Genome Medicine

MEETING REPORT

Report of the 60th annual meeting of the American Society of Human Genetics: several steps toward discoveries

Leonid Padyukov*

Abstract

A report of the 60th annual meeting of the American Society of Human Genetics in Washington, DC, USA, 2-6 November 2010.

Introduction

To say that science is about understanding the mysteries is not very new. However, even in the relatively dry and ordinary issues of statistical and genetic epidemiology there remains a lot of space for a mystery to be discovered. During the 60th annual meeting of the American Society of Human Genetics (ASHG), many topics referred to the phenomenon of 'missing heritability', which was previously coined by Maher (*Nature* 2008, **456:**18-21).

The 60th annual meeting of the AHSG was held on 2-6 November 2010, at the Walter E Washington Convention Center, Washington, DC, USA. There were more than 7,200 participants and almost 3,000 presentations at the conference, a record-breaking number.

Two lectures at the very beginning of the conference highlighted the fact that the meeting was refining plans for comprehensive research into common complex human diseases in the coming years. At the pre-conference National Institute on Alcohol Abuse and Alcoholism symposium 'Tightening the genotype-phenotype gap: from genetic variation to gene function', Dr Eric Green (Director of the National Human Genome Research Institute, Bethesda, MD, USA) made a presentation entitled 'En route to the era of genomic medicine', presenting a draft of the strategy for genetic research in this area. Second, at very beginning of the conference itself, Dr Eric S Lander (Broad Institute of Harvard and MIT, Cambridge, MA, USA) presented 'The human genome project: a decade later', which was an overview of the achievements and perspectives of human genetics. It was especially interesting to hear how the mystery of 'missing heritability' could be explained. The key word was 'interaction'. Interaction between genes, epistasis, may clarify what has been missing in our understanding of genetics of complex diseases.

The mystery of the missing heritability

According to the generally accepted view, common complex human diseases, such as type 1 or type 2 diabetes, multiple sclerosis, Alzheimer's disease, rheumatoid arthritis, asthma and many others, are the product of at least two types of factor: environmental and genetic (heritability). The impact of the latter factor is high enough to bring these diseases to the field of genetic research. However, there is a problem due to uncertain patterns of inheritance and relatively low penetrance for these diseases. In contrast, Mendelian diseases demonstrate more predictable heritability patterns and often represent highly penetrant phenotypes. Since gene mapping for Mendelian diseases has been very successful, there have been strong expectations for the discovery of genetic variations responsible for complex diseases. Very efficient and comprehensive tools for genome-wide genotyping should be the technical solution and, although these diseases are complex by nature, it was commonly believed that we were close to resolving the problem by examining each of the variants/genes involved. Since the modern version of genome-wide association studies (GWAS) was introduced in 2007, substantial numbers of genetic risk factors have been discovered for many complex diseases. However, the impact of these factors for the prediction of traits remains relatively low. This inability to explain a major part of the genetic influence by known genetic variations has been defined as 'missing heritability'.

In order to potentially explain 'the mystery', several directions for future research were suggested and discussed at the conference. The two main directions

*Correspondence: leonid.padyukov@ki.se
Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

were: broadening the discovery of genetic risk factors by increasing the statistical power of GWAS (for example, by extensive meta-analysis); and the study of interactions between genes, and between genes and the environment.

Many GWAS have been published, with a growing number of observations and large consortia collecting impressive sets of data, sometimes with sample sizes >100,000 individuals. However, for many phenotypes only slight increases in our understanding of heritability have been achieved. In the session titled 'Polygenic traits: GWAS methods and results' it was convincingly presented by Dr HL Allen *et al.* (University of Exeter, Exeter, UK) and the GIANT consortium that an additional approximately 10% of heritability variance for adult height can be explained by the sum of genetic signals with small effects from GWAS.

At the session entitled 'Autoimmunity and infection' presented by Dr EA Stahl (Brigham and Women's Hospital, Boston, MA, USA, and The Broad Institute, Cambridge, MA, USA) the data on previously undiscovered genetic variations obtained from GWAS of rheumatoid arthritis suggested that a relatively high portion of variability could be explained. However, it is difficult to pinpoint particular risk factors from the set of the candidates with small effects in GWAS.

Are interactions the answer?

Multiple pieces of evidence from the presentations at different sessions of the conference indicated that gene-gene interactions contribute substantially to human complex diseases.

In the plenary session, Dr J Knight (King's College London School of Medicine, London, UK), together with the Consortium for Genetic Analysis of Psoriasis and the Wellcome Trust Case-Control Consortium II, presented important new data on psoriasis susceptibility loci and genetic interactions between *HLA-C* and *ERAP1* (endoplasmic reticulum aminopeptidase 1, chromosome 5). Psoriasis is one of the most common human autoimmune diseases, and discovery of genetic interactions will serve as an important prototype for the study of other complex diseases.

The session 'Polygenic traits: GWAS methods and results' presented an interesting example of a gene-gene interaction, that between *APOE* and *BIN1* (bridging integrator 1, chromosome 2) and *CUGBP2* (also known as *CELF2*, Elav-like family member 2, chromosome 10). This was presented by E Wijsman *et al.* (University of Washington School of Medicine at Seattle, Seattle, WA, USA) with the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer's Disease/National Cell Repository for Alzheimer's Disease Family Study Group.

In another session entitled 'Genetic architecture of neurological diseases', TA Thornton-Wells *et al.* (Vanderbilt University's School of Medicine, Nashville, TN, USA) and The Alzheimer's Disease Genetics Consortium presented the evidence for gene-gene interactions in Alzheimer's disease, and these were replicated in independent Alzheimer's Disease Genetics Consortium datasets. By using 18 genes in a multidimensional reduction analysis with subsequent mapping back to the genes, *ASL* (argininosuccinate lyase, chromosome 7) and *CPS1* (carbamoyl-phosphate synthase 1, mitochondrial, chromosome 2) were found to potentially interact in the development of Alzheimer's disease.

The interest in genetic interactions attracted a great deal of attention to the session 'Translating GWAS statistics into biology: use of interaction studies and functional information', where the majority of invited lectures were related to gene-gene and gene-environment interactions.

In his lecture entitled 'Gene-environment interaction in the study of human complex diseases: what we can learn from rheumatoid arthritis and multiple sclerosis?' Lars Alfredsson (Karolinska Institutet, Stockholm, Sweden) raised several important methodological issues in relation to interactions. By using experimental data from two common autoimmune diseases, rheumatoid arthritis and multiple sclerosis, Dr Alfredsson demonstrated the important interaction between smoking behaviour and genetic make-up. Interestingly, substantial additional risk for both diseases was detected in the interaction of smoking with susceptibility alleles from the human leukocyte antigen (HLA) system locus. Since these alleles are not identical for the two diseases, the mechanisms of interaction could not be determined easily. In rheumatoid arthritis, the major risk from smoking and HLA shared epitope alleles is known to be associated with autoantibody-positive rheumatoid arthritis. It was not surprising that interaction with smoking was detected for this particular subgroup of the disease, but was completely absent in autoantibody-negative rheumatoid arthritis. In multiple sclerosis, serological phenotypes are not well characterized in comparison with rheumatoid arthritis, but the lesson from rheumatoid arthritis is in the evaluation of a more specific subgroup of complex disease rather than analysis of the whole heterogenic group. Another conclusion was the importance of including environmental risk factors in genetic studies of complex diseases.

Marylyn Ritchie (Center for Human Genetic Research at Vanderbilt University, Nashville, TN, USA) presented the Biofilter, an algorithm that was mentioned several times in different presentations at the conference. Biofilter is a bioinformatics approach for generating and ranking biologically supported multilocus models of disease susceptibility. The algorithm automatically accesses

and indexes data sources implying interaction of molecules, data sources for gene relationships to disease, and literature-based data sources. These resources are integrated using a 'genomic convergence' approach and an implication index that measures the number of data sources that support the model. In addition, Biofilter allows the investigator to include a subset of disease-related genes based on previous genetic linkage, genetic association, and gene expression studies. Dr Ritchie demonstrated examples of successful application of the Biofilter in identifying previously unknown interactions in human diseases and in quantitative phenotypes.

It can be a bit disheartening to find yourself as the very last lecturer of the very last session of the meeting. However, the interest in interaction studies remained high for this session, which was concluded with my well-attended lecture on genome-wide interaction studies. The data from our group illustrate a new approach in finding genetic interactions on a genome-wide scale. We performed a genome-wide interaction study in rheumatoid arthritis using HLA shared epitope alleles as an anchor in a large population-based study of rheumatoid arthritis in Sweden, and found several new candidate genes, which were replicated by similar evaluation in an independent study from the USA and were supplemented by expression analysis of the genes with highest scores for interaction. Using our GEIRA algorithm, a similar study could be performed for any disease or categorical trait with a known strong 'anchor', a robust and well-established risk factor (either genetic or environmental). Such strong contributors (usually HLA alleles for autoimmune diseases), at least in some cases, may represent 'the suzerain effect', when many genes with a small contribution for interaction with the same factor may each generate a cumulative effect that is non-detectable in generic GWAS.

The end of the meeting was illuminated by a very inspirational and energetic talk by Dr Francis Collins (Director of the National Institutes of Health (NIH), Bethesda, MD, USA) at a special symposium entitled 'Looking toward a healthier future: perspectives from the NIH'. In his lecture, Dr Collins presented the current vision of opportunities for genetic research and how the NIH is promoting this research. Substantial resources will be allocated in the future to help elucidate the genetic complexity of human diseases, with the goal to initiate early prevention programs for individuals at risk.

Similar to previous years, the ASHG meeting was an important point in my research schedule, a place to meet friends and colleagues from the USA and many other countries, a time to summarize ideas and to plan new projects. This year there was a feeling that we are a few steps further forward in understanding 'missing heritability' and that we may soon be able to explain this mystery in scientific terms.

Abbreviations

ASHG, American Society of Human Genetics; GWAS, genome-wide association studies; HLA, human leukocyte antigen; NIH, National Institutes of Health.

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