DRIVERS OF INNOVATION: THE HUMAN GENOME PROJECT, MICROARRAYS, THE HAPMAP, AND THE $1,000 GENOME

Alan E. Guttmacher, M.D.
National Human Genome Research Institute

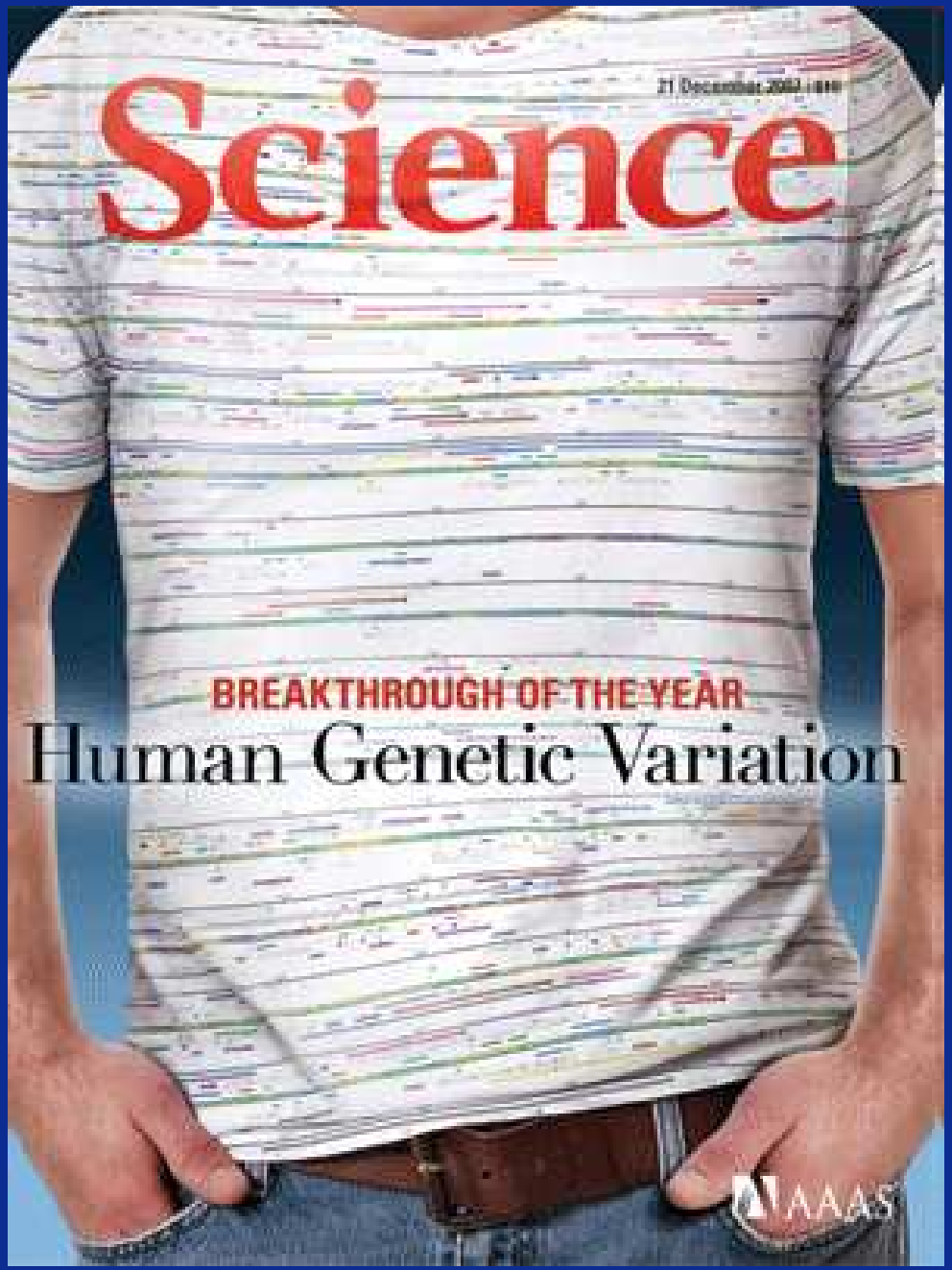
The National Academies

August 31, 2009

Or, Where Are We, How Did We Get Here, and Where Are We Headed?


National
Human Genome
Research Institute
National Institutes of Health

Where Are We?



Science

December 21, 2007

Sequencing Bonanza

NEW GENOME-SEQUENCING TECHNOLOGIES that are much faster and cheaper than the approach used to decipher the first human genome are driving a boom in sequencing.

This year, using "sequencing by synthesis" technology from 454 Sequencing, which "grows" fluorescently labeled DNA on microscopic beads, researchers produced the mitochondrial genomes of extinct cave bears and of a Neandertal, and 70% of the genome of a woolly mammoth.

A preliminary draft of the full Neandertal genome is in the works. Another new technology, developed by Solexa (now part of Illumina), made its debut in the scientific literature with the descriptions of the first genomes of an Asian, an African, and a cancer patient, shedding new light on early human migrations and candidate genes that may underlie malignancies. Illumina's technology sequences DNA in massively parallel reactions on glass plates. A proof-of-concept paper by Pacific Biosciences, a company that sequences single DNA molecules, provided an exciting glimpse of even faster sequencing. Now the goal is to make it more accurate.

Costs continue to drop; at least one company boasts that genomes for $5000 are in reach. **–THE NEWS STAFF**

Cancer Genes

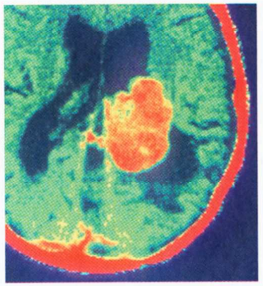
RESEARCHERS THIS YEAR TURNED A SEARCHLIGHT ON THE ERRANT DNA that leads tumor cells to grow out of control. These studies are revealing the entire genetic landscape of specific human cancers, providing new avenues for diagnosis and treatment.

Tumor cells are typically riddled with genetic mistakes that disrupt key cell pathways, removing the brakes on cell division. Thanks to the completion of the human genome and cheaper sequencing, researchers can now systematically survey many genes in cancer cells for changes that earlier methods missed. Results from the first of these so-called cancer genome projects came out 2 years ago, and the output ramped up in 2008.

Leading the list were reports on pancreatic cancer and glioblastoma, the deadliest cancers. By sequencing hundreds or thousands of genes, researchers fingered dozens of mutations, both known and new.

CREDITS (TOP TO BOTTOM): CERN; DAN MCCOY/GETTY IMAGES

For example, a new cancer gene called *IDH1* appeared in a sizable 12% of samples from glioma brain tumors. A separate glioma study revealed hints as to why some patients' tumors develop drug resistance. Other studies winnowed out abnormal DNA in lung adenocarcinoma tumors and acute myeloid leukemia.



The expanding catalog of cancer genes reveals an exciting but sobering complexity, suggesting that treatments that target biological pathways are a better bet than "silver bullet" drugs aimed at a single gene. Genome projects for at least 10 more cancers are in the works.

Breakthroughs of the Year - 2008

Science

12/19/08

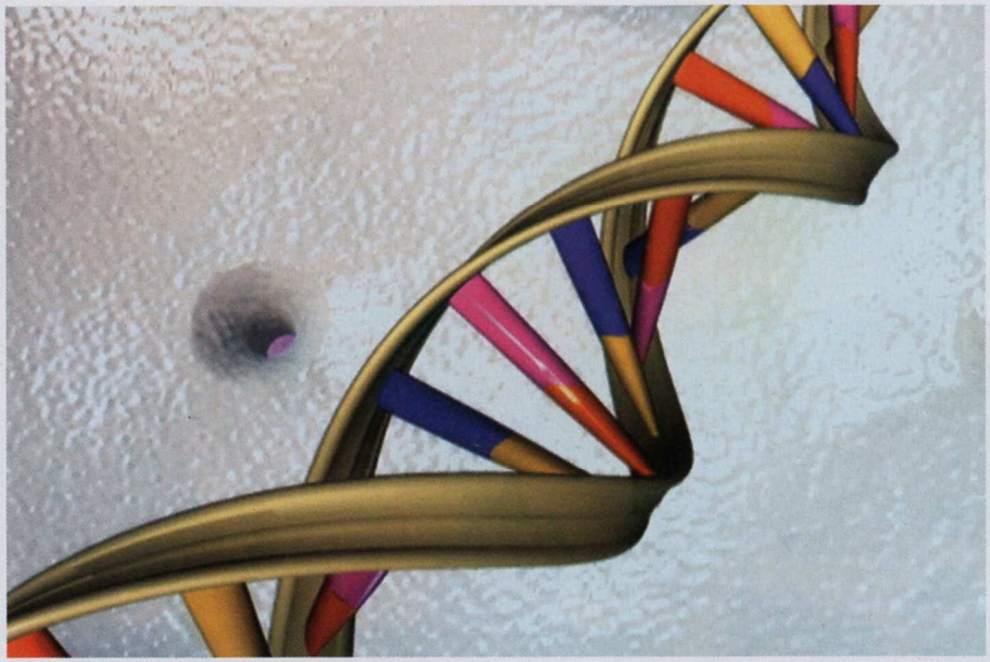
nature

Vol 456|18/25 December 2008

NEWS 2008: THE YEAR IN WHICH ...

Words: Ashley Yeager

NATL HUMAN GENOME RES. INST.



Personal genomics goes mainstream
In January, an international consortium announced the launch of the 1,000 Genomes Project, which aims to provide a catalogue of human genetic variation. In October, the Personal Genome Project, which hopes to sequence and publish the genomes of as many people as possible, released initial data for ten participants. Meanwhile, as researchers wondered what they could glean from the results coming from personal-genomics companies, the prices of such services dropped. The firm 23andMe, based in Mountain View, California, for instance, now offers personalized genetic information for $399. And finally, two more human genomes — one of an anonymous African, the other an Asian — were decoded, bringing the world's total of published human genomes to four.

Nature 12/18-25/08

nature

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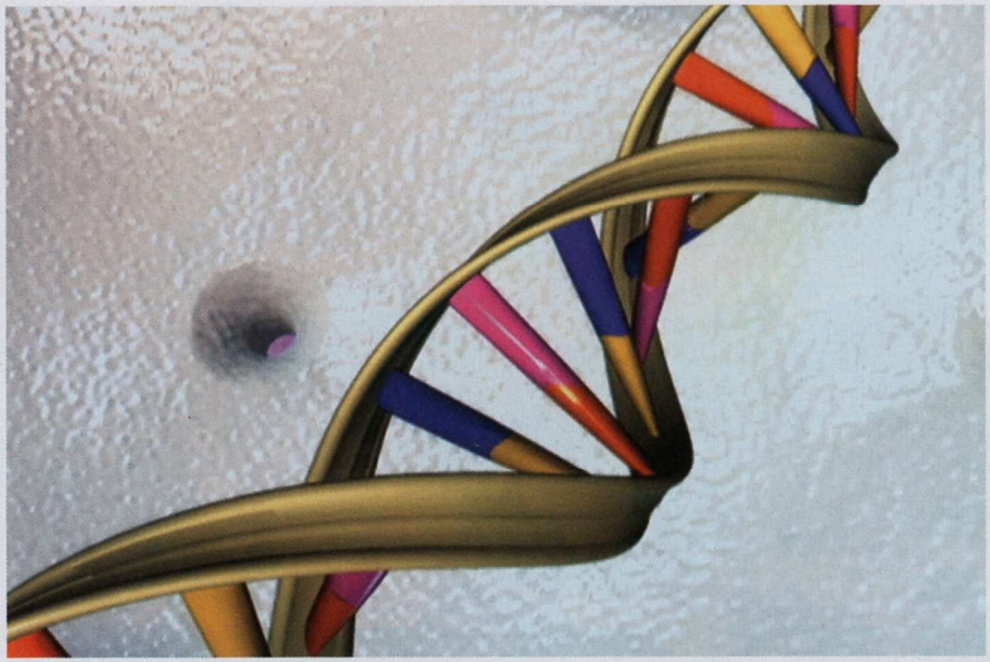

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Nature 12/18-25/08

November 6, 2008

TIME's Best Inventions of 2008

Invention of the Year

Next

1. The Retail DNA Test

By Anita Hamilton

ARTICLE TOOLS
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Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin, and she went to Yale. But after an hour chatting with her in the small office she shares with co-founder Linda Avey at 23andMe's headquarters in Mountain View, Calif., I know some things no Internet search could reveal: coffee makes her giddy, she has a fondness for sequined shoes and fresh-baked bread, and her unborn son has a 50% chance of inheriting a high risk for Parkinson's disease.

Learning and sharing your genetic secrets are at the heart of 23andMe's controversial new service — a $399 saliva test that estimates your predisposition for more than 90 traits and conditions ranging from baldness to blindness. Although 23andMe isn't the only company

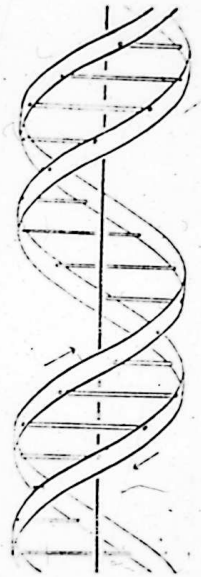
How Did We Get Here?

April, 1953

No. 4356 April 25, 1953 NATURE

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

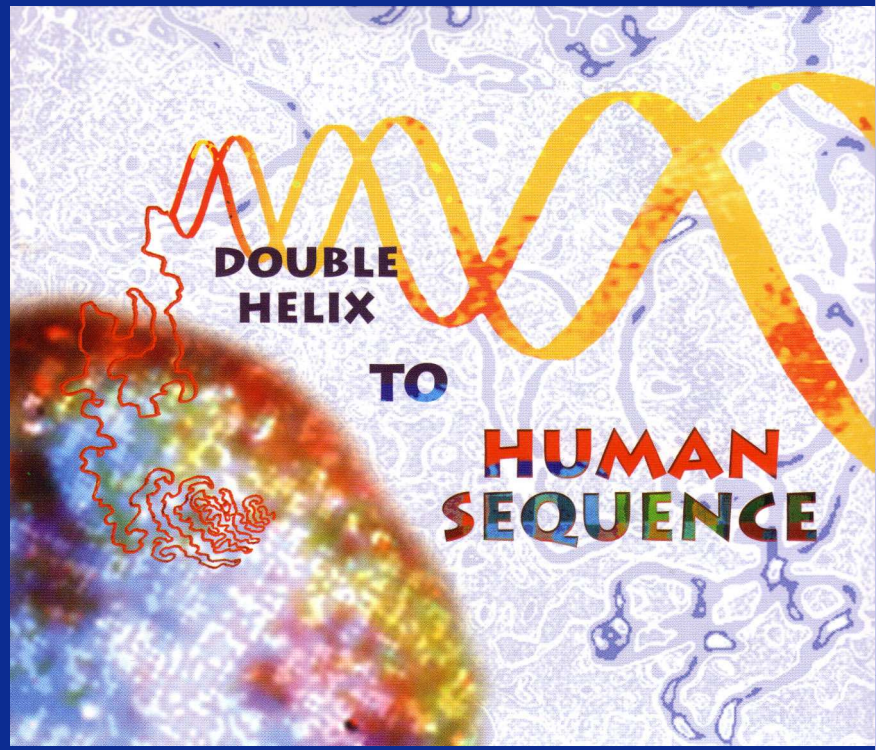
A Structure for Deoxyribose Nucleic Acid

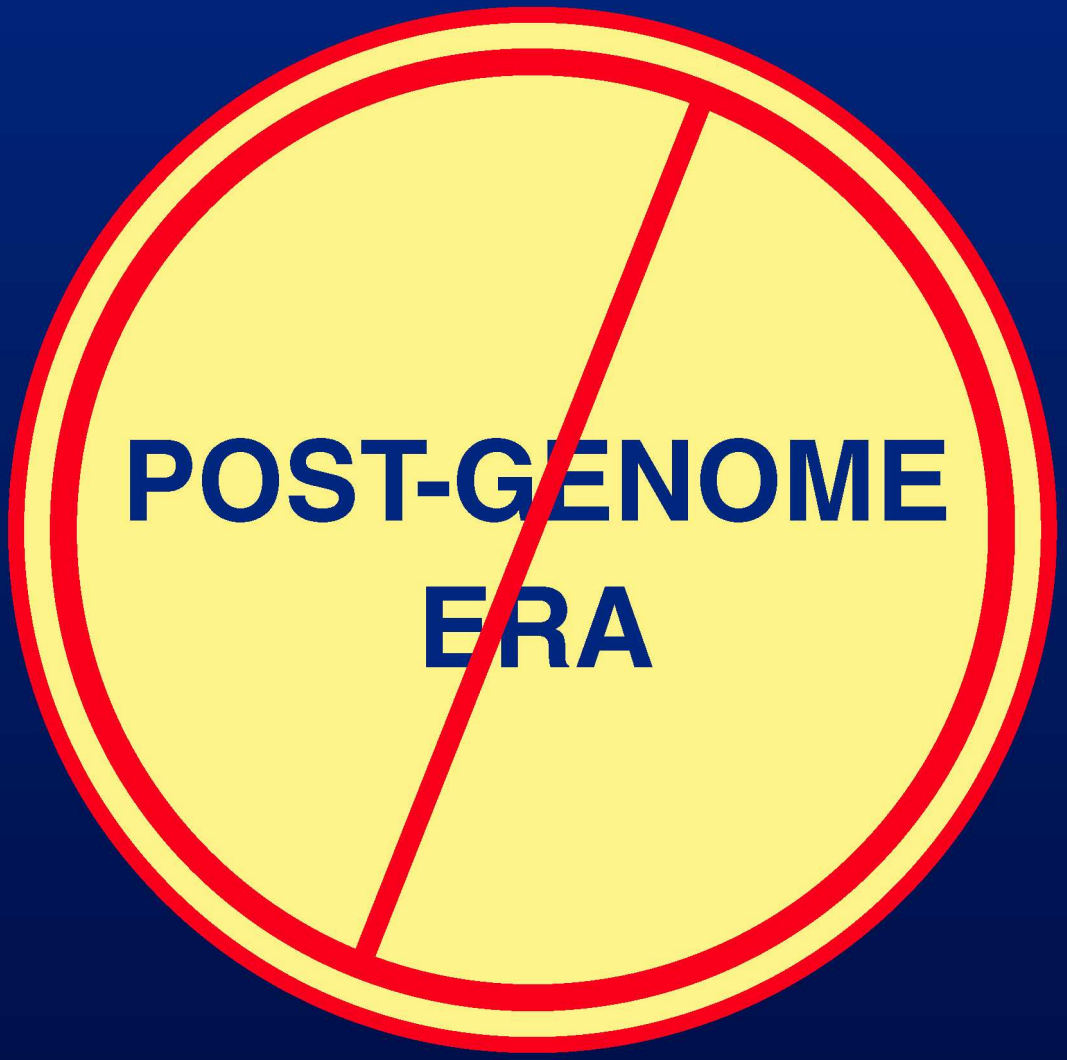


J. D. Watson
F. H. C. Crick

Medical Research Council Unit for the
Study of the Molecular Structure of
Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.

April, 2003

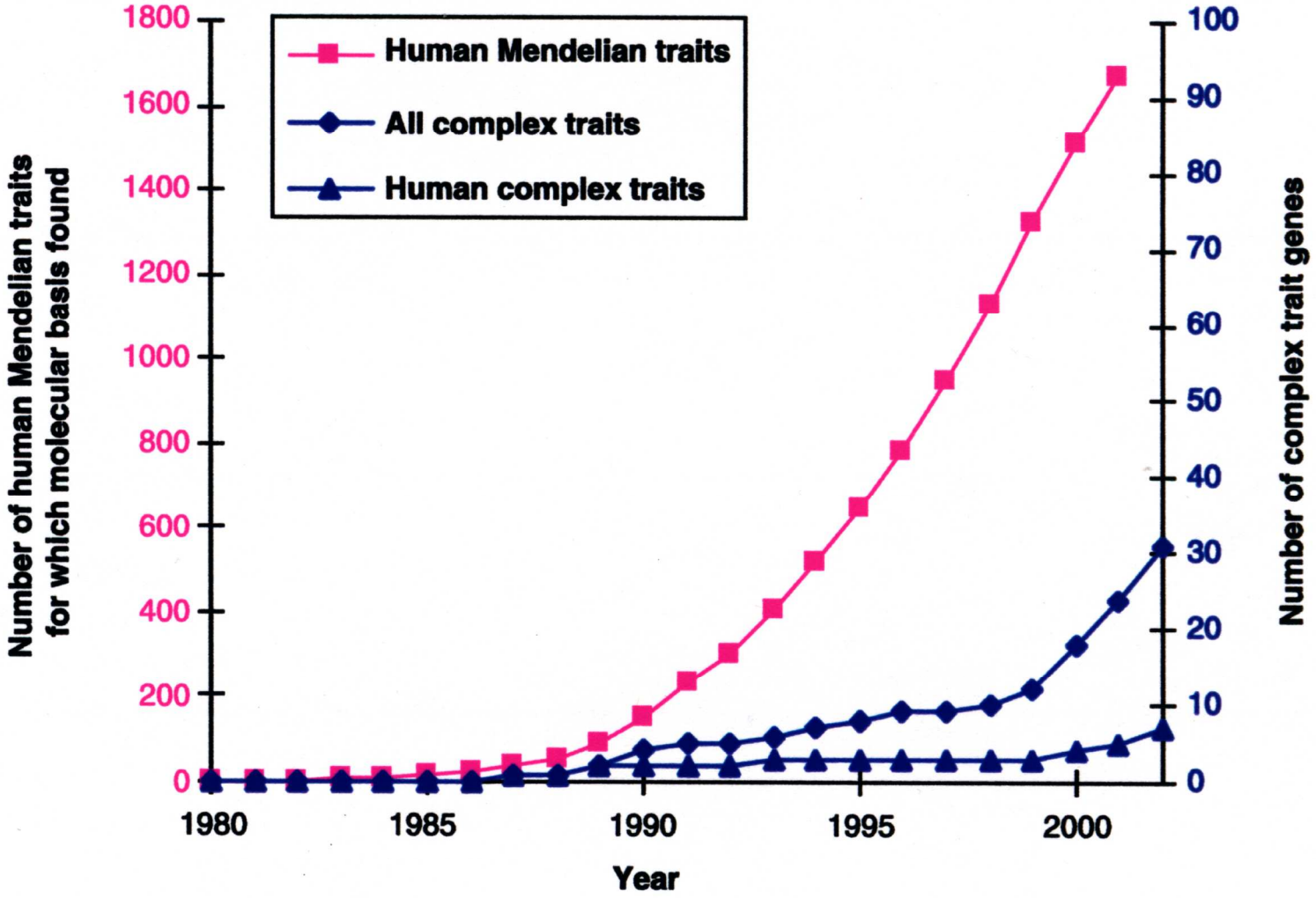




WELCOME TO THE GENOME ERA

All of the original goals of the human genome project have been accomplished

- So, what's next?



Glazier et al., Science 298:2345-9, 2002

Whole Genome Association Approach to Common Disease: The 2002 View

- Identify all 10 million common SNPs
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to 20 billion genotypes
- At 50 cents a genotype, that's **$10 billion** for each disease

International HapMap Project

www.hapmap.org

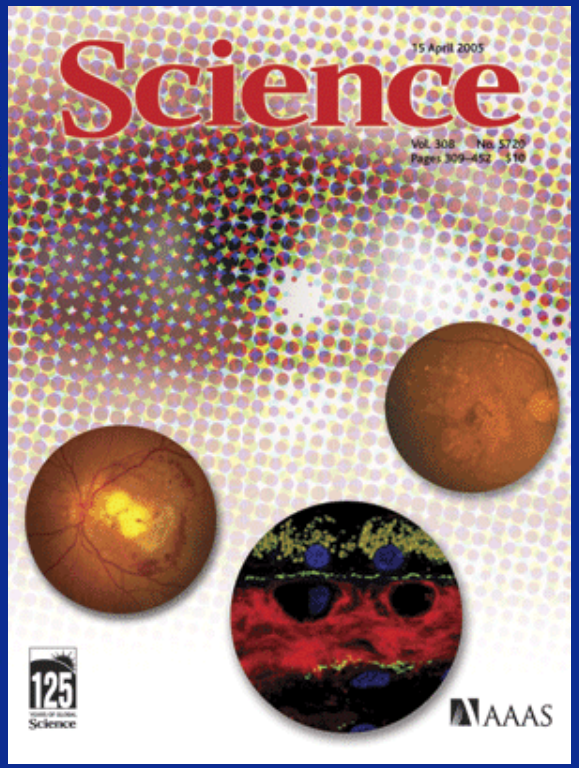
Whole Genome Association Approach to Common Disease: The 2007 View (The HapMap Era)

- Identify optimum set of ~500,000 (or more) variants
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to ~~20~~ **1** billion genotypes
- And, a genotype now costs ~~50 cents~~ 1/12 of a penny, so that's about ~~$10 billion~~ **$800,000** for each disease

An Early Result from the HapMap: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

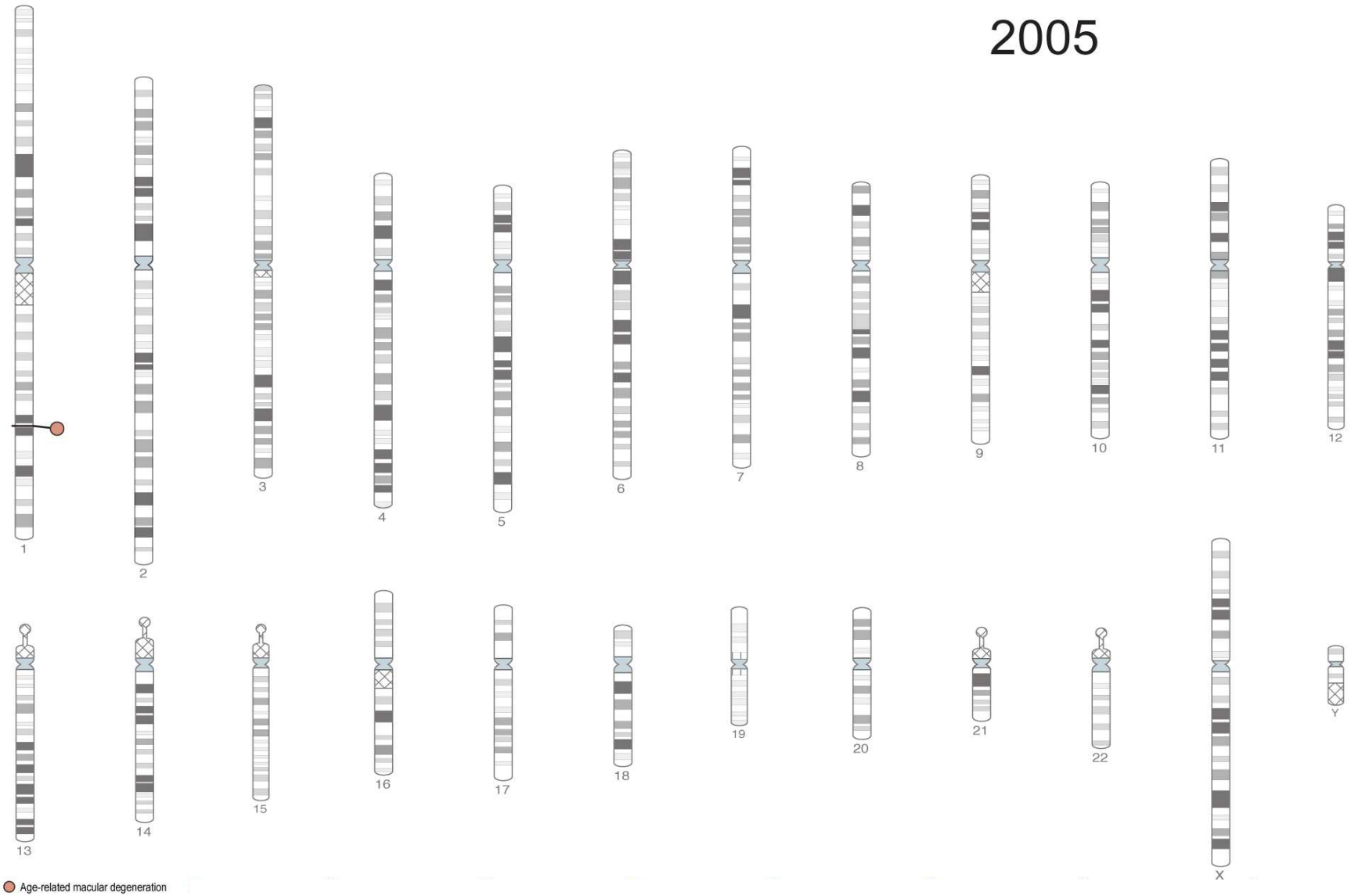


Science 2005; 308:385-9

Using the same strategy, another major risk locus was identified (HTRA1).

Together these account for ~50% of risk, suggest AMD may be an inflammatory disease, and point to new approaches to prevention and treatment.

2005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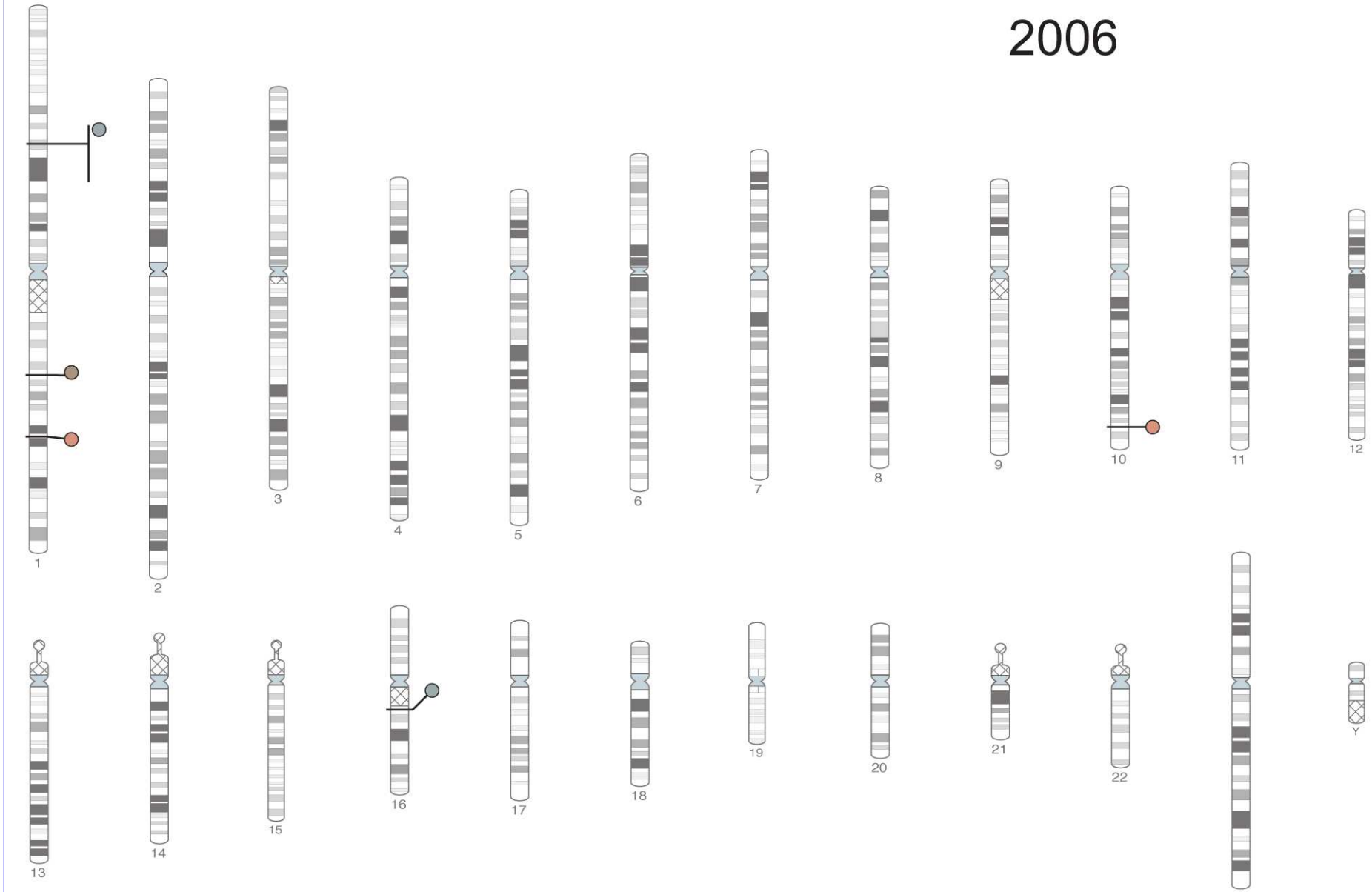
Age-related macular degeneration

2006



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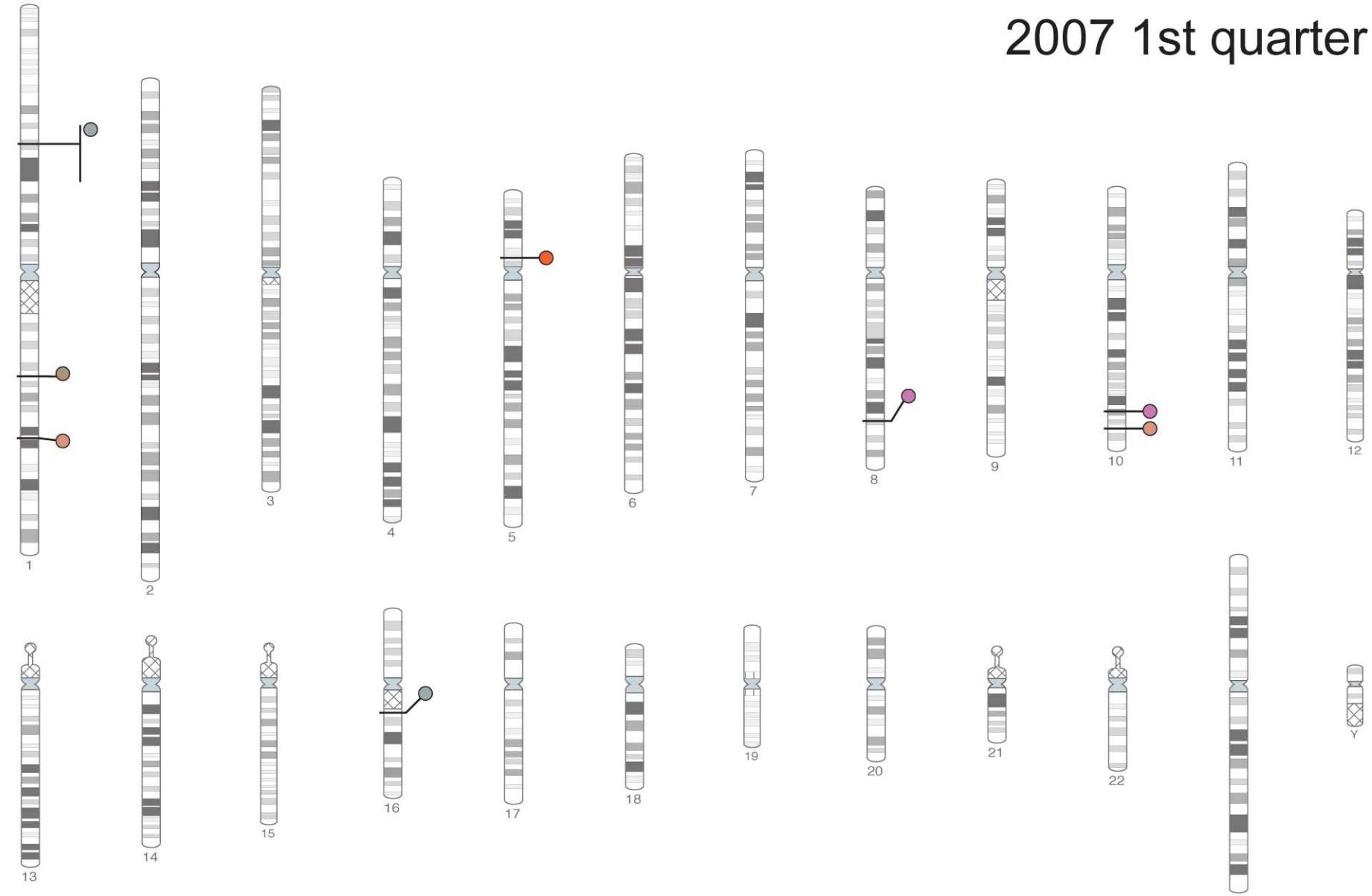
2007 1st quarter



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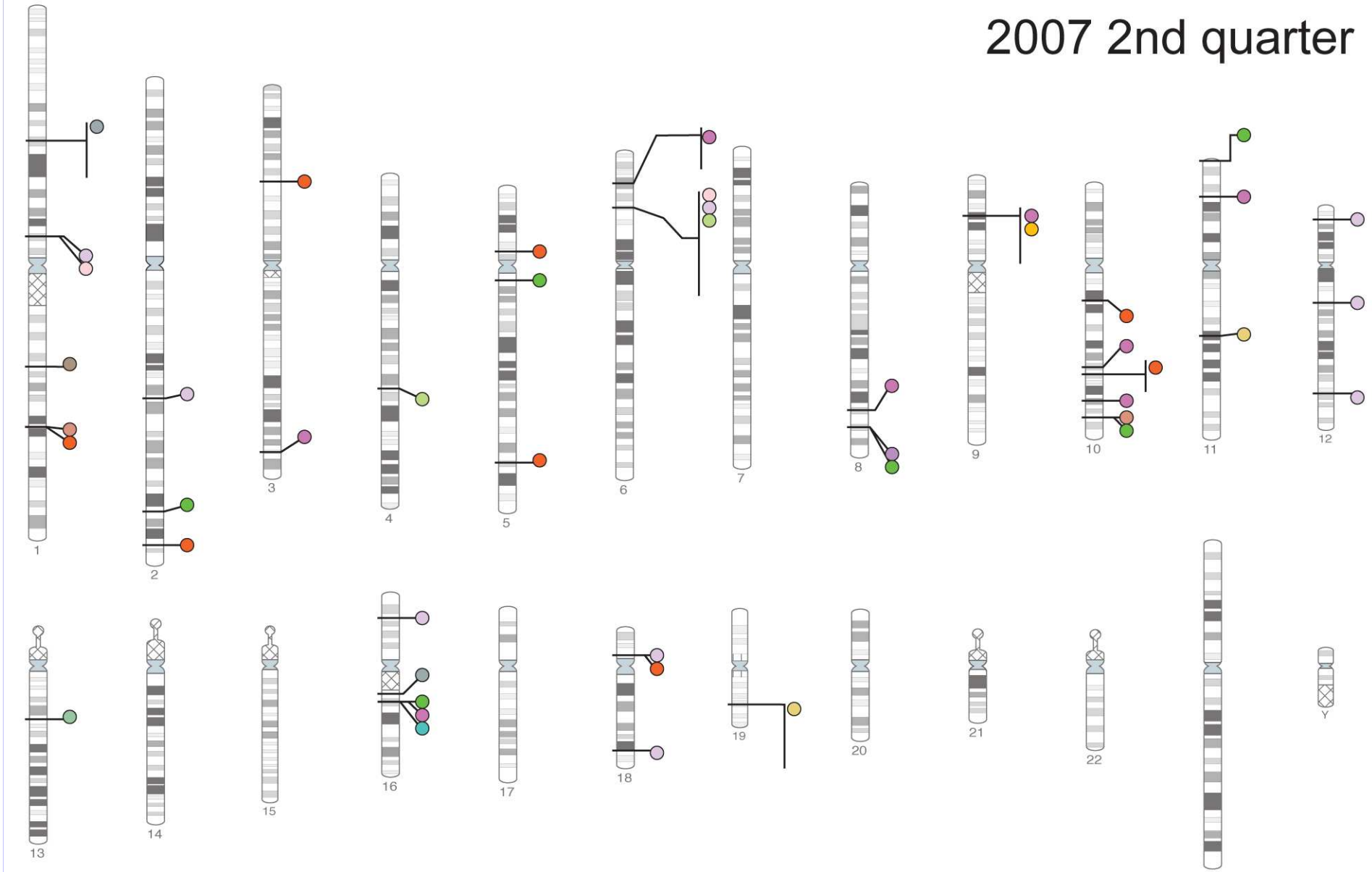
2007 2nd quarter



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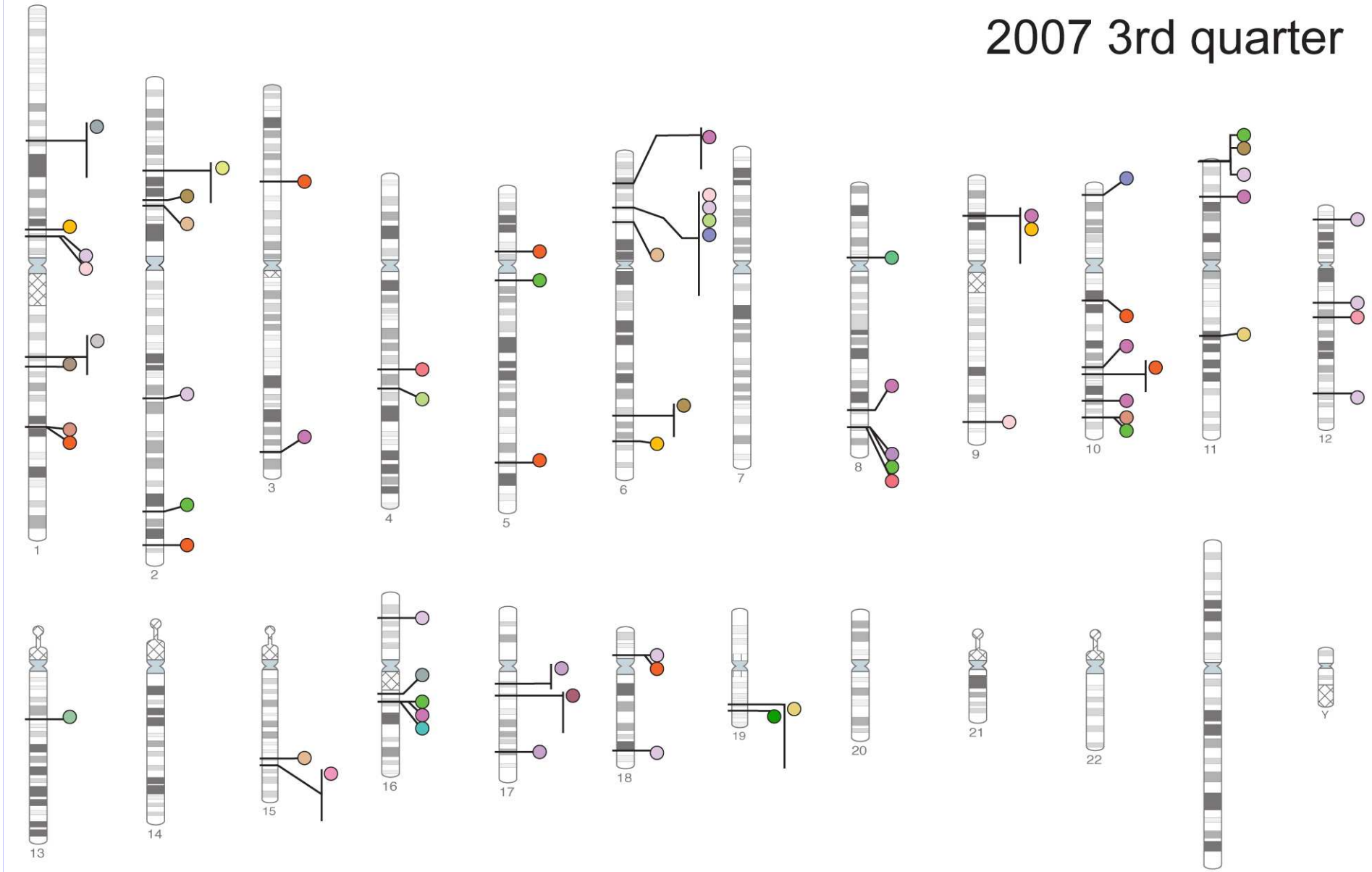
2007 3rd quarter



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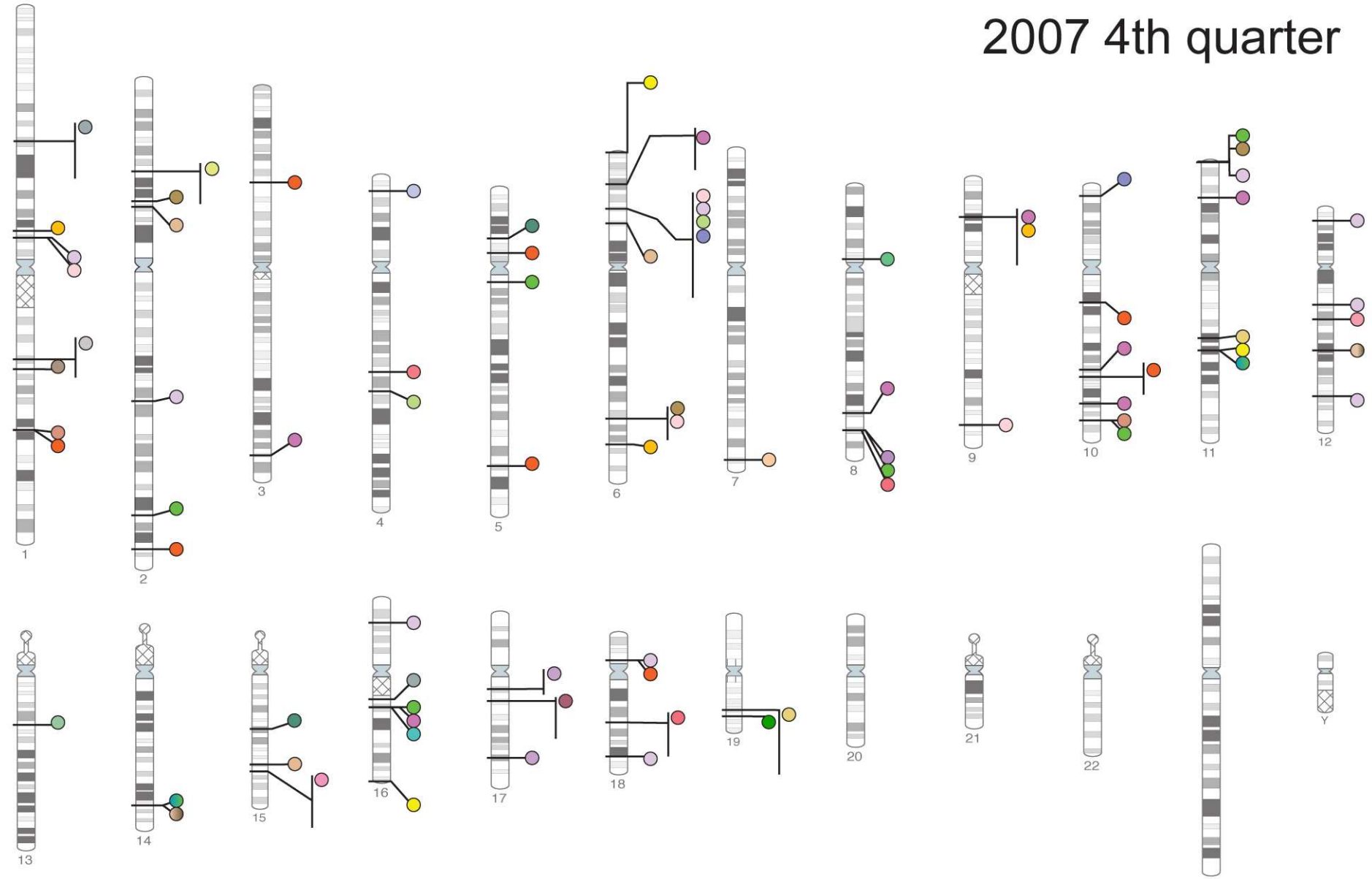
2007 4th quarter



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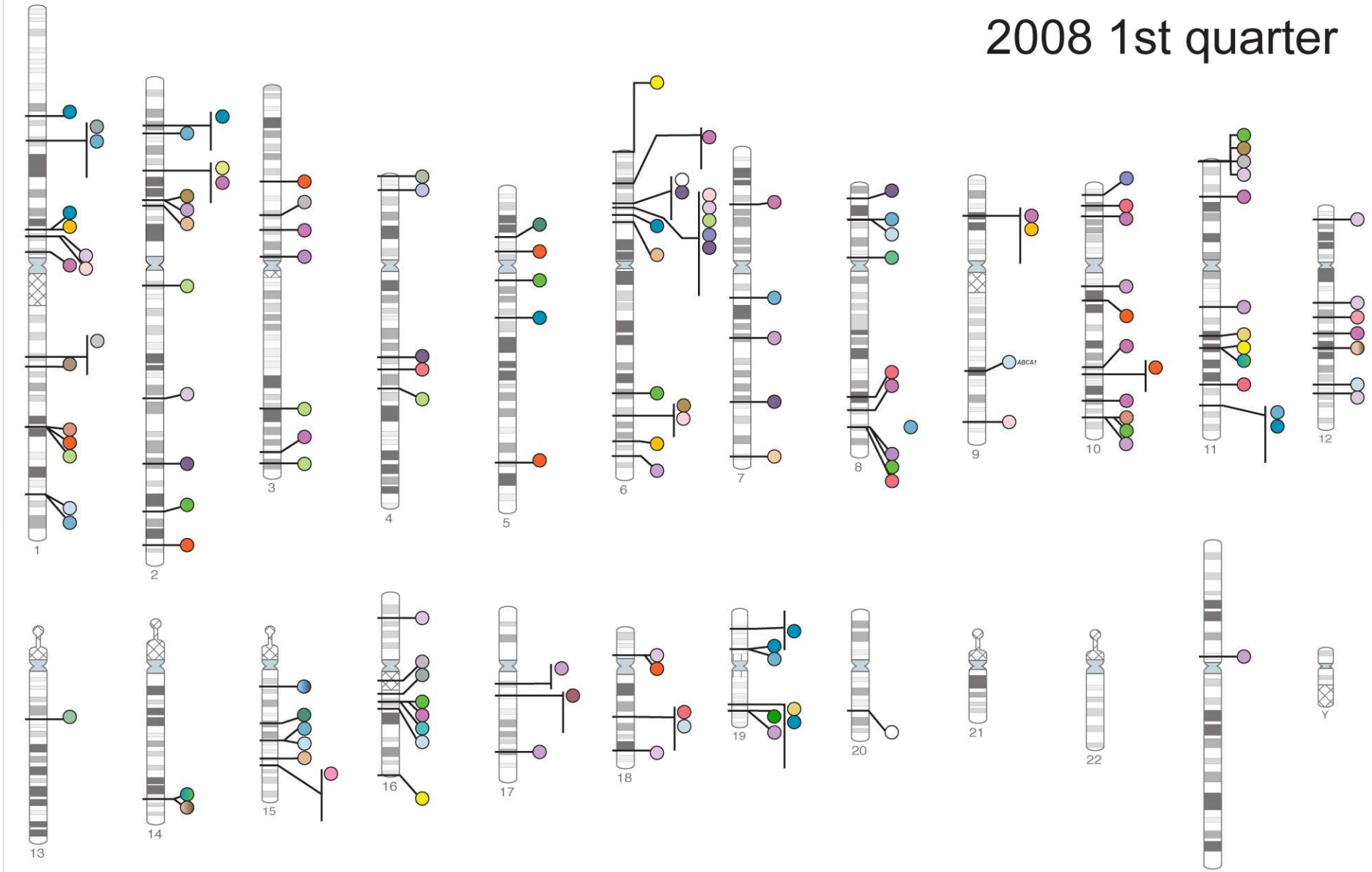
2008 1st quarter



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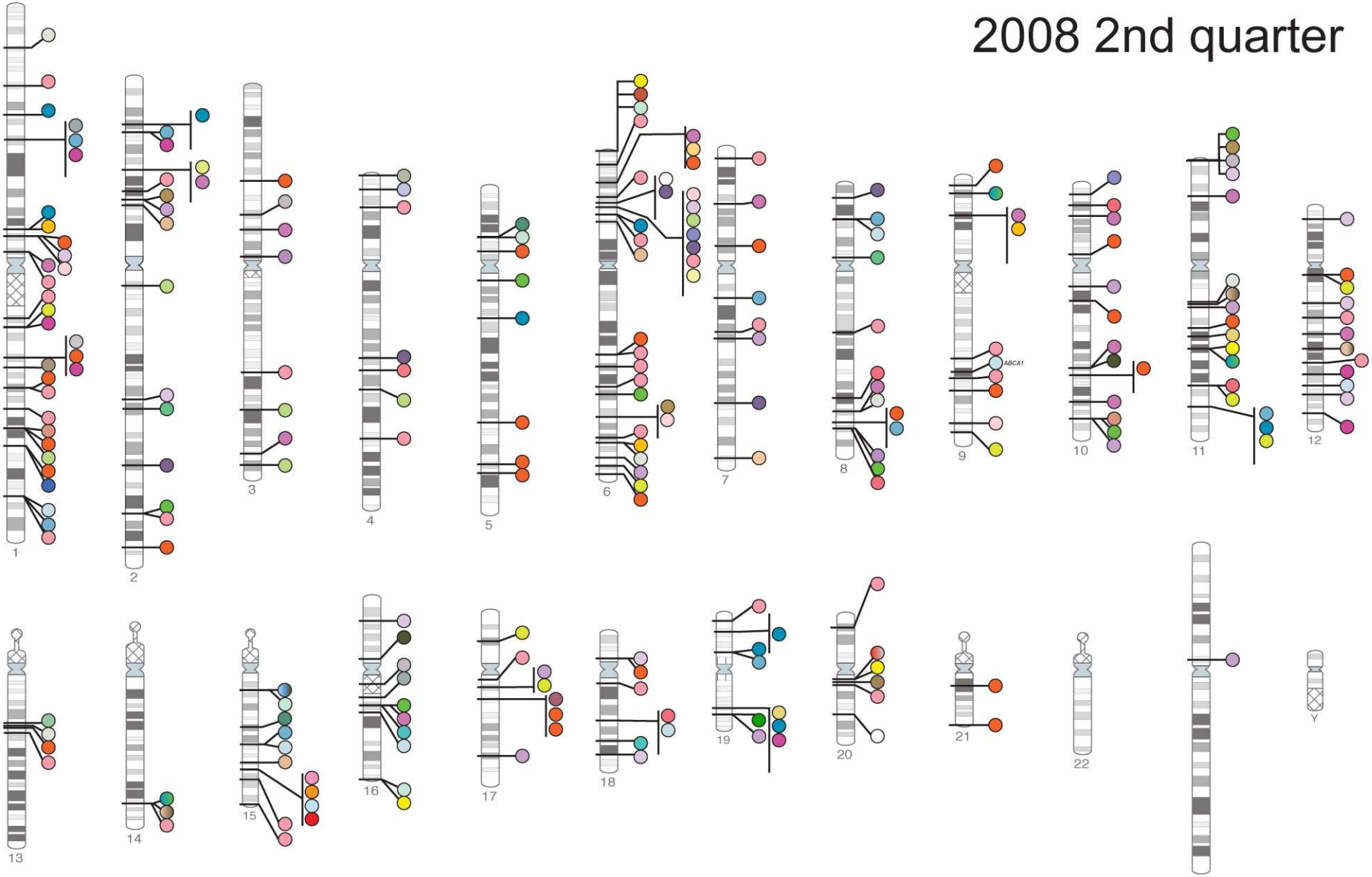
2008 2nd quarter



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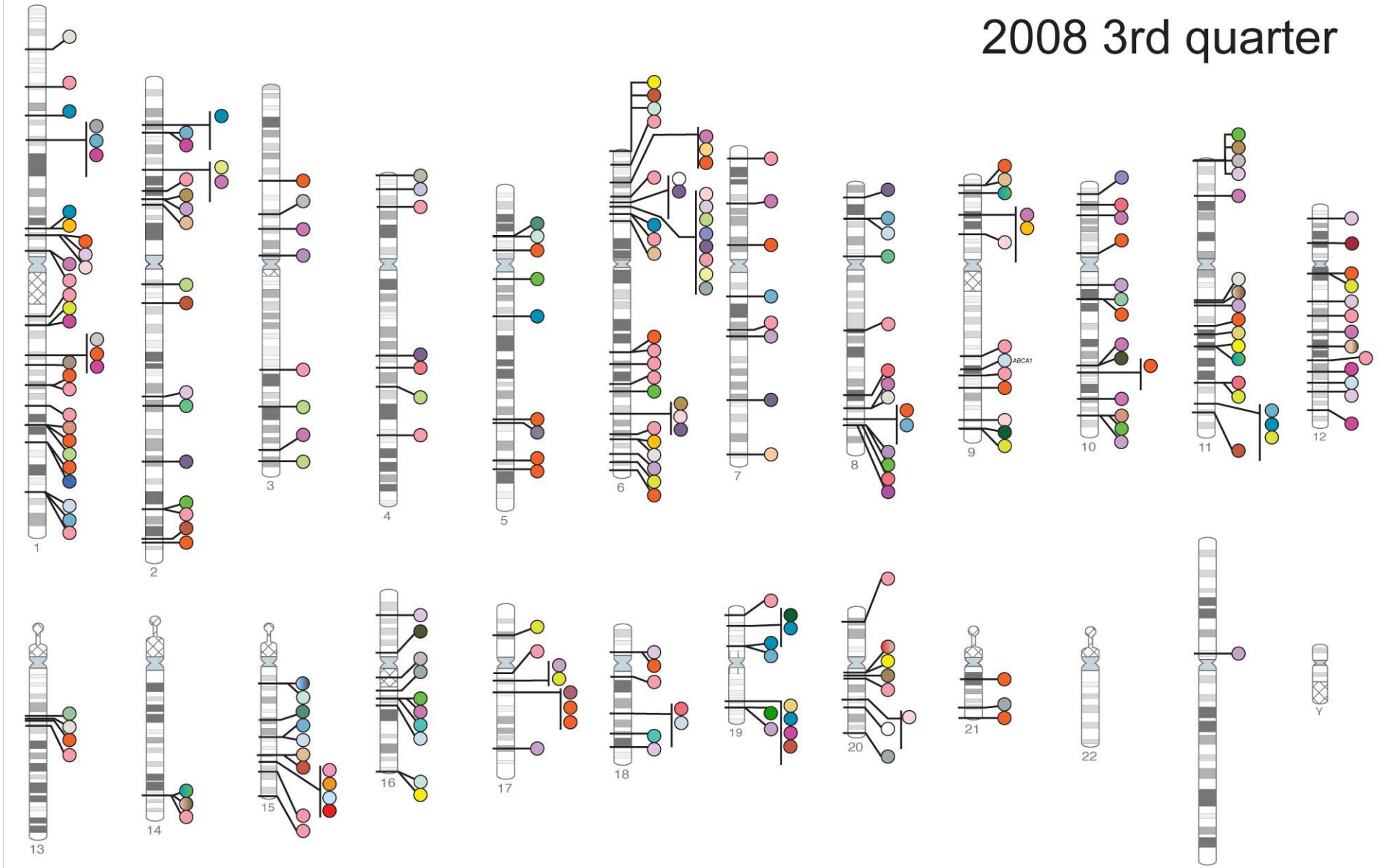
2008 3rd quarter



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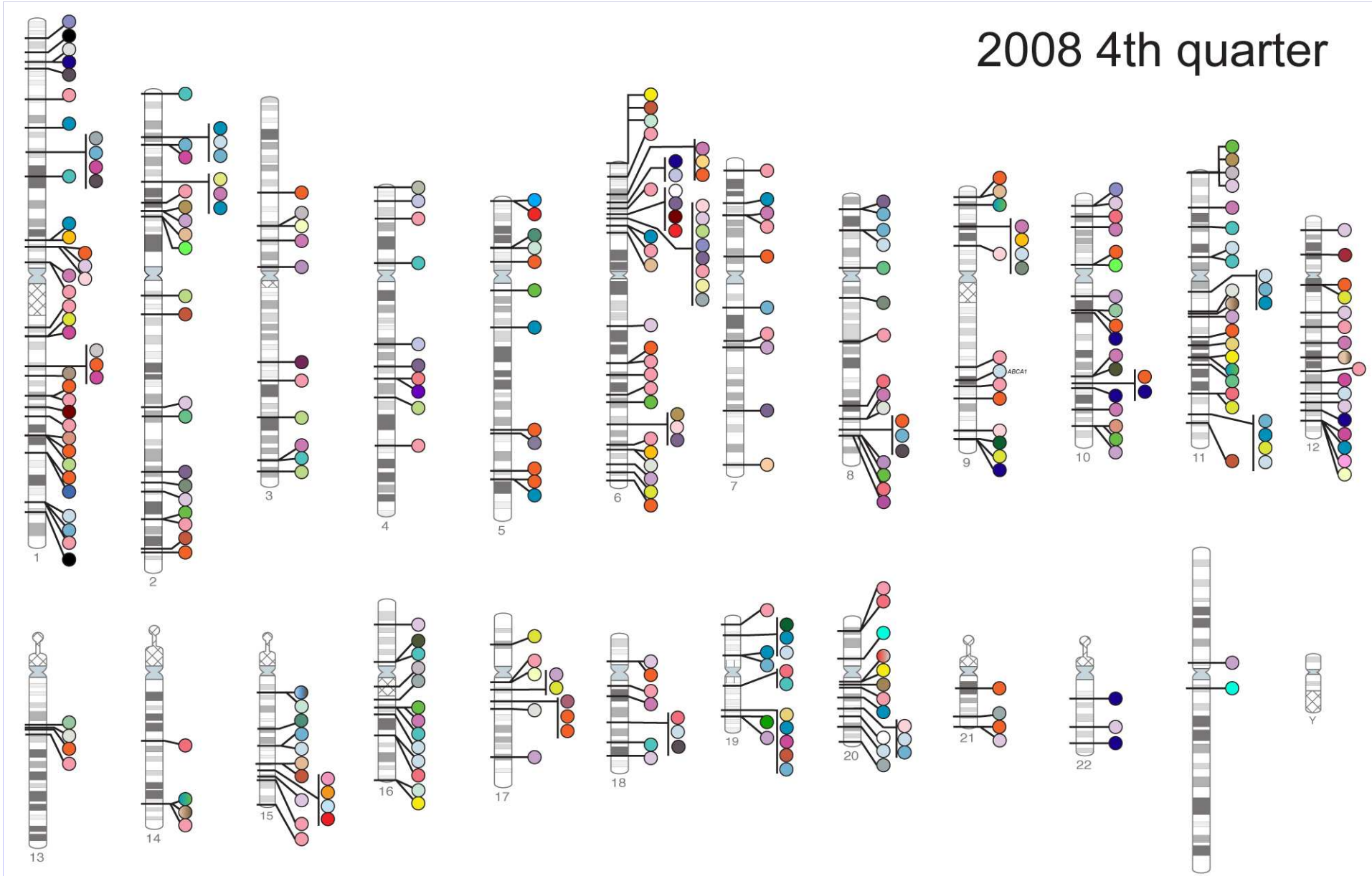
- Skin pigmentation by reflectance spectroscopy
- Soluable ICAM-1
- Statin-induced myopathy
- Systemic lupus erythematosus
- Systemic lupus erythematosus in women
- Total cholesterol
- Triglycerides
- Type 1 diabetes
- Type 2 diabetes
- Vitamin B12 levels
- Warfarin dose
- Weight
- YKL-40 levels

2008 4th quarter



- Age-related macular degeneration
- Alzheimer disease APOE*e4 carriers
- Amyotrophic lateral sclerosis
- Asthma
- Atrial fibrillation
- Basal cell cancer
- Bipolar disorder
- Bladder cancer
- Blond or brown hair
- Blue or green eyes
- BMI, waist circumference
- Bone density
- Breast cancer
- C-reactive protein
- Celiac disease
- Chronic lymphocytic leukemia
- Colorectal cancer
- Coronary disease
- Crohn's disease
- Exfoliation glaucoma
- F cell distribution
- Fasting glucose
- Freckles and burning
- Gallstones
- Hair color
- Height
- HDL cholesterol
- Idiopathic pulmonary fibrosis
- Inflammatory bowel disease
- Intracranial aneurysm
- Iris color
- Ischemic stroke
- Juvenile idiopathic arthritis
- LDL cholesterol
- Liver enzymes
- Lung cancer
- Male pattern baldness
- MCP-1
- Mean platelet volume
- Melanoma
- Multiple sclerosis
- Neuroblastoma
- Nictotine dependance
- Obesity
- Other metabolic traits
- Peripheral arterial disease
- Prostate cancer
- Protein levels
- QT interval prolongation
- Psoriasis
- Recombination rate
- Red vs.non-red hair
- Restless legs syndrome
- Rheumatoid athritis
- Serum IgE levels
- Serum markers of Iron status
- Serum metabolites
- Serum urate
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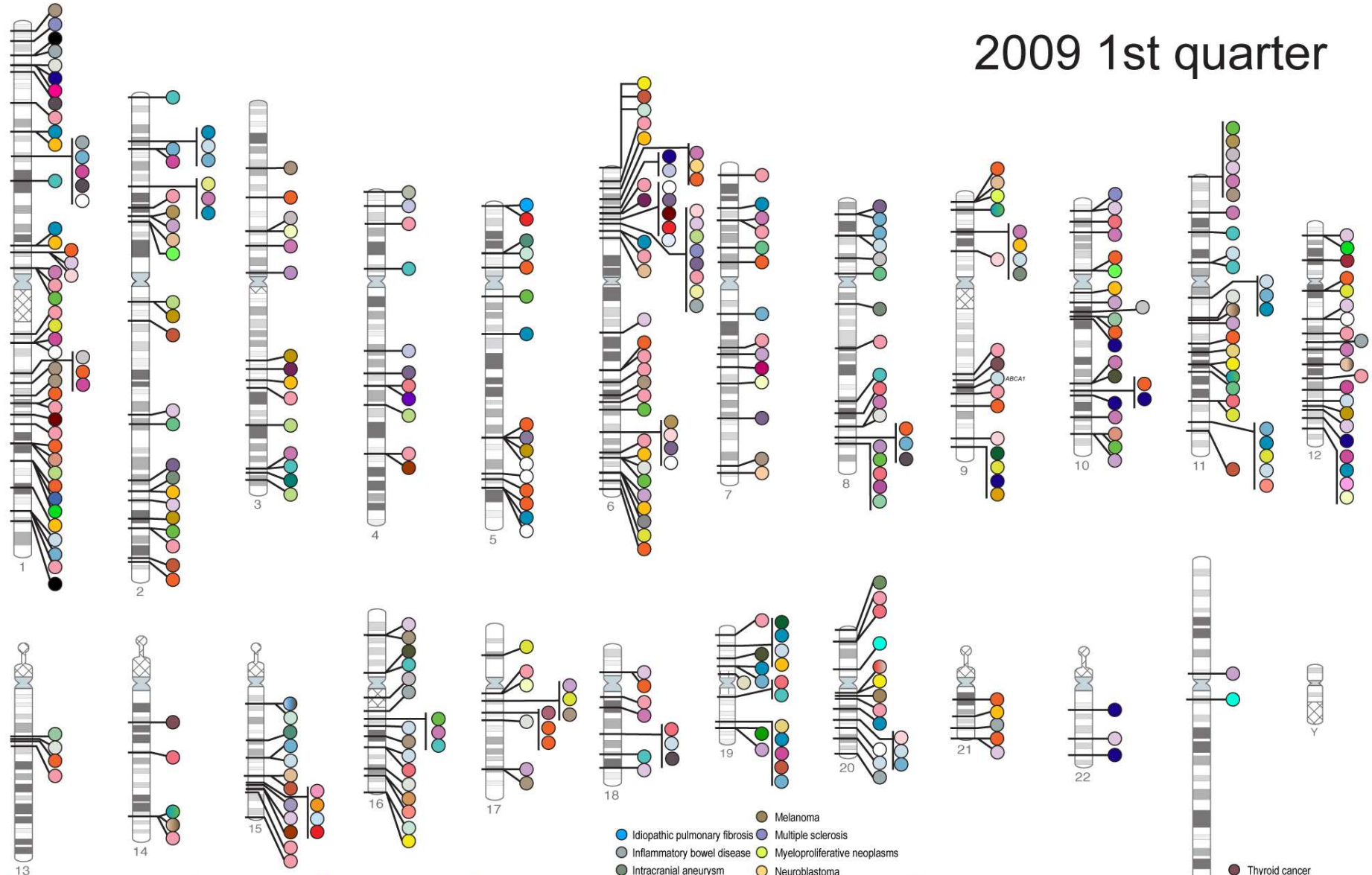
- Total cholesterol
- Triglycerides
- Type 1 diabetes
- Type 2 diabetes
- Vitamin B12 levels
- Warfarin dose
- Weight
- YKL-40 levels

2009 1st quarter



- Adiponectin levels
- Age-related macular degeneration
- AIDS progression
- Alzheimer disease APOE*e4 carriers
- Amyotrophic lateral sclerosis
- Asthma
- Atrial fibrillation
- Basal cell cancer
- Bipolar disorder
- Bladder cancer
- Blond or brown hair
- Blue or green eyes
- BMI, waist circumference
- Bone density
- Breast cancer
- C-reactive protein
- Carotenoid/tocopherol levels
- Celiac disease
- Chronic lymphocytic leukemia
- Cleft lip/palate
- Colorectal cancer
- Coronary disease
- Creutzfeldt-Jakob disease
- Crohn's disease
- Eosinophil count
- Essential tremor
- Exfoliation glaucoma
- F cell distribution
- Fasting glucose
- Folate pathway vitamins
- Freckles and burning
- Gallstones
- Hair color
- Height
- Hirschsprung's disease
- HDL cholesterol
- Idiopathic pulmonary fibrosis
- Inflammatory bowel disease
- Intracranial aneurysm
- Iris color
- Ischemic stroke
- Juvenile idiopathic arthritis
- LDL cholesterol
- Liver enzymes
- Lung cancer
- Male pattern baldness
- MCP-1
- Mean platelet volume
- Melanoma
- Multiple sclerosis
- Myeloproliferative neoplasms
- Neuroblastoma
- Nicotine dependence
- Obesity
- Otosclerosis
- Other metabolic traits
- Pain
- Panic disorder
- Peripheral arterial disease
- Plasma LP (a) levels
- Prostate cancer
- Protein levels
- Pulmonary funct./COPD
- QT interval prolongation
- Psoriasis
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- Red vs. non-red hair
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- Systemic lupus erythematosus in women
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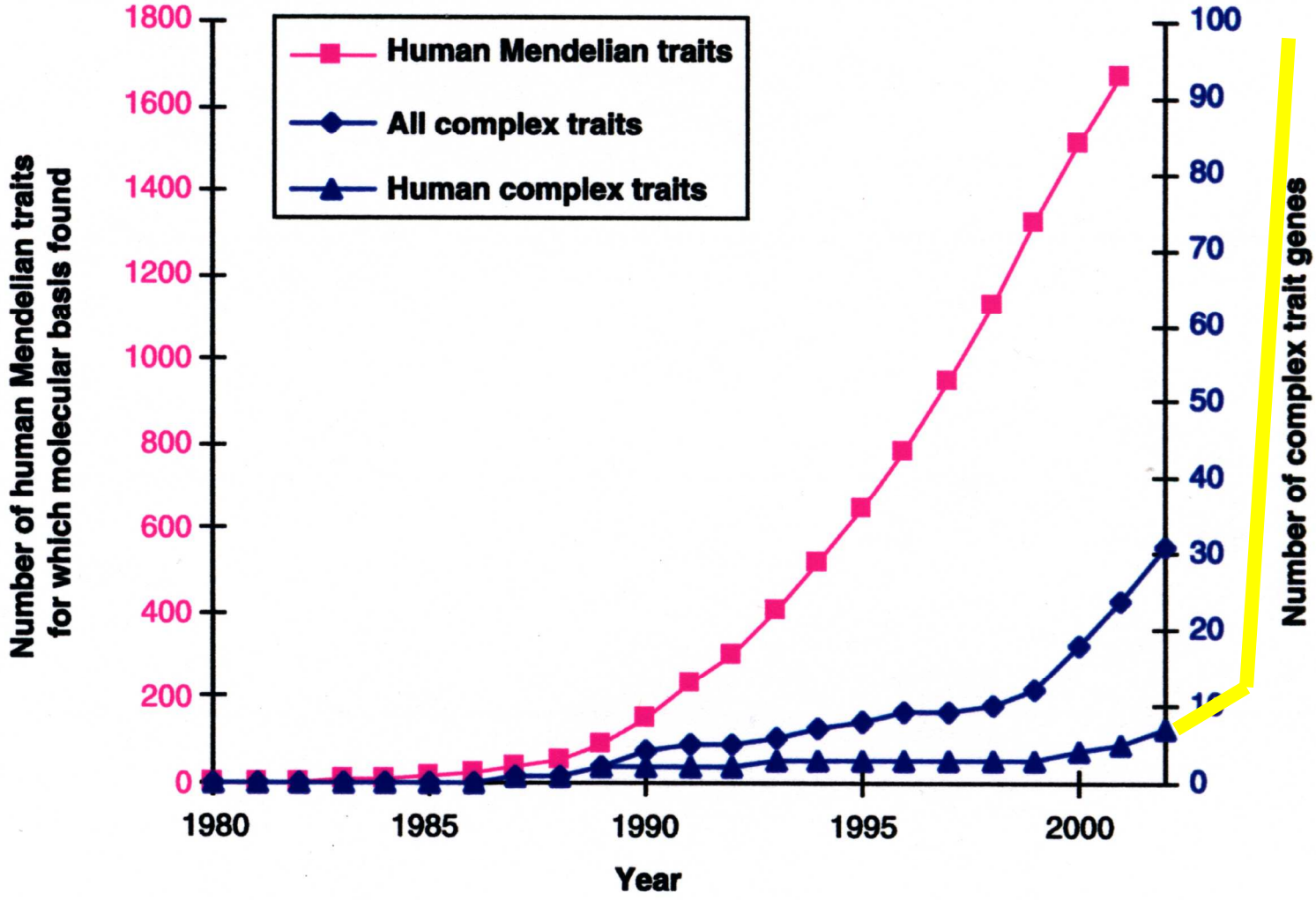
- Total cholesterol
- Triglycerides
- Type 1 diabetes
- Type 2 diabetes
- Venous thromboembolism
- Vitamin B12 levels
- Warfarin dose
- Weight
- YKL-40 levels



Glazier et al., Science 298:2345-9, 2002

A Note

- Validated and replicated GWAS are a powerful source of information about genetic predisposition to disease
- However, they are even more powerful as a source of understanding about the basic biology of disease

Where Are We Headed?

GWAS Studies Are Great, But…

- So far, they do not explain most of heritability..
- Which means they are, at least so far, only a weak forecaster of individual genetic risk for disease

Where Is the Rest of Heritability?

- Common variants with smaller effect sizes?
- Rare variants, some with quite large effect sizes?
- Copy number variants?
- Epigenetics?
- Other?
- And, could we have overestimated heritability a bit?

Anything Else Going on in Genomics?

- A small sampling…

The 1000 Genomes Project

- Goal is to catalog human variants present at ≥1% (or, within genes, ≥0.5%) frequency.
- Will include not only SNPs, but also rearrangements, deletions, and duplications.
- In its production phase, will produce ~8.2 billion bases/day (> two genomes/day).
- Samples from HapMap and extended HapMap set: Yoruba, Japanese, Chinese (Beijing and Denver), Maasai, Toscani, Gujarata Indian, CEPH, Mexican ancestry (L.A.), African ancestry (SW U.S.)

Encyclopedia of DNA Elements (ENCODE) Project

Vol 447|14 June 2007|doi:10.1038/nature05874 nature

ARTICLES

Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project

The ENCODE Project Consortium*

We report the generation and analysis of functional data from multiple, diverse experiments performed on a targeted 1% of the human genome as part of the pilot phase of the ENCODE Project. These data have been further integrated and augmented by a number of evolutionary and computational analyses. Together, our results advance the collective knowledge about human genome function in several major areas. First, our studies provide convincing evidence that the genome is pervasively transcribed, such that the majority of its bases can be found in primary transcripts, including non-protein-coding transcripts, and those that extensively overlap one another. Second, systematic examination of transcriptional regulation has yielded new understanding about transcription start sites, including their relationship to specific regulatory sequences and features of chromatin accessibility and histone modification. Third, a more sophisticated view of chromatin structure has emerged, including its inter-relationship with DNA replication and transcriptional regulation. Finally, integration of these new sources of information, in particular with respect to mammalian evolution based on inter- and intra-species sequence comparisons, has yielded new mechanistic and evolutionary insights concerning the functional landscape of the human genome. Together, these studies are defining a path for pursuit of a more comprehensive characterization of human genome function.

A Fun Fact: How Many Human Genes Do All Current Drugs Target?

1) ~500 (2.5% of the genome)
2) ~1,000 (5%)
3) ~5,000 (25%)
4) ~10,000 (50%)
5) ~ 15,000 (75%)
6) ~20,000 (100%)

A Fun Fact: How Many Human Genes Do All Current Drugs Target?

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Chemical Genomics

- Offers academic researchers access to small organic molecules for use as chemical probes to study cellular pathways in greater depth
- Will help validate new targets for drug therapy more rapidly, and enable researchers in the public and private sectors to take these targets and compounds and move them into the drug-development pipeline

Chemical Genomics Works…

April 2008
Nature Medicine

nm1737.pdf - Adobe Acrobat Professional

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nature medicine

Identification of oxadiazoles as new drug leads for the control of schistosomiasis

Ahmed A Sayed[1], Anton Simeonov[2], Craig J Thomas[2], James Inglese[2], Christopher P Austin[2] & David L Williams[1]

Treatment for schistosomiasis, which is responsible for more than 280,000 deaths annually, depends almost exclusively on praziquantel. Millions of people are treated annually with praziquantel, and drug-resistant parasites thus are likely to evolve. Phosphinic amides and oxadiazole 2-oxides, identified from a quantitative high-throughput screen, were shown to inhibit a parasite enzyme, thioredoxin glutathione reductase (TGR), with activities in the low micromolar to low nanomolar range. Incubation of parasites with these compounds led to rapid inhibition of TGR activity and parasite death. The activity of the oxadiazole 2-oxides was associated with a donation of nitric oxide. Treatment of schistosome-infected mice with 4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide led to marked reductions in worm burdens from treatments against multiple parasite stages and egg-associated pathologies. The compound was active against the three major schistosome species infecting humans. These protective effects exceed benchmark activity criteria set by the World Health Organization for lead compound development for schistosomiasis.

Schistosomiasis is a chronic disease caused by trematode flatworms of the genus *Schistosoma*. The disease remains a major, neglected, poverty-related health problem in many tropical areas[1]. The health burden resulting from schistosomiasis is estimated to include more

single drug for the treatment of schistosomiasis is not sustainable, and thus there is an urgent need to identify new targets and drugs for schistosomiasis treatment.

Schistosome parasites have a complex life cycle involving snail

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The Cancer Genome Atlas

doi:10.1038/nature07385

nature

ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Human cancer cells typically harbour multiple chromosomal aberrations, nucleotide substitutions and epigenetic modifications that drive malignant transformation. The Cancer Genome Atlas (TCGA) pilot project aims to assess the value of large-scale multi-dimensional analysis of these molecular characteristics in human cancer and to provide the data rapidly to the research community. Here we report the interim integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas—the most common type of primary adult brain cancer—and nucleotide sequence aberrations in 91 of the 206 glioblastomas. This analysis provides new insights into the roles of *ERBB2*, *NF1* and *TP53*, uncovers frequent mutations of the phosphatidylinositol-3-OH kinase regulatory subunit gene *PIK3R1*, and provides a network view of the pathways altered in the development of glioblastoma. Furthermore, integration of mutation, DNA methylation and clinical treatment data reveals a link between *MGMT* promoter methylation and a hypermutator phenotype

Rector sacked in Austrian stem-cell scandal

A fierce academic dispute in Austria reached fresh heights on 21 August when the Medical University of Innsbruck's council dismissed the rector, German immunologist Clemens Sorg, without notice.

In a letter to friends and colleagues in Austria and Germany that was later leaked to the press, Sorg had criticized Austria's academic establishment for its laxness in a case of scientific misconduct at the university's urology department.

Earlier in August, a report by the Austrian Agency for Health and Food Safety found that a clinical trial involving stem cells, run by urologist Hannes Strasser at the university, had serious flaws (see *Nature* 454, 922–923; 2008). Last week the agency announced that it will hand the report over to public prosecutors.

But the seven-strong university council says that Sorg's "public attacks" against his host country were "unjustified". It accuses Sorg of a "serious breach of duties", including violating official secrecy. In a copy of his letter that appeared in the Austrian daily *Tiroler Tageszeitung*, Sorg writes that Austria's highest "networks" were attempting hush up what he calls a "medical scandal of unprecedented scale". Sorg says that he intends to sue the Medical University of Innsbruck.

Nuclear group to rule on

In the 34 years since its first test, India's nuclear programme has been limited by the nation's refusal to put its name to the nuclear non-proliferation treaty, which all members of the NSG have signed. India wants access to international nuclear trade without restrictions on the growth of its nuclear weapons programme.

A nuclear deal between India and the United States is poised for approval by the US Congress on the condition that the NSG agrees to India's request. Any of the NSG's 45 member countries can veto the application.

NIH promises funds for cheaper DNA sequencing

The US National Human Genome Research Institute (NHGRI) is ploughing more than $20 million into new genetic sequencing technologies.

A series of grants announced on 20 August are the latest step in the institute's drive to bring down the cost of sequencing. The money will support projects such as the development of nanopores. These structures could, it is hoped, identify DNA bases threaded through them from variations in the bases' ionic or electrical properties. The largest grants will go to Daniel Branton and Jene Golovchenko of Harvard University, who are developing this technology, and Mostafa Ronaghi of Illumina in San Diego.

Jeffrey Schloss, director of the NHGRI's technology-development [illegible] that the institute's goal of a $1,000 genome by 2014 "is still realistic".

The All India Institute of Medical Sciences is investigating child deaths in several drug trials.

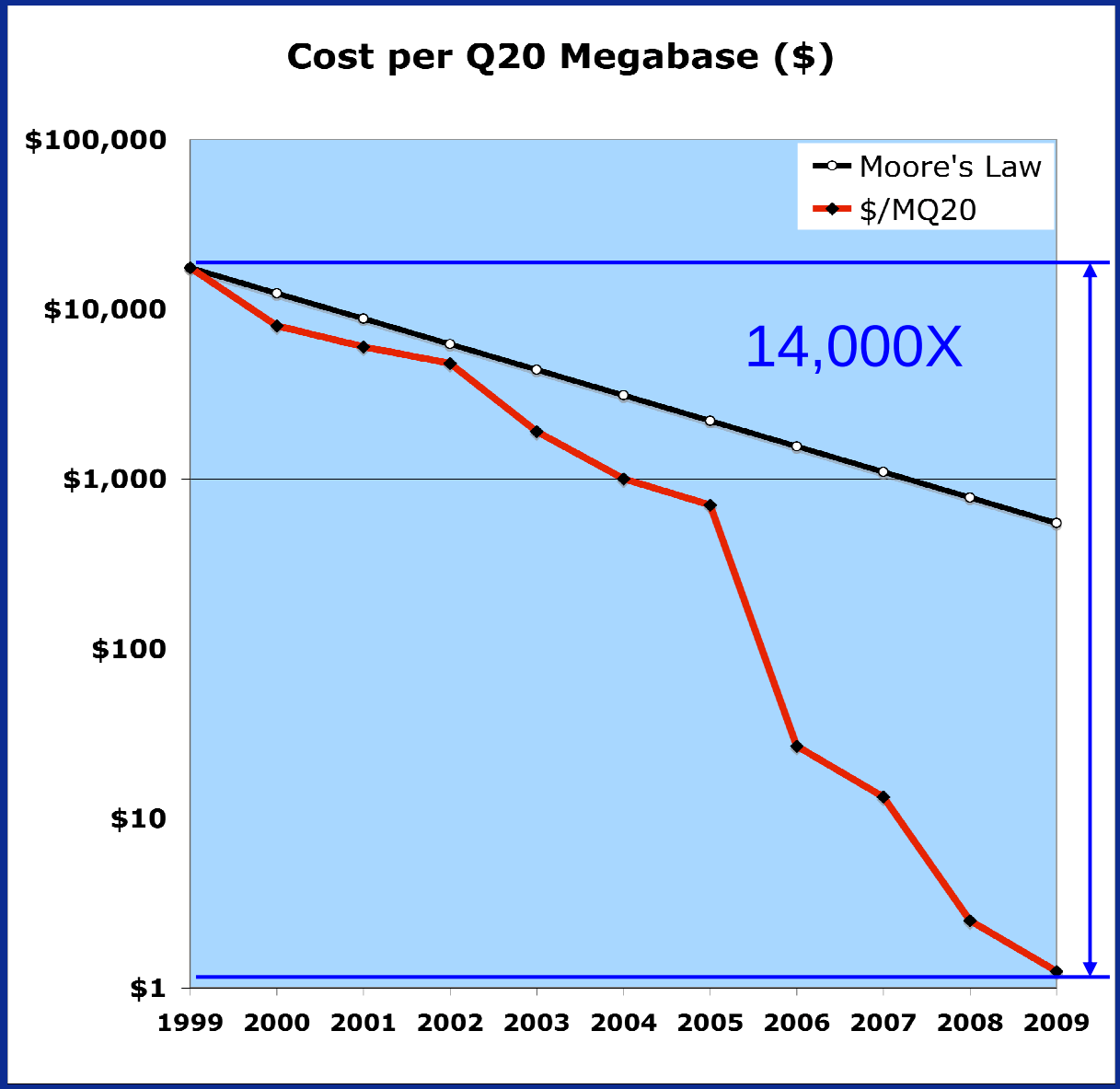
M. VATSYAYANA/AFP/GETTY IMAGES

age who have died in drug trials at the New Delhi institution since January 2006. But questions are being raised over whether the inquiry is necessary on scientific grounds.

The death rate in the 42 separate clinical trials was just over 1%. The trials involved a total of 4,142 young patients, 2,728 of whom were under a year old. Among the drugs being tested were the cancer drug rituximab, as well as olmesartan and valsartan, which lower blood pressure.

"The deaths were due to sickness only. All drugs used were of proven safety," Shakti Kumar Gupta, the head of hospital administration at AIIMS, told *Nature*. The

We Have Put Moore's Law to Shame



Graph Courtesy of Eric Lander

Where Are We Headed?