Biological Interfaces

The Biological Interfaces effort targets genes and chromosome regions associated with DNA damage and repair, mitotic stability, and chromosome structure and function as primary subjects for physical mapping and sequencing. Specific disease-associated genes on human chromosome 5 (e.g., Cri-du-Chat syndrome) and on 16 (e.g., Batten's disease and Fanconi anemia) are the subjects of collaborative biological projects.

Accomplishments

- Identification of two human 7q exons having 99% homology to the cDNA of a known human gene, vasoactive intestinal peptide receptor 2A. Preliminary data suggests that the *VIPR*2A gene is expressed.
- Identification of numerous expressed sequence tags (ESTs) localized to the 7q region. Since three of the ESTs contain at least two regions with high confidence of homology (~90%), genes in addition to *VIPR*2A may exist in the terminal region of 7q.
- Generation of high-resolution cosmid coverage on human chromosome 5p for the larynx and critical regions identified with Cri-du-Chat syndrome, the most common human terminal-deletion syndrome (in collaboration with Thomas Jefferson University).
- Refinement of the Wolf-Hirschhorn syndrome (WHS) critical region on human chromosome 4p. Using the SCAN program to identify genes likely to contribute to WHS, the project serves as a model for defining the interaction between genomic sequencing and clinical research.
- Collaborative construction of contigs for human chromosome 16, including 1.05 million bases in cosmids through the familial Mediterranean fever (FMF) gene region (with members of the FMF Consortium) and 700,000 bases in P1 clones encompassing the polycystic kidney disease gene (with Integrated Genetics, Inc.).
- Collaborative identification and determination of the complete genomic structure of the Batten's disease gene (with members of the BDG Consortium), the gamma subunit of the human amiloride-sensitive epithelial channel (Liddle's syndrome, with University of Iowa), and the polycystic kidney disease gene (with Integrated Genetics).
- Participation in an international collaborative research consortium that successfully identified the gene responsible for Fanconi anemia type A.

Chromosome 16 Physical Map (pp. 38–39). *A condensed chromosome 16 physical map constructed at Los Alamos National Laboratory (LANL) is shown in two parts on the following pages. Besides facilitating the isolation and characterization of disease genes, the map provides the framework for a large-scale sequencing effort by LANL, The Institute for Genomic Research, and the Sanger Centre.*

Distinct types of maps and data are shown as levels or tiers on the integrated map. At the top of each page is a view of the banded human chromosome to which the map is aligned. A somatic-cell hybrid breakpoint map, which divides the chromosome into 90 intervals, was used as a backbone for much of the map integration.

The physical map consists of both a low-resolution yeast artificial chromosome (YAC) contig map localized to and ordered within the breakpoint intervals with sequence tagged sites (STSs) and a high-resolution bacteria-based clone map. The YAC-STS map provides almost complete coverage of the chromosome's euchromatic arm, with STS markers on average every 100,000 bases.

A high-resolution, sequence-ready cosmid contig map is anchored to the YAC and breakpoint maps via STSs developed from cosmid contigs and by hybridizations between YACs and cosmids.

As part of the ongoing effort to incorporate all available loci onto a single map of this chromosome, the integrated map also features genes, expressed sequence tags, exons (gene-coding regions), and genetic markers.

The mouse chromosome segments at the bottom of the map contain groups that correspond to human genes mapped to the regions shown above them.
[Source: Norman Doggett, LANL]