

Introduction to the Special Issue: Genome-Wide Association Studies

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Genome-wide association studies (GWAS) have recently provided some exciting scientific advances for identifying susceptibility genes for many common diseases (e.g., WTCCC, 2007, in the June issue of *Nature*). These advances will have great impact on future genetic studies and clinical trials to understand mechanisms of common diseases. The GWAS revolution is far from having run its course. Attention is now turning from simple case-control designs to using family data or prospective cohort data that convey a wealth of phenotypic information, including life-course varying phenotypes, as well as environmental exposures. Statistical analyses of GWAS data have to date focused mainly on the simplest tests of one SNP at a time, leaving open the possibility that more sophisticated analyses may reveal further important results. These could involve results about metabolic pathways, gene-by-gene and gene-by-environment interactions, imputations and copy number variants. Funds from the US government (National Institutes of Health), the Wellcome Trust and other research organizations for genomic studies have increased substantially.

Advances in statistical methodology will be central in these developments, and we proposed this special issue to help foster them, by authoritative reviews of the current state of the art, and pointers to novel developments. Statistical issues and challenges arise from all aspects of design and analysis of GWAS. This special issue consists of 12 papers focusing on the following topics: statistical designs using case-control or family

data, two and multi-stage designs for GWAS, retrospective and prospective designs and their impact on single marker, imputation and haplotype analyses, robust single marker analysis and probability measures of detecting markers with true associations, population structure and how to detect and correct for it, multiple testing issues and weighted hypothesis testing for GWAS, strategies for analyses of gene–gene and gene–environmental interactions in the GWAS setting, novel Bayesian approaches to impute and test markers, estimating genetic effect and making predictions using significant markers from GWAS, analysis of copy number variants, and replication studies for GWAS. The authors of these reviews are widely published in this area and we thank them for their timely contributions. Without their enthusiasm this issue could not come to fruition.

Some other topics are not included in this special issue, including genotype call algorithms and methods of quality control, integration of gene expression and genetic data, random forests and machine learning methods, and methods related to resequencing genetic data. An overall review of Bayesian methods in genetic association studies, including GWAS, a topic not included in this issue, has recently been published by Stephens and Balding (2009) in the October issue of *Nature Reviews Genetics*. Much computer software is available to run analyses for GWAS. A review of these computer programs is not presented in this special issue, but a number of programs are already included in the various reviews. Study designs combining case-control and family data for GWAS are not included in this special issue.

Finally, we would like to thank Peter Donnelly and David Balding for their support of the idea to have this special GWAS issue. In particular, David made very helpful suggestions to our initial proposal of this special issue. We would also like to thank the Executive Editor, David Madigan, for his excellent editorial support. All published papers in this special issue have been through the regular peer-review process. Our thanks also go to the referees of this special issue.

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