## Correction for multiple testing (the bootstrap method of Storey and Tibshirani)

We propose applying the bootstrap method of Storey and Tibshirani [[1](#_ENREF_1),[2](#_ENREF_2)] to estimate the proportion of true null hypotheses and use this in a Bonferroni-like manner to correct for multiple testing.

The method of Storey and Tibshirani makes use of the vector of resulting *ppermut,GS*-values to determine a tuning parameter λ, in order to estimate the proportion of true null hypotheses for , where is the number of *ppermut,GS*-values less than or equal to λ and z*=1* for the finite-sample case; otherwise z*=0*. For each λ, we bootstrap on the p-values to form *B* bootstrap versions , with *b=1,…, B*, and choose the “optimum” λ that yields the minimum .

Finally the corrected p-value for each GS is calculated as:

(S6)

### Correction for multiple: Application: GO-pathways and lung cancer

Of the 421 investigated gene sets, 313 belong to *biological processes,* according to the GO hierarchy, while the remaining 108 gene sets belong to *molecular functions*. To maintain the balance between these two functional classes, we used a weighted Bonferroni adjustment to correct for multiple testing [[3](#_ENREF_3)]. In general, a null-hypothesis H0i of no association of gene set *i* (*i=1 to nGS*) is rejected if: as long as , where *α*=0.05 is the global level of significance, *t* is the effective number of tests, and *wi* is a weight assigned to each test *i* [[3](#_ENREF_3)]. Reformulated, the p-values of META-GSA adjusted for multiple testing are given as . We defined equal weights for each gene set within a function class as , with *tf* the effective number of gene sets of the function class and .

References

1. Storey JD, Tibshirani R (2003) Statistical significance for genomewide studies. Proc Natl Acad Sci USA 100: 9440-9445.

2. Publishing SAS (2010) SAS/Stat 9.22 User's Guide the MULTTEST Procedure: SAS Publishing.

3. Kang G, Ye K, Liu N, Allison DB, Gao G (2009) Weighted multiple hypothesis testing procedures. Stat Appl Genet Mol Biol 8: Article23.