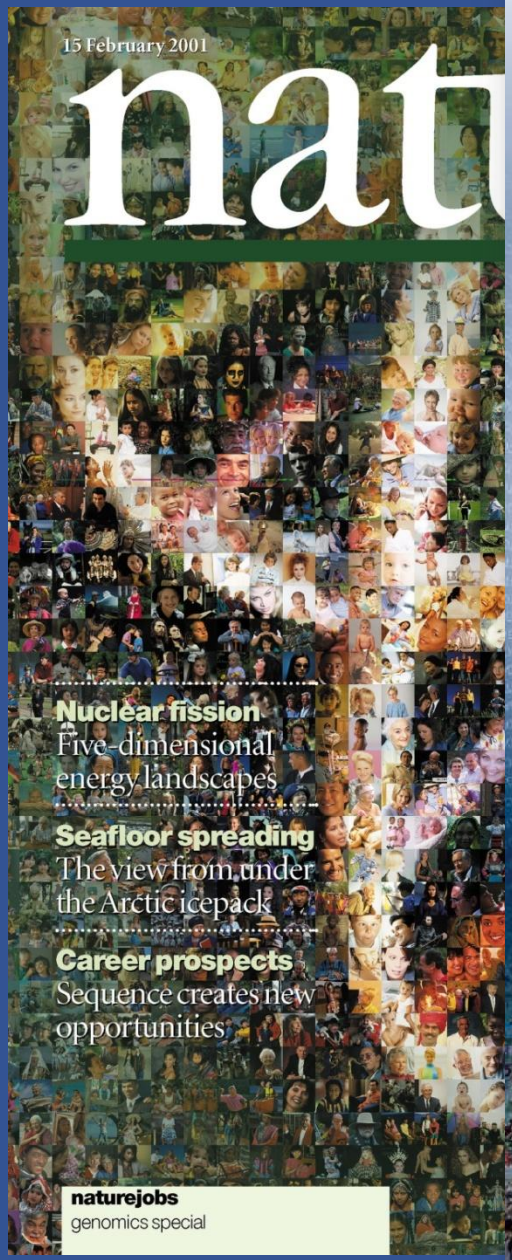
Anticipating the Next Decade of the Genome

Francis Collins, M.D., Ph.D., NIH Director

A Decade with the Human Genome Sequence:
Charting a Course for Genomic Medicine
February 11, 2011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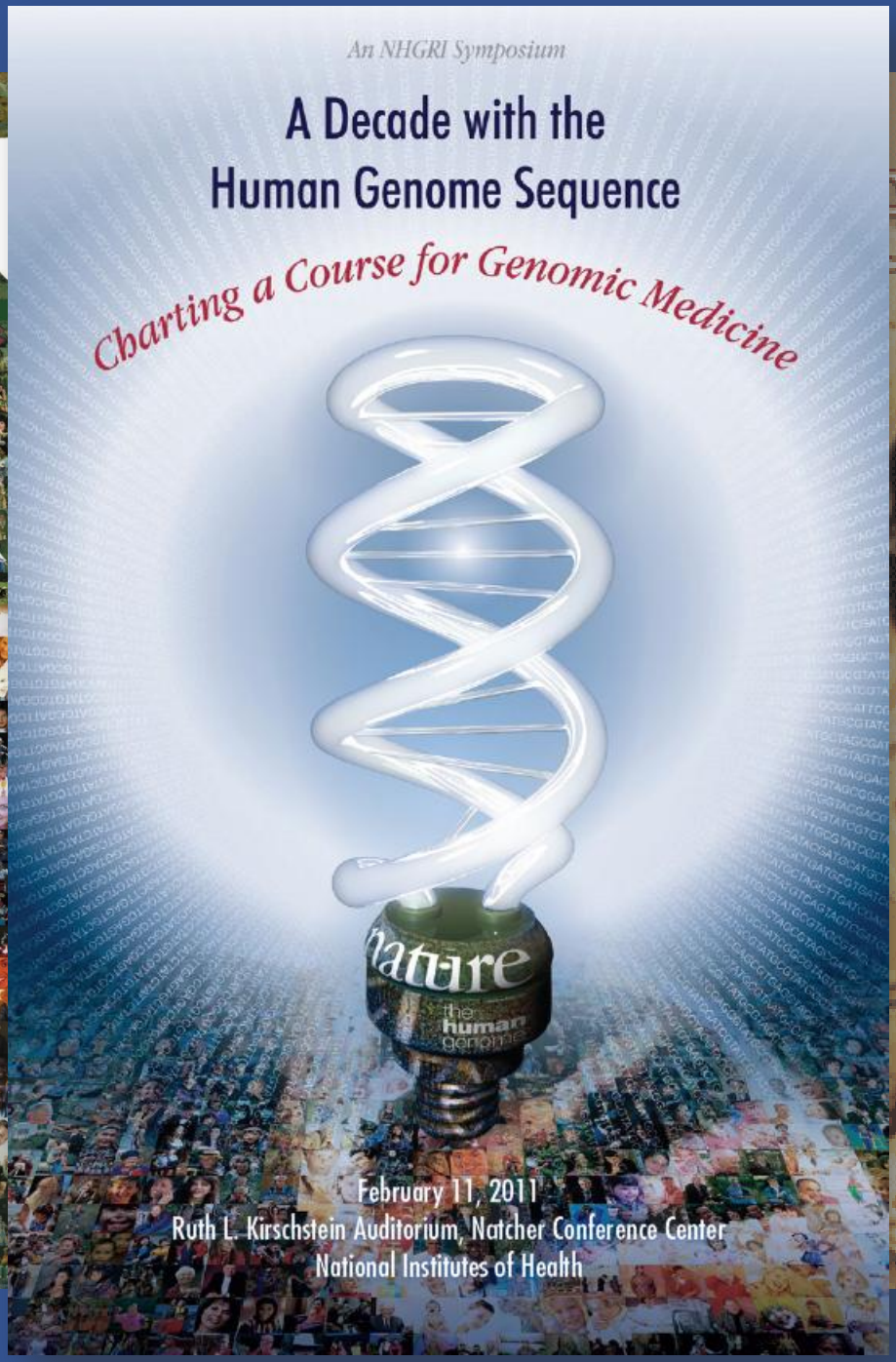
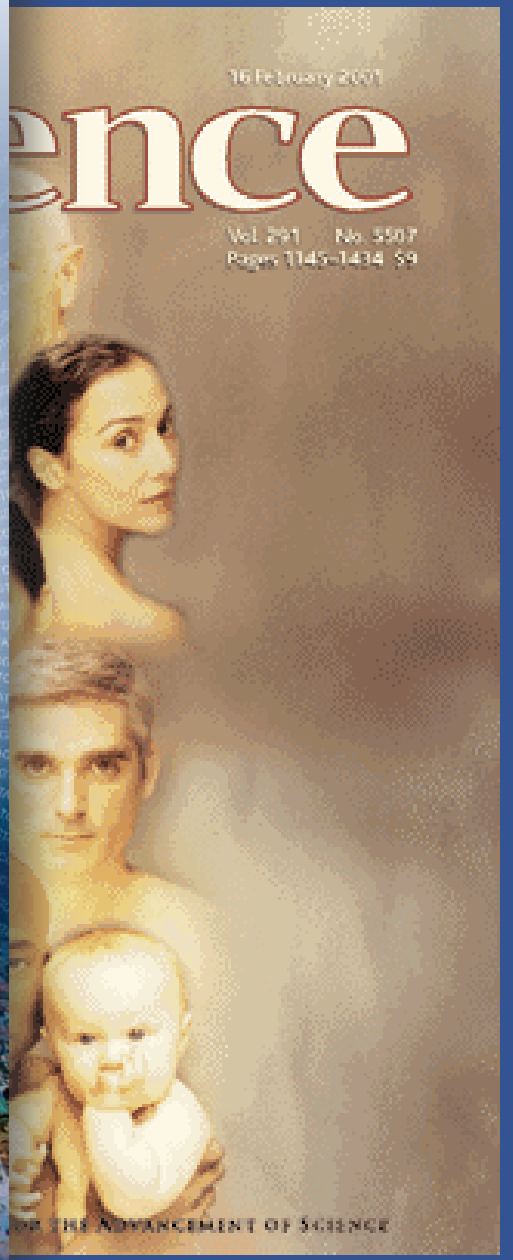
Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic icepack
Career prospects
Sequence creates new opportunities
naturejobs
genomics special


An NHGRI Symposium
A Decade with the Human Genome Sequence
Charting a Course for Genomic Medicine
nature
the human genome
February 11, 2011
Ruth L. Kirschstein Auditorium, Natcher Conference Center
National Institutes of Health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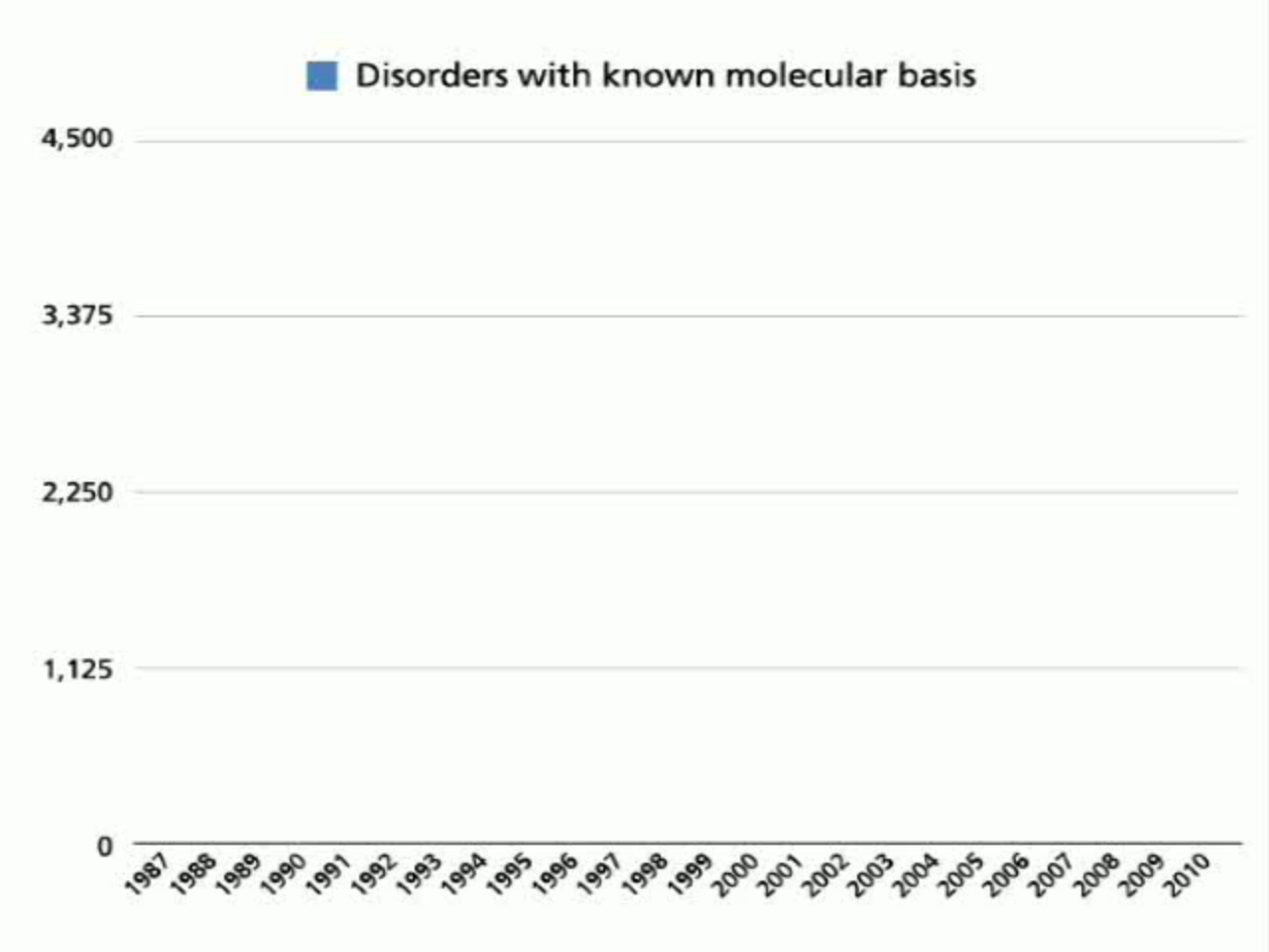
Pages 1143–1434 $9



Source: Online Mendelian Inheritance in Man

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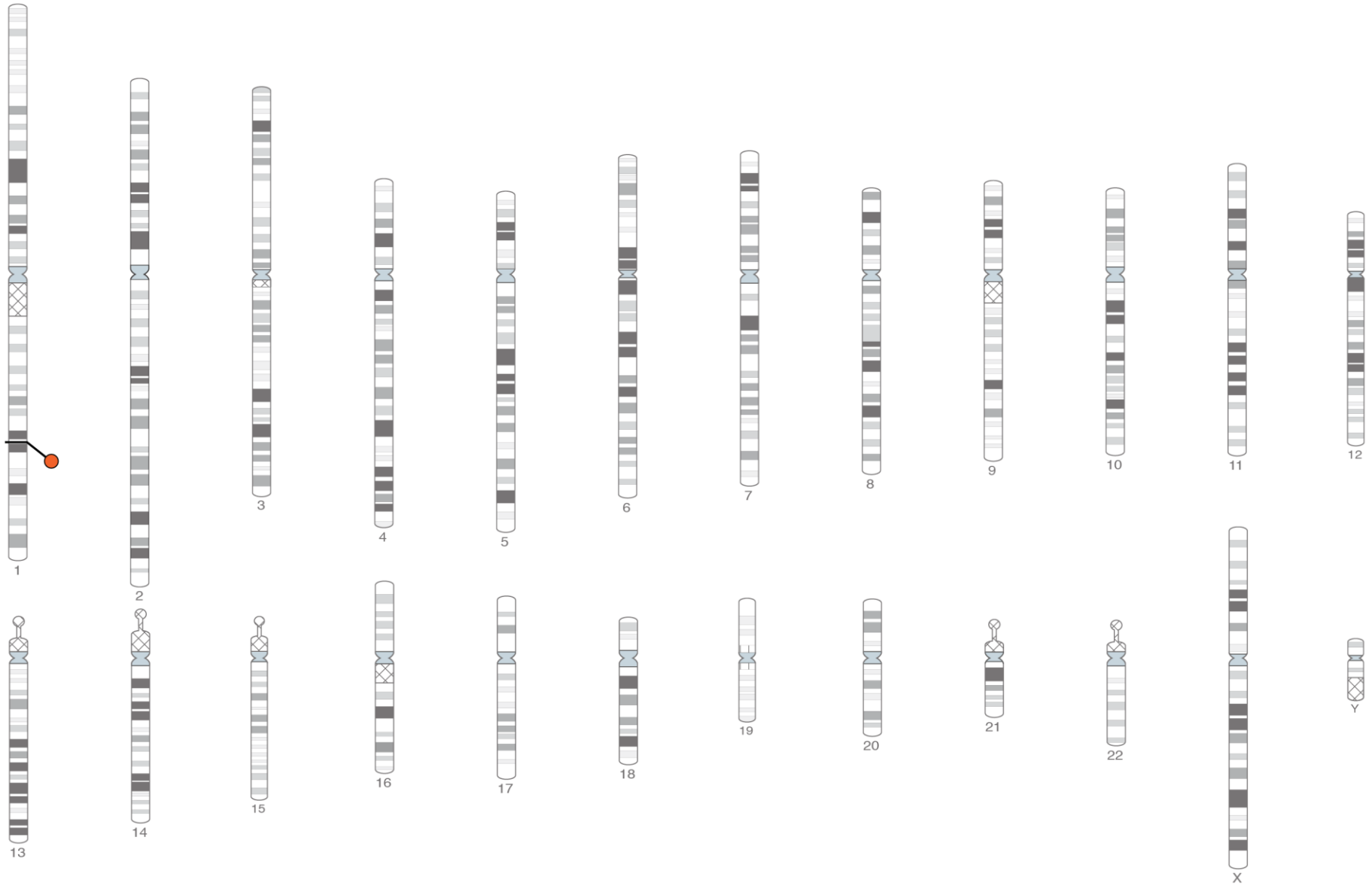

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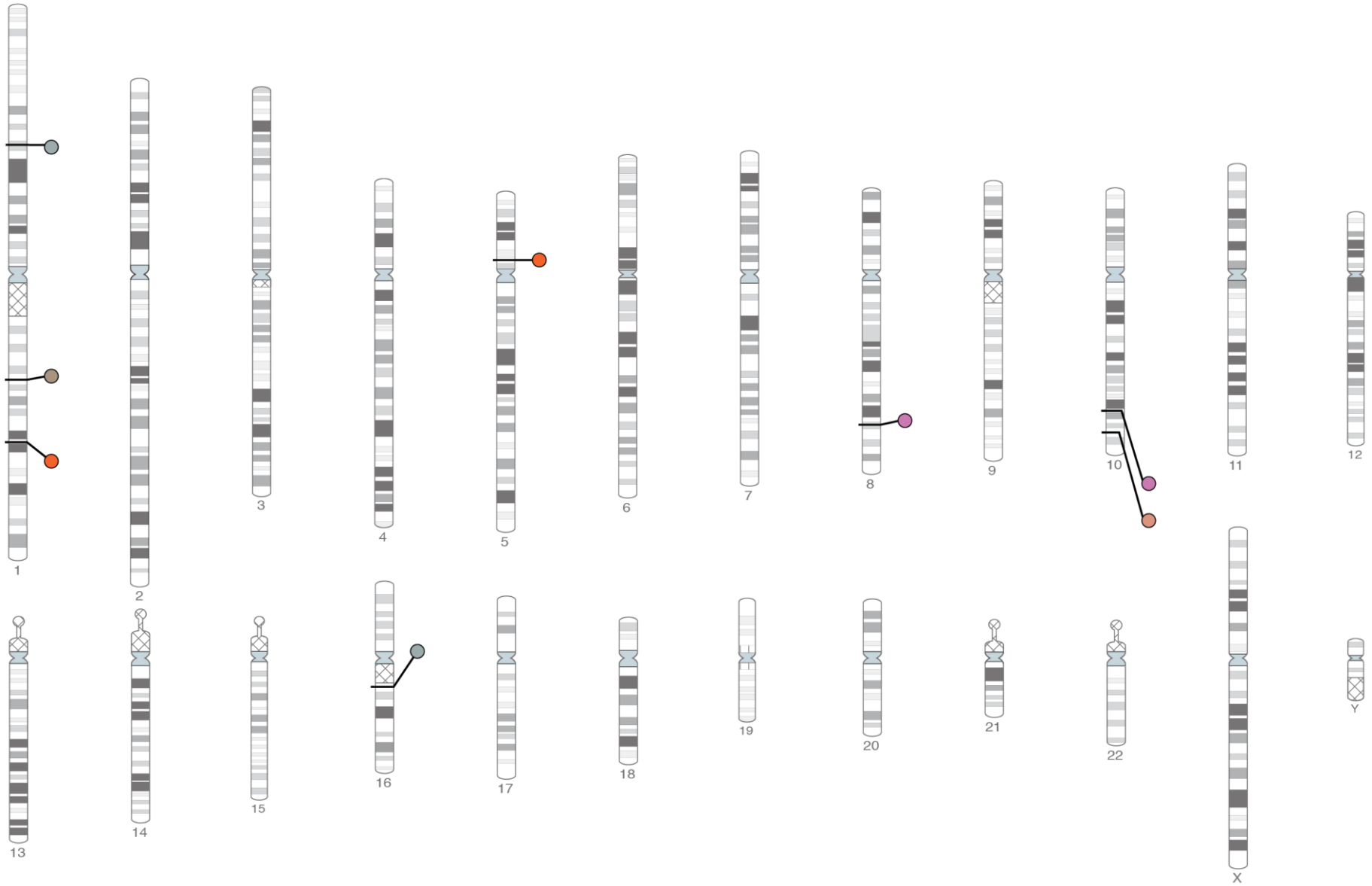

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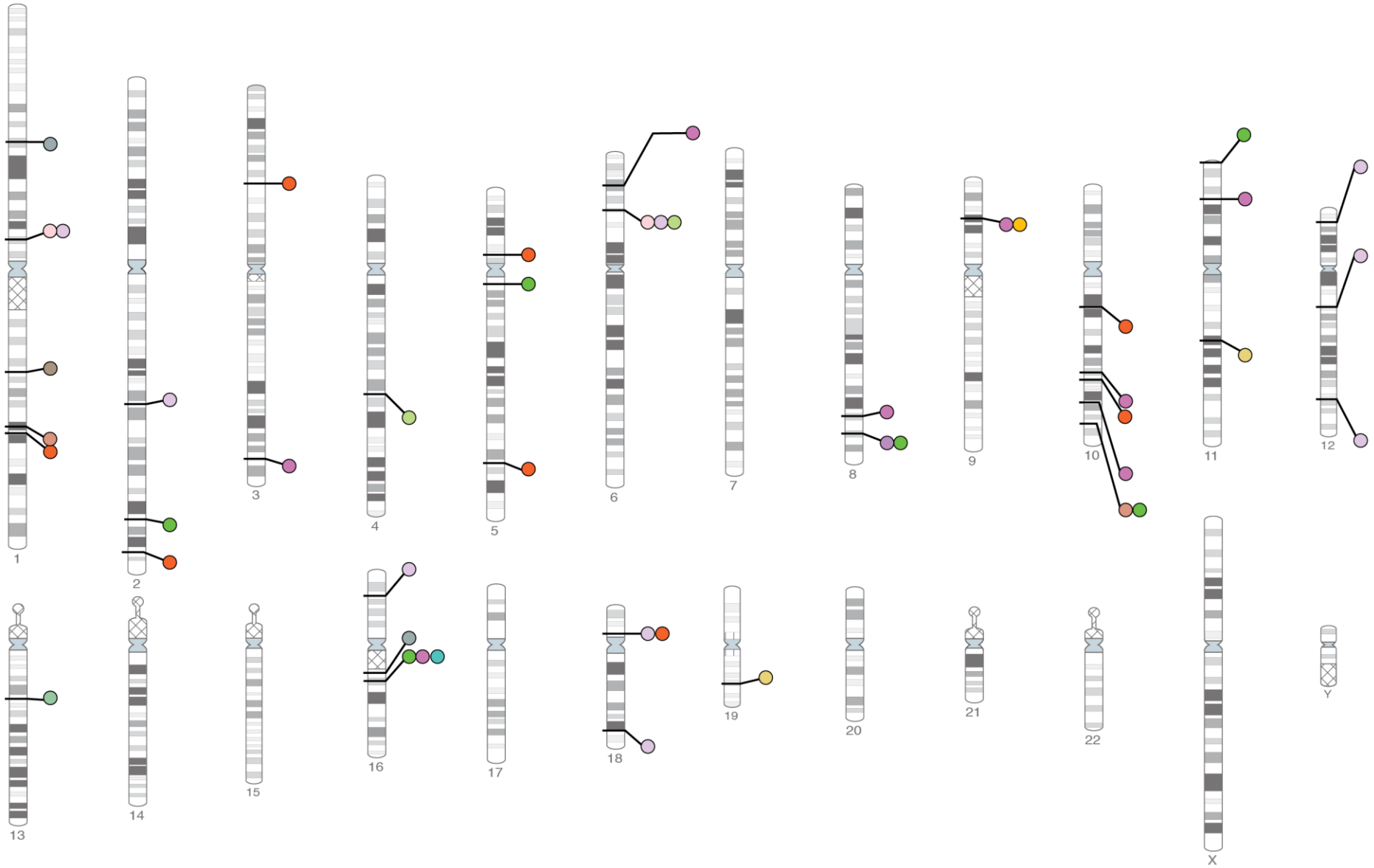

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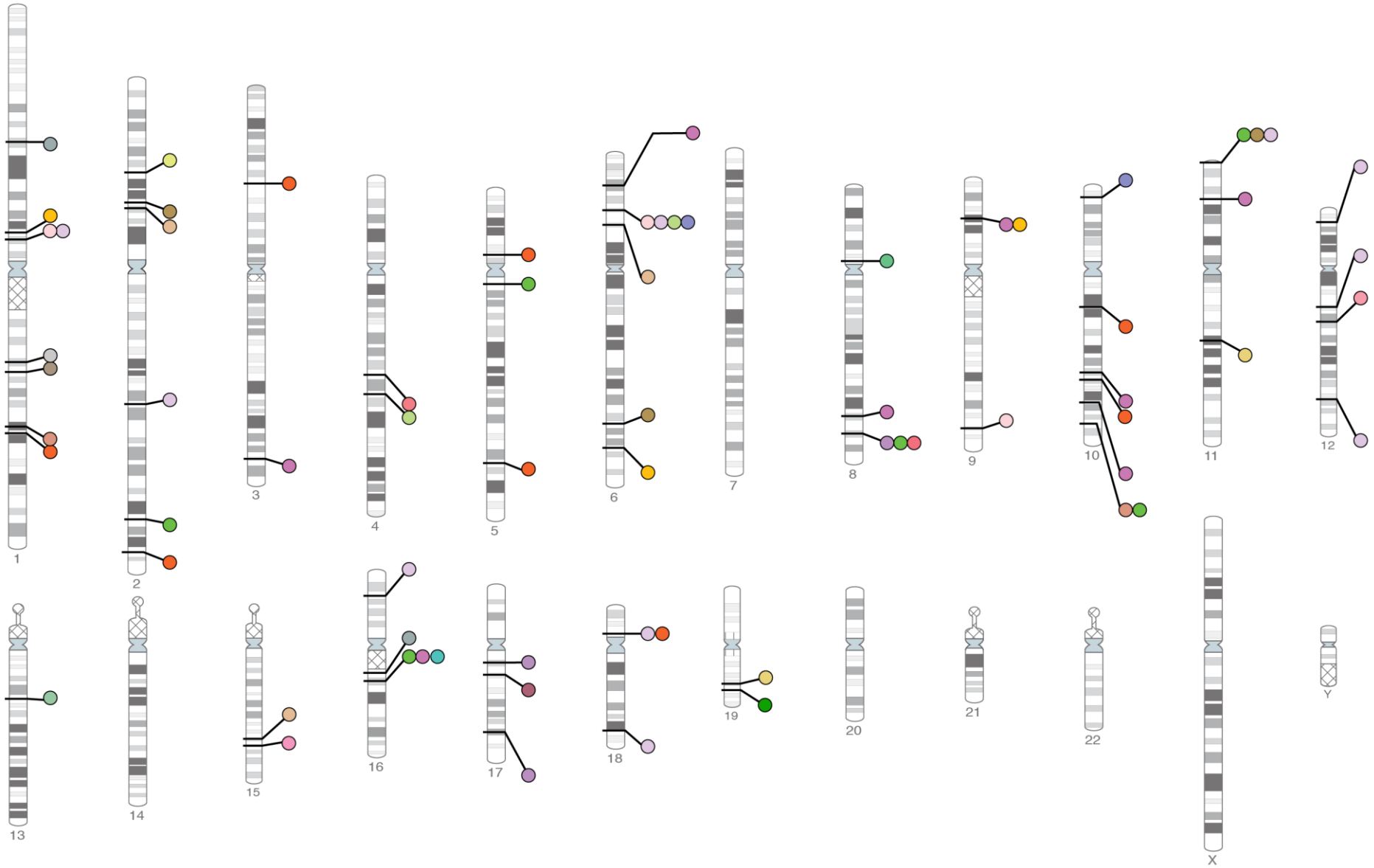

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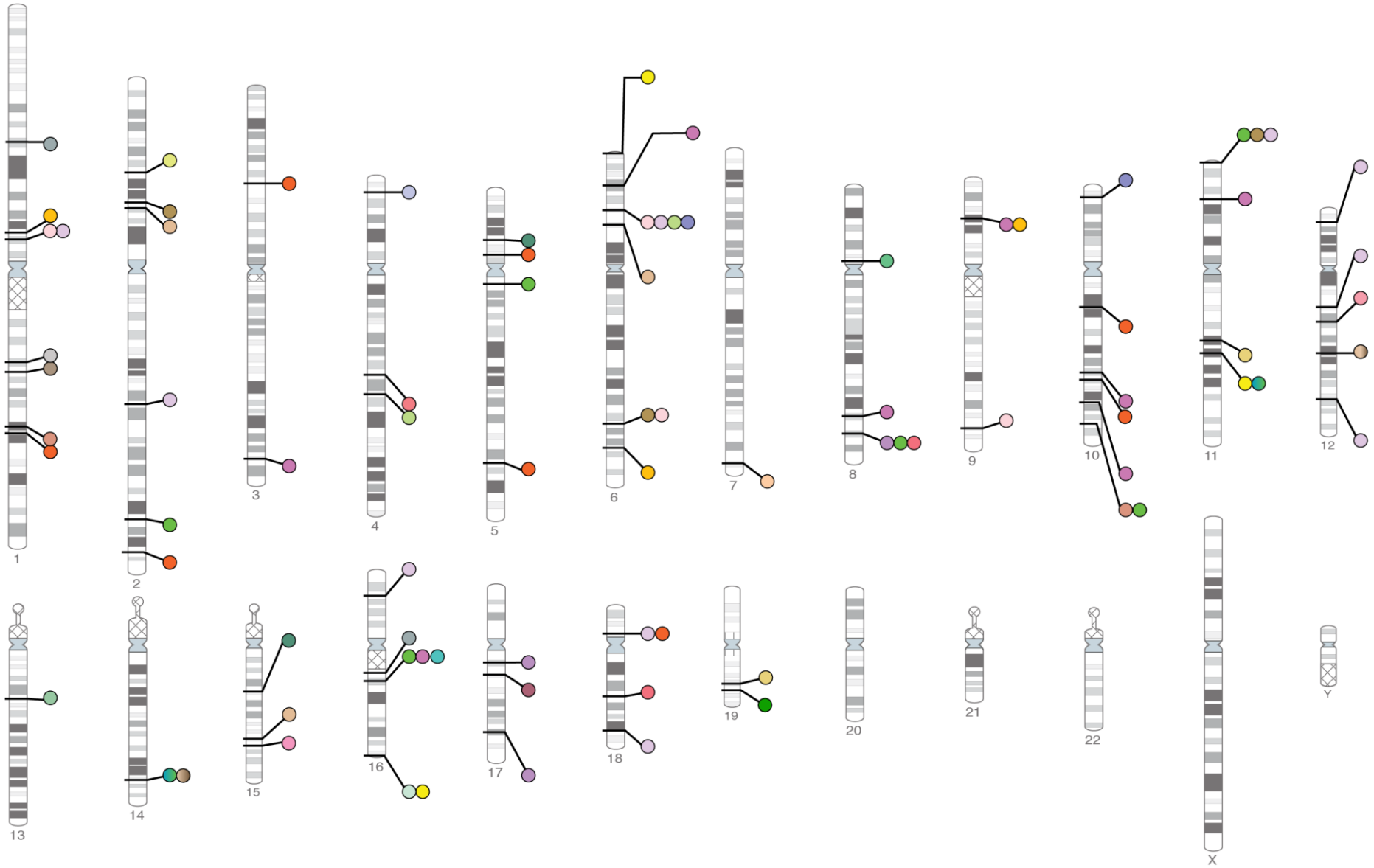

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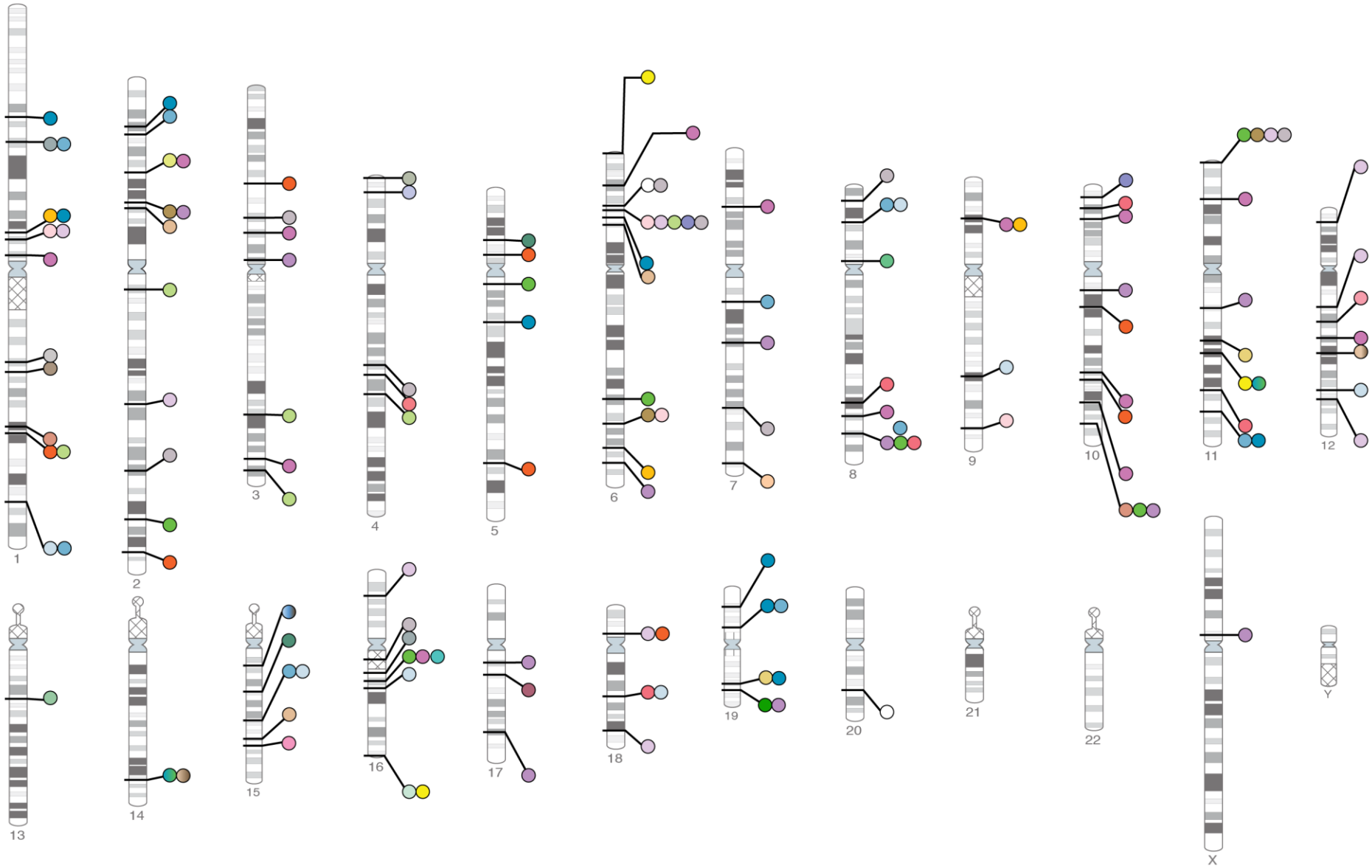

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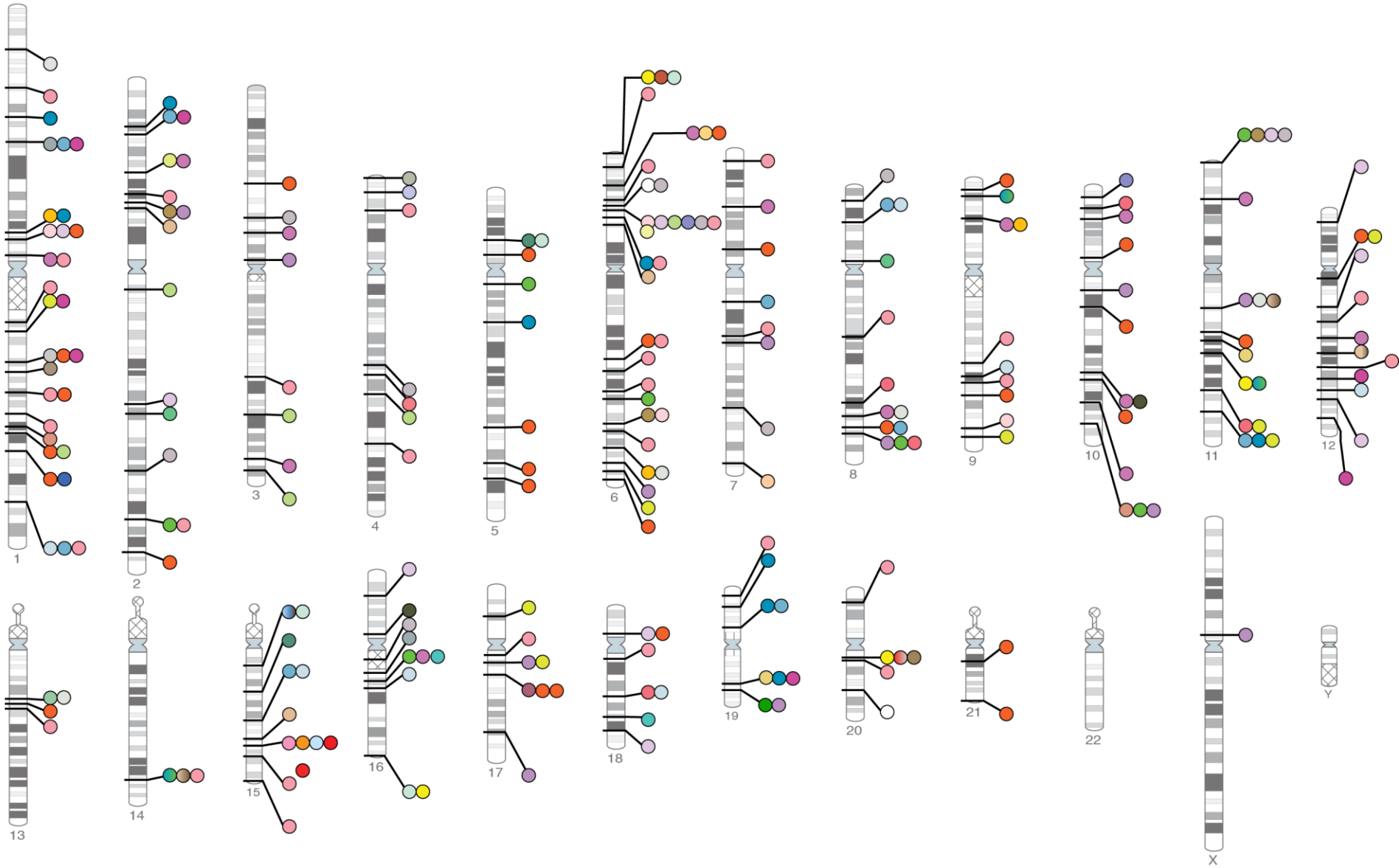

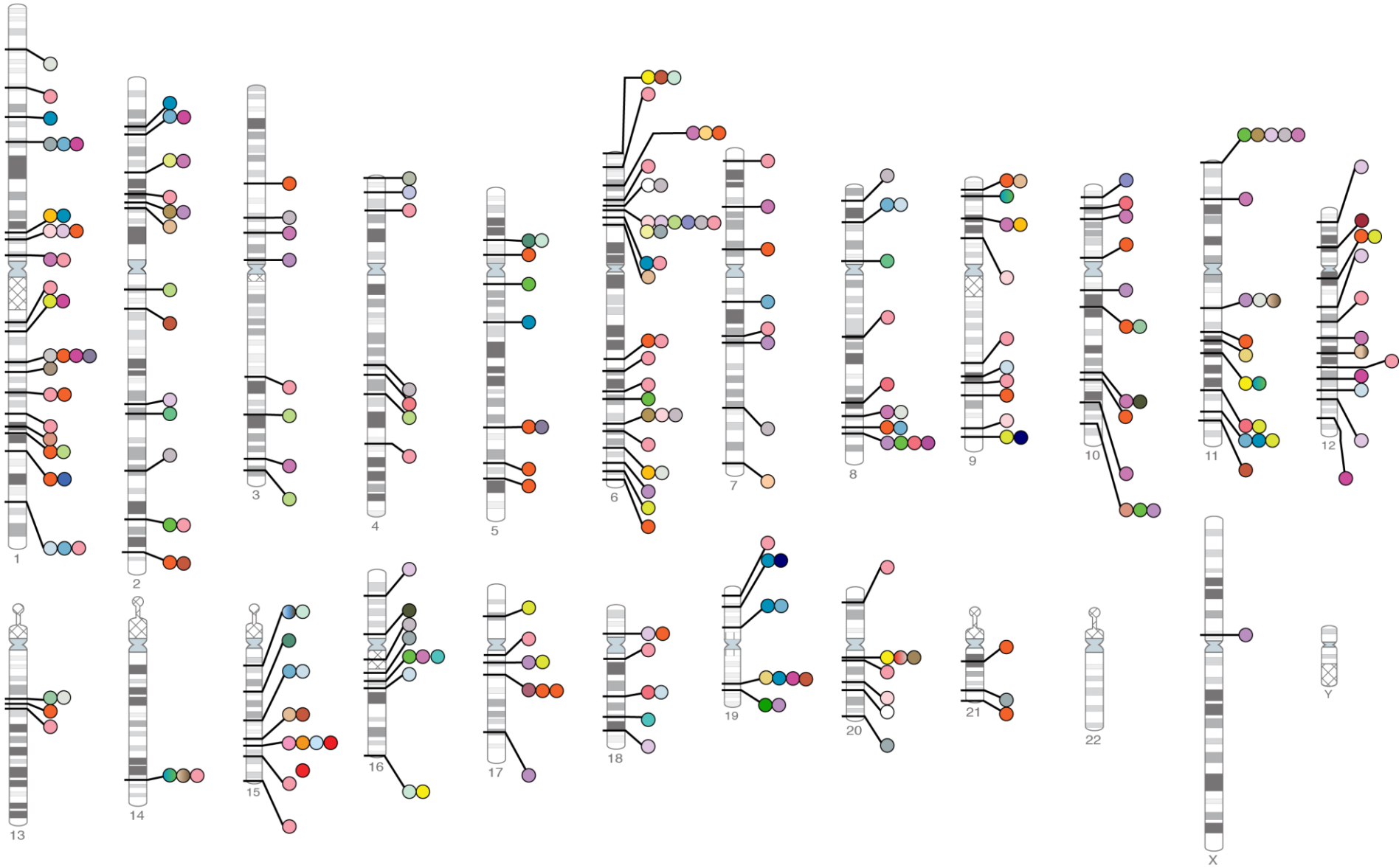
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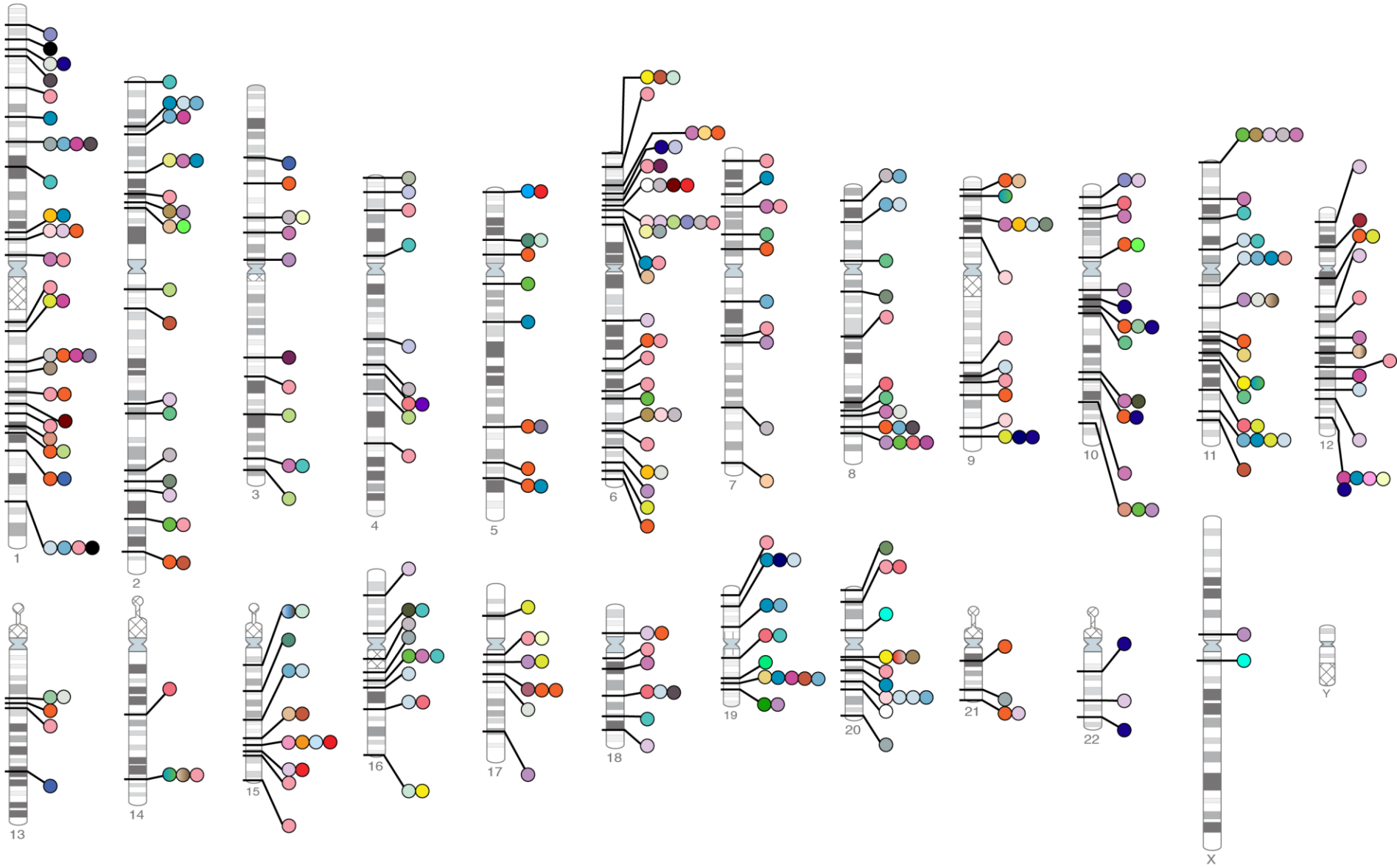

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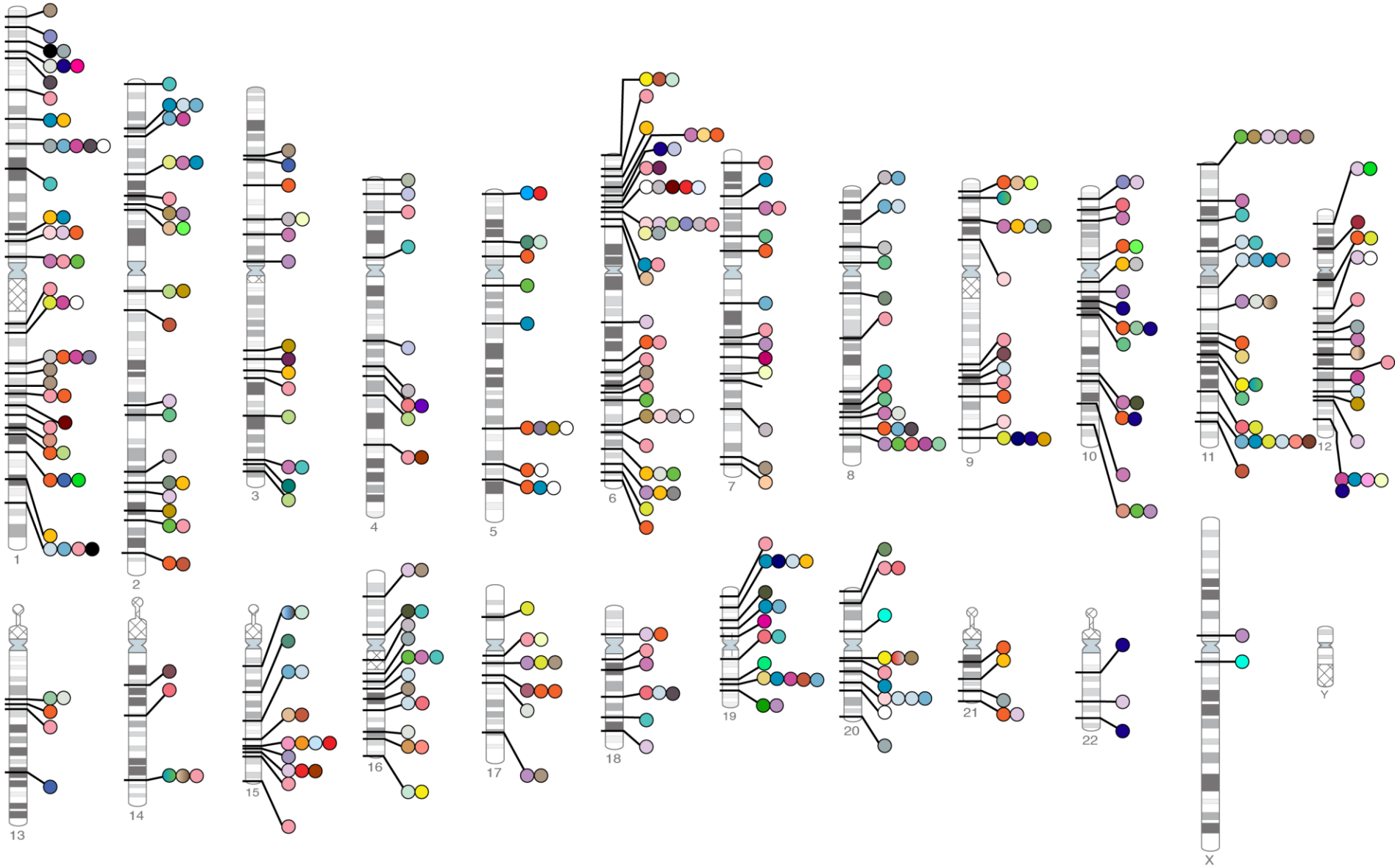

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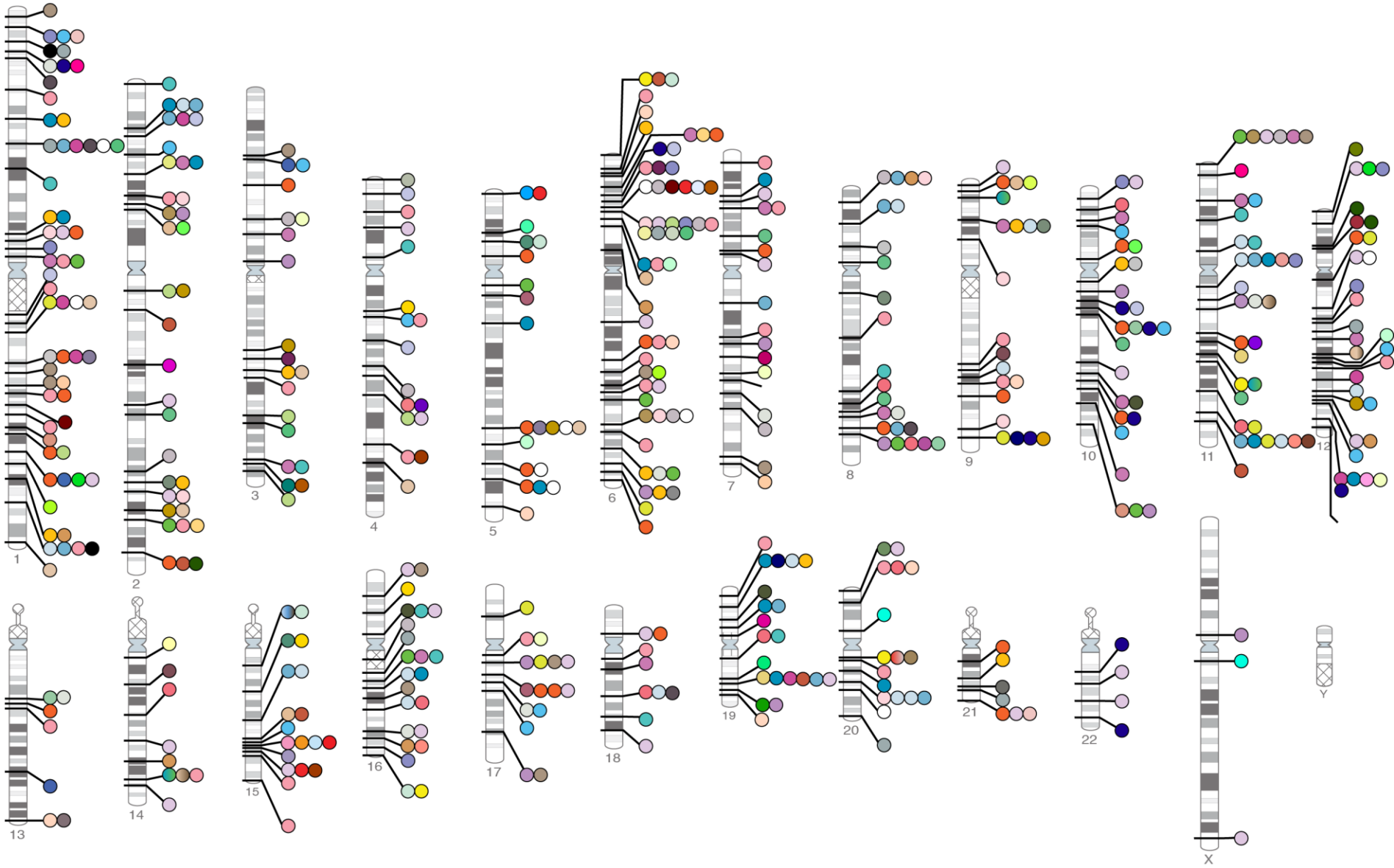


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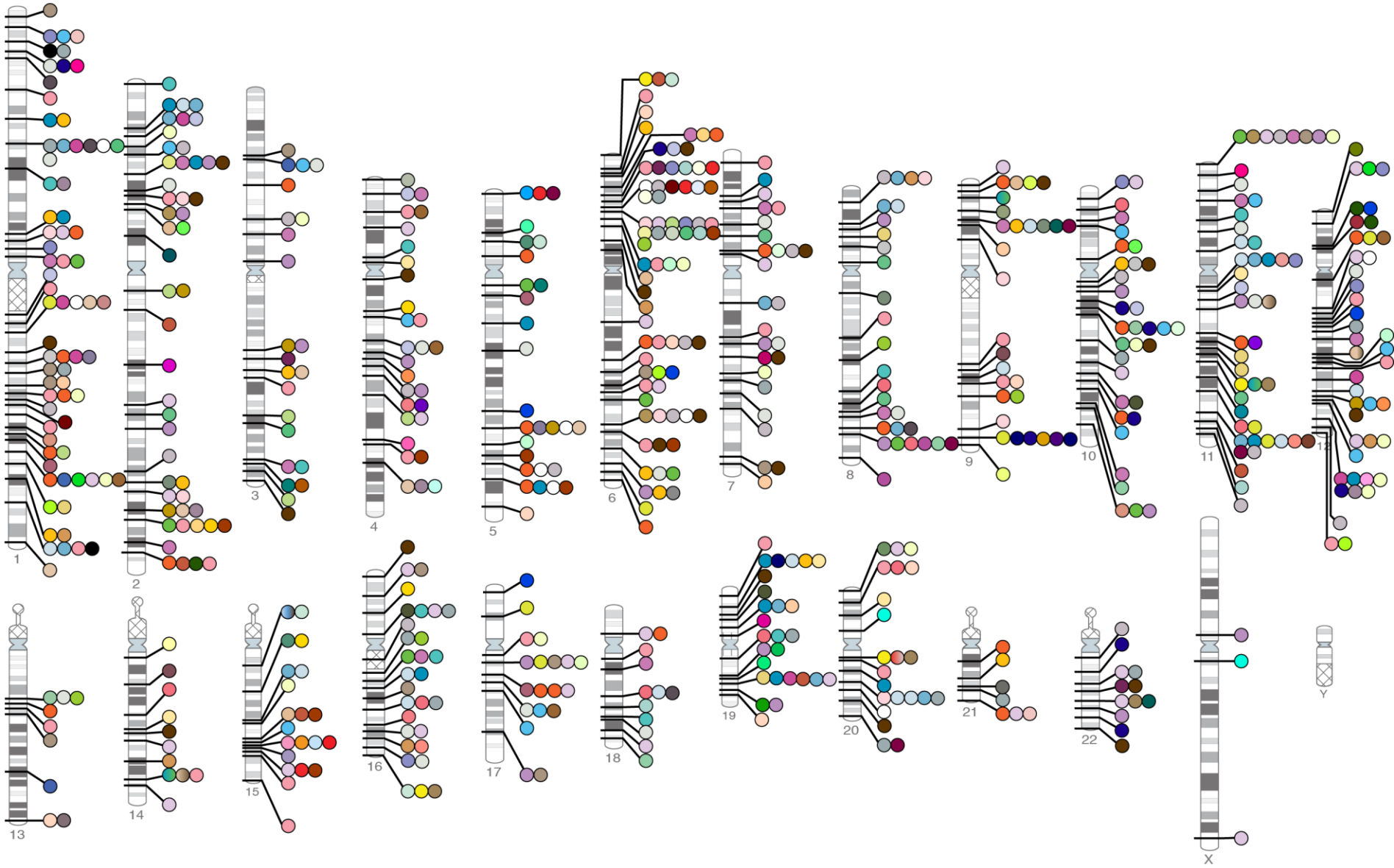
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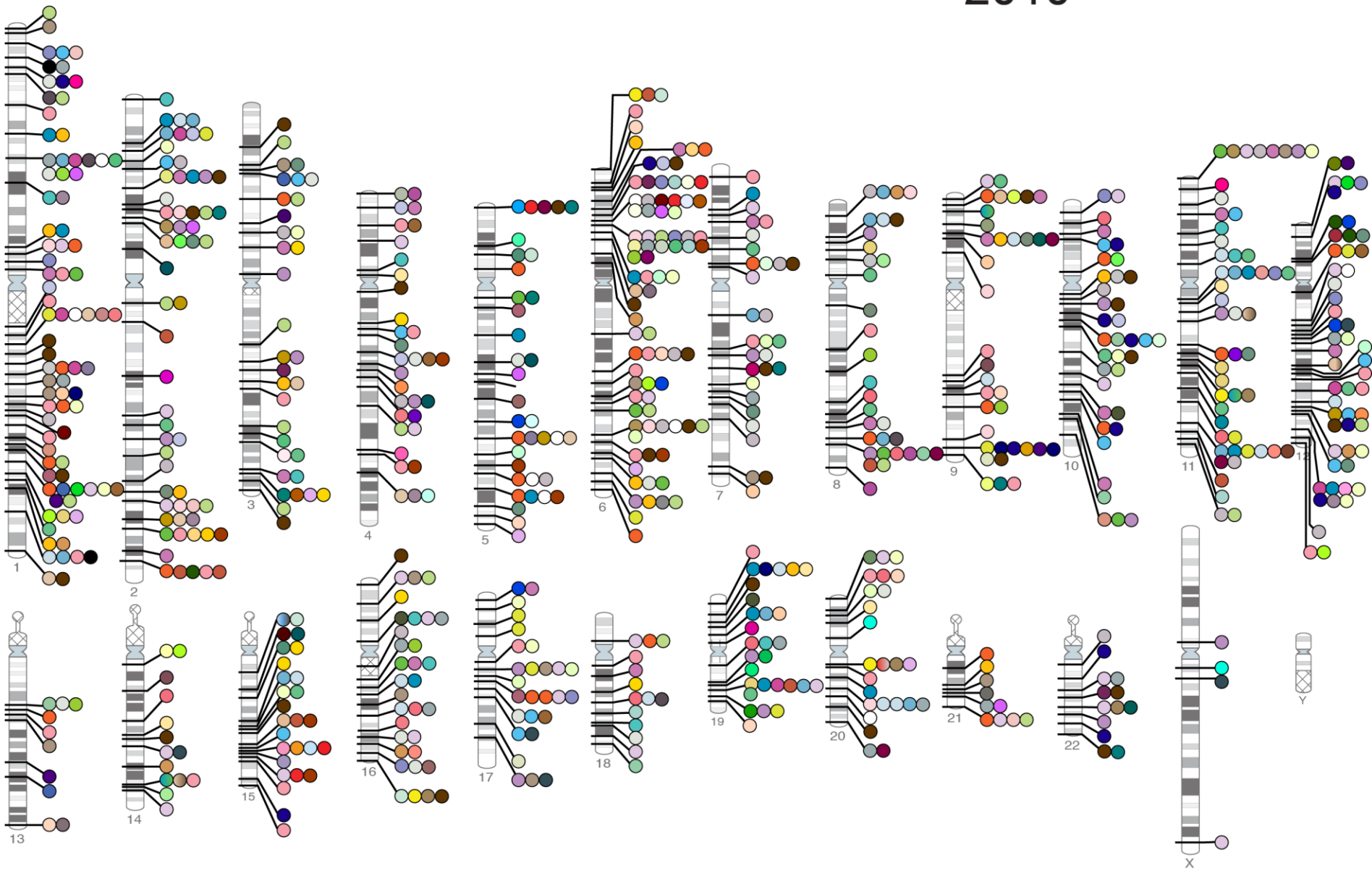
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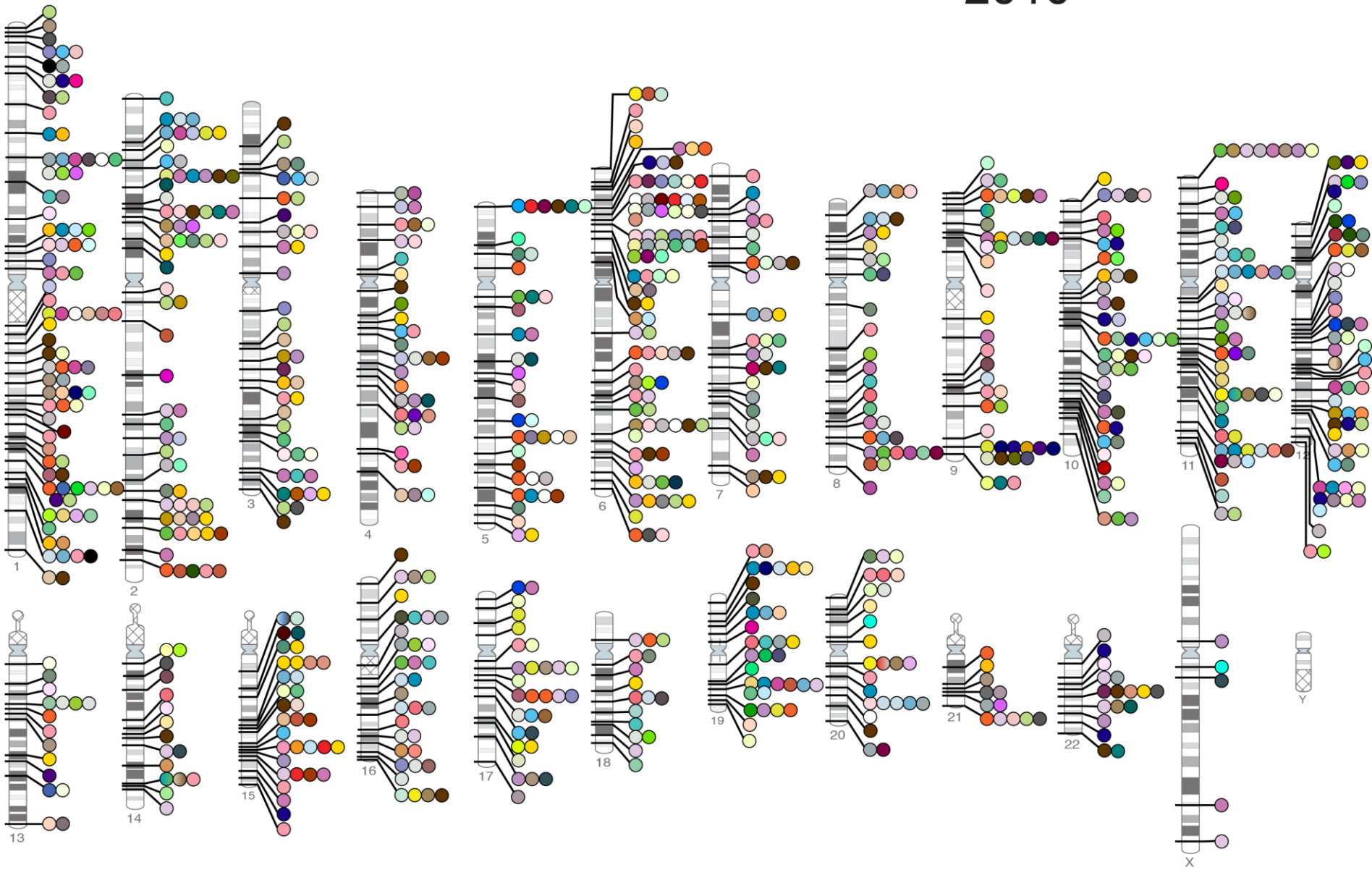

www.genome.gov/gwastudies/


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CTA
TCC
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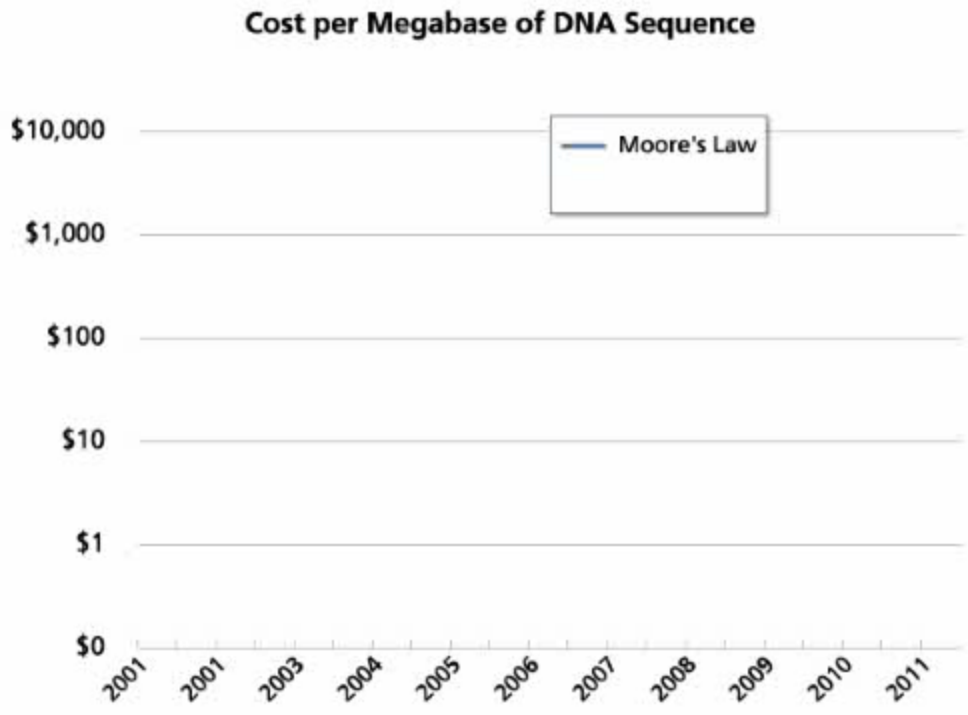
S. Myers


Cost per Megabase of DNA Sequence
$10,000
$1,000
$100
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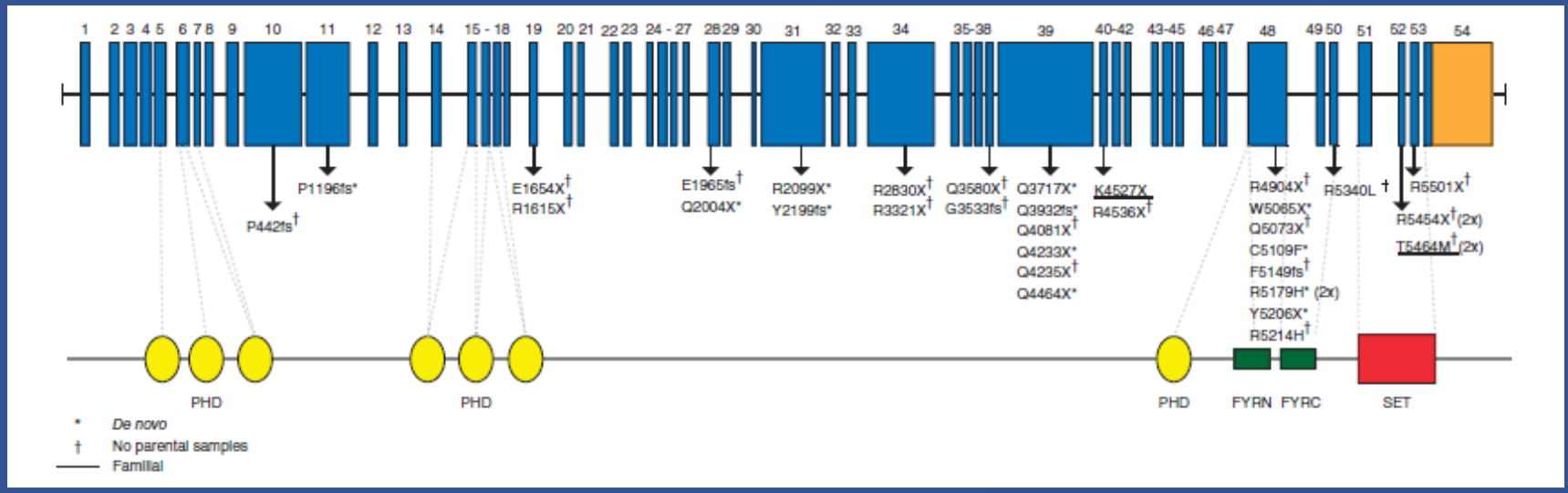
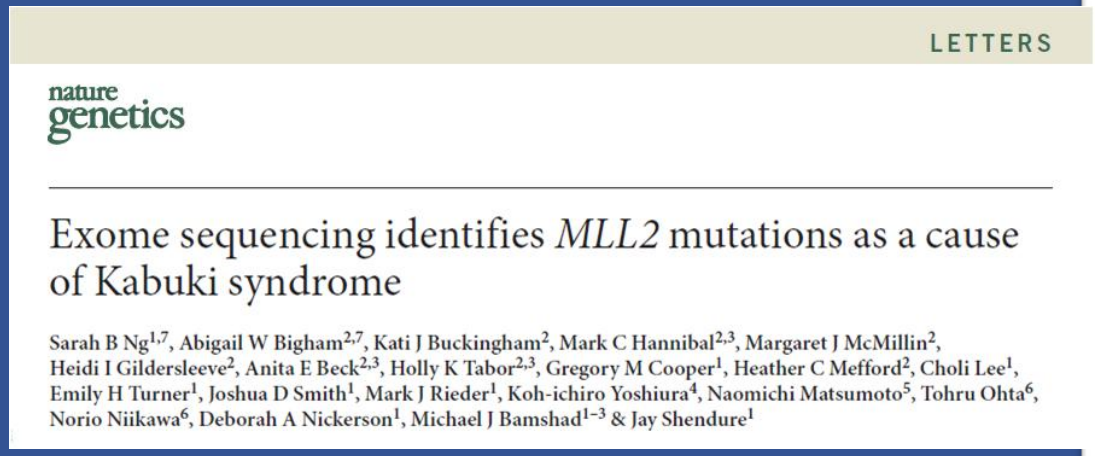
Clinical Applications of Genomic Analysis: Identifying Cause of Rare Disease



- Results confirmed by traditional Sange sequencing


LETTERS

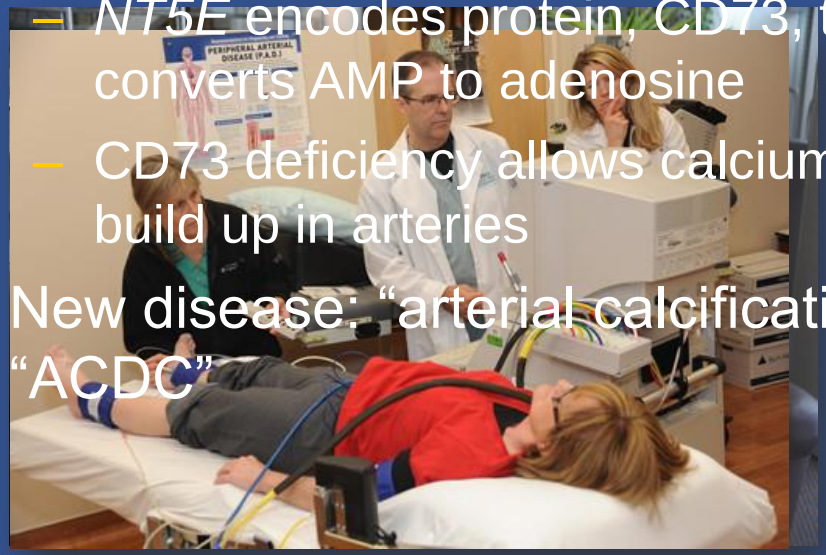
nature genetics

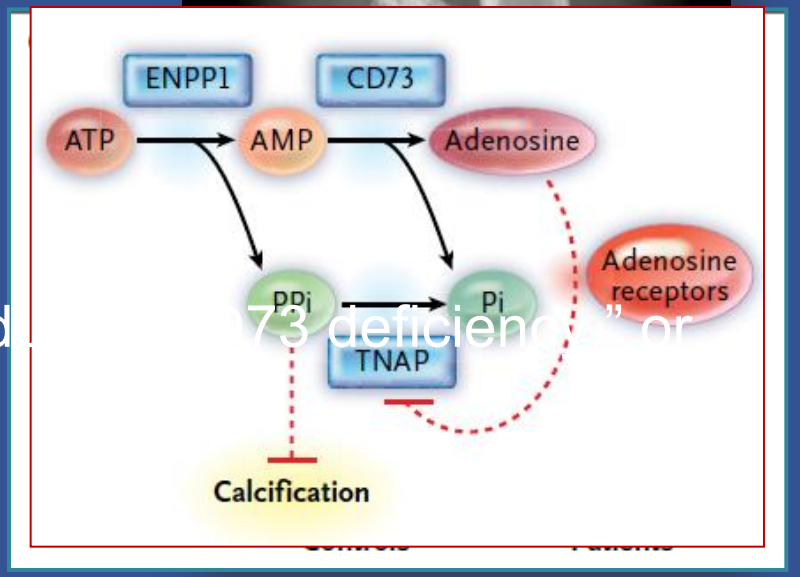
Exome sequencing identifies *MLL2* mutations as a cause of Kabuki syndrome

Sarah B Ng[1,7], Abigail W Bigham[2,7], Kati J Buckingham[2], Mark C Hannibal[2,3], Margaret J McMillin[2], Heidi I Gildersleeve[2], Anita E Beck[2,3], Holly K Tabor[2,3], Gregory M Cooper[1], Heather C Mefford[2], Choli Lee[1], Emily H Turner[1], Joshua D Smith[1], Mark J Rieder[1], Koh-ichiro Yoshiura[4], Naomichi Matsumoto[5], Tohru Ohta[6], Norio Niikawa[6], Deborah A Nickerson[1], Michael J Bamshad[1–3] & Jay Shendure[1]

Clinical Applications of Genomic Analysis: Identification of a New Disease

- Symptoms exhibited by Kentucky siblings
  - Progressive, debilitating joint pain
  - Calcium build-up in arteries of hands and feet; not heart
- Louise and Paula, sisters, seek answers at NIH Undiagnosed Diseases Program
- SNP analysis and targeted sequencing shows disease is caused by mutation in *NT5E*
  - *NT5E* encodes protein, CD73, that converts AMP to adenosine
  - CD73 deficiency allows calcium to build up in arteries
- New disease: "arterial calcification d[illegible]73 deficiency," or "ACDC"





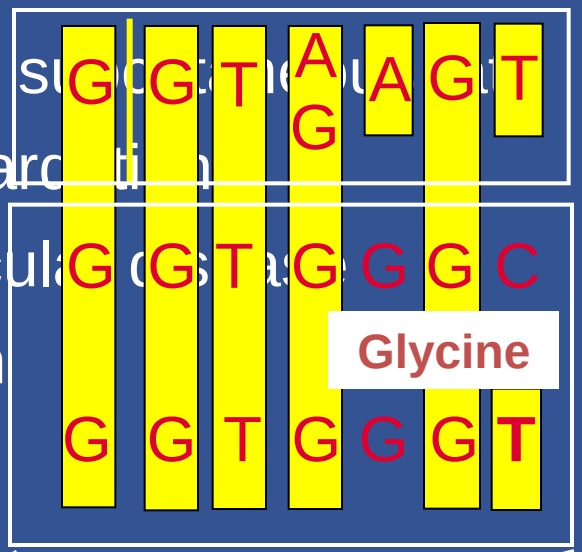
From Gene Discovery to Clinical Trial: Hutchinson-Gilford Progeria

- Loss of Hair
- Diminished subcutaneous fat
- Growth retardation
- Cardiovascular disease
- Early death

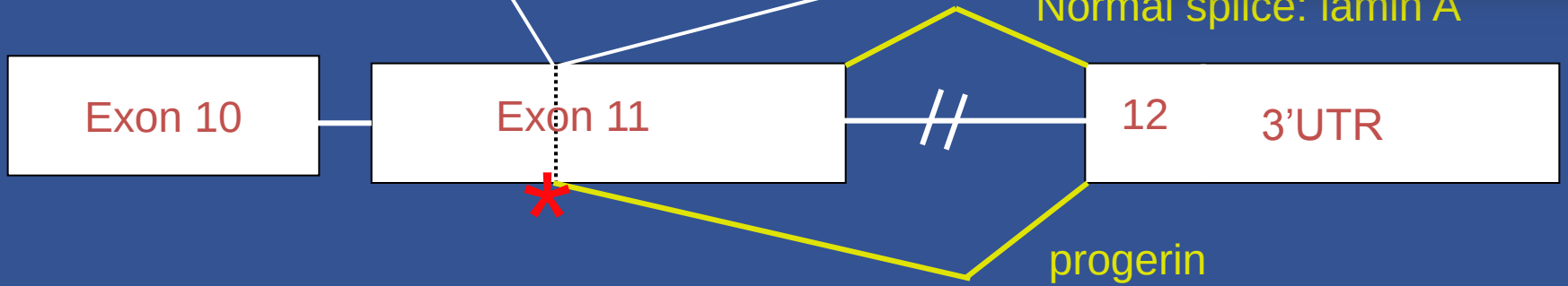
Splice donor consensus

Normal LMNA sequence

Mutation*
GGC=>GGT
(G608G)

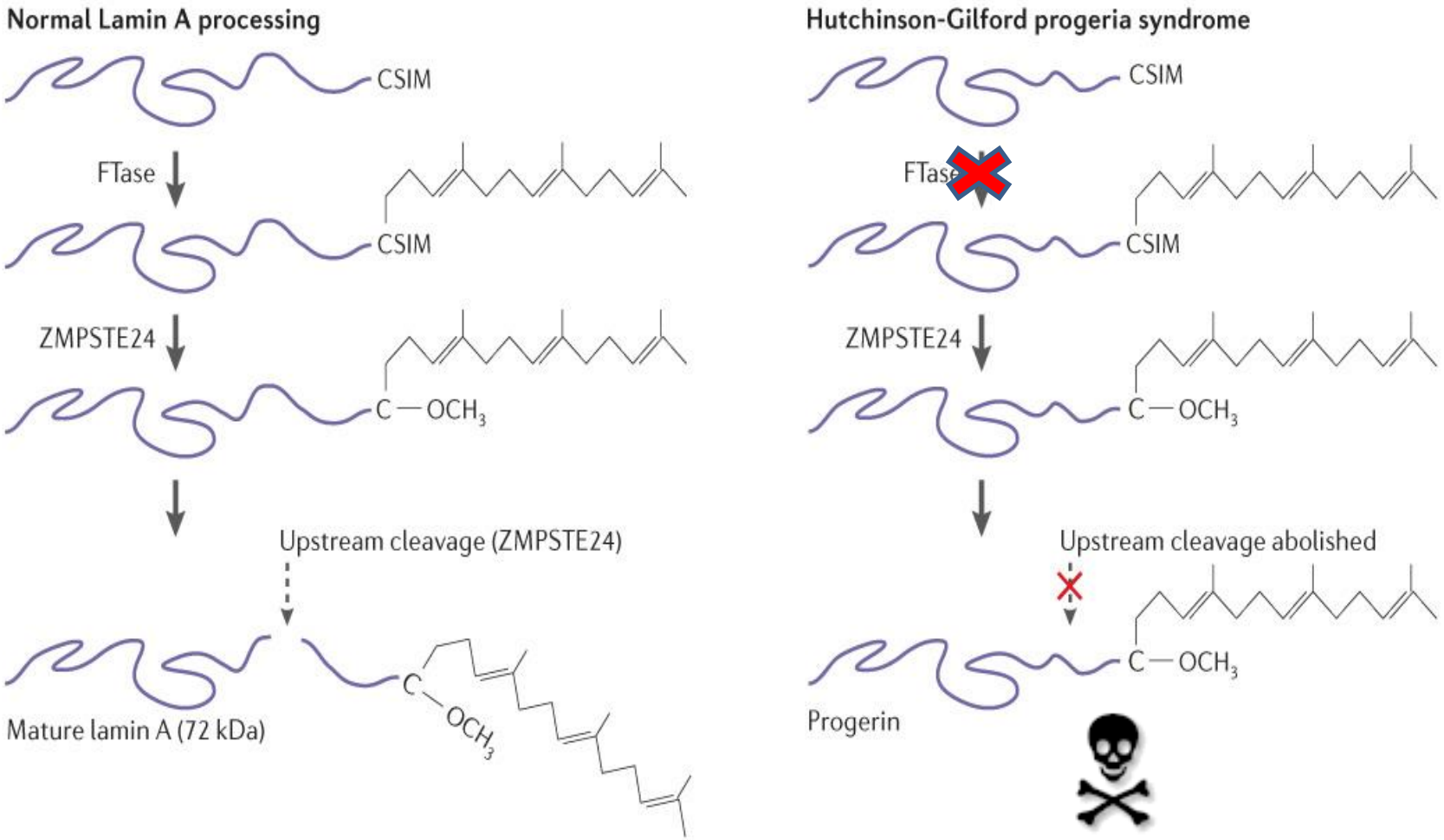


Normal splice: lamin A



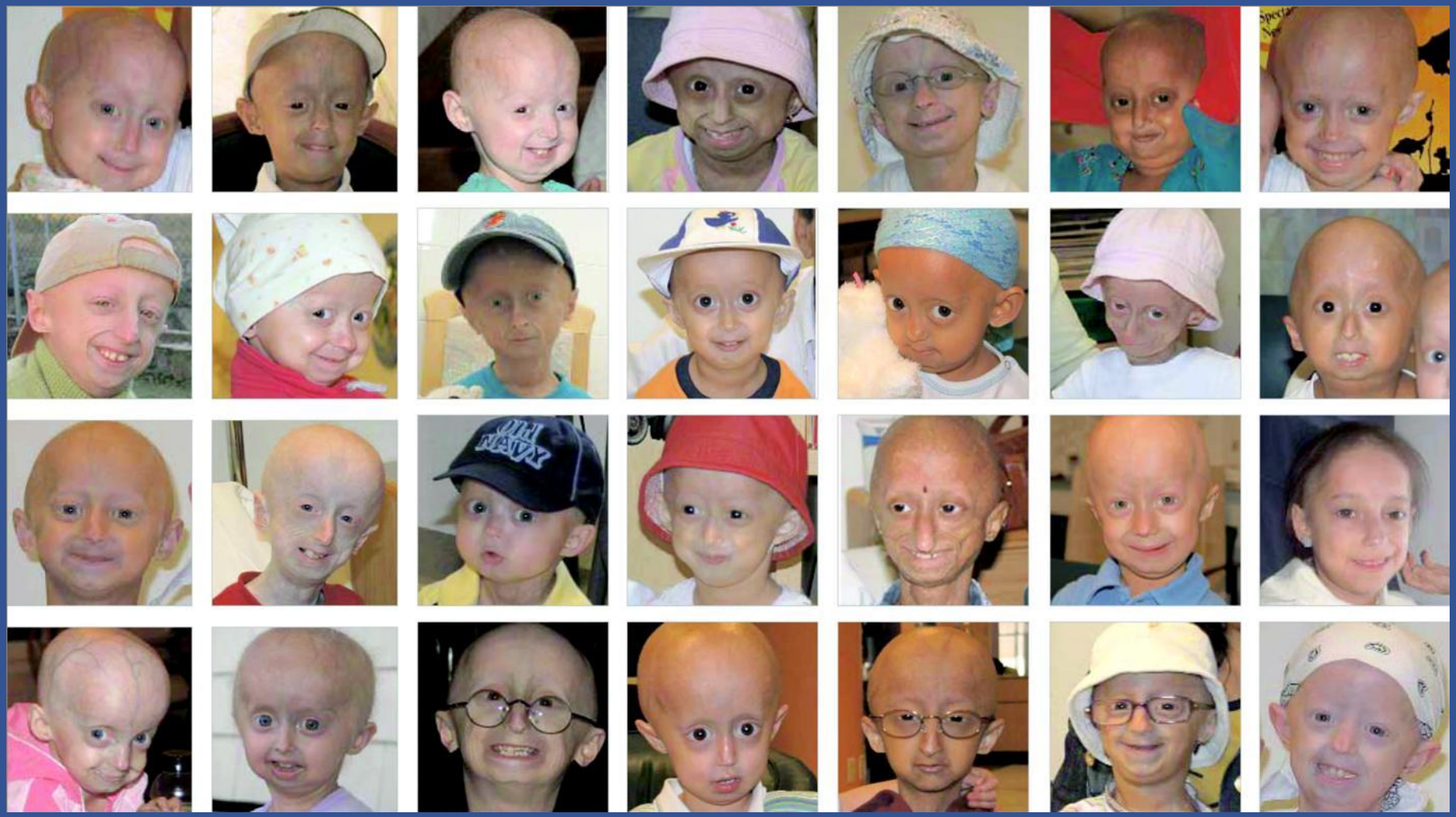
Eriksson, M. *et al*., *Nature* (2003)

Lamin A Processing



Capell B.C. & Collins F.S., *Nat. Rev. Genet.* (2006)

Children Now Enrolled In FTI Trial



Photographs Provided by The Progeria Research Foundation

Clinical Applications of Genomic Analysis: Diagnosis and Treatment

Credit: Gary Porter, Milwaukee Journal Sentinel

- Patient: 6-year-old Nic
  - Severe inflammatory bowel disease from just before 2nd birthday
  - 100+ surgeries – little solid food – **no diagnosis**
- Whole exome sequencing
  - Found mutation in *XIAP* gene
  - Gene previously linked to blood disorder; curable by bone marrow transplantation
- Diagnosis allows treatment
  - July 2010: Nic receives stem cell transplant from healthy donor
  - Today: doing well; recovery continues

MEDICAL COLLEGE OF WISCONSIN

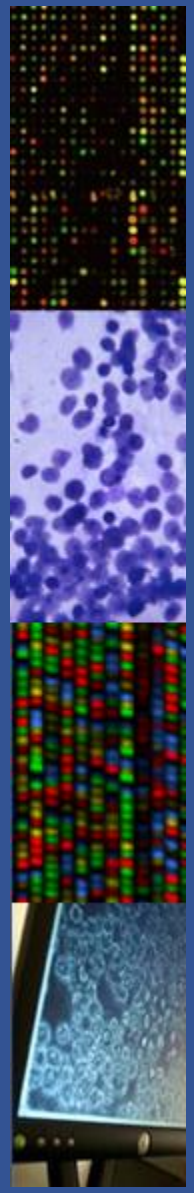
Clinical Applications of Genomic Analysis: Sequencing in a Clinical Research Setting

- ClinSeq: trans-NIH study, led by NHGRI, exploring how to apply genome sequencing in a clinical setting
- Enrolling 1,000 participants
- Initial focus: genetic risk for coronary heart disease
  - 200–400 genes implicated
  - Disease phenotypes correlated with variants
- Moving to whole-genome sequencing
  - Stay tuned for details about a healthy volunteer in this afternoon's panel discussion

Rick Del Sontro

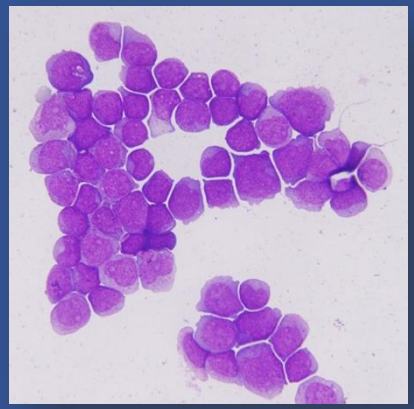
The Cancer Genome Atlas (TCGA)

- A comprehensive, collaborative effort led by NIH
  - To map genomic changes in major types, subtypes of cancer …
  - To help chart a new course in cancer research
- Pilot project initiated in 2006
  - Established scientific infrastructure; demonstrated “proof of concept”
  - Focused on 3 types of cancer: glioblastoma multiforme; ovarian; lung
  - Success of pilot → expansion: Phase II
- Now aim to characterize 20 cancer types in detail over the next four years

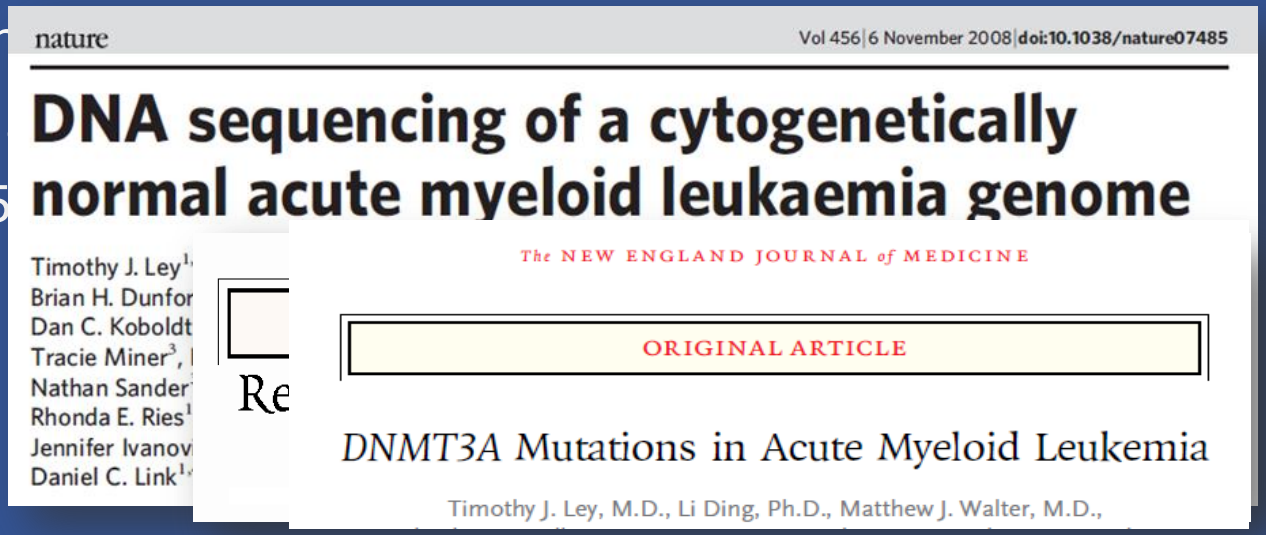


THE CANCER GENOME ATLAS

All the Mutations: Acute Myeloid Leukemia



- Acute myeloid leukemia (AML)
  - Cancer of blood-forming cells in the bone marrow
  - ~13,000 cases diagnosed in U.S. annually
  - 5-year survival rate: 21%
- Landmark study of AML genome
  - Completed DNA sequences of skin (normal) cells and tumor cells in patient; compared sequences
  - Found all mutations unique to tumor: 10
- Research has cor
  - Whole genome
  - All data, plus 15


nature

Vol 456 | 6 November 2008 | doi:10.1038/nature07485

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley[1]
Brian H. Dunfor
Dan C. Koboldt
Tracie Miner[3],
Nathan Sander
Rhonda E. Ries[1]
Jennifer Ivanov
Daniel C. Link[1]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

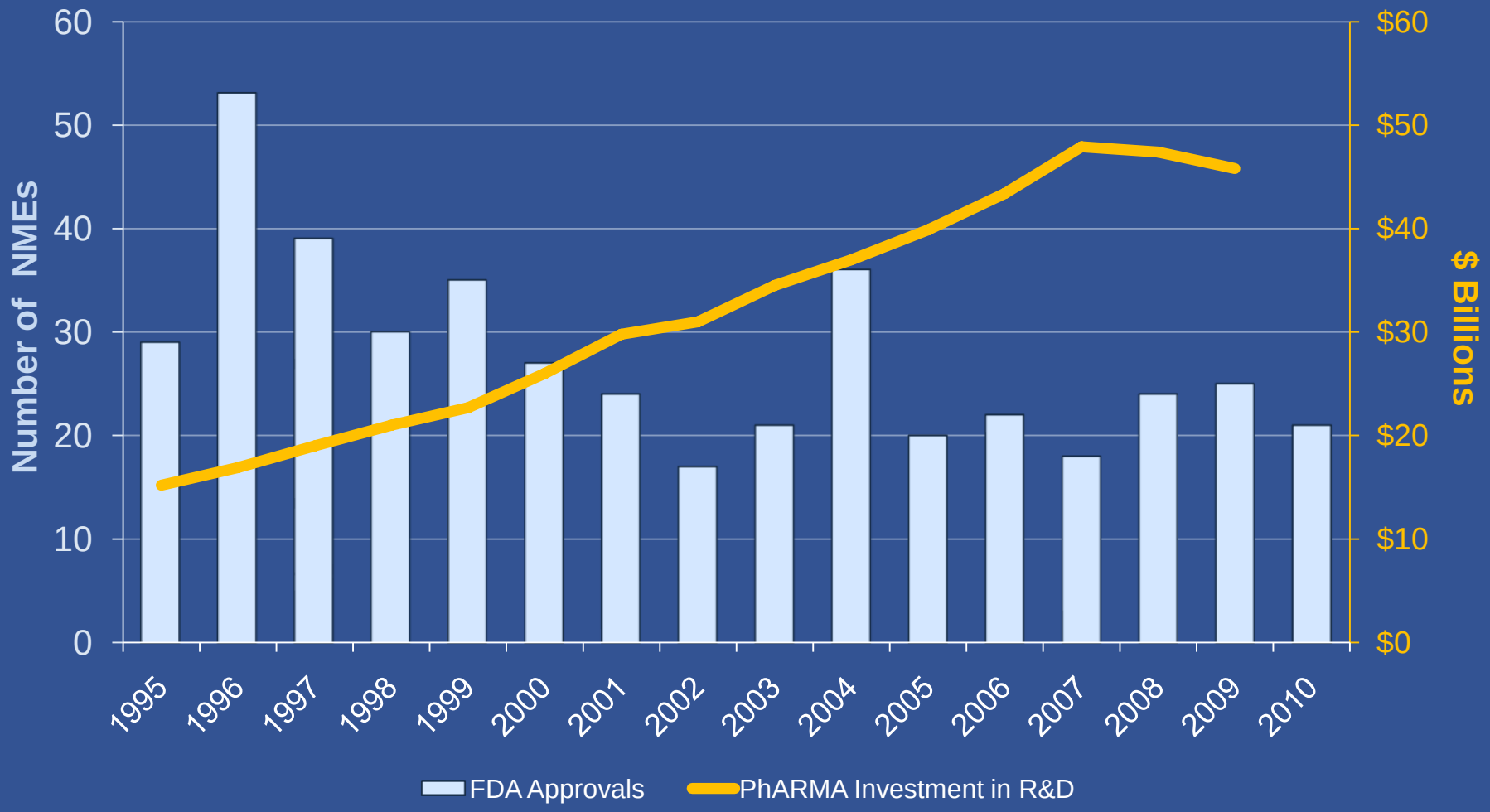
DNMT3A Mutations in Acute Myeloid Leukemia

Timothy J. Ley, M.D., Li Ding, Ph.D., Matthew J. Walter, M.D.,

Washington University in St. Louis
School of Medicine


Fundamental
Knowledge
Application of
Fundamental
Knowledge

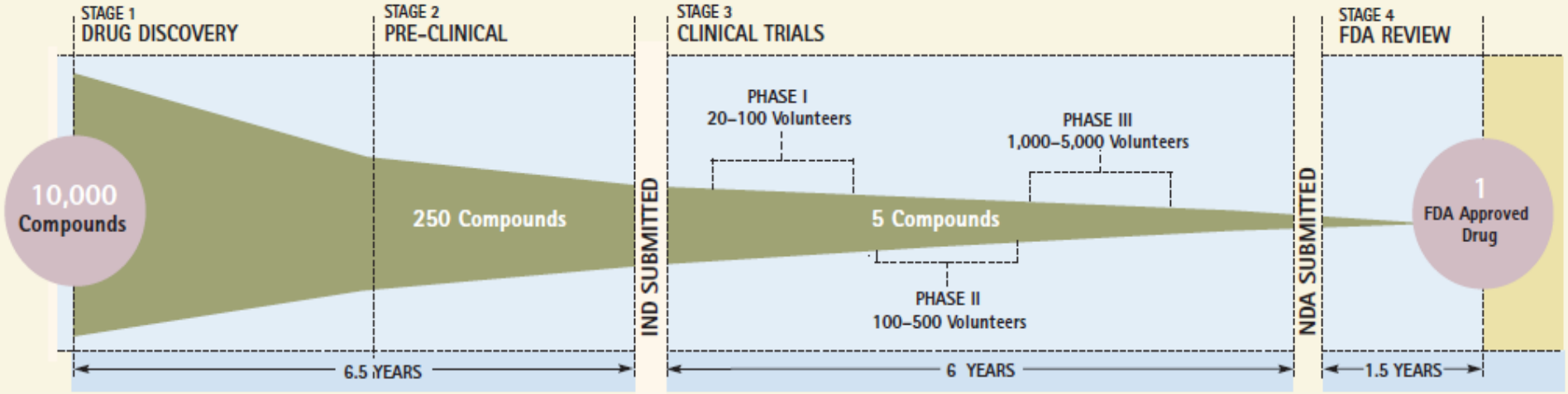
Despite greater investments in R&D by pharma, FDA approvals of new medical entities appear to be declining



Glaxo tries biotech model to spur drug innovations. *Wall Street Journal*, July 1, 2010.

Sources: Pharmaceutical Research and Manufacturers of America; FDA

Approximately 95% of Candidate Compounds Prove Ineffective



- Pharmaceutical Research and Manufacturers of America; FDA

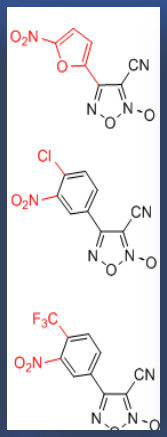
The NEW ENGLAND JOURNAL of MEDICINE

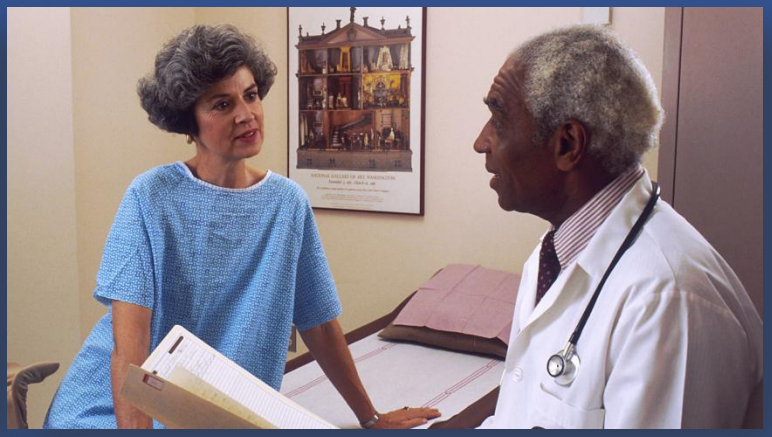
SPECIAL ARTICLE

The Role of Public-Sector Research in the Discovery of Drugs and Vaccines

Ashley J. Stevens, D.Phil., Jonathan J. Jensen, M.B.A., Katrine Wyller, M.B.E., Patrick C. Kilgore, B.S., Sabarni Chatterjee, M.B.A., Ph.D., and Mark L. Rohrbaugh, Ph.D., J.D.

N ENGL J MED 364;6 NEJM.ORG FEBRUARY 10, 2011





Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	CER

NIH Supported Basic Research

NIH Molecular Libraries Initiative

TRND

RAID

NIH Clinical Center, CTSAs

HMORN

PCORI

New NIH-FDA Partnerships

Cures Acceleration Network

The Problem of Rare and Neglected Diseases

- ~7,000 diseases affect humankind – but only a small fraction support commercial development of therapeutic agents
- Two types of neglected diseases:
  - Low prevalence, i.e., "rare" (<200,000 diagnosed in U.S.)
    - There are >6000 rare (orphan) diseases
    - Cumulative prevalence in U.S. ~ 25 – 30 million
    - Most are single gene diseases
    - <200 have any pharmacotherapy available
  - High prevalence but "neglected"
    - Occur chiefly among impoverished and marginalized populations in developing nations (treatment costs prohibitive)
    - Most are infectious

NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

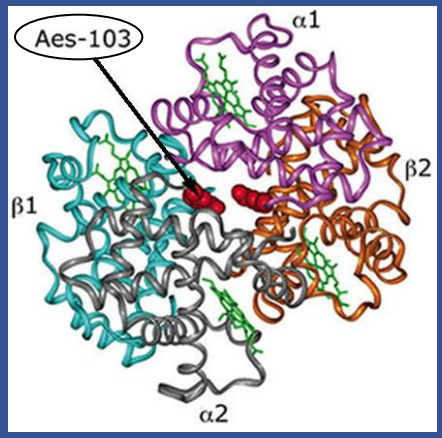
- Congressionally-mandated effort to speed development of new drugs for rare and neglected diseases
- Collaboration between NIH-intramural and extramural labs with appropriate expertise
- Projects will:
  - Enter TRND at a variety of stages of development
  - Be taken to phase needed for external organization to adopt for clinical development
  - Not duplicate PhRMA projects
- TRND will encourage creative partnerships; novel approaches to intellectual property

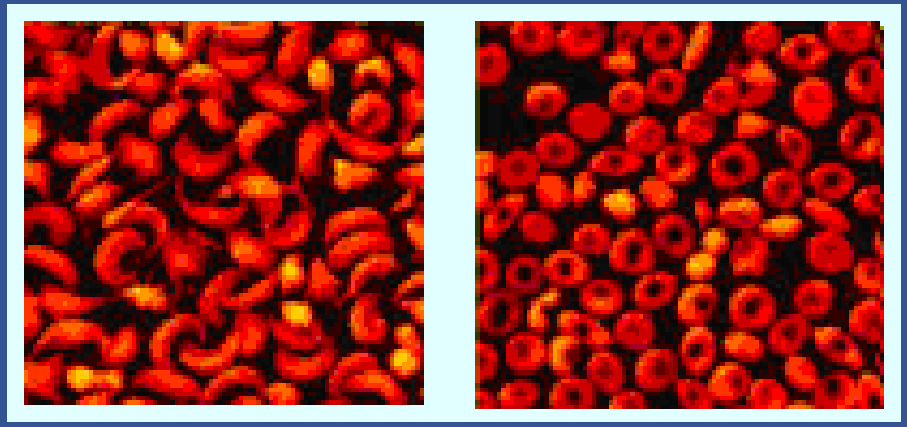
TRND Pilot Projects

Disease	Type	Pathology	Collaborators	Compound type	Stage
Schistosomiasis, Hookworm	Neglected	Infectious parasite	Extramural	NME	Early (lead optimization)
NPC	Rare	CNS, liver/spleen	Disease Fnd, Extramural, Intramural	Repurposed approved drug	Mid-stage
HIBM	Rare	Muscle	Biotech, Intramural	Intermediate replacement	Pre-IND
Sickle Cell Disease	Rare	Blood	Nonprofit, Intramural, Extramural	NME	Mid-stage
Chronic Lymphocytic Leukemia	Rare	Cancer	Disease Fnd, Extramural	Repurposed approved drug	Pre-IND

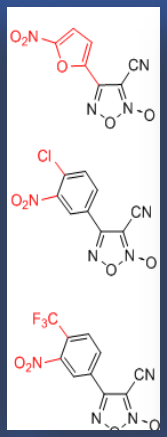
Therapeutics for Rare and Neglected Diseases (TRND): Pilot Project on SCD

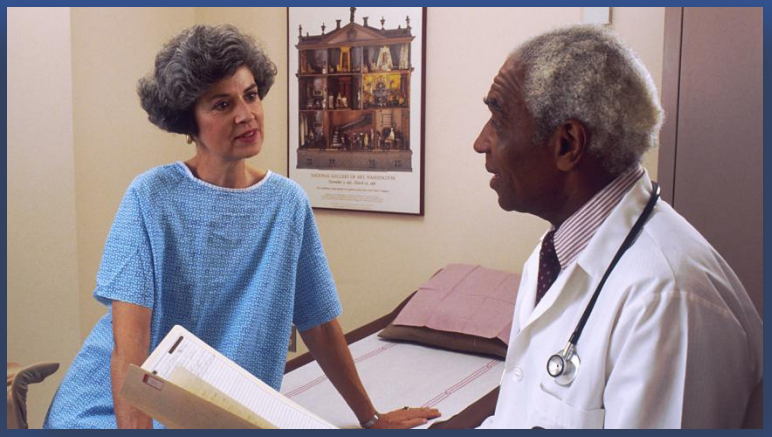
- Compound originally identified at VCU
- Structure: 5-hydroxymethyl-2-furfural (Aes-103)
  - Binds to sickle hemoglobin and increases its oxygen affinity
- Stage of project: late preclinical





Aes-103 0mM Aes-103 5mM





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NIH Supported Basic Research	NIH Molecular Libraries Initiative	TRND RAID	NIH Clinical Center, CTSAs	HMORN PCORI

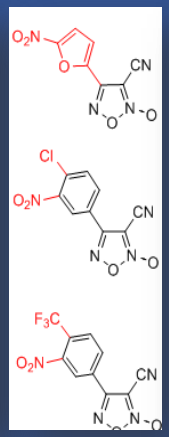
New NIH-FDA Partnerships

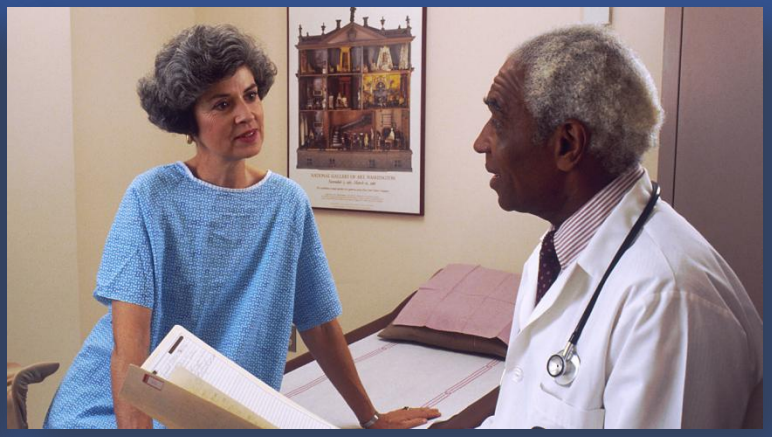
Cures Acceleration Network

New NIH-FDA Partnership

- NIH-FDA Joint Leadership Council
  - Established 2010
- NIH and FDA will:
  - Invest in advancing translational and regulatory science
  - Better define regulatory pathways for coordinated approval of co-developed diagnostics and therapeutics
  - Develop risk-based approaches for appropriate and accurate review of diagnostics
  - Make accurate information about tests readily available

National Center for Advancing Translational Sciences





Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	CER

NIH Supported Basic Research	NIH Molecular Libraries Initiative	TRND RAID	NIH Clinical Center, CTSAs	HMORN PCORI

New NIH-FDA Partnerships

Cures Acceleration Network

THE HUFFINGTON POST

Top 10 Watch

ISSUES

JANUARY

By Kathlee

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About PhR

PHRMA STATE

Washington, D.C Vice President D new drug discov

"Collaboration – particularly early progress in disco

"PhRMA agrees supports the role

"We're proud of live longer, hea serious illnesses diseases such as medicines – inc – are in develop

"The biopharma medicines in 20 remain real. In f promising molec

"We're encourag stage research i

The Dev

Jan. 23

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By: MARI

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The New York Times

SUNDAY, JANUARY 23, 2011

New Federal Research Center Will Help Develop Medicines

The Boston Globe

February 7, 2011

Opinion: Pharma needs US help; Important drugs will be slow to market if agencies don't coordinate

BY CHRISTOPH WESTPHAL

THE VAST MAJORITY of prescription drugs are discovered and developed by pharmaceutical and biotech companies, not by academic labs. Nevertheless, companies depend on vibrant academic research to feed the early stage of their new drugs pipeline — which is funded largely via the National Institutes of Health. At the late stage of the new drugs pipeline, the Food and Drug Administration weighs risks and benefits before deciding whether to grant approval to market a new medicine.

The development of important new drugs is

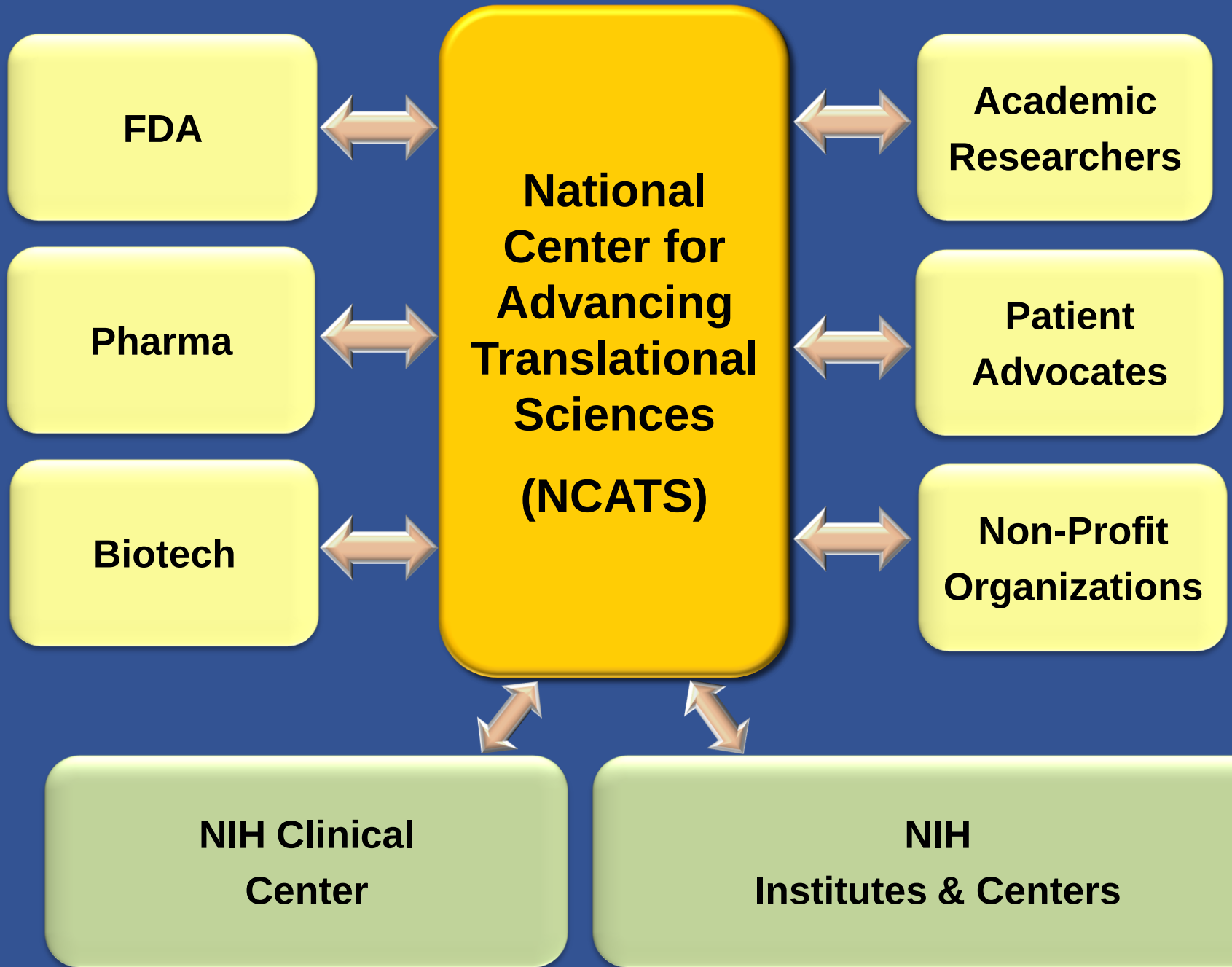
medicines to the market, to bring all the stakeholders to the table (the NIH, industry, and the FDA) in supporting the most innovative and promising new drugs in mid- and late-stage trials.

Despite vast increases in government and industry spending on research and drug discovery, fewer important new drugs are being approved now than before. From 1995 to 2004, roughly 30 new

(Boston Globe / David Gothard)

drug development pipeline, by advancing the most promising drugs quickly through human trials, should be undertaken in parallel.

A focus on improving the late stage of the new drugs pipeline is likely to be accomplished only via a close collaboration with the NIH and the FDA on the one hand and the pharmaceutical and biotech industries on the other. Think of it this way: the new NIH center may help to bring more new drugs to market — but in 12 years at the earliest. Twelve years and $1 billion are a minimum estimate for the time and money required to


FDA
Pharma
Biotech
National Center for Advancing Translational Sciences (NCATS)
Academic Researchers
Patient Advocates
Non-Profit Organizations
NIH Clinical Center
NIH Institutes & Centers

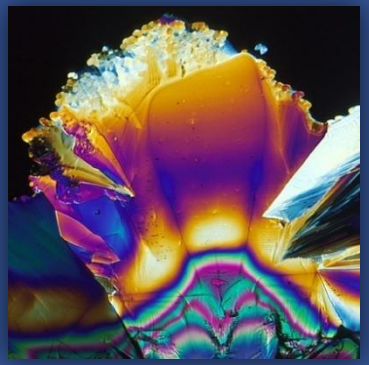
Tell us what you think…

www.nih.gov

“Cutting the deficit by gutting our investments in innovation and education is like lightening an overloaded airplane by removing its engine. It may make you feel like you're flying high at first, but it won't take long before you feel the impact.”

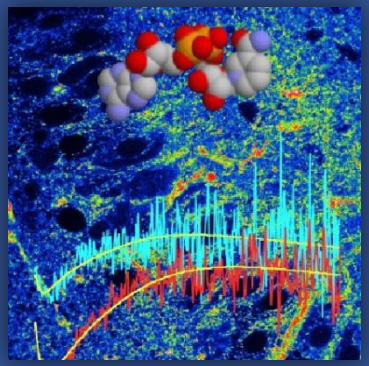
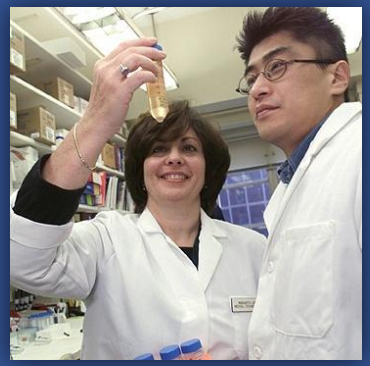
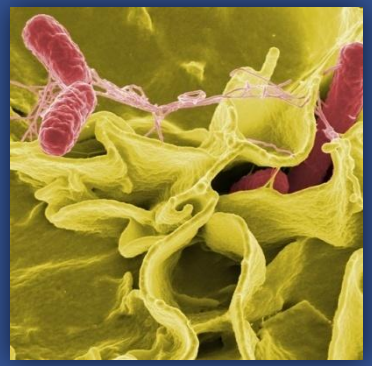
— President Barack Obama, 2011 State of the Union





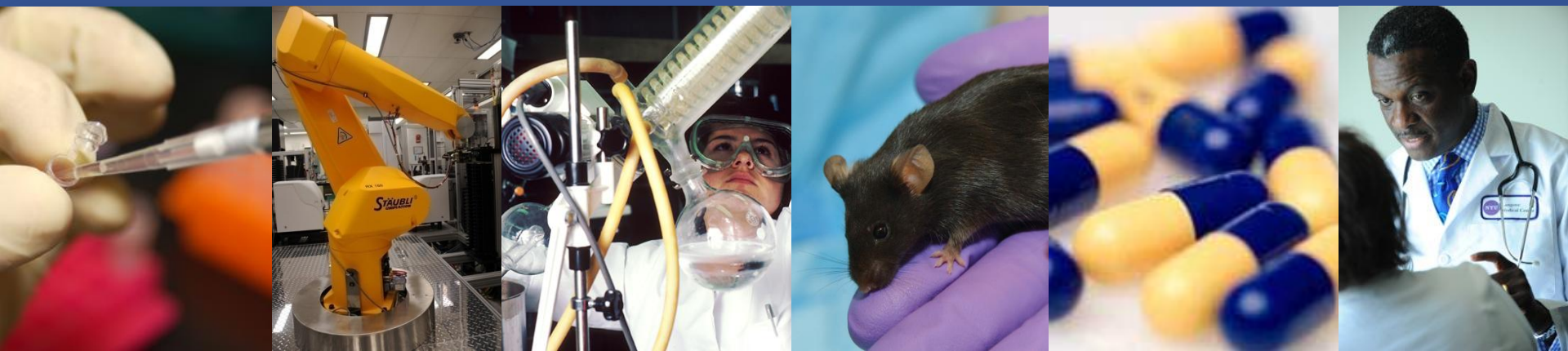

NIH

Turning discovery into health

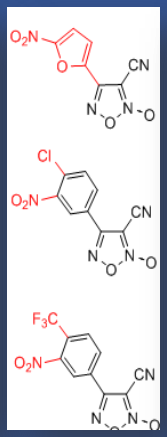





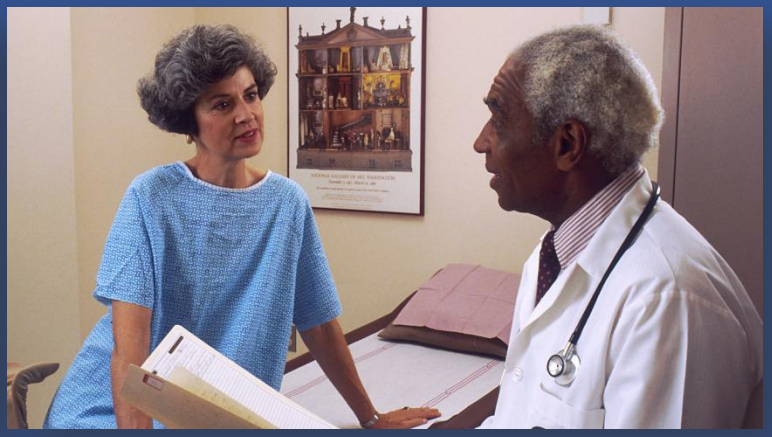
Draft Mission Statement for National Center for Advancing Translational Sciences (NCATS)

To advance the discipline of translational science and catalyze the development of novel diagnostics and therapeutics across a wide range of human diseases and conditions




nature
THE FUTURE IS BRIGHT





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New NIH-FDA Partnerships

Cures Acceleration Network

A Bold New Paradigm: Cures Acceleration Network (CAN)

- Established by the Affordable Care Act
- CAN will
  - Advance the development of "high need cures"
  - [illegible]overy and
  - [illegible] pursue i
- Rev

124 STAT. 978 PUBLIC LAW 111–148—MAR. 23, 2010

Cures Acceleration Network Act of 2009. 42 USC 201 note.

SEC. 10409. CURES ACCELERATION NETWORK.

(a) SHORT TITLE.—This section may be cited as the "Cures Acceleration Network Act of 2009".

(b) REQUIREMENT FOR THE DIRECTOR OF NIH TO ESTABLISH A CURES ACCELERATION NETWORK.—Section 402(b) of the Public Health Service Act (42 U.S.C. 282(b)) is amended—

"(c) FUNCTIONS.—The functions of the CAN are to—

"(1) conduct and support revolutionary advances in basic research, translating scientific discoveries from bench to bedside;

"(2) award grants and contracts to eligible entities to accel-

"(4) reduce the barriers between laboratory discoveries and clinical trials for new therapies; and

"(5) facilitate review in the Food and Drug Administration for the high need cures funded by the CAN, through activities

… reduce the barriers between laboratory discoveries and clinical trials for new therapies and …

Cures Acceleration Network: Funding Mechanisms

- Grant Awards:
  - Up to $15 million per award per fiscal year
- Partnership Awards:
  - $1 match for every $3 from NIH
  - Up to $15 million per award per fiscal
- Flexible Research Awards:
  - DARPA-like authority
  - Not to exceed 20% of total appropriated funds in any fiscal year

Clinical Applications of Genomic Analysis: Individualized Cancer Treatment

VANITY FAIR

FIRST PERSON

Topic of Cancer

One fine June day, the author is launching his best-selling memoir, *Hitch-22*. The next, he's throwing up backstage at *The Daily Show*, in a brief bout of denial, before entering the unfamiliar country—with its egalitarian spirit, martial metaphors, and hard bargains of people who have cancer.

By **Christopher Hitchens** • Photograph by **John Huba**
September 2010

JOINING THE RESISTANCE?
The author at home in Washington, D.C., July 18, 2010.

Christopher Hitchens

Complete sequencing of his esophageal cancer has just uncovered an "actionable" mutation.

Stay tuned!

The NEW ENGLAND JOURNAL of MEDICINE

FEBRUARY 3, 2011 364;5

ORIGINAL ARTICLE

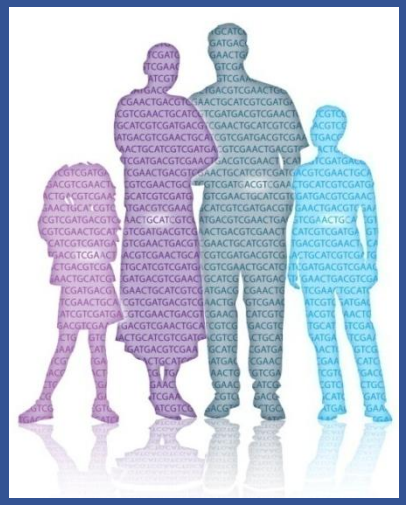
NT5E Mutations and Arterial Calcifications

Cynthia St. Hilaire, Ph.D., Shira G. Ziegler, B.A., Thomas C. Markello, M.D., Ph.D., Alfredo Brusco, Ph.D., Catherine Groden, M.S., Fred Gill, M.D., Hannah Carlson-Donohoe, B.A., Robert J. Lederman, M.D., Marcus Y. Chen, M.D., Dan Yang, M.D., Ph.D., Michael P. Siegenthaler, M.D., Carlo Arduino, M.D., Cecilia Mancini, M.Sc., Bernard Freudenthal, M.D., Horia C. Stanescu, M.D., Anselm A. Zdebik, M.D., Ph.D., R. Krishna Chaganti, M.D., Robert L. Nussbaum, M.D., Robert Kleta, M.D., Ph.D., William A. Gahl, M.D., Ph.D., and Manfred Boehm, M.D.

- Sisters and siblings now have their diagnosis
- New knowledge of this disease mechanism:
  - Will guide treatment development
  - May illuminate metabolic pathways involved in calcification – including osteoporosis

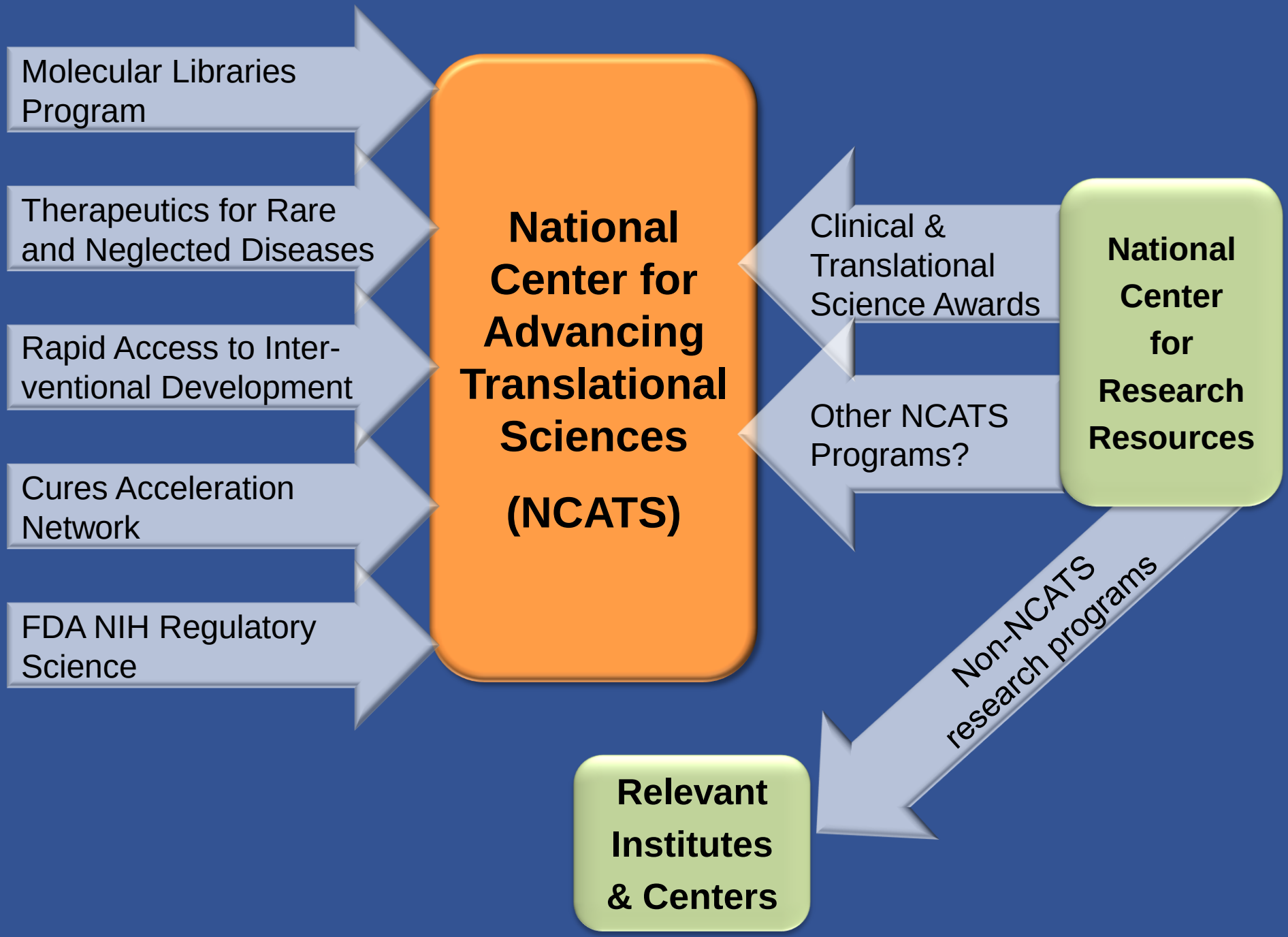
TCGA: Phase II

- FY2010 – FY 2011 budget: $275M
- Expansion: to identify recurrent genomic and epigenomic drivers for at least 20 cancers over next 5 years
  - 6 decided: lung, breast, kidney, endometrial, colon, and acute myeloid leukemia
  - Others to be added based on prevalence
- Data are made available rapidly to worldwide research community



NIH and AesRx partnership: next stage

- Will take Aes-103 beyond pre-clinical development and into initial clinical trials
- Trials (2) to be conducted in NIH Clinical Center
- Supported by NIH through TRND; Clinical Center; National Heart, Lung, and Blood Institute


Molecular Libraries Program
Therapeutics for Rare and Neglected Diseases
Rapid Access to Inter-ventional Development
Cures Acceleration Network
FDA NIH Regulatory Science
National Center for Advancing Translational Sciences (NCATS)
Clinical & Translational Science Awards
Other NCATS Programs?
National Center for Research Resources
Non-NCATS research programs
Relevant Institutes & Centers


National Center for Advancing Translational Sciences
(NCATS)
NIH Clinical Center
Relevant Institutes & Centers