The Genomic Control for Fisher's Exact Test.

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Abstract

Population structure can produce variable inflation of test statistics in genome-wide association (GWA) study, and genomic control (GC) is one of the method to correct the inflation of χ^2 statistics for contingency tables of case-control independency tests. When the tables have low expected values, χ^2 test is inaccurate and Fisher's exact test should be substituted for χ^2 test. However, the GC for Fisher's exact test has not been indicated.

We propose the application of GC to Fisher's exact test, using mid-P value. The method transforms the observed mid-P values into the corresponding χ^2 values ($\chi^2_{\text{mid-P}}$), and estimates the coefficient of the variable inflation.

We generated simulation case-control data sets in a range of population structures, sample sizes and minor allele frequencies, and applied both GC methods.

GC for Fisher's exact test achieved more accurate type I error rates for nominal significance level, compared with GC for χ^2 test, especially in small sample sizes (N≤1,000) and low minor allele frequencies (MAF:0-0.1)

We propose our application of GC to Fisher's exact test gives significant contributions in the field of GWA studies.

Population Structure and Genomic Control

GC assumes the impact of variable inflation induced by population structure to be constant among samples and markers[1]. For 2x2 χ^2 test, variable inflation is estimated as a single coefficient λ_{GC}, by dividing the median value of observed χ^2 statistics by median value of χ^2 distribution of 1.d.f.

$$\lambda_{GC} = \frac{median(\chi^2_{chi})}{0.455}.$$

Mid-P Value of Fisher's Exact Test

We adopted mid-P value of Fisher's exact test, which include a half of the probability of observed table in the estimation of exact P value[2], known to be less conservative than original exact test P-value.

Original Fisher's exact test p-value:

$$p = \sum_{P(\mathbf{t}) \le P(t_{obs})} P(\mathbf{t}).$$

Mid-P value of Fisher's exact test:

$$mid-p = \frac{1}{2}P(t_{obs}) + \sum_{P(\mathbf{t}) < P(t_{obs})} P(\mathbf{t}).$$

Genomic Control for Fisher's Exact Test

Observed mid-P values are translated into corresponding χ^2 values of 1.d.f. ($\chi^2_{\text{mid-P}}$), and the coefficient of variable inflation ($\lambda_{GC,\text{mid-P}}$) was estimated by comparing the distribution of $\chi^2_{\text{mid-P}}$ with χ^2 distribution of 1 d.f. Finally, $\chi^2_{\text{mid-P}}$ were divided by $\lambda_{GC,\text{mid-P}}$, and re-translated into the corresponding p-value.

$$\lambda_{GC,mid-P} = \frac{median(\chi^2_{mid-P})}{0.455}.$$

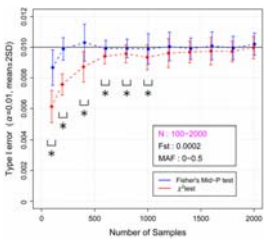
Simulation Analysis

We generated simulation case-control data sets in a range of population structures (*Fst*=0-0.001), sample sizes (N=100-2,000, cases: controls=1:1) and minor allele frequencies (MAF:0-0.5). For each condition, data were created 30 sets. Both χ^2 test and Fisher's mid-p exact test were performed for 2x2 allelic associations.

After GC of both tests were applied, type I error rates of GC corrected p-values were assessed for nominal significance level of α=0.01. Deviations of type I error rates from α=0.01 were compared using t-test between both tests.

Type I Error Rates (after GC)

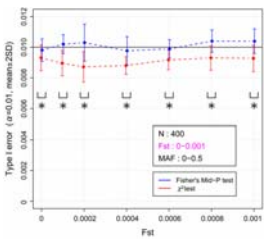
N = 100-2,000



When the number of samples (N) was changed,

GC for Fisher's exact test achieved more accurate type I error rates for small sample sizes (N ≤ 1,000) than GC for χ^2 test.

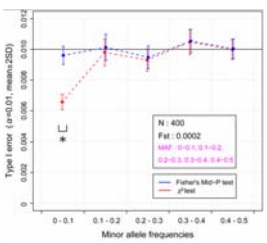
Fst = 0-0.001



When the degree of population structure (*Fst*) was changed,

GC for Fisher's exact test achieved more accurate type I error rates regardless of *Fst* than GC for χ^2 test.

MAF: 0-0.5



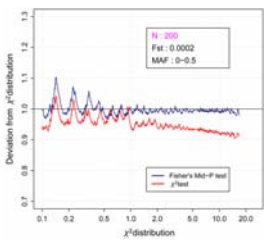
When the range of MAF was changed,

GC for Fisher's exact test achieved more accurate type I error rates for low MAF (MAF:0-0.1) than GC for χ^2 test.

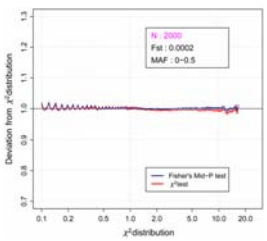
*: GC corrected Fisher's exact test mid-P values showed significantly accurate estimation of type I error rates than GC corrected χ^2 test p-values (p<0.01).

Quantile Plot† of Test Statistics (after GC)

N = 200



N = 2,000

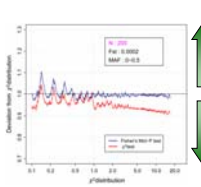


For small sample sizes (N=200), GC corrected mid-P values showed better fitness to uniform distribution, than GC corrected χ^2 test p-values.

For large sample sizes (N=2,000), differences between both tests were not apparent.

† Quantile Plot of Test Statistics

Deviations of quantiles of observed test statistics (χ^2_{chi}, χ^2_{mid-P}), compared with χ^2 distribution of 1.d.f. were on y-axis. Quantile values of χ^2 distribution were on x-axis. When GC was appropriate, corrected p-values followed uniform distribution, and the plot became flat on y=1.



Anti-conservative correction of test statistics.

Uniform distribution of corrected p-values.

Conservative correction of test statistics.

Conclusions

(1). GC for Fisher's exact test achieved more accurate type I error rates compared with original GC for χ^2 test.

(2). Differences between both GC methods became apparent in small sample sizes (N≤1,000) and low minor allele frequencies (MAF:0-0.1).

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References

(1). Delvin, B.& Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997-1004 (1999).

(2). Martin, A.A. Fisher's mid-p-value arrangement in 2x2 comparative trials. *Comput. Stat. Data Anal.* **29,** 107-115 (1998).