Clone-Based Physical Mapping of the Human Genome

- YACs for '1st Generation' Clone-Based Physical Maps
- Options for Landmarks:

  Fingerprints
  Hybridization Probes (e.g., Alu-PCR Products)
  STSs

- Strategic Issue: Genome-Wide vs. Chromosome-Specific Efforts
- 1st Generation Clone-Based Physical Maps of Human Chromosomes:

  Strategies for Construction
  Characteristics
  Lessons Learned
  Progress to Date

Early Successes in Human Chromosome Mapping

• Chromosome Y [Foote et al. (1992), Vollrath et al. (1992)]

The Human Y Chromosome: Overlapping DNA Clones Spanning the Euchromatic Region

Simon Foote, Douglas Vollrath, Adrienne Hilton, David C. Page

The Human Y Chromosome: A 43-Interval Map Based on Naturally Occurring Deletions

Douglas Vollrath, Simon Foote, Adrienne Hilton, Laura G. Brown, Peggy Beer-Romero, Jonathan S. Bogan, David C. Page

• Chromosome 21 [Chumakov et al. (1992)]

Continuum of overlapping clones spanning the entire human chromosome 21q

Ilya Chumakov[*†], Philippe Rigault[†], Sophie Guillou[†], Pierre Ougen[*], Alain Billaut[*], Ghislaine Guasconi[†], Patricia Gervy[†], Isabelle LeGall[*], Pascal Soularue[*], Laurent Grinas[†], Lydie Bougueleret[*], Christine Bellanné-Chantelot[*], Bruno Lacroix[*], Emmanuel Barillot[†], Philippe Gesnouin[†], Stuart Pook[†], Guy Vaysseix[*†], Gerard Frelat[‡], Annette Schmitz[‡], Jean-Luc Sambucy[*], Assumpcio Bosch[‖], Xavier Estivill[‖], Jean Weissenbach[†‖], Alain Vignal[†], Harold Riethman[¶], David Cox[◇], David Patterson[**], Kathleen Gardiner[**], Masahira Hattori[††], Yoshiyuki Sakaki[††], Hitoshi Ichikawa[‡‡], Misao Ohki[‡‡], Denis Le Paslier[*], Roland Heilig[§§], Stylianos Antonarakis[‖‖] & Daniel Cohen[*†††]

The CEPH/Genethon Map of the Human Genome

- Bellanne-Chantelot et al. (1992)

Mapping the Whole Human Genome by Fingerprinting Yeast Artificial Chromosomes

Christine Bellanné-Chantelot,* Bruno Lacroix,*
Pierre Ougen,* Alain Billault,* Sandrine Beaufils,†
Stéphane Bertrand,† Isabelle Georges,†
Fabrice Gilbert,† Isabelle Gros,†
Georges Lucotte,† Laurent Susini,†
Jean-Jacques Codani,‡ Philippe Gesnouin,†
Stuart Pook,† Guy Vaysseix,* Jennifer Lu-Kuo,§
Thomas Ried,§ David Ward,§ Ilya Chumakov,*
Denis Le Paslier,* Emmanuel Barillot,†
and Daniel Cohen*†

- Cohen et al. (1993)

A first-generation physical map of the human genome

D. Cohen*†, I. Chumakov*† & J. Weissenbach†‡

- Chumakov et al. (1995)

A YAC contig map of the human genome

Ilya M. Chumakov*, Philippe Rigault*, Isabelle Le Gall*, Christine Bellanné-Chantelot*, Alain Billault*, Sophie Guillou*, Pascal Soularue*, Ghislaine Guasconi*, Eric Poullier*, Isabelle Gros*, Maria Belova*, Jean-Luc Sambucy*, Laurent Susini*, Patricia Gervy*, Fabrice Gilbert*, Sandrine Beaufils*, Hung Bui*, Catherine Massart*, Marie-France De Tand*, Frédérique Dukasz*, Sandrine Lecoulant*, Pierre Ougen*, Virginie Perrot*, Martial Saumier*, Catherine Soravito*, Rita Bahouayila*, Annick Cohen-Akenine*, Emmanuel Barillot†, Stéphane Bertrand†, Jean-Jacques Codani†, Dominique Caterina*, Isabelle Georges†, Bruno Lacroix*, Georges Lucotte*, Mourad Sahbatou*, Christian Schmit*, Muriel Sangouard*, Emmanuel Tubacher*, Colette Dib†, Sabine Fauré†, Cécile Fizames†, Gabor Gyapay†, Philippe Millasseau†, Simon NGuyen†, Delphine Muselet†, Alain Vignal†, Jean Morissette†¶, Joan Menninger‡, Jonathan Lieman‡, Trushna Desai‡, Amy Banks‡, Patricia Bray-Ward‡, David Ward‡, Thomas Hudson§, Sebastian Gerety§, Simon Foote§, Lincoln Stein§, David C. Page§||, Eric S. Lander§||, Jean Weissenbach†, Denis Le Paslier* & Daniel Cohen*

CEPH/Genethon Strategy for Map Construction

- Experimental Data Set

  Hybridization-Based Fingerprint Analysis
  Hybridization Analysis (YAC x YAC):

    Alu-PCR YAC Probes → Alu-PCR Products from YACs

  Alu-PCR Hybridization Assignment of YACs to Chromosomes
  FISH-Based Assignment of YACs to Chromosomes
  *Assignment of Genethon Genetic Markers (STSs) to YACs

- Data Analysis

  Complicated!!!
  Suite of Programs to 'Disambiguate' the Data (*Quickmap*)
  Heavy Reliance on Genethon Genetic Map for Contig Assembly
  Predict 'Most Likely' **Paths** Among Overlapping Clones

- Map Highlights

  Clone-Based Map (Mostly Based on Intrinsic Landmarks)
  225 Contigs Averaging 10 Mb, 75% of Genome Covered
  Potentially Useful for Positional Cloning Projects
  Poor Scaffold for DNA Sequencing (Sparse STS Density)

- Data and Map Availability

  http://www.cephb.fr/bio/ceph-genethon-map.html

Example of a CEPH/Genethon Map

The Whitehead Map of the Human Genome

- Hudson et al. (1995)

An STS-Based Map of the Human Genome

Thomas J. Hudson,* Lincoln D. Stein, Sebastian S. Gerety, Junli Ma, Andrew B. Castle, James Silva, Donna K. Slonim, Rafael Baptista, Leonid Kruglyak, Shu-Hua Xu, Xintong Hu, Angela M. E. Colbert, Carl Rosenberg, Mary Pat Reeve-Daly, Steve Rozen, Lester Hui, Xiaoyun Wu, Christina Vestergaard, Kimberly M. Wilson, Jane S. Bae, Shanak Maitra, Soula Ganiatsas, Cheryl A. Evans, Margaret M. DeAngelis, Kimberly A. Ingalls, Robert W. Nahf, Lloyd T. Horton Jr., Michele Oskin Anderson, Alville J. Collymore, Wenjuan Ye, Vardouhie Kouyoumjian, Irena S. Zemsteva, James Tam, Richard Devine, Dorothy F. Courtney, Michelle Turner Renaud, Huy Nguyen, Tara J. O'Connor, Cécile Fizames, Sabine Fauré, Gabor Gyapay, Colette Dib, Jean Morissette, James B. Orlin, Bruce W. Birren, Nathan Goodman, Jean Weissenbach, Trevor L. Hawkins, Simon Foote, David C. Page, Eric S. Lander*

- Web Site: http://www-genome.wi.mit.edu

- ~25,000 STSs Mapped on a Genome-Wide Basis by YAC-Based STS-Content Mapping, Radiation Hybrid (RH) Mapping, **and/or** Genetic Mapping

- Strategy for Map Construction

  Genetic and Radiation Hybrid Maps Provide Global Framework ('Top-Down Mapping')

  YAC-Based STS-Content Map Provides Local Ordering of STSs ('Bottom-Up Mapping')

  Cross-Reference the Top-Down and Bottom-Up Maps to Deduce an 'Integrated Map' of Each Chromosome

The Whitehead Map: Data Generation and Analysis

- Integrated Approach for Physical Mapping of STSs

  1. YAC-Based STS-Content Mapping
     ~11,000 STSs, CEPH Mega-YACs

  2. Radiation Hybrid Mapping of STSs
     ~15,000 STSs, GeneBridge 4 RH Panel

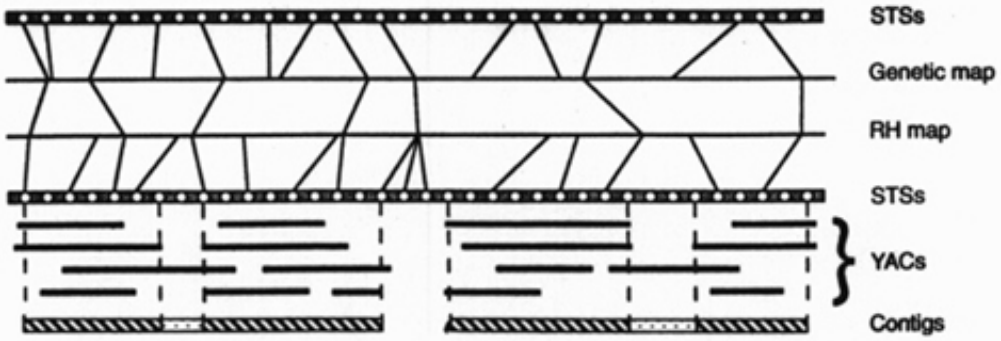
  3. Genethon Genetic Maps
     ~5,300 STSs

- PCR Analysis: ***Genomatron***

  Massively-Parallel, Factory-Style Automation System
  1536 Position Arrays
  ~150,000 PCR Assays Per Run, >25,000,000 PCR Assays Total

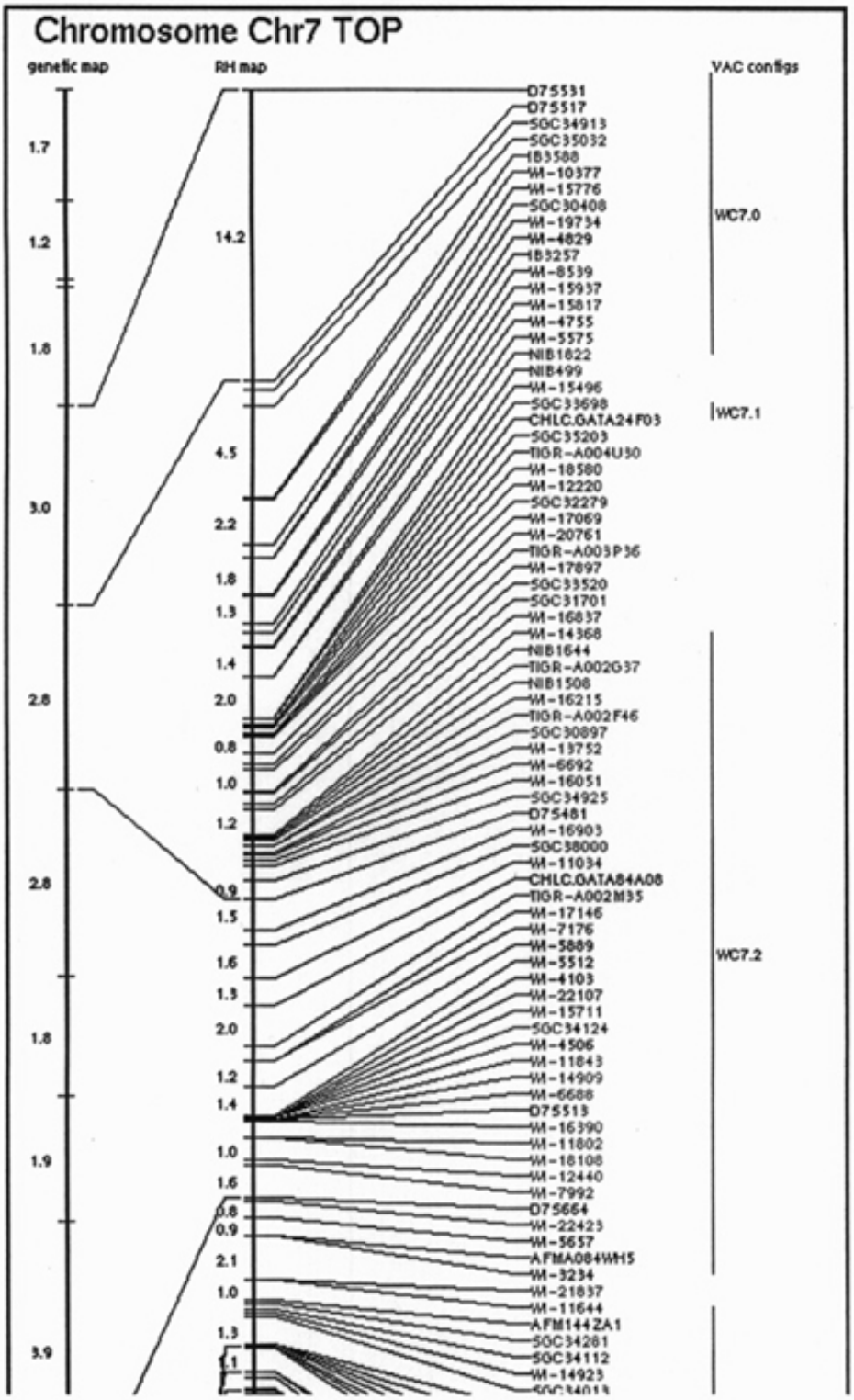
- Average STS Resolution: ~120 kb

- Integration of Top-Down and Bottom-Up Maps



- Availability of Data and Maps: http://www-genome.wi.mit.edu

The Whitehead Map: An Example



Chromosome-Specific Mapping Efforts

- Chromosome 3 (U. of Colorado, U. of Texas-San Antonio)
  Gemmill et al. (1995)
  http://www-eri.uchsc.edu/Welcome.html
  http://mars.uthscsa.edu/DB

- Chromosome 4 (Stanford U.)
  Goold et al. (1993)
  http://www-shgc.stanford.edu

- Chromosome 7 (NHGRI, U. of Toronto)
  Green et al. (1994, 1995), Bouffard et al. (1997)
  http://www.nhgri.nih.gov/DIR/GTB/CHR7
  http://www.genet.sickkids.on.ca/chromosome7/

- Chromosome 10 (Genome Therapeutics)
  http://www.cric.com/htdocs/sequences/chr10-mapping/index.html

- Chromosome 11 (U. of Texas-Southwestern, Roswell Park)
  Smith et al. (1993), Quackenbush et al. (1995)
  Qin et al. (1996)
  http://mcdermott.swmed.edu/datapage
  http://shows.med.buffalo.edu/home.html

- Chromosome 12 (Albert Einstein U.)
  Krauter et al. (1995)
  http://paella.med.yale.edu/chr12/Home.html

Chromosome-Specific Mapping Efforts [con't]

- Chromosome 16 (Los Alamos Labs)
  Doggett et al. (1995)
  http://www-ls.lanl.gov

- Chromosome 19 (Lawrence Livermore Labs)
  Ashworth et al. (1995)
  http://www-bio.llnl.gov/bbrp/genome/genome.html

- Chromosome 21 (U. of Colorado, CEPH)
  http://www-eri.uchsc.edu/Welcome.html

- Chromosome 22 (U. of Pennsylvania, Sanger Centre)
  Bell et al. (1995)
  Collins et al. (1995)
  http://www.cbil.upenn.edu/HGC22.html
  http://www.sanger.ac.uk

- Chromosome X (Washington University, Baylor University)
  Nagaraja et al. (1997)
  http://genome.wustl.edu/cgm/cgm.html
  http://gc.bcm.tmc.edu:8088/home.html

- Chromosome Y
  Foote et al. (1992), Vollrath et al. (1992)
  http://www-genome.wi.mit.edu

'100-kb STS Maps' of Human Chromosomes

• Nagaraja et al. (1997)

RESEARCH

X Chromosome Map at 75-kb STS Resolution, Revealing Extremes of Recombination and GC Content

Ramaiah Nagaraja, Sandra MacMillan, Juha Kere, Carmela Jones, Stephanie Griffin, Matthew Schmatz, Jennifer Terrell, Michael Shomaker, Christopher Jermak, Christian Hott, Mochubeloa Masisi, Steven Mumm, Anand Srivastava, Giuseppe Pilia, Terence Featherstone, Richard Mazzarella, Sheila Kesterson, Brigid McCauley, Brian Railey, Frank Burough, Volker Nowotny, Michele D'Urso, David States, Bernard Brownstein, and David Schlessinger[1]

• Bouffard et al. (1997)

RESEARCH

A Physical Map of Human Chromosome 7: An Integrated YAC Contig Map with Average STS Spacing of 79 kb

Gerard G. Bouffard,[1] Jacquelyn R. Idol,[1] Valerie V. Braden,[1] Leslie M. Iyer,[1] Aimee F. Cunningham,[1] Lauren A. Weintraub,[1] Jeffrey W. Touchman,[1] Rose M. Mohr-Tidwell,[2] Dale C. Peluso,[2] Robert S. Fulton,[2] Melinda S. Ueltzen,[2] Jean Weissenbach,[3] Charles L. Magness,[4] and Eric D. Green[1,5]