The Human Genome and Individualized Medicine

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What is "Individualized Medicine" ??

"At it's most basic, personalized medicine refers to using information about a person's genetic makeup to tailor strategies for the detection, treatment or prevention of disease"

Francis Collins

Interview published July 17, 2005 in the Boston Globe

*Genetics & medicine, 2011: Some terms **

- Personal
  - ✓ Relating to somebody's private life, intimacy
  - ✓ Relating to one person, a particular individual
- Individual
  - ✓ A particular person, distinct from others

* Encarta World English Dictionary, 1999

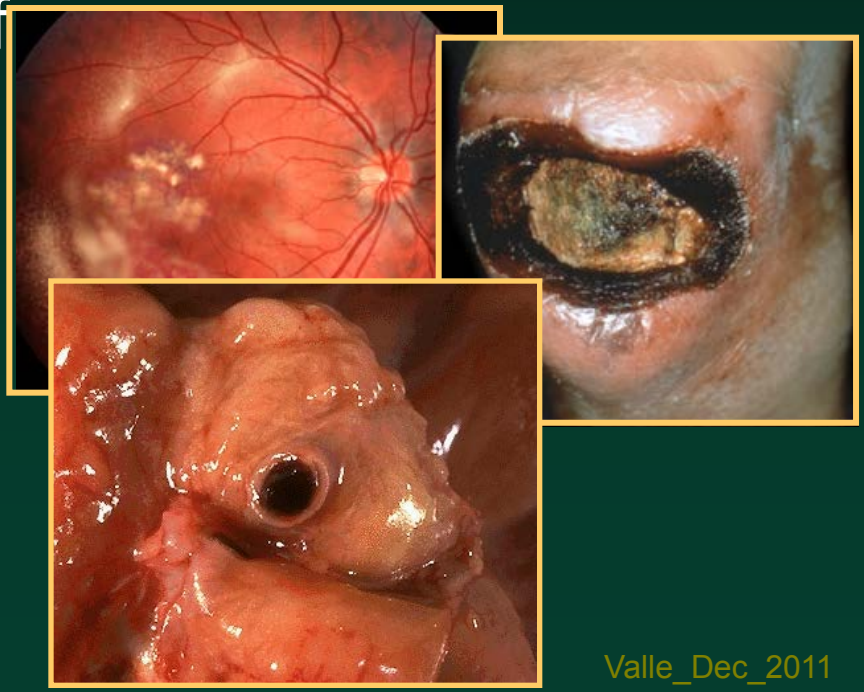
Individualized Medicine: Why now?

- Enormous success of modern medicine
  - ✓ Prolongation of lifespan
  - ✓ Improved quality of life
- Ongoing concerns
  - ✓ Many diseases with increasing incidence
  - ✓ Unacceptable frequency of adverse events
  - ✓ Increasing expense

Type 2 Diabetes

- Incidence increasing throughout the industrialized world and intertwined with obesity

- Chronic illness with an array of complications
  - ✓ Microvascular
  - ✓ Macrovascular



Suppose a member of your family develops type II diabetes …..

- Would you like to know the prognosis and response to existing treatments for the average patient?
- Or, would you like to know as precisely as possible the specific features, prognosis and response to therapy for your loved one?
- Even better, would you like to know ahead of time, assuming preventative measures were available???

Medicine of the 20th Century

- "Average medicine" – medicine for the average patient (the "classic case" mentality)

The “classic case” mentality

Medicine of the 20th Century

- "Average medicine" – medicine for the average patient (the "classic case" mentality)

- "Trial and error medicine" – trying possible treatments sequentially until you find one that works

Individualized medicine

"The experienced physician knows that no two patients are exactly alike"

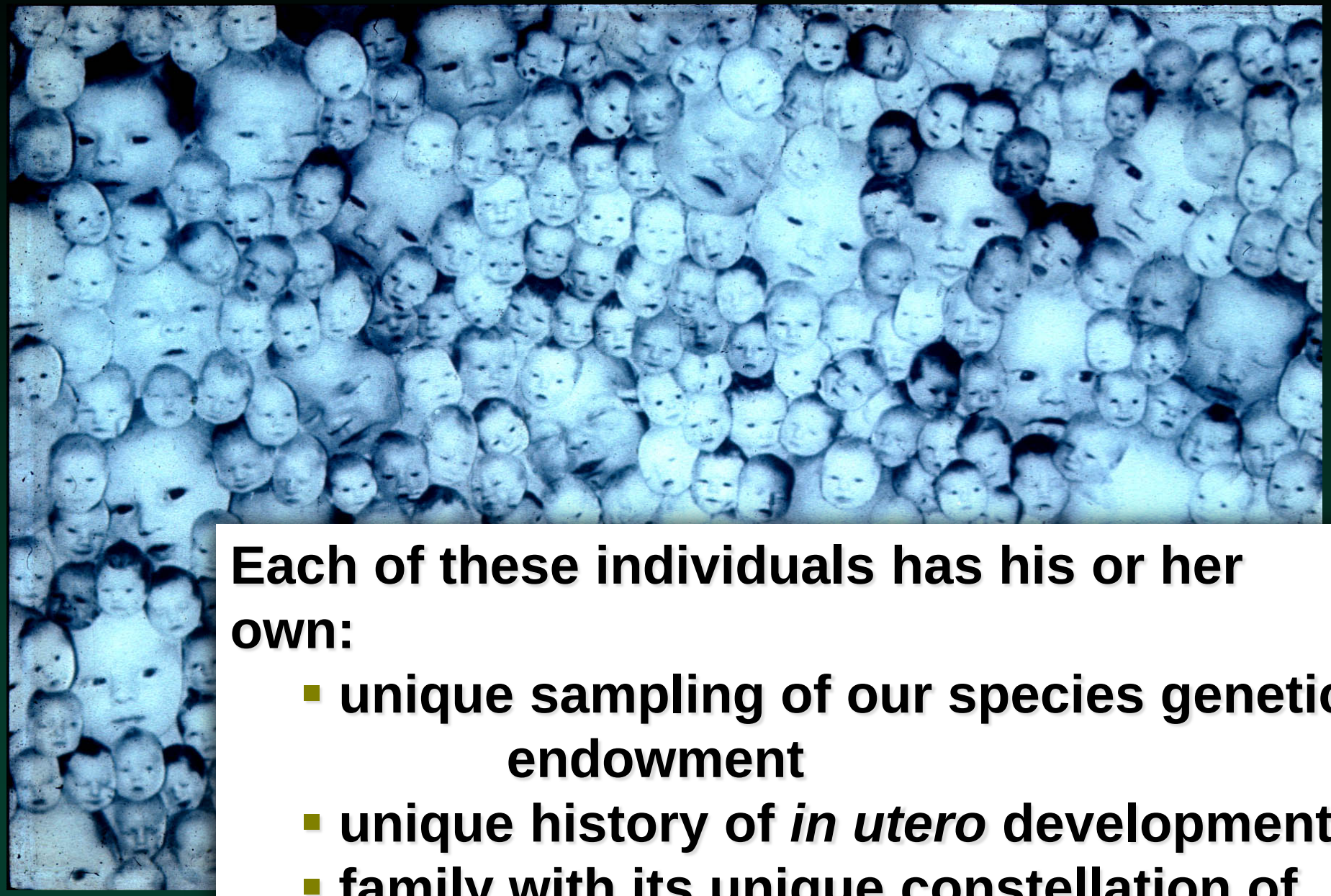
"There is no science of the individual, and medicine suffers from a fundamental contradiction: its practice deals with the individual while its theory grasps universals only"

O. Temkin, 1963

Not a new idea…..

"The doctor does not treat 'man' except accidentally; he treats Calius or Socrates or someone else... So if someone …knows the universal without knowing the individuals contained in it, he will often fail in his treatment; for it is the individual who has to be treated"

- Aristotle **~350 BC**



Each of these individuals has his or her own:

- **unique sampling of our species genetic endowment**
- **unique history of *in utero* development**
- **family with its unique constellation of socio-economic variables**

What has changed ??

- HGP, sequencing technology and appreciation of sequence variation
- Whole Genome Sequence (WGS) biology
- Increasing prominence of evolutionary thinking in medicine
- Disease gene identification

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- Individual genome sequences

Human Genome Project

- Conceived in the mid 1980's
- Debated and argued
- Oct 1, 1990 start date
- Initially focused on technology, maps & model organisms
- Reference human sequence complete in 2003

"All the News That's Fit to Print"

The New York Times

Washington Edition

Washington and Baltimore: Th storms by afternoon, high ne Tonight, showers end, lows in th 60's. Tomorrow, showers. Highs low 80's. Weather map is on Pag

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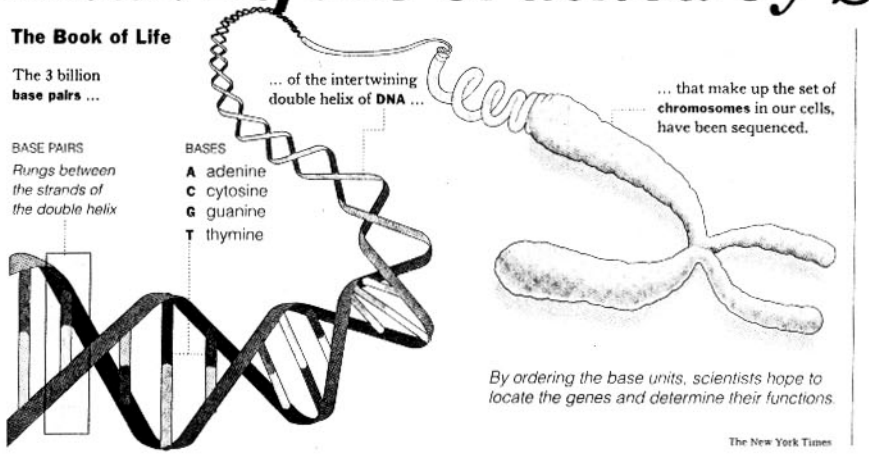
Genetic Code of Human Life Is Cracked by Scientists

The Book of Life

The 3 billion **base pairs** ... ... of the intertwining double helix of **DNA** ... ... that make up the set of **chromosomes** in our cells, have been sequenced.

BASE PAIRS
Rungs between the strands of the double helix

BASES
A adenine
C cytosine
G guanine
T thymine



By ordering the base units, scientists hope to locate the genes and determine their functions.

The New York Times

Science Times
A special issue

- Putting the genome to work.
- Some information has already paid research dividends.
- Two research methods, two results
- More articles, charts and photos of the genome effort.
- From Mendel to helix to genome.

Section D

Francis S. Collins, head of the Human Genome Project, right, with J. Craig Venter, head of Celera Genomics, after the announcement yesterday that they had finished the first survey of the human genome.

Paul Hosefros/The New York Times

A SHARED SUCCI

2 Rivals' Announcem Marks New Medic Era, Risks and All

By NICHOLAS WADE

WASHINGTON, June 26 — achievement that represents nacle of human self-knowledge rival groups of scientists said that they had deciphered the h tary script, the set of instruc that defines the human organis

"Today we are learning the guage in which God created President Clinton said at a W House ceremony attended by m bers of the two teams and, via s lite, Prime Minister Tony Bla England. [Excerpts, Page D8.]

The teams' leaders, Dr. J. C Venter, president of Celera G mics, and Dr. Francis S. Collins rector of the National Human nome Research Institute, pra each other's contributions and naled a spirit of cooperation f now on, even though the two eff will remain firmly independent.

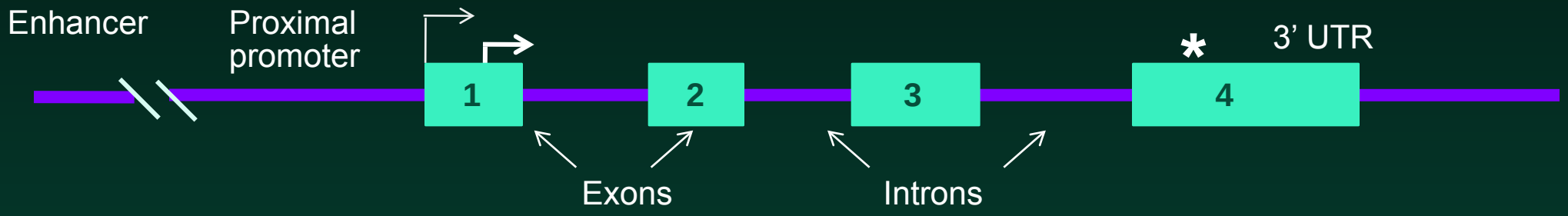
The human genome, the anc script that has now been deciphe consists of two sets of 23 giant D molecules, or chromosomes, each set — one inherited from e parent — containing more than th billion chemical units.

The successful deciphering of vast genetic archive attests to extraordinary pace of biology's

A Pearl and a Hodgepodge: Human DNA

Collins, director of the National Hu- Though scientists underscore the

What is a gene?



Some features of the reference genome

	Human (3.0 Gb)	Mouse (2.5 Gb)
Genes (protein coding)	~ 22,000	~ 22,000
known function	~ 75%	~ 75%
exons / transcript	8.7	8.4
total exons “exome”	~ 220,000	~ 210,000
the “exome”	~ 50 Mb (1.5%)	

DNA Sequence: Are We All the Same ?

- Humans are 99.6% identical at the sequence level
- Evolutionary perspective:
  - ✓ *H. sapiens* a young species (100 K yr) with a small founding population (~ 10,000)
  - ✓ Similarity with our relatives
    - 70-90% identity with mouse
    - 98.5% identity with chimp

27 October 2005

HapMap : A Database of Human Sequence Variation

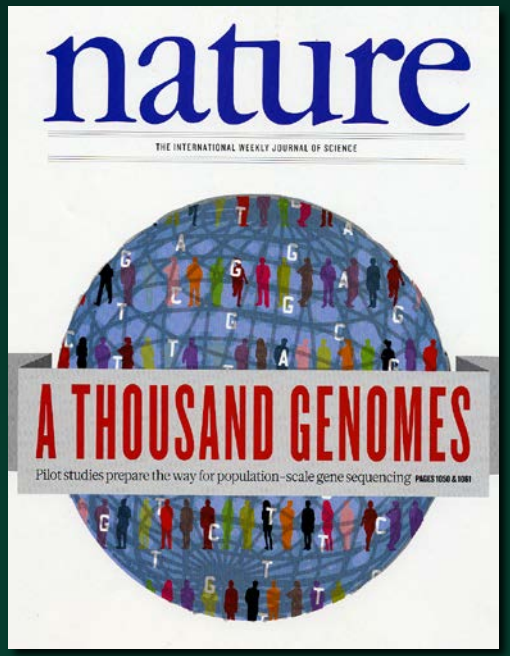
www.hapmap.org

A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

Nature 467: 1061, 2010

- Study ~2,500 individuals from ~50 populations
- Catalog >95% of variants with an allele frequency ≥ 1% across the genome
- Catalog lower frequency alleles (≥ 0.1%) in coding sequence



Sources of Genetic Variation

- Insertions / deletions -“indels” ~10%
- Length polymorphisms - STRp ~ 5%
- Single nucleotide polymorphisms (SNPs) ~ 45%
- Copy number variants (CNVs) ~
- Recombination
- Inversions ?

Single Nucleotide Polymorphisms (SNPs)

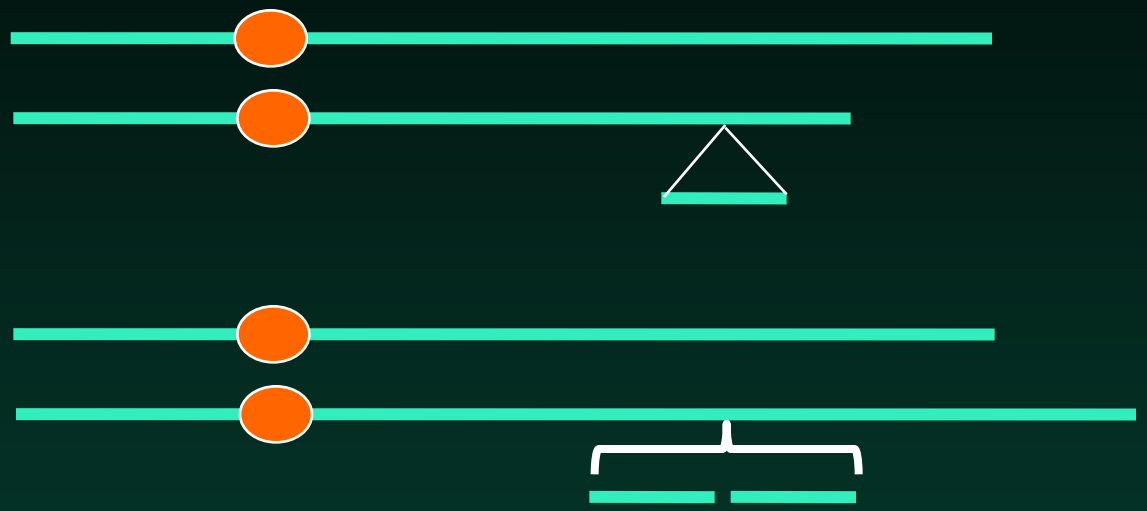
- Single base pair variant with both possibilities relatively frequent

  allele 1 … G A T C A …

  allele 2 … G A G C A …

- Frequent ~ 1/1000 bp or at least 3 x 10^6 per haploid genome
- Current SNP genotyping platforms score >1 x10^6 SNPs across the genome

Copy Number Variants (CNVs)



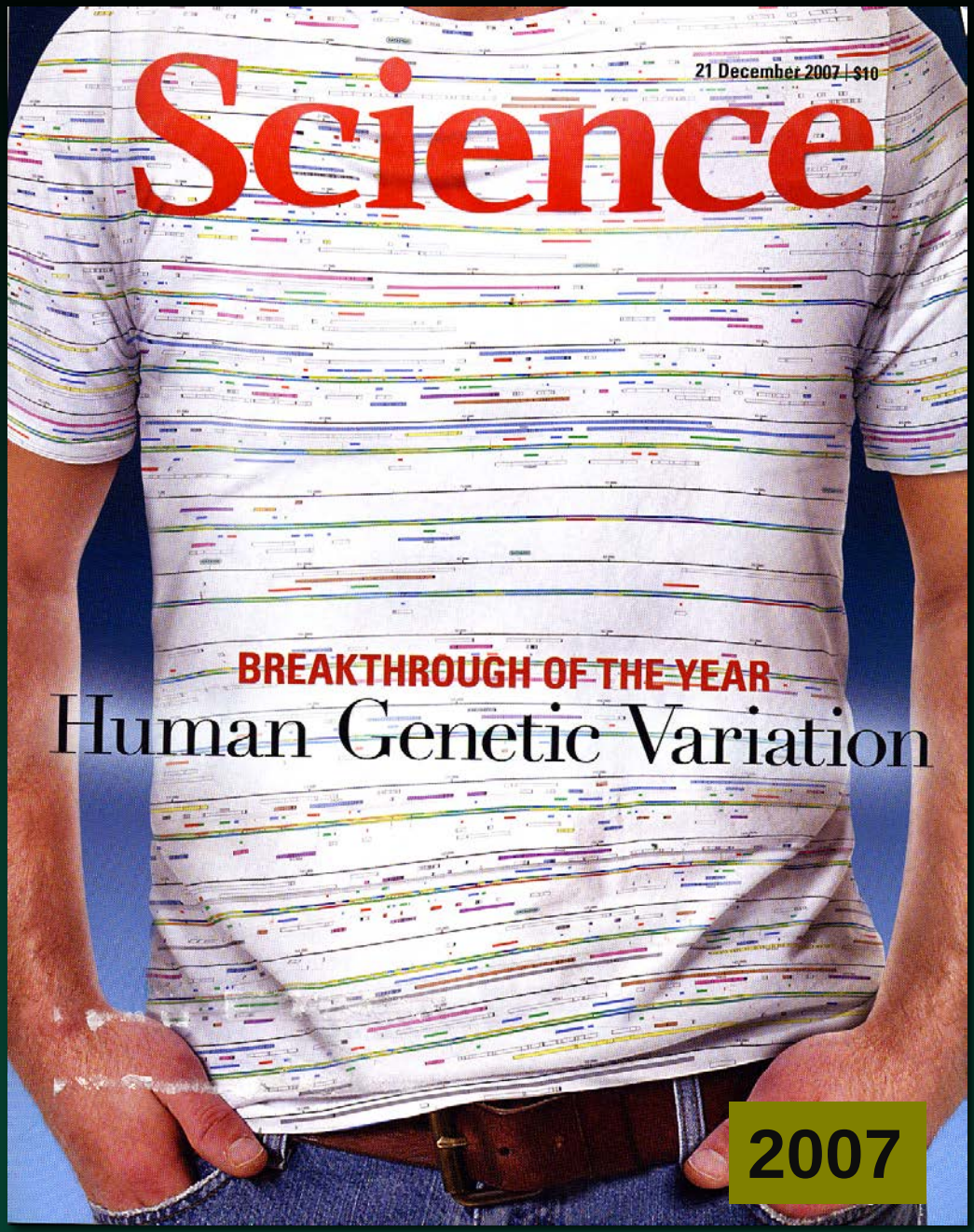
Deletion

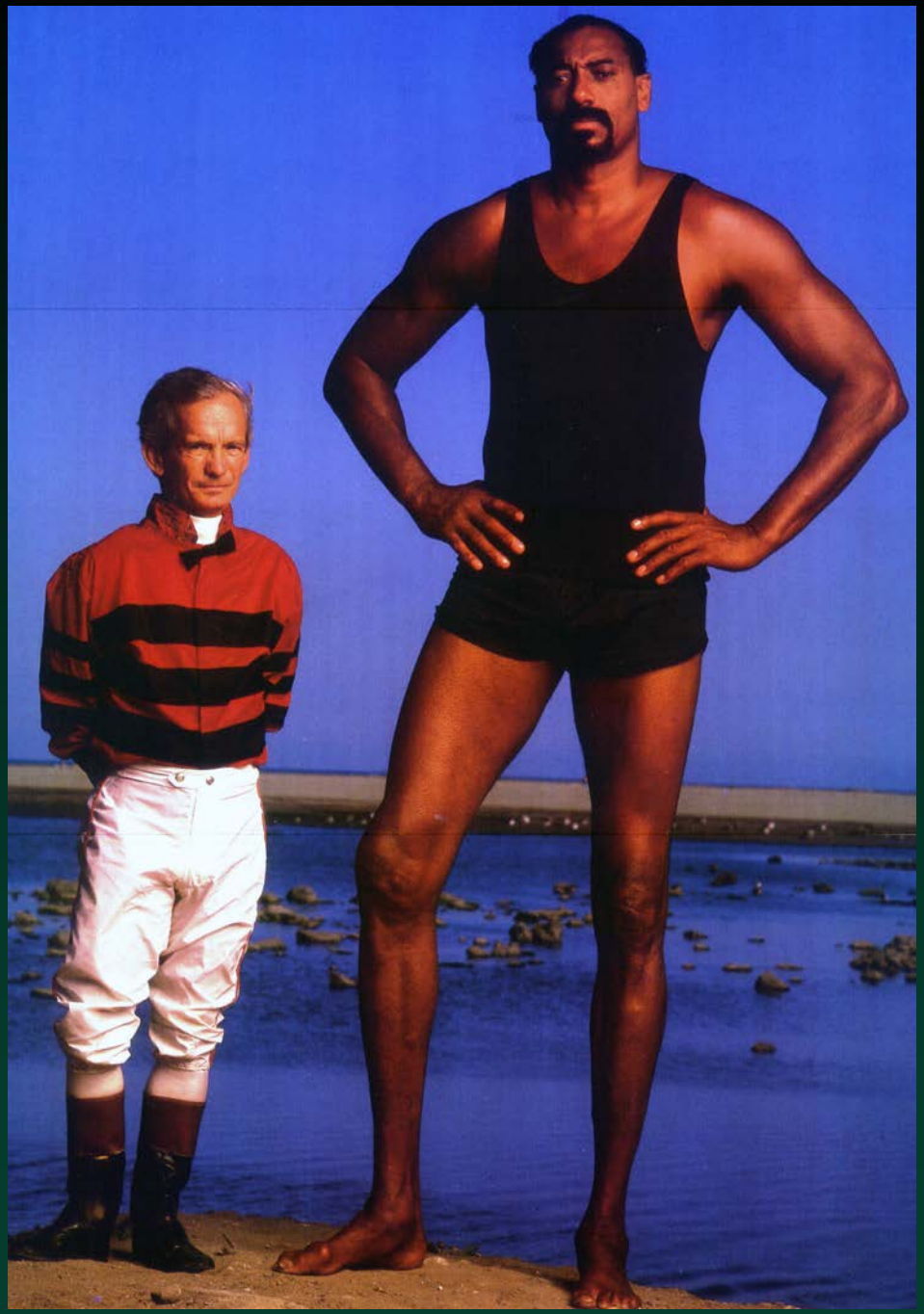
Duplication

- Expose dosage sensitive genes
- For deletions, expose otherwise “normal variation” on the remaining allele
- Create “fusion” genes with new functions

Increasing appreciation for human genetic variation

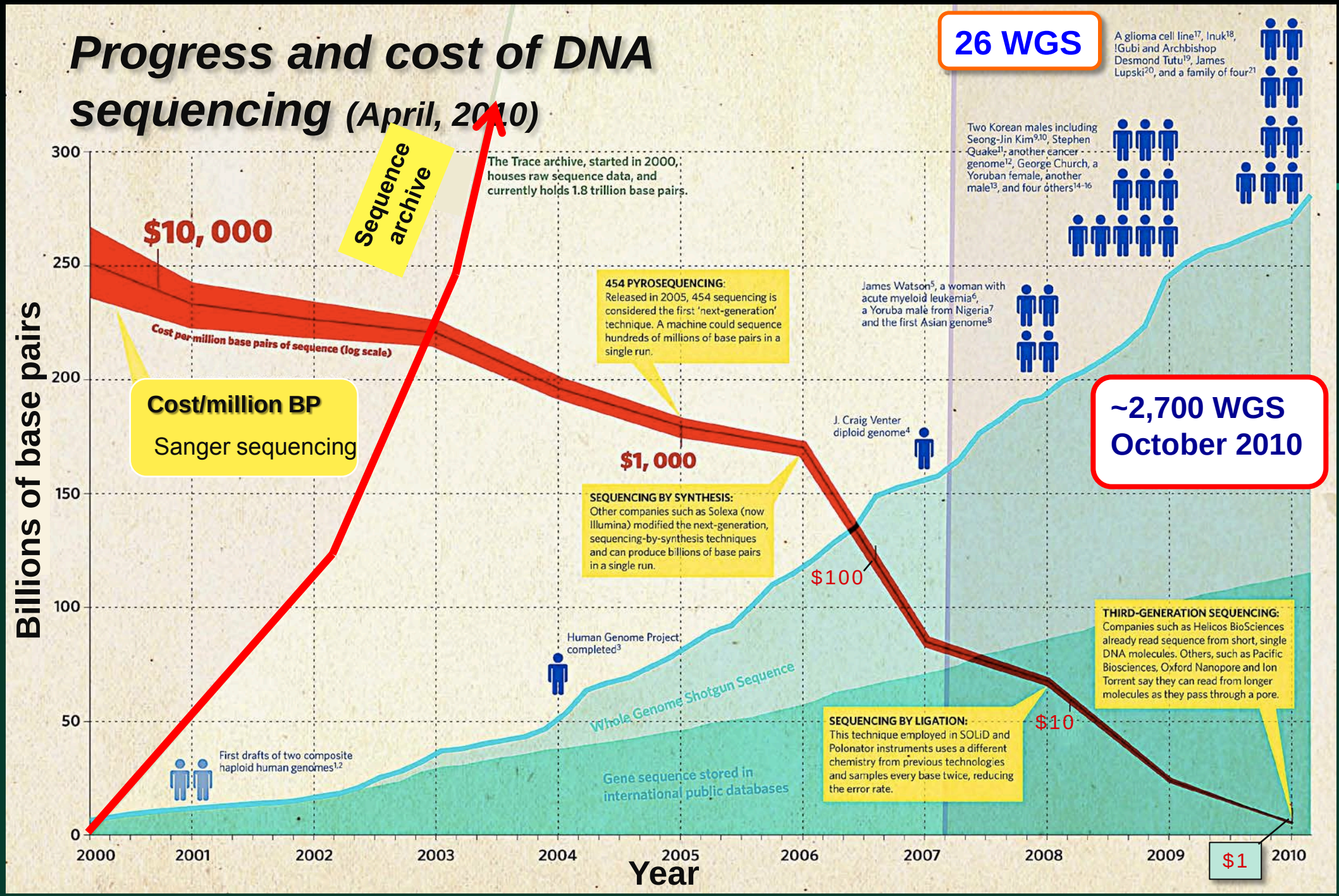
- SNPs
  - ✓ > 30 M in our species
  - ✓ ~ 3 M differences between individuals
- CNVs
  - ✓ 3-7 large CNVs/individual
  - ✓ 5-10% have 1 CNV > 100kb
  - ✓ 1-2 % have 1 CNV > 1 Mb





Human Variation

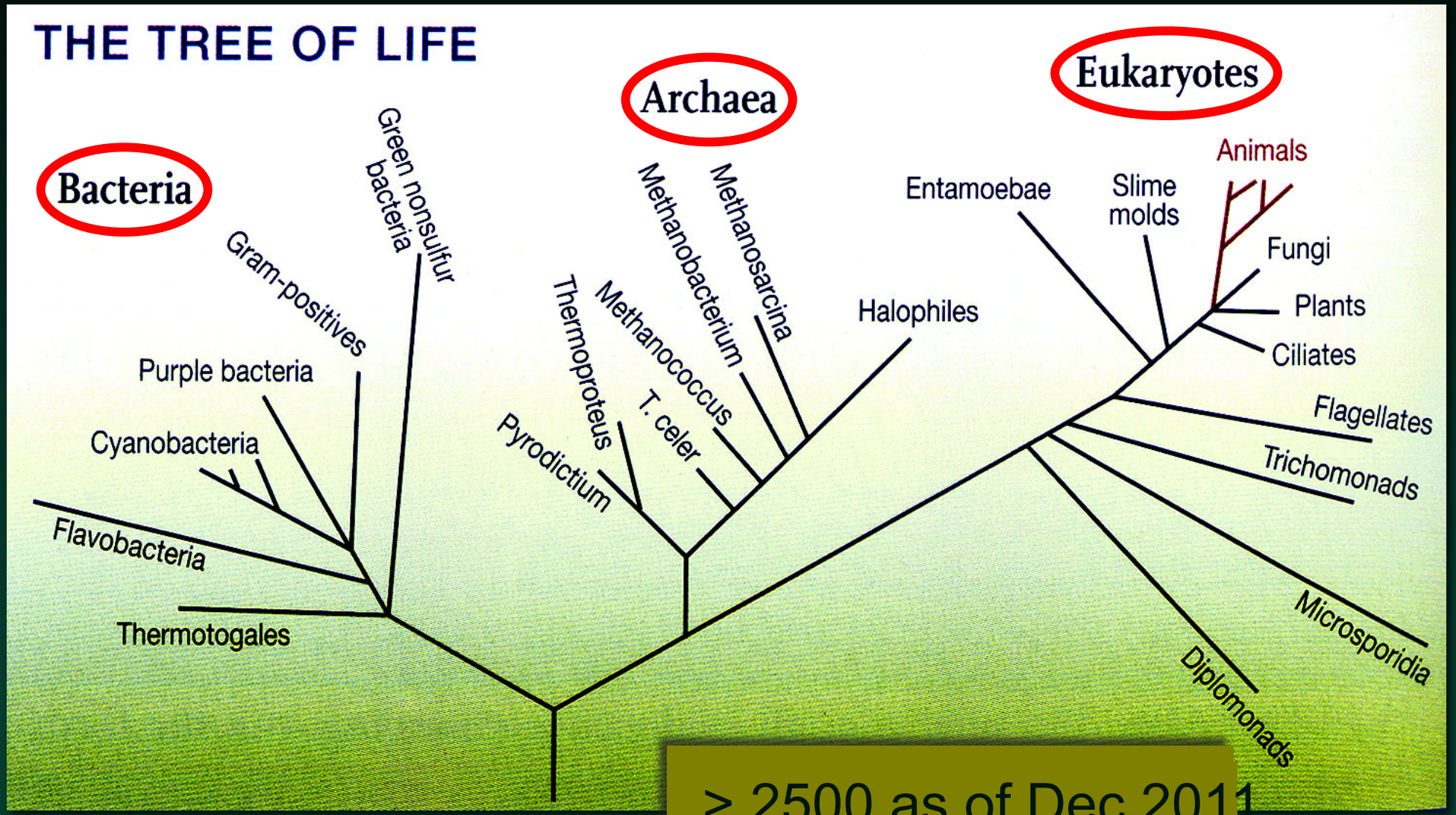
Differ at
only
~ 1 / 1000 bp !!


Progress and cost of DNA sequencing (April, 2010)
26 WGS
A glioma cell line[17], Inuk[18], !Gubi and Archbishop Desmond Tutu[19], James Lupski[20], and a family of four[21]
Two Korean males including Seong-Jin Kim[9,10], Stephen Quake[11], another cancer genome[12], George Church, a Yoruban female, another male[13], and four others[14-16]
Sequence archive
The Trace archive, started in 2000, houses raw sequence data, and currently holds 1.8 trillion base pairs.
$10, 000
Cost per million base pairs of sequence (log scale)
Cost/million BP
Sanger sequencing
454 PYROSEQUENCING: Released in 2005, 454 sequencing is considered the first 'next-generation' technique. A machine could sequence hundreds of millions of base pairs in a single run.
James Watson[5], a woman with acute myeloid leukemia[6], a Yoruba male from Nigeria[7] and the first Asian genome[8]
J. Craig Venter diploid genome[4]
$1, 000
SEQUENCING BY SYNTHESIS: Other companies such as Solexa (now Illumina) modified the next-generation, sequencing-by-synthesis techniques and can produce billions of base pairs in a single run.
~2,700 WGS October 2010
$100
Human Genome Project completed[3]
Whole Genome Shotgun Sequence
THIRD-GENERATION SEQUENCING: Companies such as Helicos BioSciences already read sequence from short, single DNA molecules. Others, such as Pacific Biosciences, Oxford Nanopore and Ion Torrent say they can read from longer molecules as they pass through a pore.
SEQUENCING BY LIGATION: This technique employed in SOLiD and Polonator instruments uses a different chemistry from previous technologies and samples every base twice, reducing the error rate.
$10
First drafts of two composite haploid human genomes[1,2]
Gene sequence stored in international public databases
$1
Billions of base pairs
0
50
100
150
200
250
300
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
Year

What has changed ??

- HGP, sequencing technology and appreciation of sequence variation
- Whole Genome Sequence (WGS) biology
- Increasing prominence of evolutionary thinking in medicine
- Disease gene identification
- Individual genome sequences

Whole genome sequences: bridges that connect all biology



> 2500 as of Dec 2011

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*Evolutionary thinking and medicine**

- Centrality of variation
- Continuity and consequences of natural selection
- Evolvability and systems biology
- Emphasis on integrated biology
- Individuality-- Selection acts on individuals

* Making evolutionary biology a basic science for medicine
Nesse et al, PNAS, Jan 2010

Comparative Genomics of Higher Primates

A Draft Sequence of the Neandertal Genome

Science 328: 710, 201

Richard E. Green,[1]*†‡ Johannes Krause,[1]†§ Adrian W. Briggs,[1]†§ Tomislav Maricic,[1]†§ Udo Stenzel,[1]†§ Martin Kircher,[1]†§ Nick Patterson,[2]†§ Heng Li,[2]† Weiwei Zhai,[3]†|| Markus Hsi-Yang Fritz,[4]† Nancy F. Hansen,[5]† Eric Y. Durand,[3]† Anna-Sapfo Malaspinas,[3]† Jeffrey D. Jensen,[6]† Tomas Marques-Bonet,[7,13]† Can Alkan,[7]† Kay Prüfer,[1]† Matthias Meyer,[1]† Hernán A. Burbano,[1]† Jeffrey M. Good,[1,8]† Rigo Schultz,[1] Ayinuer Aximu-Petri,[1] Anne Butthof,[1] Barbara Höber,[1] Barbara Höffner,[1] Madlen Siegemund,[1] Antje Weihmann,[1] Chad Nusbaum,[2] Eric S. Lander,[2] Carsten Russ,[2] Nathaniel Novod,[2] Jason Affourtit,[9] Michael Egholm,[9] Christine Verna,[21] Pavao Rudan,[10] Dejana Brajkovic,[11] Željko Kucan,[10] Ivan Gušic,[10] Vladimir B. Doronichev,[12] Liubov V. Golovanova,[12] Carles Lalueza-Fox,[13] Marco de la Rasilla,[14] Javier Fortea,[14]¶ Antonio Rosas,[15] Ralf W. Schmitz,[16,17] Philip L. F. Johnson,[18]† Evan E. Eichler,[7]† Daniel Falush,[19]† Ewan Birney,[4]† James C. Mullikin,[5]† Montgomery Slatkin,[3]† Rasmus Nielsen,[3]† Janet Kelso,[1]† Michael Lachmann,[1]† David Reich,[2,20]*† Svante Pääbo[1]*†

Some genes with positive selection around the time of divergence:

- *THADA – energy metab*
- *DYRK1A - cognition*
- *NRG3 - neurodevelopment*
- *several microRNAs*

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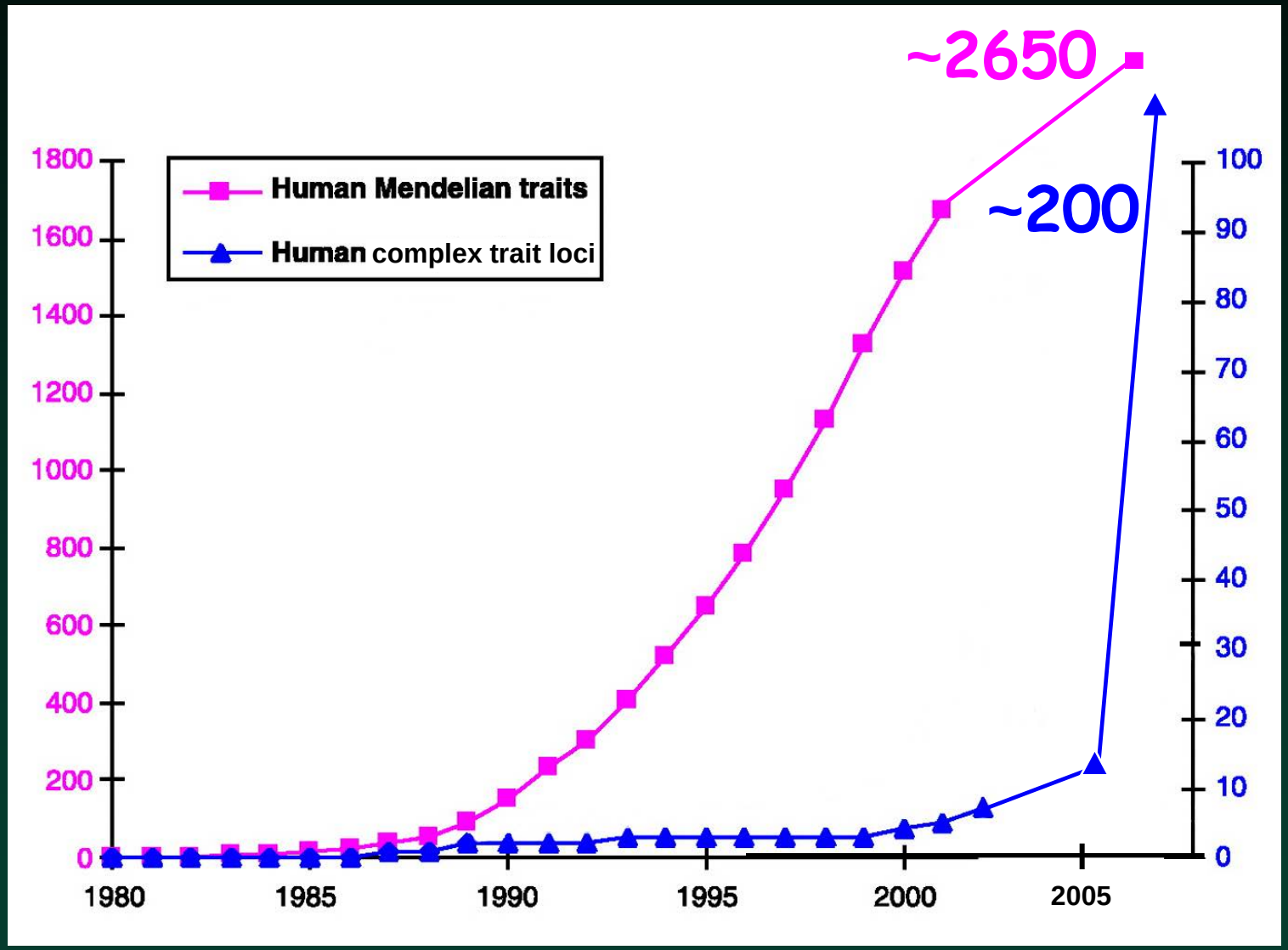
Progress in Disease Gene Identification – Dec 2

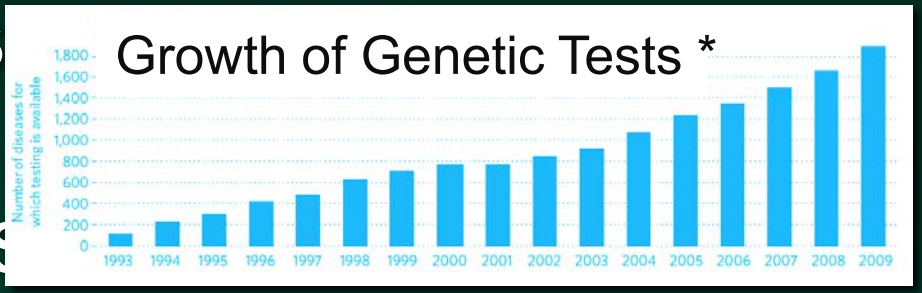


Number of monogenic disease genes

Number of complex trait genes

Progress in disease gene identification

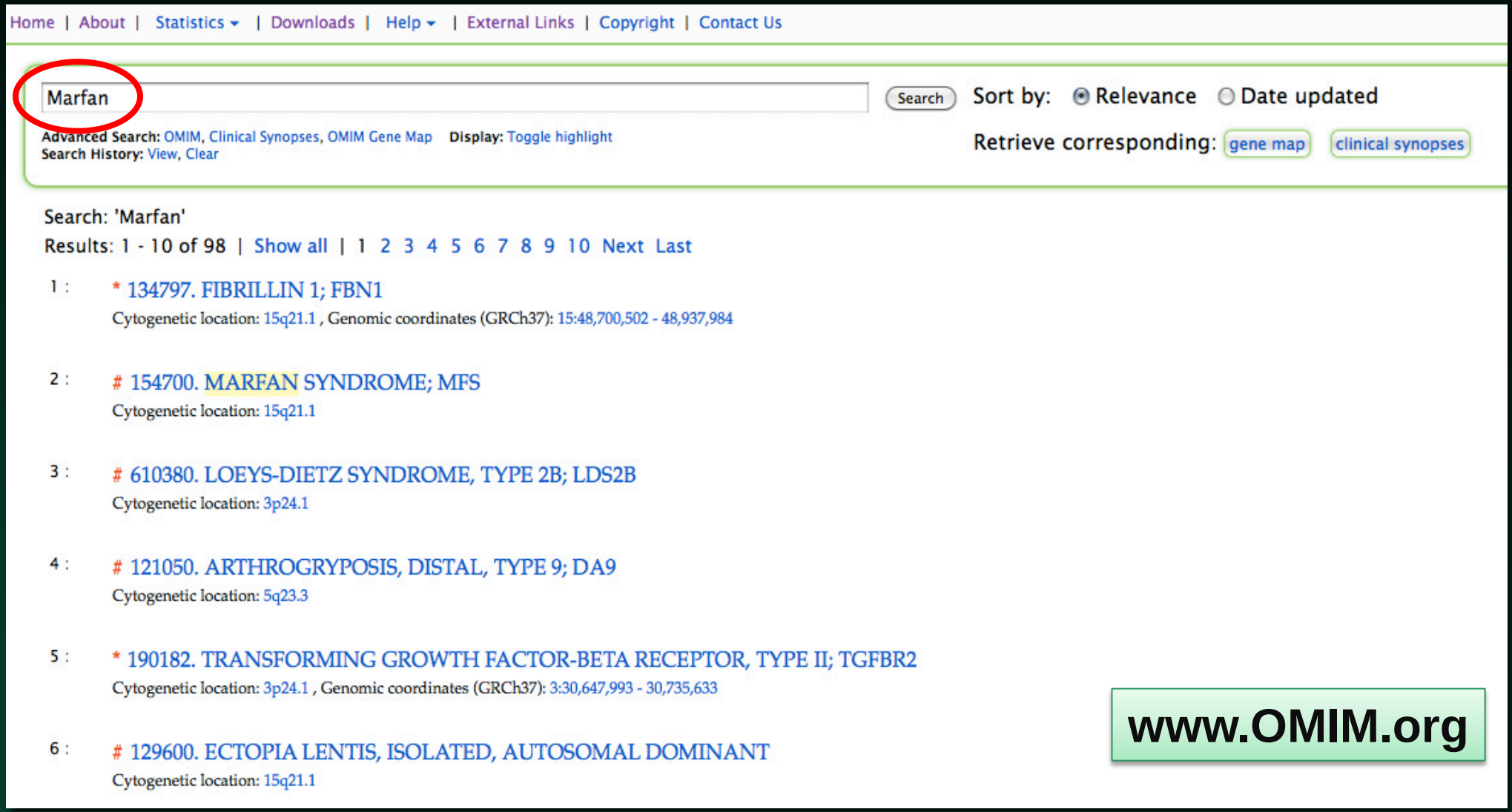
- OMIM lists ~2500 disease gen ~15% of total
- GeneTests lists >1900 diseases with molecular tests
- Molecular cytogenetics
- Progress in identifying genes contributing risk for complex traits



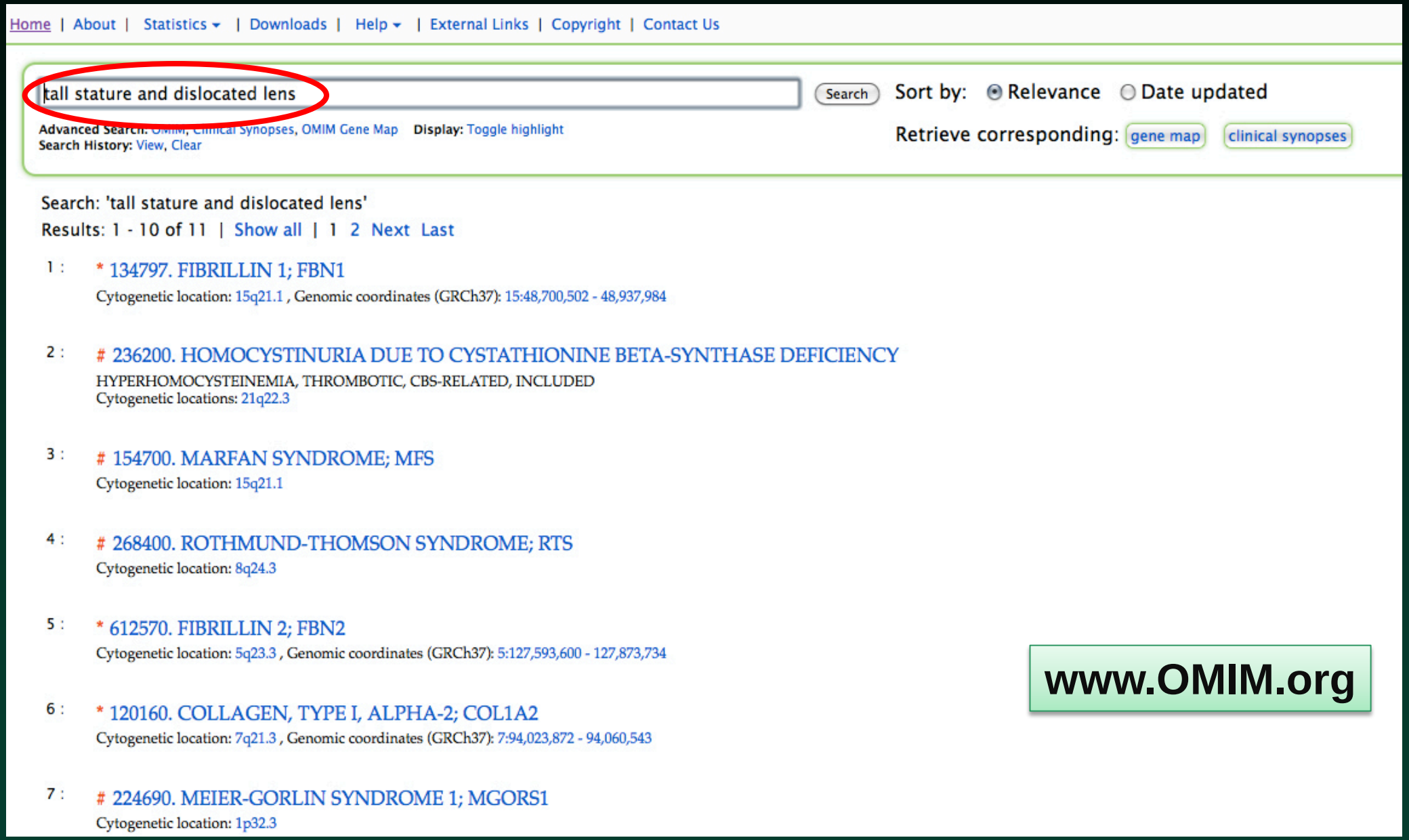
* Beaudet, Nature 466: 816, 201

Online Mendelian Inheritance in Man

Online Mendelian Inheritance in Man



Online Mendelian Inheritance in Man



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tall stature and dislocated lens

Search

Sort by: Relevance Date updated

Advanced Search: OMIM, Clinical Synopses, OMIM Gene Map Display: Toggle highlight

Search History: View, Clear

Retrieve corresponding: gene map clinical synopses

Search: 'tall stature and dislocated lens'

Results: 1 - 10 of 11 | Show all | 1 2 Next Last

1 : * 134797. FIBRILLIN 1; FBN1

Cytogenetic location: 15q21.1 , Genomic coordinates (GRCh37): 15:48,700,502 - 48,937,984

2 : # 236200. HOMOCYSTINURIA DUE TO CYSTATHIONINE BETA-SYNTHASE DEFICIENCY

HYPERHOMOCYSTEINEMIA, THROMBOTIC, CBS-RELATED, INCLUDED

Cytogenetic locations: 21q22.3

3 : # 154700. MARFAN SYNDROME; MFS

Cytogenetic location: 15q21.1

4 : # 268400. ROTHMUND-THOMSON SYNDROME; RTS

Cytogenetic location: 8q24.3

5 : * 612570. FIBRILLIN 2; FBN2

Cytogenetic location: 5q23.3 , Genomic coordinates (GRCh37): 5:127,593,600 - 127,873,734

6 : * 120160. COLLAGEN, TYPE I, ALPHA-2; COL1A2

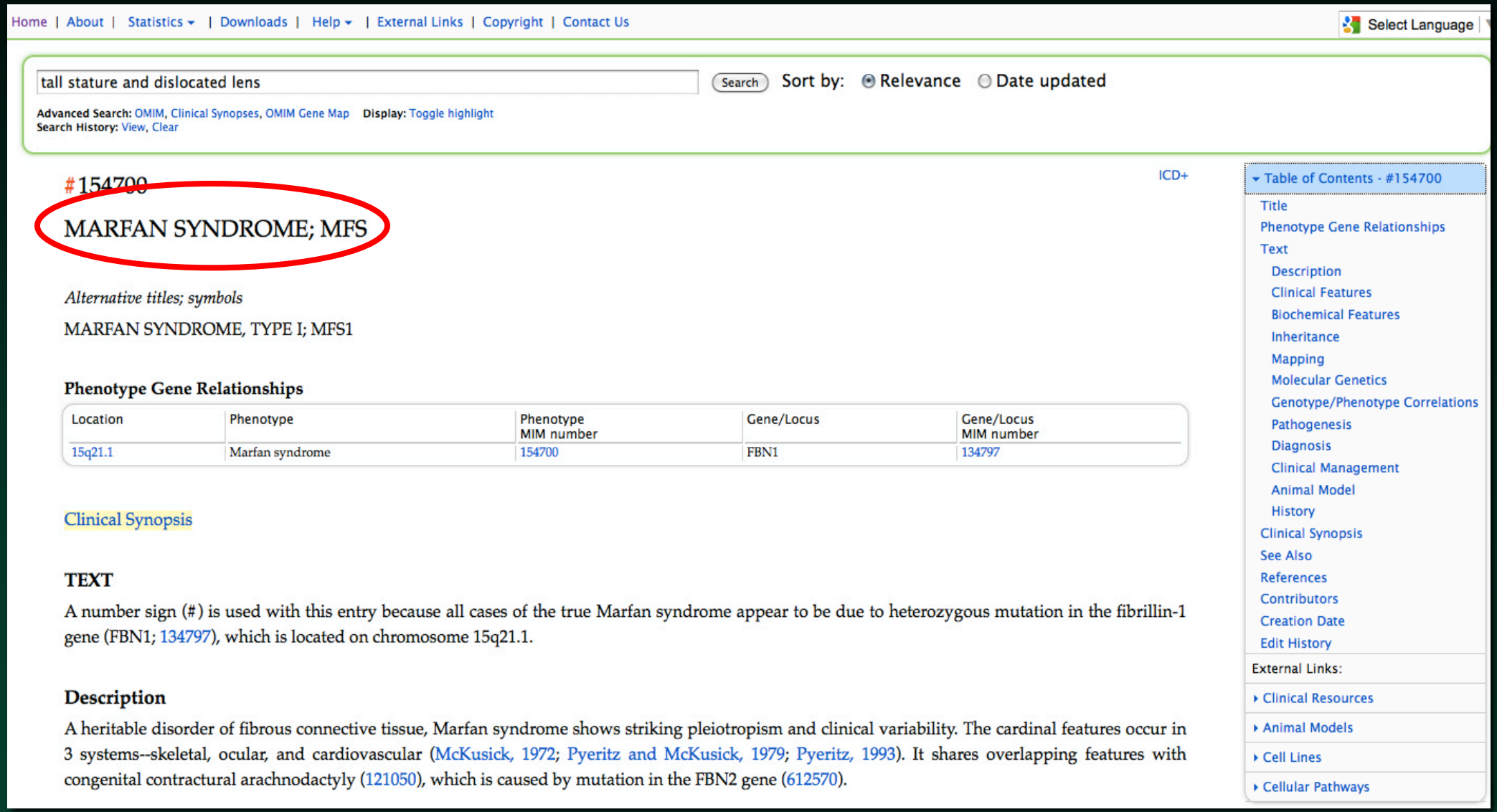
Cytogenetic location: 7q21.3 , Genomic coordinates (GRCh37): 7:94,023,872 - 94,060,543

7 : # 224690. MEIER-GORLIN SYNDROME 1; MGORS1

Cytogenetic location: 1p32.3

www.OMIM.org

Online Mendelian Inheritance in Man



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Select Language

tall stature and dislocated lens

Search

Sort by: Relevance Date updated

Advanced Search: OMIM, Clinical Synopses, OMIM Gene Map **Display:** Toggle highlight
Search History: View, Clear

ICD+

#154700

MARFAN SYNDROME; MFS

Alternative titles; symbols

MARFAN SYNDROME, TYPE I; MFS1

Phenotype Gene Relationships

Location	Phenotype	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
15q21.1	Marfan syndrome	154700	FBN1	134797

Clinical Synopsis

TEXT

A number sign (#) is used with this entry because all cases of the true Marfan syndrome appear to be due to heterozygous mutation in the fibrillin-1 gene (FBN1; 134797), which is located on chromosome 15q21.1.

Description

A heritable disorder of fibrous connective tissue, Marfan syndrome shows striking pleiotropism and clinical variability. The cardinal features occur in 3 systems--skeletal, ocular, and cardiovascular (McKusick, 1972; Pyeritz and McKusick, 1979; Pyeritz, 1993). It shares overlapping features with congenital contractural arachnodactyly (121050), which is caused by mutation in the FBN2 gene (612570).

Table of Contents - #154700

- Title
- Phenotype Gene Relationships
- Text
  - Description
  - Clinical Features
  - Biochemical Features
  - Inheritance
  - Mapping
  - Molecular Genetics
  - Genotype/Phenotype Correlations
  - Pathogenesis
  - Diagnosis
  - Clinical Management
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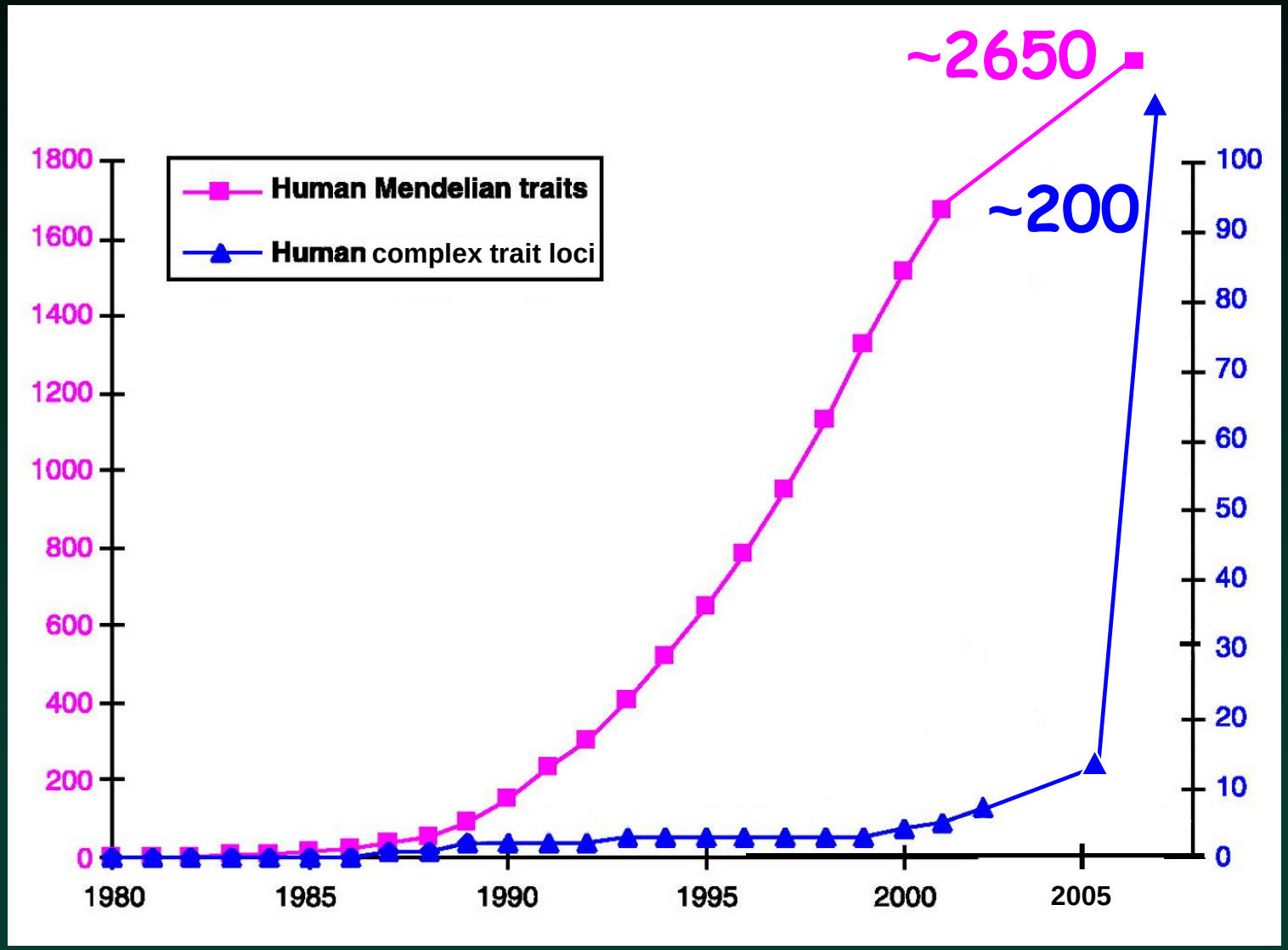
- See Also
- References
- Contributors
- Creation Date
- Edit History

External Links:

- Clinical Resources
- Animal Models
- Cell Lines
- Cellular Pathways

Progress in Disease Gene Identification – Dec 2



Number of monogenic disease genes

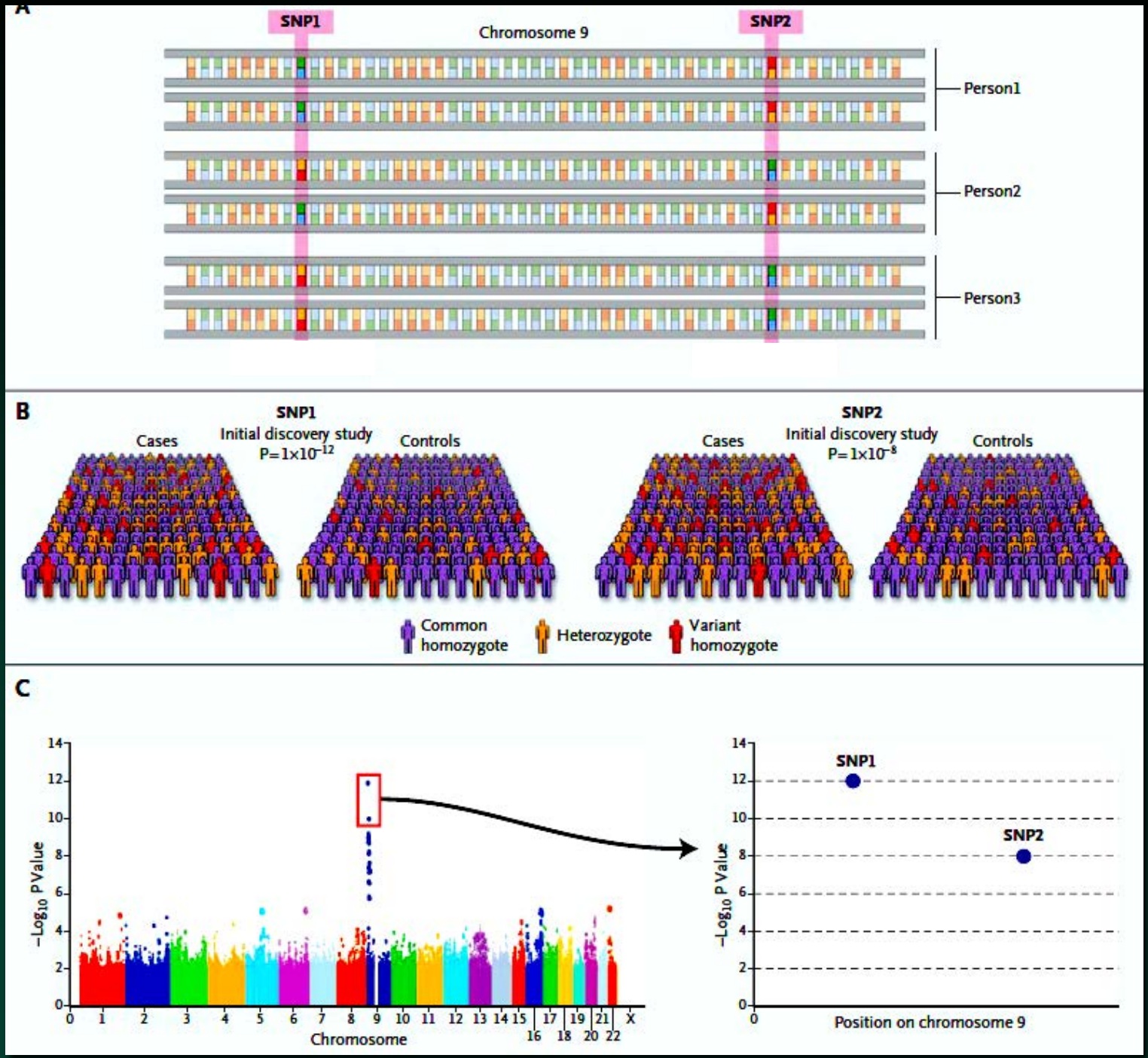
Number of complex trait genes

Genome wide association studies (GWAS)

- Agnostic approach that identifies SNP markers enriched in cases as compared to controls

- Identification of causative variants in LD with the marker leads to definition of genes & biological systems involved in the disease of interest

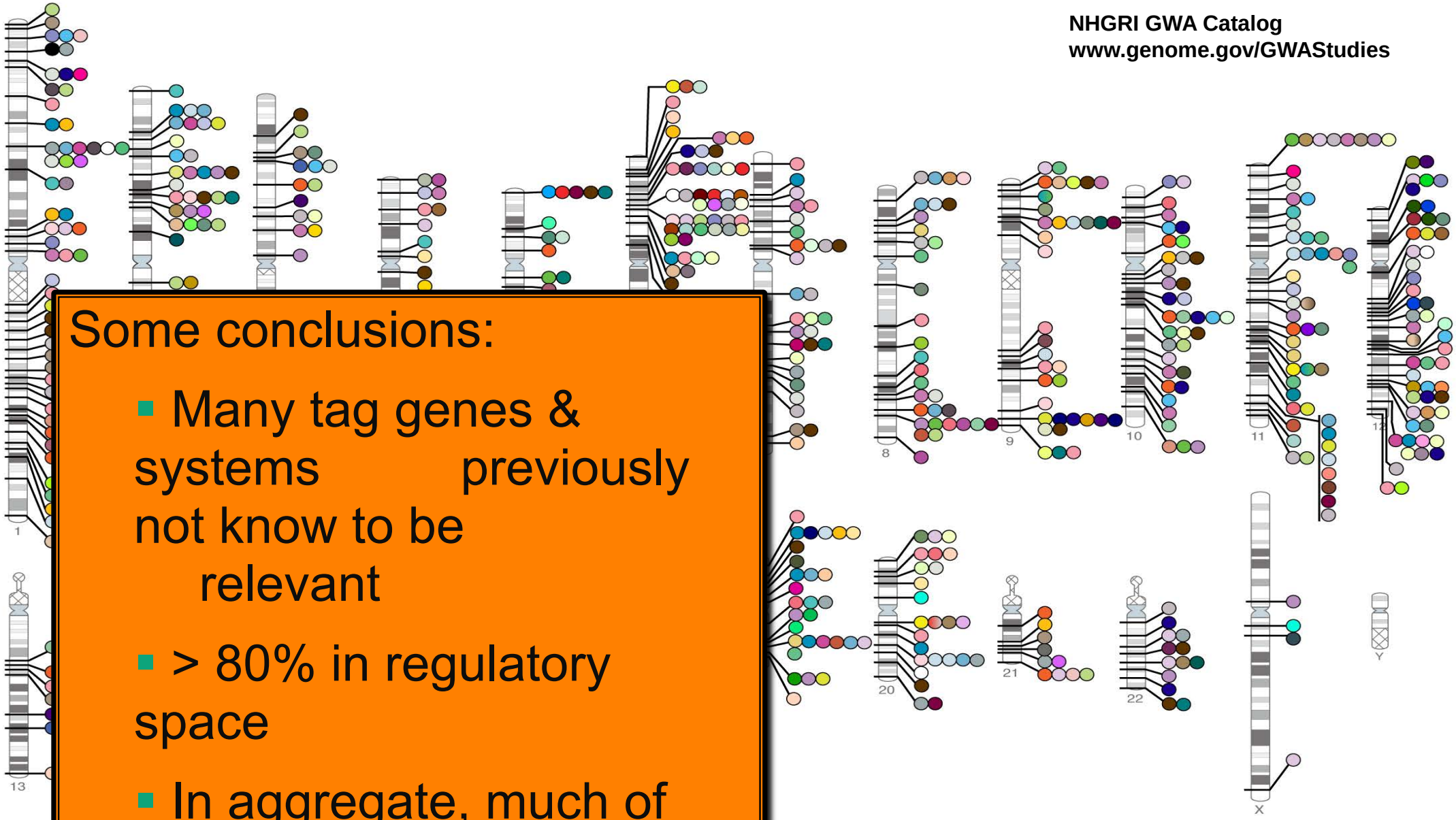
- Understanding pathophysiology increases the opportunity for prevention and/or treatment



Manolio, NEJM 363: 166, 2010

Published Genome-Wide Associations through 3/2011,
779 published GWA at $p \leq 5 \times 10^{-8}$ for 205 traits

NHGRI GWA Catalog
www.genome.gov/GWAStudies



Some conclusions:

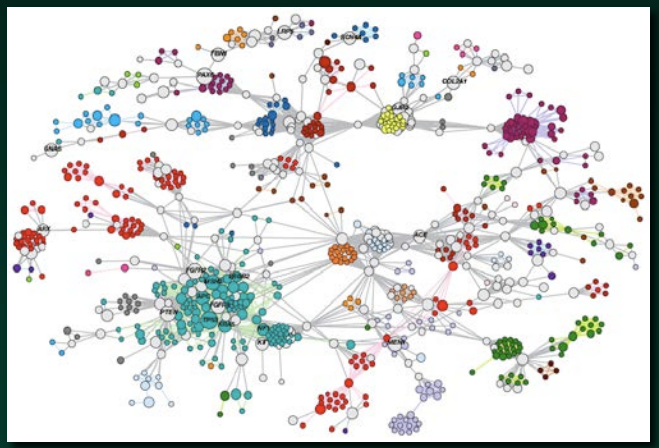
- Many tag genes & systems previously not know to be relevant
- > 80% in regulatory space
- In aggregate, much of heritability remains to

The missing “Dark Matter”

Variants so far identified explain from < 5% - 60% of the variation for various phenotypes

The problem of poor predictive valu

"the risk allele at this SNP confers a risk to individuals that is only 1.2 x greater than those who do not have the risk allele"



- Calculated in populations, applied to individuals
- Biologically naïve
- Need for a biologically – based analytic methods that consider the constellation of variants as well as developmental, environmental and epigenetic variants in a particular individual

Table 1 | Thirty-seven loci that displayed genome-wide significance in the meta-analysis

Locus & SNP id	Metabolic trait	*P* value	Relationship between gene function and the associated metabolic traits	Biomedical and pharmaceutical interest
ACADS rs2066938	Butyrylcarnitine/propionylcarnitine	$< 4.4 \times 10^{-305}$	Butyrylcarnitine$^+$ and propionylcarnitine$^+$ are substrates/products of ACADS	ACADS is a key enzyme in mitochondrial fatty acid β-oxidation
NAT8 rs13391552	N-acetylornithine	5.4×10^{-252}	N-acetyltransferase function of NAT8 matches the associating metabolite N-acetylornithine$^+$	Association with **glomerular filtration** and **CKD**; association of N-acetylornithine$^+$ with eGFR in this study
FADS1 rs174547	1-arachidonoylglycerophosphoethanolamine/ 1-linoleoylglycerophosphoethanolamine	8.5×10^{-116}	FADS1 substrate/product pair ratio arachidonate (20:4n6)$^+$/dihomo-linolenate (20:3n3 or n6)$^+$ is among the top associations	Association with **LDL cholesterol, HDL cholesterol and triglycerides, fasting glucose and homeostatic model assessment B (HOMA-B) Crohn's disease** and **resting heart rate**
UGT1A rs887829	Bilirubin (E,E)/oleoylcarnitine	2.9×10^{-74}	Bilirubin$^+$ is a substrate of UGT1A1	Association with **hyperbilirubinaemia**; low serum concentrations of bilirubin associate with increased risk of CAD; a SNP in *UGT1A1* is a pharmacogenetic risk factor for irinotecan toxicity
ACADM rs211718	Hexanoylcarnitine/oleate (18:1n9)	2.2×10^{-71}	Hexanoylcarnitine$^+$ is a substrate of ACADM	ACADM is a key enzyme in mitochondrial fatty acid β-oxidation
OPLAH rs6558295	5-oxoproline	1.5×10^{-59}	5-oxoproline$^+$ is a substrate of 5-oxoprolinase OPLAH	
SCD rs603424	Myristate (14:0)/myristoleate (14:1n5)	2.9×10^{-57}	SCD catalyses the Δ-9-desaturation of fatty acids, such as myristate (14:0)$^+$ to myristoleate (14:1n5)$^+$ and palmitate (16:0)$^+$ to palmitoleate (16:1n7)$^+$	Palmitoleate (16:1n7) is a lipokine linking adipose tissue to systemic metabolism
GCKR rs780094	Glucose/mannose	5.5×10^{-53}	GCKR has a role in glucose homeostasis; strong association with mannose$^+$ to glucose$^+$ ratios matches the gene's function	Association with **type 2 diabetes, fasting glucose, fasting insulin; serum uric acid; triglyceride levels; C-reactive protein; serum creatinine (eGFRcrea), Crohn's disease** and **hypertriglyceridaemia**

What has changed ??

- HGP, sequencing technology and appreciation of sequence variation
- Whole Genome Sequence (WGS) biology
- Increasing prominence of evolutionary thinking in medicine
- Disease gene identification
- Individual genome sequences

OPEN ACCESS Freely available online

4 September, 2007 PLOS BIOLOGY

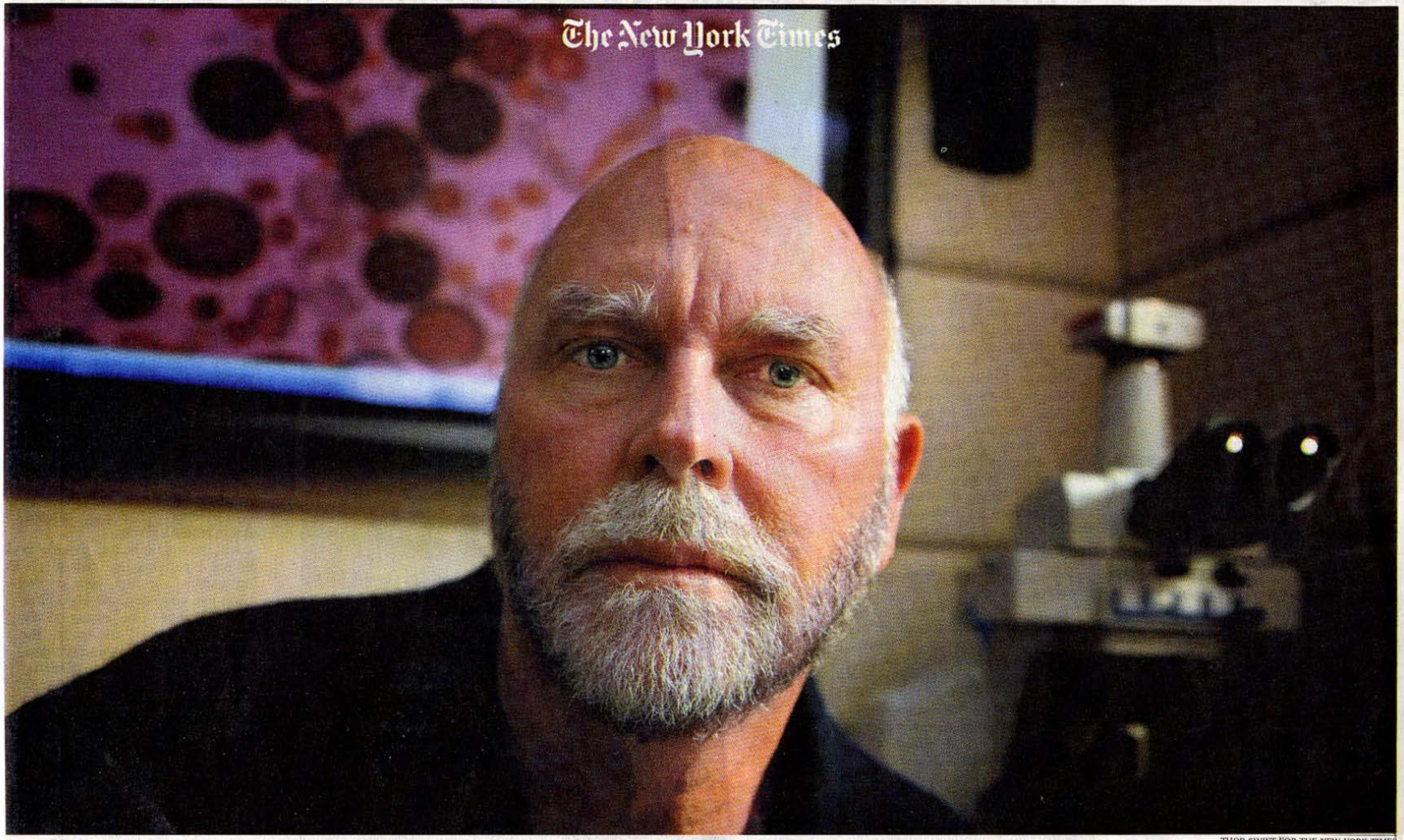
The Diploid Genome Sequence of an Individual Human

Samuel Levy[1*], Granger Sutton[1], Pauline C. Ng[1], Lars Feuk[2], Aaron L. Halpern[1], Brian P. Walenz[1], Nelson Axelrod[1], Jiaqi Huang[1], Ewen F. Kirkness[1], Gennady Denisov[1], Yuan Lin[1], Jeffrey R. MacDonald[2], Andy Wing Chun Pang[2], Mary Shago[2], Timothy B. Stockwell[1], Alexia Tsiamouri[1], Vineet Bafna[3], Vikas Bansal[3], Saul A. Kravitz[1], Dana A. Busam[1], Karen Y. Beeson[1], Tina C. McIntosh[1], Karin A. Remington[1], Josep F. Abril[4], John Gill[1], Jon Borman[1], Yu-Hui Rogers[1], Marvin E. Frazier[1], Stephen W. Scherer[2], Robert L. Strausberg[1], J. Craig Venter[1]

1 J. Craig Venter Institute, Rockville, Maryland, United States of America, **2** Program in Genetics and Genomic Biology, The Hospital for Sick Children, and Molecular and Medical Genetics, University of Toronto, Toronto, Ontario, Canada, **3** Department of Computer Science and Engineering, University of California San Diego, La Jolla, California, United States of America, **4** Genetics Department, Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain

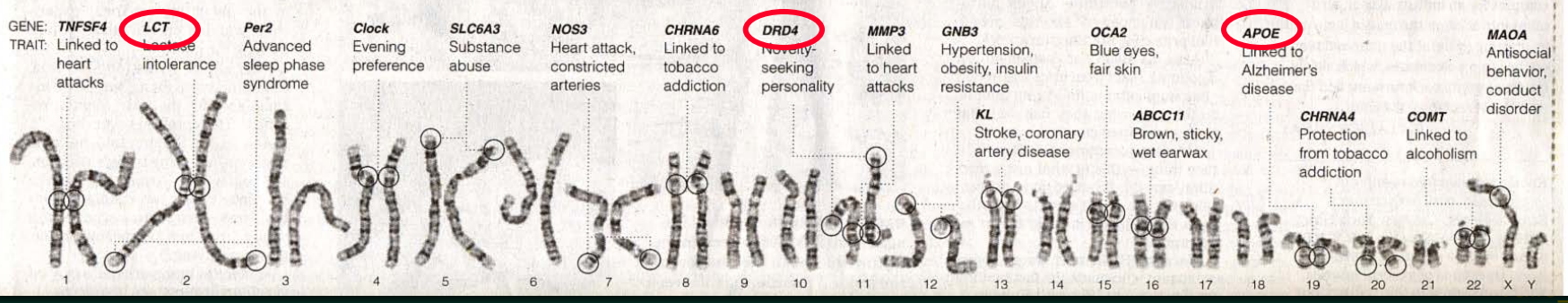
- 4.1 million variants vs. reference sequence including
- 3.2 million SNPS
- ~ 300,000 CNVs
- 90 inversions
- total covers 12.3 MB

The New York Times



THOR SWIFT FOR THE NEW YORK TIMES

DECODING HIMSELF A team led by J. Craig Venter, above, has finished the first mapping of a full, or dilpoid, genome, made up of DNA inherited from both parents. The genome is Dr. Venter's own.



Dr. Cerani on rounds,
Eugene Smith

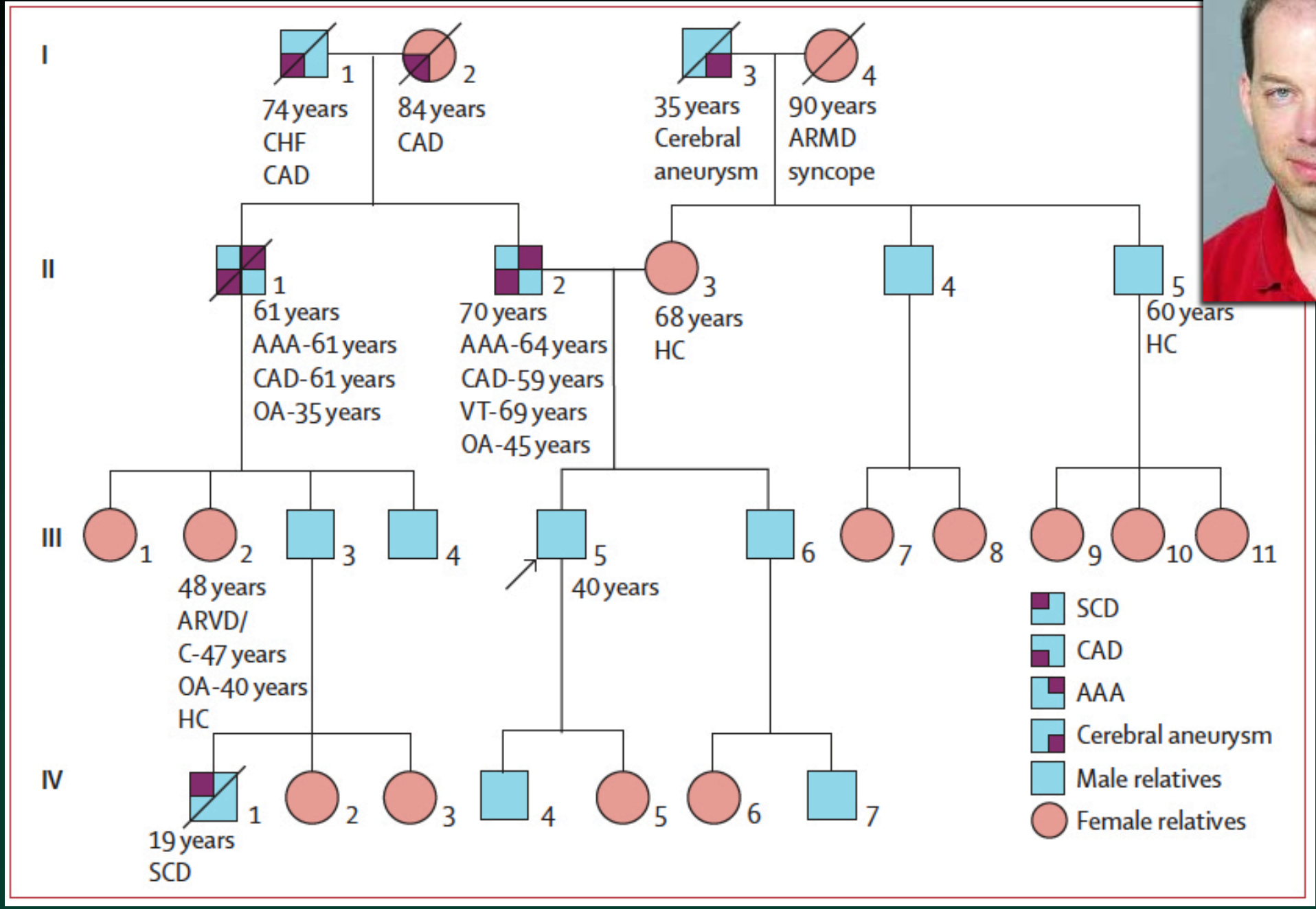
What does this all mean for medicine?

Science of the Individual: Some Consequences for Medicine

- Exposes the pitfalls of typological thinking - the classical case mentality
- Confirms physiologic view of disease - each individual has their own disease
- Emphasizes the importance of asking:

  " Why does this patient have this illness at this time?"
- What prevention/treatment best for this individual?

The stimulus of sudden cardiac death (SCD)



1 Medical geneticist
1 Genetic counselor

Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Lancet 375: 1525, 2010

"The explanatory power and path to clinical translation of risk estimates for common variants reported in GWAS remain unclear. …present analytical methods are insufficient to make genetic data accessible in a clinical context, and the clinical usefulness of these data for individual patients has not been formally assessed. We aim to undertake an integrated analysis of a complete human genome in a clinical context."

Going forward: the path to individualized medicine

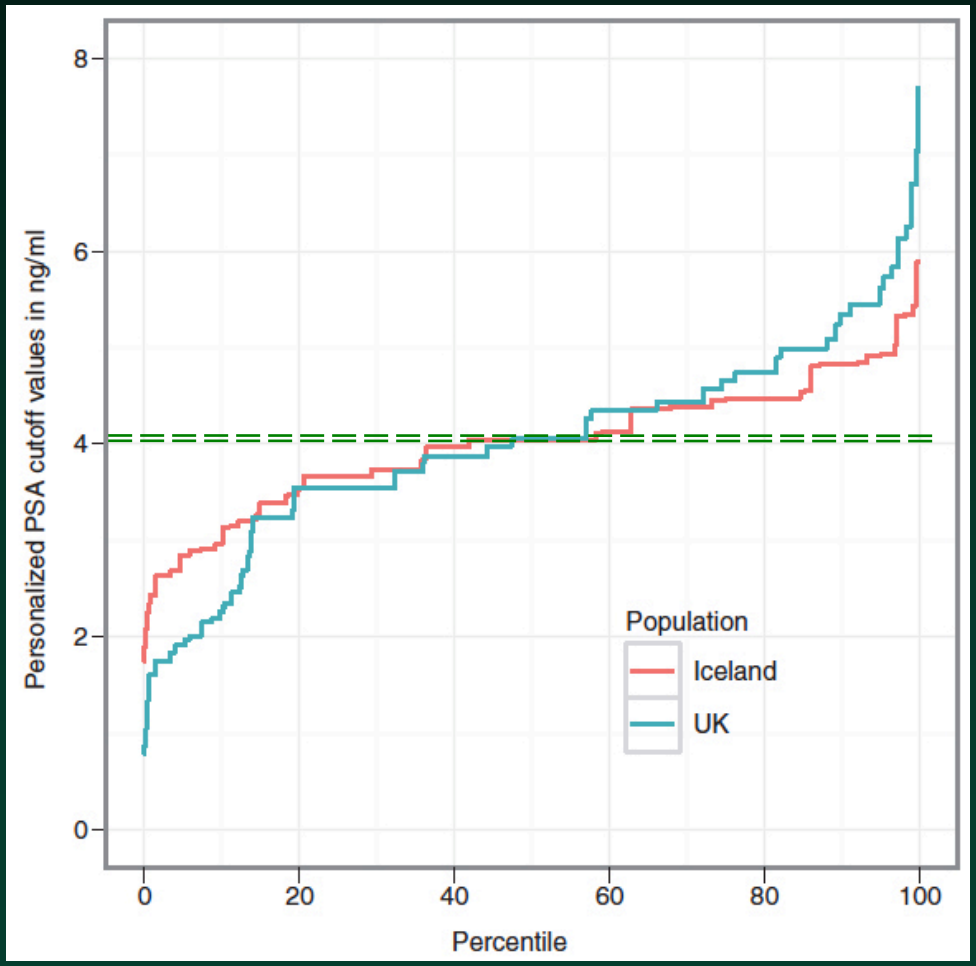
- Rigorous research – basic, translational and clinical
- New technology will greatly accelerate the pace
- Will not be quick but has already begun…
  - ✓ Acute lymphoblastic leukemia
  - ✓ Sickle cell disease
  - ✓ Glioblastoma multiforme & isocitrate dehydrogenase I (12% of tumors het for

HUMAN GENETICS

Genetic Correction of PSA Values Using Sequence Variants Associated with PSA Levels

Gudmundsson … Stefansson, Sci Transl Med 2: 62ra92, 2010

- ~40% variation in PSA levels is genetic
- Influenced by at least 6 loci
- 3834 men with PSA levels and prostate bx
- Suggests individualized PSA cutoff value (i.e. the population average) too high for some and too low for others



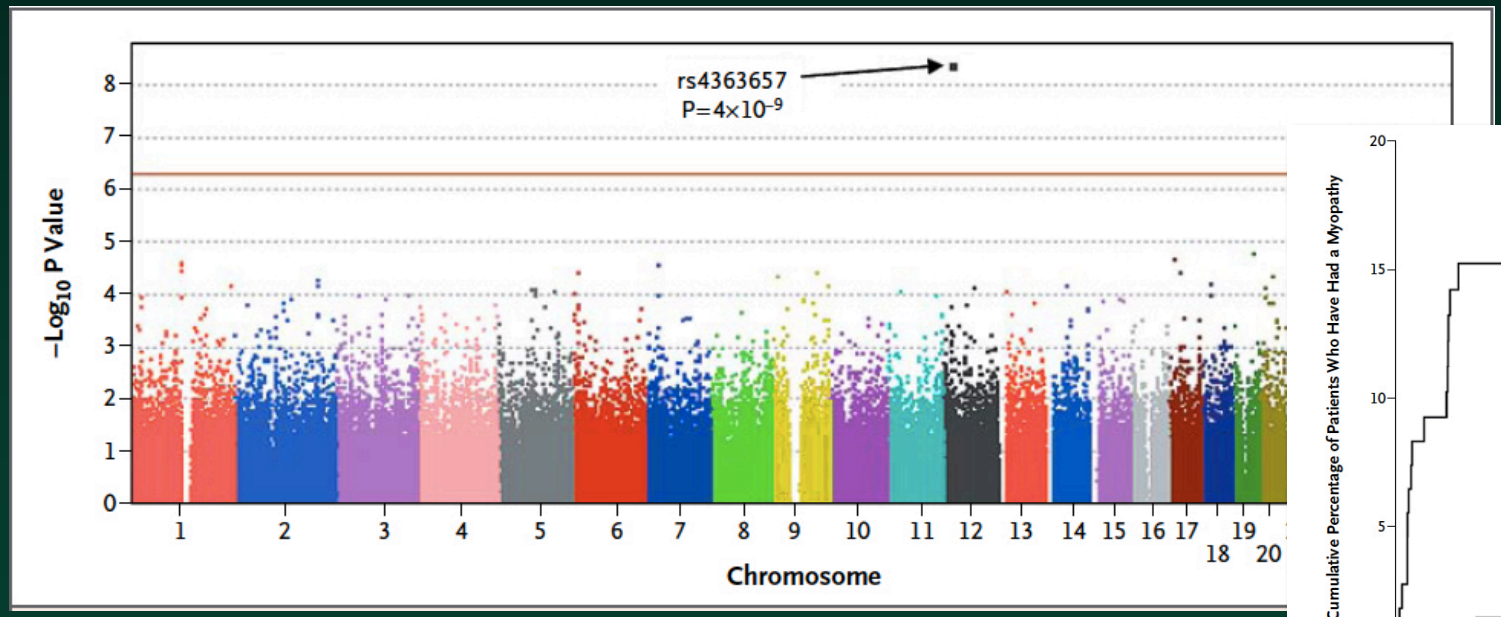
The special case of pharmacogenetics

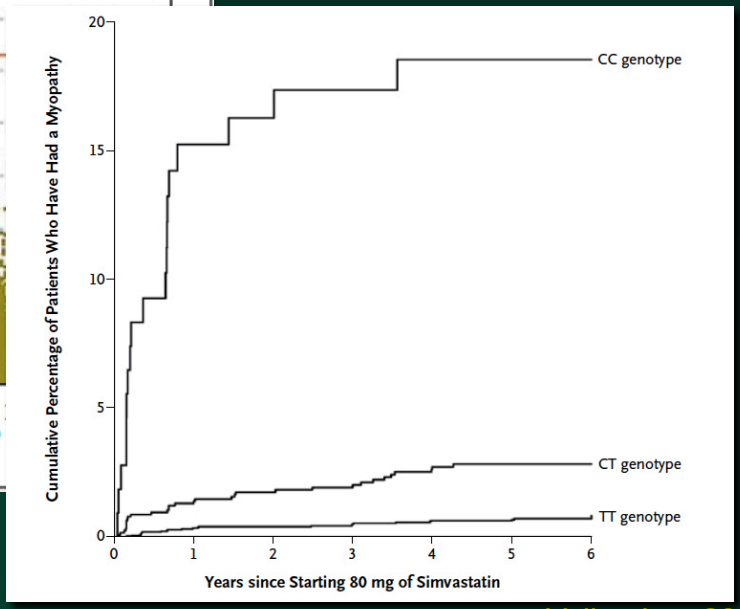
- Environmental variable well defined in terms of timing and amount
- Drug and drug metabolites can be measured
- Metabolism often known
- Alternatives available

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

Search Collaborative Group, NEJM 359: 789, 20

- Odds ratio for myopathy 4.3 in heterozygotes; 17.4 in homozygotes



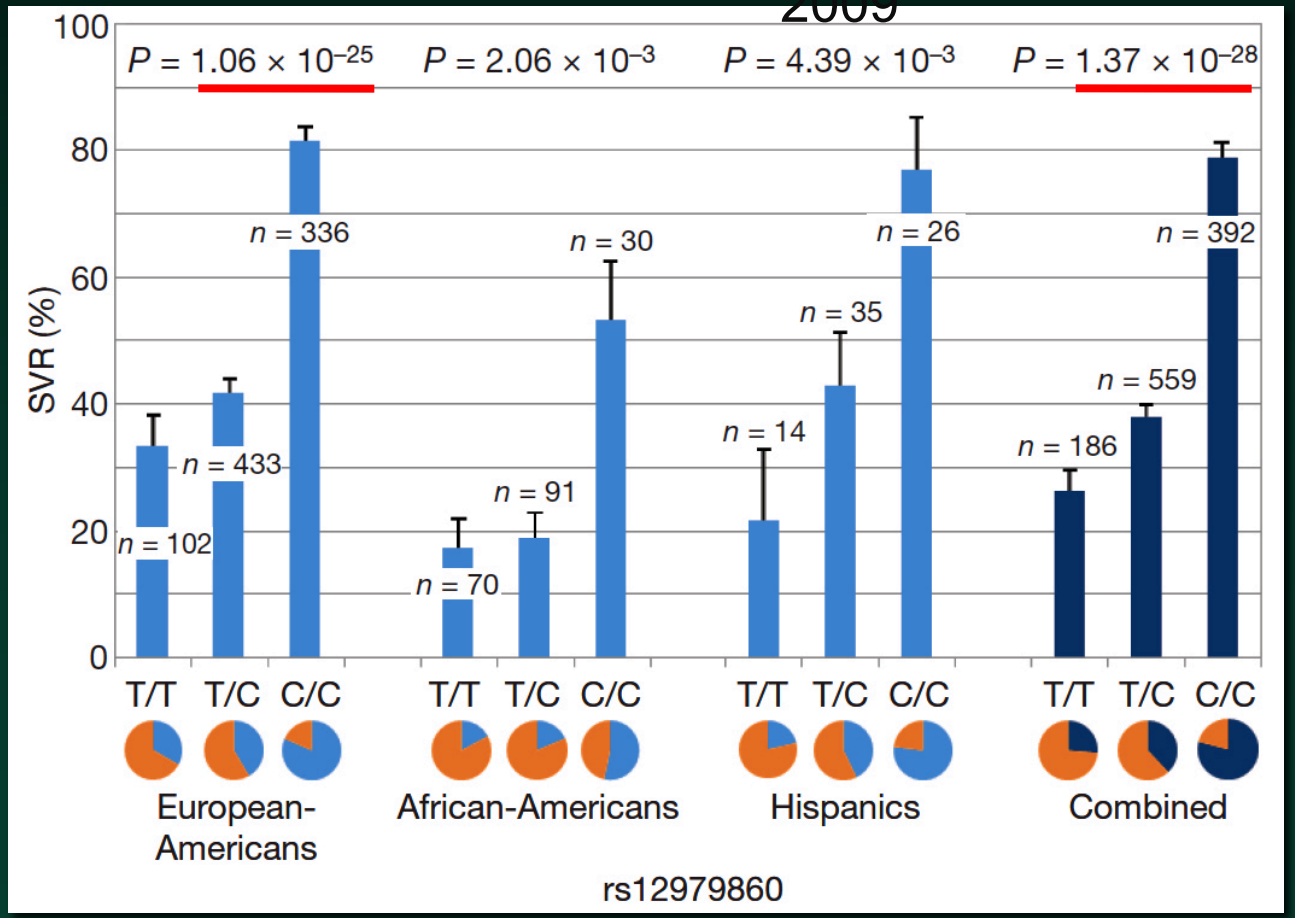


Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

Dongliang Ge[1], Jacques Fellay[1], Alexander J. Thompson[2], Jason S. Simon[3], Kevin V. Shianna[1], Thomas J. Urban[1], Erin L. Heinzen[1], Ping Qiu[3], Arthur H. Bertelsen[3], Andrew J. Muir[2], Mark Sulkowski[4], John G. McHutchison[2] & David B. Goldstein[1]

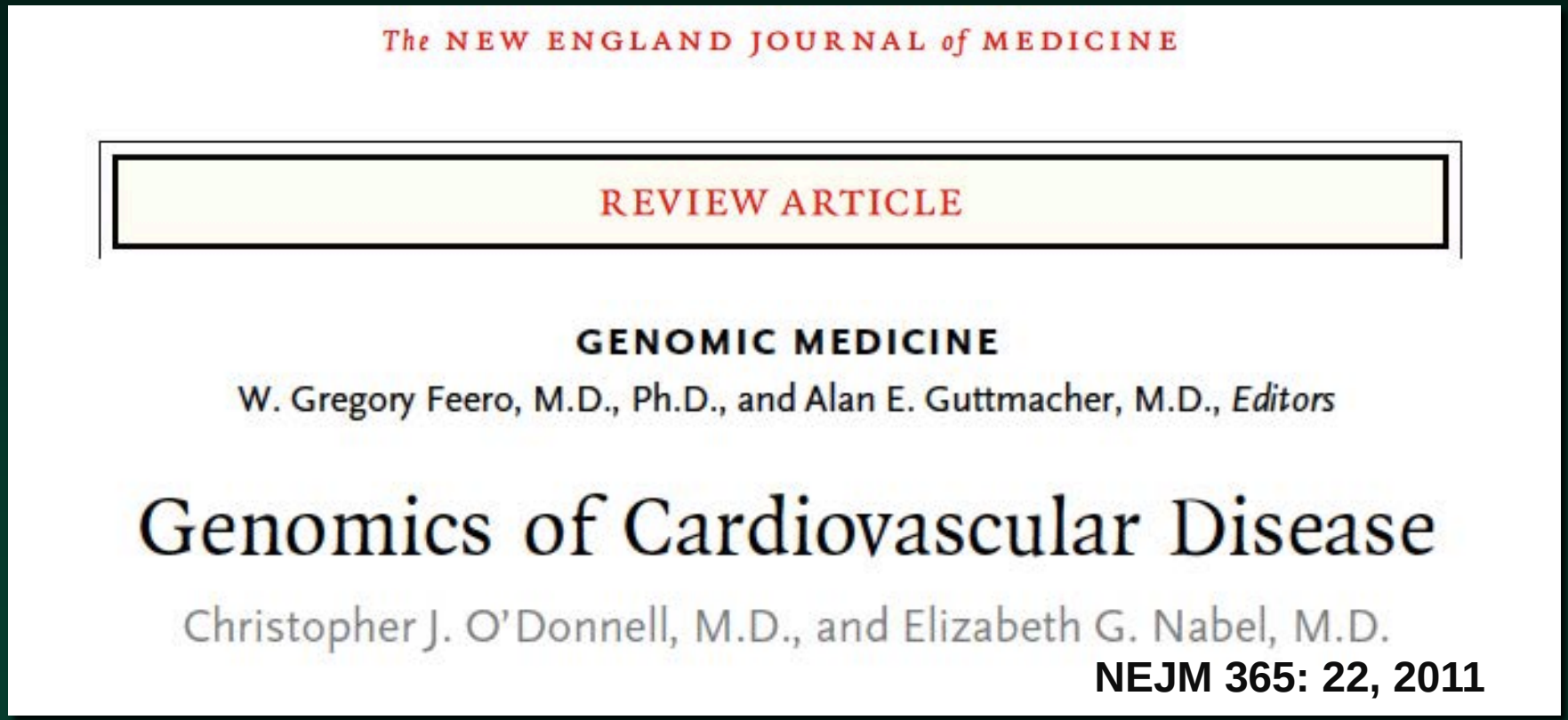
Nature 461: 399, 2009

- rs12979860, 3 kb upstream of *IL28B*, encoding Interferon λ3
- Response to treatment with PEG-IFN-α-2a or 2b
- OR for SVR ~7 for CC vs, CT or TT



Sir Luke Fildes, The Doctor, 1891

Thanks for your attention!



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

GENOMIC MEDICINE

W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D., *Editors*

Genomics of Cardiovascular Disease

Christopher J. O'Donnell, M.D., and Elizabeth G. Nabel, M.D.

NEJM 365: 22, 2011

dvalle@jhmi.edu

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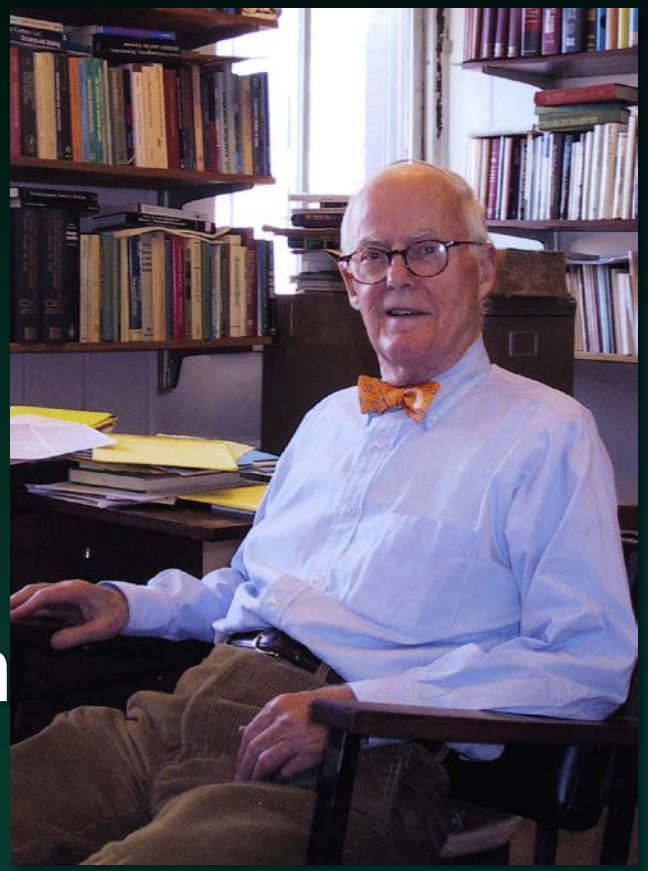
- Barton Childs
- Victor McKusick
- Colleagues in the IGM and throughout Johns Hopkin



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