

SKAT Package

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1 Overview

SKAT package has functions to 1) test for associations between SNP sets and continuous/binary phenotypes with adjusting for covariates and kinships and 2) to compute power/sample size for future studies.

2 Association test

An example dataset (`SKAT.example`) has a genotype matrix (Z) of 2000 individuals and 67 SNPs, vectors of continuous ($y.c$) and binary ($y.b$) phenotypes, and a covariates matrix (X).

```
> library(SKAT)
> data(SKAT.example)
> names(SKAT.example)
```

```
[1] "Z"  "X"  "y.c" "y.b"
```

```
> attach(SKAT.example)
```

To test for associations, `SKAT_Null_Model` function should be used in prior to run `SKAT` to estimate parameters under the null model of no associations.

```
> # continuous trait
> obj<-SKAT_Null_Model(y.c ~ X, out_type="C")
> SKAT(Z, obj)$p.value
```

```
[1] 0.002877041
```

```
> # dichotomous trait
> obj<-SKAT_Null_Model(y.b ~ X, out_type="D")
> SKAT(Z, obj)$p.value
```

```
[1] 0.1401991
```

```
>
```

When the trait is binary and the sample size is small, SKAT can produce conservative results. We developed a moment matching adjustment (MA) that adjusts the asymptotic null distribution by estimating empirical variance and kurtosis. By default, SKAT will conduct the MA adjustment when the sample size < 2000 . In the following code, we use only 200 samples to run SKAT.

```
> IDX<-c(1:100,1001:1100)
> # With-adjustment
> obj.s<-SKAT_Null_Model(y.b[IDX] ~ X[IDX,],out_type="D")
```

Sample size (non-missing y and X) = 200, which is < 2000 . The small sample adjustment is applied.

```
> SKAT(Z[IDX,], obj.s, kernel = "linear.weighted")$p.value
```

```
[1] 0.1332123
```

```
>
```

If you don't want to use the adjustment, please set Adjustment=FALSE in the SKAT_Null_Model function.

```
> # Without-adjustment
> obj.s<-SKAT_Null_Model(y.b[IDX] ~ X[IDX,],out_type="D", Adjustment=FALSE)
> SKAT(Z[IDX,], obj.s, kernel = "linear.weighted")$p.value
```

```
[1] 0.147093
```

Resampling based approaches to adjust for binary traits have been developed and implemented in SKATBinary function. When you use the SKATBinary function, Adjustment=TRUE in SKAT_Null_Model is not necessary. Implemented methods are 1) Efficient resampling (ER); 2) ER with adaptive resampling (ER.A); 3) Quantile adjusted moment matching (QA); 4) Moment matching adjustment (MA); 5) No adjustment (UA); and 6) Hybrid. "Hybrid" (default method) selects a method based on the total minor allele count (MAC), the number of individuals with minor alleles (m), and the degree of case-control imbalance. Detailed description of these methods can be found in the following reference:

Lee, S., Fuchsberger, C., Kim, S., Scott, L. (2016) An efficient resampling method for calibrating single and gene-based rare variant association analysis in case-control studies. *Biostatistics* (2016) 17 (1): 1-15.

```
> # default hybrid approach
> out<-SKATBinary(Z[IDX,], obj.s, kernel = "linear.weighted")
> out$p.value
```

```
[1] 0.147093
```

```
>
```

We have recently developed more scalable and accurate method for binary traits, which is implemented in `SKATBinary_Robust` function. Detailed description of these methods can be found in the following reference:

Zhao, Z., Bi, W., Zhou, W., VanderHaar, P., Fritsche, L.G., Lee, S. (2019) UK Biobank Whole-Exome Sequence Binary Phenome Analysis with Robust Region-based Rare-Variant Test. *AJHG*, in press, doi:<https://doi.org/10.1016/j.ajhg.2019.11.012>

```
> # Robust approach
> out<-SKATBinary_Robust(Z[IDX,], obj.s, kernel = "linear.weighted")
> out$p.value

[1] 0.1511487

>
```

2.1 Assign weights for each SNP

It is assumed that rarer variants are more likely to be causal variants with large effect sizes. To incorporate this assumption, the linear weighted kernel uses a weighting scheme and is formulated as $ZWWZ'$, where Z is a genotype matrix, and $W = \text{diag}\{w_1, \dots, w_m\}$ is a weight matrix. In the previous examples, we used the default `beta(1,25)` weight, $w_i = \text{dbeta}(p_i, 1, 25)$, where `dbeta` is a beta density function, and p_i is a minor allele frequency (MAF) of SNP i . Different parameters for the beta weight can be used by changing `weights.beta`. For example, `weights.beta=c(0.5,0.5)` will use the Madsen and Browning weight.

```
> SKAT(Z, obj, kernel = "linear.weighted", weights.beta=c(0.5,0.5))$p.value

[1] 0.4931639
```

You can use your own weight vector by using the `weights` parameter. For the logistic weight, we provide a function to generate the weight.

```
> # Shape of the logistic weight
>
> MAF<-1:1000/1000
> W<-Get_Logistic_Weights_MAF(MAF, par1=0.07, par2=150)
> par(mfrow=c(1,2))
> plot(MAF,W,xlab="MAF",ylab="Weights",type="l")
> plot(MAF[1:100],W[1:100],xlab="MAF",ylab="Weights",type="l")
> par(mfrow=c(1,2))
> # Use logistic weight
> weights<-Get_Logistic_Weights(Z, par1=0.07, par2=150)
> SKAT(Z, obj, kernel = "linear.weighted", weights=weights)$p.value

[1] 0.3293643
```

2.2 SKAT-O: Combined Test of burden test and SKAT

A test statistic of the combined test is

$$Q_\rho = (1 - \rho)Q_S + \rho Q_B,$$

where Q_S is a test statistic of SKAT, and Q_B is a score test statistic of the burden test. The ρ value can be specified by using the `r.corr` parameter (default: `r.corr=0`).

```
> #rho=0, SKAT
> SKAT(Z, obj, r.corr=0)$p.value

[1] 0.1401991

> #rho=0.9
> SKAT(Z, obj, r.corr=0.9)$p.value

[1] 0.06031026

> #rho=1, Burden test
> SKAT(Z, obj, r.corr=1)$p.value

[1] 0.06095529
```

If `method="optimal.adj"` or `"SKATO"` (both are equivalent), SKAT-O method will be performed, which computes p-values with eight different values of $\rho = (0, 0.1^2, 0.2^2, 0.3^2, 0.4^2, 0.5^2, 0.5, 1)$ and then uses the minimum p-value as a test statistic. If you want to use the original implementation of SKAT-O, use `method="optimal"`, which uses eleven equally spaced ρ values from 0 to 1 as a grid of ρ s. We recommend to use `"SKATO"` or `"optimal.adj"`, since it has a better type I error control.

```
> #Optimal Test
> SKAT(Z, obj, method="SKATO")$p.value

[1] 0.1008976

>
```

2.3 Combined test of common and rare variants

It is possible that both common and rare variants are associated with phenotypes. To test for combined effects of common and rare variants, `SKAT_CommonRare` function can be used. The detailed description of the combined test can be found in the following reference:

Ionita-Laza, I., Lee, S., Makarov, V., Buxbaum, J. Lin, X. (2013). Sequence kernel association tests for the combined effect of rare and common variants. *AJHG*, 92(6):841-53.

```
> # Combined sum test (SKAT-C and Burden-C)
>
> SKAT_CommonRare(Z, obj)$p.value
```

```

[1] 0.2238025

> SKAT_CommonRare(Z, obj, r.corr.rare=1, r.corr.common=1 )$p.value

[1] 0.1546374

> # Adaptive test (SKAT-A and Burden-A)
>
> SKAT_CommonRare(Z, obj, method="A")$p.value

[1] 0.4372293

> SKAT_CommonRare(Z, obj, r.corr.rare=1, r.corr.common=1, method="A" )$p.value

[1] 0.1548059

>

```

2.4 Impute missing genotypes.

If there are missing genotypes, SKAT automatically imputes them based on Hardy-Weinberg equilibrium. You can choose from “bestguess”, “fixed” or “random”. The “bestguess” imputes missing genotypes as most likely values (0,1,2), the “fixed” imputes missing genotypes by assigning the mean genotype value ($2p$, p is the MAF) and the “random” imputes missing genotypes by generating binomial(2, p) random variables. The default imputation method for the SKAT function is “fixed” and for the SKATBinary function is “bestguess”.

```

> # Assign missing
> Z1<-Z
> Z1[1,1:3]<-NA
> # bestguess imputation
> SKAT(Z1,obj,impute.method = "bestguess")$p.value

[1] 0.1401991

> # fixed imputation
> SKAT(Z1,obj,impute.method = "fixed")$p.value

[1] 0.1401982

> # random imputation
> SKAT(Z1,obj,impute.method = "random")$p.value

[1] 0.1401991

>
>

```

2.5 Resampling

SKAT package provides functions to carry out resampling method to compute empirical p-values and to control for family wise error rate. Two different resampling methods are implemented. “bootstrap” conducts a parametric bootstrap to resample residuals from H_0 with adjusting for covariates. When there is no covariate, “bootstrap” is equivalent to the permutation. “perturbation” perturbs the residuals by multiplying standard normal random variables. The default method is “bootstrap”. From ver 0.7, we do not provide the “perturbation” method.

```
> # parametric bootstrap.
> obj<-SKAT_Null_Model(y.b ~ X, out_type="D", n.Resampling=5000,
+ type.Resampling="bootstrap")
> # SKAT p-value
> re<- SKAT(Z, obj, kernel = "linear.weighted")
> re$p.value          # SKAT p-value

[1] 0.1401991

> Get_Resampling_Pvalue(re)          # get resampling p-value

$p.value
[1] 0.1463707

$is_smaller
[1] FALSE

> detach(SKAT.example)
```

When there are many genes/SNP sets to test, resampling methods can be used to control family-wise error rate. Examples are provided in the next section.

2.6 Adjust for kinship

If related individuals exist in your data, you need to adjust for kinship. SKAT_NULL_emmaX function uses linear mixed model (EMMAX) to estimate the variance component, which will be subsequently used to adjust for kinship. For the kinship adjustment, SKAT_NULL_emmaX function should be used instead of SKAT_Null_Model.

```
> data(SKAT.fam.example)
> attach(SKAT.fam.example)
> # K: kinship matrix
> obj<-SKAT_NULL_emmaX(y ~ X, K=K)
> SKAT(Z, obj)$p.value

[1] 0.2123192

> # SKAT-O
> SKAT(Z, obj, method="SKATO")$p.value

[1] 0.352943

> detach(SKAT.fam.example)
```

2.7 X chromosome test

Since male has only one copy of X-chromosome, special care is needed to test for associations in X-chromosome. We have developed a method to test for X-chromosome in region based rare variant test with and without X-inactivation. To use it, you need to use `SKAT_Null_Model_ChrX` to fit the null model and `SKAT_ChrX` for association tests. Detailed description of association tests in X-chromosome can be found in the following reference:

Ma, C., Boehnke, M., Lee, S., the GoT2D Investigators (2015) Evaluating the Calibration and Power of Three Gene-based Association Tests of Rare Variants for the X Chromosome, *Genetic Epidemiology*, 39 (7): 499-508.

```
> data(SKAT.example.ChrX)
> attach(SKAT.example.ChrX)
> Z = SKAT.example.ChrX$Z
> #####
> #           Compute the P-value of SKAT
>
> # binary trait
> obj.x<-SKAT_Null_Model_ChrX(y ~ x1 +x2 + Gender, SexVar="Gender", out_type="D", data=SKAT.example.ChrX)
> # run SKAT-O
> SKAT_ChrX(Z, obj.x, method="SKATO")$p.value

[1] 0.9156629

> detach(SKAT.example.ChrX)
```

3 Plink Binary format files

For the genome-wide data analysis, plink binary format files can be used in SKAT. To use plink files, plink bed, bim and fam files, and your own setid file that contains information of SNP sets are needed. Example files can be found on the SKAT/MetaSKAT google group page.

```
> # To run this code, first download and unzip example files
>
> #####
> #           Generate SSD file
>
> # Create the MW File
> File.Bed<-"./Example1.bed"
> File.Bim<-"./Example1.bim"
> File.Fam<-"./Example1.fam"
> File.SetID<-"./Example1.SetID"
> File.SSD<-"./Example1.SSD"
> File.Info<-"./Example1.SSD.info"
> # To use binary ped files, you have to generate SSD file first.
```

```
> # If you already have a SSD file, you do not need to call this function.
> Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)
```

```
Check duplicated SNPs in each SNP set
No duplicate
1000 Samples, 10 Sets, 984 Total SNPs
[1] "SSD and Info files are created!"
```

Now you can open SSD and Info file and run SKAT.

```
> FAM<-Read_Plink_FAM(File.Fam, Is.binary=FALSE)
> y<-FAM$Phenotype
> # To use a SSD file, please open it first. After finishing using it, you must close it.
>
> SSD.INFO<-Open_SSD(File.SSD, File.Info)
```

```
1000 Samples, 10 Sets, 984 Total SNPs
Open the SSD file
```

```
> # Number of samples
> SSD.INFO$nSample
```

```
[1] 1000
```

```
> # Number of Sets
> SSD.INFO$nSets
```

```
[1] 10
```

```
> obj<-SKAT_Null_Model(y ~ 1, out_type="C")
```

```
> out<-SKAT.SSD.All(SSD.INFO, obj)
```

```
> out
```

```
$results
```

	SetID	P.value	N.Marker.All	N.Marker.Test
1	GENE_01	0.77747880	94	94
2	GENE_02	0.06245208	84	84
3	GENE_03	0.38416582	108	108
4	GENE_04	0.46179268	101	101
5	GENE_05	0.18548863	103	103
6	GENE_06	0.93255760	94	94
7	GENE_07	0.18897220	104	104
8	GENE_08	0.73081683	96	96
9	GENE_09	0.67366458	100	100
10	GENE_10	0.40310682	100	100


```
$P.value.Resampling
NULL
```

```
attr("class")
[1] "SKAT_SSD_ALL"
```

If you have a plink covariate file, `Read_Plink_FAM_Cov` function can be used to read both FAM and covariate files.

```
> File.Cov<-"/Example1.Cov"
> FAM_Cov<-Read_Plink_FAM_Cov(File.Fam, File.Cov, Is.binary=FALSE)
> # First 5 rows
> FAM_Cov[1:5,]
```

	FID	IID	PID	MID	Sex	Phenotype	X1	X2
1	FID454	1	0	0	1	0.679793	1.0297614	1
2	FID977	1	0	0	1	0.836566	0.1846235	1
3	FID462	1	0	0	1	-0.408388	-0.6141158	1
4	FID958	1	0	0	1	-0.522305	-2.0226759	0
5	FID668	1	0	0	1	-0.328300	-0.8213776	0

```
> # Run with covariates
> X1 = FAM_Cov$X1
> X2 = FAM_Cov$X2
> y<-FAM_Cov$Phenotype
> obj<-SKAT_Null_Model(y ~ X1 + X2, out_type="C")
> out<-SKAT.SSD.All(SSD.INFO, obj)
> out
```

```
$results
```

	SetID	P.value	N.Marker.All	N.Marker.Test
1	GENE_01	0.77771227	94	94
2	GENE_02	0.06157071	84	84
3	GENE_03	0.39818504	108	108
4	GENE_04	0.46548442	101	101
5	GENE_05	0.18981516	103	103
6	GENE_06	0.94073952	94	94
7	GENE_07	0.18779019	104	104
8	GENE_08	0.74559501	96	96
9	GENE_09	0.66573796	100	100
10	GENE_10	0.40204308	100	100

```
$P.value.Resampling
NULL
```

```
attr("class")
[1] "SKAT_SSD_ALL"
```

To use custom weight, you need to make a weight file and read it using “Read_SNP_WeightFile” function. The weight file should have two columns, SNP ID and weight values. The output object of “Read_SNP_WeightFile” can be used as a parameter in SKAT.SSD functions

```
> # Custom weight
> # File: Example1_Weight.txt
> obj.SNPWeight<-Read_SNP_WeightFile("./Example1_Weight.txt")

> out<-SKAT.SSD.All(SSD.INFO, obj, obj.SNPWeight=obj.SNPWeight)

> out
```

```
$results
  SetID   P.value N.Marker.All N.Marker.Test
1 GENE_01 0.58647860         94          94
2 GENE_02 0.03286684         84          84
3 GENE_03 0.25752493        108         108
4 GENE_04 0.18486050        101         101
5 GENE_05 0.43670123        103         103
6 GENE_06 0.98039703         94          94
7 GENE_07 0.12460640        104         104
8 GENE_08 0.78814493         96          96
9 GENE_09 0.80206141        100         100
10 GENE_10 0.34070404        100         100
```

```
$P.value.Resampling
NULL
```

```
attr("class")
[1] "SKAT_SSD_ALL"
```

The output object of SKAT.SSD.All has an output dataframe object “results”. You can save it using write.table function.

```
> output.df = out$results
> write.table(output.df, file="./save.txt", col.names=TRUE, row.names=FALSE)
>
```

If more than one gene/SNP sets are to be tested, multiple test should be adjusted to control for family-wise error rate. It can be done by the bonferroni correction. If gene/SNP sets are correlated, however, this approach can be conservative. Alternatively, you can directly control family wise error rate (FWER) using the resampling method.

```
> obj<-SKAT_Null_Model(y ~ 1, out_type="C", n.Resampling=1000, type.Resampling="bootstrap")
> out<-SKAT.SSD.All(SSD.INFO, obj)

> # No gene is significant with controlling FWER = 0.05
> Resampling_FWER(out,FWER=0.05)
```

```
$result
```

```
NULL
```

```
$n
```

```
[1] 0
```

```
$ID
```

```
NULL
```

```
> # 1 gene is significant with controlling FWER = 0.5
```

```
> Resampling_FWER(out,FWER=0.5)
```

```
$result
```

```
      SetID      P.value N.Marker.All N.Marker.Test
2 GENE_02 0.06245208           84           84
```

```
$n
```

```
[1] 1
```

```
$ID
```

```
[1] 2
```

“SKAT.SSD.OneSet” or “SKAT.SSD.OneSet_SetIndex” functions can be used to test for a single gene/SNP set. Alternatively, you can obtain a genotype matrix using “Get_Genotypes_SSD” function and then run SKAT.

```
> obj<-SKAT_Null_Model(y ~ 1, out_type="C")
```

```
> # test the second gene
```

```
> id<-2
```

```
> SetID<-SSD.INFO$SetInfo$SetID[id]
```

```
> SKAT.SSD.OneSet(SSD.INFO,SetID, obj)$p.value
```

```
[1] 0.06245208
```

```
> SKAT.SSD.OneSet_SetIndex(SSD.INFO,id, obj)$p.value
```

```
[1] 0.06245208
```

```
> # test the second gene with the logistic weight.
```

```
> Z<-Get_Genotypes_SSD(SSD.INFO, id)
```

```
> weights = Get_Logistic_Weights(Z, par1=0.07, par2=150)
```

```
> SKAT(Z, obj, weights=weights)$p.value
```

```
[1] 0.7227001
```

```
>
```

SKAT_CommonRare function also can be used with SSD files.

```
> # test all genes in SSD file
> obj<-SKAT_Null_Model(y ~ X1 + X2, out_type="C")
> out<-SKAT_CommonRare.SSD.All(SSD.INFO, obj)
>
```

```
> out
```

```
$results
```

	SetID	P.value	Q	N.Marker.All	N.Marker.Test	N.Marker.Rare
1	GENE_01	0.69065787	7793.492	94	94	0
2	GENE_02	0.01627559	10487.653	84	84	0
3	GENE_03	0.57047824	9340.646	108	108	0
4	GENE_04	0.31381746	9743.714	101	101	0
5	GENE_05	0.21088057	10224.331	103	103	0
6	GENE_06	0.91250955	6734.116	94	94	0
7	GENE_07	0.26552996	10193.704	104	104	0
8	GENE_08	0.64072991	8087.342	96	96	0
9	GENE_09	0.65984552	8376.438	100	100	0
10	GENE_10	0.28938130	9502.883	100	100	0

```
N.Marker.Common
```

1	94
2	84
3	108
4	101
5	103
6	94
7	104
8	96
9	100
10	100

```
$P.value.Resampling
```

```
NULL
```

```
attr(,"class")
```

```
[1] "SKAT_SSD_ALL"
```

After finishing to use SSD files, please close them.

```
> Close_SSD()
```

```
Close the opened SSD file: /tmp/Rtmp2qFoAG/Rbuild254a76a7c2ce/SKAT/vignettes/Example1.SSD
```

3.1 Plink Binary format files: SKATBinary

SKATBinary functions can also be used with plink formatted files. This section shows an example code. Example plink files can be found on the SKAT/MetaSKAT google group page.

```

> # File names
> File.Bed<-"./SKATBinary.example.bed"
> File.Bim<-"./SKATBinary.example.bim"
> File.Fam<-"./SKATBinary.example.fam"
> File.Cov<-"./SKATBinary.example.cov"
> File.SetID<-"./SKATBinary.example.SetID"
> File.SSD<-"./SKATBinary.example.SSD"
> File.Info<-"./SKATBinary.example.SSD.info"
> # Generate SSD file, and read fam and cov files
> # If you already have a SSD file, you do not need to call this function.
> Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)

Check duplicated SNPs in each SNP set
No duplicate
2000 Samples, 30 Sets, 340 Total SNPs
[1] "SSD and Info files are created!"

> FAM<-Read_Plink_FAM_Cov(File.Fam, File.Cov, Is.binary=TRUE, cov_header=FALSE)
> # open SSD files
>
> SSD.INFO<-Open_SSD(File.SSD, File.Info)

2000 Samples, 30 Sets, 340 Total SNPs
Open the SSD file

> # No adjustment is needed
> obj<-SKAT_Null_Model(Phenotype ~ COV1 + COV2, out_type="D", data=FAM, Adjustment=FALSE)

> # SKAT
> out.skat<-SKATBinary.SSD.All(SSD.INFO, obj, method="SKAT")
> # SKAT-0
> out.skato<-SKATBinary.SSD.All(SSD.INFO, obj, method="SKATO")

> # First 5 variant sets, SKAT
> out.skat$results[1:5,]

```

	SetID	P.value	N.Marker.All	N.Marker.Test	MAC	m	Method.bin	MAP
1	1	0.92753378	11	11	18	17	ER 2.512149e-07	
2	2	0.24947578	2	2	3	3	ER 3.544808e-02	
3	3	0.60706345	7	7	19	19	ER 3.312382e-08	
4	4	0.08566388	11	11	19	18	ER 6.640864e-08	
5	5	0.63625247	4	4	18	18	ER 2.721199e-07	

```

>

```

The effective number of tests and QQ plots can be obtained using the minimum achievable p-values (MAP).

```

> # Effective number of test is smaller than 30 (number of variant sets)
> # Use SKAT results
> Get_EffectiveNumberTest(out.skat$results$MAP, alpha=0.05)

[1] 28

> # QQ plot
> QQPlot_Adj(out.skat$results$P.value, out.skat$results$MAP)
>

```

4 Power/Sample Size calculation.

4.1 Dataset

SKAT package provides a haplotype dataset (SKAT.haplotypes) which contains a haplotype matrix of 10,000 haplotypes over 200kb region (Haplotype), and a dataframe with information on each SNP. These haplotypes were simulated using a calibrated coalescent model (cosi) with mimicking linkage disequilibrium structure of European ancestry. If no haplotype data are available, this dataset can be used to compute power/sample size.

```

> data(SKAT.haplotypes)
> names(SKAT.haplotypes)

[1] "Haplotype" "SNPInfo"

> attach(SKAT.haplotypes)

```

4.2 Power/Sample Size calculation

The following example uses the haplotypes in SKAT.haplotypes with the following parameters.

1. Subregion length = 3k bp
2. Causal percent = 20%
3. Negative percent = 20%
4. For continuous traits, $\beta = c|\log_{10}(MAF)|$ (BetaType = "Log") with $\beta = 2$ at $MAF = 10^{-4}$
5. For binary traits, $\log(OR) = c|\log_{10}(MAF)|$ (OR.Type = "Log") with $OR = 2$ at $MAF = 10^{-4}$, and 50% of samples are cases and 50% of samples are controls

```

> set.seed(500)
> out.c<-Power_Continuous(Haplotype,SNPInfo$CHROM_POS, SubRegion.Length=5000,
+ Causal.Percent= 20, N.Sim=10, MaxBeta=2,Negative.Percent=20)

[1] "10/10"

> out.b<-Power_Logistic(Haplotype,SNPInfo$CHROM_POS, SubRegion.Length=5000,
+ Causal.Percent= 20, N.Sim=10 ,MaxOR=7, Negative.Percent=20)

```

```

[1] "10/10"

> out.c

$Power
      0.01      0.001      1e-06
500 0.6175978 0.4876905 0.2812231
1000 0.8196568 0.6959138 0.4967577
1500 0.9260644 0.8176848 0.6047217
2000 0.9795038 0.9033846 0.6978467
2500 0.9964443 0.9611981 0.7625096
3000 0.9996061 0.9888946 0.8168844
3500 0.9999708 0.9977467 0.8687841
4000 0.9999985 0.9996697 0.9163105
4500 0.9999999 0.9999641 0.9541347
5000 1.0000000 0.9999970 0.9789134

$R.sq
[1] 0.07804945

attr("class")
[1] "SKAT_Power"

> out.b

$Power
      0.01      0.001      1e-06
500 0.3195274 0.1838831 0.03372994
1000 0.5729441 0.3887094 0.15492725
1500 0.7488294 0.5687846 0.25885689
2000 0.8557195 0.7085993 0.37007813
2500 0.9189064 0.8044937 0.48059575
3000 0.9569876 0.8689837 0.58421719
3500 0.9790826 0.9146539 0.67116819
4000 0.9907789 0.9475064 0.73753304
4500 0.9963200 0.9700309 0.78656221
5000 0.9986658 0.9842302 0.82447737

attr("class")
[1] "SKAT_Power"

> Get_RequiredSampleSize(out.c, Power=0.8)

$`alpha` = 1.00e-02`
[1] 951.3587

$`alpha` = 1.00e-03`

```

```

[1] 1427.385

$`alpha = 1.00e-06`
[1] 2844.741

> Get_RequiredSampleSize(out.b, Power=0.8)

$`alpha = 1.00e-02`
[1] 1739.361

$`alpha = 1.00e-03`
[1] 2476.569

$`alpha = 1.00e-06`
[1] 4677.209

>

```

In this example, N.Sim=10 was used to get the result quickly. When you run the power calculation, please increase it to more than 100. When BetaType = “Log” or OR.Type = “Log”, the effect size of continuous trait and the log odds ratio of binary traits are $c|\log_{10}(MAF)|$, where c is determined by Max_Beta or Max_OR. For example, $c = 2/4 = 0.5$ when the Max_Beta = 2. In this case, a causal variant with MAF=0.01 has $\beta = 1$. For binary traits, $c = \log(7)/4 = 0.486$ with MAX_OR=7. And thus, a causal variant with MAF=0.01 has $\log OR = 0.972$.

Power_Continuous_R or Power_Logistic_R functions can be used to compute power with with non-zero r.corr (ρ). Since these functions use slightly different method to compute power, power estimates from Power_Continuous_R and Power_Logistic_R can be slightly different from estimates from Power_Continuous and Power_Logistic even when r.corr=0. If you want to computer the power of SKAT-O by estimating the optimal r.corr, please use r.corr=2. The estimated optimal r.corr is

$$r.corr = p_1^2(2p_2 - 1)^2,$$

where p_1 is the proportion of nonzero β s, and p_2 is the proportion of negative (or positive) β s among the non-zero β s.

```

> set.seed(500)
> out.c<-Power_Continuous_R(Haplotype,SNPInfo$CHROM_POS, SubRegion.Length=5000,
+ Causal.Percent= 20, N.Sim=10, MaxBeta=2,Negative.Percent=20, r.corr=2)

[1] "10/10"

> out.c

$Power
      0.01      0.001      1e-06
500 0.6143437 0.4867279 0.2821814
1000 0.8155499 0.6904465 0.4962072

```



```
1500 0.9246785 0.8124547 0.5991376
2000 0.9798723 0.9006001 0.6923563
2500 0.9967484 0.9611003 0.7558941
3000 0.9996732 0.9894869 0.8095854
3500 0.9999783 0.9980407 0.8629075
4000 0.9999990 0.9997413 0.9136032
4500 1.0000000 0.9999749 0.9542956
5000 1.0000000 0.9999981 0.9801759
```

```
$R.sq
```

```
[1] 0.07804945
```

```
$r.corr
```

```
[1] 0.0144
```

```
attr(,"class")
```

```
[1] "SKAT_Power"
```

```
> Get_RequiredSampleSize(out.c, Power=0.8)
```

```
$`alpha = 1.00e-02`
```

```
[1] 961.3582
```

```
$`alpha = 1.00e-03`
```

```
[1] 1448.959
```

```
$`alpha = 1.00e-06`
```

```
[1] 2910.736
```

```
>
```