

# Package ‘CSeQTL’

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**Type** Package

**Title** Cell Type-Specific Expression Quantitative Trail Loci Mapping

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**Description** Perform bulk and cell type-specific expression quantitative trail loci mapping with our novel method (Little et al. (2023) <[doi:10.1038/s41467-023-38795-w](https://doi.org/10.1038/s41467-023-38795-w)>).

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**LinkingTo** Rcpp, RcppArmadillo

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**License** GPL (>= 3)

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**VignetteBuilder** knitr

**NeedsCompilation** yes

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|                |                       |
|----------------|-----------------------|
| CSeQTL_dataGen | <i>CSeQTL_dataGen</i> |
|----------------|-----------------------|

---

## Description

Simulates a gene/SNP pair with baseline covariates *XX*, cell type compositions *true\_RHO*, phased SNP genotypes *true\_SNP*, and total (TReC) and allele-specific read counts (ASReC) contained in *dat*.

## Usage

```
CSeQTL_dataGen(
  NN,
  MAF,
  true_BETA0 = log(1000),
  true_KAPPA,
  true_ETA,
  true_PHI = 0.1,
  true_PSI = 0.05,
  prob_phased = 0.05,
  true_ALPHA = NULL,
  batch = 1,
  RHO = NULL,
  cnfSNP = FALSE,
  show = TRUE
)
```

## Arguments

|            |  |
|------------|--|
| NN         | Positive integer for sample size.  |
| MAF        | Positive numeric value between 0 and 1 for the minor allele frequency to simulate phased SNP genotypes assuming Hardy-Weinberg.  |
| true_BETA0 | A positive numeric value denoting the reference cell type and reference base's expression multiplied by two and log transformed. For example, if the TReC for reference base and cell type is 500, then $\text{true\_BETA0} = \log\{2 * 500\}$ . |
| true_KAPPA | A numeric vector denoting the baseline fold change in TReC between a cell type and reference. By definition, the first element is 1.   |
| true_ETA   | A numeric vector where each element denotes the fold change in TReC between the non-reference and reference base in a cell type.   |

|             |  |
|-------------|--|
| true_PHI    | A non-negative numeric value denoting the over-dispersion term associated with TReC. If $\text{true\_PHI} > 0$ , TReC is simulated with the negative binomial. If $\text{true\_PHI} = 0$ , TReC is simulated with the poisson.   |
| true_PSI    | A non-negative numeric value denoting the over-dispersion term associated with ASReC. If $\text{true\_PSI} > 0$ , ASReC is simulated with the beta-binomial, otherwise it is simulated with the binomial distribution.   |
| prob_phased | A positive numeric value denoting the simulated proportion of simulated TReC that are ASReC.   |
| true_ALPHA  | By default, it is set to NULL setting each cell type with an eQTL to be cis-eQTL. Otherwise, a positive numeric vector of fold changes between TReC eQTL effect sizes and ASReC eQTL effect sizes.   |
| batch       | A numeric value set to 1 by default to allow underlying batch effects. Set to zero to eliminate batch effects.   |
| RHO         | A numeric matrix of cell type proportions where each row sums to one. If set to NULL, a matrix of cell type proportions will be simulated.   |
| cnfSNP      | A boolean value where TRUE re-arranges simulated SNPs to correlate with baseline bulk expression. When fitting the marginal model (not accounting for cell type proportions) and in the presence of cell type-specific differentiated expression, a marginal eQTL may be incorrectly inferred. |
| show        | A boolean value to display verbose output and plot intermediate simulated results.   |

**Value**

A R list containing true parameters governing the simulated dataset, simulated covariate matrix *XX*, observed outcomes in *dat*.

---

CSeQTL\_full\_analysis    *CSeQTL\_full\_analysis*

---

**Description**

Performs marginal and cell type-specific eQTL analysis with both CSeQTL and OLS models for simulation and comparative purposes.

**Usage**

```
CSeQTL_full_analysis(
  TREC,
  hap2,
  ASREC,
  PHASE,
  SNP,
  RHO,
  XX,
```

```

log_lib_size,
vec_MARG = c(TRUE, FALSE),
vec_TRIM = c(TRUE, FALSE),
vec_PERM = c(TRUE, FALSE),
thres_TRIM = 10,
ncores = 1,
show = TRUE
)

```

### Arguments

|              |   |
|--------------|---|
| TREC         | An integer vector of total read counts.   |
| hap2         | An integer vector of second haplotype counts  |
| ASREC        | An integer vector of total haplotype counts   |
| PHASE        | An integer vector of 0s and 1s denoting if a subject has available haplotype counts.  |
| SNP          | An integer vector of phased genotypes coded 0 (AA), 1 (AB), 2 (BA), 3 (BB), and 5 (NA).   |
| RHO          | A numeric matrix of cell type proportions. Rows correspond to subjects and columns correspond to cell types.                                      |
| XX           | A numeric design matrix of baseline covariates including the intercept in the first column and centered continuous covariates.                    |
| log_lib_size | A positive numeric vector of log transformed library sizes per subject.   |
| vec_MARG     | A boolean vector for marginal and/or cell type-specific analyses to be run. By default, both sets of analyses are run.                            |
| vec_TRIM     | A boolean vector for whether or not analyses with trimmed outcomes are included. By default, both sets of analyses are run.                       |
| vec_PERM     | A boolean vector for whether or not permuted SNP analyses are included. By default, both sets of analyses are run.                                |
| thres_TRIM   | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed. |
| ncores       | A positive integer specifying the number of threads available to decrease computational runtime.  |
| show         | A boolean value to display verbose output and plot intermediate simulated results.  |

### Value

A R list containing multiple objects. `res` is a R dataframe containing the model fitted, marginal model indicator, TRIM indicator, permutation indicator, cell types, utilized allele-specific reads indicator, A and B allele-specific expression, eta/eqtl fold change estimate, p-value. `out` contains lists of detailed estimates per model fit.

---

CSeQTL\_GS

*CSeQTL\_GS*


---

### Description

Main function that performs eQTL mapping on one gene with its associated SNPs.

### Usage

```
CSeQTL_GS(
  XX,
  TREC,
  SNP,
  hap2,
  ASREC,
  PHASE,
  RHO,
  trim = TRUE,
  thres_TRIM = 20,
  numAS = 5,
  numASn = 5,
  numAS_het = 5,
  cistrans = 0.01,
  ncores = 1,
  show = TRUE
)
```

### Arguments

|       |   |
|-------|---|
| XX    | A numeric design matrix of baseline covariates including the intercept in the first column and centered continuous covariates. One of the non-intercept columns should correspond to centered log-transformed library size. The rownames(XX) needs to be specified. |
| TREC  | An integer vector containing one gene's total read counts. The names(TREC) needs to be specified.   |
| SNP   | A nonnegative integer matrix with genotypes. Values should be coded 0, 1, 2, 3, 5 for genotypes AA, AB, BA, BB, NA, respectively. Rows correspond to SNPs and columns correspond to subjects. The rownames(SNP) needs to be specified.                              |
| hap2  | An integer vector of the second haplotype's counts for the gene. The names(hap2) needs to be specified and match names(TREC).   |
| ASREC | An integer vector of the total haplotype counts (ASReC) for the gene. The names(ASREC) needs to be specified and match names(TREC).   |
| PHASE | A binary 0/1 vector indicating if haplotype counts for the gene will be used. The names(PHASE) needs to be specified and match names(TREC).   |

|            |  |
|------------|--|
| RHO        | A numeric matrix of cell type proportions. Rows correspond to subjects and columns correspond to cell types. The rownames(RHO) needs to be specified and match names(TREC). The colnames(RHO) also needs to be specified.  |
| trim       | Boolean value set to FALSE by default to prevent outcome trimming. If TRUE, the CSeQTL model will be fitted without SNP genotype to calculate each subject's Cooks' distance for the gene.   |
| thres_TRIM | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed.  |
| numAS      | A positive integer to determine if a subject has enough total haplotype counts.  |
| numASn     | A positive integer to determine how many subjects have at least numAS to use the haplotype counts.   |
| numAS_het  | A positive integer to determine how many subjects with at least numAS are heterozygous (AB or BA). If $\text{sum}(\text{PHASE} == 1 \ \& \ \text{ASREC} \geq \text{numAS} \ \& \ (\text{SNP} == 1 \   \ \text{SNP} == 2)) \geq \text{numAS\_het}$ , those subjects haplotype counts will be used for TReCASE and cis/trans testing and estimation. |
| cistrans   | A numeric value specifying the cis/trans test p-value cutoff to determine if the eQTLs from TReC-only or TReCASE model is reported.  |
| ncores     | A positive integer specifying the number of threads available to decrease computational runtime when performing trimming and looping through SNPs.   |
| show       | A boolean value to display verbose output.   |

### Value

A R list of statistics and metrics after optimizing the model across multiple SNPs. The list contains parameter MLEs, gene expression estimates, fold change estimates, convergence indicators, likelihood ratio test statistics, and associated p-values.

---

|                   |                          |
|-------------------|--------------------------|
| CSeQTL_linearTest | <i>CSeQTL_linearTest</i> |
|-------------------|--------------------------|

---

### Description

Runs marginal and cell type-specific analysis using ordinary least squares.

### Usage

```
CSeQTL_linearTest(
  input,
  XX,
  RHO,
  SNP,
  YY = NULL,
  MARG = FALSE,
  impute_genotype = FALSE,
  trim = FALSE,
```

```

    thres_TRIM = 10,
    show_plot = TRUE,
    main_plot = "",
    CTs = NULL
  )

```

### Arguments

|             |   |
|-------------|---|
| input       | A data.frame containing columns total (total read counts) and log_lib_size (log transformed library size).  |
| XX          | A numeric design matrix of baseline covariates including the intercept in the first column and centered continuous covariates.  |
| RHO         | A numeric matrix of cell type proportions. Rows correspond to subjects and columns correspond to cell types.  |
| SNP         | An integer vector of phased genotypes coded 0 (AA), 1 (AB), 2 (BA), 3 (BB), and 5 (NA).   |
| YY          | Default is NULL. By default, the outcome for OLS is the inverse rank quantile normalized TReC after library size correction. Otherwise, the user can input their own transformed outcome as a numeric vector.                                     |
| MARG        | Boolean value. Set to TRUE to fit the marginal OLS model. Default is set to FALSE to fit the cell type-specific interaction OLS model.  |
| impute_geno | Boolean value. Default is set to FALSE to only analyze subjects with non-missing genotype. If TRUE, missing genotypes are imputed with the mean of non-missing genotypes mimicing MatrixEQTL.   |
| trim        | Boolean value set to FALSE by default to prevent outcome trimming. If TRUE, the OLS model will be fitted without covariates containing SNP genotype to calculate each subject's Cooks' distance.  |
| thres_TRIM  | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed.   |
| show_plot   | Boolean value set to TRUE to visualize boxplot or interactions.   |
| main_plot   | Character string for the visual's main title.   |
| CTs         | Set to NULL by default. If NULL and show_plot = TRUE, all cell type interaction plots are shown. Otherwise a subset of cell types can be displayed using an integer vector of columns or character vector of column names of RHO can be provided. |

### Value

A R list containing `lm()` output for `lm_out`, a R dataframe for `out_df` containing regression estimates, standard errors, p-values. `res_trim` provides a summary of trimmed results over a grid of cut-off values and number of samples trimmed. `cooksd` is a numeric vector of median shifted and MAD scaled Cook's distances per sample. `prop_trim`, a numeric value for number of samples with outcome values trimmed for the user-specified `thres_TRIM` value.

---

CSeQTL\_oneExtremeSim *CSeQTL\_oneExtremeSim*

---

### Description

Performs a simulation with multiple replicates for a pre-specified set of arguments.

### Usage

```
CSeQTL_oneExtremeSim(
  NN,
  MAF,
  true_BETA0,
  true_KAPPA,
  true_ETA,
  true_PHI = 0.1,
  wRHO,
  noiseRHO = 0,
  RR = 50,
  vec_MARG = c(TRUE, FALSE),
  vec_TRIM = c(TRUE, FALSE),
  vec_PERM = c(TRUE, FALSE),
  thres_TRIM = 10,
  ncores = 1,
  sim_fn
)
```

### Arguments

|            |  |
|------------|--|
| NN         | Positive integer for sample size.  |
| MAF        | Positive numeric value between 0 and 1 for the minor allele frequency to simulate phased SNP genotypes assuming Hardy-Weinberg.  |
| true_BETA0 | A positive numeric value denoting the reference cell type and reference base's expression multiplied by two and log transformed. For example, if the TReC for reference base and cell type is 500, then $\text{true\_BETA0} = \log\{2 * 500\}$ . |
| true_KAPPA | A numeric vector denoting the baseline fold change in TReC between a cell type and reference. By definition, the first element is 1.   |
| true_ETA   | A numeric vector where each element denotes the fold change in TReC between the non-reference and reference base in a cell type.   |
| true_PHI   | A non-negative numeric value denoting the over-dispersion term associated with TReC. If $\text{true\_PHI} > 0$ , TReC is simulated with the negative binomial. If $\text{true\_PHI} = 0$ , TReC is simulated with the poisson.                   |
| wRHO       | Takes integer values 1, 2, or 3 to simulate three scenarios of cell type proportions.  |
| noiseRHO   | A positive numeric value to purposely distort simulated cell type compositions.  |



|            |   |
|------------|---|
| RR         | A positive integer for number of replicates to generate and analyze.  |
| vec_MARG   | A boolean vector for marginal and/or cell type-specific analyses to be run. By default, both sets of analyses are run.                            |
| vec_TRIM   | A boolean vector for whether or not analyses with trimmed outcomes are included. By default, both sets of analyses are run.                       |
| vec_PERM   | A boolean vector for whether or not permuted SNP analyses are included. By default, both sets of analyses are run.                                |
| thres_TRIM | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed. |
| ncores     | A positive integer specifying the number of threads available to decrease computational runtime.  |
| sim_fn     | Character value specifying the full path and filename to store intermediate simulation replicates should errors arise.                            |

**Value**

A R list containing the results of a small-scale simulation. `res` contains replicate-specific results while `ures` contains overall simulation results include power, frequency of replicates with constrained eta estimates and gene expressions inferred to be zero after optimization.

---

CSeQTL\_run\_MatrixEQTL *CSeQTL\_run\_MatrixEQTL*

---

**Description**

CSeQTL\_run\_MatrixEQTL

**Usage**

```
CSeQTL_run_MatrixEQTL(TREC, RD, XX, SNP, out_cis_fn, cisDist = 1e+06)
```

**Arguments**

|            |  |
|------------|--|
| TREC       | A matrix of integer total read counts, rows are genes with row labels with syntax "gene_name:chrom:start:end", columns are samples with column labels. |
| RD         | A positive numeric vector of library sizes per sample.   |
| XX         | A numeric design matrix of baseline covariates including the intercept in the first column and centered continuous covariates.                         |
| SNP        | An integer matrix, rows are genomic loci with row labels such as "chrom:pos", columns correspond to samples with column labels.                        |
| out_cis_fn | A full path filename string to store MatrixEQTL output   |
| cisDist    | A positive integer for number of SNPs to include relative to the gene body   |

**Value**

The MatrixEQTL output file/R dataframe generated containing genes, SNPs, associated p-values, effect sizes, etc.

---

CSeQTL\_smart

*CSeQTL\_smart*


---

### Description

A function to understand the novelties within CSeQTL. The user can experiment with trimming TReC, assess parameter estimation, perform hypothesis testing, actively constrain cell type-specific parameters, when analyzing a single gene/SNP pair.

### Usage

```
CSeQTL_smart(
  TREC,
  hap2,
  ASREC,
  PHASE,
  SNP,
  RHO,
  XX,
  upPHI,
  upKAPPA,
  upETA,
  upPSI,
  upALPHA,
  iFullModel = FALSE,
  trim = FALSE,
  thres_TRIM = 10,
  hypotest = TRUE,
  swap = TRUE,
  numAS = 5,
  numASn = 5,
  numAS_het = 5,
  cistrans_thres = 0.01,
  gr_eps = 0.01,
  conv_eps = 0.001,
  ncores = 1,
  show = FALSE
)
```

### Arguments

|       |  |
|-------|--|
| TREC  | An integer vector of total read counts.  |
| hap2  | An integer vector of second haplotype counts   |
| ASREC | An integer vector of total haplotype counts  |
| PHASE | An integer vector of 0s and 1s denoting if a subject has available haplotype counts. |

|                |  |
|----------------|--|
| SNP            | An integer vector of phased genotypes coded 0 (AA), 1 (AB), 2 (BA), 3 (BB), and 5 (NA).  |
| RHO            | A numeric matrix of cell type proportions. Rows correspond to subjects and columns correspond to cell types.   |
| XX             | A numeric design matrix of baseline covariates including the intercept in the first column and centered continuous covariates.   |
| upPHI          | A value of 0 or 1 indicating if a Poisson or Negative binomial distribution is fitted, respectively.   |
| upKAPPA        | An integer vector of zeroes and ones where $\text{length}(\text{upKAPPA}) == \text{ncol}(\text{RHO})$ . A requirement is $\text{upKAPPA}[1] = 1$ . Cell types with indices equal to one have the baseline fold change between the q-th and reference cell type are estimated. Otherwise that cell type's parameter is constrained to zero.         |
| upETA          | An integer vector of zeroes and ones where $\text{length}(\text{upETA}) == \text{ncol}(\text{RHO})$ indicating which cell types eQTL parameters are estimated or constrained to their null.  |
| upPSI          | A value of 0 or 1 indicating if a Binomial or Beta-binomial distribution is fitted, respectively.  |
| upALPHA        | An integer vector of zeroes and ones where $\text{length}(\text{upALPHA}) == \text{ncol}(\text{RHO})$ indicating which cell types' cis-trans parameters are estimated or constrained to their null.  |
| iFullModel     | A boolean that if set to TRUE will determine the submodel of the full model, based by upKAPPA, upETA, and upALPHA parameters, that can be estimated with stability.  |
| trim           | Boolean value. If TRUE, the TReC model will be fitted without SNP genotype to calculate each subject's Cooks' distance.  |
| thres_TRIM     | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed.  |
| hypotest       | A boolean to perform eQTL significance testing and cis-trans eQTL testing.   |
| swap           | A boolean to determine if the reference cell type should be swapped with the cell type with highest TReC across alleles.   |
| numAS          | A positive integer to determine if a subject has enough total haplotype counts.  |
| numASn         | A positive integer to determine how many subjects have at least numAS to use the haplotype counts.   |
| numAS_het      | A positive integer to determine how many subjects with at least numAS are heterozygous (AB or BA). If $\text{sum}(\text{PHASE} == 1 \ \& \ \text{ASREC} \geq \text{numAS} \ \& \ (\text{SNP} == 1 \   \ \text{SNP} == 2)) \geq \text{numAS\_het}$ , those subjects haplotype counts will be used for TReCASE and cis/trans testing and estimation. |
| cistrans_thres | A numeric value to determine the cis/trans test p-value cutoff.  |
| gr_eps         | A numeric value to determine if convergence is achieved based on the L2 norm of the gradient.  |
| conv_eps       | A numeric value to determine if convergence is achieved based on the L2 norm of the product of the inverse hessian and gradient.   |

|        |  |
|--------|--|
| ncores | A positive integer specifying the number of threads available to decrease computational runtime. |
| show   | A boolean value to display verbose output and plot intermediate simulated results.               |

**Value**

A R list of statistics and metrics after optimizing the model for a single SNP. The list contains parameter MLEs, gradient vectors, covariance matrices, gene expression estimates, fold change estimates, convergence indicators, likelihood ratio test statistics, and associated p-values.

---

|                     |                     |
|---------------------|---------------------|
| <i>gen_true_RHO</i> | <i>gen_true_RHO</i> |
|---------------------|---------------------|

---

**Description**

Simulates cell type proportions under three scenarios.

**Usage**

```
gen_true_RHO(wRHO = 1, NN, QQ, RHO = NULL)
```

**Arguments**

|      |  |
|------|--|
| wRHO | An integer taking values 1, 2, or 3 for one of the three scenarios. For wRHO equal to 2 or 3, QQ needs to be set to 3 cell types.              |
| NN   | Positive integer for sample size.  |
| QQ   | Positive integer for number of cell types.   |
| RHO  | Default to NULL leads to simulating cell type proportions. If a matrix of proportions is supplied, this function will append row/column names. |

**Value**

A numeric matrix with QQ columns and NN rows of cell type proportions per sample and cell type.

---

 OLS\_sim
 

---



---

 OLS\_sim
 

---

**Description**

OLS\_sim

**Usage**

```

OLS_sim(
  NN,
  MAF,
  true_BETA0,
  true_KAPPA,
  true_ETA,
  wRHO,
  RR,
  trim = FALSE,
  thres_TRIM = 10,
  showRHO = TRUE
)

```

**Arguments**

|            |  |
|------------|--|
| NN         | Positive integer for sample size.  |
| MAF        | Positive numeric value between 0 and 1 for the minor allele frequency to simulate phased SNP genotypes assuming Hardy-Weinberg.  |
| true_BETA0 | A positive numeric value denoting the reference cell type and reference base's expression multiplied by two and log transformed. For example, if the TReC for reference base and cell type is 500, then $\text{true\_BETA0} = \log\{2 * 500\}$ . |
| true_KAPPA | A numeric vector denoting the baseline fold change in TReC between a cell type and reference. By definition, the first element is 1.   |
| true_ETA   | A numeric vector where each element denotes the fold change in TReC between the non-reference and reference base in a cell type.   |
| wRHO       | Takes integer values 1, 2, or 3 to simulate three scenarios of cell type proportions.  |
| RR         | A positive integer for number of replicates to generate and analyze.   |
| trim       | Boolean value set to FALSE by default to prevent outcome trimming. If TRUE, the OLS model will be fitted without covariates containing SNP genotype to calculate each subject's Cooks' distance.   |
| thres_TRIM | A positive numeric value to perform subject outcome trimming. Subjects with standardized Cooks' Distances greater than the threshold are trimmed.  |
| showRHO    | Boolean for seeing a preview of how proportions are distributed.   |

**Value**

Simulation results for OLS-based approach with per replicate and per cell type metrics including p-values, OLS effect sizes, and proportion of samples with trimmed outcomes.

---

|          |                 |
|----------|-----------------|
| plot_RHO | <i>plot_RHO</i> |
|----------|-----------------|

---

**Description**

plot\_RHO

**Usage**

```
plot_RHO(RHO, main_plot = "", ...)
```

**Arguments**

|           |  |
|-----------|--|
| RHO       | A numeric matrix of cell type proportions. Rows correspond to subjects and columns correspond to cell types. |
| main_plot | Character string for the visual's main title.  |
| ...       | Arguments for <code>plot(x,y,bty = "n", ...)</code> .  |

**Value**

Null. A plot of cell type proportions per cell type across NN samples.

---

|                |                       |
|----------------|-----------------------|
| prep_gene_info | <i>prep_gene_info</i> |
|----------------|-----------------------|

---

**Description**

Prepare GTF files for gene and exon level information

**Usage**

```
prep_gene_info(work_dir, gtf_gz_fn = NULL)
```

**Arguments**

|           |  |
|-----------|--|
| work_dir  | A character string specifying the working directory to store gene and exon data. |
| gtf_gz_fn | A character string full path of the gz compressed gtf file                       |

**Value**

Null. No value returned.

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