**Package ‘BayesMetaPenetrance’**

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**Type** Package

**Title** Bayesian meta-analysis to estimate age-specific penetrance of getting cancer due to pathogenic variants of a given gene

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**Description**
Estimate meta-analytic age-specific risk of getting cancer (penetrance) due to pathogenic variants of a given gene by integrating information from studies reporting different types of risk measures on that particular gene. These risk measures include age-specific penetrance, relative risk (RR), standard incidence ratio (SIR), and odds ratio (OR).

**Depends** R (>= 3.6.0)

**License** GPL-2

**LinkingTo** Rcpp

**Imports** dplyr (>= 1.0.9), mvtnorm (>= 1.1-3), rlist (>= 0.4.6.2), Rcpp (>= 1.0.9)

**R topics documented:**

| BayesMetaPenetrance | Estimates consensus age-specific penetrance of cancer for carriers of a pathogenic gene mutation |

**Description**
BayesMetaPenetrance is used to estimate meta-analytic age-specific risk of getting cancer (penetrance) for carriers of pathogenic variants of a specific gene. Information from studies reporting different types of risk measures (these risk measures include age-specific penetrance, relative risk (RR), standard incidence ratio (SIR), and odds ratio (OR)) on that gene are integrated to give the age-specific penetrance for carriers up to age 85. In this package, SIR is treated in the same manner as RR under the assumption of rare disease.
BayesMetaPenetrance

Usage

BayesMetaPenetrance(penet, RR_studies=TRUE, OR_studies=TRUE, OR, zero_studies=FALSE, zero_OR, ages=seq(40, 80, 10), n.iter=30000, n.burn=15000, CrI=FALSE, pl=FALSE, ylim=c(0, 1), xlim=c(40, 80))

Arguments

penet A data frame containing information for studies reporting age-specific penetrance with following columns:

study_label label to identify the set of penetrance values from a single study.
penetrance age-specific penetrance value.
penet_ci_lower lower 95% confidence limit.
penet_ci_upper upper 95% confidence limit.
ages_penet ages at which penetrance is reported.

RR_studies A logical variable to indicate whether studies reporting RR or SIR are included in the meta analysis. Default is TRUE.

RR If RR_studies is TRUE, a data frame containing information for all RR and SIR studies with following columns where each row corresponds to a single study

R.est reported RR/SIR value.
RR.ci.lower lower 95% confidence limit.
RR.ci.upper upper 95% confidence limit.

A mean age of onset for carriers. Default is 63.
V sd of age of onset for carriers. Default is 14.00726.
A.lo minimum possible age of onset for carriers. Default is 20.
A.hi maximum possible age of onset for carriers. Default is 95.
A0 mean age of onset for non-carriers. Default is 63.
V0 sd of age of onset for non-carriers. Default is 14.00726.
A0.lo minimum possible age of onset for non-carriers. Default is 20.
A0.hi maximum possible age of onset for non-carriers. Default is 95.

OR_studies A logical variable to indicate whether studies reporting OR are included in the meta analysis. Default is TRUE.

OR If OR_studies is TRUE, a data frame containing information for all OR studies with following columns where each row corresponds to a single study

OR.est reported OR value.
OR.ci.lower lower 95% confidence limit.
OR.ci.upper upper 95% confidence limit.

A mean age of onset for cases. Default is 63.
V sd of age of onset for cases. Default is 14.00726.
A.lo minimum possible age of onset among cases. Default is 20.
A.hi maximum possible age of onset among cases. Default is 95.
A0 mean age of controls (at inclusion in study). Default is value A.
V0 sd of age of controls (at inclusion in study). Default is value V.
A0.lo minimum possible age of controls (at inclusion in study). Default is value A.lo.
A0.hi maximum possible age of controls (at inclusion in study). Default is value A.hi.

zero_studies A logical variable to indicate whether information from case control studies where no mutations were detected in controls are included in the meta analysis. These studies should not be included in OR. Default if FALSE.
zero_OR

If zero_studies is TRUE, a data frame containing information for such studies with following columns where each row corresponds to a single study

carrier.cases  number of carrier cases.
non_carrier.cases  number of non-carrier cases.
non_carrier.controls  number of non-carrier controls.
A.lo  minimum possible age of onset among cases. Default is 20.
A.hi  maximum possible age of onset among cases. Default is 95.
A0  mean age of controls (at inclusion in study). Default is value A.
V0  sd of age of controls (at inclusion in study). Default is value V.
A0.lo  minimum possible age of controls (at inclusion in study). Default is value A.lo.
A0.hi  maximum possible age of controls (at inclusion in study). Default is value A.hi.

ages  Ages at which penetrance values are required in the output. Default is 40 to 80 years at increments of 10.
n.iter  Number of MCMC iterations to run. Default is 30000.
n.burn  Number of MCMC iterations to burn-in. Default is 15000.
CrI  If CrI=TRUE, returns the 95% credible intervals of the estimated age specific penetrance values. Default is FALSE.
pl  If pl=TRUE, returns a plot of the estimated age specific penetrance value vs age along with 95% credible intervals. Default is FALSE.
ylim  If pl=TRUE, numeric vector of length 2, giving the y coordinates. Default is c(0,1).
xlim  If pl=TRUE, numeric vector of length 2, giving the x coordinates. Default is c(40,80).

Details

The BayesMetaPenetrance function estimates age-specific risks of developing cancer associated with mutations in a specific gene, i.e., penetrance estimation. A meta-analysis approach based on a Bayesian hierarchical random-effects model is used to obtain penetrance estimates integrating studies reporting different types of risk measures (e.g., penetrance, relative risk, odds ratio, and standard incidence ratio) while accounting for associated uncertainties.

The cumulative penetrance $F_s(t|\kappa_s, \lambda_s)$ at age $t$ for study $s$ is assumed to be given by the c.d.f. of a Weibull distribution with shape parameter $\kappa_s$ and scale parameter $\lambda_s$.

The prior distributions are $\pi(\kappa_s|a, b) = \text{Gamma}(a, b)$, $\pi(\lambda_s|c, d) = \text{Gamma}(c, d)$, where $a$ and $c$ are shape parameters and $b$ and $d$ are scale parameters.

Continuous uniform distributions are assumed for all the hyper-parameters. Specifically, $\pi(a|l_a, u_a) = \text{U}(l_a, u_a)$, $\pi(b|l_b, u_b) = \text{U}(l_b, u_b)$, $\pi(c|l_c, u_c) = \text{U}(l_c, u_c)$, and $\pi(d|l_d, u_d) = \text{U}(l_d, u_d)$ with $l_a, u_a, l_b, u_b, l_c, u_c, l_d, u_d$ pre-specified.

Posterior distributions are obtained via a Markov chain Monte Carlo algorithm. The default values for age distributions are based on the distribution of age of onset of breast cancer for US general population (https://seer.cancer.gov/statfacts/html/breast.html). Credible interval at a given age is the $0.025^{th}$ and $0.975^{th}$ quantiles of the posterior distribution of penetrance estimate at that age.

Value

BayesMetaPenetrance returns a list of two objects

Ages  Ages corresponding to the estimated penetrance values
penetrance  Estimated age-specific penetrance values
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References

Examples
#penetrance value
set.seed(123)
penet1=c(0.134,0.230,0.400,0.571,0.706) #penetrance values from study 1
penet2=c(0.092,0.146,0.260,0.403,0.556) #penetrance values from study 2

penet1_ci_low=c( 0.113, 0.203,0.369,0.539,0.675) #lower 95% confidence limit of values in penet1
penet1_ci_hi=c(0.155,0.256,0.430,0.601,0.734) #upper 95% confidence limit of values in penet1

penet2_ci_low=c( 0.066,0.114, 0.221,0.359,0.508) #lower 95% confidence limit of values in penet2
penet2_ci_hi=c(0.117,0.176,0.298,0.446,0.600) #upper 95% confidence limit of values in penet2

ages_penet1=c(35,40,50,60,70) # ages corresponding to values in penet 1
ages_penet2=c(40,50,60,70,80) # ages corresponding to values in penet 2

study_number=c(rep(1,5),rep(2,5)) # 1 for 5 records of study 1, 2 for study 2.

penet=data.frame('
penetrance'=c(penet1,penet2),
'penet_ci_lower'=c(penet1_ci_low,penet2_ci_low),
'penet_ci_upper'=c(penet1_ci_hi,penet2_ci_hi),
'ages_penet'=c(ages_penet1,ages_penet2),
'study_label'=study_number)

## RR values
R.est=c(4.71) #RR or SIR values reported by each study
RR.ci.lower=c(3.80) #corresponding 95% lower limit
RR.ci.upper=c(5.84) #corresponding 95% upper limit

## Age related summaries from each study
A=c(60.21)
V=c(17.34)
A.lo=c(20)
A.hi=c(95)
A0=c(67.61)
V0=c(14.33)
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A0.lo = c(20)
A0.hi = c(95)

RR = data.frame(R.est, RR.ci.lower, RR.ci.upper, A, V, A.lo, A.hi, A0, V0, A0.lo, A0.hi)
colnames(RR) = c("R.est", "RR.ci.lower", "RR.ci.upper", "A", "V", "A.lo", "A.hi", "A0", "V0", "A0.lo", "A0.hi")

### OR values
OR.est = c(6.25) # OR value reported by each study
OR.ci.lower = c(1.38) # corresponding 95% lower limit
OR.ci.upper = c(28.23) # corresponding 95% lower limit

# Age related summaries from each study
A = c(66.69)
V = c(15.34)
A.lo = c(20)
A.hi = c(95)
A0 = c(66.69)
V0 = c(15.34)
A0.lo = c(20)
A0.hi = c(95)

OR = data.frame(OR.est, OR.ci.lower, OR.ci.upper, A, V, A.lo, A.hi, A0, V0, A0.lo, A0.hi)
colnames(OR) = c("OR.est", "OR.ci.lower", "OR.ci.upper", "A", "V", "A.lo", "A.hi", "A0", "V0", "A0.lo", "A0.hi")

####### studies with no mutations in controls

carrier.cases = c(1)
non_carrier.cases = c(99)
non_carrier.controls = c(100)

# Age related summaries from each study
A = c(48)
V = c(13.57)
A.lo = c(25)
A.hi = c(78)
A0 = c(48)
V0 = c(13.57)
A0.lo = c(25)
A0.hi = c(78)

zero.OR = data.frame(carrier.cases, non_carrier.cases, non_carrier.controls, 
A, V, A.lo, A.hi, A0, V0, A0.lo, A0.hi)
colnames(zero.OR) = c("carrier.cases", "non_carrier.cases", "non_carrier.controls", 
"A", "V", "A.lo", "A.hi", "A0", "V0", "A0.lo", "A0.hi")

# The following example command uses a very small number of MCMC iterations
# to allow a quick initial check of the code but for actual analysis, it is recommended
# to use the default number of iterations and burn-in.

BayesMetaPenetrance(penet, RR_studies = TRUE, RR = RR, OR_studies = TRUE, OR = OR, zero_studies = TRUE, zero.OR = zero.OR, ages = seq(40, 80, 10), n.iter = 10000, n.burn = 100, CrI = FALSE, pl = FALSE)