Research

Comparative and Medical Genomics

We are using a comparative genomics approach to better understand the structure, function and evolution of the human genome. Our group is one of the pioneers in the field of comparative genomics. We proposed the compact genome of the fugu (*Takifugu rubripes*) as a model vertebrate genome in 1993 (*Nature* 366: 265-268, 1993) and determined its whole genome sequence in 2002 (*Science* 297: 1301-1310, 2002). Fugu genome was the first vertebrate genome to be sequenced soon after the completion of the human genome. It is being widely used as a reference genome for comparative analysis of human and other vertebrate genomes. More recently, we identified elephant shark (*Callorhinchus milii*) as having the smallest genome among cartilaginous fishes and initiated the Elephant Shark Genome Project (*PLoS Biol* 5(4): e101, 2007). Cartilaginous fishes are the oldest living group of jawed vertebrates (gnathostomes) and serve as a critical reference for understanding the evolution of vertebrate genomes. We have also initiated a genome project for a model jawless vertebrate, the Japanese lamprey (*Lethenteron japonicum*), which has a smaller genome than the sea lamprey. Jawless vertebrates (cyclostomes), comprising lampreys and hagfishes, are the most basally branching lineage of vertebrates and hence an important reference for understanding the origin and evolution of vertebrates. In addition, we are exploring other model vertebrate genomes such as coelacanth, gar and cichlid fishes that can contribute to our understanding of human and other vertebrate genomes. Our group is also participating in "Genome 10K", an international project which aims to sequence the genomes of 10,000 vertebrates.

Medical Genomics

We apply our high-throughput next-generation sequencing and bioinformatics capabilities for identifying variants associated with genetic diseases. The main collaborators of our Medical Genomics projects are scientists from the Institute of Medical Biology (IMB) and the Translational Laboratory in Genetic Medicine (TLGM), and clinicians from the KK Women's and Children's Hospital and the National University Hospital. A major ongoing project is aimed at identifying variants associated with rare genetic diseases, whose precise diagnosis is often a challenge to clinicians due to the diagnosis odyssey of patients with uncommon symptoms. By sequencing whole-exomes of patients, their unaffected parents and other family members, we have been able to identify causative variants for 150 rare and undiagnosed genetic diseases. Besides helping clinicians in the precise diagnosis of the disease and deciding appropriate therapeutic measures, these findings have improved our understanding of the functions of many human genes. The objective of another ongoing project is to identify germline and somatic mutations associated with neuroblastoma, which is the most common

extracranial solid tumour in children. This project is based on sequencing and analysis of a large number of FFPE tumour and normal tissue samples collected by clinicians at the KK Women's and Children's Hospital over several years.

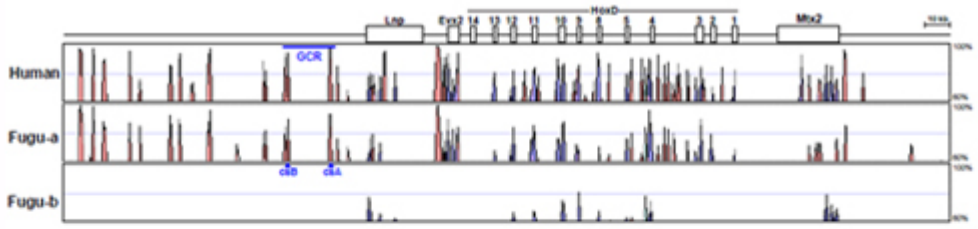

Figure 1. Conserved noncoding elements (CNEs) in the elephant shark (base sequence), human and fugu HoxD locus. Pink peaks (>70% identical across ≥100 bp) represent CNEs. GCR, Global control region.

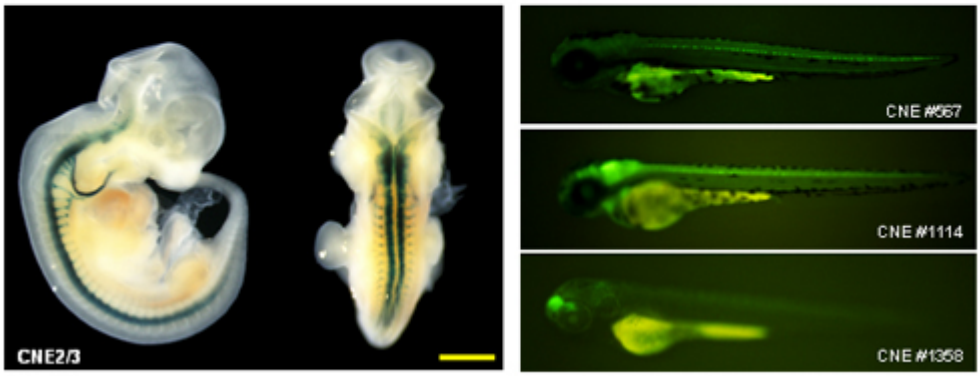

Figure 2. Human conserved noncoding elements (CNEs) direct expression of a reporter gene to specific domains in developing mouse and zebrafish embryos.

Besides sequencing and annotation of whole genomes and transcriptomes, our research interests include the role of gene and genome duplications in the evolution of vertebrate genomes; and evolution of *cis*-regulatory elements and its contribution to the morphological diversity of vertebrates. Prediction of conserved noncoding elements and their assay in transgenic zebrafish and mouse have proved to be an effective strategy for discovering *cis*-regulatory elements in the human genome, and for understanding the role of regulatory evolution in the phenotypic diversity of vertebrates.