Meeting report

ASHG 2008 Annual Meeting: from enormous cohorts to individual genomes

Lars Feuk

Address: Program in Genetics and Genomic Biology, The Hospital for Sick Children, MaRS Centre - East Tower, 101 College Street, Room 14-701, Toronto, Ontario, M5G 1L7 Canada. Email: lars@genet.sickkids.on.ca

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A report of The 58th Annual Meeting of the American Society for Human Genetics (ASHG), Philadelphia, Pennsylvania, USA, 11-15 November, 2008.

The 58th Annual Meeting of the American Society for Human Genetics (ASHG) gathered experts in all areas of genetics and genomics from around the world. In total, there were nearly 5,000 people registered for the meeting this year. The meeting is one of the best opportunities for geneticists to catch up on the latest research breakthroughs, but also presents an excellent setting for meeting old friends and colleagues in the field. This year's meeting also saw an increase in the number of exhibitor booths, clearly demonstrating how genetics is going mainstream in the health care industry.

One of the best attended sessions was the presidential address, delivered by ASHG President Aravinda Chakravarti (Johns Hopkins University, Baltimore, USA) [Session 1]. In his talk, entitled 'Principia Genetica: our future science', Chakravarti outlined the great achievements made in genetics to date, but also reminded us that there is plenty of work ahead. He emphasized that we must take full advantage of the knowledge gleaned from the large genome projects and to use this towards understanding the basic mechanisms of our genome. Chakravarti stated that great progress has been made in describing the genome and genetic variation, but we now need to go from description to prediction. Only when the basic mechanisms of our genome are well understood will we be able to take that step. He also cautioned that there have been many unexpected findings in the genome in the past decade - for example, the low number of genes, the large amounts of variation, the complexity of transcriptional regulation - and our genome probably has a few more surprises in store for us in the future.

In terms of new discoveries and trends in the field, there were four major themes in which significant progress has been made over the last year. The success of identification of variants associated with complex traits using genome-wide association studies (GWASs) has been established over the past two years. This year, one major theme was that data from several of the main cohorts in the initial wave of GWASs had been pooled, leading to better power to detect novel loci. As an example, the GIANT consortium study of body mass index, presented by Cristen Willer (University of Michigan, Ann Arbor, USA) [Abstract 105], made an initial meta-analysis of 13 cohorts of over 32,000 individuals, followed by a replication in over 58,000 samples from 14 independent studies. These types of meta-analysis, performed for many common diseases, identified many new risk alleles. There was also a trend among the GWAS presentations to study non-disease-related traits, such as height, or traits indirectly linked to disease, for example, blood-lipid and cholesterol levels. Two of the key messages coming out of the GWASs were that many of the genes identified would not have been on anyone's list of candidates and also that the variants identified explain a very small fraction of the overall disease burden in the population. There was also agreement on the challenges that lie ahead, namely how we best use this knowledge of low-penetrance risk alleles and how this knowledge can be translated into clinical utility.

Another area in which major progress has been made is in the field of structural variation, and specifically copy number variation (CNV). Since the discoveries that this type of variation is abundant in the human genome were

published, the interest in making better CNV maps and linking CNVs to disease has grown rapidly. This year, there were over 200 abstracts related to this form of variation and the session entitled 'Structural variation and disease' was one of the most popular. Don Conrad and Emmanouil Dermitzakis, both from the Wellcome Trust Sanger Institute (Hinxton, UK) [Abstracts 150, 149], described large collaborative efforts towards better annotating CNVs at high resolution with better information about variation boundaries, population frequencies and breakpoint mechanisms. The main purpose of creating better CNV maps is to enable studies of the correlation of CNV with human traits. It was clear from the meeting that ample progress is already being made in this area. Several talks were focused on the characterization of CNVs in patient cohorts, describing associations with various forms of cancer, schizophrenia and Crohn's disease. It is likely that this will remain a hot topic over the next few years, especially when CNVs can be used in a better way in GWAS designs.

In terms of complex traits, one of the most challenging areas is to understand the etiology of neuropsychiatric disorders. This year, this field of research received plenty of attention, with two sessions on neuropsychiatric disorders and two sessions related to autism. Several important genetic discoveries over the past years have led to an increased understanding of the complexity of these disorders. The studies of CNV in neuropsychiatric disorders in general, and in autism and schizophrenia in particular, have led to the discovery of specific genes and loci that are strongly associated or directly causative. Large collaborative efforts to study the genetics of autism were reported in several talks. Jim Sutcliffe (Vanderbilt University, Nashville, USA) [Abstract 220], representing the Autism Genome Project, gave an update on the progress of phase II of the project, which is a study using high-resolution single nucleotide polymorphism (SNP) arrays in a large cohort of autism trios. Maja Bucan (University of Pennsylvania, Philadelphia, USA) [Abstract 219], representing a collaboration mainly involving University of Pennsylvania and the Children's Hospital of Philadelphia (USA), used a similar strategy but on a different set of samples. Both studies are using the array data for both SNP-based and CNV-based analysis. A theme that has been emerging over the past year and that was reiterated in the presentations this year is that these disorders can be caused by a large number of genes. However, although many of the genes and CNVs identified seem to have very high penetrance, each locus seems to make a very small contribution to the total patient population. Despite this low contribution overall, these are extremely important findings as they represent targets that can be used to untangle the complex pathways involved.

The most dramatic development since last year's ASHG meeting has been the completion of several individual human genome sequences. Not only has this led to an increased understanding of individual genome variation, but it has given us a glimpse of the future of genomics. Personalized genome sequencing was one of the main topics of the meeting and was discussed in depth both in the genomics and the ethical, legal and social issues sessions. Two of the highlights of the individual genome sequencing talks were delivered by David Altshuler (The Broad Institute, Boston, USA) [Abstract 84] and Craig Venter (J Craig Venter Institute, Rockville, USA) [Abstract 37], respectively. Altshuler gave a presentation on the aims, design and progress of the '1000 Genomes' Project. This is a two year project with the goal of sequencing 1,000 or more individual genomes to create a detailed map of human genetic variation. The pilot phase, which aims to answer questions about what strategies and approaches to use for the next stage of the project, is now well underway. In a separate session entitled 'Presidential Symposium: genome stories', Craig Venter gave a talk entitled 'My genome' [Abstract 37]. Venter, who is one of only two identified individuals who have had their genome sequences published so far (along with James Watson of Cold Spring Harbor Laboratory, Cold Spring Harbor, USA), gave a very personal account of the characterization of his own genetic code and the implications this has had for himself. There have only been four individual genome sequences published to date. It will be interesting to see what that number is by the time of next year's ASHG meeting.

The feeling I came home with after the 5 days filled with presentations, meetings and vendor lunch seminars was that the increased pace and reduced cost of producing large amounts of genomic data have led to impressive progress over the past year, but as a result data analysis is becoming a bottleneck, and making sense of the results is the real challenge. The stage we are currently at in genomics research, taking the impressive achievements over the past year into account, was summarized nicely by ASHG president Aravinda Chakravarti, who stated that "We live in a very different world in genetics than we did a short time ago. Clearly we have exciting times ahead."

Abbreviations

ASHG, American Society for Human Genetics; CNV, copy number variation; GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

Acknowledgements

All abstracts in the reference list were presented at the annual meeting of The American Society of Human Genetics, November 11-15, 2008, Philadelphia, Pennsylvania, USA [1].

References

1. **The American Society of Human Genetics 2008 Meeting** [http://www.ashg.org/2008meeting/]