The Epistatic Interaction Package

Version 1.0

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1. Introduction

The Epistatic Interaction Package (Eip) is developed to estimate the epistatic effector in a candidate-gene case-control data set based on the Tian's model [1, 2]. In general, the case-control data has two groups, one group includes m cases who display a disease, and another group includes n control with no disease. All the cases and controls are genotyped for some SNPs. This package can calculate the p-value for all the combinations of 2 SNPs and 3 SNPs of case-control data. Based on the p-values results, some significant SNP combinations with epistatic effector are selected to export in the summary. This guide gives some brief instructions on how to perform the tasks of epistatic interaction detection. The outline of this guide is as follows.

Section 2: How to install the Eip pakage.
Section 3: Data format for the Eip package.
Section 4: Main function.
Section 5: One Snp analysis.
Section 6: Two Snps analysis.
Section 7: Three Snps analysis.
Section 8: Correction method
Section 9: Output description
Section 10: Function details
Section 11: System configuration

We refer to Tian et at.(2010) and Zhong et al.(2010) for the theoretical foundation of this package, If you appreciate this software then please cite the following papers in your work:

1. Tian Liu, A,Thalamuthu, J.J.Liu, C.Chen,Yao Li,and Rongling Wu. A Model for testing epistatic interactions of complex diseases in Case-Control studies.

2. Zhong Wang, Zhenwu Lin, Arthur Berg, John Hegarty, Walter A. Koltun and Rongling Wu. A general model for multilocus epistatic interactions in Case-Control studies..

2. Installation

The Eip package does not depend on any package, so it is very easy to install. After you download this package file, please type the following command or click the menu item “Install packages from local zip files”.

```
>install.packages( c( "C:¥¥path¥¥epinteraction_0.1.zip"), repos=NULL )
```

3. Data format

The goal of the Eip package is to find the significant SNP combination with epistatic effector from the candidate-gene case-control data set. The data set should be a CSV file, and at least includes one case-control column and some SNP columns. Now the current package supports 4 SNP formats. Hereby, we describle 4 types of data format in this guide.

3.1. Type A

One SNP column includes one allele. In following table three SNP columns are listed with one case-control column.

Individual ID, …,	Case,	**SNP 1,**	SNP 2,	SNP 3,	…
1 , …,	1,	GG,	CC,	CC,	…
2 , …,	1,	AA,	CT,	CA,	…
3 , …,	0,	AG,	CC,	CC,	…
……					

3.2. Type B

One SNP data is splited into three columns that includs two homczygous alleles and one heterozygote allele. Above data set can be converted into the following table.

Individual ID, …,	Case,	**SNP 1,**	**SNP 1-1,**	**SNP 1-2,**	SNP 2,	SNP 2-1,	SNP 2-2,……
1, …,	1,	GG,	,	,	CC,	,	,
2, …,	1,	,	,	AA,	,	CT,	,
3, …,	0,	,	AG,	,	CC,	,	,
……							

3.3. Type C

One SNP data is splited into two columns that every column includes one nucleotide. The following table is still same data set as the above.

Individual ID, …,	Case,	SNP 1,	SNP 1-1,	SNP 2,	SNP 2-1,	……
1, …,	1,	G,	G,	C,	C,	……
2, …,	1,	A,	A,	C,	T,	……
3, …,	0,	A,	G,	T,	T,	……
……						

3.4. Type D

The type D is kind of same as the type A. Every column is an allele, but in Type D, the allele is mapped to 0, 1, 2, which means qq, Qq, QQ.

```
Individual ID, …, Case, SNP 1, SNP 2, SNP 3, SNP 4, ……
1,             …,    1,      1,     2,     0,     1, ……
2,             …,    1,      0,     1,     0,     1, ……
3,             …,    0,      1,     2,     1,     0, ……
……
```

4. Main function

Our model uses Mather and Jinks model to describe different epistatic effector in case-control study. For 1 SNP, the model can calculate the additive and dominance effector. For *n* SNPs, 3^n-1 epistatic effectors can be estimated in theoretic analysis.

Although our model can be used to any number SNPs, the current package implements 1 SNP, 2 SNPs and 3 SNPs analysis. The users can select some or all of the analysis methods to estimate the epistatic effector.

If many SNPs are provided in a case-control data set, the package will calculate all combinations of 2 SNPs or 3 SNPs. Because these SNPs are estimated at the same time, the correction method of multiple tests is required. In this package, *Bonferroni*, *Holm* and *FDR* correction are implemented. The users can select the correction method by the parameters.

This package provides a very easy function to do the analysis. So if the data set complies with the data format described previous section, input the following command, all results can be outputted automatically.

```
> library(Eip);
> TIAN.full_test( "file.csv", output="file.csv.ret");
```

TIAN.full_test function can load the csv file and try to read the SNP columns and case-control column. If the data set is understandable, firstly this function can analyzer every SNP by the method for 1 SNP and output the results to log file, figure or CSV file. Secondly all combinations of 2 SNPs are analyzered by the 2 SNPs method and output the result immediately. Finally, all combinations of 3 SNPs can be done as the combination of 2 SNPs.

The results have three output formats. The significant effectors are selected to log file and the result details are exported to the CSV file as the table. For 2 SNPs analysis and 3 SNPs analysis, the epistatic effectors between 2 SNPs or 3 SNPs can be expressed in a correlation figure. All output files have a filename started with the output parameter of TIAN.full_test.

TIAN.full_test function has three optional arguments besides CSV file name, including
1) Options.
2) Output file name
3) Analysis method, the value is 1,2,3, corresponding the 1 SNP, 2 SNPs, 3SNPs analysis.

The following snippet shows the complete usage of the TIAN.full_test function.

```
  options <- list(
```

```
          type       = "auto",
          correction = "FDR, Holm",
          case_col    = "Disease",
          case_values= c("CD"),
          ctrl_values= c("Healthy"),
          snp_cols   = c("C.Ins","T.mut","X380Mut","Arg30Gln","L503F"),
          filters    = c("C.Ins==¥"TT¥""),
          ignoreRow  = NULL,
          bHead      = TRUE );

TIAN.full_test( "file.csv", options=options, output="file.csv.ret")
```

The *options* argument restricts the model to extract the SNPs and case-control information. It can define the following restriction.

No	Plus	Default	Minus
1	type	auto	The format of data set. Optional values: TA, TB, TC and TD.
2	correction	NA	The correction method of multiple tests. Optional values: Bonferroni, Holm, FDR or combination of these methods.
3	case_col	1	This optional argument shows which column provides the case-control information. Default the first colum provides case-control values.
4	case_values	1	The case_values indicates which items in case-control column will be regarded as case value.
5	ctrl_values	0	The ctrl_values indicates which items in case-control column will be regarded as control value.
6	snp_cols	NA	The snp_cols indicated which columns provide the SNP information.
7	filters	NA	This optional argument defines some filter ceriations. The individual data will be removed if some columns meet these ceriations.
8	ignoreRow	NULL	This optional argument indicates whether the n row below the head will be removed.
9	bHead	TRUE	Whether the CSV includes a data head.

5. One SNP Analysis

For single SNP analysis, addititive and dominance effector can be estimated by the chi-square test. Table 1 and table 2 show how to get addititive and dominance effector by a chi-square test. N_{xx} and M_{xx} indicate the number of SNP xx in the group of case and control. The chi-square value and p-value of ervery SNP in the data set are estimated by this analysis method.

Table 1: Chi-square table for addititive estimation of 1 SNP.

	u + a	u - a
Case	N_{AA}	N_{aa}
Control	M_{AA}	M_{aa}

Table 2: Chi-square table for dominance estimation of 1 SNP.

	u	u + d
Case	$N_{AA} + N_{aa}$	$2N_{Aa}$
Control	$M_{AA} + M_{aa}$	$2M_{Aa}$

Besides the TIAN.full_test function, the function TIAN.snp1_test is also provided as a special method to analyze 1 SNP. The argument *options* and output are same as TIAN.full_test.

```
# options setting is same as TIAN.full_test

TIAN.snp1_test( "file.csv", options=options, output="file.csv.ret")
```

When the data set is being analyzed, the progress hints are displayed in the R console. The following is a demonstration for the progress hints.

```
Execute the model(1 SNP) task, data file:test¥zhong.csv, SNP count:6.
Task Index:1/6, 00 seconds  has elapsed, left time:  00 seconds .
Task Index:2/6, 00 seconds  has elapsed, left time:  00 seconds .
Task Index:3/6, 00 seconds  has elapsed, left time:  00 seconds .
Task Index:4/6, 00 seconds  has elapsed, left time:  00 seconds .
Task Index:5/6, 00 seconds  has elapsed, left time:  00 seconds .
Task Index:6/6, 01 seconds  has elapsed, left time:  00 seconds .
The model(1 SNP) task is done.
```

6. Two SNPs Analysis

For 2 SNPs A and B, there are 8 genetical effectors of a1, a2, d1, d2, i_{a1a2}(additive*additive), i_{a1d2}(additive*dominance), i_{d1a1}(dominance*additive) and i_{d1d2}(dominance*dominance).

No.	Effectors	Description for 2 SNPs A and B
1	a_1	Additive of SNP A
2	a_2	Additive of SNP B
3	d_1	Dominance of SNP A
4	d_2	Dominance of SNP B
5	a_1a_2	Additive of SNP A × Additive of SNP B
6	a_1d_2	Additive of SNP A × Dominance of SNP B
7	d_1a_2	Dominance of SNP A × Additive of SNP B
8	d_1d_2	Dominance of SNP A × Dominance of SNP B

According to the model of Mather-Jinks that the genotypic value can be specified by the count of an arbitrary genotype, the epistasis effectors can be expressed by the statistical value conversely. For example, the interaction between the dominance of SNP A and the additive of SNP B, it can be expressed by the following equation.

$$I_{d1a2} = ½(2\mu_{12} + \mu_{20} + \mu_{00} - 2\mu_{10} - \mu_{22} - \mu_{02})$$

In this equation, I_{d1a2} is separated to the plus and minus group and a 2*2 contingency table will be built as following table for hypothesis test of I_{d1a2}. The parameter of m_{xy} and n_{xy} indicate the observed numbers of genotypes x(x=0,1,2) at SNP A and y(y=0,1,2) at SNP B in case and control group. So the number in the subscript, such as 00, 01, 02, 10, 11, 12, 20, 21 and 22, indicates the genotype of AABB, AABb, AAbb, AaBB, AaBb, Aabb, aaBB, aaBb and aabb.

	$2\mu + d_2 + i_{ad}$	$2\mu + d_2 - i_{ad}$
Cases	$m_{21} + \frac{1}{2}m_{02} + \frac{1}{2}m_{00}$	$m_{01} + \frac{1}{2}m_{20} + \frac{1}{2}m_{22}$
Controls	$n_{21} + \frac{1}{2}n_{02} + \frac{1}{2}n_{00}$	$n_{01} + \frac{1}{2}n_{20} + \frac{1}{2}n_{22}$

In view of the case and control, the chi-square test is used to test the significance (p-value) of epistasis componenets. In this package, a specific function TIAN.snp2_test is provided to analyze every combination of 2 SNPs in the data set. The parameters of TIAN.snp2_test are also same as the TIAN.full_test function.

```
# options setting is same as TIAN.full_test

TIAN.snp2_test( "file.csv", options=options, output="file.csv.ret")
```

The progress hints are also outputted to the console when this analysis task is being executed.

7. Three SNPs Analysis

3 SNPs analysis is more complex than 2 SNPs because there are 26 epistasis effectors in a combination of 3 SNPs. According to the Mather-Jinks model, these 26 epistasis effectors can be expressed by the statistical value of the genotypes. In similar way, every epistasis effector can be calculated from a two*two consitency table by chi-sequare test. The following table lists all 26 epistasis effectors.

No.	Effectors	Description for 3 SNPs A , B and C
1	a_1	Additive of SNP A
2	a_2	Additive of SNP B
3	a_3	Additive of SNP C
4	d_1	Dominance of SNP A
5	d_2	Dominance of SNP B
6	d_3	Dominance of SNP C
7	a_1a_2	Additive of SNP A × Additive of SNP B
8	a_1a_3	Additive of SNP A × Additive of SNP C
9	a_2a_3	Additive of SNP B × Additive of SNP C
10	d_1d_2	Dominance of SNP A × Dominance of SNP B
11	d_2d_3	Dominance of SNP B × Dominance of SNP C
13	d_1d_3	Dominance of SNP A × Dominance of SNP C

12	a_1d_2	Additive of SNP A × Dominance of SNP B
14	a_1d_3	Additive of SNP A × Dominance of SNP C
15	d_1a_2	Dominance of SNP A × Additive of SNP B
16	d_1a_3	Dominance of SNP A × Additive of SNP C
17	a_2d_3	Additive of SNP B × Dominance of SNP C
18	d_2a_3	Dominance of SNP B × Additive of SNP C
19	$a_1a_2a_3$	Additive of SNP A × Additive of SNP B × Additive of SNP C
20	$a_1a_2d_3$	Additive of SNP A × Additive of SNP B × Dominance of SNP C
21	$a_1d_2a_3$	Additive of SNP A × Dominance of SNP B × Additive of SNP C
22	$a_1d_2d_3$	Additive of SNP A × Dominance of SNP B × Dominance of SNP C
23	$d_1a_2a_3$	Dominance of SNP A × Additive of SNP B × Additive of SNP C
24	$d_1a_2d_3$	Dominance of SNP A × Additive of SNP B × Dominance of SNP C
25	$d_1d_2a_3$	Dominance of SNP A × Dominance of SNP B × Additive of SNP C
26	$d_1d_2d_3$	Dominance of SNP A × Dominance of SNP B × Dominance of SNP C

3 SNPs analysis is easy to do by the TIAN.full_test function. Besides TIAN.full_test, the user can use the TIAN.snp3_test to do same anlysis. The p-value can be corrected by 3 correction method if it is necessary for too many combinations.

```
# options setting is same as TIAN.full_test

TIAN.snp3_test( "file.csv", options=options, output="file.csv.ret")
```

8. Correction methods

When many pairs of SNPs are calculated at the same data file, the correction of multiple tests becomes an important issue. This package provides 3 correction methods listed in the following table. Among these correction methods, Bonferrorni approach is too conservative, but FDR is not strong relatively.

No.	Value	Correction method
1	***bonf***	Bonferroni
2	***holm***	HOLM correction
3	***fdr***	FDR correction

All corrections are used to adjust the p-values by default. The user can customize the correction method by specifying the correction attribute of parameter *options*. For example,

```
Options$correction = c("fdr","holm");
TIAN.full_test( "file.csv", options=options, output="file.csv.ret")
```

If multiple corrections are used in the analysis, every correction outputs the results independently. Above example shows two corrections are applied to full test, including 1 SNP, 2SNPs and 3SNPs analysis. Every analysis generates 3 results of non-correction, HOLM correction and FDR correction.

9. Output

While computational task is being processed, the progress is indicated in R console and the left time is estimated simultaneously. Besides the progress hints, 3 kinds of result information is exported to the files or the console.
1) The summary report for every analysis.
2) The full data set stored in the CSV format.
3) The significant figure for 2 SNPs and 3 SNPs analysis

The filename of summary report can be customized in the output parameter, such as TIAN.full_test. In the summary report, the following of 4 data objects can be summarized.
1) Raw data set
2) Results of 1 SNP analysis
3) Results of 2 SNP analysis
4) Resultsof 3 SNP analysis

9.1. Raw data object

Based on the parameter *options*, the package builds a raw data object to store the input data. The summary of data object gives the genotype information at every SNP. It looks like the following secion.

```
-----------------------------------
 Data File: zhong.csv
     Date: 2010-04-21 09:27:18
 File type: TA
SNPs Count: 6
    Cases: 192
  Controls: 298
-----------------------------------

SNPs List:
Name      Pos.    AA(case:ctrl)   Aa              aa
C.Ins     3       TT(123:291)     TC(26:7)        CC(5:0)
T.mut     4       CC(119:277)     CT(30:20)       TT(5:1)
X380Mut   5       GG(139:291)     GT(11:7)        TT(4:0)
Arg30Gln  6       GG(128:242)     GA(39:46)       AA(0:6)
L503F     7       TT(34:41)       TC(88:141)      CC(44:101)
R381Q     8       GG(163:257)     GA(7:38)        AA(0:0)
```

9.2. 1 SNP analysis

1 SNP analysis calculates additive and dominance effectoror by the new method. It also provides the calculation for 3 genotypes at one SNP by conventional case-control. The following summary summarizes 1 SNP analysis with Bonferrioni correction for a data set of 192 cases and 298 control individuals. The phrase of "AA:Aa:aa" stands for right conventional calculation in this summary.

```
Epistatic Interaction Analysis Report
-------------------------------------
 Data File: zhong.csv
     Date: 2010-04-21 09:27:19
    Cases: 192
  Controls: 298
SNPs Count: 6
    Model: 1 SNPs
Correction: Bonferroni
-------------------------------------

p-Value <= 1e-08:
1:          C.Ins     Dominance x2=56.84903471    0.00000000

p-Value <= 1e-06:
1:          C.Ins     AA:Aa:aa  x2=39.26004787    0.00000002
2:          T.mut     Dominance x2=29.31486810    0.00000037

p-Value <= 1e-04:
1:          T.mut     AA:Aa:aa  x2=24.29700914    0.00003178

p-Value <= 0.05:
1:          X380Mut   AA:Aa:aa  x2=11.54530913    0.01866892
2:          C.Ins     Additive  x2=8.03191867     0.02757608
3:          T.mut     Additive  x2=7.86648189     0.03021572
4:          Arg30Gln  Dominance x2=6.98508967     0.04931492

#1: Full p-value data is exported to the CSV file(zhong-CD.txt.s1.Bonferroni.pvalue.csv).
#2: Full chi2-value data is exported to the CSV file(zhong-CD.txt.s1.Bonferroni.chi2.csv).
```

In the summary there are five criterias to select the significant values from the results. The criterias are 10^{-8}, 10^{-6}, 10^{-4}, 10^{-2} and 0.05. For every criterias, the selected epistatis effectors will be listed with the SNP name, chi-square value and p-value.

At the end of the summary, the full data of chi-square and p-value are exported to two CSV files.

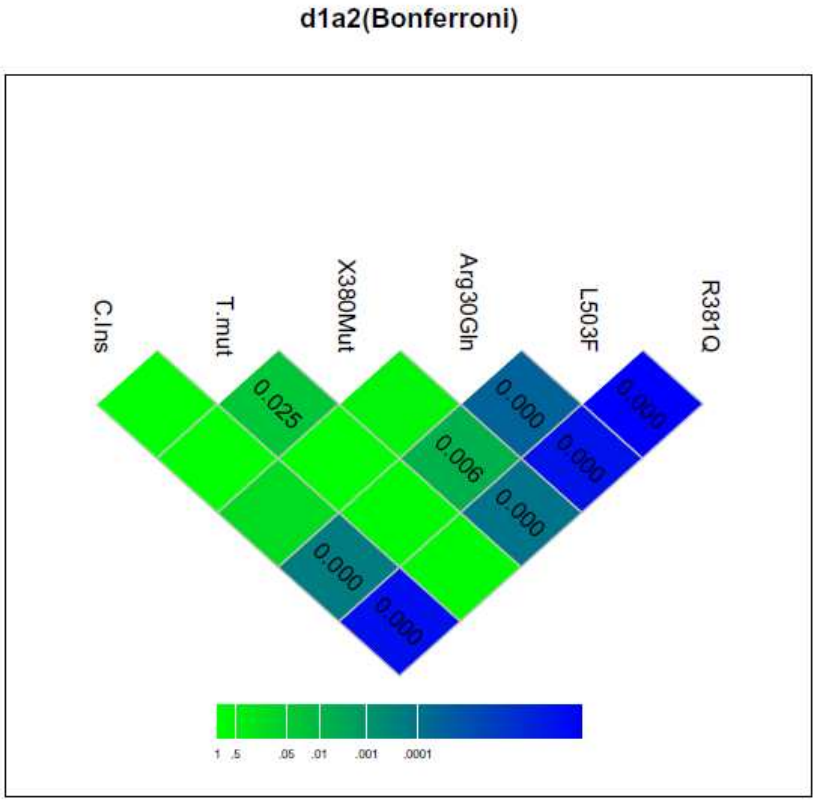
9.3. 2 SNPs analysis

2 SNPs analysis can generate 8 effectors listed in the section 6. The output format is same as 1 SNP analysis. The following shows the result of 2 SNPs analysis. The result data of 2 SNPs can be drawn into a correlation figure and the message for correlation figure is prompted in the summary.

```
Epistatic Interaction Analysis Report
-------------------------------------
 Data File: test¥zhong.csv
     Date: 2010-04-21 09:27:24
    Cases: 192
  Controls: 298
SNPs Count: 6
    Model: 2 SNPs
```

```
Correction: Bonferroni
-----------------------------------

p-Value <= 1e-08:
1:          C.Ins,X380Mut      d1       x2=26.77265758     0.00000000
2:          C.Ins,R381Q        d1       x2=24.99898330     0.00000001

p-Value <= 1e-06:
1:          C.Ins,T.mut        d1       x2=22.72850734     0.00000006
2:                             d1a2     x2=26.85122152     0.00000004
…

p-Value <= 0.05:
1:          C.Ins,T.mut        a2       x2=9.40514814      0.01991434
2:          T.mut,X380Mut      a1d2     x2=7.93984962      0.04444913
……
8:          L503F,R381Q        d2       x2=6.26980082      0.04680578

#1: Full p-value data is exported to a CSV file(zhong-CD.txt.s2.Bonferroni.pvalue.csv).
#2: Full chi2-value data is exported to a CSV file(zhong-CD.txt.s2.Bonferroni.chi2.csv).
#3: Correlation figure is exported to a PDF file(zhong-CD.txt.s2.Bonferroni.pdf).
```

The following figure is a demonstration with Bonferronl correction for the dominance×additive effector. The significant values (p-value<0.05) are labelled in dark green or blue box. The criteria of significant value can be customized in the system configuration.



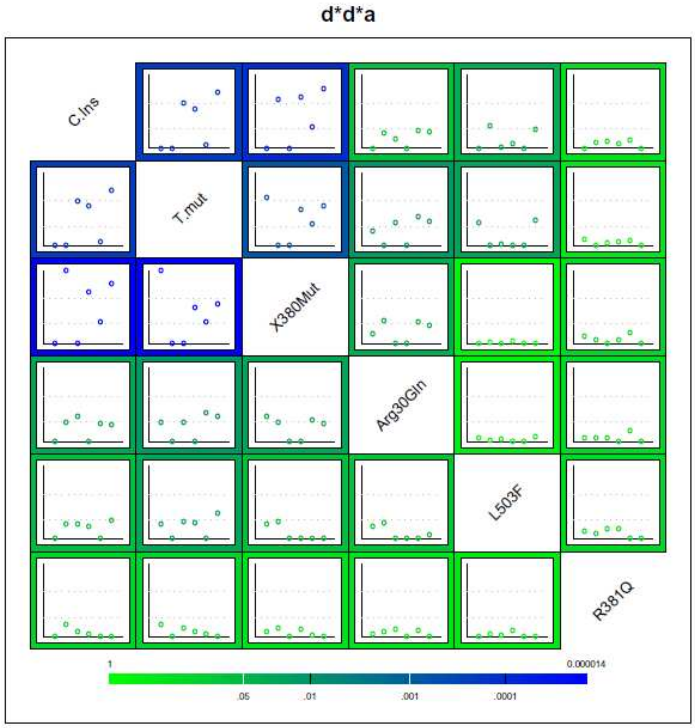
9.4. 3 SNPs analysis

3 SNPs analysis can generate 26 effectors listed in the section 7. The summary is same as 1 SNP analysis and 2 SNPs analysis.

```
Epistatic Interaction Analysis Report
-------------------------------------
 Data File: test¥zhong.csv
     Date: 2010-04-21 09:28:25
    Cases: 192
  Controls: 298
SNPs Count: 6
    Model: 3 SNPs
Correction: Bonferroni
---------------------------------

p-Value <= 1e-08:
1:          C.Ins,X380Mut,R381Q          d1        x2=23.38357198     0.00000001

p-Value <= 1e-06:
1:          C.Ins,T.mut,X380Mut          d1        x2=20.43275815     0.00000011
2:                                       d1a2      x2=24.71905601     0.00000059
……
p-Value <= 0.05:
1:          C.Ins,T.mut,X380Mut          a2        x2=9.89930833      0.03790009
```

```
2:                                      a*d*d     x2=7.95251067      0.01234702
……
32:          X380Mut,Arg30Gln,R381Q     d1        x2=7.29796565      0.02180795
33:                                     a2d3      x2=9.31272259      0.01775092
34:                                     a*a*d     x2=8.35778523      0.02043801

#1: Full p-value data is exported to the CSV file(zhong-CD.txt.s3.Bonferroni.pvalue.csv).
#2: Full chi2-value data is exported to the CSV file(zhong-CD.txt.s3.Bonferroni.chi2.csv).
#3: Correlation figure is exported to a PDF file(zhong-CD.txt.s3.Bonferroni.pdf).
```

3 SNPs analysis also outputs the correlation figure based on the results. The following figure shows the effector of Dominance (SNP A)*Dominance (SNP B)*Additive (SNP C) with Bonferrion correction. In this example small boxes are firstly drawn by the correlation of Dominance (SNP A)*Dominance (SNP B). So the boxes at top line imply Dominance (C.Ins) * Dominance (T.mut), Dominance (C.Ins) * Dominance (X380Mut), Dominance (C.Ins) * Dominance (Arg30Gln), Dominance (C.Ins) * Dominance (L503F) and Dominance (C.Ins) * Dominance (R381Q) respectively. Inside the correlation box for 2 SNPs, there is a scatter diagram that every circle gives the p-value of SNP A*SNP B *SNP C. For example, inside the left box at the first line, first two circles indicate Dominance (C.Ins)* Dominance (T.mut)* Additive (C.Ins) and Dominance (C.Ins) * Dominance (T.mut)* Additive (T.mut). Because these two combinations are invalid, the first two p-values are zero. The rest circles indicate Dominance (C.Ins) * Dominance (T.mut)* Additive (X380Mut), Dominance (C.Ins) * Dominance (T.mut)* Additive (Arg30Gln), Dominance (C.Ins) * Dominance (T.mut)* Additive(L503F) and Dominance (C.Ins) * Dominance (T.mut)* Additive (R381Q).



10. Function details

No	Function description
1	***TIAN.full_test (sCsvFile, options, output_file=NULL, model=NULL)*** The main function to analyze the data set. sCsvFile: CSV data file, it must meet the format of section 3. options: parameters for the data file, see section 3 to get the details. output_file: file name for the summary report. model: 1,2,3 are available that indicate the interaction of 1 SNP, 2 SNPs, 3 SNPs.
3	***TIAN.snp1_test (sCsvFile, options, output_file=NULL)*** 1 SNP analysis The parameters are same as the main function.
4	***TIAN.snp2_test (sCsvFile, options, output_file=NULL)*** 2 SNPs analysis The parameters are same as the main function.
5	***TIAN.snp3_test (sCsvFile, options, output_file=NULL)*** 3 SNPs analysis The parameters are same as the main function.

11. System configuration

sys object is a global object for system configuration. Before the analysis procedure is called, some adjustments for the correlation figure are available in current package.

No	Variable	Description
1	display.cross	Indicate whether the significant values are labeled or drawn in 2D correlation graph.
2	color.cross	Indicate the color of significant values in 2D correlation graph.
3	color.v0	Indicate the color of p-value 0
4	color.v1	Indicate the color of p-value 1
5	legend.peak	Indicate the minimal value in the legend bar.

The following code shows how to use sys object.

```
sys$set_value("legend.peak" , 0.000001);
sys$set_value("display.cross " ,FALSE);

sCsvFile <- "test¥¥zhong2.csv";
options  <- list(
        type      = "auto",
        case_cols  = "Disease",
        snp_cols   = c("X1007FS","R702W","G908R"),
        ignoreRow  = NULL,
```

```
          bHead     = TRUE );

 TIAN.full_test( sCsvFile, options, output="log.txt", model=2 );
```

12. References

(1). Tian Liu, A,Thalamuthu, J.J.Liu, C.Chen,Yao Li,and Rongling Wu. A Model for testing epistatic interactions of complex diseases in Case-Control studies.

(2). Zhong Wang, Zhenwu Lin, Arthur Berg, John Hegarty, Walter A. Koltun and Rongling Wu. A general model for multilocus epistatic interactions in Case-Control studies..

13. Appendix: version history.

Up to now, the version 1.0 has been released.