Genome Medicine

MEETING REPORT

Using DNA sequencers as stethoscopes

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Abstract

A report on the Cold Spring Harbor Laboratory meeting on 'Personal Genomes', Cold Spring Harbor, New York, USA, 30 September to 2 October, 2011.

Bench-to-bedside transition in personal genomics

The era of personal genomics emerged four years ago with the publication of the first complete human genome sequences by Craig Venter and by Jim Watson. Since the completion of these multi-million dollar genome projects, breathtaking developments have occurred at a pace exceeding that predicted by Moore's law. As of today, whole-genome sequencing (WGS) data have become a commodity, with applications spanning oncology, pediatrics, and medical genetics and with a price tag of only a few thousand dollars.

The 'Personal Genomes' meeting at Cold Spring Harbor Laboratory is a relatively intimate gathering focusing on recent developments and forthcoming challenges in the crosstalk between genome sequencing and personalized medicine. Although just three years had elapsed since the last meeting, both the subject matter and the list of participants were significantly different for this year's meeting, highlighting the swift advancements in this field. Three years ago, sequencing technologies and front-line bioinformatics analysis techniques, such as assembly and variant calling, were among the hottest topics. But this time, the spotlight had moved on toward clinical applications - how sequencing technologies can affect patient care and improve diagnosis and treatment. The speakers themselves were mostly clinicians who apply 'bench-to-bedside sequencing' to their patients. In this meeting report, we discuss their success stories, the challenges of translating genomic research into clinical treatments, the ethical issues surrounding post-genomic medicine, and the directions the field is taking as it attempts to tackle these challenges.

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Success stories (and failures) in clinical sequencing

Wojciech Wiszniewski and Richard Gibbs (Baylor College of Medicine, USA) presented the case of the Beery twins, a brother and sister who suffer from Segawa dystonia, a rare and heterogeneous movement disorder. Prior to the study, the twins were given the standard L-dopa treatment, which alleviated some of their symptoms. Nonetheless, the twins continued to suffer from respiratory difficulties and attention problems. Using WGS, the Baylor team identified the pathogenic mutation in the sepiapterin reductase gene that participates in both dopaminergic and serotonergic metabolism. Accordingly, they supplemented the L-dopa with a 5-hydroxytryptophan treatment, which dramatically improved the twins' symptoms. This was a remarkable demonstration of successful personalized treatment based on WGS results.

David Dimmock (Children's Hospital of Wisconsin (CHW), USA) described how the clinical WGS program at CHW had succeeded in improving the course of treatment in several pediatric cases. The focal point of his talk was the burning need to make WGS a first-line clinical test, like computed tomography (CT) or magnetic resonance imaging (MRI). To emphasize this need, he presented the case of a child with cobalamin E disease, a treatable inborn error in vitamin B12 metabolism. Although the child had first come to their clinic several years ago, routine tests had failed to provide a conclusive diagnosis. Only recently, through their new WGS program, were clinicians able to identify the genetic pathology. It is too late, however, to mitigate the neurological damage for this particular child, who is confined to a wheelchair. Dimmock used this case to motivate participants to move clinical WGS forward: 'I want to be able to do it faster, more efficiently, cheaper, and with a better turnaround time… This is my challenge to you.' Despite the need for routine WGS, participants acknowledged that sequencing is not a magical solution. David Valle (Johns Hopkins Medicine, USA) and Gholson Lyon (University of Utah, USA) cautioned that WGS should not replace a thoughtful integrative process for diagnosing and treating a patient's condition.

Interpreting sequencing results - are we ready for prime time?

As WGS enters the clinic, one recurring question is whether current variant databases are adequate for

clinical diagnosis. Stephen Kingsmore (Children's Mercy Hospital, USA), who presented a targeted sequencing approach for the diagnosis of Mendelian disorders, found that 22% of all literature-cited disease mutations were mis-annotated and sometimes pointed to common polymorphisms as the pathological variant. Atul Butte (Stanford University School of Medicine, USA) added that in the major database for complex diseases, namely the National Human Genome Research Institute (NHGRI) genome-wide association study (GWAS) catalog, 26% of the records do not report the odds ratio prediction, and 33% do not specify the protective and risk alleles. To provide a solution, he has embarked upon a project to build a clinical-grade variant database by manually scanning 5,500 GWAS papers. In his perspective, manual processing is required to reach clinical-grade results because most papers report their results in formats that are hard to process by automatic procedures.

Even basic resources, such as the human reference genome, contain errors that can confound clinical analysis. Daniel MacArthur (Wellcome Trust Sanger Institute, UK) found hundreds of allegedly severe loss-of-function (LoF) mutations, namely premature stop codons, frameshifts, and splice site disruptions, in the personal genomes of healthy individuals. According to his analysis, a large portion of these LoF variations are false positives attributed to both sequencing errors and annotation errors in the reference. These annotation errors include, for example, inaccurate gene models with misplacement of the stop codon. His team has been working to fix these errors in Gencode (http://genome.crg.es/gencode/) and Ensembl (http://useast.ensembl.org/index.html).

In addition to improving the grade of current databases, careful attention must be paid to what results are reported and how they are interpreted. Mark Boguski (Beth Israel Deaconess Medical Center, USA) suggested that clinical databases should be separated into pre-symptomatic databases, for exploratory predictions of general conditions, and post-diagnosis databases, for treatment decisions. 'A patient with a stage 4 melanoma does not care about his Alzheimer risk', he said. Another question that Boguski discussed was that of who is going to analyze the data in clinical sequencing. He argued that molecular pathologists, who currently receive all cancerous specimens, who are empowered by Clinical Laboratory Improvement Amendments (CLIA)-certification, and who have a workforce of the necessary scale, should be the ones to interpret clinical sequencing information, especially for tumor re-sequencing. Boguski also described the Genomic Medicine Initiative (http://genomicmedicineinitiative.org), which aims to create a nationwide program to train pathologists in interpreting genomic results.

OK, we've got the mutation, now what?

Beyond scientific challenges, the era of personalized genomic medicine presents complicated ethical challenges to patients, researchers, and clinicians. The meeting held an open ethics session to discuss these issues, but this topic was featured in talks at each session of the meeting, emphasizing its growing importance to the community.

Ethical issues surface even before sequencing takes place. Dimmock mentioned that 2 out of 17 families that were deemed eligible for their clinical WGS program decided to opt out. One family worried about loss of genetic privacy and the other family was concerned that the DNA results could identify an intractable condition that would reduce their ability to access medical care. Although this is a small sample, it is striking that around 10% of families strictly opposed a procedure that might improve their clinical outcome. This could be a warning sign that suggests that the community must seek to increase the public's trust in clinical genomics.

Ellen Clayton (Vanderbilt University, USA) stated that as personal genomics reaches medicine, it is important to sharpen the increasingly blurred lines between research and clinical care. Research is aimed towards the systematic evaluation and dissemination of information and the wide application of results, whereas clinical care is intended solely to benefit the individual patient.

Highlighting the complexities of the hybrid research-clinical nature of personal genomics, Lyon described his experience of a moment dreaded by every researcher. During his group's study of an extended family with an X-linked terminal pediatric disorder, Lyon received a phone call from one of the participants revealing that she was four months pregnant with a boy and fearful about the outcome. At this stage, Lyon had multiple layers of data, including a functional assay in yeast, which unequivocally pointed to the causative gene and showed that the expectant mother is a carrier. He decided not to disclose this information to the mother, rationalizing 'I am a physician but not her physician … and this was not a diagnostic test'. The baby was affected and died three months after birth, during the same week that Lyon's work was published. The disorder was named Ogden syndrome, in honor of the Utah town in which the family lives.

Future perspectives

As personal genomics moves forward, technology is no longer the major barrier to clinical sequencing; as Butte pointed out, WGS has become cheaper than a colonoscopy. Having conquered the cost mountain, the community has begun to approach the next hurdle: how to integrate WGS into clinical settings. Presenters stressed that this will require the development of routine clinical-grade procedures for the interpretation of data and return of results.

But who is going to oversee the development of clinical sequencing procedures? The range of clinical sequencing applications is steadily increasing to include the diagnosis of idiopathic genetic disorders, tumor sequencing, and microbiome profiling. One potential solution is to take a divide-and-conquer approach: medical geneticists will develop sequencing procedures for the diagnosis of idiopathic genetic disorders, molecular pathologists and oncologists will develop cancer sequencing procedures, and so on. Such a solution could, however, be prone to overlapping investments in the development of data analysis techniques and to knowledge fragmentation that will reduce the integrative power of high-throughput sequencing. Interestingly, the 100-year-old field of medical imaging has adopted an alternative solution in which radiology is a medical specialty. This raises the question of whether the field would benefit most from treating clinical sequencing as a new medical specialty.

Meeting tweets are available online at #cshlpg

Abbreviations

GWAS, genome-wide association study; LoF, loss-of-function; NHGRI, National Human Genome Research Institute; WGS, whole-genome sequencing.

Competing interests

YE serves on the scientific advisory board of Knome and Kailos Genetics.

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