Conference Scene

Biomarkers in the next decade

The Inaugural Australian Biomarker Discovery Conference Shoal Bay, NSW, Australia, 6–10 December 2010

In the next decade, biomarker research is increasingly likely to incorporate multivariate associations utilizing diverse molecular data types. This meeting surveyed some emerging technologies for profiling on the genomic scale in hundreds of patients, discussed the computational challenges in data reduction and interaction analysis and collated numerous success stories where multiple markers jointly associate with disease.

A small but eclectic mix of computational biologists, technology advocates and human geneticists met at the Shoal Bay Resort 2 hours north of Sydney, Australia, for the Inaugural Australian Biomarker Discovery Conference, which took place on 6–10 December 2010. The theme for the meeting was that the era of univariate biomarkers is passing, and that emerging bioinformatics applications applied to genome-scale datasets will provide fresh ways to think about the risks of disease.

New technologies

The meeting opened with a series of talks that looked beyond the now-established genotyping and gene-expression profiling platforms. Charles Cantor (Sequenom, CA, USA) demonstrated how mass spectrometry-based genotyping provides quantitative measures of rare variants in complex mixtures of DNA. Intuitively, we think of peripheral blood samples as a pool of red and white blood cell types, but the serum is also contaminated with free DNA from other sources, such as the fetus in pregnant women, or apoptosed cancer cells. Sequenom's platform allows these species to be detected, and the company is developing multiplex assays that will allow clinicians to detect the appearance of the most drugable mutations that genome sequencing projects indicate drive metastasis.

A number of talks by Philip Low (Neurovigil, CA, USA) introduced a novel technology for monitoring sleep patterns as biomarkers of neuropathologies. He noted that up to 30% of adults have sleep disturbance that, until now, could only be studied with a complex semi-invasive series of electrodes covering the head. Neurovigil's iBrain™ is a skull cap that picks up a

single channel of brain waves, and a novel algorithm deconvolutes the EEG into fractions that provide a high resolution view of altered brain activity in victims of stroke, dementia and congenital brain disease.

Illumina (CA, USA) and Affymetrix (CA, USA) representatives presented the companies' latest round of amazing whole-genome assays for the genome, methylome and transcriptome, but commercial displays also highlighted some emerging technologies, of which Fluidigm (CA, USA) deserves a mention. This company has developed a microfluidic device that mixes 96 samples and 96 primer sets in nano-scale assay chambers that support over 9000 parallel quantitative reverse transcription PCR reactions. The device can also be adapted for genotyping and targeted sequence capture and seems set to fill the gap between biomarker evaluation of a handful of candidate genes, and the hundreds of markers that emerge from genome-scale studies.

Computational biomarker discovery

Several speakers focused on the advances in computing that will facilitate finding the 'needles in the haystacks' of modern data. Mike Langston (University of Tennessee, TN, USA) and Vladimir Brusic (Dana Farber Cancer Institute, MA, USA) gave general overviews of the advances in high-performance computing and of modeling of the immune system. Biological systems tend to present NP-hard problems that can only be partially overcome by ever-larger mainframe clusters of processors, but new approaches to breaking down the problems into manageable units will facilitate analyses on cleverly aligned processors that even

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incorporate principles of green computing. These will also allow us to add biological insight by modeling how molecules interact in the transduction of signals to different cellular responses, and nowhere are these approaches more fascinating than the complex organ systems of the brain and immune system.

A good example of a computationally demanding problem is the detection of epistasis, namely genotype-by-genotype interactions, in genome-wide association study data. Jason Moore (Dartmouth, NH, USA) outlined how multidimensional reduction algorithms can be used to detect interaction effects that explain a significant amount of nonadditive variation for bladder cancer. It is unlikely that such approaches will be broadly seen as a solution to the missing heritability problem in contemporary genetics until such time as more and more instances of epistasis are firmly established. New approaches that incorporate pathway knowledge, reducing the search space, are now being developed. Moore also briefly presented exciting new computational research using 3D imaging, borrowing the power of video games, to facilitate exploration of high-dimensional datasets.

Conference convenor Pablo Moscato (University of Newcastle, NSW, Australia) departed from the traditional approach to biomarkers, which assumes that genotypes or transcripts are most interesting when they differ in frequency or abundance between cases and controls, and argued for entropy-based measures. One of the hallmarks of disease states is that they have increased disorder, most obviously in cancer, but also likely in psychological and immunological disease. New computational methods explore the relationship between complexity and entropy, and can be very effective in finding novel biomarkers, some of which highlight the transition to alternate pseudostable states. Information theory meets biology in interesting ways that are only just beginning to be explored.

Genomic biomarkers

It is astonishing how rapidly genomics has come to dominate genetic research, and numerous presenters discussed applications to a wide range of diseases from

asthma to autism, macular degeneration to metabolic syndrome. Greg Gibson (Georgia Tech, GA, USA) emphasized that in comparing transcriptional profiles we need to recognize that there is a wide range of diversity within and among human groups, and that the environment and culture interact with the genome in profound ways that shape the distribution of normality. Various presenters expressed a range of views, some despondent, some excited, regarding their efforts to find methylome, proteome and transcriptome biomarkers of disease and/or response to therapy. Ultimately, biomarkers must be understood, not just for their association with abnormality, but also on the basis of their biological mechanism.

In addition, genomicists are digging ever more deeply into those mechanisms. A great example is the revelation that long ncRNAs are also increasingly seen as functional genes. Marcel Dinger (University of Queensland, Brisbane, Australia) gave an overview of the field, including a call for an ordered nomenclature for ncRNAs, and then focused on two examples where a role in cancer progression is quite clear: ZNF1-NA1 in breast cancer, and SPRY4-IN in melanoma. It will be fascinating to see how variation in these structural RNAs affects secondary structure, and how often it predisposes to disease. Archa Fox (Western Australian Institute for Medical Research, Perth, Australia) also described how the NEAT1 long ncRNA organizes the assembly of nuclear paraspeckles, which regulate gene expression at the level of nuclear export of RNA-edited transcripts, and may have an important role in Alzheimer's progression.

Several speakers updated the Australian contribution to the International Cancer Genome Consortium (ICGC), through the deep sequencing of hundreds of pancreatic cancer genomes and transcriptomes in particular. Andrew Biankin (Garvan Institute, Sydney, Australia) outlined the general paradigm for genome sequence-enabled personalized medicine, which sees drug therapy targeted not so much to the cancer type as to the molecular profile of mutations. Once a bank of typical mutations has been established, and drugs that target specific lesions have been identified and approved, therapy will be directed in

a personalized manner. Since many mutations are beginning to be found to contribute to diverse types of cancer, this also raises the prospect that boutique drugs that are currently formulated for a particular sub-type of tumor may find broader application in different oncologies.

The idea that expensive high-volume genotyping will pay off in terms of expanding the range of biomarkers for chronic diseases, is also gaining traction. Genome-wide association studies have been criticized for ‘only’ uncovering the genetic basis for up to 10% of disease risk, but as the number of cases increases into the hundreds of thousands, several hundred genes emerge. These turn out also to be shared across disease classes, and provide a validated pool of variability for biologists to study. At some point, we would expect genetics to return to family and pedigree studies once these markers are in hand, since this is where the science translates to individual outcomes.

The meeting concluded with a glimpse in this direction with a talk from Lyn Griffiths (Griffith University, Gold Coast, Australia) who described her studies of migraine on Norfolk Island. This is a fascinating population since almost all of the residents derive from a founder population of around 20 Polynesian women and

Bounty mutineers, who were resettled from remote Pitcairn Island in the deep South Pacific 200 years ago. An 11-generation pedigree of over 5700 people is being studied, and genome-wide association studies has provided suggestive evidence for a couple of genes that may contribute to the doubling of migraine incidence on the island. In addition, candidate approaches have demonstrated that a mutation in the *MTHFR* gene associates with migraine with aura. For almost 20% of these patients, folate/vitamin B supplementation seems to provide an effective intervention. Such results remind us that biomarker research need not immediately impact the lives of everyone we study, or lead to effective interventions for all diseases: the clear successes, however occasional they occur, do make a real difference.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.