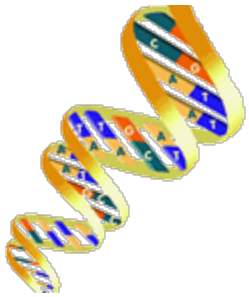

Exceptional Chromosome Regions I

May 15, 2000

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Agenda

Abstracts and References

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- One Origin of Man: Primate Evolution Through Genome Duplication
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- Nucleic Acid Strands Specific for Binding via Non-Denaturing Triple Helix Formation (TISH) to Centromeric DNAs of Each of the Human Chromosomes and to the DNA Common to the Tips of the Achrocentrics
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- References on sequencing through difficult chomosomal regions
  John Dunn
- References on duplicated regions
  Barbara Trask
- Finding Genes in Centromeric Regions of the Genome
  Jim Tucker

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Please contact Marvin Stodolsky (Marvin.Stodolsky@science.doe.gov) with updates or corrections.

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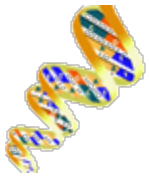

Exceptional Chromosome Regions Workshop I

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Agenda

May 15, 2000

7:30 Continental Breakfast

8:30 Workshop begins,. Chairs are Robert Moyzis and Julie Korenberg

Presentations will each be about 20 minutes long, with 10 minutes of following discussion.
* indicate remote participation, subject to time changes.

Status of human centromeric regions
R. Moyzis

Chromosome 16&19 centromeric regions and short arms.
EE. Eichler

Duplications revealed by FISH analyses of BACs/PACs
J. Korenberg

10:30 Coffee break

Arabidopsis centromers
G. Copenhaver

* Drosophila centromeric regions.
G. Karpen

Optical Mapping across ECR
D. Schwartz

12:00 Lunch

1PM Technologies session

cDNA candidates for centromeric regions
J. Quackenbush

Triplex probe technologies
Jacques Fresco

* PCR of chromosomal regions

J. Tucker

2:30 Coffee break

Cloning human centromeric DNAs
N. Kouprina & V. Larionov

* Sequencing difficult regions
J. Dunn

3:30 Round table discussion

5 PM Adjourn

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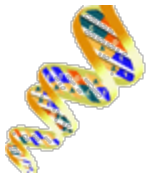

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Human Telomere Mapping and Sequencing

R.K.Moyzis, H. Chi, D.L. Grady, and H. Riethman
Dept of Biol Chem, College of Med, Univ of CA, Irvine, CA 92697, and The Wistar Institute, Philadelphia, PA 19104

The Human Genome Project has accomplished the goal of obtaining a "working draft" sequence of human DNA this year. Such a framework sequence will catalyze gene discovery and functional analysis, and allow finished sequencing to be focused on regions of the highest biomedical priority. Such finished sequence can be obtained in the next few years by highly automated, high throughput sequencing centers. However, a significant fraction of the human genome will not be sequenced and/or assembled to completion by such approaches, as demonstrated by the recent sequence of human chromosome 22 (Dunham et. al., Nature 402, 489-495, 1999). These are regions that contain 1) a high percentage of repetitive DNA sequences; 2) internal tandem duplications, including multigene families; and/or 3) are unstable in all current sequencing vectors. Producing quality DNA sequence of these regions, which faithfully represents genomic DNA, will be a continuing challenge.

Telomeres, the ends of the linear DNA molecules in human chromosomes, exhibit both high levels of repetitive DNA composition and cloning instability. In addition, extensive heterogeneity exists in these regions between various individuals. Half-YAC clones are uniquely suited as starting material for the sequence analysis of human telomeric regions. The inability to clone the extreme end of human chromosomes in bacterial vectors, including BACs, is well known. Due to the lack of appropriate restriction sites in the terminal (TTAGGG)n regions, as well as the necessary size selection involved in BAC library construction, the most terminal BAC clones will be 20-200Kb from the true DNA ends. By functional complementation in yeast, however, the true human telomeric end can be cloned. To date, 44 of the 46 unique human telomeres have been obtained as half-YACs.

Using RARE (RecA-Assisted Restriction Endonuclease) cleavage, 22 of these telomere half-YAC clones (representing the telomeres of human chromosomes 1p,1q,2p,2q,4p,6q,7p,7q,8p,8q,9p,11p,12q,13q,14q,16p,17p,17q,18p,18q,19p,and 21q) have now been confirmed to represent the true telomere. Further, the majority of these YAC clones have been integrated with the BAC contigs being used for large-scale sequencing (either by hybridization of DNA probes with these BAC libraries or by DNA sequence matches). Given the new goals of the Human Genome Project, we have initiated framework sequencing on these clones, as well as the most terminal BACs identified from our chromosome 5 mapping project (Peterson et.al., Genome Res 9, 1250-1267, 1999). A combination of cosmid and plasmid end sequence analysis, combined with extensive restriction enzyme mapping of the original YAC, results in highly ordered framework sequences. To date, framework sequence of 17 half-YAC clones has been completed (1q,2p,2q,7p,7q,8p,9q,10p,10q,11p,11q,13q,15q,16q,17p,18p,and 18q), as well as the most distal BAC localized to 5p. An important QC/QA aspect of our sequence analysis is the extensive confirmation of the sequence against genomic DNA by PCR-resequencing, and somatic cell hybrid mapping. This analysis has uncovered extensive polymorphism in these regions, including SNPs, VNTRs, and widespread genomic rearrangements and duplications. Despite this complicated repetitive genomic organization, many confirmed and putative protein

coding regions are found as well.

Many of the techniques used successfully to map and sequence human telomeric regions (especially RARE cleavage) should be applicable to other human ECRs, including centromeric regions. Given the high level of polymorphism uncovered, however, it is proposed that extensive human population sampling and primate DNA characterization be incorporated into such studies.

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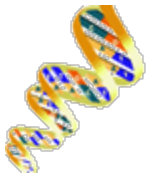

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One Origin of Man: Primate Evolution Through Genome Duplication

Julie R. Korenberg, Xiao-Ning Chen, Steve Mitchell, Rajesh Puri, Zheng-Yang Shi and Dean Yimlamai
Medical Genetics Birth Defects Center, The CSMC Burns & Allen Research nstitute, UCLA School of Medicine, Los Angeles, CA

Chromosome duplication is a force that drives evolution. We now suggest that this may also be true of the primates and that the resulting duplications in part determine the spectrum of human chromosomal rearrangements. To investigate the existence and origin of duplications in the human genome, and their consequences, 5,000 bacterial artificial chromosomes (BACs) were mapped at 2-5 Mb resolution on human high resolution chromosomes by using fluorescence in situ hybridization. A subset of 469 of these was defined that generated two or more signals, excluding those located in regions of known repeated sequences, viz., the regions of centromeres, telomeres and ribosomal genes. Although a subset of these multiple site BACs represent the chimeric artifacts of cloning, derived from two different chromosomal regions, others reflect regions of true homology in the human genome.

Two questions were considered; first, the extent to which the multiple sites of hybridization of single BACs within single chromosomes reflected the breakpoints of naturally occurring human inversions, and second, the extent to which these same multiple hybridization points reflected the chromosomal inversion points in primate evolution. For human inversions, the results of the analyses revealed a total of 124 BACs (2.5%) mapping to two or more sites on the same chromosome, of which 81 (65%) mapped to one of 27 distinct human inversion sites, the largest share of which recognized the well-established pericentromeric inversions of chromosomes 1, 2, 9, and 18, as well as the paracentric inverted region of chromosome 7q11/q22. From this, we infer that meiotic mispairing involving the homologous regions may be responsible for the inversions.

With respect to primate evolution, a significant proportion of inversion breakpoints that characterize the chromosomal changes seen in the evolution of the great apes through man, are also reflected in the distribution of BAC multiple intrachromosomal sites. Further analyses of the 29 independent BACs recognizing the pericentromeric region of human chromosome 9 suggest at least three classes, two of which recognize only single sites in Pan troglodytes.

These data suggest that inversions occurring through primate evolution may generate small duplications that, although they can cause chromosomal imbalance in single individuals, they also provide the additional genetic material for speciation.

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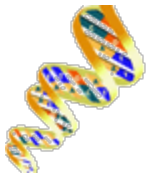

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Home

Abstract

Evan E. Eichler
Case Western Reserve University

A series of chromosome 19, p12-specific repeat probes have been generated and have been used to screen two genomic library sources (RPCI11 and CIT-D BAC libraries). Probes were generated using a degenerate 19p12-specific beta-satellite PCR assay. The initial target region focussed primarily on the existing 8 gap regions within the physical map of 19p12. To date, a total of 403 BAC clones have been identified (192 RPCI-11 BACs and 211 CIT-D BACs) representing an estimated ~2.5 Mb of the 19p12 region. A subset (74) of these BAC clones have been selected for BAC-end sequence analysis. These BAC-ends in conjunction with existing BAC-end sequences deposited in GenBank have successfully been used to extend 12 of the 16 BAC contigs in the region. This includes extension of the most proximal contig to include the transition into heterochromatic alpha-satellite DNA. An additional 120 kb of pericentromeric DNA has been added to the map, including higher-order alpha satellite DNA. Four of the original eight gap regions have been tentatively closed based on this analysis. In collaboration with Dr. Anne Olsen (LLNL), 57 BACs have been selected for integration into the 19p12 physical map. Incorporation of these clones into the 19p12 physical map is currently being used to complete sequence analysis in this region.

The short arm of chromosome 16 is also under analysis.

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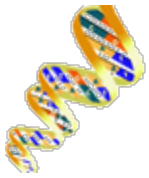

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References for *Arabidopsis* centromer studies

Greg Copenhaver & Daphne Pruess

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   Abstract:
   High precision genetic mapping was used to define the regions that contain centromere functions on each natural chromosome in *Arabidopsis thaliana*. These regions exhibited dramatic recombinational repression and contained complex DNA surrounding large arrays of 180-bp repeats. Unexpectedly, the DNA within the centromeres was not merely structural, but also encoded several expressed genes. The regions flanking the centromeres were densely populated by repetitive elements yet experienced normal levels of recombination. The genetically defined centromeres were well conserved between *Arabidopsis* ecotypes but displayed limited sequence homology between different chromosomes, excluding repetitive DNA. This investigation provides a platform for dissecting the role of individual sequences in higher eukaryotic centromeres
2. Copenhaver, G.P. and Preuss, D. (1999) Centromeres in the genomic era: Unraveling paradoxes. Curr. Op. Plant Biol. 2: 104-108.
   Abstract:
   The centromeres of higher plants and animals share many common features, though current models fail to account for all aspects of centromere composition and function. This dilemma will likely be resolved in the next few years in *Arabidopsis* where robust assays for centromere function are available and the sequence of the entire genome will be determined.
3. Copenhaver, G.P., Browne, W.E. and Preuss, D. (1998) Assaying genome-wide recombination and centromere functions with *Arabidopsis* tetrads. Proc. Natl. Acad. Sci 95:247-252.
   Abstract:
   During meiosis, crossover events generate new allelic combinations, yet the abundance of these genetic exchanges in individual cells has not been measured previously on a genomic level. To perform a genome-wide analysis of recombination, we monitored the assortment of genetic markers in meiotic tetrads from *Arabidopsis*. By determining the number and distribution of crossovers in individual meiotic cells, we demonstrate i) surprisingly precise regulation of crossover number in each meiosis, ii) considerably reduced recombination along chromosomes carrying ribosomal DNA arrays, and iii) an inversely proportional relationship between recombination frequencies and chromosome size. This use of tetrad analysis also achieved precise mapping of all five *Arabidopsis* centromeres, localizing centromere functions in the intact chromosomes of a higher eukaryote.

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map the position and internal organization of the nucleolus organizer region on chromosome 2 in *Arabidopsis thaliana.* The Plant Journal 7(2): 273-286.
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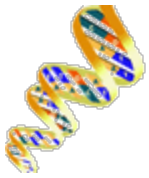

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Home

Abstract

Gary H. Karpen
The Salk Institute

Our laboratory investigates the structure and function of chromosomes and nuclei. We are particularly interested in understanding the basic mechanisms responsible for ensuring normal chromosome inheritance, a process that is fundamental to all aspects of biology. Our long term goal is to utilize a basic understanding of inheritance in the diagnosis and treatment of human disorders caused by defective chromosome behavior, such as birth defects (e.g., Down's Syndrome) and cancer. Cancer is in part caused by failures in chromosome transmission during cell division, and in the normal monitoring systems (checkpoints) that signal a cell to cease dividing until genome integrity can be restored. For example, tumor progression is characterized by genomic instability and increasing levels of aneuploidy. What are the mechanisms responsible for gain and loss of chromosomes? Unfortunately, we know far too little about the DNA elements and proteins responsible for normal chromosome inheritance in multicellular eukaryotes. Clearly, cancer diagnosis and treatment would be greatly aided by a better understanding of components and mechanisms that act to ensure genome continuity and stability. We have developed the Drosophila Dp1187 minichromosome as a model system for studying chromosome structure and function in higher organisms. In the last year, we have completed molecular-genetic studies that determined the sequence composition of a key cis-acting component of inheritance (the centromere), and studied novel genes and proteins involved in normal inheritance and in linking chromosome and nuclear organization to gene expression.

There are sub-projects on:

- Centromere Structure and the Determinants of Centromere Identity
- Proteins Required for Centromere Function and Other Aspects of Chromosome Inheritance
- Nuclear Organization and Long Distance Regulation of Gene Expression

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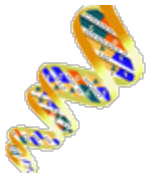

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Home

Abstract

David C. Schwartz
University of Wisconsin, Madison

Our laboratory has developed Optical Mapping, a single molecule system for the construction of ordered restriction maps. Optical Mapping dispenses with electrophoretic approaches, and uses fluorescence microscopy to directly image individual DNA molecules bound to derivatized glass surfaces, after cleavage by restriction enzymes. Cleaved fragments retain their original order, and cut sites are flagged by small, visible gaps. Optical Mapping solves the problem of determining fragment order, and when working with clones, works with only a handful of molecules. By determining the existence of these sequence-specific cut sites and the distances between them, we can create a landmark map of the DNA sequence. Efforts in our laboratory, over the last two years have been to automate Optical Mapping, with the goal of creating high throughput systems for the analysis of a wide range of sample types. This work has entailed the fusion of advanced optical, and biochemical techniques with novel statistical and algorithmic developments.

Optical Mapping of clones
Optical Mapping is now a robust system for the analysis of cloned DNA samples. We have mapped cosmid and yeast (YAC), or bacterial artificial chromosome (BAC) clones. We have mapped to high resolution BACs derived from the human Y chromosome which contain numerous repeated regions and are considered difficult to map by conventional means.

Optical Mapping of genomic DNA
We are now also able to map genomic DNA directly which enables large stretches of the genome to be mapped, simplifying contig formation. Library construction is obviated enabling mapping of organisms with DNA which is difficult to clone. Also, cloning artifacts are precluded enabling more accurate maps to be generated. Furthermore, small amounts of starting material are required, enabling mapping of microorganisms which are problematic to culture. We benchmarked our genomic mapping system by mapping E. coli K12 strain which has been completely sequenced, and then mapped the microbial genomes Plasmodium falciparum and Deinococcus radiodurans. Such maps have proved invaluable as a scaffold for assembling of sequence contigs and as a means of sequence verification.

We then went on to map the human genome with 0.6-fold coverage. We project that a whole genome map of high accuracy and minimal gaps will be obtained when approximately 5 genome equivalents are mapped and contiged. We expect to link these contigs and close a large portion of gaps by the Optical Mapping of BAC or YAC contigs previously assigned to the physical map. The complete reference map will serve as a database by which inherited genetic aberrations and genomic rearrangements associated with tumors can be characterized at the molecular level.

Software tools for Optical Mapping.

We have developed an integrated microscope control, machine vision and statistical anlysis system to fully automate image collection, processing and map construction (Optical Map Maker). A number of other software tools have been developed to aid in manipulating large pieces of data such as images of long DNA molecules which span multiple microscope fields (Gencol). Marking of restriction site cuts in images is now semi-automated (Visionade) and multiple maps can be aligned and oriented to form contigs (Gentig).

It is our hope that the Optical Mapping system will be broadly used for large scale genomic analysis and a means to perform population-based genomic studies.

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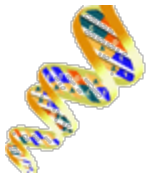

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Reconstruction and Annotation of Transcribed Sequences: The TIGR Gene Indices

John Quackenbush, Ingeborg Holt, Feng Liang, Geo Pertea, Jonathan Upton, and Thomas S. Hansen
The Institute for Genomic Research, Rockville, MD 20850

A goal of the Human Genome Project is identification of the complete set of human genes and the role played by these genes in development and disease. The sequencing of Expressed Sequence Tags (ESTs) has provided a first glimpse of the collection of transcribed sequences in humans and other organisms, but significant additional information can be obtained by a thorough analysis of the EST data. TIGR's analysis of the world's collection of EST sequence data, captured in our Gene Indices, provides assembled consensus sequences that are of high confidence and represent our best estimate of the collection of transcribed sequences underlying the ESTs. In addition to the Human Gene Index (HGI), we maintain Gene Indices for a variety of other species, including mouse, rat, *Drosophila*, zebrafish, rice, tomato, and *Arabidopsis*. Collectively, the Gene Indices represent a unique resource for the comparative analysis of mammalian genes and may provide insight into gene function, regulation, and evolution.

We have recently expanded the TIGR Gene Index project to include quarterly releases, expanded annotation, integration with mapping and genomic sequence data, and more robust search capabilities. In addition, we are developing a database of mammalian orthologues based on comparison of the human, mouse, and rat TC sequences and a web-based presentation to allow the data to be effectively explored. This database will provide direct links between the human, mouse, and rat assemblies and represent the most extensive catalog of eukaryotic orthologues available, providing a valuable resource for gene identification, elucidation of functional domains, and analysis of gene and genome evolution.

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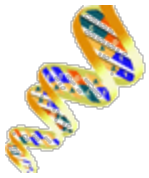

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Direct isolation of a centromeric region from the human Y chromosome by TAR cloning for structural and functional studies

Natalay Kouprina and Vladimir Larionov
Laboratory of Molecular Genetics, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC 27709
kouprina@niehs.nih.gov

Isolation of specific chromosomal regions and entire genes has typically involved cloning of random fragments as BACs or YACs followed by a long and laborious process to identify the region of interest. Using the TAR cloning technique in yeast[1], it is possible to directly isolate specific chromosomal regions and genes from complex genomes as large linear or circular YACs. We applied a TAR cloning technique for isolation of a centromeric region of the human mini-chromosome [delta]1 containing 5 Mb of the human chromosome Y[2]. This mini-chromosome was generated by two rounds of telomere-directed chromosome breakage leading to a loss of sequences from both arms of the chromosome. Despite the small size and loss of a significant part of centromeric repeats (only 140 kb of alphoid DNA left), the[delta]1 mini-chromosome segregates accurately in mitosis, suggesting that this block of alphoid DNA alone or along with the short arm flanking sequence is sufficient for a centromere function. The centromeric region containing an entire block of alphoid DNA was rescued in yeast as a circular YAC. To simplify physical analysis of the cloned material and prevent its rearrangements due to the presence of multiple repeats, the YAC was retrofitted into YAC/BAC with the *Neo*^{R} gene and transferred into the *E. coli* cells. No detectable changes in a BAC DNA were observed during propagation in bacterial cells that allowed a complete sequencing of the block of alpha satellite repeats. Because the BAC also contains a mammalian selectable marker, it can be transferred into human cells for further functional analysis.

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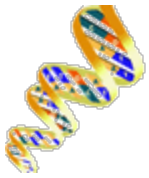

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Nucleic Acid Strands Specific for Binding via Non-Denaturing Triple Helix Formation (TISH) to Centromeric DNAs of Each of the Human Chromosomes and to the DNA Common to the Tips of the Achrocentrics

Jacques R. Fresco
Dept. of Molecular Biology, Princeton University, Princeton, N. J. 08544

Marion Johnson and I have developed a methodology for binding single nucleic acid strands specifically to purine-rich.pyrimidine-rich sequences of protein-depleted chromosomes under conditions that are non-denaturing to double helical DNA. The binding occurs by triple helix formation and is remarkably sequence-specific under conditions of appropriate stringency. The probe strands are 15-25 residues in length, can distinguish a single base pair difference in the target sequence, the binding is quantitative, and the method should be relatively easy to adapt for the isolation of a long DNA chain in which a target is present. So far we have used this approach to develop fluorescent cytogenetic probes in human and drosophila chromosomes (cf. M. D. Johnson and J. R. Fresco, CHROMOSOMA (1999) 108:181-189.Currently, we are using it as the basis of a novel approach to gene therapy and also to develop cytogenetic probes for genes amplified in various types of Cancer.

My laboratory will be pleased to collaborate, help, or otherwise interact with anyone interested in exploiting this technology.

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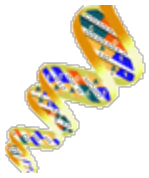

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Brookhaven National Lab.

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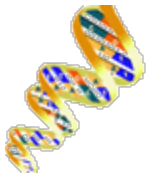

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