Human Genome news

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NIH Initiates Clinical Studies on Cystic Fibrosis Testing, Education, and Counseling

The recent development of a clinical test for major DNA mutations causing cystic fibrosis (CF) is the culmination of years of intense research. Clinical tests for other disease-producing genetic mutations will become available much more quickly, partly because of research tools to be generated by the Human Genome Project. Thus, professional practices governing the use of the CF test will be relevant to a wide range of future genetic testing services.

CF is a disorder that affects mucous membranes, particularly in the lungs, where a thick mucous buildup makes the individual more susceptible to infections and other complications. Until recently, most people with CF did not live into their thirties.

CF, a single-gene recessive disorder—caused by two altered copies of the gene, one from each parent—is one of the most common hereditary diseases in the United States. A single copy of the CF gene mutation is inherited by an estimated 1 in 25 Americans of European ancestry; 1 in 2500 inherits 2 altered copies of the gene and has the disorder.

Through genetic testing, couples can determine their risk of having a child with CF. The current test detects 85 to 95% of all CF mutations. If neither prospective parent tests positive for a CF mutation, the risk is substantially below the risk for the general population. If both partners carry a mutation, they face a 1 in 4 chance of having a child with CF. If only one partner carries a mutation, the risk depends on whether or not the other partner carries a CF mutation not yet detectable with current methodologies.

Explaining this information to individuals, helping them decide whether or not to be tested, and counseling them about the results can be a sensitive, complex, and time-consuming process for genetics professionals. Increasingly, individuals with no known family history of CF are also asking their health professionals about testing. Because the number of trained genetics professionals is unlikely to be sufficient to meet the rising demand for genetic services, other health providers must know how to respond to such requests.

Recognizing this need, several professional groups called for a coordinated effort to identify testing, education, and counseling practices that would increase patient understanding of the CF-carrier test and protect people from test-related psychological harm, stigmatization, and discrimination. These groups were (1) participants in the 1990 NIH Workshop on Population Screening for Cystic Fibrosis; (2) the American Society of Human Genetics; and (3) the Joint NIH-DOE Working Group on the Ethical, Legal, and Social Implications (ELSI) of Human Genome Research.

(continued)

In This Issue...

NIH CF Studies

Studies Will Identify Best Professional Practices and Serve as Paradigms for Other Genetic Tests

Three NIH components—the National Center for Human Genome Research (NCHGR), the National Institute of Child Health and Human Development, and the National Center for Nursing Research—responded to these concerns by initiating a 3-year research project to define the best methods of educating and counseling individuals who want to be tested for CF mutations. Seven research teams across the country will conduct eight studies to address the following issues in testing, education, and counseling:

- Levels of understanding and interest in CF-carrier testing among different populations.
- Optimum forms of pretest education for different populations.
- Most effective posttest counseling strategies, in terms of the understanding and psychological health of tested individuals and families.
- Optimum locations for CF-carrier testing services.
- Recordkeeping and disclosure policies to protect against stigmatization, discrimination, and breaches of confidentiality.
- Accuracy and cost-effectiveness of various types of tests.

Two studies will address these questions as they apply to families with known histories of CF, and the remaining studies will evaluate methods of educating and counseling people not known to have relatives affected with CF.

These eight coordinated projects address a broad range of issues important in developing sound public and professional policies to guide the integration of genetic tests into clinical practice. Findings from interstudy comparisons should serve as paradigms for the introduction of DNA-based genetic tests for other common, single-gene recessive disorders.

To foster cooperation among the seven CF investigative groups coordinated by NCHGR, the Cystic Fibrosis Studies Consortium (CFSC) held its first meeting on the NIH campus on November 1 and 2, 1991. Principal investigators of each study and other research team members attended. Experts gave brief presentations in the areas of laboratory procedures, psychological testing and evaluation, informed consent and confidentiality, development of educational materials, assessment of costs, and ethnocultural issues. A representative from the Cystic Fibrosis Foundation and a physician specializing in the care of CF patients were invited participants in the discussion.

Where appropriate, some features of the research, such as evaluation measures and tools, cost assessment, laboratory quality-control procedures, and protection of human subjects, will be standardized among participating sites. CFSC members agreed to

- explore quality control and proficiency testing issues,
- use a core set of psychological evaluation instruments,
- develop a common guide to describing CF for consortium reference, and
- circulate educational materials developed by each research team among the consortium members.

To facilitate such coordination, the group will meet regularly to refine methodologies, exchange information, and share unique components of their projects. ◇

Reported by Elinor J. Langfelder, Eric T. Juengst, and Elizabeth Thomson ELSI Program, NIH NCHGR

NIH CF Studies (First-Year Funding)

- "An Evaluation of Testing and Counseling for CF Carriers," **James Sorenson,** *University of North Carolina, Chapel Hill* ($231,916)
- "Perception of Carrier Status by Cystic Fibrosis Siblings," **Joanna Fanos,** *Children's Hospital Oakland Research Institute, Oakland, California* ($73,196)
- "Cystic Fibrosis Screening: An Alternative Paradigm," **John Phillips,** *Vanderbilt University, Nashville, Tennessee* ($206,513)
- "Testing and Counseling for Cystic Fibrosis Mutations," **Peter Rowley,** *University of Rochester, Rochester, New York* ($274,110)
- "Cystic Fibrosis Mutation Screening and Counseling," **Wayne Grody,** *University of California School of Medicine, Los Angeles* ($179,067)
- "Ethical and Policy Issues in Cystic Fibrosis Screening," **Neil A. Holtzman,** *Johns Hopkins University, Baltimore ($314,449)*
- "Prescriptive Decision Modeling for Cystic Fibrosis Screening" and a complementary clinical study, "How Much Information Do Couples Want?" **David Asch,** *University of Pennsylvania, Philadelphia* ($197,634 and $180,201)

LLNL Licenses Chromosome Painting

Lawrence Livermore National Laboratory (LLNL) announced in October that chromosome painting, a new staining technology with the potential to improve dramatically the diagnosis of many cancers, has been transferred to Imagenetics, a medical diagnostics company based in Naperville, Illinois. LLNL officials see this as one of the laboratory's most important technology transfers to the private sector.

The key discovery, made by an LLNL biomedical team led by Joe Gray and Dan Pinkel, is that very complex DNA probes can be used for fluorescently staining the entire length of any specific chromosome. Different chromosomes in the same cell can be made to fluoresce different colors, a technique that makes chromosome abnormalities such as translocations easy to see. A translocation occurs when a piece of one chromosome is exchanged with a piece of another; in chronic myelogeneous leukemia, for example, pieces of chromosomes 9 and 22 are exchanged. Chromosome painting is particularly effective in metaphase when the chromosomes are condensed and easily visible as distinct objects in a microscope.

With conventional techniques, says Robert Jenkins (Mayo Clinic), "Sometimes analysis is much more difficult because parts of one chromosome will look like a natural part of another chromosome. But with the paints, the fluorescent dyes light up the different chromosomes in two distinct colors, showing the translocation."

Imagenetics research led to development of methods that permit at least five different chromosomes to be analyzed at once. Commercial availability will make the paints much cheaper to most researchers, who will not have to grow and label the DNA in their laboratories. Thus the number of investigators using the probes will be expanded, and research progress will be speeded up.

Researchers hope that improved detection of chromosome abnormalities will assist in better understanding the multiple genetic changes involved in the development and progression of cancer and may eventually permit treatment to be tailored to specific abnormalities present in particular tumors. To further their research and explore its medical value, Gray, Pinkel, and their team moved in July 1991 from LLNL to the University of California, San Francisco.

Chromosome painting has also proven valuable in detecting chromosome translocations caused by exposure to radiation and chemicals. This feature may help determine cumulative lifetime exposure doses and allow estimation of health risks.

Under a 1989 funding and licensing agreement, Whole Chromosome Paints™ has become a product line of Imagenetics and will be sold worldwide by Life Technologies, Inc., through the GIBCO BRL brand as WCP™ DNA Probes. Of 24 paints, 9 became available in October and the remaining 15 should be out in 6 to 12 months, according to Imagenetics' Tom Mozer. ◇

Chromosome Painting:

- **Simplifies staining procedures,**
- **Makes alterations more visible,**
- **Is potentially automatable.**

For more information, contact

- **Candy Voelker**
  University of California
  Technology Transfer Office
  510/748-6600

HUGO Names 1992 Council, Requests YAC Library Information

The Human Genome Organization (HUGO) has announced its 1992 Council, with the terms of new members expiring in 1994.

Other HUGO activities involve the small HUGO task force on yeast artificial chromosomes (YACs), chaired by Gert-Jan van Ommen (Leiden University, Netherlands). The group is now compiling inventories of both chromosome-specific and genomic YAC libraries [see *HGN* **3**(4), 12–13 (November 1991)]. Information on these libraries will be available through the HUGO offices and in *Human Genome News*.

To make the inventories as complete and useful as possible, the task force requests that investigators making and screening YAC libraries contact HUGO with information such as insert size and co-ligation frequency. A list of other needed data can be faxed to investigators upon request.

- Contact: Liz Evans
  HUGO Europe; 179 Great Portland Street, 5th Floor; London W1N 5TB, U.K.
  Fax: (Int.) 44/71-436-1988 ◇

HUGO COUNCIL 1992

Terms Expire December 1992	
Walter Bodmer	United Kingdom
Charles R. Cantor	United States
Malcolm Ferguson Smith	United Kingdom
Victor McKusick	United States
Glauco Tocchini-Valentini	Italy
Lennart Philipson	Germany
Terms Expire December 1993	
Francis Collins	United States
H. John Evans	United Kingdom
Leroy Hood	United States
Andrei Mirzabekov	Russia
Grant Sutherland	Australia
James Wyngaarden	United States
Terms Expire December 1994	
Kay E. Davies	United Kingdom
Eric Lander	United States
Jean-Louis Mandel	France
Kenichi Matsubara	Japan
Ulf Pettersson	Sweden
Nobuyoshi Shimizu	Japan

Genome News

Ann M. Barber
Computational Biologist
DOE Human Genome Program

Barber Named Computational Biologist at DOE

Ann M. Barber recently joined the Human Genome Program staff of the DOE Office of Health and Environmental Research (OHER) in Washington, D.C., where her responsibilities as Computational Biologist will encompass a wide range of challenges in genome informatics.

In 1974 Barber received both her B.S. and M.S. mathematics degrees from Stanford University. She conducted image-processing research and worked in medical informatics before entering Northwestern University Medical School, from which she received her M.D. degree in 1981. After a 3-year residency in internal medicine, Barber served as Medical Staff Fellow at the NIH National Cancer Institute (NCI) in Bethesda, Maryland; her research years were spent at the NCI Laboratory of Mathematical Biology, where she became Senior Staff Fellow in 1987.

During 6 years at the NCI Supercomputer Center, Barber developed models and theories on DNA-protein interactions, created Unix/C software for aligning multiple sequences, and tested her hypotheses with molecular biology benchwork. Her SequenceEditingAligner, distributed internationally, helps find commonalities between different genes or species in hundreds of nucleic acid or protein sequences. Her work in DNA-protein interactions has revealed a new structural class of catabolite gene activator protein (CAP) DNA binding sites.

Barber's tasks at OHER include establishing goals and objectives of computer applications in the DOE Human Genome Program, promoting networking within the genome community for better interagency and international communication, and developing computational resources and techniques to elucidate biological structures and establish structure-function relationships.

Barber represents OHER at Protein Data Bank meetings and on the following groups: Genome Data Base Coordinating Committee, Energy Research Network Advisory Committee, GenBank® Advisors Committee, and GenBank Sponsors Forum. She is a member of OHER Structural Biology Task Group and the Human Genome Task Group. ◊

Contact information:
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Internet: "barber@mailgw.er.doe.gov"

Howard University Plans Genetics Resource for African-American Families

Researchers at Howard University in Washington, D.C., are planning to expand the university's human genome research program by setting up the African-American Reference Family Panel, an organized collection of family histories and DNA samples. The panel will be modeled on the French Centre d'Etude du Polymorphisme Humain (CEPH) collection, which consists of information from 61 Caucasian families and is used worldwide in genetic mapping studies.

African-American genetic data will help scientists identify gene-based differences already known to exist among population subgroups in sensitivity to drugs, immune response to organ transplants, susceptibility to diseases such as high blood pressure and diabetes, and the influence of environment on health.

A team led by Howard University microbiologist Georgia Dunston will develop procedures for recruiting subject families, establishing a resource laboratory that will share information with other investigators, and managing research data by computer.

The 2-year planning project, expected to cost around $425,000, will be supported by the NIH National Center for Human Genome Research. These funds supplement a Research Centers in Minority Institutions grant from the NIH National Center for Research Resources. After the planning period, the research team will apply for NIH funding to support the family panel as a resource for Howard University scientists and other genetics researchers. ◊

NCHGR Genome Project Booklet Available

The Human Genome Project: New Tools for Tomorrow's Health Research, a new 19-page booklet, explains the basic science of the project, reviews its history, and briefly assesses progress. It was prepared by the Office of Communications, NIH National Center for Human Genome Research (NCHGR). 1991, free. [Office of Communications; NCHGR; Building 38A, Room 617; 9000 Rockville Pike; Bethesda, MD 20892; 301/402-0911, Fax: 301/480-2770.] ◊

LLNL, GDB Transfer Map Data

The success of the Human Genome Project requires efficient, automated transfer of physical mapping data from laboratories to large public databases such as Genome Data Base (GDB) at Johns Hopkins University. An effort to develop such a transfer system is described below.

GDB and the physical mapping project at Lawrence Livermore National Laboratory (LLNL) have been cooperating to develop a prototype approach to automated data transfer. Physical mapping data from LLNL is now uploaded to GDB automatically and becomes part of the public release from GDB. The system will evolve through continued evaluation.

Certain generic constraints were recognized in planning the approach. Concern for the security and integrity of both the sending and receiving databases required that (1) the receiving database not be allowed unlimited access to all data in the sending database and (2) the sending database could not inject data into the receiving database without the knowledge, consent, and active participation of the recipient system's staff.

Other considerations involved minimizing adverse effects on both the sending and receiving databases: neither should have to reconfigure its internal data representations to meet the needs of the other. Efficient transfer dictated that the sending and receiving databases not be required to prepare or parse each data shipment, either manually or with ad hoc programs.

Both GDB and LLNL store data using commercial client-server-type relational database management systems (RDBMSs) running on workstation-class computers with Internet access. Although both data sets are maintained using a system from Sybase, this is a convenience but not a necessity. Database design at the two sites did not allow a direct data transfer, but addressing the generic aspects of data transfer made possible an automated system that met system constraints.

Efforts to automate the transfer of data involved the following steps:

1. GDB and LLNL staff determined what data at LLNL would be appropriate for transfer to GDB. Data models at each site were compared to determine how LLNL data structures might map to those at GDB.
2. An intermediate relational schema was designed with tables that could hold contig-type physical mapping data in a format consistent with GDB needs and with LLNL designs. Data in these tables describe the contigs, the cloned elements in the contigs (cosmids thus far), and all biologically interesting attributes that have been determined for these cloned elements.
3. These tables were installed at LLNL as an adjunct database, the "GDB Interface" (GDBI). GDBI and the LLNL main mapping database are managed by the server component of the DBMS.
4. At timely intervals, LLNL updates the tables in its GDBI database with data from its own mapping database. Although this transfer can be executed automatically as a database transaction, at present LLNL reviews all transferred data for accuracy and consistency with release policy.
5. GDB has been given unlimited read-only permission for GDBI, to be used in any fashion and at any time. For automated transfer, however, a Sybase "Client" software package at GDB queries the LLNL system to capture GDBI data and transfer it directly via Internet into database tables managed by the GDB Sybase-server.

(continued)

Investigators interested in experimenting with this system at their sites should contact

- **Elbert Branscomb (510/422-5681, Fax: 510/422-2282, Internet: "elbert@alu.llnl.gov")**

GDB/OMIM Sets Training Course Schedule

Two comprehensive hands-on training courses on the use of GDB and OMIM are being scheduled in Baltimore and other locations:

- The general course for scientific users provides a basic understanding of the databases and the relationships among the different types of data.
- The course for users with editing privileges includes instructions on adding, modifying, and deleting GDB data.

Class frequency and location will be determined by demand (see the Baltimore schedule at right). Courses are free, but attendees must pay their own travel and lodging expenses. Hotel information and directions will be mailed with registration materials.

Contact: GDB/OMIM User Support; 410/955-7058, press 4 after greeting; Fax: 410/955-0054; Internet: "help@welch.jhu.edu". ◊

BALTIMORE CLASSES

Course	Dates
Editing	Mar 22–24
Editing	May 3–5
General User (Two 1-day courses for MLA attendees)	May 16 May 17
General User	June 15–16
General User	July 12–13
General User	Sep 21–22
General User	Nov 23–24

GDB/OMIM will also have an exhibit booth at several meetings. See the Calendar of Events, p. 14.

GDB Forum

GDB User Support, Registration

To become a registered GDB/OMIM user, contact one of the User Support offices listed below (a user may register to access both Baltimore and a remote site). Questions, problems, or user-registration requests may be sent by telephone, fax, or e-mail. (Note change in GDB and OMIM telephone numbers in Baltimore.)

User-registration requests should include name, institutional affiliation, and title (if applicable), street address (no P.O. box numbers), telephone and fax numbers, and e-mail address.

The Help Line is staffed from 9 a.m. to 5 p.m. EST for information on accounts, technical support, data questions, and training courses. Calls received after hours will be forwarded to the appropriate voicemail and returned as soon as possible.

User Support Offices

United States
GDB/OMIM User Support
William H. Welch Medical Library
Baltimore, MD
410/955-7058
Fax: 410/955-0054
Internet: "help@welch.jhu.edu".
Office hours: 9 a.m. to 5 p.m. EST.

To obtain a user's local SprintNet (Telenet) number for locations within the United States: 800/736-1130.

United Kingdom
Christine Bates
Human Gene Mapping Program Resource Center
Harrow, U.K.
(Int.) 44/81-869-3446
Fax: (Int.) 44/81-869-3807
E-mail: "cbates@uk.ac.crc"

Germany
Otto Ritter
Molecular Biophysics Group
German Cancer Research Center
Heidelberg, FRG
(Int.) 49/6221-42-2372
Fax: (Int.) 49/6221-40-1271;
E-mail: "dok261@cvx12.dkfz.heidelberg.de"

The main characteristics of this interface design are the following:

- GDB has access only to GDBI and not to other LLNL databases or computer systems (i.e., no login privileges). Thus, LLNL computers and main database are insulated from uncontrolled outside access.
- LLNL does not actively enter data into GDB. After being notified of updates via e-mail, GDB uses procedures under its control to obtain LLNL data.
- Neither the sending nor the receiving database was required to modify its internal working data representations. However, both were obliged to cooperate in developing the appropriate intermediate interface database.
- Both data addition by LLNL and data extraction by GDB can be accomplished automatically by invoking the appropriate routines. No manual preparation or parsing of data is required.
- Both LLNL and GDB can modify internal data representations without "breaking" the transfer system, provided that mapping between the interface database and the new internal representations is consistent. Thus, a stable interface allows the continued evolution of both sending and receiving databases without endangering data flow.
- Direct, transnetwork, machine-to-machine transfer is achieved, and no tapes need be prepared and shipped. With this system, LLNL contig-mapping and attribute data appears in the form GDB desires, not as LLNL sees and stores the same data. Thus GDB is insulated from LLNL conceptions of data.

The generic nature of GDBI may allow the interface tables used at LLNL to be used by other supplier laboratories to hold data for transfer to GDB. The use of equivalent interface databases would spare other laboratories from devising systems de novo and would ensure that biologically similar data are entered into GDB in a logically similar manner. The figure shows the arrangement of the system's main components.

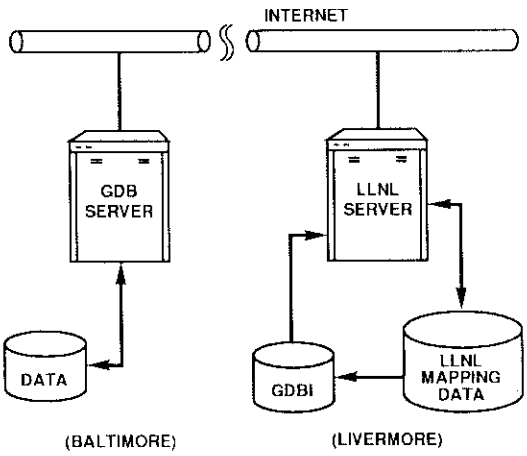
GDBI consists of some 11,750 different data items arranged in 15 tables (presently aggregating to 3 megabytes). These data comprise some 26 contigs, 320 cosmids, and a total of 815 attribute facts about these cosmids.

The GDBI database will contain information on all contigs for which some useful biological fact has been ascertained. Biological facts about the contigs include finding positive hybridization to member cosmids of a unique sequence element (e.g., cDNA probes), in situ hybridization mapping results, and repetitive element content. Contigs are described according to their cosmid membership and the order of a minimal covering subset of elements.

Whereas this approach nominally requires that the supplier laboratory use a relational client-server DBMS and provide direct Internet access, the server need not use the same vendor as GDB. For example, the Sybase "Open-Server" software interface allows remote RDBMS servers supplied by other vendors to be accessed directly through standard relational database query language (SQL). With significantly more effort, the Open-Server package can be used to access supplier DBMSs that are neither client-server nor relational in design, as long as they afford Internet connection and an appropriate application program interface.

At tolerable cost, the Internet connection requirement can be relaxed and the

(see GDB Forum: LLNL, p. 7)



LLNL-GDB Map Data Transfer System.

First International Workshop on the Identification of Transcribed Sequences

Twenty-four investigators met on October 4–5, 1991, at the NIH National Institute of Mental Health (NIMH) in Bethesda, Maryland, for the First International Workshop on the Identification of Transcribed Sequences, sponsored by the DOE Human Genome Program. The purpose of the workshop was to exchange information on the systematic identification of transcribed sequences and the construction of transcriptional maps for large chromosomal regions.

Investigators discussed the broad areas of (1) identification of expressed sequences from genomic clones and (2) cDNA library analysis. The group also considered strategies for the most reliable and exhaustive search for gene sequences from any chromosomal region.

J. Gregor Sutcliffe (Scripps Research Institute) defined three data requirements for including a gene on a transcriptional map: sequence, physical and genetic map location, and pattern of expression. Katheleen Gardiner (Eleanor Roosevelt Institute) described the striking variation in gene and potential CpG island density found on human chromosome 21 and suggested that different approaches may be required for gene-rich and gene-poor regions.

Sequence Analysis

Several presentations were devoted to the analysis of genomic sequence information. Andrzej Konopka (National Cancer Institute) discussed basing the detection of coding sequences on statistical characteristics (such as complexity) of textual elements, using as an example protein-coding sequences.

Steen Knudson (Boston University) is investigating a neural network approach to predicting splice sites and open reading frames. Richard Mural (Oak Ridge National Laboratory) reported considerable success with a neural network/rule-based inference system. This program identifies about 90% of protein-coding exons 100 or more bases long and has predicted 14 exons in a region near the Huntington's disease locus that have been experimentally confirmed.

(see cDNA Sequences, p. 8)

Sequence Workshop Considers Strategies for Gene Searches in any Chromosomal Region

GDB Forum: LLNL *(from p. 6)*

telephone lines made to appear to the computers at both ends as reasonably high speed "Internet" links. A suitable interface that is programmable to a supplier database and a willingness to cooperate are the only real requirements for putting such systems in place. To provide reasonable functionality, the supplier database should be maintained on a workstation-class, multitasking computer; however, this need not be excessively expensive. ◇

Elbert Branscomb and Tom Slezak (LLNL) and Robert Robbins (GDB) contributed to this article. Many more people, especially those at GDB, were critically involved in the project itself. Richard Lucier (now at the University of California, San Franciso) and Peter Pearson (GDB) played essential roles in responding favorably and aggressively to original suggestions that this data transfer experiment be undertaken; many GDB technical staff members worked very hard to make the project successful.

GDB Files Available via Anonymous FTP

To expand methods of distributing data to the scientific community, a set of GDB data files and other materials are now available via Anonymous FTP (file transfer protocol) from the host "mendel.welch.jhu.edu" (128.220.59.42).

Initial files include data files (as tab-delimited ASCII tables) generated weekly from GDB tables, schema files, forms for submission of data, and user documentation. The "gdb" directory includes a README file describing what is available and an INDEX file listing all the files in each subdirectory.

In addition, GDB will soon begin to generate standard report files containing results from a series of predefined searches and to make these reports available via FTP. GDB staff asks users to specify the types of reports that would be valuable; e-mail the message to "help@welch.jhu.edu".

Space will be available on the server for software tools and utilities developed by the user community. Use the e-mail address above to request information on how to submit software. Users of this service should be familiar with FTP access and downloading procedures. ◇

Meeting Reports

Approaches to Direct Isolation of Coding Sequences:

- Exon Trapping
- Exon Amplification
- 3′ Exon Trapping
- Isolation of cDNAs Encoded in YACs

cDNA Sequences *(from p. 7)*

Direct Exon Identification

Four speakers addressed three approaches to direct isolation of coding sequences from genomic clones. Geoffrey Duyk (Harvard Medical School) discussed current and proposed modifications of the "exon trapping" procedure; Alan Buckler (Massachusetts Institute of Technology) described experience with the related "exon amplification" system. Nine of ten putative exons obtained with the latter system subsequently identified clones in a cDNA library.

Susan Berget (Baylor College of Medicine) presented a scheme for trapping 3′ exons; such an approach would have the advantage of isolating larger exons (typically, around 600 nucleotides, compared with 100 to 200 nucleotides for internal exons).

These three approaches still require library screening to obtain a complete cDNA. Alternatively, David Kurnit (Howard Hughes Medical Institute and University of Michigan Medical School) described his recombination-based assay system in the isolation of cDNAs encoded in yeast artificial chromosome (YAC) clones. A lambda cDNA library is replicated in the presence of a plasmid library made from YAC DNA. The progeny phage are then grown in an *Escherichia coli* host that requires plasmid sequences; only those phage that have integrated a plasmid are viable. This system has been used to obtain many cDNAs from several human chromosome 21 YACs.

cDNA Library Construction and Screening

Two approaches for identifying human cDNAs from somatic cell hybrids were discussed. David Nelson (Baylor College of Medicine) has used *Alu*-specific polymerase chain reaction (PCR) primers to amplify human hnRNA from the Xq28 region. Michael Siciliano (M. D. Anderson Cancer Center) used splice donor site-specific PCR primers to construct libraries of amplified material and screened the libraries with human repeat sequences. False positives continue to present some difficulties, although both methods are rapid and successful.

Bento Soares (Columbia University) discussed the use of lafmid vectors in cDNA library construction. Such libraries can be normalized efficiently and used in subtractive hybridizations.

Fa-Ten Kao (Eleanor Roosevelt Institute) described the identification of 7 chromosome 21 cDNAs, obtained by screening cDNA libraries with 200 microdissection genomic clones. Large pools of clones facilitated the screening, as did the use of normalized cDNA libraries [Sherman Weissman (Yale University School of Medicine)].

cDNAs as Probes

Direct cDNA screening of large (>10,000) arrayed genomic libraries has been used to identify genomic clones containing transcribed sequences. Ute Hochgeschwender (NIMH) presented results for mouse chromosome 16, reporting improved sensitivity by using cDNA probes with (1) decreased complexity or (2) enrichment for low-abundance transcripts. A second application, presented by Anne Marie Poutska (German Cancer Research Fund, Heidelberg), used pig cDNA probes to screen a human Xq28–specific genomic library. This is an alternative solution to the problem of repetitive sequences and identifies conserved, transcribed sequences.

Hans Lehrach (Imperial Cancer Research Fund, London) discussed using arrayed cDNA and region-specific genomic libraries to map particular cDNAs to genomic clones. Possibilities include the use of clone pools and cDNAs from various tissues and oligonucleotide fingerprinting of both cDNA and genomic libraries.

Hybrid-selection schemes to isolate cDNA clones from YACs and from pools of cosmids were described by Mike Lovett (Genelabs, Inc.) and Weissman. In these methods, cDNAs are annealed to immobilized clones of genomic DNA, and the annealed fraction is recovered, amplified, and cloned. Impressive enrichments of >1000-fold were reported for specific cDNAs.

MaryKay McCormick (Los Alamos National Laboratory) outlined an alternative strategy that would use homologous recombination and fragmentation to locate the gene position within a YAC. Then cDNAs of interest are cloned into an appropriate vector and transformed into a yeast clone containing a YAC. Truncation of the original YAC will occur where it contains sequences homologous to the cDNA.

(see cDNA Sequences, p. 9)

This newsletter is prepared at the request of the DOE Office of Health and Environmental Research and the NIH National Center for Human Genome Research by the Biomedical and Environmental Information Analysis Section of the Health and Safety Research Division at Oak Ridge National Laboratory, which is managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy, under Contract DE-AC05-84OR21400.

Second Chromosome 11 Workshop

The Second Chromosome 11 Workshop, held in Paris May 27–29, 1991, was organized by a scientific committee chaired by Claudine Junien (see side column). About 80 participants from Europe, North America, New Zealand, and Japan gathered to discuss progress after HGM 10.5 and the future direction of chromosome 11 mapping.

Several French, European, and U.S. organizations sponsored the meeting.

Chromosome 11 has been extensively studied because of the biologically interesting regions p15, p13, q13–14, q22–23, and q25—all positive gene-rich R-bands. Interest is reflected in patches of high marker density around these sites and an uneven distribution of highly polymorphic reference markers along the chromosome. The regions of interest are listed below, along with their associated disorders.

- *11p13 and 11p15*: Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR). Imprinting related to the Beckwith-Wiedemann syndrome (BWS) and associated tumors, loss of heterozygosity, and breakpoints in T-cell leukemias;
- *11cen to 11q21*: multiple endocrine neoplasia (MEN1), atopy, major mental illness, including schizophrenia and bipolar affective disorder, amplification of 11q13 genes, and loss of constitutional heterozygosity in tumors;
- *11q23 to 11q25*: tuberous sclerosis (TSC2), ataxia telangiectasia (AT), and breakpoints in translocations associated with the Ewing sarcoma/peripheral neuroepitheliomas (ES/PNE), the constitutional t(11;22), and T/B cell leukemias.

Most disease associations with chromosome 11 were not established by linkage studies, but the Centre d'Etude du Polymorphisme Humain (CEPH) is now compiling a consensus linkage map.

(see Chromosome 11, p. 10)

Chromosome 11 contact:
- **Claudine Junien**
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  Fax: (Int.) 33/1-46-47-95-01

cDNA Sequences *(from p. 8)*

Sequencing cDNAs

James Sikela (University of Colorado Health Sciences Center) and Mark Adams [National Institute of Neurological Disorders and Stroke (NINDS)] reported on projects to sequence 100 to 200 nucleotides from the 3′ (and possibly 5′) ends of a large number of random human brain cDNAs. The usefulness of this approach will depend partly on the generation of sufficient sequence to permit protein motif identification and also on the ability to map accurately the genomic sequences. Some regional clone localization by fluorescence in situ hybridization has been proposed (Adams).

Chris Fields (NINDS) discussed database formats for the storage of cDNA sequence information.

Summary

Participants agreed that conventional techniques, including cDNA library screening with YAC clones and searches of CpG islands and conserved sequences, can be informative but are not likely to be comprehensive. However, at this time no one technique is completely satisfactory; an exhaustive gene search will require several complementary methodologies. Many techniques discussed are still very new and have not been applied extensively.

The group recommended that another workshop be held in 1992, when experience in different laboratories will allow more critical technique evaluation. Future considerations also will include how best to approach the thorny problem of determining expression patterns, both in developmental timing and tissue specificity. ◊

Reported by Katheleen Gardiner
Eleanor Roosevelt Institute
and
Miles Brennan
National Institute of Mental Health

Upcoming Chromosome Workshops Listed on Next Page

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Marcel Mannens
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On the Agenda: "Who's in Your Genes?"

"Who's in Your Genes?" will be presented at 2:00 p.m. on Thursday, March 19, at the second annual Conference on Computers, Freedom, and Privacy (CFP-2), sponsored by the Association for Computing Machinery, to be held on March 18–20 in Washington, D.C. The conference, which is partially funded by the DOE and NIH Human Genome Programs, will feature privacy and constitutional issues as they relate to rapidly expanding electronic information technology. Contact: Division of Continuing Education/Conferences and Institutes; George Washington University; 2003 G Street NW; Washington, DC 20052; 202/994-7238, Fax: 202/994-7048; Internet: "cfp2@seas.gwu.edu". ◊

Meeting Reports

Human Genome news

National Center for Human Genome Research

This newsletter is intended to facilitate communication among genome researchers and to inform persons interested in genome research. Suggestions are invited.

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Chromosome 11 *(from p. 9)*

At the workshop, important contributions were made to the construction and integration of genetic and physical maps of disease loci on chromosome 11.

Many new polymorphic markers have been identified and provisionally placed on the map. Although linkage studies in the CEPH pedigrees had been undertaken for many of these and other reference markers, data analysis was not complete, and therefore the likely order of 11q could not be given. Nevertheless, independent genetic linkage maps of normal and affected chromosomes were consistent, with a few exceptions.

The consensus genetic map was also in close accord (at least in terms of linear order) with physical maps, including breakpoint maps produced over the years and, more recently, with radiation hybrids. Pulsed-field gel electrophoresis (PFGE) in the 11q13 region agrees with the genetic map. Contig analysis with cosmids and yeast artificial chromosome (YAC) clones is proceeding for several chromosome 11 regions. Knowledge of established maps, such as the 16-Mb PFGE map for 11p13, is used for cloning specific genes and for revealing disease-associated gross alterations (e.g., the WAGR region where candidate genes have been recently isolated).

The maps under construction in various laboratories clearly are progressing rapidly, but direct fine-structure comparisons were often compromised by the lack of common reference markers and mapping resources. The value of open-access cosmid and YAC libraries was discussed; making such resources available on gridded filters and as DNA pools for the isolation of specific probes was enthusiastically supported. This effort must be linked to continuing genetic mapping, which requires the development of more and better polymorphic markers to fill gaps on both chromosome arms. There is also a need to define map ends by producing telomere and centromere markers. The evolution of computing tools for collecting and collating mapping data into maps was also seen as an essential requirement for rapid progress.

Workshop participants also felt that identified sets of hybrids for coarse regional maps and finer subregional localization should be readily accessible, possibly through national or international cell repositories. A very extensive set of somatic cell hybrids carrying translocation or deletion chromosomes 11, with in vivo– or in vitro–induced breakpoints, are available and widely used. A proposal that an agreed set of ten well-characterized reference hybrids be made freely available to the community was enthusiastically supported. The means must now be found to make the efficient distribution of these cell lines possible.

The Genome Data Base was available and demonstrated during the workshop by Peter Pearson (Johns Hopkins University). ◇

Reported by Claudine Junien

Upcoming Chromosome Workshops

Upcoming chromosome workshops, to be held June–September, are listed below. Please consult the Calendar of Genome Events for meetings scheduled before June. Readers should inform HGMIS of other meetings to include in the calendar.

June 7–9	**International Workshop on Chromosome 6,** Ann Arbor, MI [*J. Trent, 313/764-4509*]	**July 20–21**	**First International Workshop on Chromosome 18,** Chicago, IL [*M. LeBeau, 312/702-0795*]
June 12–14	**Second Chromosome 4 Workshop,** Leiden, Netherlands [*G.-J. van Ommen, (Int.) 31/71-276075*]	**September 13–15**	**Third International Workshop on Human Chromosome 11,** San Diego, CA [*G. Evans, 619/453-4100, ext. 279*]
June 18–19	**Chromosome 15 Workshop,** Tucson, AZ [*T. Donlon, 451/723-4923*]	**September 17–20**	**Third International Chromosome 22 Workshop,** Philadelphia, PA [*B. Emanuel, 215/590-3856, ext. 2930*]
July 17–19	**Chromosome 12 Gene Mapping Workshop,** Oxford, England [*I. Craig, (Int.) 44/865-275-259*]	**September 20–23**	**Chromosome 13 Workshop,** New York, NY [*A. Bowcock, 214/688-3896*]

Workshop on Computational Molecular Biology

The international workshop "Open Problems in Computational Molecular Biology" was held in Telluride Summer Research Center (Telluride, Colorado) on June 2–8, 1991. Sponsored by the DOE Human Genome Program, the meeting was organized by Andrzej Konopka (National Cancer Institute), Hugo Martinez (University of California, San Francisco), and Peter Salamon (San Diego State University) with Danielle Konings (University of Colorado at Boulder) as events coordinator.

The workshop brought together key researchers in computational biology, coding theory, and biomathematics from nine countries (Canada, China, France, Germany, Netherlands, Israel, Scotland, United States, and the former U.S.S.R.) to address the problem of identifying the kind of phenomena and principles that constitute biological coding (not only the mRNA protein-translation code).

Sequence-analysis software, which is becoming progressively faster and more powerful, graphical, and user friendly, is now routinely used. New computational architectures are beginning to be implemented for searching databases and comparing sequences.

Many studies in computer-assisted sequence research have been based on the assumption that the genomic code can be compared to a text carrying many messages written in many languages. Although this linguistic analogy was originally meant to be just a metaphor, it has been taken quite literally. An arbitrarily defined pattern in a nucleotide sequence has often been given the rank of a *word* in an alleged *language* responsible for an alleged (but often unknown) *function*. Published sequence-analysis papers are full of references to *signals, codes, languages, texts, information*, and similar terms that do not refer to any precise concept or phenomenon. As a result, most scientific conclusions of the last 10 years were based on speculation and premature inferences from incomplete evidence.

Use of these arbitrary standards has created a real need for computational biologists to formulate carefully the very foundations of their field; the Telluride workshops are planned as a systematic forum for the exchange of pertinent ideas and results. The 1991 workshop, devoted entirely to the foundations of biolinguistics, dealt with several general topics, and participants reached the following conclusions.

Legitimacy of the linguistic metaphor as a research tool

Conclusions:

- Detailed methodological guidelines for conducting statistical and heuristic experiments are urgently needed.
- Computational sequence research logic and terminology should be developed.

Structural patterns and the physiological conditions in which they can be expressed as "signals"

Conclusions:

- No methodology exists for assessing structural pattern significance to allow systematic consideration of conditions in which patterns are to be expressed.
- This methodology gap urgently needs to be addressed because a large amount of sequence and structure data will emerge from genome sequencing efforts.

Methods of assessing functional significance without knowing sequence function

Conclusions:

- A given biological function can be represented as a collection of properly aligned sequences or structures [functionally equivalent sequences (FES)].
- A set of properties (a profile) can be systematically assigned to a given FES or even to particular FES regions.
- The vocabulary of profiles assigned to a given FES can be considered a classification code and used for discriminant analysis purposes.
- No clear methodology exists for deciding whether and to what extent a given classification code corresponds to the actual functional code. The correlation would have to account for overlapping messages, which are inevitable because two or more different functions can be (and often are) encoded in a given nucleic acid sequence.

Technical aspects of biomathematics

Conclusions:

- Statistically, genomic sequences are inhomogeneous, and models that require knowledge of prior distributions

Participants Reach Conclusions on These Topics:

- **What constitutes biological coding?**
- **How much sense does the concept of sequence "signal" really make?**
- **Why is the new, pragmatic information theory needed in molecular biology?**

1992 Conference Planned for July 19–August 2 in Telluride, Colorado

Meeting Reports

Note to DOE Human Genome Program Awardees:

DOE Plans 1993 Contractor-Grantee Workshop for February 7–10 in Santa Fe, New Mexico

of predefined patterns are usually arbitrary (i.e., their selection cannot be justified by sufficient knowledge of the modeled system).

- Many statistical dependencies in genomic sequences exist at various levels of pattern definition, and most are not detectable by routine statistical approaches.
- Methods for identifying hidden dependencies need to be developed to design correct statistical models of genomic sequences. Alternatively, statistical techniques not requiring knowledge of prior distributions could be formulated.

Coding theory, cryptology, and information theory

Conclusions:

- To understand sequence data through a linguistic framework, focus is needed on alleged-language pragmatics (i.e., *utterance* of predefined patterns in a set of known conditions).
- Complex cellular *machinery* and insufficient knowledge of its detailed workings prevent consideration of alleged-message syntactic and semantic aspects in genomic sequences at this time.
- Existing coding theory deals with decoder properties that were designed to serve telecommunication systems and digital computers, a basis with little relevance to systems of unknown design (i.e., to most communication models involving genome expression).
- A biolinguistics coding theory is required to establish code words of undetermined message units (i.e., words in an unknown language). Before possible theories can be explored, however, databases of significant patterns and associated conditions of their expression must be created.
- A new, pragmatic information theory is likely to emerge as the body of available sequence and structure data grows.

The workshop promoted formal and informal exchanges of ideas, and sessions were vigorous and lively. Many promising collaborations were initiated, including a nonorthodox application of Kullback entropy to computational molecular biology, a study of the evolution of recombination machinery as a pattern-recognition system, statistical modeling, and the inclusion of thermodynamic properties of sequence fragments in sequence-analysis tasks. ◇

Reported by Andrzej Konopka and Peter Salamon

Resources

¶Genome Publications

Scope Note 17: The Human Genome Project, written by Sharon J. Durfy and Amy E. Grotevant, is part of the *Scope Note* series of the *Kennedy Institute of Ethics Journal*. It provides a brief survey of the Human Genome Project, an overview of related issues and viewpoints, and an annotated bibliography. The bibliography is divided into sections, including general surveys; international involvement; history of the U.S. project; mapping; and ethical, social, and legal considerations. [*Kennedy Institute of Ethics Journal* 1(4), 347–62 (December 1991)]. *Scope Notes* are also available separately for $3 prepaid. [National Reference Center for Bioethics Literature; Kennedy Institute of Ethics; Georgetown University; Washington, DC 20057; 800/633-3849 or 202/687-6738.]

Trends in Biotechnology has published "Genome Mapping and Sequencing," a special issue on innovative technologies being developed for large-scale genome analysis. Topics include targeted genome analysis–cDNA cloning; laser microdissection and microcloning; flow cytometry sequencing technology; advanced cloning vectors; international perspectives on project structuring; model genomes; in situ hybridization and structural analysis in relation to function and mapping; database organization and coordination of international data networks; artificial intelligence and sequence feature recognition; and descriptions of biological resources available from nonprofit organizations. Special issue, £8.50 or $15.00. Discount available on bulk orders. [Elsevier Trends Journals; 68 Hills Road, Cambridge, CB2 1LA, U.K. ; Fax: (Int.) 44/223-321410.] ◇

Utah Workshop To Prepare Scientists, Physicians for Genome Research

The Utah Genome Center at the University of Utah in Salt Lake City plans an intensive 3-week training workshop, sponsored by the NIH National Center for Human Genome Research. To be held July 13–August 1, "Genome Technology" is designed to prepare scientists and physicians for genome research. Students may take 1 or more weeks of the course, which will examine a different research perspective each week. Instruction will be offered in large-scale DNA sequencing, informatics tools, and medical applications for genome technology. Students will receive hands-on laboratory and computer experience and will interact with outstanding faculty and speakers. Classes are limited to 16 students.

- Contact: Raymond F. Gesteland, 801/581-5190, Fax: 801/585-3910. ◇

Training, Sequencing Funding

The NIH National Center for Human Genome Research (NCHGR) reminds the scientific community that institutional grants and individual fellowships for training at the predoctoral, postdoctoral, and advanced career levels are available through the National Research Service Awards. Senior scientists may use the fellowships to support sabbatical leaves, acquire skills in a new research area, or update skills in their current area. Although the emphasis is on interdisciplinary training, applications will be accepted for advanced instruction in genomic analysis or technology. NCHGR is also encouraging training in areas of interest to its Ethical, Legal, and Social Implications (ELSI) Program.

Recipients must be U.S. citizens or permanent residents. Next application receipt date: May 10.

■ PA-92-22

NCHGR also announces its broadly based program to train individuals to (1) develop new technology, mapping research programs, or sequencing projects or (2) analyze and apply resulting data for solving problems of biological interest. These research training opportunities will be supported through predoctoral institutional training grants (T32s), individual postdoctoral fellowships (F32s), and senior fellowships (F33s). Application receipt dates for institutional training grant and fellowships: May 10, September 10, and January 10.

NIH contacts:

- Eric Juengst; ELSI Program; 301/402-0911; BITNET: "ejs@nihcu"; Internet: "ejs@cu.nih.gov"
- Bettie J. Graham, Genomic Analysis and Technology Training; 301/496-7531; BITNET: "b2g@nihcu"; Internet: "b2g@cu.nih.gov" ◇

■ RFA HG-92-01 (R21, R01, P01, and P20)

Applications are encouraged to address the development of new large-scale DNA sequencing methods that (1) cost significantly less than $.50 per base pair or (2) improve current techniques by at least tenfold. Receipt dates – letter of intent: January 31; application: March 17.

- Contact: Robert Strausberg (301/496-7531, Fax: 301/480-2770; Internet: "cxr@cu.nih.gov"); NIH NCHGR: Building 38A, Room 610; Bethesda, MD 20892. ◇

U.S. Genome Research Funding Guidelines

Note: Investigators wishing to apply for NIH funding are urged to discuss their projects with agency staff before submitting formal proposals. DOE requires no prior discussion on preproposals.

NIH National Center for Human Genome Research (NCHGR)

Application receipt dates:

- R01, P01, R21, R29, P30, P50, and R13 grants – February 1, June 1, and October 1.
- Individual postdoctoral fellowships and institutional training grants – January 10, May 10, and September 10.
- Small Business Innovation Research Grants (SBIR: firms with 500 or fewer employees) – April 15, August 15, and December 15.
- Research supplements for underrepresented minorities – applications are accepted on a continuing basis.
- Requests for Applications (RFAs) – receipt dates are independent of the above dates. Notices will appear in *HGN* and other publications.

Program announcements are listed in the weekly *NIH Guide for Grants and Contracts*, which is available by

- Hard-copy subscription – call 301/496-7441.
- Remote login via modem to NIH Grant Line – call John James, 301/496-7554.
- Listserver computer network subscription – call Dottie Baker, 919/966-5625; BITNET: "pjones@uncvx1.bitnet" or Internet: "jones@samba.acs.unc.edu".

Expanded statements of RFAs listed in the NIH grants guide may be obtained from either of the two electronic sources or from NIH NCHGR in Bethesda, MD (301/496-0844).

DOE Human Genome Program

Solicitations for proposals will be announced in the February 1992 issues of the *Federal Register* and *Science* and in other publications. Formal proposals are due in August 1992.

For further information, contact the program office via

- 301/903-5037 or FTS 233-5037; Fax: 301/903-5051 or FTS 233-5051; or Internet: "genome@oerv01.er.doe.gov".

SBIR Grants. DOE also invites small business firms to submit grant applications addressing the human genome topic of SBIR programs, which are designed to strengthen innovative firms in areas of research and development and to contribute to the growth and strength of the nation's economy. The human genome topic emphasizes instrumentation development for automated clone processing, improvements in DNA sequencing technologies, and enhanced sequence data storage and processing capabilities. Next submission date: fall 1992. For more information, contact

- Samuel Barish; SBIR Program Manager, ER-16; DOE; Washington, DC 20585; 301/903-5707.

Human Genome Distinguished Postdoctoral Fellowships
Next deadline: February 1. For further information, see *HGN* **3**(3), 5 (September 1991) or contact

- Oak Ridge Associated Universities: 615/576-4805. ◇

Calendar of Genome Events*

February	7	***National Advisory Council for Human Genome Research**; Bethesda, MD
	6–11	**GDB** exhibit presented at **AAAS**; Chicago, IL [*AAAS Meetings Office, 202/326-6450*]
	9–13	**Joint Meeting of the American Society for Biochemistry & Molecular Biology & Biophysical Society**; Houston, TX [*M. Sternberg, 301/530-7010, Fax: 301/530-7014*]
	20	**NCHGR Lecture Series: High-Speed DNA Sequencing in Ultrathin Gels**; Bethesda, MD [*C. Dahl, 301/402-0838*]
	23–26	***Human Genetics and Genome Analysis: A Practical Workshop for the Nonscientist**; Cold Spring Harbor, NY [*J. Witkowski, 516/549-0507*]
	26–28	**Chromosome 16 Workshop**; Adelaide, Australia [*E. Hildebrand, 505/667-2746, Fax: 505/665-3024 or G. Sutherland, (Int.) 61/8-204-7284, Fax: (Int.) 61/8-204-7342*]
March	5–6	***Joint Working Group on the Mouse**; Bethesda, MD
	7–8	**Third International Workshop on Chromosome 3**; Toyko, Japan [*Y. Nakamura, (Int.) 81/3-918-0342, Fax: (Int.) 81/3-918-0342*]
	11–13	***Genome Research Review Committee**; Bethesda, MD
	13–14	**Chromosome 17 Workshop**; Park City, UT [*P. Fain, 801/581-5270, Fax: 801/581-6052*]
	13–15	***Second Invitational Conference on Genetics, Religion, and Ethics**; Houston, TX [*R. Nelson, 713/797-0600, Fax: 713/797-9199*]
	15–18	**30th Annual Meeting of the American Cytogenetics Conference**; Virginia Beach, VA [*A. Brothman, 804/446-5670, Fax: 804/624-2255 or P. Jacky, 503/652-2880, Fax: 503/652-5783*]
	19	**"Who's in Your Genes?"**at the **Conference on Computers, Freedom, and Privacy**, Washington, DC [*George Washington University, 202/994-7238, Fax: 202/994-7048, Internet: "cfp2@seas.gwu.edu"*]
	19	**NCHGR Lecture Series: Social Implications: Genetics and Popular Culture**; Bethesda, MD [*see contact: Feb. 20*]
	22–25	**Chromosome 9 Workshop**; Cambridge, England [*M. Smith, 714/856-6684, Fax: 714/725-2089 or S. Povey, (Int.) 44/71-387-7050, ext. 7410, Fax: (Int.) 44/71-387-3496*]
April	3–4	**Chromosome X Workshop**; Amalfi, Italy [*D. Toniolo, (Int.) 39/382-422286, Fax: (Int.) 39/382-527967*]
	3–10	**Keystone Symposia Meeting: Molecular Biology of Human Genetic Disease**; Copper Mountain, CO [*Keystone Symposia, 303/262-1230, Fax: 303/262-1525*]
	5–10	**GDB** exhibit presented at **FASEB**; Anaheim, CA [*FASEB Office of Scientific Meetings, 301/530-7010*]
	13–15	**Second HUGO European Conference: Human Genome Diversity**; Alghero, Sardinia [*HUGO Conference, Tel. & Fax: (Int.) 39/6-324-4340*]
	16	**NCHGR Lecture Series: Genome Mapping and Functional Organization of the Interphase Nucleus**; Bethesda, MD [*see contact: Feb. 20*]
	20–21	**Third International Workshop on Chromosome 21**; Baltimore, MD [*S. Antonarakis or J. Amberger, 301/955-7872, Fax: 301/955-0484, Internet: "joanna@welchlab.welch.jhu.edu"*]
	27–28	**Annual Biotechnology Patent Conference**; ATCC, Washington, DC [*ATCC Workshop Manager, 301/231-5566, Fax: 301/770-1805*]
	27–29	**Third European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumors**; Porto, Portugal [*S. Castedo, (Int.) 351/2-497-833, Fax: (Int.) 351/2-410-3940*]
May	1–4	**GDB** exhibit presented at **AAP/AFCR/ASCI**; Baltimore, MD [*K. Lodge, 609/848-1000, ext. 208*]
	6–8	**6th Annual Seminar on Analytical Biotechnology**; Barr Enterprises, Cambridge, MA (Deadline for poster abstracts: April 24) [*J. Cunningham, 301/898-3772, Fax: 301/898-5596*]
	6–10	***Genome Mapping and Sequencing Workshop** (GDB exhibit displayed); Cold Spring Harbor, NY
	12–13	**Second International Workshop on Chromosome 5**; Chicago, IL [*W. Neuman, 312/702-6201, Fax: 312/702-3163*]

*Attendance at meetings listed with asterisk is either limited or restricted. Dates may change; check with contact person.

Training Calendar: Workshops and Coursework*

February	20–21	**Molecular Cytogenetics: Chromosome In Situ**; Oncor, Inc., Gaithersburg, MD (also offered April 23–24) [*M. Williams, 301/963-3500, Fax: 301/926-6129*]
March	2–6	**Recombinant DNA Methodology**; CATCMB/CUA, Washington, DC [*M. Miller, 202/319-5276, Fax: 202/319-5721*]
	2–17	**Carolina Workshop on Yeast Molecular Genetics**; Chapel Hill, NC [*W. Litaker, 919/966-1730, Fax: 919/966-6821*]
	9–10	**Introduction to IG Suite**; IntelliGenetics, Mountain View, CA (also offered May 18–19 and Nov. 9–10) [*N. Robinson, 415/962-7300, Fax: 415/962-7302*]
	9–13	**DNA-Protein Interactions**; LTI, Germantown, MD [*L. Kerwin, 301/921-2250, Fax: 301/258-8212*]
	11–12	**Advanced Data Banks**; IntelliGenetics, Mountain View, CA (also offered Nov. 11–12) [*see contact: Mar. 9–10*]
	22–23	**GDB/OMIM General User Course**; Baltimore, MD (also offered May 16–17) [*GDB/OMIM User Support, 410/955-7058, press 4, Fax: 410/955-0054, Internet: "help@welch.jhu.edu"*]
	23–27	**Recombinant DNA Methodology**; Exon-Intron, Inc., Columbia, MD (also offered June 15–19) [*Workshop Coordinator, 410/730-3984, Fax: 410/730-3983*]
	23–27	**Recombinant DNA Techiques & Applications**; ATCC, Rockville, MD [*ATCC Workshop Manager, 301/231-5566, Fax: 301/770-1805*]
	23–27	**Recombinant DNA Techniques I**; LTI, Germantown, MD (also offered April 27–May 1 and July 13–17) [*see contact: Mar. 9–13*]
	30–April 1	**PCR Applications/Cycle DNA Sequencing**; ATCC, Rockville, MD [*see contact: Mar. 23–27*]
April	2–16	†**Cloning & Analysis of Large DNA Molecules**; Cold Spring Harbor, NY [*CSHL, 516/367-8343, Fax: 516/367-8845*]
	6–9	**PCR Methodology**; Exon-Intron, Inc., Columbia, MD (also offered Sept. 14–17) [*see contact: Mar. 23–27*]
	6–11	**cDNA Library Techiques**; LTI, Germantown, MD (also offered June 15–20 and Aug. 10–15) [*see contact: Mar. 9–13*]
May	3–5	**GDB/OMIM Editing Course**; Baltimore, MD [*see contact: Mar. 22–23*]
	4–9	**Recombinant DNA Techniques II**; LTI, Germantown, MD (also offered July 20–25 and Sept. 21–26) [*see contact: Mar. 9–13*]
	13	**Introduction to PCR**; BTP, Durham, NC (also offered June 16 in Lincoln, NE) [*S. Chance, 515/232-8306*]
	18–20	**Cloning and Hybridization Analysis of PCR Products**; BTP, Durham, NC (also offered June 17–19 in Lincoln, NE) [*see contact: May 13*]
	19–22	†**Introductory Linkage Course**; New York, NY [*K. Montague, 212/960-2507, Fax: 212/568-2750*]
	20–21	**Advanced IG Suite;** IntelliGenetics, Mountain View, CA [*see contact: Mar. 9–10*]
June	15–19	†**Ethics and the Human Genome Project**; Seattle, WA (application deadline: Mar. 15) [*B. Brownfield, 206/543-5447*]
	22–26	**Advanced Topics in Recombinant DNA**; Exon-Intron, Inc., Columbia, MD (also offered July 20–24) [*see contact: Mar. 23–27*]
August	2–14	**Molecular Evolution**; MBL, Woods Hole, MA [*F. Dwane, 508/548-3705, ext. 216, Fax: 508/540-6902*]
	10–14	**RNA Isolation and Characterization**; Exon-Intron, Inc., Columbia, MD [*see contact: Mar. 23–27*]
	17–18	**PC/GENE**; IntelliGenetics, Mountain View, CA [*see contact: Mar. 9–10*]
	19–20	**GeneWorks**; IntelliGenetics, Mountain View, CA [*see contact: Mar. 9–10*]
	24–27	†**Partnerships in Teaching Biotechnology: Human Genome Technology Workshop**; Ann Arbor, MI (also offered Aug. 28–29) [*P. Gregory, 313/764-8050, Fax: 313/764-4133*]
October	26–Nov. 4	†**Essential Computational Genomics for Biologists**; Cold Spring Harbor, NY [*T. Marr, 516/367-8393, Fax: 516/367-8389*]

*Dates and course status may change, and courses may be offered at other times and places; check with contact person.
†NCHGR-funded event.

Acronym List

Acronyms listed were chosen because they were either used in the text or are relevant to the human genome research community. Listed in parentheses after an organization is the branch of government or the organization to which it is responsible.

*Denotes U.S. Department of Energy organizations.
†Denotes U.S. Department of Health and Human Services organizations.

AAAS	American Association for the Advancement of Science
AAP	Association of American Physicians
AFCR	American Federation of Clinical Research
ASCI	American Society for Clinical Investigation
ASHG	American Society of Human Genetics
ATCC	American **Type Culture** Collection
BTP	Biotechnology Training Programs
cDNA	complementary DNA
CATCMB	Center for Advanced Training in Cell and Molecular Biology
CEPH	Centre d'Etude du Polymorphisme Humain
CF	cystic fibrosis
CSHL	Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
CUA	Catholic University of America
DBMS	database management system
DHHS	Department of Health and Human Services (U.S.)
DOE	Department of Energy (U.S.)
ELSI	Ethical, Legal, and Social Issues
FASEB	Federation of American Societies for Experimental Biology
FES	functionally equivalent sequences
FRG	Federal Republic of Germany
GDB*†	Genome Data Base
GDBI	GDB Interface
HGMIS*	Human Genome Management Information System (ORNL)
HGN*†	**Human Genome News**
HHMI	Howard Hughes Medical Institute
HUGO	Human Genome Organization [International]
IG	IntelliGenetics
JITF*†	Joint Informatics Task Force
LANL*	Los Alamos National Laboratory, Los Alamos, N.M.
LBL*	Lawrence Berkeley Laboratory, Berkeley, Calif.
LLNL*	Lawrence Livermore National Laboratory, Livermore, Calif.
LTI	Life Technologies, Inc.
MBL	Marine Biological Laboratory
MLA	Medical Library Association
NCHGR†	National Center for Human Genome Research (NIH)
NIH†	National Institutes of Health
NIMH†	National Institute of Mental Health
NINDS†	National Institute of Neurological Disorders and Stroke
OER*	Office of Energy Research
OHER*	Office of Health and Environmental Research (OER)
OMIM™	Online **Mendelian Inheritance in Man**
ORNL*	Oak Ridge National Laboratory,
PACHG†	Program Advisory Committee on the Human Genome (NIH)
PCR	polymerase chain reaction
PFGE	pulsed-field gel electrophoresis
RDBMS	relational database management system
SBIR	Small Business Innovation Research
SQL	standard relational database query language
WAGR	Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation
YAC	yeast artificial chromosome

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