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Genetic Analysis Workshop 15: Gene expression analysis and approaches to detecting multiple functional loci

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Genetic Analysis Workshop 15: gene expression analysis and approaches to detecting multiple functional loci

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Preface

This issue of *BMC Proceedings* contains the proceedings of Genetic Analysis Workshop (GAW) 15, which was held November 11–15, 2006, in St. Pete Beach, Florida, USA. The GAWs began in 1982 and are now held in even-numbered years. They provide a forum for investigators interested in identifying genetic effects on complex diseases to evaluate and compare novel and existing statistical methods. The purpose of these Workshops is to allow the comparison of statistical methodologies for genetic epidemiology using common, well described data sets. Prior to each GAW, topics are chosen, one or more existing data sets are selected, and a set of simulated data is created that permits investigation of current questions of broad interest in statistical genetics. These data are made available to any scientist who requests them, and their analyses of these data are presented at the Workshop. Participation in the Workshop is open to anyone who submits an analysis of one of these data sets, provides data, or participates in Workshop organization. More information about GAW, including details of upcoming Workshops, may be found at <http://www.gaworkshop.org>.

Three data sets (two empirical and one simulated) were distributed for GAW15, addressing two general classes of problems: 1) the genetics of expression, and 2) methods for dissection of complex traits. For the first time, one of the real data sets included RNA expression data from microarrays (Problem 1). Analyses of these data by GAW15 participants were focused primarily on expression data as quantitative traits in linkage and association scans and on methods for extracting additional information from the massively multivariate nature of the data set, which included literally thousands of quantitative traits. The second real data set (Problem 2) provided opportunities to address such methodological problems as separating multiple functional loci within a region of linkage or association, and linkage and association analyses of markers in the pseudoautosomal region of the X chromosome. The simulated data set (Problem 3) for GAW15 was based on the Problem 2 data set to allow participants to address complementary questions in a data set with a known genetic architecture. Here we provide a brief summary of the data sets; further details can be found in Cheung and Spielman [1], Amos et al. [2], and Miller et al. [3] in this issue.

The Problem 1 data set included microarray expression profiles originally investigated by Morley et al. [4]. Data were provided for 14 three-generation Centre d'Etude du Polymorphisme Humain (CEPH) Utah families (approximately 8 offspring per sibship and approximately 14 individuals per family). Phenotypes included expression level of genes in lymphoblastoid cells of these family members, obtained using the Affymetrix Human Focus

Arrays that contain probes for 8500 transcripts. Among these, Morley et al. [4] found greater variation among individuals than between replicate determinations on the same individual for 3554 expression phenotypes (expressed genes); these were provided to GAW15. For approximately 100 individuals, array hybridizations were performed in duplicate. The Affymetrix CEL files for all array hybridizations were provided to GAW15 participants. Genotypes for members of the 14 families were provided for 2882 autosomal and X-linked single-nucleotide polymorphisms (SNPs). The genotypes were generated by The SNP Consortium. This data set provided the opportunity to develop and apply methods for simultaneous analysis of a variety of related traits. Natural variation in gene expression is a new idea, and this collection is the first to provide such a large number of phenotypes in a family study.

The Problem 2 data set consisted of family- and population-based data from the North American Rheumatoid Arthritis Consortium study (NARAC) and from collaborators in Canada, France, and England. The goal of these studies is to understand the etiology of rheumatoid arthritis. It is highly likely that multiple interacting loci influence disease risk, as evidenced by the considerably higher recurrence risk for this disease to siblings as opposed to more distant relatives. The data provided by NARAC to GAW15 included 757 multiplex families genome scanned with microsatellites (511 families) and/or SNPs (746 families), candidate gene data for the *PTPN22* locus from a study of 1519 controls and 1393 cases (and for additional candidate loci in a separate sample of 855 controls and 839 cases), dense genotyping data from a panel of 2300 SNPs for an approximately 10-kb region of chromosome 18q (genotyped on 460 cases and 460 controls), and further data on a number of quantitative phenotypes and clinical measures. The Canadian group provided data from 60 families that had been genotyped using the same Illumina platform used by NARAC as well as 79 families that were genotyped using an Affymetrix 100 K platform. The European Consortium on Rheumatoid Arthritis Families provided high-density microsatellite data from 88 families typed with 1089 microsatellite markers. The UK group provided microsatellite genome screen data from 174 families, of which 157 were also genotyped at 10,156 SNPs. A further set of 195 families genotyped at selected microsatellites was also provided.

The Problem 3 data set included 100 replicates of simulated data, modeled after the rheumatoid arthritis data set. Each replicate included 1500 nuclear families of size four (two parents and an affected sib pair (ASP)) and 2000 unrelated controls. Three sets of autosomal markers were generated: 1) a set of 730 microsatellite markers spaced on average 5 cM apart; 2) a set of 9187 SNPs distributed on

the genome to mimic a 10 K SNP chip set; and 3) a very dense map of 17820 SNPs on chromosome 6 (an average inter-marker spacing of 9586 bp). The data included map information, with lists of markers and their locations, and simulated family, marker, and phenotype/covariate data. "Answers" (the locations/effects of true causal loci and a description of the underlying generating model) were provided to GAW15 participants on request.

The availability of the GAW15 data was announced by email in the Spring of 2006, to the more than 2600 individuals on the GAW mailing list. A total of 179 groups requested GAW15 data. The Problem 1 data were requested by 133 groups, the Problem 2 data by 142 groups, and the Problem 3 data by 128 groups (with many groups requesting access to more than one data set). In the Summer of 2006, 252 contributed papers were received describing analyses of these data sets. A book and CD containing these contributions plus descriptions of the data sets were distributed to GAW15 participants.

The GAW15 participants included 350 individuals from 20 countries on four continents – Asia, Australia, Europe, North and South America. The 252 contributions submitted to GAW15 were organized into 17 presentation groups of 11 to 18 papers each, grouped based on common methodological themes. The 17 presentation groups were organized around the following themes: association analysis (Problem 1); association analysis (Problem 2); association analysis (Problem 3); combining linkage and association; data mining, neural networks, and gene networks (Problem 1); data mining, neural networks, and trees (Problems 2 and 3); gene \times gene interaction; gene \times environment interaction; linkage analysis (Problem 1); linkage analysis (Problems 2 and 3); model selection and Bayesian methods; multivariate analysis; candidate gene association; multistage designs; multiple testing and false discovery rate; processing and normalization of expression traits and their effect on analysis; and SNP selection, ancestry informative markers, and linkage disequilibrium between markers. For each presentation group, a group leader was chosen who had previous GAW experience. This person facilitated group discussion, organized the group's oral presentation to the general GAW meeting, and took the lead in writing the group summary paper to be published in *Genetic Epidemiology*.

Members of most presentation groups began interacting by email and/or conference call before GAW15, comparing and contrasting their approaches and results. Each presentation group also met at least once during the Workshop, where they continued their discussions and finalized a group presentation that was delivered to the full GAW15 audience during the general sessions. The group meetings were attended mostly by group partici-

pants but were open to all GAW15 attendees. During poster sessions, 118 individual contributions were presented. There also was a special general session on "Novel Methods" at which four of the contributions (selected prior to GAW15 on the basis of the submitted papers) that had used or developed novel analytical approaches were highlighted and presented.

The 162 GAW contributions included in this issue of *BMC Proceedings* are a subset of the 252 contributions presented at GAW15. All of these papers have been peer-reviewed and were selected on the basis of scientific merit. First come three papers that describe the data sets. These are followed by the 162 individual GAW15 contributions organized by presentation group, and alphabetically by first author within each group. Additionally, in a forthcoming supplement to the journal *Genetic Epidemiology*, a paper by each presentation group summarizes the contributions to that group and the lessons learned, comparing and contrasting contributions and describing their main themes and results. Overall, GAW15 generated many interesting discussions and some conclusions concerning appropriate approaches to the analysis of massively multivariate data, and methods for separating multiple functional loci within a region of linkage or association. These discussions also highlighted areas in which further methodological development is needed.

Competing interests

The author(s) declare that they have no competing interests.

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The GAWs succeed because of the dedication of hundreds of individuals who help to select Workshop topics, provide real and simulated data, prepare and distribute data to participants, prepare Workshop contributions, organize the Workshop, lead presentation groups and chair sessions, write summary papers, review manuscripts, and edit the Workshop proceedings.

We are extremely grateful to the investigators who provide data for the Genetic Analysis Workshops for analysis by workshop participants. The workshops would not be possible without their generosity. Many investigators contributed data to GAW15: **Problem 1:** Drs. Vivian Cheung and Richard Spielman provided their microarray expression data from CEPH families. The generation of these data was supported by NIH grant HG002386 from the National Human Genome Research Institute (NHGRI). **Problem 2:** Rheumatoid arthritis data were provided by investigators in the US (Peter Gregersen, Elaine Remmers, Lindsey Criswell, Ann Begovich, Robert Plenge, Chris Amos, Wei V. Chen, Dan Kastner, Michael Seldin, Annette Lee), Canada (Katherine Siminovitch), the UK (Jane Worthington, Sally John, Neal Shephard), and France (François Cornelis). Dakai Zhu helped with organization of the data and Toi Soh assisted with preparation of the summary. The rheumatoid arthritis studies were supported by NIH grant AR44422, NIH contract N01-AR-7-2232, funding from Genome Canada and Associations AFP, Polyarctique-Groupe Taitbout and Rhumatisme et Travail. Funding for UK researchers was provided by the Arthritis Research Campaign. **Problem 3:** The GAW15 simulated data set was generated by Michael B. Miller in collaboration with Gregg R. Lind, Na Li,

and Soon-Young Jang, with assistance from Octave developer John Eaton. Chris Amos was especially helpful in guiding choices in model selection. Support for generation of the simulated data was provided from NIH grants 5R01-HL049609-14, 1R01-AG021917-01A1, the University of Minnesota, and the Minnesota Supercomputing Institute.

The GAW15 contributions were organized by theme into presentation groups. Seventeen people generously volunteered for the difficult task of group leader, which involved initiating interactions among group members before GAW15, leading group meetings at GAW15, organizing summary presentations for the larger GAW15 audience, and taking responsibility for the preparation of a summary paper for *Genetic Epidemiology*. Their efforts deserve special recognition. We are grateful to the following people who led the group discussions and preparation of summary presentations (in group numerical order): John Witte, Marsha Wilcox, Heike Bickeböllner, L. Adrienne Cupples, Cathy Falk, Andreas Ziegler, Veronica Vieland, Rob Culverhouse, Ellen Wijsman, Saurabh Ghosh, Duncan Thomas, Joseph Beyene, Mariza de Andrade, Beth Hauser, Lisa Martin, Maria Martinez, and Josée Dupuis.

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Since GAW7 in 1991, Vanessa Olmo has had major responsibility for all aspects of Workshop organization. Over the years, as the Workshops have increased in size and complexity, she has taken on greatly increased responsibilities. She has primary responsibility for Workshop logistics, including interaction with participants, organizers, editors, and publisher; data distribution; site selection and liaison with local organizers; maintenance of the GAW web site and mailing list; and preparation of the proceedings. The

GAWs could not succeed without her commitment and her enthusiasm. We also thank Selina Flores who helped with data distribution, communications with participants, and preparation of the pre-GAW volume; and Richard Polich, Tom Dyer, Laura Almasy, Linda Freeman-Shade, and Gerry Vest, who worked on preparing the data for distribution. As for past GAWs, April Hopstetter, Director of Technical Publications and Printing at the Southwest Foundation for Biomedical Research, assisted with editing of the GAW15 proceedings, while Maria Messenger and Malinda Mann typeset the articles. Rene Sandoval and Rudy Sandoval were responsible for putting together the final pre-GAW book.

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The GAW Advisory Committee, which has a rotating membership, has overall responsibility for long-term planning for the GAWs. Its membership at the time of GAW15 included Laura Almasy, Joan Bailey-Wilson, Heike Bickeböllner, Ingrid Borecki, Françoise Clerget-Darpoux, Heather Cordell, Lynn Goldin, Jean MacCluer (chairman), Duncan Thomas, John Witte, and Andreas Ziegler.

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