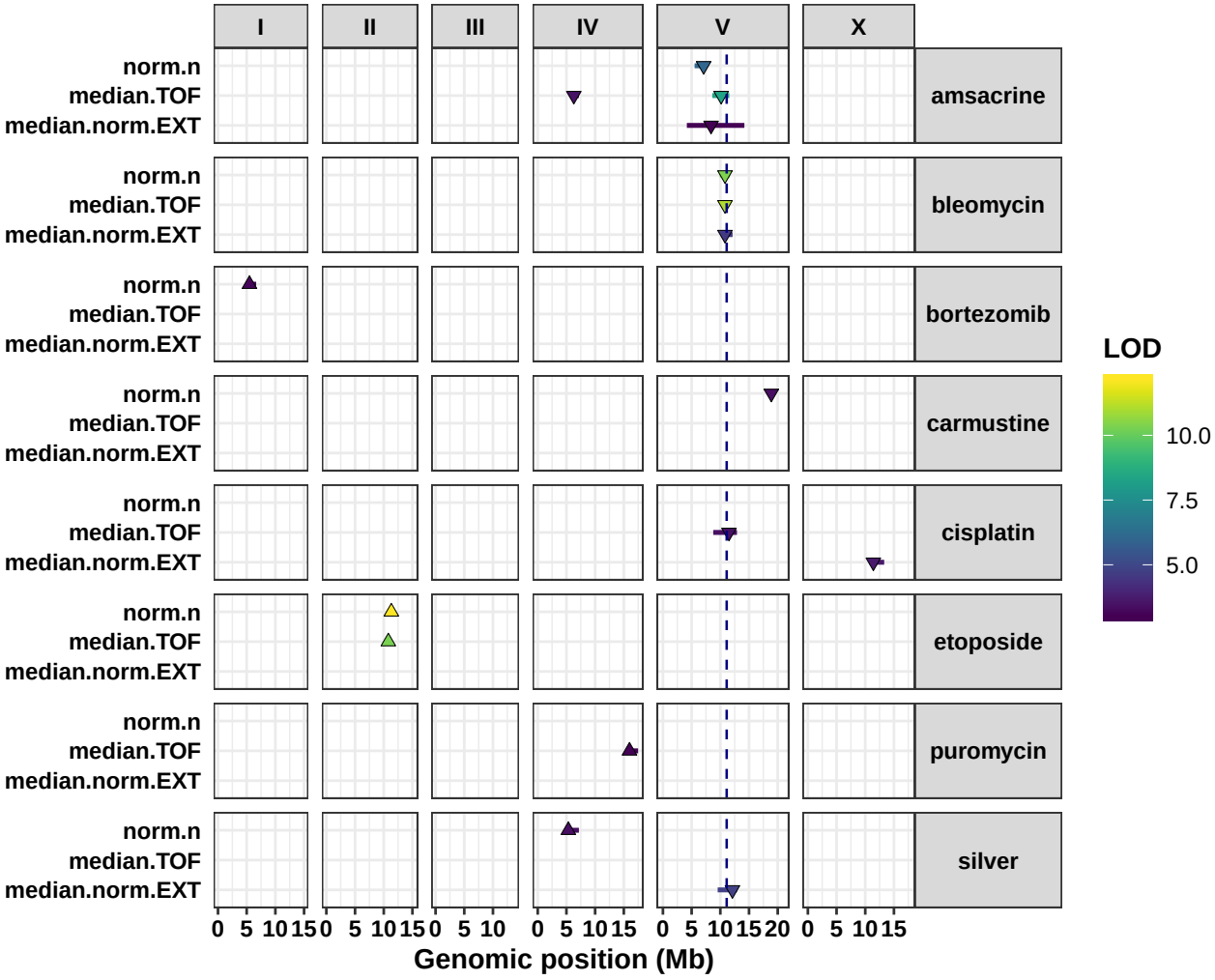

Figure S5 Linkage mapping summary for drug-response traits in the set 1 RIAILs. Genomic positions (x-axis) of all QTL identified from linkage mapping are shown for each drug-trait (y-axis). Each QTL is plotted as a triangle at the genomic location of the peak marker and a line that represents the 95% confidence interval. QTL with right side up triangles have a negative effect size (N2 allele is resistant), and QTL with upside down triangles have a positive effect size (CB4856 allele is resistant). QTL are colored by the logarithm of the odds (LOD) score, increasing in significance from purple to green to yellow. The dotted vertical line represents the genomic position of *scb-1*.

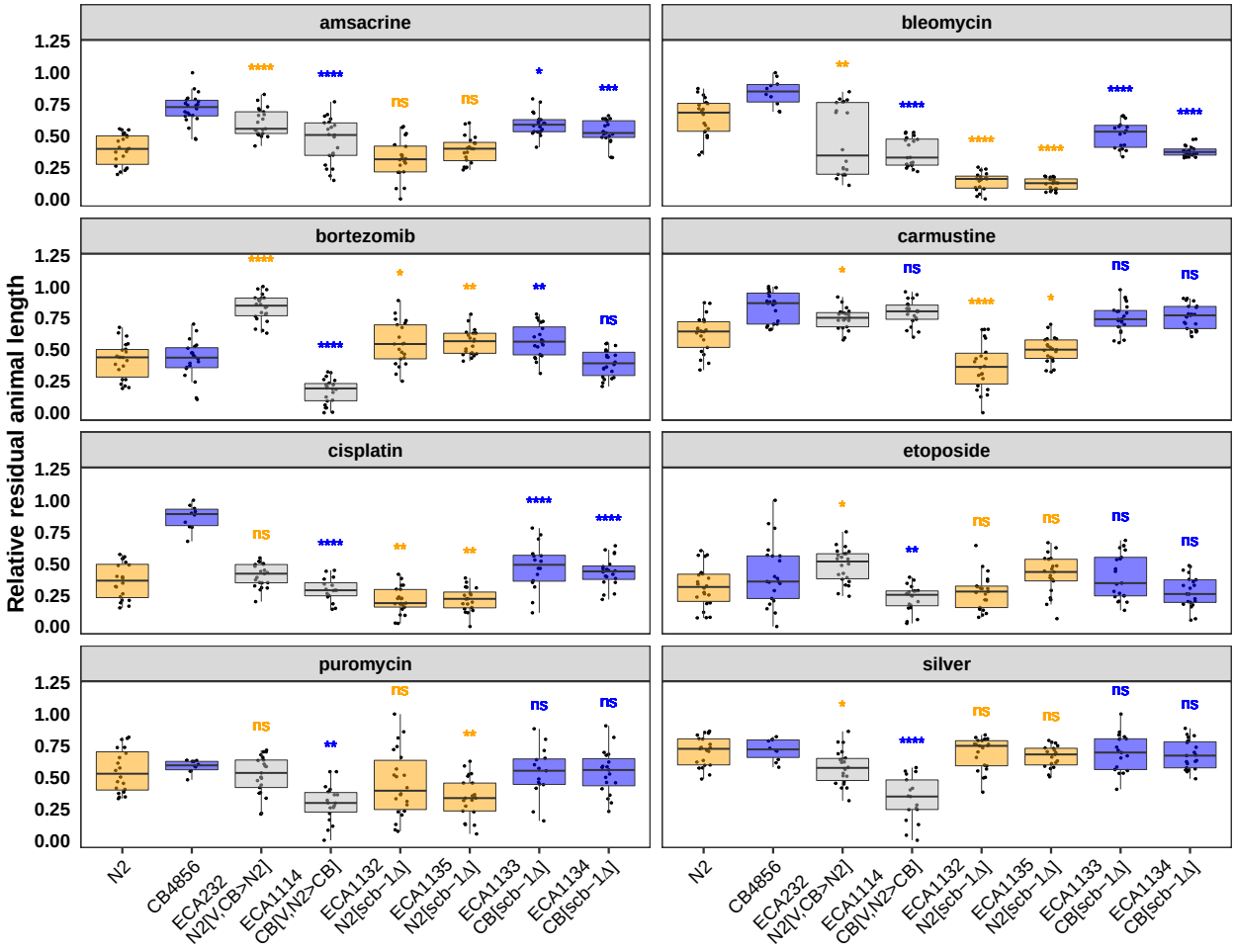

Figure S6 Testing the role of *scb-1* in drug responses. Drug phenotypes are plotted as Tukey box plots with strain (x-axis) by relative residual animal length (median.EXT, y-axis). Strains with an N2 background are colored orange and strains with a CB4856 background are colored blue. NILs are colored grey. Statistical significance of each strain compared to its parental strain (ECA232, ECA1132, and ECA1135 to N2 and ECA1114, ECA1133, and ECA1134 to CB4856) is shown above each strain and colored by the parent strain it was tested against (ns = non-significant (p-value > 0.05); *, **, ***, and **** = significant (p-value $<$ 0.05, 0.01, 0.001, or 0.0001, respectively).

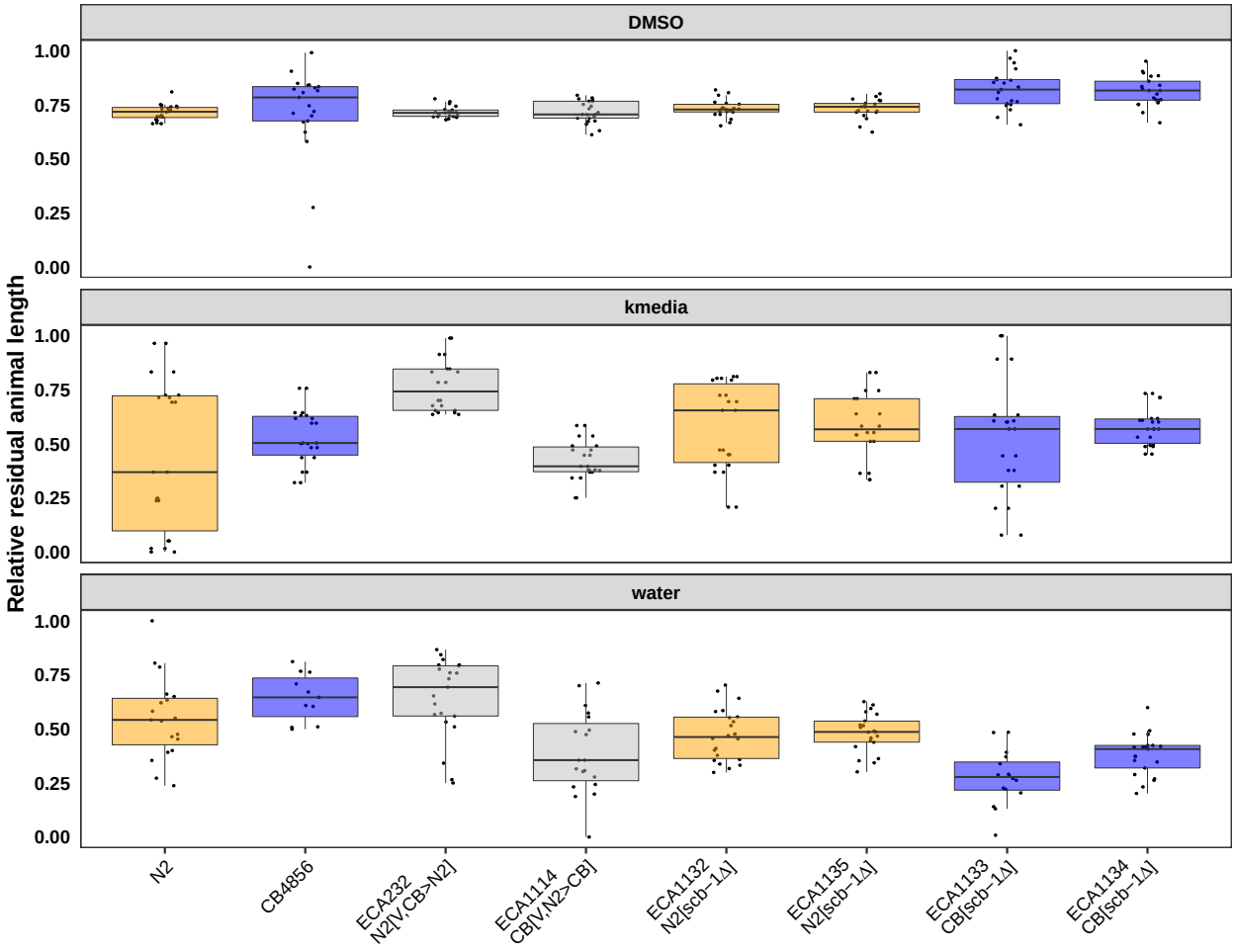

Figure S7 Control conditions for *scb-1* deletion test. Control phenotypes are plotted as Tukey box plots with strain (x-axis) by relative residual animal length (median.EXT, y-axis). Strains with an N2 background are colored orange and strains with a CB4856 background are colored blue. NILs are colored grey.