Genome Medicine

Meeting report

The 2009 European Society of Human Genetics Meeting: novel technologies driving change

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Abstract
A report on the meeting of the European Society of Human Genetics, Vienna, Austria, 23-26 May 2009.

This is the premier European meeting for those with an interest in any aspect of human genetics, with some 3,000 attendees, more than 1,800 abstracts submitted as talks and posters, over 100 exhibitors, and many corporate workshops, satellite and business meetings held annually over a four-day period. From such a large conference where five or six sessions can run concurrently and with diverse topics ranging from ethics, to clinical and molecular diagnostic genetics, to pure research, it is impossible to digest anything but a fraction of what is on offer, and inevitably the highlights of the conference will vary depending on your background. Here I discuss what I considered to be the most interesting developments of the vast selection that was on offer.

The importance of conserving copy number

The emerging role of copy number variation in human disease has been a common theme of many genetics conferences over the last five years, and this meeting was no exception. With microarrays now being routinely used in most clinical genetics laboratories, several participants presented data describing the characterization of novel aneuploidies, and the emerging heterogeneity of some recently described syndromes such as recurrent deletions of 15q13.3.

The leading manufacturers of microarray platforms each hosted a scientific symposium, which, while obviously designed to showcase the capabilities of their respective products, can be an excellent way to gain insights into up and coming or recently released technologies. Dr Ingrid Simonic (Department of Medical Genetics, Cambridge University Hospital, UK), Dr Joris Veltman (Department of Human Genetics, St Radboud University Medical Center Nijmegen, The Netherlands), and Dr Alistair Reid (Division of Investigative Science, Imperial College, London, UK) presented results of trials using arrays consisting of several million probes for the investigation of both germline rearrangements in patients with genetic syndromes, and somatic rearrangements in cancer. These demonstrated how the increased resolution of such platforms results in not only higher rates of diagnosis of pathogenic changes, but also an increased rate of detection of variants of unknown clinical significance, something that is becoming a common theme in both the clinical and diagnostic setting.

Eva Klopocki (Institute of Medical Genetics, Charité Universitätsmedizin, Berlin, Germany) presented results demonstrating that copy number changes of conserved non-coding elements can cause human disease, providing the first definitive example of how mutations of these non-genic elements can influence human phenotypes. Using array comparative genomic hybridization (aCGH) to study large kindreds with autosomal dominant forms of brachydactyly (digital anomalies) for which the causative gene, *BMP2*, is already known, Dr Klopocki was able to identify duplications that affect regulatory elements located outside the affected gene. In one case, the duplication identified was only 6 kb in size and lay >100 kb from *BMP2*. In most clinical situations, such a small change located outside any genes would likely be ignored and presumed to represent a benign variant unrelated to the patient's phenotype. However, here the segregation of this duplication with the disease in a large pedigree, the detection of several other overlapping larger duplications in different families, and some very elegant data in which the insertion of this duplicated element in a transgenic *lacZ* reporter mouse recapitulated perfectly the expression of *BMP2* in the developing digits of the embryo proved that this was the causative mutation. These data should make anyone who routinely performs aCGH in a clinical setting sit up and reconsider how they interpret the wealth of copy number alterations that are generated from the analysis of even a single disease patient, and show that the gene-centric approach to genetic disease is a rather short-sighted one.

aCGH, array comparative genomic hybridization; SNP, single nucleotide polymorphism.

Targeted resequencing

Just as microarrays have breathed new life into the world of cytogenetics, the advent of next-generation sequencing is causing a revolution in the field of molecular genetics. Alexander Hoischen (Department of Human Genetics, St Radboud University Medical Center Nijmegen, The Netherlands) presented results of a proof-of-principle study in which oligonucleotide arrays were first used to perform targeted enrichment of the coding regions of genes underlying ataxia, which were then selectively resequenced by 454 technology. This protocol resulted in a high specificity for the targeted regions, with approximately 90% of the 454 reads mapping to the regions present on the enrichment array, allowing accurate detection of SNPs and point mutations in the genes of interest using a single sequencing run. Even though all of the mutations in the study population were already known, this study opens the door to the use of new sequencing technologies in the clinic.

The power of decoding in Iceland

Augustine Kong (deCODE Genetics, Reykjavik, Iceland) presented a fascinating review of what has been achieved through the large-scale population genetic studies that have been performed by deCODE Genetics in Iceland. Approximately 12% of the Icelandic population has now been genotyped for hundreds of thousands of SNPs, and together with the isolated nature of this population and the availability of national family trees going back almost a millennium, this allows incredibly powerful insights to be made into their genetic structure. deCODE has undoubtedly been the biggest single contributor to the growing list of genetic variants linked to human phenotypes through genome-wide association studies. However, Dr Kong showed that by leveraging the available data on the small proportion of the population that has been tested, and combining this with their known genealogies, it is now possible to fill in the data on the remaining 88% of the population by a process of imputation, and to predict the genotypes of the entire Icelandic population with >90% accuracy. This astounding result is given even more weight when one considers that most mutations in the Icelandic population can be traced on founder haplotypes. This includes, for example, mutations in the *BRCA1* gene, essentially allowing highly accurate population-wide carrier prediction for many genetic diseases to be performed computationally without even testing a single individual! From a public health and disease-prevention point of view, this represents a dream scenario, but also goes hand in hand with immense ethical issues that have yet to be addressed. However, while the incredible power that comes from having such data is truly eye-opening, whether such techniques would be successful in a more heterogeneous population is currently unclear.

Inspiring personalized genomics

For me the most inspiring lecture of the four days was reserved for those who stayed right to the end of the conference. In a lecture entitled 'I have seen the future, and it works', John Burn (Institute of Human Genetics, Newcastle University, UK) gave a thoroughly entertaining and insightful reminder of where we should all be heading as researchers in the field of human genetics. Drawing on his experience as both a clinician and researcher, he focused everyone's mind on the many ways in which recent advances in our knowledge are now able to bring direct benefits to patients in the clinic, and how these might be applied in the future. One example used was the antibiotic flucloxacillin. Although safe in the vast majority of individuals, a small proportion of people who take this drug suffer severe liver damage, which is generally fatal unless a liver transplant is given. Genome-wide association studies have recently shown that this adverse reaction is a genetically determined trait that is explained by a specific genotype of the HLA-B gene cluster, presenting a perfect opportunity to use 'personalized genomics' to avoid life-threatening side-effects. Burn's vivid imagination foresees a day when all boxes of flucloxacillin will come with a special patch on the side which, when licked, changes color to indicate if the user should take the contents or not! However, this was just one story from a wide-ranging discussion as to how we, as human geneticists, should be focusing our research on what is really our *raison d'être*: improving human health. Other topics he raised included how microarrays and high-throughput sequencing are transforming patient diagnosis, the efficacy of aspirin as a long-term treatment to reduce the incidence of colon cancer, and an amusing but very informative discussion about why genetics may apparently only be able to identify variants that explain a minority of the variance in a particular trait. My only regret for this talk was that, unfortunately for the listeners, some of his extremely entertaining dry wit was lost on many of those listening who do not speak (Northern) English as a first language.

Concluding remarks

Held against the backdrop of one of the great European cities, this was a fine conference. Driven by new technologies that are becoming available, it is clear that there are many advances to be made in research, and that will improve the diagnosis and treatment of patients in the clinical setting. Next year's meeting will be held in Gothenburg, Sweden, 12-15 June, 2010.

Competing interests

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