

SKAT Package

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1 Overview

SKAT package has functions to 1) test an association between a SNP set and continuous/binary phenotypes and 2) to compute power/sample size for future sequence association studies.

2 Testing an association between a SNP set and outcome phenotypes.

2.1 Example Dataset

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 an association, `SKAT_Null_Model` function should be first used to estimate parameters and to obtain residuals under the null model of no associations. And then, `SKAT` function can be used to get p-values.

```
> # 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 method that adjusts the asymptotic null distribution by estimating empirical variance and kurtosis. By default, SKAT (\geq ver 0.7) will conduct a small sample adjustment when the sample size < 2000 . In the following code, we only use 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] 0.1322255
```

```
>
```

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
```

We recently developed efficient resampling methods to compute p-values for binary traits, and the methods are implemented in SKATBinary function. When you use this 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.

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

```
[1] 0.1352503
```

```
>
```

2.2 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 . You can use different parameters for the beta weight by changing the `weights.beta` parameter. For example, if you want to use Madsen and Browning weight, use `weight.beta=c(0.5,0.5)`.

```
> SKAT(Z, obj, kernel = "linear.weighted", weights.beta=c(0.5,0.5))$p.value
[1] 0.4931639
```

You can make your own weight vector and use it for the weighting. 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
```

2.3 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. You can specify ρ value using the `r.corr` parameter (default: `r.corr=0`).

```
> #rho=0
> 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", SKAT-O method is 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 uses the minimum p-value as a test statistic. If you want to use the original implementation of SKAT-O, use method="optimal". We recommend to use "optimal.adj", since it has a better type I error control.

```

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

[1] 0.1008976

>

```

2.4 Combined test of rare and common variants

If you want to test combined effects of common and rare variants, you can use SKAT_CommonRare function.

```

> # 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

>

```

The detailed description of each method 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. *American Journal of Human Genetics*, in press.

* contributed equally.

2.5 Imputing missing genotypes.

If there are missing genotypes, SKAT automatically imputes them based on Hardy-Weinberg equilibrium. You can choose either “random” or “fixed” imputation (default=“fixed”). The “random” imputation generates $\text{binomial}(2, p_i)$ random numbers to impute missing values, where p_i is the MAF of SNP i calculated from non-missing genotypes, and the “fixed” imputation uses the mean genotype value, $2p_i$, to impute missing values.

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

[1] 0.1401991

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

[1] 0.1401982
```

2.6 Resampling

SKAT package provides functions to carry out resampling to compute empirical p-values and to control family wise error rate. Two different resampling methods are implemented. “bootstrap” conducts the parametric bootstrap to resample residuals from H_0 with considering 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] 0.1361728

$is_smaller
[1] FALSE

```

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

2.7 Plink Binary format files

SKAT package can use plink binary format files for genome-wide data analysis. 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. After finishing it, you must call close function to close SSD file.

```

> 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, you can use Read_Plink_FAM_Cov file 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	0.77771227	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"
```

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, you should adjust for multiple testing to control for family-wise error rate. It can be done 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. Example code is given in following.

```
> 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 significnat 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 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 N.Marker.All N.Marker.Test N.Marker.Rare N.Marker.Common
1 GENE_01 0.70833804           94           94           0           94
2 GENE_02 0.01961982           84           84           0           84
3 GENE_03 0.53912934          108          108           0          108
4 GENE_04 0.34134633          101          101           0          101
```

5	GENE_05	0.20548007	103	103	0	103
6	GENE_06	0.92017774	94	94	0	94
7	GENE_07	0.24712642	104	104	0	104
8	GENE_08	0.66303494	96	96	0	96
9	GENE_09	0.66044604	100	100	0	100
10	GENE_10	0.30882075	100	100	0	100

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

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

```
>
>
```

After finishing, please close the SSD file.

```
> Close_SSD()
```

Close the opened SSD file: /private/var/folders/zs/nf_6qpd12r1dm4v3y2y298fr0000gn/T/Rtmpuox

2.8 Plink Binary format files: SKATBinary

SKATBinary functions can be used with plink formatted files. This section shows 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-O
> 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)
>
```

3 Power/Sample Size calculation.

3.1 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 informations of each SNP. These haplotypes were simulated using a calibrated coalescent model with mimicking linkage disequilibrium structure of European ancestry. If you don't have any haplotype information, please use this dataset to compute power/sample size.

```
> data(SKAT.haplotypes)
> names(SKAT.haplotypes)
[1] "Haplotype" "SNPInfo"
> attach(SKAT.haplotypes)
```

3.2 Power/Sample Size calculation

SKAT package provides functions to compute the power/sample size for future sequence association studies. 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 0.5601495 0.4507543 0.2745436
1000 0.6983510 0.6372979 0.4477310
1500 0.7393476 0.6978347 0.5840998
2000 0.7741144 0.7169529 0.6649380
2500 0.8041370 0.7386689 0.6938517
3000 0.8224103 0.7660432 0.6997755
3500 0.8349515 0.7896737 0.7015918
4000 0.8484832 0.8037123 0.7049269
4500 0.8647970 0.8109526 0.7122846
5000 0.8834324 0.8165985 0.7253563

$R.sq
[1] 0.0693529

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

```

> out.b

$Power
      0.01      0.001      1e-06
500 0.3894872 0.2757429 0.1330505
1000 0.5888308 0.4573657 0.2436726
1500 0.7021843 0.5859396 0.3485361
2000 0.7763091 0.6650800 0.4668508
2500 0.8234240 0.7280271 0.5483447
3000 0.8516985 0.7775865 0.5943673
3500 0.8718116 0.8108489 0.6269605
4000 0.8899993 0.8317031 0.6603647
4500 0.9081573 0.8464714 0.6968862
5000 0.9262225 0.8594656 0.7324297

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

> Get_RequiredSampleSize(out.c, Power=0.8)

$`alpha` = 1.00e-02`
[1] 2431.102

$`alpha` = 1.00e-03`
[1] 3867.782

$`alpha` = 1.00e-06`
[1] "> 5000"

> Get_RequiredSampleSize(out.b, Power=0.8)

$`alpha` = 1.00e-02`
[1] 2251.417

$`alpha` = 1.00e-03`
[1] 3336.919

$`alpha` = 1.00e-06`
[1] "> 5000"

>

```

In this example, N.Sim=10 was used to get results quickly. When you do 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.

If you consider non-zero r.corr (ρ) values to compute the power, Power_Continuous_R or Power_Logistic_R functions can be used instead. Since they 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 although r.corr=0.

If you want to compute the power of SKAT-O by estimating the optimal r.corr, 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 0.5584048 0.4465557 0.2700370
1000 0.6980094 0.6374870 0.4403217
1500 0.7367947 0.6977547 0.5830013
2000 0.7707641 0.7148115 0.6664808
2500 0.8032711 0.7341910 0.6946357
3000 0.8253110 0.7606592 0.6998229
3500 0.8407660 0.7863270 0.7011542
4000 0.8569269 0.8038311 0.7035340
4500 0.8759197 0.8137950 0.7089662
5000 0.8968032 0.8214246 0.7192218

$R.sq
[1] 0.0693529

$r.corr
[1] 0.0144

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

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

```
$`alpha = 1.00e-02`  
[1] 2449.686
```

```
$`alpha = 1.00e-03`  
[1] 3890.566
```

```
$`alpha = 1.00e-06`  
[1] "> 5000"
```

```
>
```