Meeting report

Human genome research enters a new phase

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A report on HGM2005, the tenth annual Human Genome Meeting, Kyoto, Japan, 18-21 April 2005.

The Human Genome Meeting (HGM) is an annual event organized by the Human Genome Organization (HUGO) for scientists working on the human genome. This year's HGM was the tenth anniversary meeting, with approximately 500 presentations covering a wide variety of work on the human genome. In his opening remarks, the president of HUGO, Yoshiyuki Sakaki (RIKEN Genomic Sciences Center, Yokohama, Japan), commented that participants would have plenty of opportunities to find out "what is going on in the post (human) genome sequencing era". This report discusses a few of the latest research findings that were presented at the meeting.

It is clear that large-scale sequencing facilities are still important, and indeed essential, for genome science. Richard Gibbs (Baylor College of Medicine, Houston, USA) reported that the genome sequencing projects of many animal species, including the Rhesus macaque, orangutan, Tammar wallaby, cow, and the honeybee, are ongoing and will soon provide us with valuable resources for the analysis of these organisms and for comparative genomics. He also reported that the phase I plan of the human HapMap project, in which common single-nucleotide polymorphisms (SNPs) are covered at a resolution of 5 kilobases (kb), has now been completed.

The completion of the human genome sequence and the progress of the HapMap project have facilitated genetic approaches to disease-associated genes and regions. Kari Stefansson (deCODE Genetics, Reykjavik, Iceland) described the genetics of complex traits in the Icelandic population: among more than 50 ongoing projects, 30 are focused on the mapping of disease-associated loci, 15 on gene isolation and eight on drug development. He reported that LTA4 hydrolase, an enzyme involved in leukotriene B4 biosynthesis, is associated with myocardial infarction (MI), and that LTB4 upregulation by ionomycin stimulation of neutrophils is higher in MI patients than in healthy people. The deCODE team has recently developed a drug, DG-031, which acts as an inhibitor of LTA4 hydrolase.

Leena Peltonen (National Public Health Institute, Helsinki, Finland) showed that isolated populations, like that in Finland, are ideal for mapping and cloning disease genes because of the low level of genetic and environmental variation between individuals. She also reported a successful example of this mapping, showing that the gene encoding upstream transcription factor 1 (*USF1*) is associated with familial combined hyperlipidemia.

Once genomes have been sequenced, the most important follow-ups are large-scale projects for analyzing the function of the genome. Despite our knowledge of the sequences of the genome and the transcriptome (the genes transcribed into RNA), we still know comparatively little about the function of many of the genes, which requires further research. Anindya Dutta (University of Virginia, Charlottesville, USA) introduced an overview plan of the ENCODE (Encyclopedia of DNA elements) project. The initial stage of the project, now under way, involves using a variety of techniques to investigate 44 selected human genomic regions, corresponding to 1% of the genome. Dutta described his studies profiling the replication of DNA within chromosomes 21 and 22 and of the ENCODE regions. The results from these studies using HeLa cells demonstrated that 440 regions (56% of the examined sequence) showed replication in either early (0 to 4 hours) or late (6 to 10 hours) S phase, and the remaining 44% of the region was replicated throughout S phase. Early replication was correlated with regions of high gene density, a result consistent with ENCODE data showing that the

early-replicating regions are rich in transcripts and contain a higher density of DNase I hypersensitive sites (an indicator of transcribable genes).

We described the Genome Network, a project led by Japanese researchers that aims to use genome structural data such as genome and transcript sequences to create experimental resources for genome-wide functional analysis of components such as expression regulatory regions and protein-protein interactions. These datasets will eventually be integrated in order to systematically explore the pathways connecting genes to the organism's phenotype at the molecular level. One of us (Y.H.) also discussed the high complexity of the transcriptome, the existence of many non-coding RNAs, and the importance of natural antisense transcripts. The functional significance of the sense-antisense relationship of transcripts was also discussed by Dvir Dahary (Compugen, Tel Aviv, Israel), using a comparative analysis of the genomic organization of genes between human and *Fugu*.

In the symposium on comparative genomics Svante Pääbo (Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany) described a comparison of the expression level of 12,000 transcripts between human and chimpanzee, looking at various different tissues. He reported that approximately 10% of transcripts showed differences in their expression level in the brain in the two species, and that the divergence of gene expression between the brain tissue of humans and chimps was smaller than that in the liver and testis. He also suggested that a change in expression is under positive selection for some genes, although the evolution of gene expression is generally neutral and occurs at a constant rate. Eddy Rubin (DOE Joint Genome Institute, Walnut Creek, USA) discussed the extraction of non-coding (non-open reading frame) elements on human chromosome 16 that are highly conserved between human and *Fugu* and which may regulate downstream genes, and the characterization of these elements using a transgenic mouse reporter assay. He stressed the importance of computational modeling using a gene-regulatory 'training set' in order to understand more about the rules of gene-regulatory mechanisms and sequences underlying tissue-specific gene expression, and to identify significant DNA motifs that are involved.

Two particularly interesting technological developments were reported. Simon Bennett (Solexa, Little Chesterford, UK) described the company's novel 'single-molecule-based sequencing technology', which simultaneously reads 25 bases of each of 10 to 20 million fragments of an individual's genomic DNA. The sequencing is carried out by 25 cycles of a one-base extension reaction of fluorescently labeled nucleotides on the genomic DNA fragments, which are attached to a solid surface to form a 'single molecule array'. The method is reported to be between 100 to 1,000 times more efficient and cost-effective than conventional sequencing technology and will be available at the beginning of 2006. Kunihisa Nagino (Toray Industries, Kamakura, Japan) reported a novel DNA microarray chip technology that achieves a level of sensitivity up to 100 times higher than conventional DNA microarrays, with an extremely high signal-to-noise ratio. This technology is still new but the rapid development of a practical DNA microarray chip, together with the appropriate software, would be of great benefit to researchers working on genome sequencing and analysis.

This year's meeting was a stimulating and interesting opportunity to share information and results with researchers in both academia and industry, and it is hoped that the HGM will continue to initiate collaborations and ideas that will promote great progress in genome research.