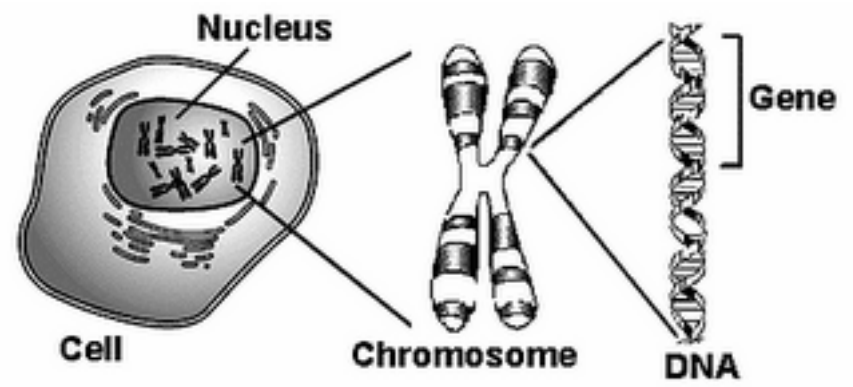
Il genoma umano: oltre la sequenza del DNA

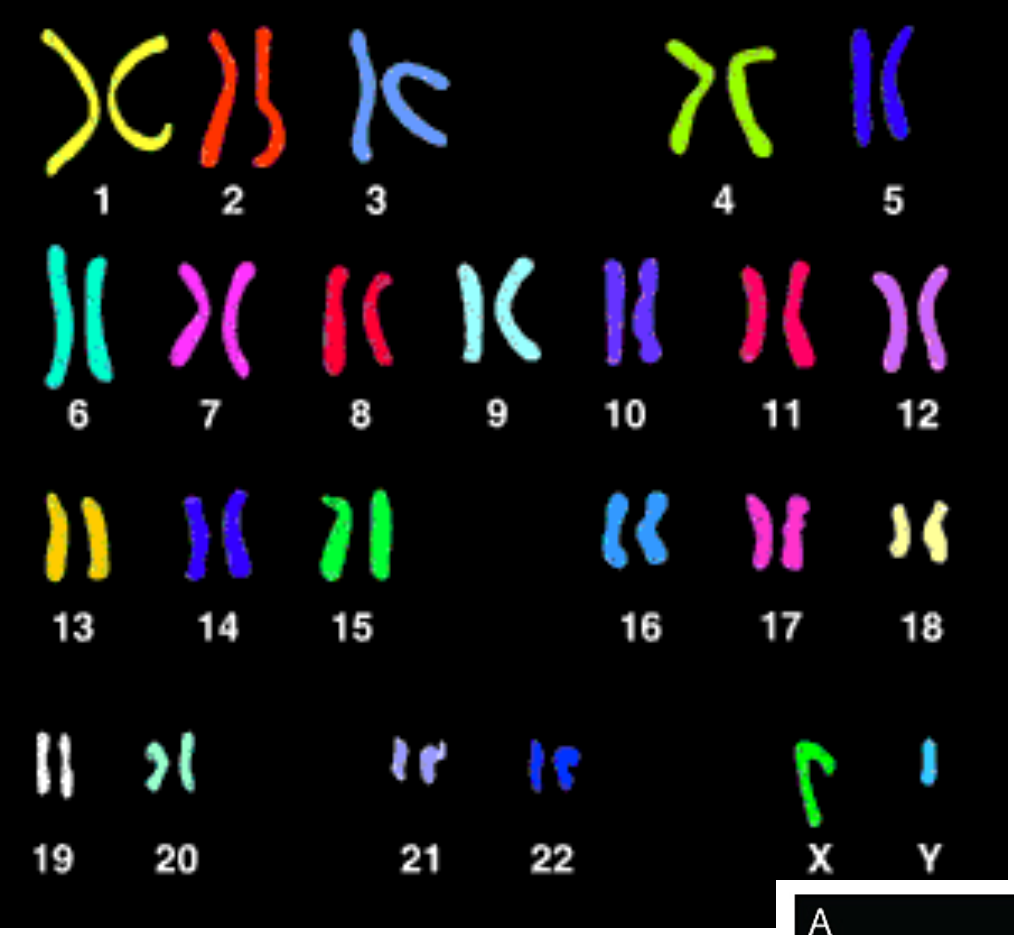
Guglielmina Nadia Ranzani

A few basic (“classical”) concepts…

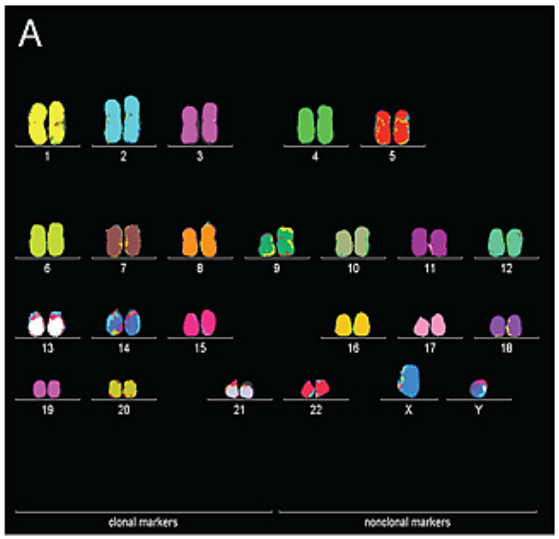
The genome

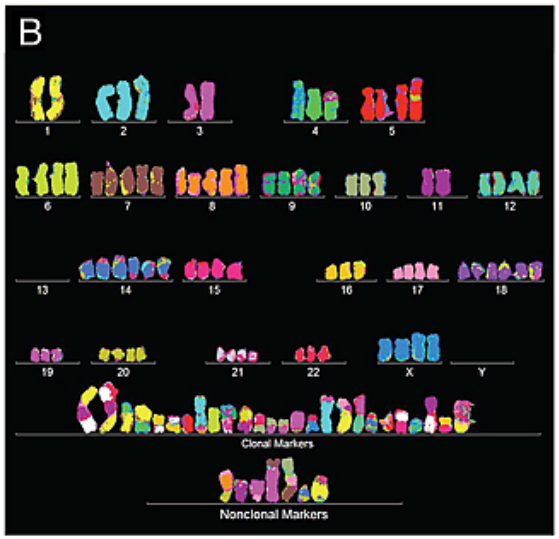
- the genome is an organism's complete set of DNA
- the genome is organized into chromosomes
- the chromosomes contain genes
- genes carry information for making the proteins required by the organism
- proteins determine, among other things, how the organism looks, how well its body metabolizes food or fights infection, and even how it behaves





Human karyotype by sky fish





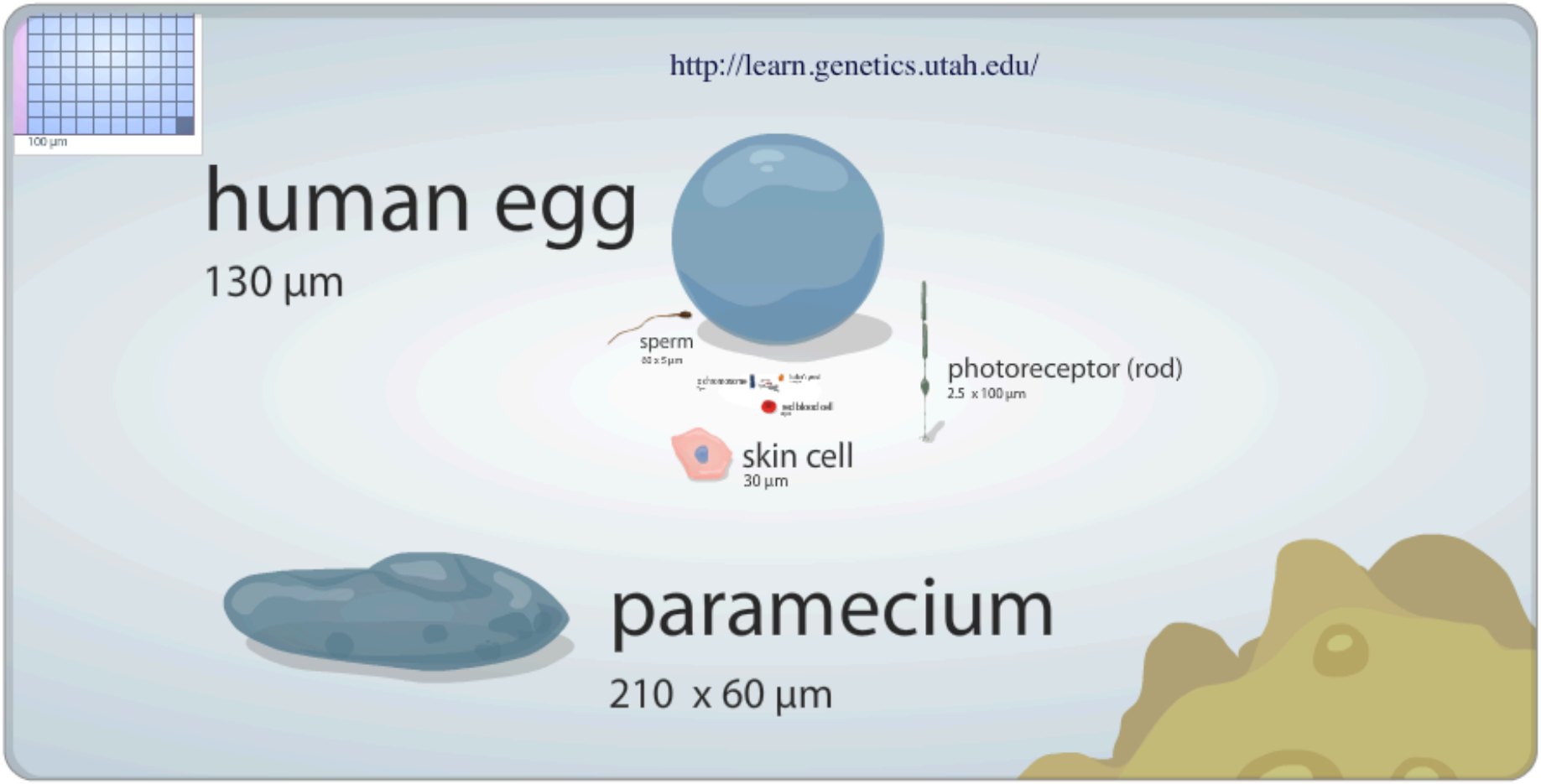
The genome

- Each genome contains all of the information needed to **build** and **maintain** the organism

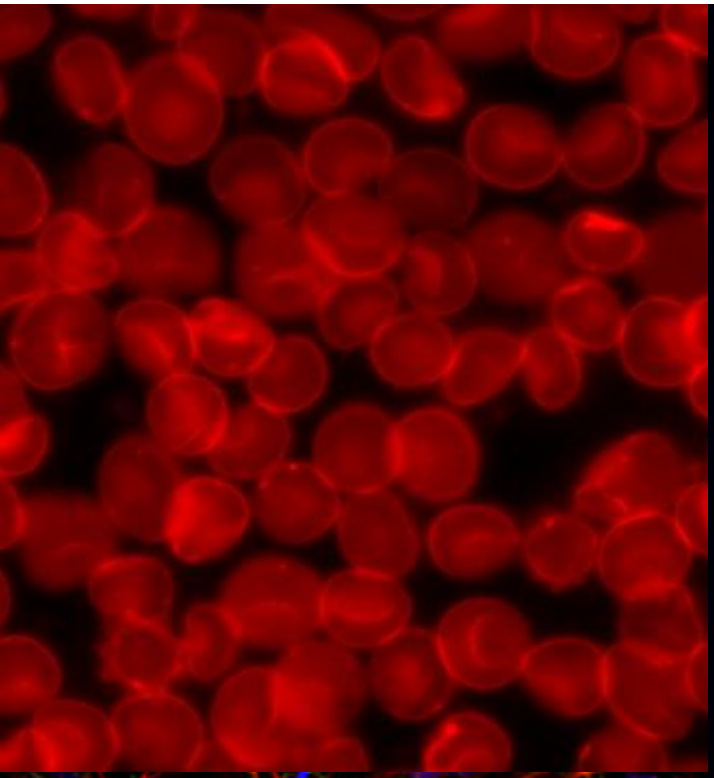
- The human body contains about 6×10^{13} cells of different types (> 300)
  - number of neurons (whole nervous system): 85,000,000,000
  - synapses for average adult: 10^{14}–10^{15} (2,000-5,000 per neuron)

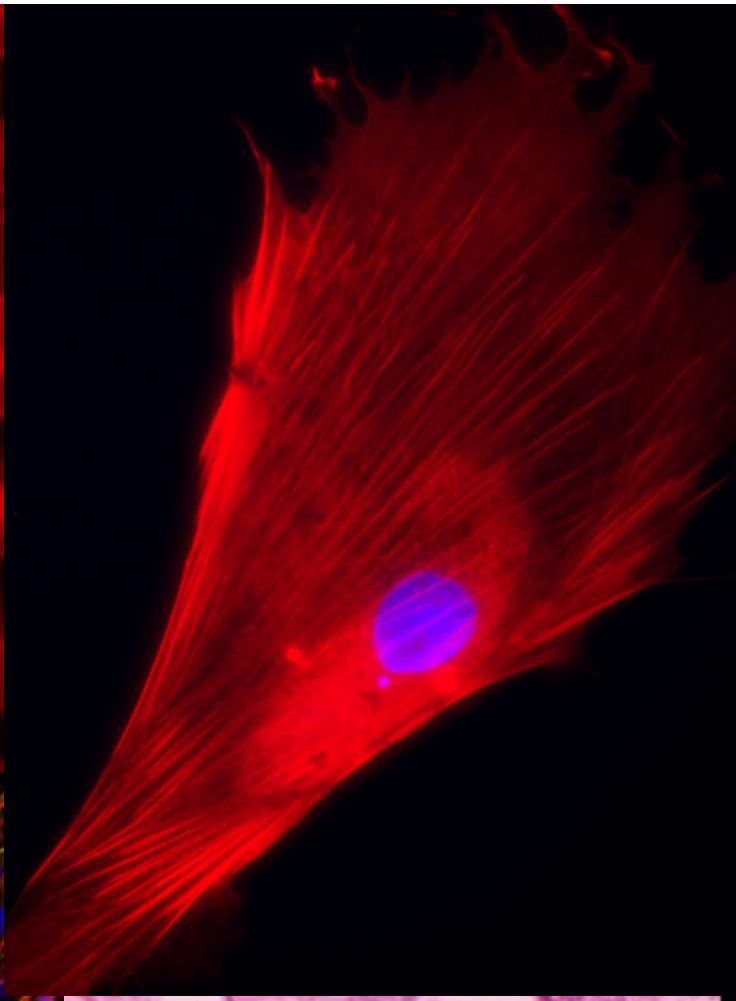
- Each somatic cell contains a complete set of genetic information (a genome) and is theoretically able to regenerate the whole organism

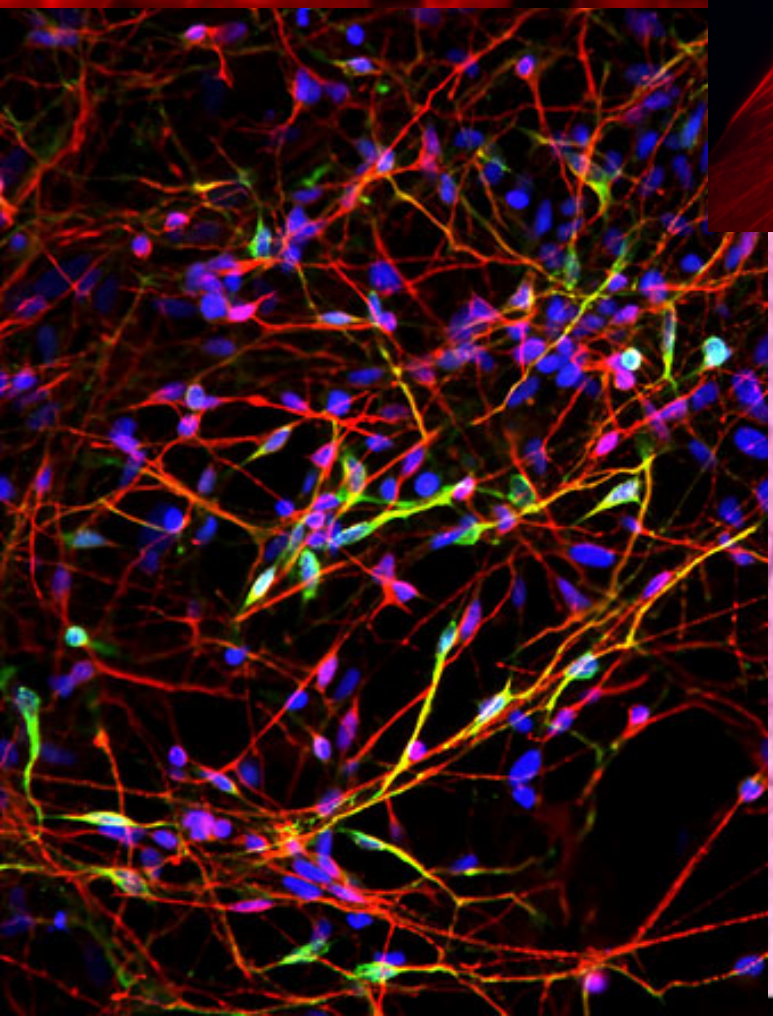
CELL SIZE AND SCALE

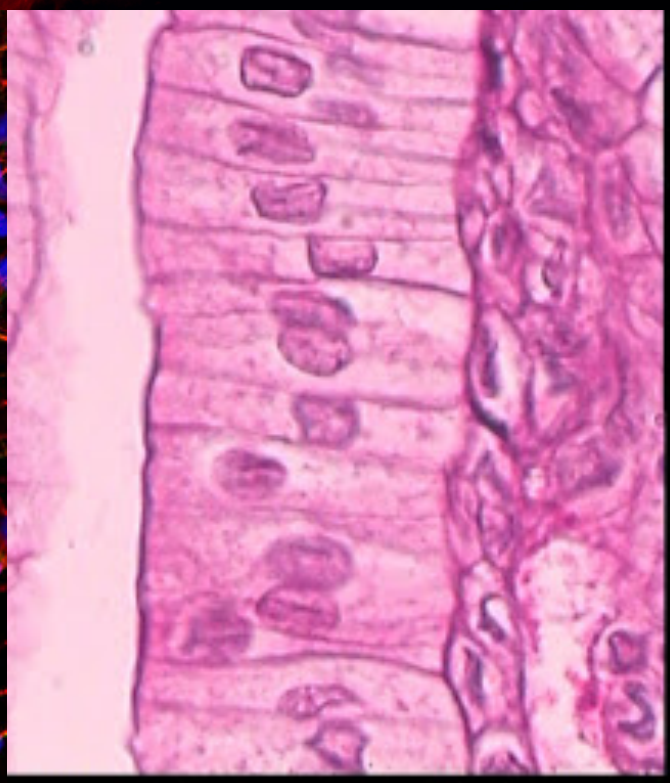


> 300 different cell types





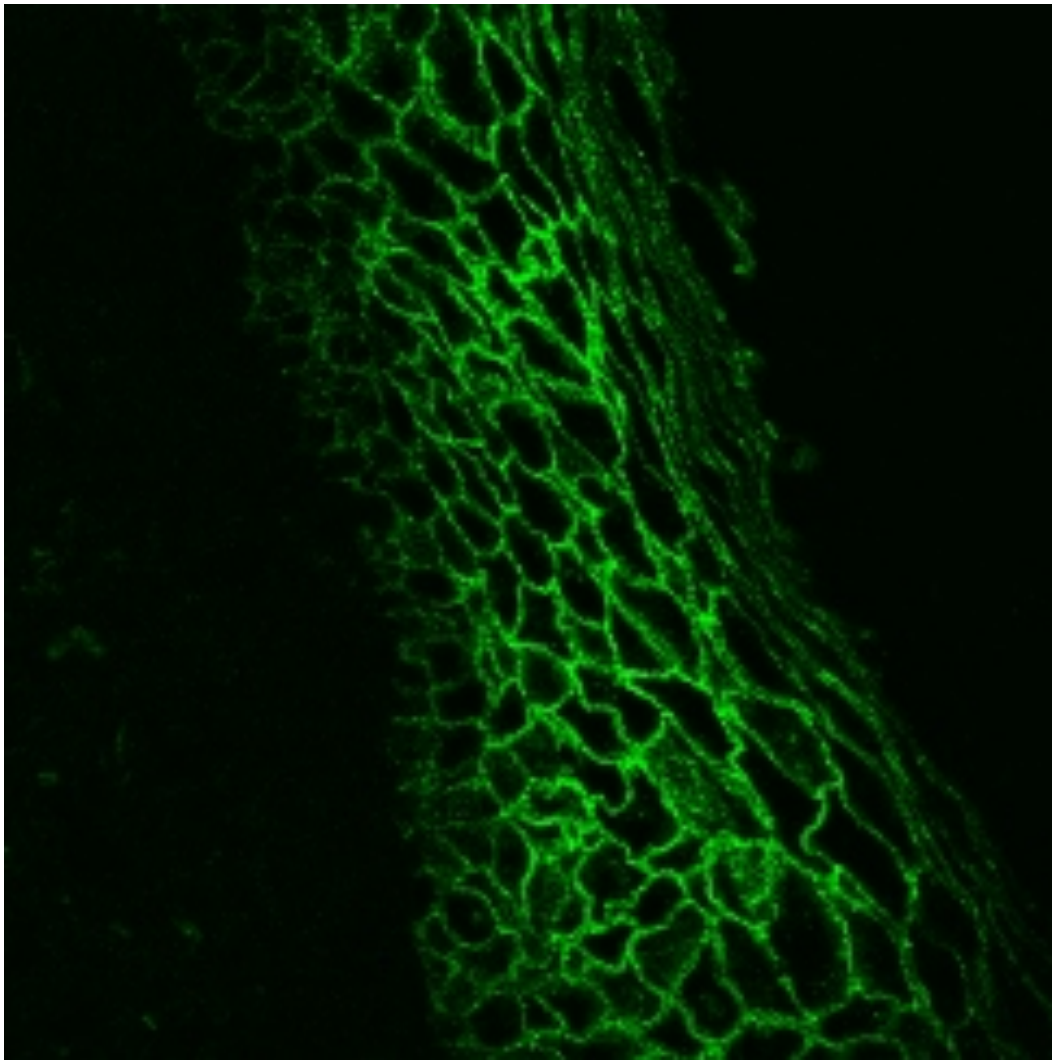




The proteins

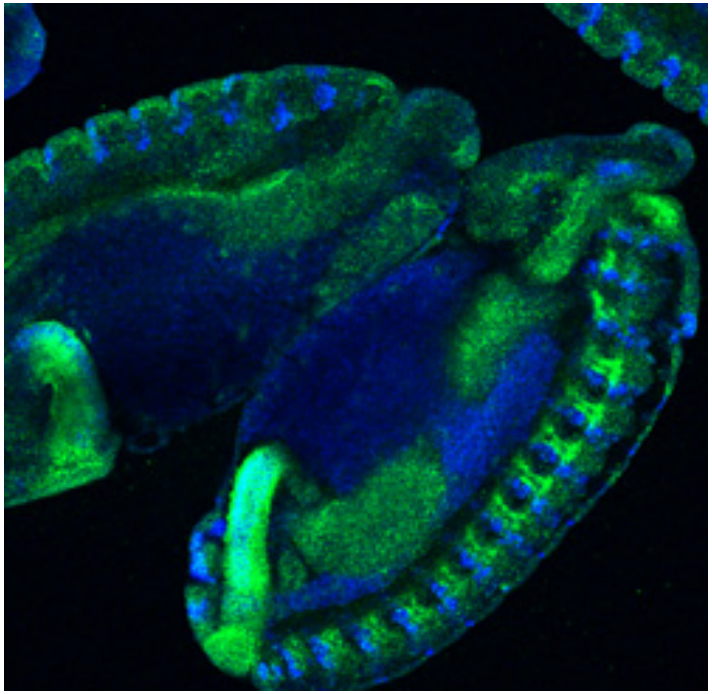
- proteins are one of the basic building blocks of the human body, making up about 16% of our total body weight (muscle, hair, skin, and connective tissue are mainly made up of protein)
- protein plays a major role in all of the cells (enzymes, hormones, neurotransmitters……)
- tissue-specific proteins: e.g. hemoglobin
- ubiquitous proteins: e.g. DNA-repair proteins

Tissue-specific expression of the human E-cadherin protein

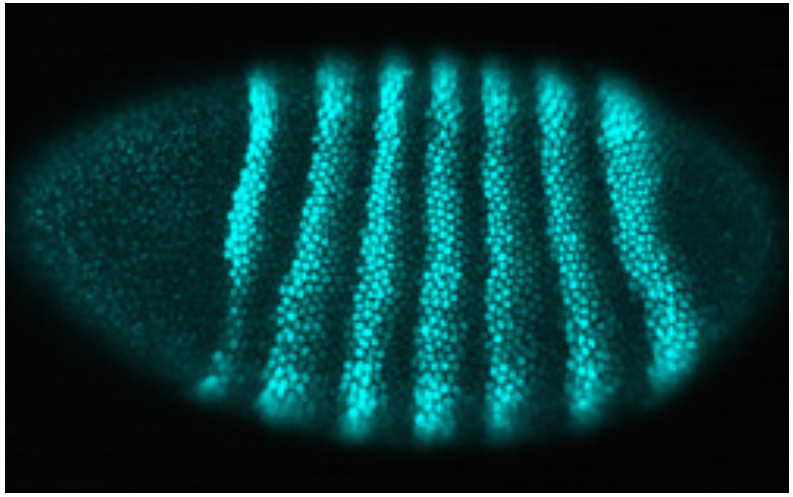


The protein is expressed in the epithelial cells, at the membrane level, but is absent in the adjacent connective tissue

Protein expression during the embryonic development of *Drosophila melanogaster*

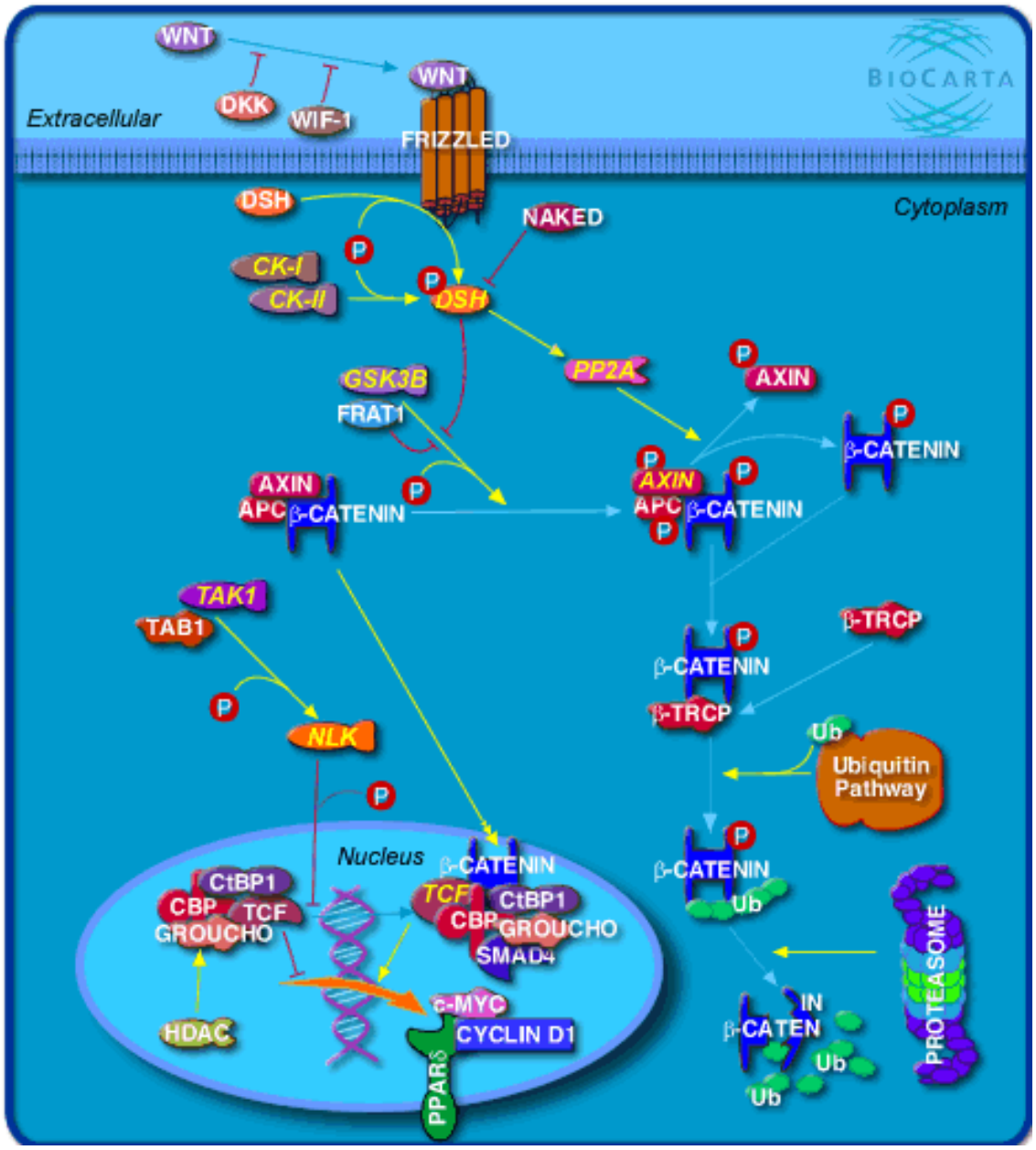


Co-expression of Dally-like and Engrailed (embryo, stage 13)



Expression of even-skipped (early stage embryo)

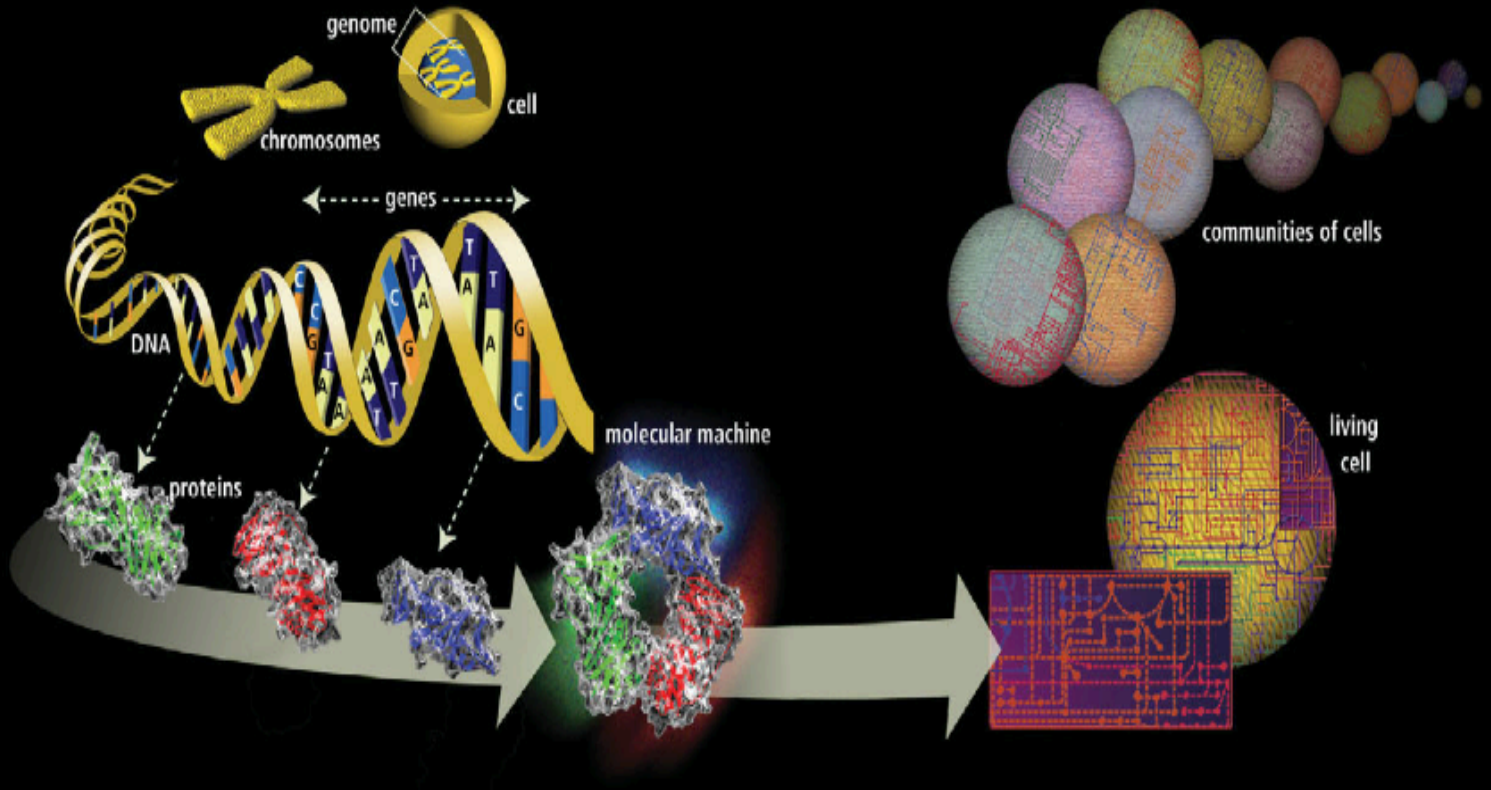
The Wnt pathway



Cells contain DNA—the hereditary material of all living systems.

The **genome** is an organism's complete set of DNA and is organized into **chromosomes**.

DNA contains **genes** whose sequence specifies how and when to build proteins.



Proteins perform most essential life functions, often working together as molecular machines.

Molecular machines interact through complex, interconnected pathways and networks to make the cell come alive.

Communities of cells range from associations of microbes (each a single cell) to the hundred trillion cells in a human being.

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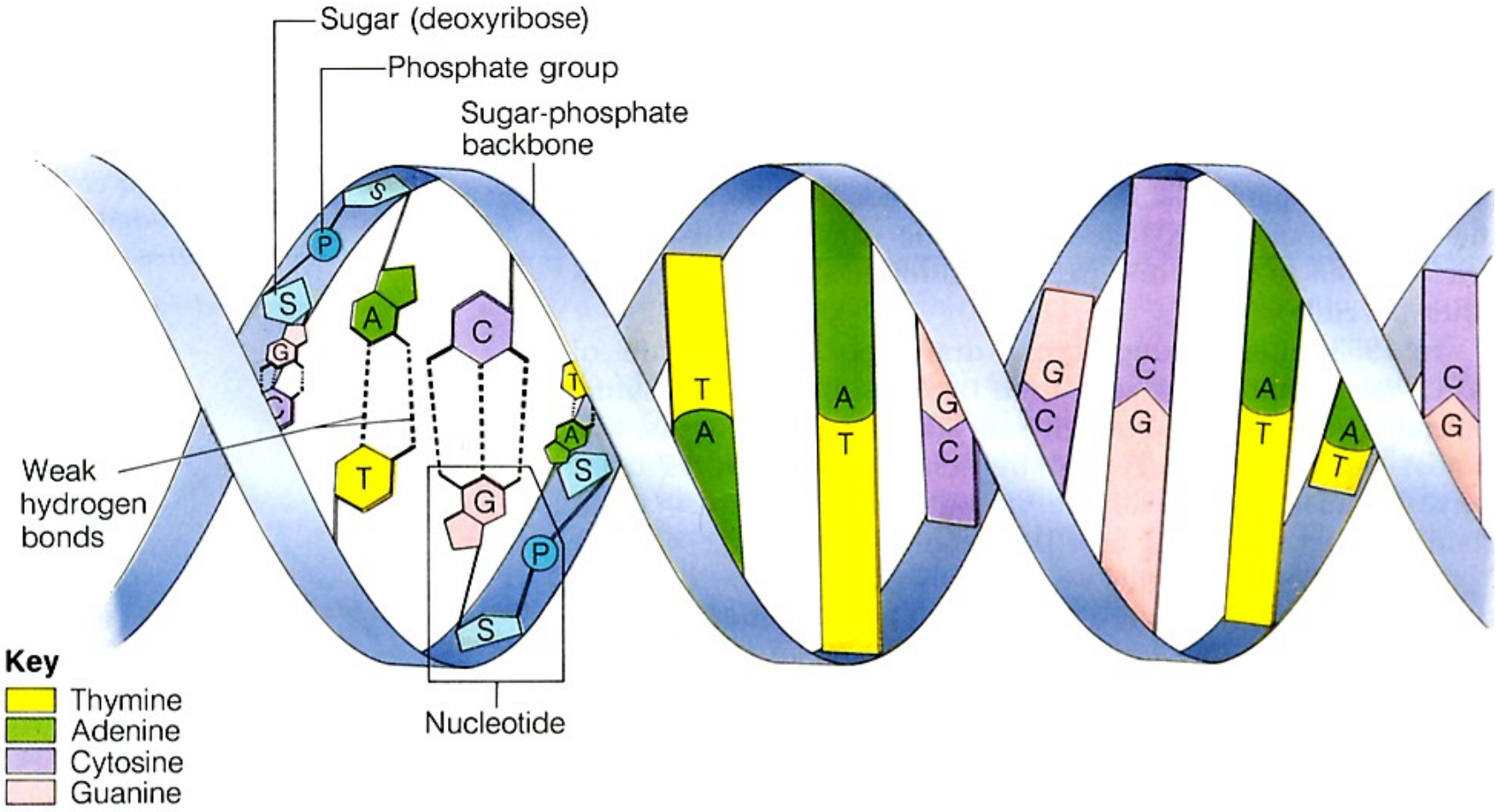
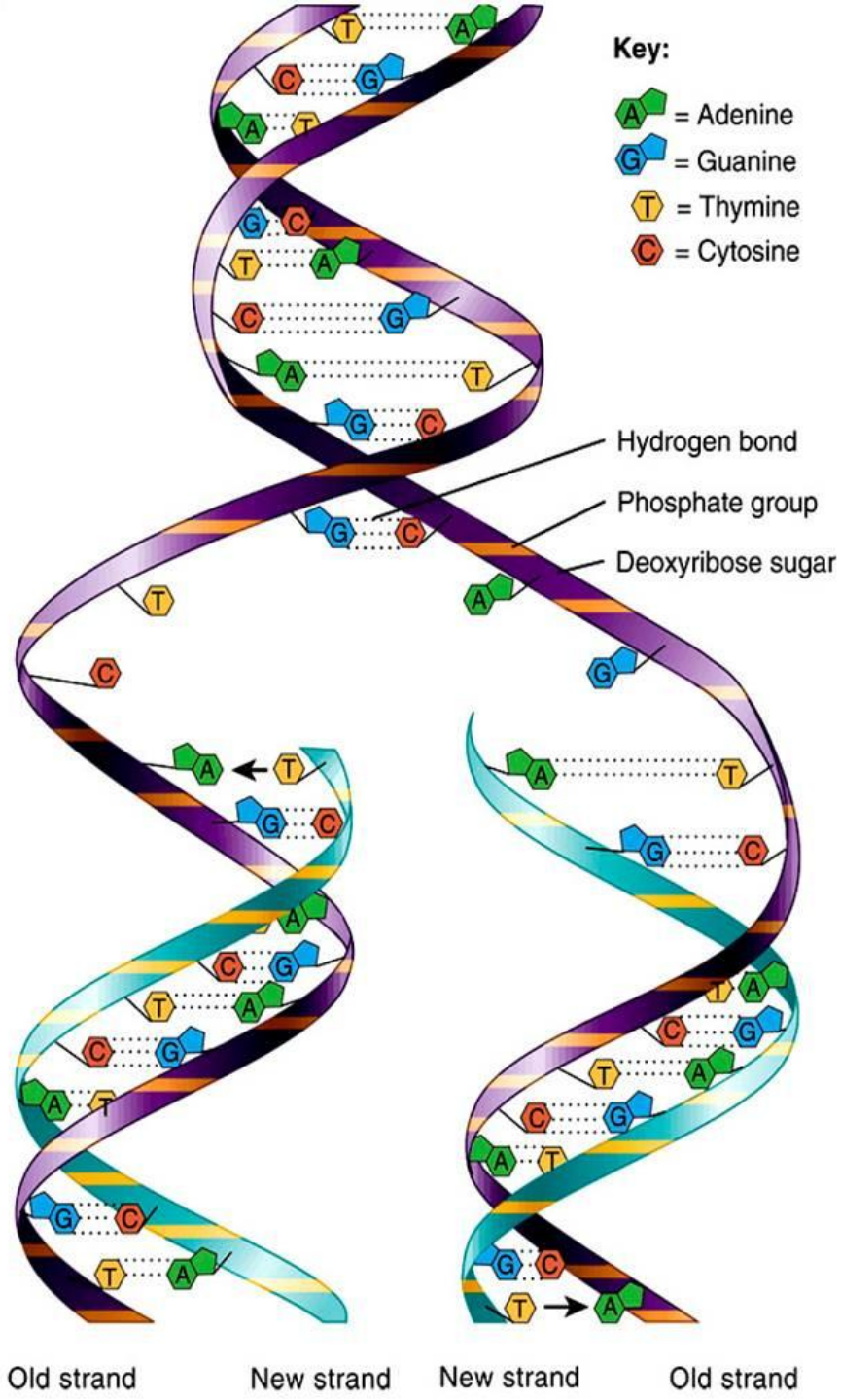
DNA structure





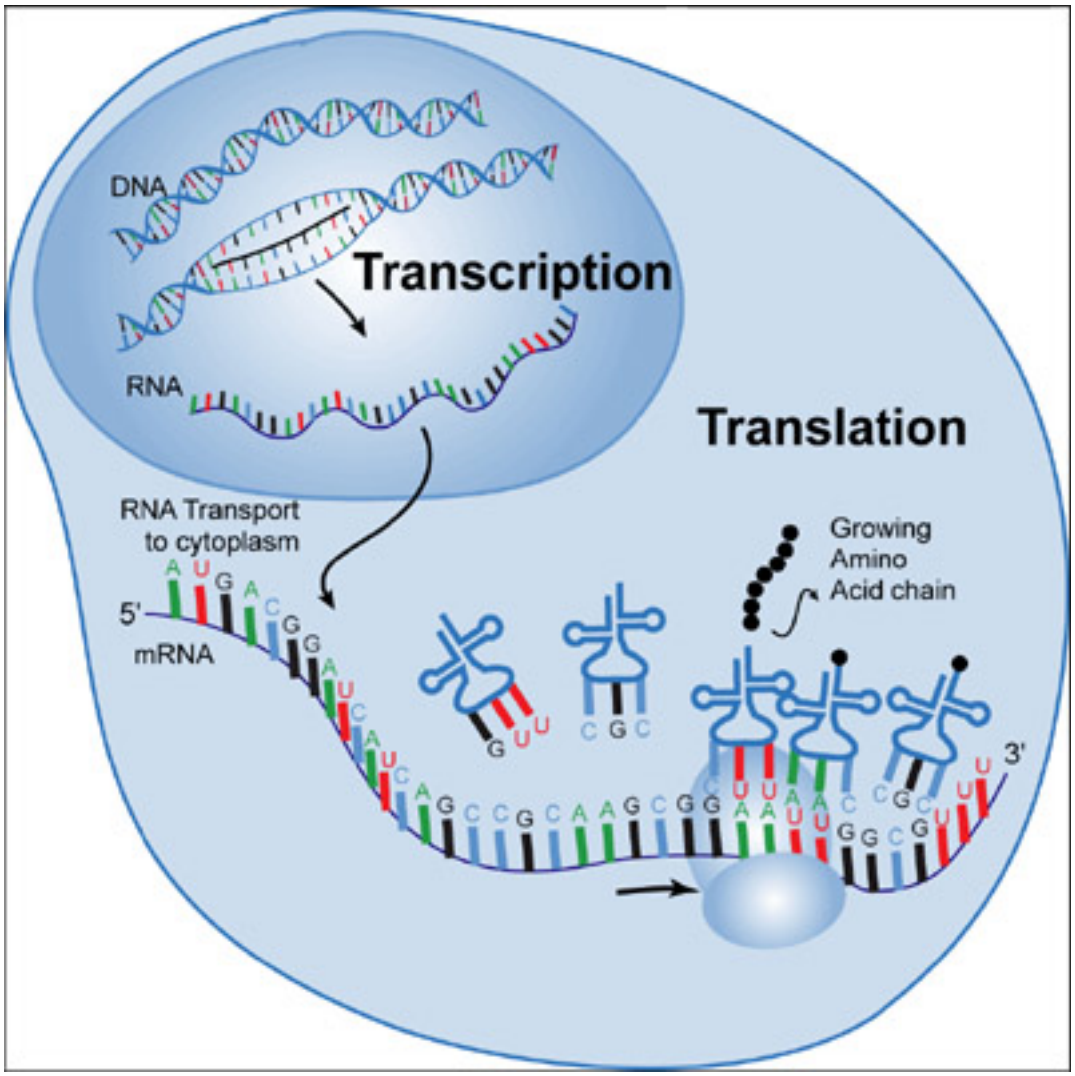
DNA REPLICATION PRIOR TO CELL DIVISION:

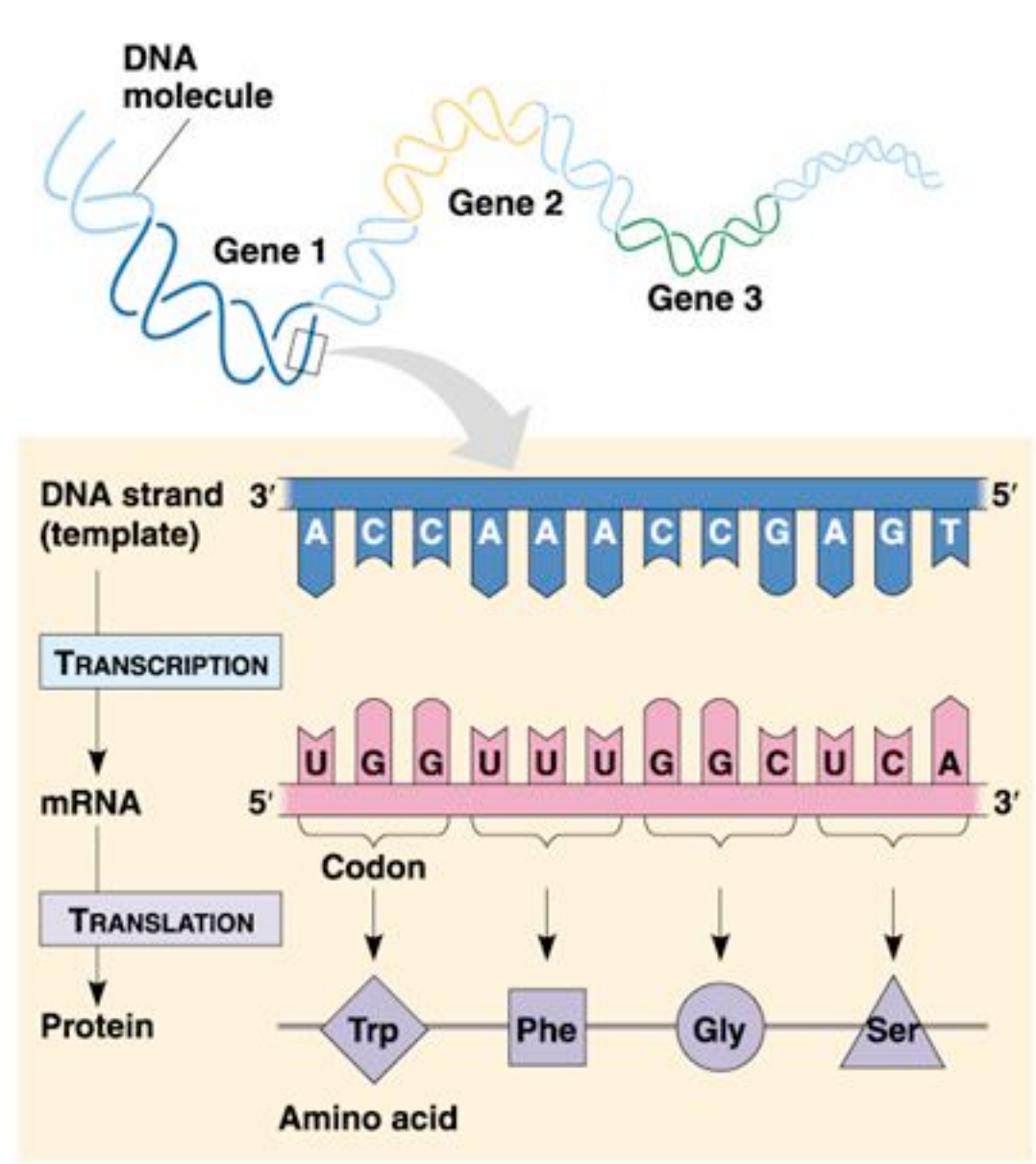
the double helix of DNA unwinds and each side serves as a pattern to make a new molecule

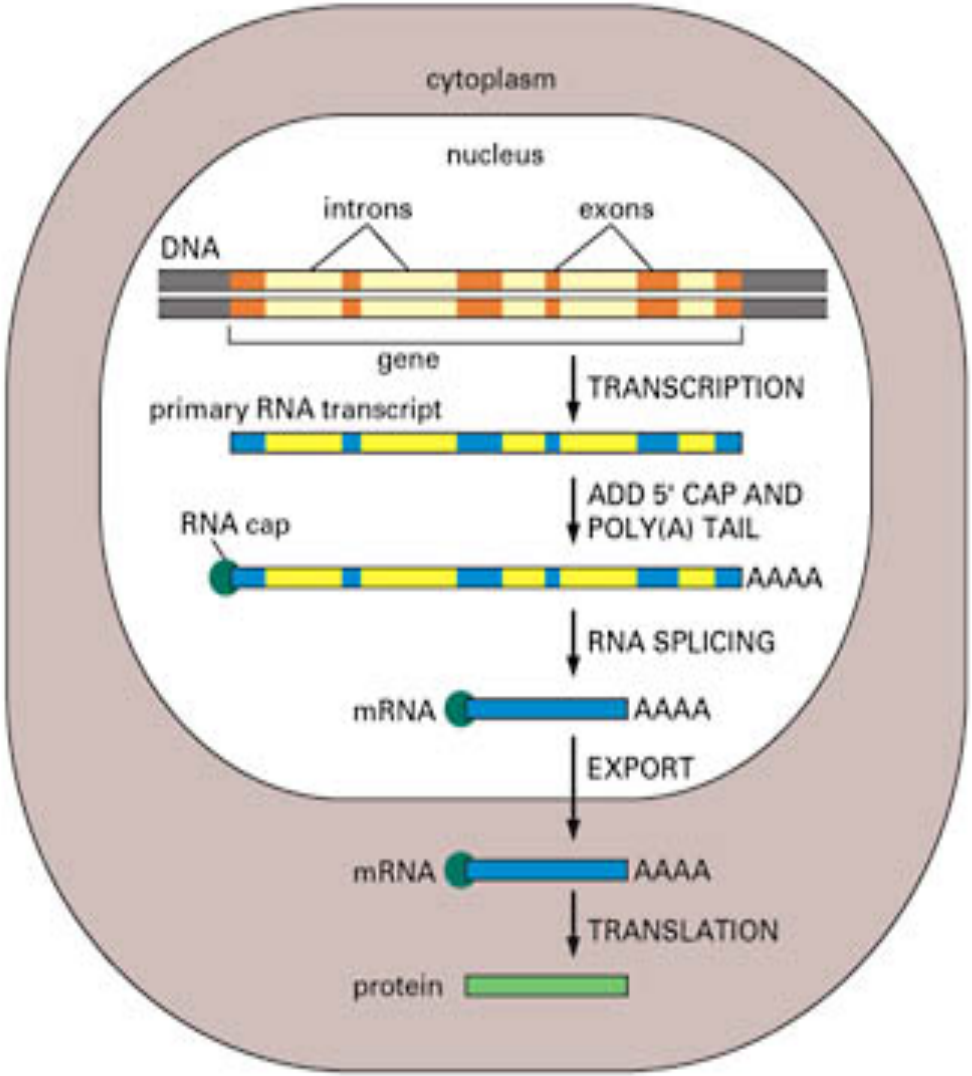
DNA

RNA

Protein







TRANSCRIPTION

⇩

SPLICING

⇩

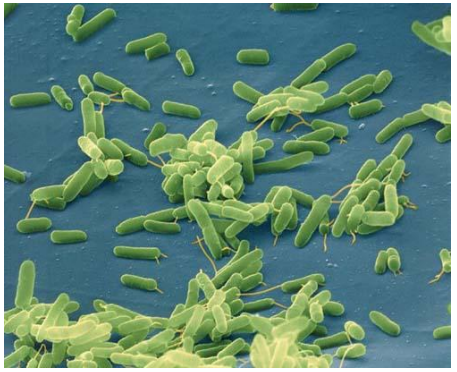
TRANSLATION

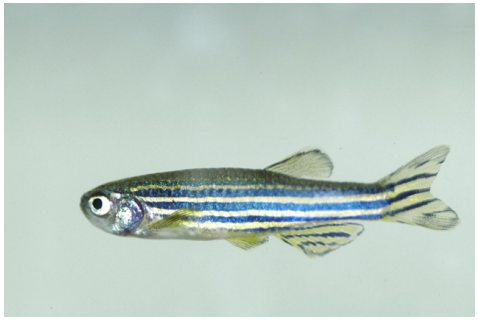
THE HUMAN GENOME PROJECT

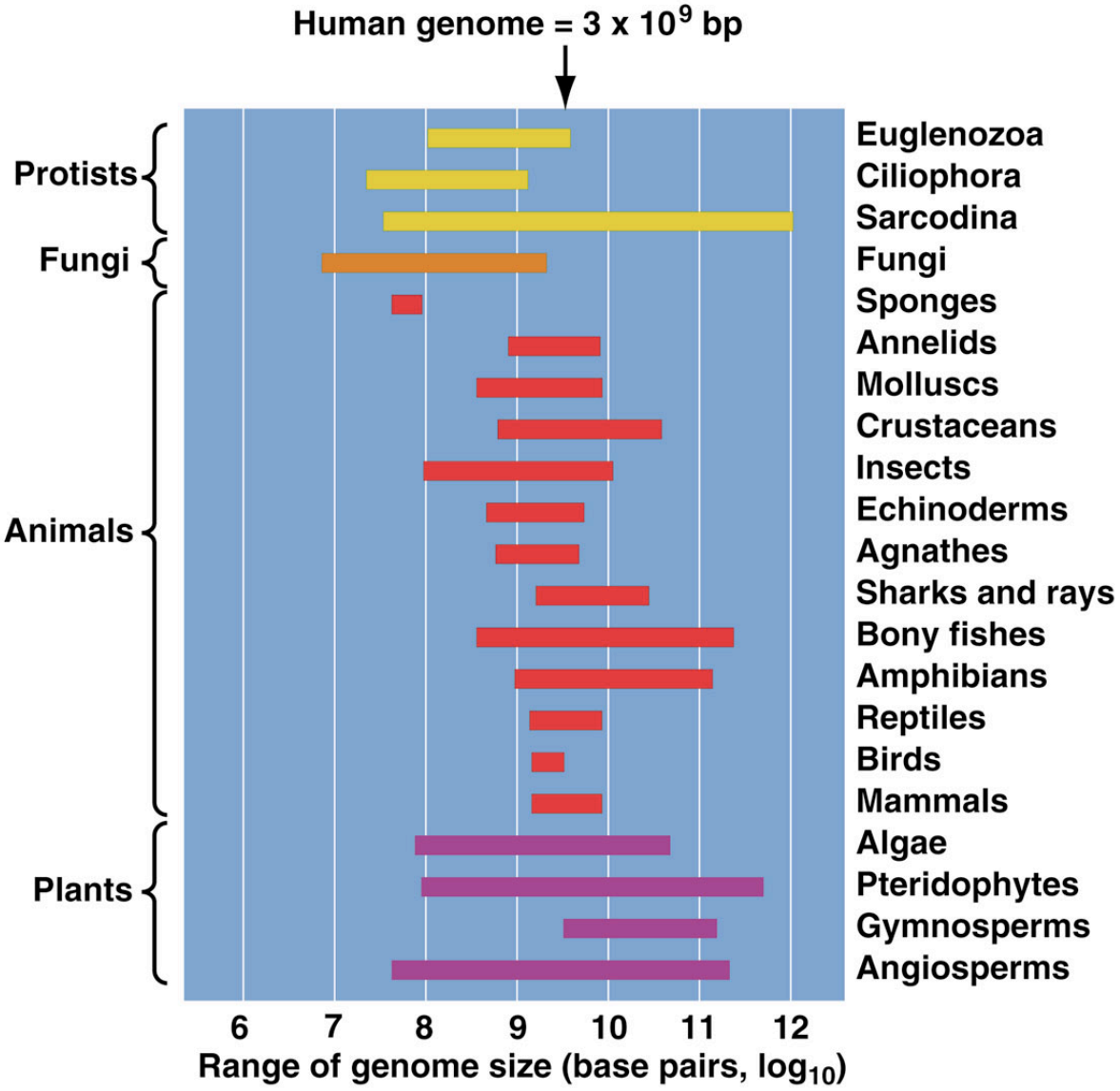
The human DNA

Total number of cells in an adult human body	6×10^{13}
DNA sequence (haploid genome)	3×10^{9} base pairs
Total length	1.2×10^{14} m

Which organism has the largest genome?







There is no correlation between complexity and genome size

Xenopus laevis  *3,000,000,000*

Rattus norvegicus *3,000,000,000*

Mus musculus  *3,000,000,000*

Homo sapiens *3,000,000,000*

Bos taurus  *3,000,000,000*

Number of Chromosomes

	Organism	Number of chromosomes
	pea plant	14
	sun flower	34
	cat	38
	puffer fish	42
	human	46
	dog	78

Highlights of Human Genome Project Timetable

- Proposed in 1990 as 3 billion dollar joint venture between DOE and NIH with 15 year completion goal
- Private efforts by Celera Genomics in 1998 helped to accelerate project completion
- In 2000, working “draft” of human genome announced (95% complete); draft sequence published in 2001
- Work completed in April 2003 (only ~300 small gaps remaining)

Goals of the Human Genome Project

- Create genetic and physical maps of the 22 autosomes and the X and Y chromosomes
- **Identify the entire set of genes in DNA**
- Determine the nucleotide sequence of 3 billion base pairs of DNA in the haploid genome
- Analyze genetic variations among humans (identify polymorphisms)
- Map and sequence the genomes of model organisms (e.g., bacteria, yeast, nematodes, fruit flies, mice, etc)
- Develop the necessary laboratory and computational tools to assist in analyzing and understanding gene structure and function
- Disseminate genome information to scientists and the public
- Examine ethical, social, and legal issues

Nature. 2001 Feb 15;409(6822):860-921.

Initial sequencing and analysis of the human genome.

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann N, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB, Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Raymond C, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blocker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C, Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowski J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ; International Human Genome Sequencing Consortium.
Whitehead Institute for Biomedical Research, Center for Genome Research, Cambridge, Massachusetts 02142, USA. lander@genome.wi.mit.edu

The human genome holds an extraordinary trove of information about human development, physiology, medicine and evolution. Here we report the results of an international collaboration to produce and make freely available a draft sequence of the human genome. We also present an initial analysis of the data, describing some of the insights that can be gleaned from the sequence.

Science. 2003 Apr 11;300(5617):286-90.

The Human Genome Project: lessons from large-scale biology.

Collins FS, Morgan M, Patrinos A.
National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, 9000 Rockville Pike, Bethesda, MD 20892, USA. fc23a@nih.gov

Publication Types:
* Historical Article

The number of human genes

Organism	Number of bp	Genes
ΦX-174	5386	10
Human mitochondrion	16569	37
Mycoplasma pneumoniae	816394	680
Hemophilus influenzae	1830138	1738
E. Coli	4639221	4406
Saccharomyces cerevisiae	12.1×10^6	5885
C. Elegans	95.5×10^6	19099
Drosophilia melanogaster	1.8×10^8	13601
Human	3.2×10^9	22.000?

100.000

(estimated number)

↓

35.000

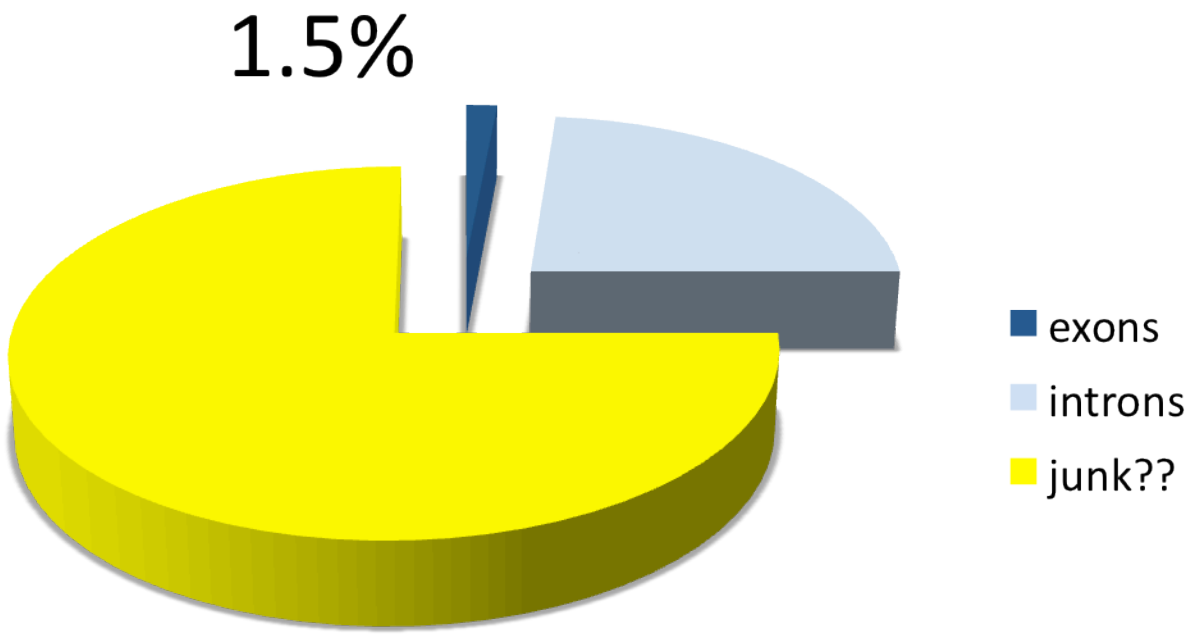
(HGP, first data)

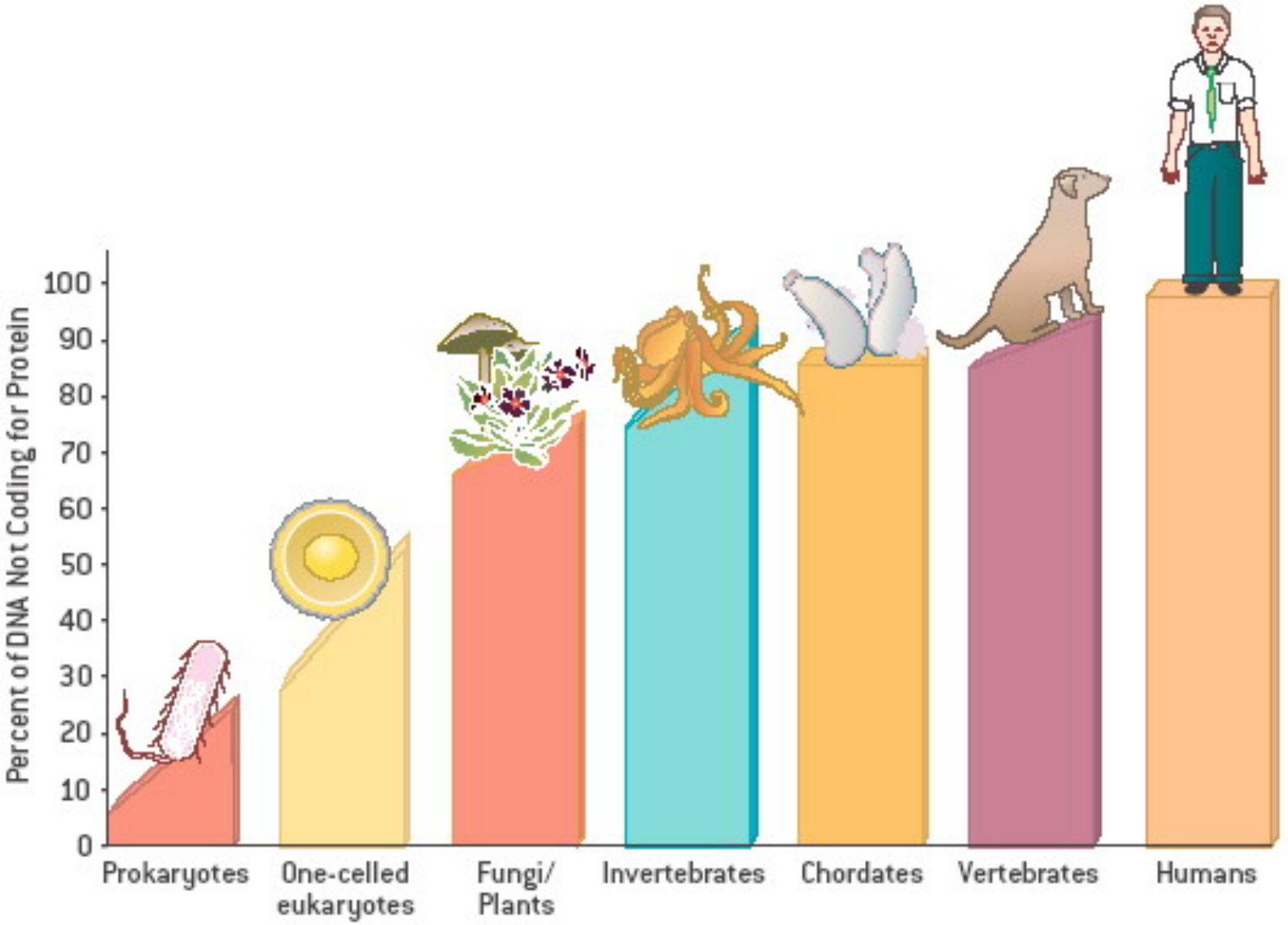
↓

22.000!!

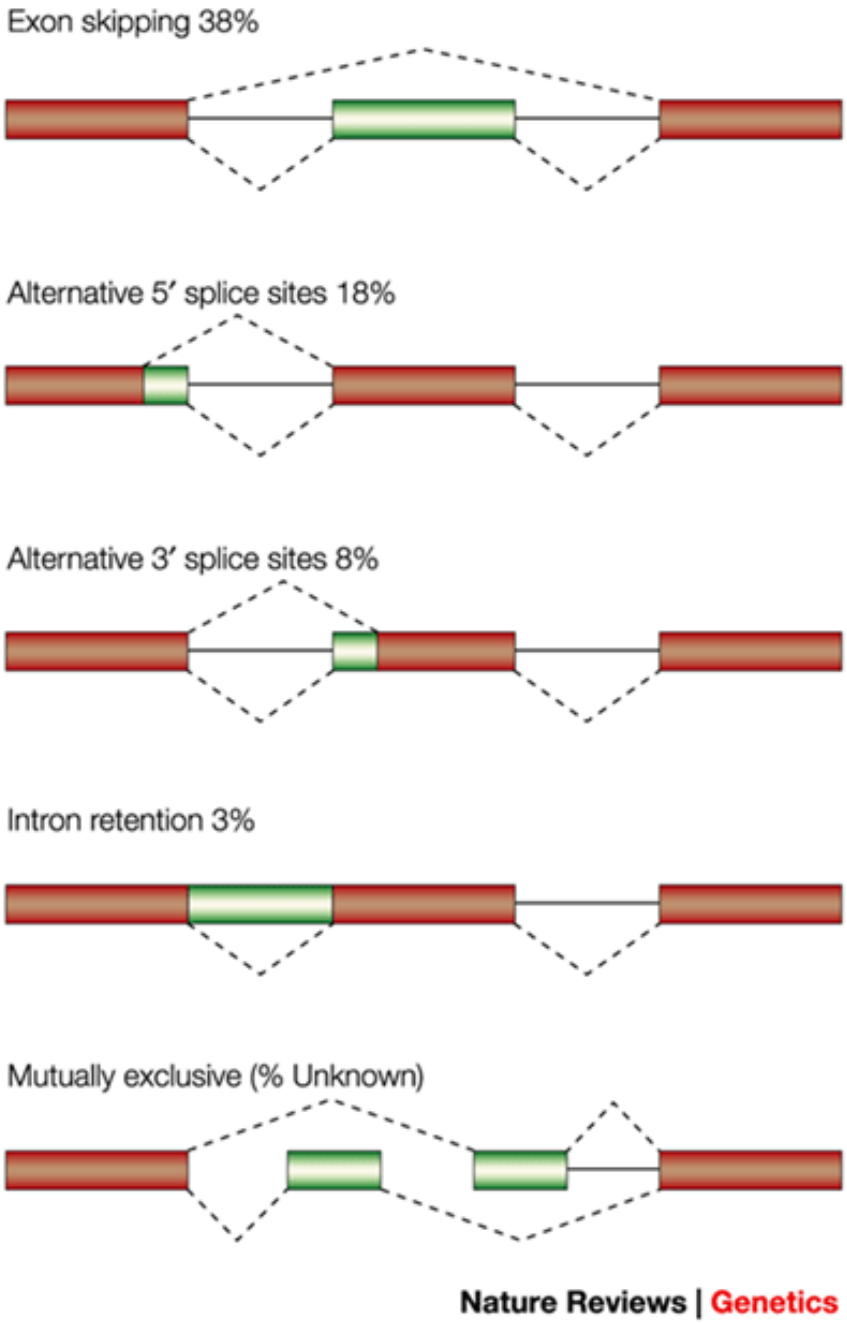
(HGP, 2005)

>95% of our DNA consists of non-protein-coding DNA





NONPROTEIN-CODING SEQUENCES make up only a small fraction of the DNA of prokaryotes. Among eukaryotes, as their complexity increases, generally so, too, does the proportion of their DNA that does not code for protein. The noncoding sequences have been considered junk, but perhaps it actually helps to explain organisms' complexity.

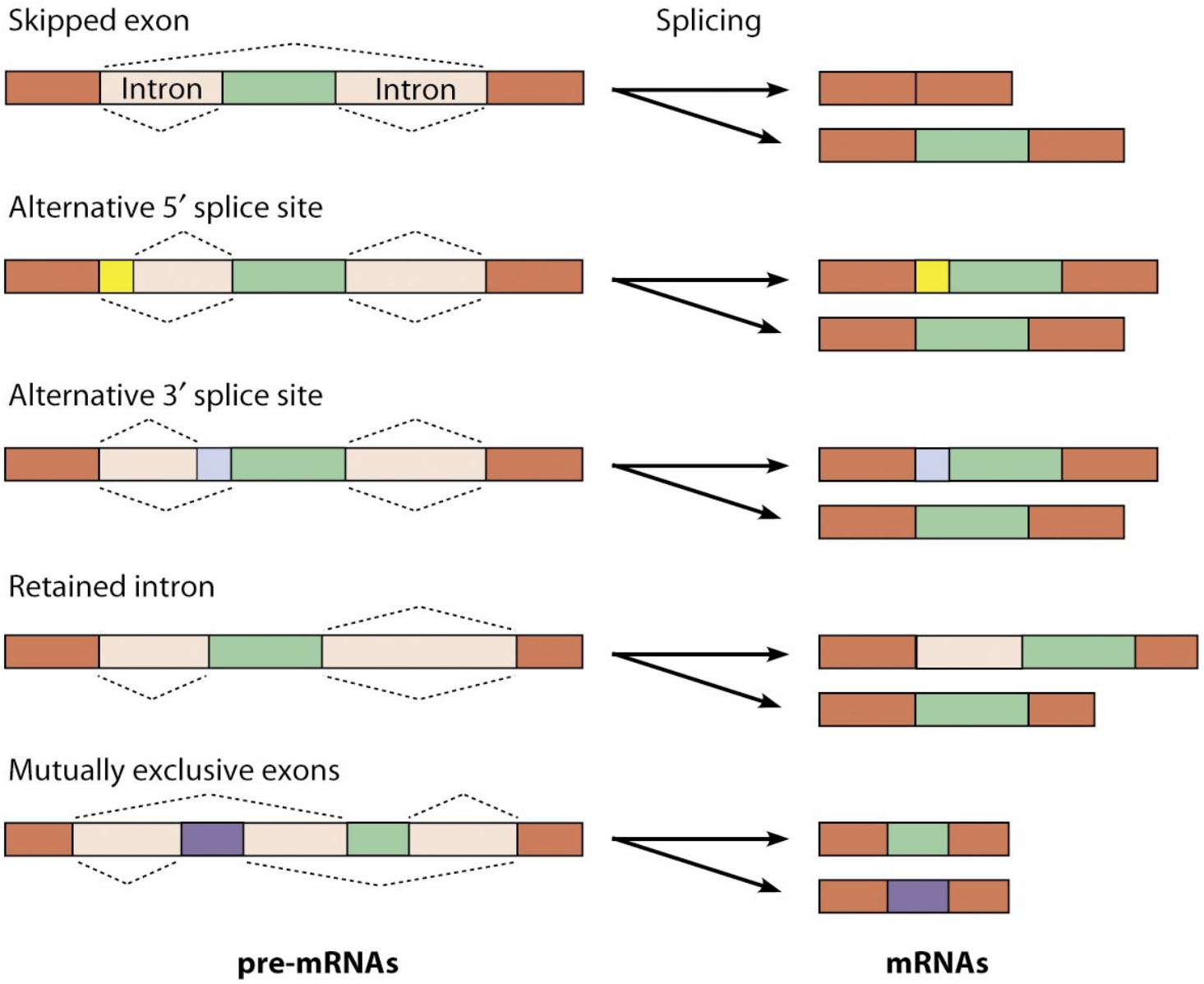


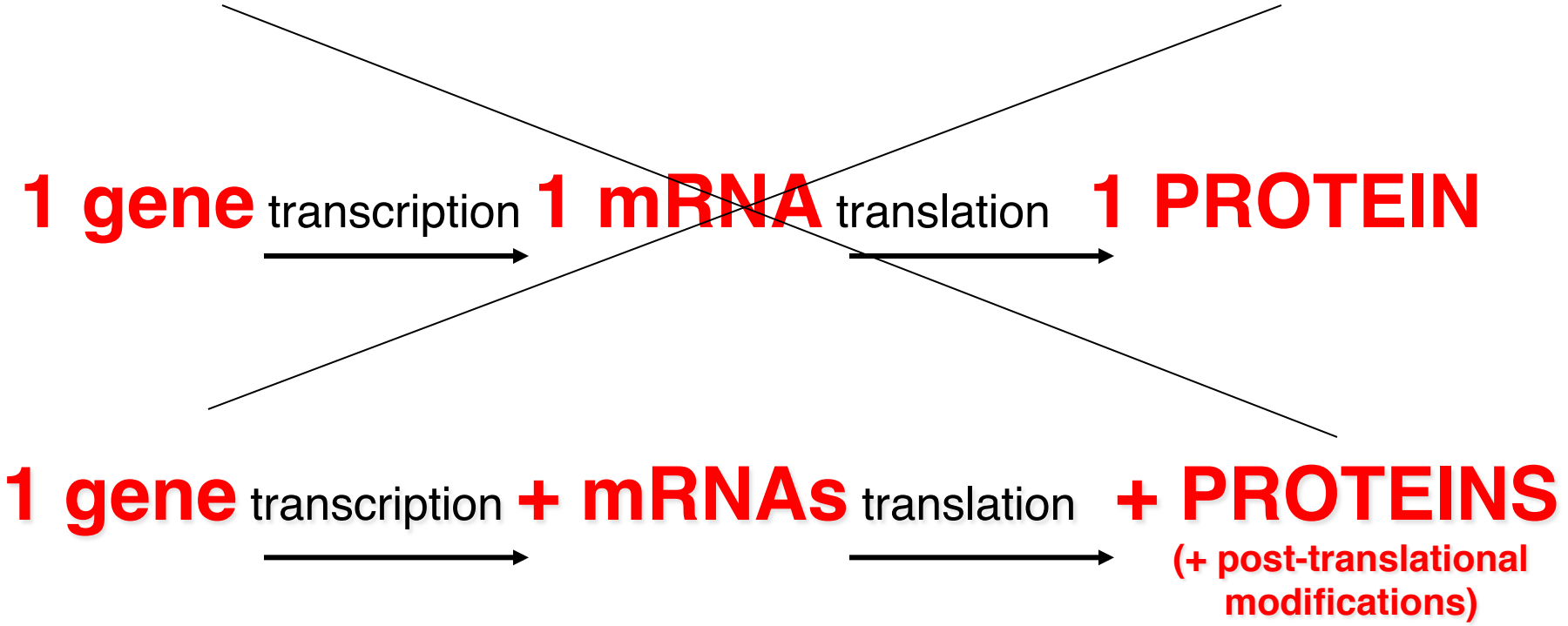
ALTERNATIVE SPLICING (tissue-specific A.S.)

One gene

↓

many possible mRNAs





In man (on the average): 1 GENE → 12 PROTEINS

Just how unique are humans?

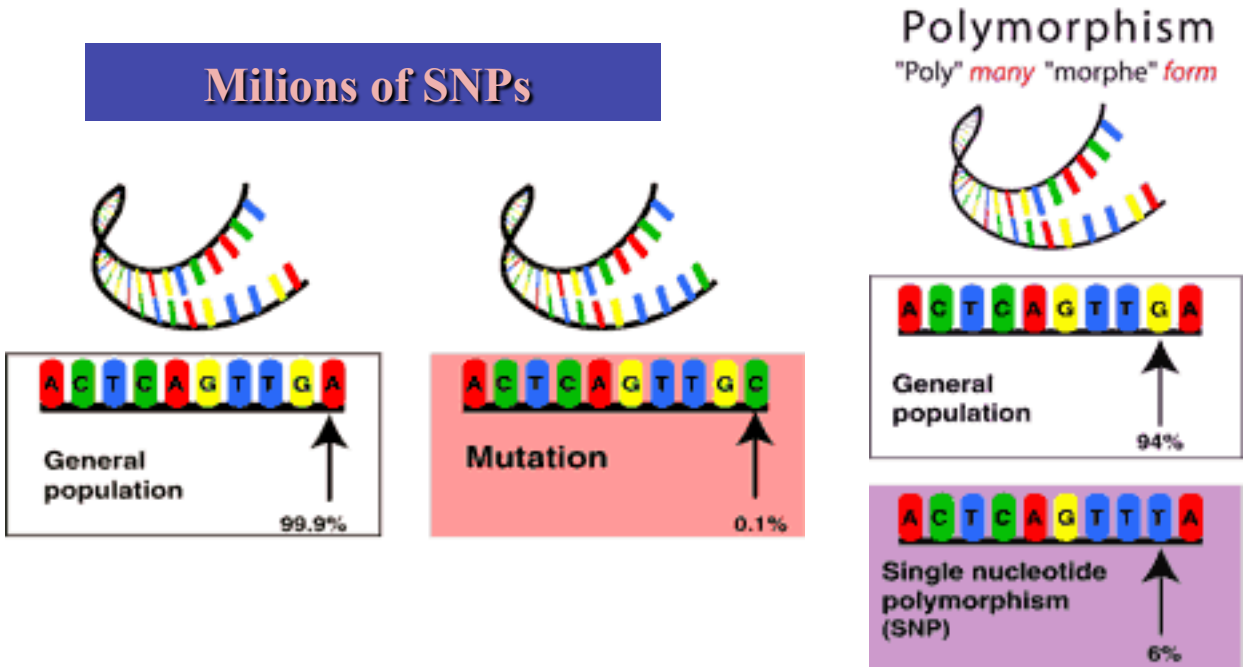
- Large number of genes are in common with other organisms

  ~ 50% of our genes are also found in fruit flies
  ~ 30% of our genes are also found in yeast
  ~ 80% of our genes are shared with the mouse
  ~ 96% of our genes are shared with chimpanzees
  ~ 100 of our genes are even shared with bacteria

Genomic comparisons between mice and men

- Both organisms have same number of genes
- Most of the common genes share the same intron and exon arrangement
- Nucleotide sequences within common gene exons are conserved to a high degree
- 1/4 of alternatively spliced exons are specific either to human or mouse
- Species specific proteins likely account for the differences between species

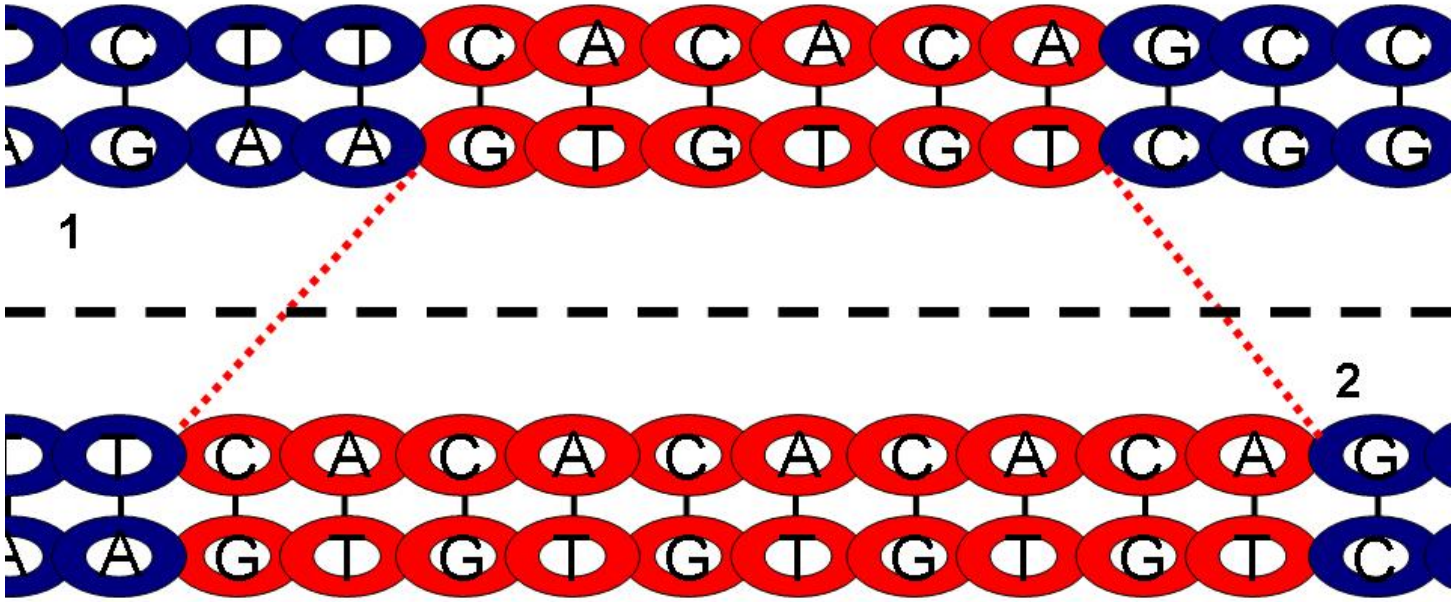
Human genome variability



SNPs

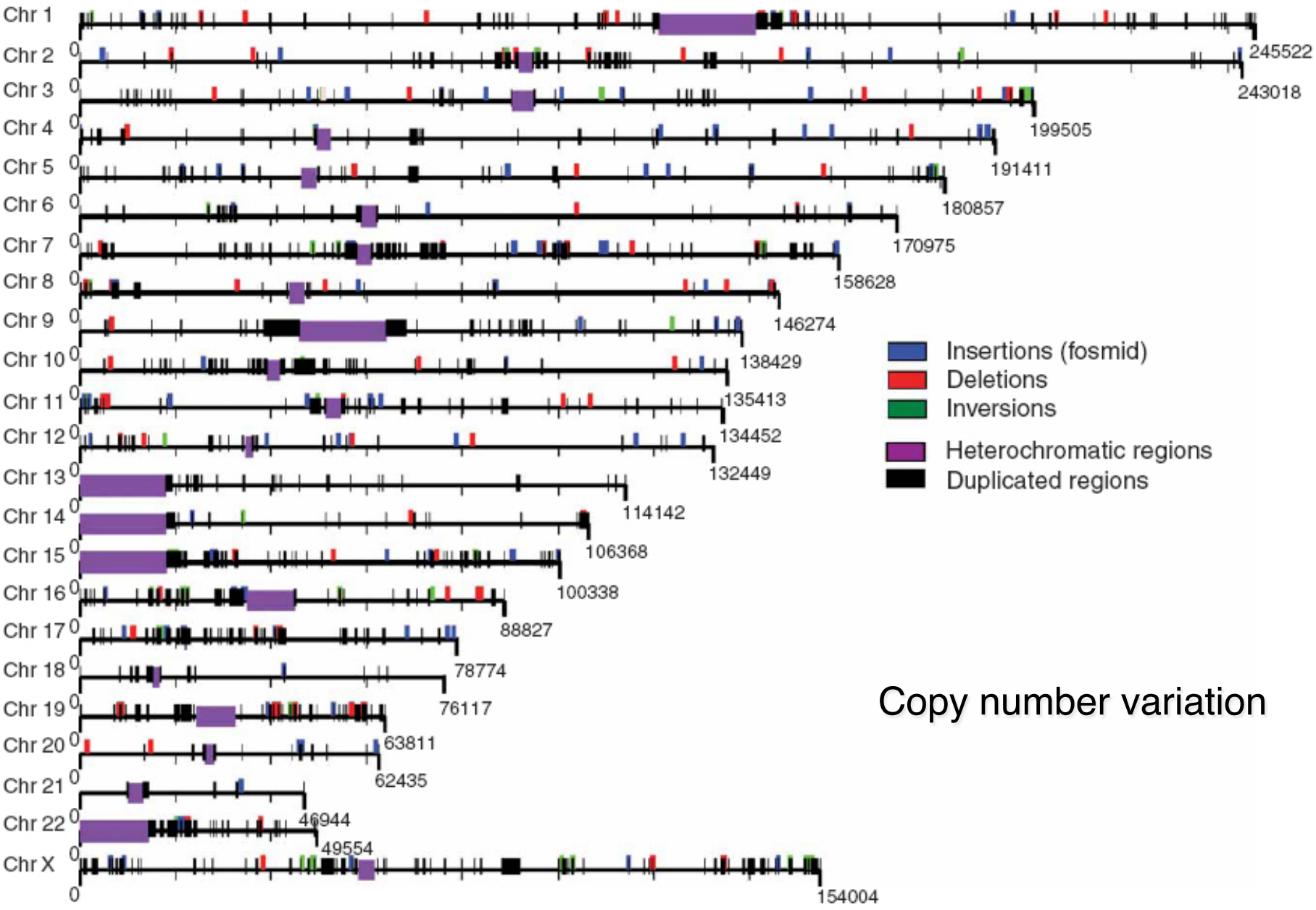
- Occur every 100 to 300 bases along the 3-billion-base human genome
- Two of every three SNPs involve the replacement of cytosine (C) with thymine (T)
- SNPs can occur in coding (gene) and noncoding regions of the genome

Microsatellites



CNVs

- A copy number variation (CNV) is a segment of DNA in which copy-number differences have been found by comparison of two or more genomes
- The segment may range from one kilobase to several megabases in size
- DNA copy number variation is a widespread and common phenomenon among humans: it is estimated that approximately 0.4% of the genomes of unrelated people typically differ with respect to copy number



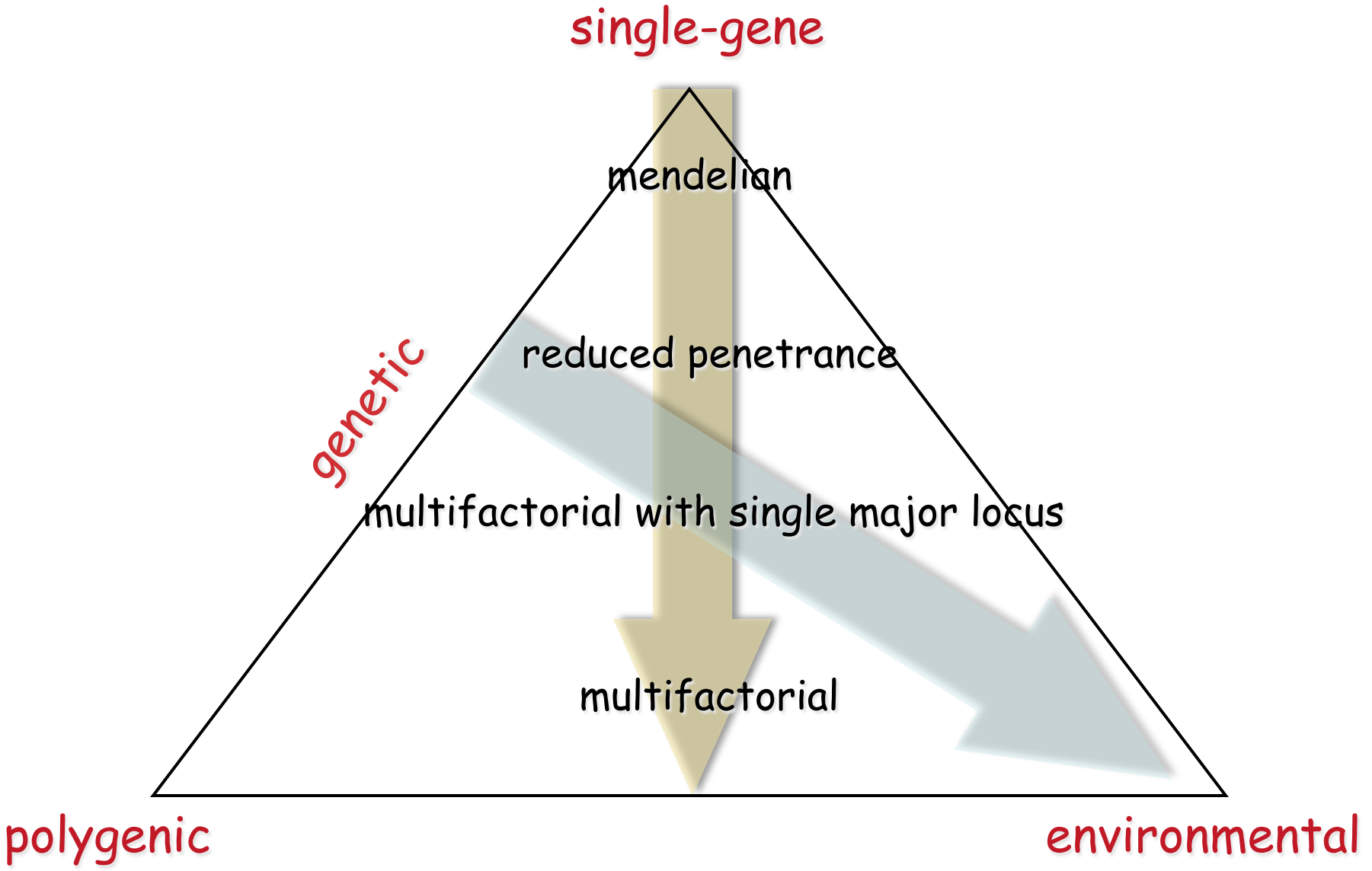
Copy number variation

What are some practical benefits to learning about DNA?

GWAS:
genome-wide association studies to identify the genetic component of complex diseases (multigenic/multifactorial)

THE SPECTRUM OF HUMAN CHARACTERS

few characters are purely mendelian, purely polygenic or purely environmental

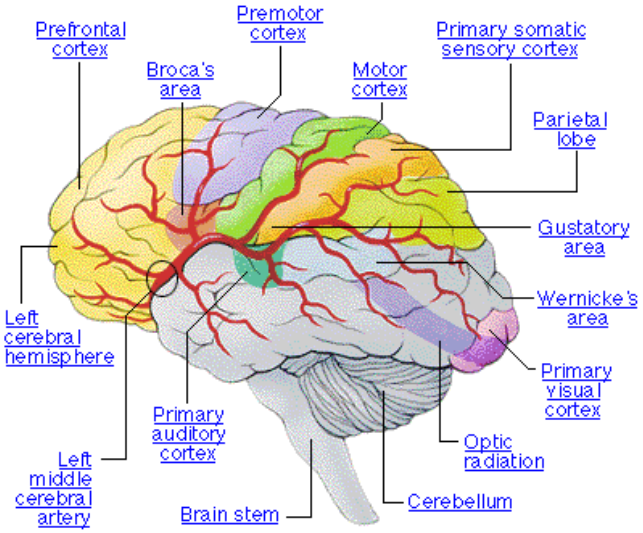


Multifactorial determination of a disease:

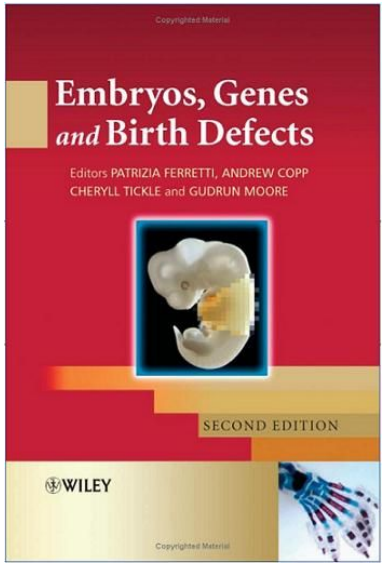
black and pink spheres represent any combination
of genetic and environmental factors
adding an extra black or an extra pink sphere can tip the balance,
without that particular factor being the cause of the disease

Complex Diseases

Cardio-vascular diseases



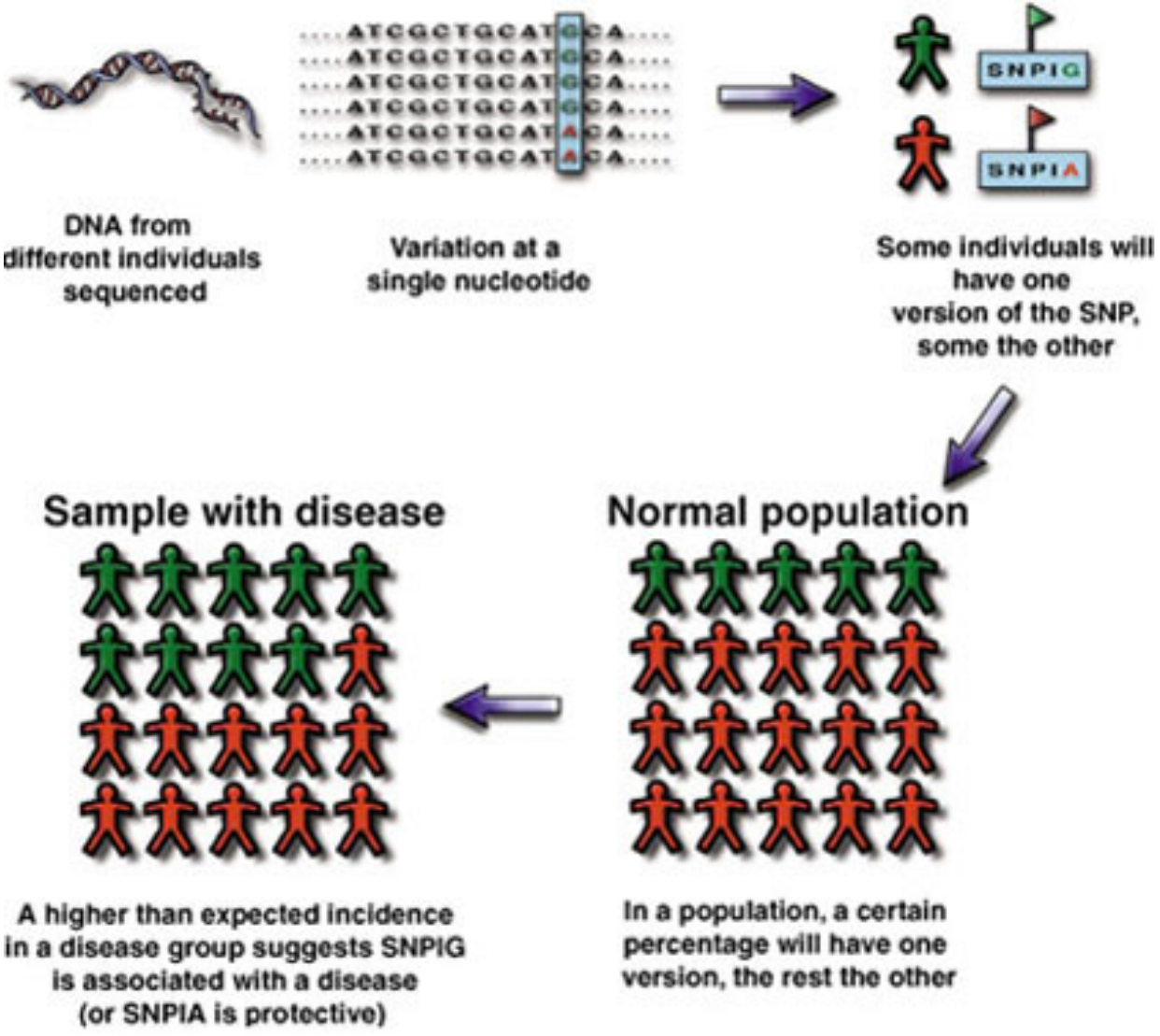
Psychiatric and degenerative disease of brain



Non-syndromic birth defects

Cancer

Using SNPs to track predisposition to complex diseases



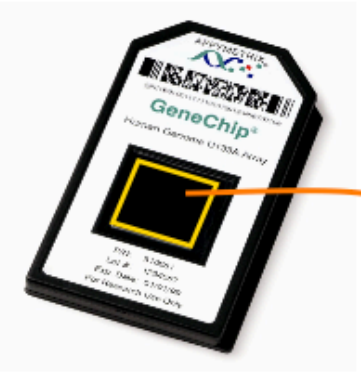
Affymetrix SNP microarrays
(Mapping 10K, 100K, 500K)
(Genome-Wide Human 5.0 and 6.0)

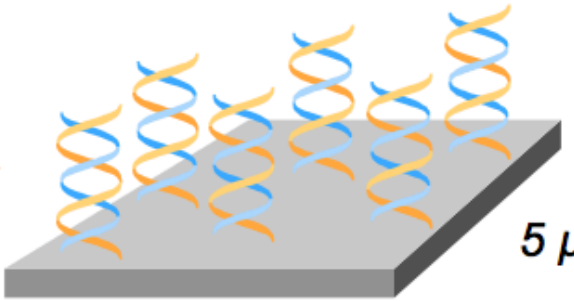
GeneChip® Mapping Assay Kit

GeneChip® Mapping 100K/500K Set

GCS 3000 7G

Affymetrix microarrays
high-density oligonucleotide chips



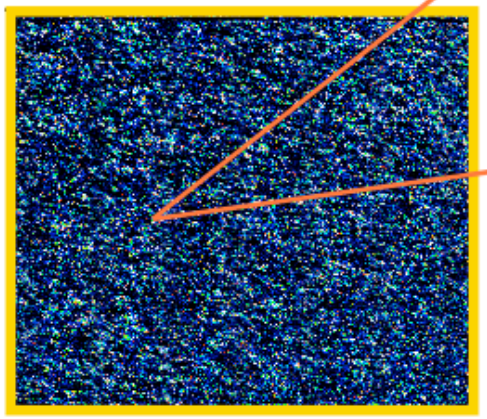


5 μm

1.28 cm

5 μm

1.28 cm

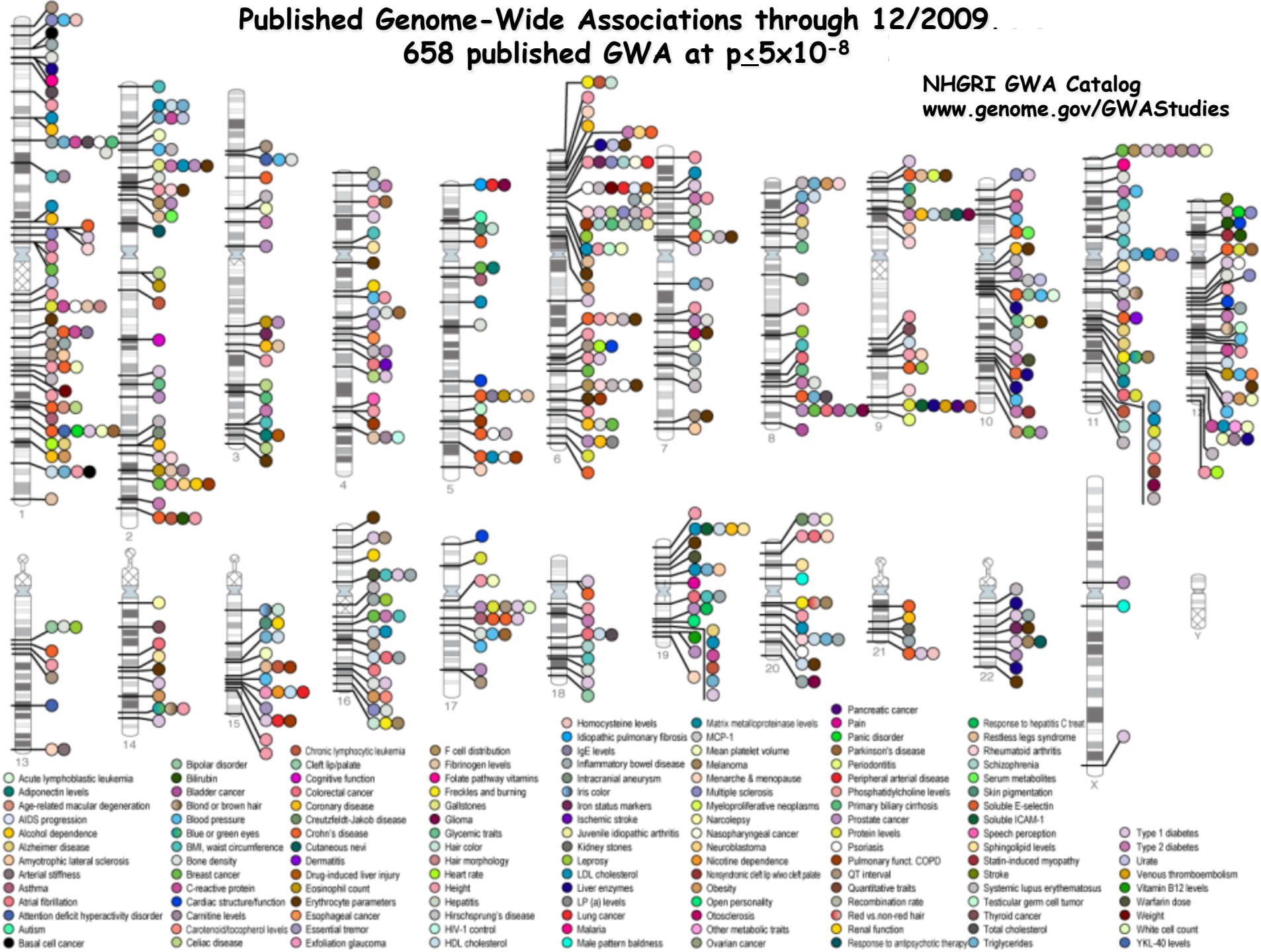


1 million identical
25-mer sequences

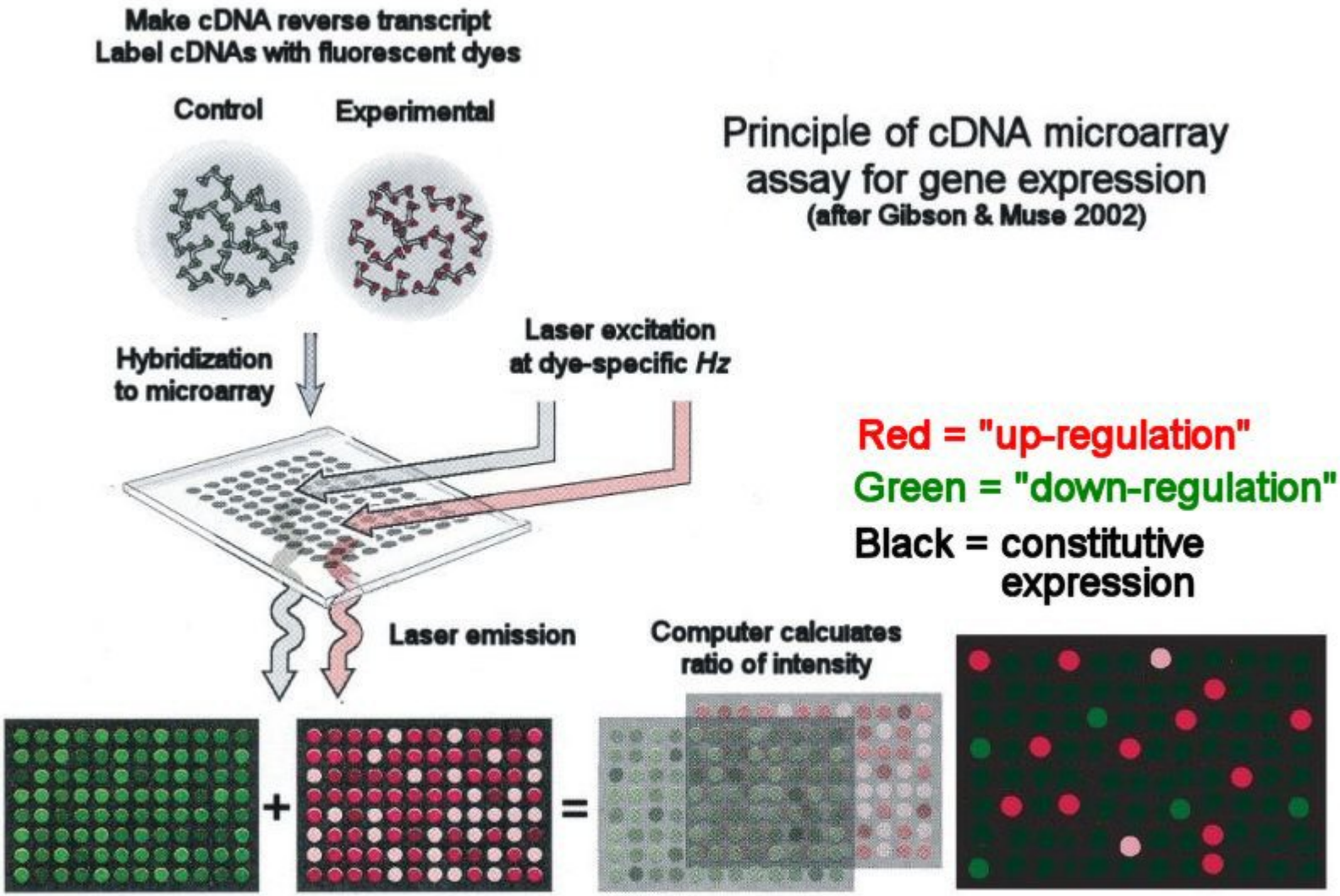
6.5 million probes/chip

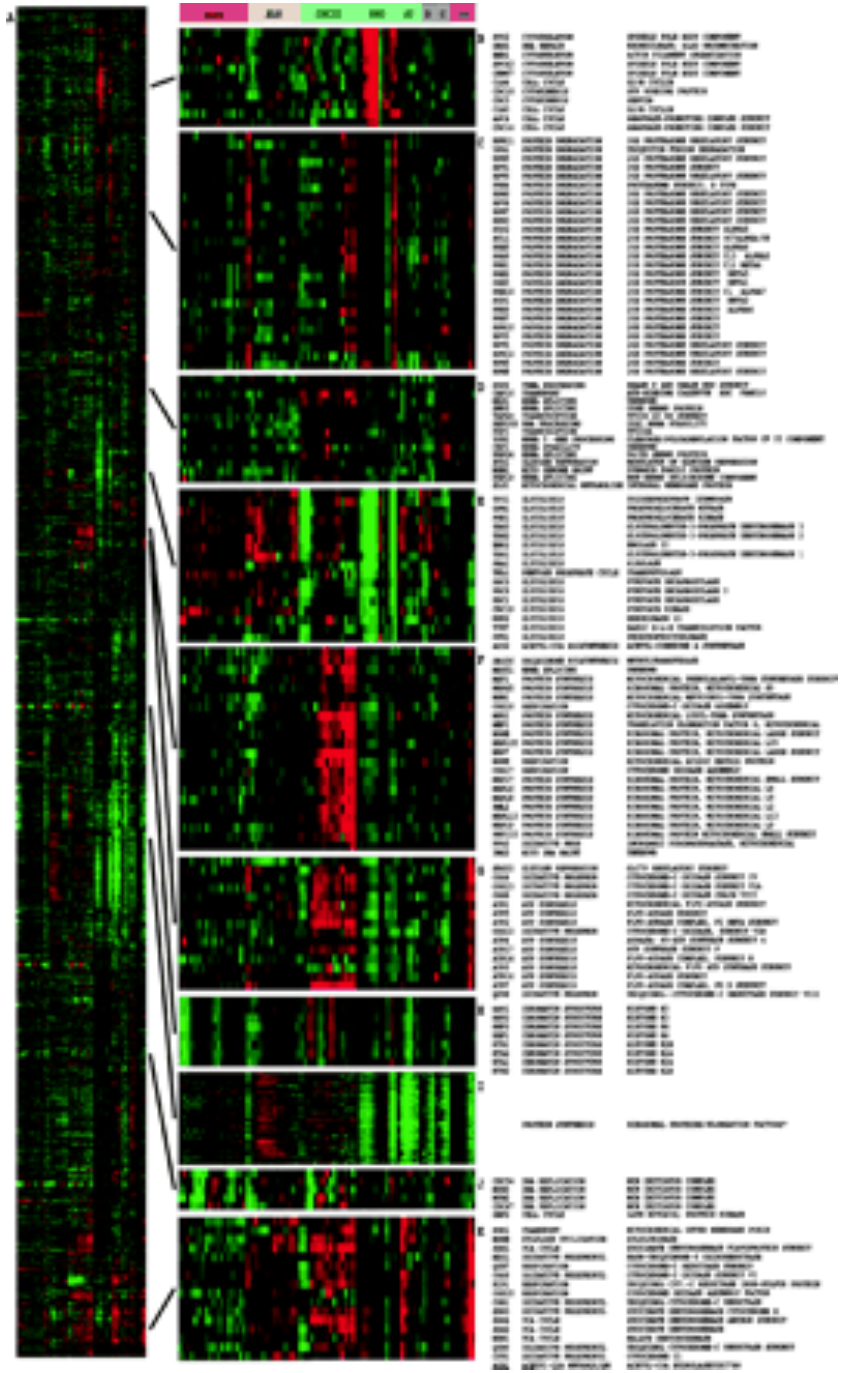
Published Genome-Wide Associations through 12/2009.
658 published GWA at $p \leq 5 \times 10^{-8}$

NHGRI GWA Catalog
www.genome.gov/GWAStudies

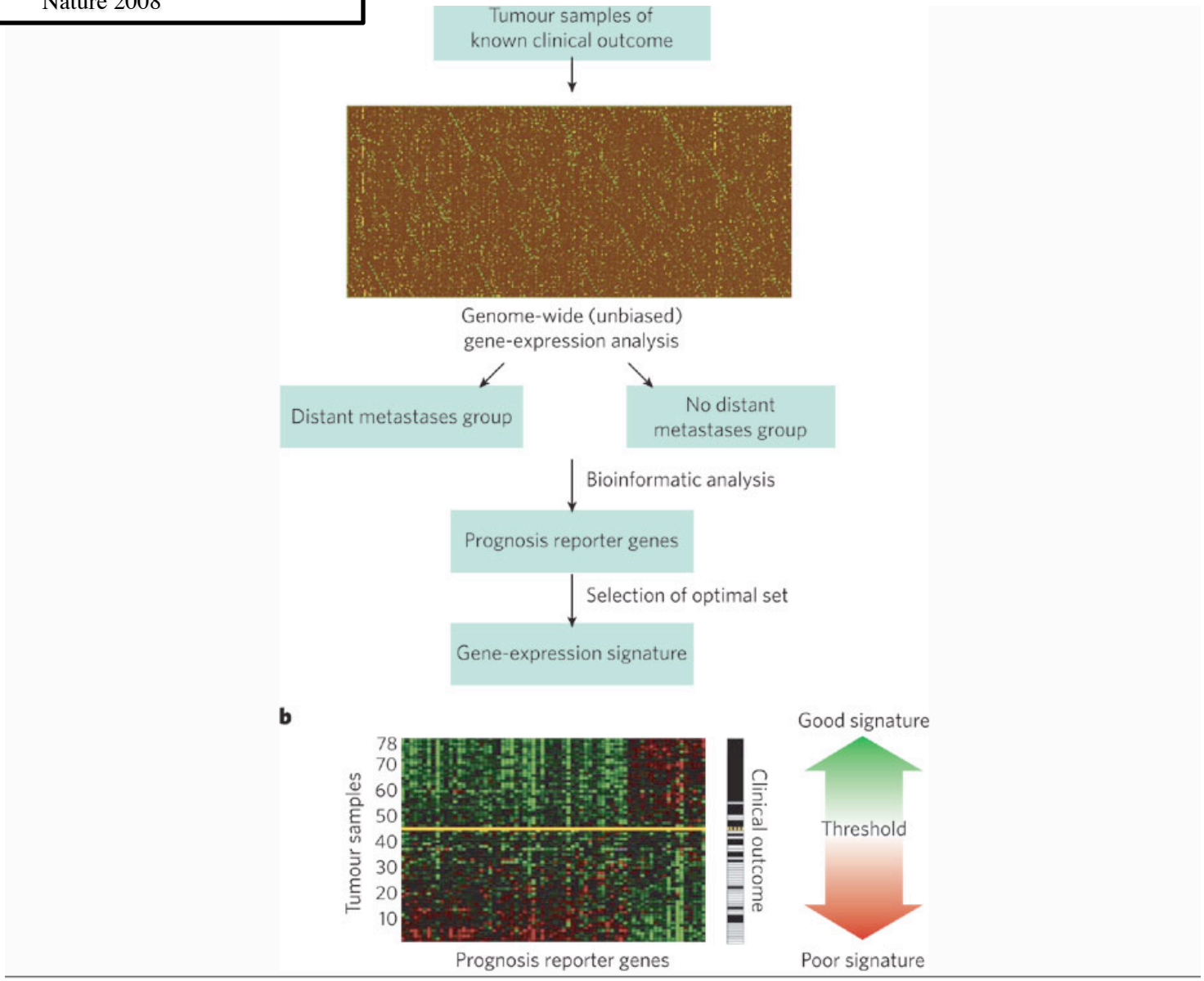


Genome-wide expression analysis





Laura J. van 't Veer and René Bernards,
Nature 2008

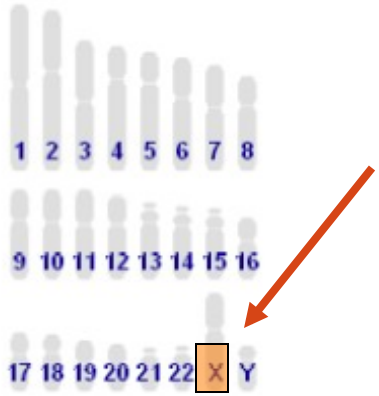


Analysis “in silico”

http://www.ncbi.nlm.nih.gov/genome/guide/human/

Browse your Genome
Click on the Chromosome to show

Genes



The NCBI Handbook

An online guide to the use of NCBI resources. Titles of selected chapters that refer to human genome resources are shown below.

The Single Nucleotide Polymorphism Database (dbSNP) of Nucleotide Sequence Variation
Adrienne Kitts and Stephen Sherry

Online Mendelian

A challenge facing researchers today is that of piecing together and analyzing the plethora of data currently being generated through the Human Genome Project and scores of smaller projects. NCBI's Web site serves an an integrated, one-stop, genomic information infrastructure for biomedical researchers from around the world so that they may use these data in their research efforts.
More...

Genes and Human Health

OMIM
A guide to human genes and inherited disorders maintained by Johns Hopkins University and collaborators.

RefSeq
Reference sequences of chromosomes, genomic contigs, mRNAs, and proteins for human and major model organisms.

dbSNP
A database of single nucleotide polymorphisms (SNPs) and other nucleotide variations.

Gene Database
A new database of genes and associated information is now available for searching in Entrez.

Search Genes
from All species
with words Go

Locus Link
A comprehensive catalog of genes and other genetic loci.

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Human Maps Help
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Region Shown:
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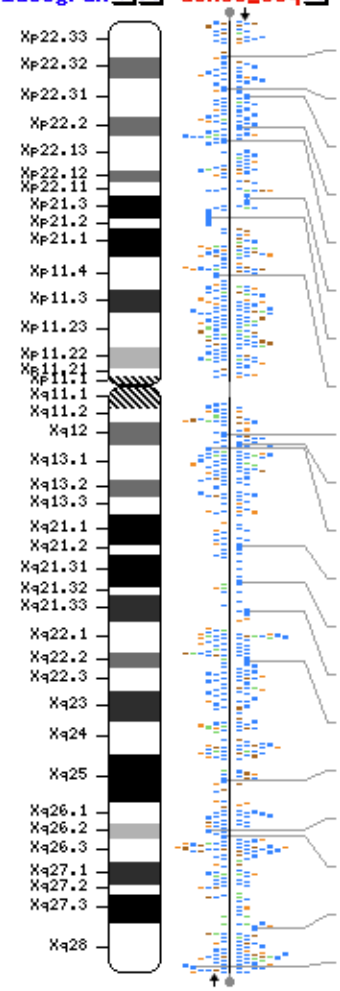
You are here:
Ideogram
default
master

Chromosome: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 [X] Y MT

Master Map: Genes On Sequence — Summary of Maps — Maps & Options

Region Displayed: **0-154M bp** — Download/View Sequence/Evidence



Symbol	O	LinkOut	E	Cyto	Description
NLGN4X	↑	OMIM sv pr dl ev mm hm ccds	C	Xp22.32-p22.31	neuroligin 4, X-linked
ARHGAP6	↑	OMIM sv pr dl ev mm hm ccds	C	Xp22.3	Rho GTPase activating protein 6
PDZK10	↓	sv pr dl ev mm hm	C	Xp22.2	PDZ domain containing 10
NHS	↓	OMIM sv pr dl ev mm hm ccds	C	Xp22.13	Nance-Horan syndrome (congen
SH3KBP1	↑	OMIM sv pr dl ev mm hm ccds	C	Xp22.1-p21.3	SH3-domain kinase binding prot
IL1RAPL1	↓	OMIM sv pr dl ev mm hm ccds	C	Xp22.1-p21.3	interleukin 1 receptor accessory p
DMD	↑	OMIM sv pr dl ev mm hm ccds	C	Xp21.2	dystrophin (muscular dystrophy,
CASK	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.4	calcium/calmodulin-dependent se
OPHN1	↑	OMIM sv pr dl ev mm hm ccds	C	Xq12	oligophrenin 1
ED1	↓	OMIM sv pr dl ev mm hm ccds	C	Xq12-q13.1	ectodermal dysplasia 1, anhidroti
TEX11	↑	OMIM sv pr dl ev mm	C	Xq13.1	testis expressed sequence 11
DACH2	↓	sv pr dl ev mm hm ccds	C	Xq21.3	dachshund homolog 2 (Drosophi
PCDH11X	↓	OMIM sv pr dl ev mm hm ccds	C	Xq21.3	protocadherin 11 X-linked
DIAPH2	↓	OMIM sv pr dl ev mm hm ccds	C	Xq22	diaphanous homolog 2 (Drosoph
IL1RAPL2	↓	OMIM sv pr dl ev mm hm ccds	C	Xq22.2-q22.3	interleukin 1 receptor accessory p
ODZ1	↑	sv pr dl ev mm hm ccds	C	Xq25	odz, odd Oz/ten-m homolog 1(D
HS6ST2	↑	sv pr dl ev mm hm	C	Xq26.2	heparan sulfate 6-O-sulfotransfer
GPC3	↑	OMIM sv pr dl ev mm hm ccds	C	Xq26.1	glypican 3
FMR2	↓	OMIM sv pr dl ev mm hm ccds	C	Xq28	fragile X mental retardation 2
F8	↑	OMIM sv pr dl ev mm hm	C	Xq28	coagulation factor VIII, procoagu

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Maps & Options
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49M
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Ideogram
default
master

Chromosome: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 [X] Y MT

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Region Displayed: **29M-49M bp**

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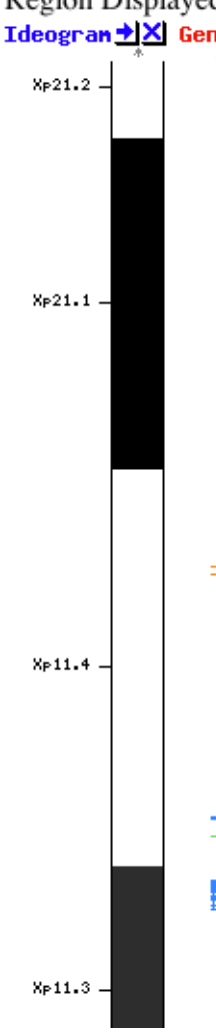


Symbol	C	LinkOut	E	Cyto	Description
IL1RAPL1	↓	OMIM sv pr dl ev mm hm ccds	C	Xp22.1-p21.3	interleukin 1 receptor accessory pro
GK	↓	OMIM sv pr dl ev mm hm ccds	C	Xp21.3	glycerol kinase
TAB3	↑	OMIM sv pr dl ev mm hm ccds	C	Xp21.3	TAK1-binding protein 3
DMD	↑	OMIM sv pr dl ev mm hm ccds	C	Xp21.2	dystrophin (muscular dystrophy, D
CXorf22	↓	sv pr dl ev mm ccds	C	Xp21.1	chromosome X open reading frame
FLJ36601	↓	sv pr dl ev mm ccds	C	Xp21.1	hypothetical protein FLJ36601
PRRG1	↓	OMIM sv pr dl ev mm hm ccds	C	Xp21.1	proline rich Gla (G-carboxyglutami
FLJ42925	↓	sv pr dl ev mm hm ccds	C	Xp21.1	FLJ42925 protein
XK	↓	OMIM sv pr dl ev mm hm ccds	C	Xp21.1	Kell blood group precursor (McLe
SYTL5	↓	sv pr dl ev mm hm ccds	C	Xp21.1	synaptotagmin-like 5
SRPX	↑	OMIM sv pr dl ev mm hm ccds	C	Xp21.1	sushi-repeat-containing protein, X-l
RPGR	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.4	retinitis pigmentosa GTPase regula
OTC	↓	OMIM sv pr dl ev mm hm ccds	C	Xp21.1	ornithine carbamoyltransferase
TM4SF2	↓	OMIM sv pr dl ev mm hm ccds	C	Xp11.4	transmembrane 4 superfamily mem
BCOR	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.4	BCL6 co-repressor
CRSP2	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.4-p11.2	cofactor required for Sp1 transcript
USP9X	↓	OMIM sv pr dl ev mm hm	C	Xp11.4	ubiquitin specific protease 9, X-link
CASK	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.4	calcium/calmodulin-dependent seri
MAOA	↓	OMIM sv pr dl ev mm hm ccds	C	Xp11.4-p11.3	monoamine oxidase A
MAOB	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.23	monoamine oxidase B

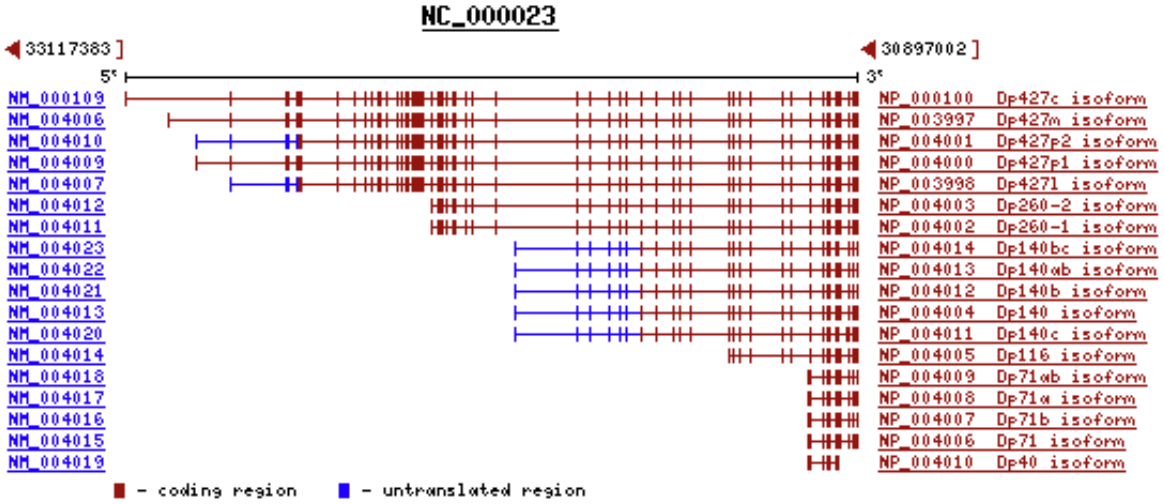
1: DMD dystrophin (muscular dystrophy, Duchenne and Becker types) [*Homo sapiens*]

Links

GeneID: 1756 Locus tag: HGNC:2928; MIM: 300377 updated 19-Mar-2005

Official Symbol: DMD **and Name:** dystrophin (muscular dystrophy, Duchenne and Becker types) **provided by** HUGO Gene Nomenclature Committee

Transcripts and products: (shown on reverse complement genome) RefSeq below



Genomic context: chromosome: X; **Maps:** Xp21.2

Gene type: protein coding
Gene name: DMD
Gene description: dystrophin (muscular dystrophy, Duchenne and Becker types)
RefSeq status: Reviewed
Organism: *Homo sapiens*
Lineage: *Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae; Homo*
Gene aliases: BMD; DXS142; DXS164; DXS206; DXS230; DXS239; DXS268; DXS269; DXS270; DXS272; dystrophin
Summary: The dystrophin gene is the largest gene found in nature, measuring 2.4 Mb. The gene was identified through a positional cloning approach, targeted at the isolation of the gene responsible for Duchenne (DMD) and Becker (BMD) Muscular Dystrophies. DMD is a recessive, fatal, X-linked disorder occurring at a frequency of about 1 in 3,500 new-born males. BMD is a milder allelic

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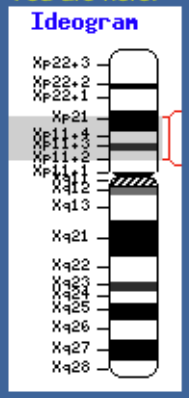

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master

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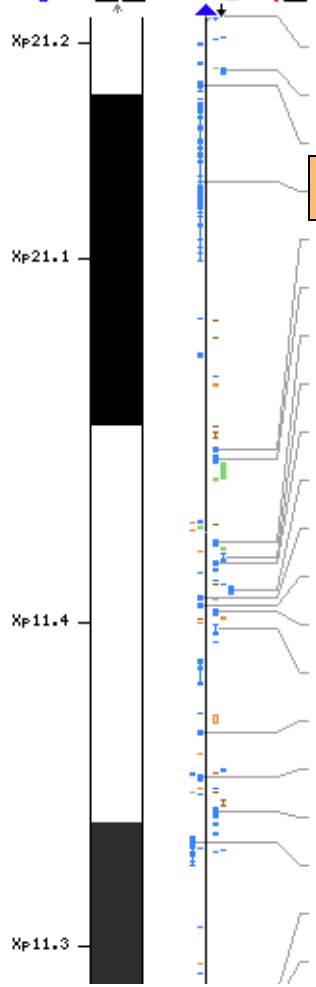

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MAOA	↓	OMIM sv pr dl ev mm hm ccds	C	Xp11.4-p11.3	monoamine oxidase A
MAOB	↑	OMIM sv pr dl ev mm hm ccds	C	Xp11.23	monoamine oxidase B

GeneTests, Links

*300377
DYSTROPHIN; DMD

Alternative titles; symbols

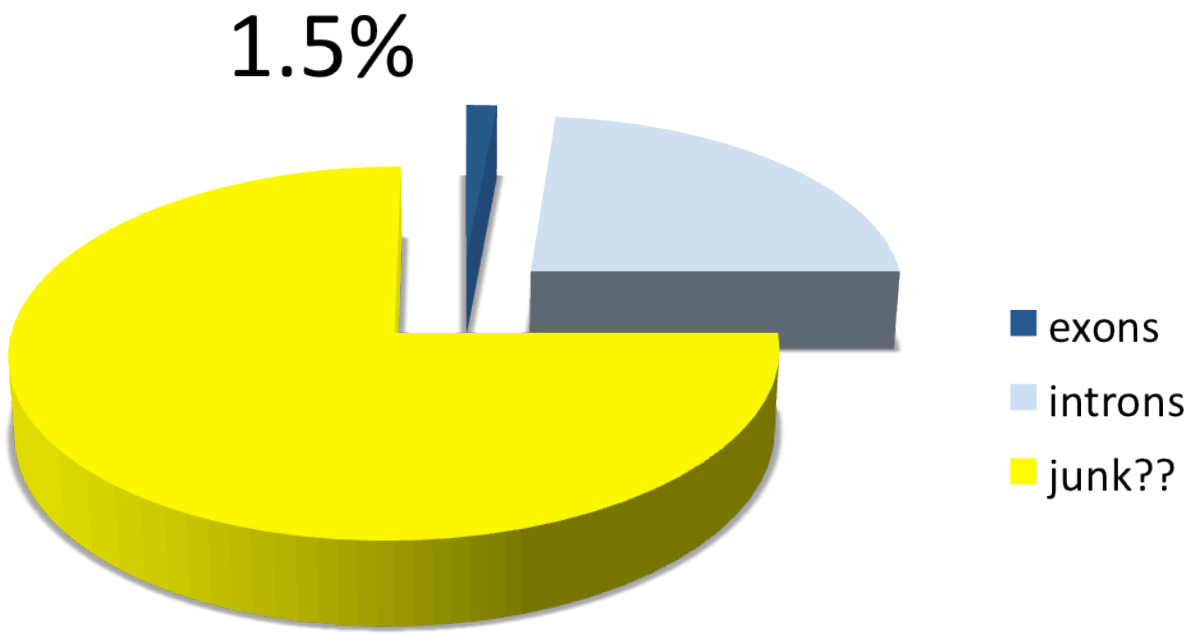
APO-DYSTROPHIN 1, INCLUDED

Gene map locus Xp21.2

TEXT

In addition to the classic dystrophies of Duchenne (310200) and Becker (300376), defined as progressive deterioration of muscle tissue and resultant weakness, other types of skeletal muscle dysfunction have been occasionally reported in association with abnormalities of the dystrophin gene. Gospe et al. (1989) described an extraordinary family with X-linked myalgia and cramps due to a nonprogressive myopathy associated with and presumably caused by a deletion in the dystrophin gene. Nine affected male family members had high resting serum levels of creatine kinase and well-developed musculature with calf hypertrophy but no evidence of muscular weakness. Symptoms began in childhood and did not progress. Electromyographic findings were consistent with myopathy while muscle biopsies showed nonspecific myopathic changes without evidence of storage of glycogen or

>95% of our DNA consists of non-protein-coding DNA



Tomorrow……

Junk-DNA is not junk at all

The DNA sequence is just the blueprint