

# Revised Regression of Offspring on Mid-Parent

ROMP<sub>rev</sub>

Suite of R functions

User's guide

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## 1. Overview

### 1.1. Introduction

Testing for associations between polymorphisms and quantitative traits provides a tool that can help to identify the genetic effects underlying multifactorial disease. In addition to testing for association, the ability to estimate how much of the variation in a quantitative trait is attributable to variation at a given marker locus, i.e. the heritability attributable to the locus (or the locus-specific heritability), can help to assess the importance of a polymorphism found through association testing, and may help to prioritize subsequent studies. Locus-specific heritability can be used in a manner similar to the use of attributable risk in assessing what proportion of the disease in the population is attributable to a risk factor. This can be especially helpful in studying the etiology of multifactorial disease in which several loci and environmental factors are likely to play a role.

The Regression of Offspring on Mid-Parent (ROMP) method [Pugh et al. 2001; Roy-Gagnon 2004] is a test of association between a quantitative trait and a candidate locus. ROMP also estimates the trait heritability and the heritability attributable to a locus and requires genotyping offspring only. The revised version of the ROMP method (ROMP<sub>rev</sub>) [Roy-Gagnon et al. 2008] is implemented in this R suite of functions.

### 1.2. Features of the ROMP<sub>rev</sub> R suite

The suite includes functions to:

- (1) Read in pedigree, phenotype, and SNP genotype data in a comma-delimited format (see Input File section) and reformat the data for ROMP<sub>rev</sub> analysis (**ROMP<sub>rev</sub>Prep** function).
- (2) Perform ROMP<sub>rev</sub> or ROOP<sub>rev</sub> analyses using parametric (**ROMP<sub>rev</sub>** and **ROOP<sub>rev</sub>** functions) standard error and test of significance for the total and locus-specific heritability estimates. ROMP<sub>rev</sub> uses the mid-parent trait value while ROOP<sub>rev</sub> uses one parental value.
- (3) Define nicely printed output (**print.romp** function).

## 2. Methods

Suppose that a quantitative trait  $y$  is a linear function of three independent effects: a locus effect  $l$ , a polygenic effect  $P$ , and a residual effect  $e$ , such that individual  $i$  has trait value  $y_i = \mu + l_i + P_i + e_i$ , where  $\mu$  is the overall mean. The genotypic value,  $l_i$ , is the effect on the trait associated with the individual's genotype at locus  $L$ . The variance of the trait is  $\sigma_y^2 = \sigma_l^2 + \sigma_P^2 + \sigma_e^2$ . The genetic components of the variance,  $\sigma_l^2$  and  $\sigma_P^2$ , can further be decomposed in terms of additive, dominance and epistatic variance components. The additive genetic variance,  $\sigma_a^2 = \sigma_{a_i}^2 + \sigma_{a_p}^2$ , is used in the estimation of the narrow sense heritability of the trait. The heritability in the narrow sense, simply called heritability hereafter, is the ratio of the

additive genetic variance to the phenotypic variance:  $h^2 = \sigma_a^2 / \sigma_y^2$ . A traditional estimate of heritability is obtained from the linear regression of the offspring's phenotype,  $y_o$ , on the average phenotype of his parents, the mid-parent value:  $y_{mp} = (y_f + y_m) / 2$ , where  $y_f$  and  $y_m$  represent the father's and mother's phenotypes, respectively [Fisher 1918; Kempthorne and Tandon 1953; Falconer and Mackay 1996]. Assuming, without loss of generality, that the variables are centered around the sample means, this regression can be written as

$$y_o = \beta_{o,mp} y_{mp} + \varepsilon, \quad (1)$$

where  $\varepsilon$  is a normally distributed residual effect. Assuming that the relationship between  $y_o$  and  $y_{mp}$  is truly linear, the regression coefficient  $\beta_{o,mp}$  is equal to the offspring-mid-parent covariance divided by the mid-parent variance. Assuming random mating, no selection, no gene-environment interaction, and no parental environmental effects, it can be shown that the offspring-mid-parent covariance is one-half the additive genetic variance, i.e.,  $\sigma_{y_o, y_{mp}} = \sigma_a^2 / 2$ . The variance of the mid-parent value is one-half the phenotypic variance, i.e.,  $\sigma_{y_{mp}}^2 = \sigma_y^2 / 2$ , so that  $\beta_{o,mp} = \sigma_a^2 / \sigma_y^2$  [Lynch and Walsh 1998]. Hence, the estimate of the slope of the regression of offspring phenotype on mid-parent phenotype is an estimate of the heritability ( $h^2$ ) of the trait.

The effect of a locus can be added to the above regression model by including the genotype of the offspring at the locus,  $g_o$ , as a covariate in the model:

$$y_o = \beta_r y_{mp} + \gamma_l g_o + \nu, \quad (2)$$

where  $\nu$  is a normally distributed residual effect. The genotype of the offspring is entered in the regression model assuming an additive allelic effect, i.e.,  $g_o$  equals 0, 1, or 2 for the number of copies of the 'variant' allele. Using equation (2), a test of the locus effect on the trait can be obtained by testing whether its coefficient,  $\gamma_l$ , equals zero. If the locus is responsible, at least in part, for the variation of the trait, the coefficient of  $y_{mp}$  will be reduced in model (2) compared to model (1). With the assumptions noted above, the coefficient of the mid-parent value in model (2) is  $\beta_r = \sigma_{a_p}^2 / (\sigma_y^2 (1 - h_l^2 / 2))$ , where  $h_l^2 = \sigma_{a_l}^2 / \sigma_y^2$  is the locus-specific heritability. Because  $\beta_{o,mp} = \sigma_a^2 / \sigma_y^2$ , an estimator of  $h_l^2$  can be obtained from  $\beta_{o,mp}$  and  $\beta_r$  by noting that

$$h_l^2 = \frac{\sigma_{a_l}^2}{\sigma_y^2} = \frac{\sigma_a^2 - \sigma_{a_p}^2}{\sigma_y^2}, \quad (3)$$

and that the difference in slopes between models (1) and (2) is

$$\beta_{o,mp} - \beta_r = \frac{\sigma_a^2}{\sigma_y^2} - \frac{\sigma_{a_p}^2}{\sigma_y^2 (1 - h_l^2 / 2)}. \quad (4)$$

When there is only one locus responsible for some of the variation in the trait,  $\sigma_{a_p}^2 = 0$ ,  $h_l^2 = h^2$ , and the difference in slopes,  $\beta_{o,mp} - \beta_r$ , is equal to the heritability attributable to the locus. However, when more than one locus determines the trait, the difference in slopes is a biased estimator of  $h_l^2$ . Using equation (3) and (4), solving for  $h_l^2$  and replacing the regression coefficients by their usual least-squares estimators, the estimator of  $h_l^2$  is:

$$\hat{h}_l^2 = \frac{\hat{\beta}_{o,mp} - \hat{\beta}_r}{1 - \hat{\beta}_r/2}. \quad (5)$$

Conditioning on  $y_{mp}$  and  $g_o$  and assuming that the errors from the regression model (2) are normally distributed with mean 0 and variance  $\sigma_v^2$ , the locus-specific heritability estimator is a function of two normally distributed random variables:  $\hat{\beta}_{o,mp}$ , and  $\hat{\beta}_r$ . The variance of  $\hat{h}_l^2$  can be approximated by using the delta method:

$$\text{Var}(\hat{h}_l^2) \approx \frac{(1 - \beta_r/2)(\beta_{o,mp} - \beta_r/2 - 1) \text{Var}(\hat{\beta}_{o,mp}) + (1 - \beta_{o,mp}/2)^2 \text{Var}(\hat{\beta}_r)}{(1 - \beta_r/2)^4}, \quad (6)$$

where

$$\text{Var}(\hat{\beta}_{o,mp}) = \frac{\sigma_v^2}{\sum y_{mp}^2}, \text{ and}$$

$$\text{Var}(\hat{\beta}_r) = \frac{\sigma_v^2 \sum g_o^2}{\sum y_{mp}^2 \sum g_o^2 - (\sum y_{mp} g_o)^2}.$$

An estimate of  $\text{Var}(\hat{h}_l^2)$  can be obtained by replacing, in equation (6), the coefficients  $\beta_{o,mp}$  and  $\beta_r$  by their least-squares estimates, and  $\sigma_v^2$  by the residual sum of squares from regression (2) divided by its degrees of freedom,  $n - 3$ . This estimated variance can then be used to obtain a test of significance for the locus-specific heritability estimate based on a  $t$  distribution with  $n - 3$  degrees of freedom because  $\hat{h}_l^2 / \hat{\sigma}_{\hat{h}_l^2}$  approximately follows a  $t_{n-3}$  under the null hypothesis that  $h_l^2 = 0$ . A 95% confidence interval can also be obtained by taking  $\hat{h}_l^2 \pm t_{0.975, n-3} \hat{\sigma}_{\hat{h}_l^2}$ .

The  $\text{ROMP}_{\text{rev}}$  functions provides the following: 1) estimates of the heritability of the trait and of its standard error ( $\hat{h}^2 \pm \hat{\sigma}_{\hat{h}^2}$ ), and a test of the null hypothesis that  $h^2 = 0$  by using the traditional regression of offspring on mid-parent [Falconer and Mackay 1996]; 2) estimates of the heritability attributable to a locus and of its standard error ( $\hat{h}_l^2 \pm \hat{\sigma}_{\hat{h}_l^2}$ ) by adding a locus effect in the regression model as described above; and 3) a test of association between the trait and a locus by testing either the null hypothesis that  $\gamma_l = 0$ , or that  $h_l^2 = 0$ . Clogg et al. (1992) showed that testing for  $\gamma_l = 0$  was equivalent to testing for  $\beta_{o,mp} - \beta_r = 0$  when the latter was done conditional on  $y_{mp}$  and  $g_o$ . The test for  $h_l^2 = 0$  based on  $\hat{h}_l^2$  from equation (5) is derived in a similar manner as the test described in Clogg et al. (1992) and has a similar behavior. It is slightly more powerful in the specific case of testing for significant locus-specific heritability since it corrects for the inherent bias of  $\beta_{o,mp} - \beta_r$ . Hence,  $\hat{h}_l^2 / \hat{\sigma}_{\hat{h}_l^2}$  is used to test for association in  $\text{ROMP}_{\text{rev}}$ .

Three approaches providing a standard error and/or a test of significance for the locus-specific heritability estimate are available in the  $\text{ROMP}_{\text{rev}}$  functions: the parametric  $\text{ROMP}_{\text{rev}}$  method as described above, a nonparametric bootstrap approach, and a permutation test approach. Bootstrap samples consist of  $nb$  samples (e.g., 1000) with replacement of trios ( $y_{o_i}, y_{mp_i}, g_{o_i}$ ). The bootstrap percentile 95% confidence interval are provided, i.e., the 2.5 and 97.5 percentiles of the bootstrap distribution are taken as the confidence limits [Efron and Tibshirani 1993]. The bootstrap test is based on the bootstrap confidence interval, i.e., the null hypothesis is rejected whenever the bootstrap confidence interval does not include 0. The bootstrap p-value is thus the percentile value for which the lower-bound of the bootstrap confidence interval equals 0. For the permutation test of the null hypothesis that  $h_l^2 = 0$ , the phenotypes of the offspring and parents, ( $y_{o_i}, y_{mp_i}$ ), is kept together while genotypes of the offspring is permuted. The locus-specific heritability estimator is used as the test statistic in  $nb$  (e.g., 1000) permuted samples to obtain an empirical p-value [Good 2000].  $nb$  can be specified in the functions.

Simulations [Roy-Gagnon et al. 2008] showed that the coverage probability of the  $\text{ROMP}_{\text{rev}}$  parametric 95% confidence intervals for the locus-specific heritability was consistently lower than 95%, despite a powerful test of significance having appropriate type I error. This apparent disagreement between the biased standard error and the accurate type I error may reflect a different distribution of the statistic when a locus effect is present compared to no locus effect. A similar problem was previously reported in the literature in the context of the study of intervening variables effects or mediation [MacKinnon et al. 2002], which is closely related to  $\text{ROMP}_{\text{rev}}$ . The bootstrap standard errors and confidence intervals yields larger confidence intervals and reduced power of the test of association compared to the parametric test. In addition, the bootstrap approach is computationally intensive. Hence, a two-step approach is suggested. First, a  $\text{ROMP}_{\text{rev}}$  heritability estimate (along with its parametric standard error) combined with the parametric test of association, which showed good properties, should provide a quick result for a large number of SNPs. Once association is established, obtaining a bootstrap confidence interval around the locus-specific heritability estimate seems to be worthwhile to

refine the estimation as a second step for polymorphisms of interest. A similar two-step approach for testing and parameter estimation was previously suggested in the context of linkage analysis [Liang et al. 2001]. Both the parametric and bootstrap approaches are provided in the  $\text{ROMP}_{\text{rev}}$  functions.

It is important to note that  $\text{ROMP}$  requires phenotypic data on both parents and on the offspring but genotypic data for the offspring only. In situations where phenotypic data are available for only one parent, a variation of the  $\text{ROMP}$  method can be used. A regression of offspring on one parent (ROOP) uses the trait value of a single parent rather than the mid-parent value. Twice the regression coefficient is then an estimate of the heritability of the trait under the same assumptions as for  $\text{ROMP}$ , i.e.,  $\hat{h}_{\text{ROOP}}^2 = 2\hat{\beta}_{o,op}$ . The locus-specific heritability estimate and its standard error can be derived in a similar manner as for  $\text{ROMP}_{\text{rev}}$ , resulting in

$$\hat{h}_{\text{ROOP}}^2 = 2(\hat{\beta}_{o,op} - \hat{\beta}_r) / (1 - \hat{\beta}_r/2). \text{ ROOP}_{\text{rev}} \text{ functions are also provided.}$$

$\text{ROMP}_{\text{rev}}$  is best suited for a sample of independent parent-offspring trios. However, simulations showed that the type I error of the parametric and bootstrap approaches is not greatly inflated by using nuclear families of size 3 or smaller. The type I error of the permutation test approach was somewhat less robust. If the sample consists of large families, selecting one parent-offspring trio at random is recommended prior to  $\text{ROMP}_{\text{rev}}$  analyses.

The trait can easily be adjusted for relevant covariates by performing a regression on all available data (parents as well as offspring) and then providing the residuals of this regression as the trait to the  $\text{ROMP}_{\text{rev}}$  functions.

### 3. Installing R

The  $\text{ROMP}_{\text{rev}}$  suite of functions are implemented within the R software [Ihaka and Gentleman 1996]. R is a free software environment for statistical computing and graphics that compiles and runs on most UNIX platforms, Windows and MacOS. Please refer to the R Project website (<http://www.r-project.org/>) for instructions on how to download and install R on your computer.

A basic knowledge of the R (or S) language is required in order to use the  $\text{ROMP}_{\text{rev}}$  functions. Free documentation on how to use R is available on the R Project website (<http://www.r-project.org/>). Books are also available (e.g., Venables and Ripley (2002) Modern Applied Statistics with S, 4th edition, Springer.)

### 4. Using the $\text{ROMP}$ functions

#### 4.1. Downloading the $\text{ROMP}_{\text{rev}}$ functions

The file containing the  $\text{ROMP}_{\text{rev}}$  functions ( $\text{ROMPrev\_v0.2.1.r}$ ) is freely available for download from the website: <http://research.nhgri.nih.gov>. The file can be saved in any directory. Example data file, sample R code to call the functions, and example of output are also available for download.

## 4.2. Defining the $\text{ROMP}_{\text{rev}}$ functions in R

The  $\text{ROMP}_{\text{rev}}$  functions first need to be defined within R before they can be used. This can be done in at least 2 ways:

- (1) Within R, use the command `source("filename")`, where `filename` is the name of the file containing the R functions (including the path indicating where the file is saved if not in current directory). The functions will only be available for the current R session unless the workspace from the session is saved at the end of the session.
- (2) R can be called from a Unix shell script or from a Windows command line by using `R --save < path/filename`, where `path/filename` indicate the location and name of the file containing the  $\text{ROMP}_{\text{rev}}$  functions. The `--save` option will allow the workspace to be saved for use in the same script.

Please refer to the R Project website (<http://www.r-project.org>) for further information on how to invoke R and save the workspace.

## 4.3. Calling the $\text{ROMP}_{\text{rev}}$ functions

Once the  $\text{ROMP}_{\text{rev}}$  functions are defined, they can be invoked by name with appropriate parameters passed on to them. The different functions can be called in the following way:

- (1)  **$\text{ROMPrevPrep}$ ("path/filename")**: reads in input file **filename** located in the directory indicated by **path** and reformats the data for  $\text{ROMP}_{\text{rev}}$  analyses. The function returns a *list* object which elements can be passed on to the  $\text{ROMPrev}$  or  $\text{ROOPrev}$  functions. The elements of the *list* object are:

- `y` = vector of offspring trait values
- `xmp` = vector of mid-parent trait values
- `xfa` = vector of fathers' trait values
- `xmo` = vector of mothers' trait values
- `xop` = vector of one-parent trait values (the parent is chosen at random if both father's and mother's values are available)
- `z` = matrix of SNP genotypes (coded as 0, 1, or 2 for number of copies of the allele coded 2 in the input data.)

The command

```
data<-ROMPrevPrep("path/filename")
```

puts the *list* object defined by the function  $\text{ROMPrevPrep}$  into the object called `data`. The elements of the list can then be accessed by using `data$y`, for example, to get the `y` vector.

- (2)  **$\text{ROMPrev}$ (**yin,xin,zin**)**: calculates  $\text{ROMP}_{\text{rev}}$  trait heritability and locus-specific heritability estimates along with their standard error and test of significance from the parametric method. **xin** is a vector of mid-parent values, **yin** is a vector of offspring values, and **zin** is a vector (not a matrix) of SNP genotypes for one SNP. **xin**, **yin**, and

**zin** can be obtained from the ROMPrevPrep function. The ROMPrev function returns a *list* object with the following 11 elements:

- n = number of parent-offspring trios used in analysis
- h2 = trait heritability estimate
- seh2 = standard error for h2
- cih2 = 95% confidence interval limits for h2
- th2 = test statistic for h2
- ph2 = p-value for h2
- h2l = locus-specific heritability estimate
- seh2l = standard error for h2l
- cih2l = 95% confidence interval limits for h2l
- th2l = test statistic for h2l
- ph2l = p-value for h2l

- (3) **ROOPrev(yin,xin,zin)**: calculates  $ROOP_{rev}$  trait heritability and locus-specific heritability estimates along with their standard error and test of significance from the parametric method. **xin** is a vector of parental values (from one parent: mother, father, or available parent), **yin** is a vector of offspring values, and **zin** is a vector (not a matrix) of SNP genotypes for one SNP. **xin**, **yin**, and **zin** can be obtained from the ROMPrevPrep function. The ROOPrev function returns a *list* object with same elements as the ROMPrev function described above.
- (4) **ROMPrevRS and ROOPrevRS** are not included in the ROMPrev v0.2.1 package but will be added at a future date.
- (5) **print.romp** provides nicely printed output for results from the ROMPrev and ROOPrev functions. This print function does not need to be called. Results from the ROMPrev and ROOPrev functions are defined as *romp* objects and are automatically printed using the corresponding print function.

## 5. Input File

The input data file must be in comma-delimited format and must contain the following fields in the following order: family id, individual id, father id, mother id, sex, trait value, SNP genotype data. No header row is allowed. There is no format restriction for the fields of family id, individual id, father id, mother id, and sex. The trait value field must be a numeric field containing data from a quantitative trait. SNP genotype data must be coded as 11, 12, or 22. See example.

## 6. Example

An example of input file is provided with the file ROMPrev\_example.data. The file ROMPrev\_example.r is an R script that provides R commands to analyze the data from this file with all ROMPrev functions. The commands can be copied and pasted to an R command line or the file can be called with the R *source* command. Note that the paths indicating the locations of files need to be changed in the script. Output from this file is shown in the files ROMPrev\_example.out and ROMPrev\_example\_out.csv.

## 7. Copyright, Disclaimer, and References

**Copyright:** Programs and documentation for ROMP<sub>rev</sub> are within the public domain. ROMP<sub>rev</sub> may be freely distributed and copied. However, appropriate acknowledgement (see below) must be given when ROMP<sub>rev</sub> is used.

**Disclaimer:** No warranty, either expressed or implied, is made with respect to the functioning and accuracy of this program. No responsibility is assumed by the authors. Please report any problems or bugs to the authors.

**Acknowledgement:** Please acknowledge the use of ROMP<sub>rev</sub> with the following citation in any publication that uses the program:

Roy-Gagnon M-H, Mathias RA, Fallin MD, Jee SH, Broman KW, Wilson AF (2008). An extension of the Regression of Offspring on Mid-Parent to test for association and estimate locus-specific heritability: The revised ROMP method. *Ann. Hum. Genet.* 72:115-125.

## 8. Future developments

The ROMP<sub>rev</sub> suite of functions is currently being implemented in an R package (or R extension) that will include improved versions of all functions along with R help files available within R. This will make the use of ROMP<sub>rev</sub> easier. The following are among the improvements planned for the ROMP<sub>rev</sub> R package:

- (1) Inclusion of ROMPrevRS and ROOPrevRS functions and corresponding print function `print.romprs`
- (2) Automated ROMP<sub>rev</sub> analyses of all SNPs provided in input file or possibility of sub-selection of SNPs by SNP names
- (3) Adjustment for covariates within ROMP<sub>rev</sub>
- (4) Additional function to select one offspring at random from large families
- (5) More flexible input data format

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