GENOMICA APPLICATA

The Human Genome

Intro

- Understanding
  - the organization,
  - variation,
  - and expression of the **human genome** is central to the principles of genomic and precision medicine.

- The comparison of individual genomes underlies the conclusion that **virtually every individual has his or her own unique constitution of gene products**

The «chemical individuality»

Archibald Garrod

From Wikipedia, the free encyclopedia

Sir Archibald Edward Garrod KCMG FRS[1] (25 November 1857 – 28 March 1936) was an English physician who pioneered the field of inborn errors of metabolism. He also discovered alkaptonuria, understanding its inheritance. He served as Regius Professor of Medicine at the University of Oxford from 1920 to 1927.[2]

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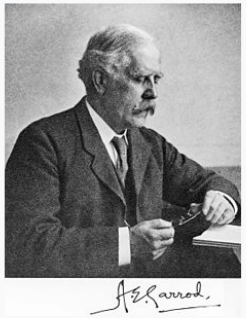
Archibald Garrod



Born	25 November 1857 London
Died	28 March 1936 (aged 78) Cambridge
Nationality	English
Known for	alkaptonuria
Awards	Fellow of the Royal Society[1]
Scientific career	
Fields	medicine
Institutions	University of Oxford

Education and personal life [edit]

Brilliancy ran in Garrod's family. Archibald was the fourth son of Sir Alfred Baring Garrod, a renowned physician who received his medical degree at the age of 23 and became a professor of medicine at University College, London by the time he was 32. He discovered the abnormal uric acid metabolism associated with gout.[2] Garrod's father also successfully estimated the weight of crystals he obtained from a known quantity of blood, resulting in what Garrod called "the first quantitative biochemical investigation made on the living human body".[3] Garrod's two older brothers also had successful careers.

Charles Keene, a cousin, frequently visited Garrod's childhood home. Keene was a illustrator for the magazine Punch for over 40 years. Influenced by Keene, Garrod wrote an illustrated booklet called *A Handbook of Classical Architecture*. According to Krishna Dronamraju, Garrod displayed an interest in natural history from an early age and was particularly interested in butterflies. At the age of 12, he began collecting them and noted how few female butterflies were present, musing over possible inheritance patterns in mammals.[4]

He was educated at Marlborough College and Christ Church, University of Oxford. He performed poorly at Marlborough, struggling due to his lack of interest in classics, especially Latin prose and grammar. He graduated with a First-class Honours (or a "First") degree in natural science in 1878.[4]

In 1880, he received further medical training at St. Bartholomew's Hospital in London, where he obtained several scholarships including the competitive Brackenbury Scholarship. Garrod graduated in 1884 and then spent a year studying in Vienna at the general hospital, known as the Allgemeines Krankenhaus. His experiences in Vienna formed the basis for his 1886 work, *An Introduction to the Use of the Laryngoscope*, which was very well received. In 1885 he

The «chemical individuality»

Eur J Pediatr. 1986 Apr;145(1-2):2-5.

"Inborn errors of metabolism" and "chemical individuality", two ideas of Sir Archibald Garrod briefly revisited 50 years after his death.

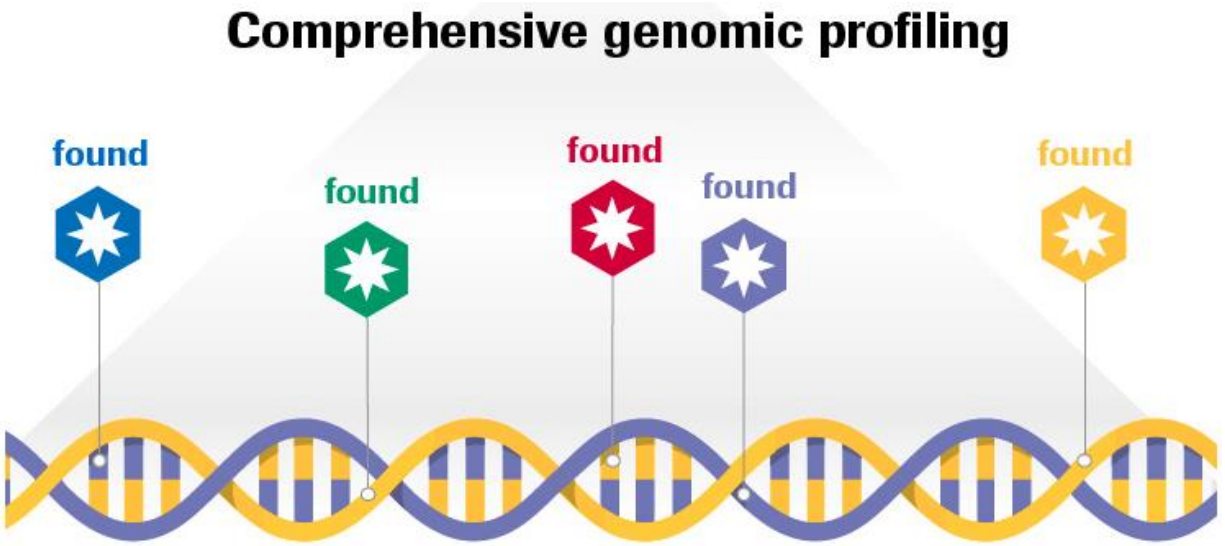
Burgio GR.

Abstract

Two ideas of Sir A. Garrod, "chemical individuality" (1902) and "inborn errors of metabolism" (1908) have proved fundamental for the development of medical knowledge. The latter idea was more fortunate than the former which, however has been extremely heuristic. On the other hand the two ideas are not entirely independent of each other: in fact, a third Garrodian concept, "inborn factors in disease", represents a significant link between them. "Inborn errors of metabolism" revived the laws of genetics and opened the way to interpretation of the molecular diseases with all their inherent practical modern implications (neonatal screening, prenatal diagnosis, and in perspective, genetic engineering). "Chemical individuality" still constitutes a valid premise for knowledge of biological individuality (in other words, the "biological ego") fundamentally programmed for conservation of self and for continuous discrimination of self versus non-self.

Variation in the human genome

- Variation in the human genome has long been the cornerstone of the field of human genetics, and its study led to the establishment of the medical specialty of **medical genetics.**



Genetics or Genomics

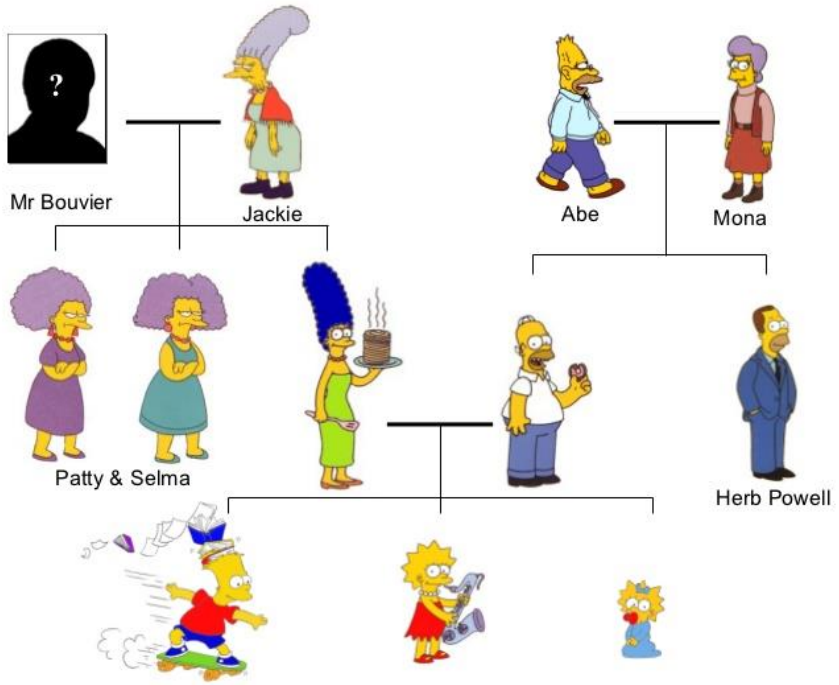
- While these terms seem similar, they in fact describe quite distinct (though frequently overlapping) approaches in biology and in medicine.
- Having said that, there are inconsistencies in the way the terms are used, even by those who work in the field.

Genetics or Genomics

- The field of *genetics* is the scientific study of heredity and of the genes that provide the physical, biological, and conceptual bases for heredity and inheritance.
- To say that something—a trait, a disease, a code, or an information—is "genetic" refers to its basis in genes and in DNA.

Genetics or Genomics

- *Heredity* refers to the familial phenomenon whereby traits (including clinical traits) are transmitted from generation to generation, due to the transmission of genes from parent to child.



Genetics or Genomics

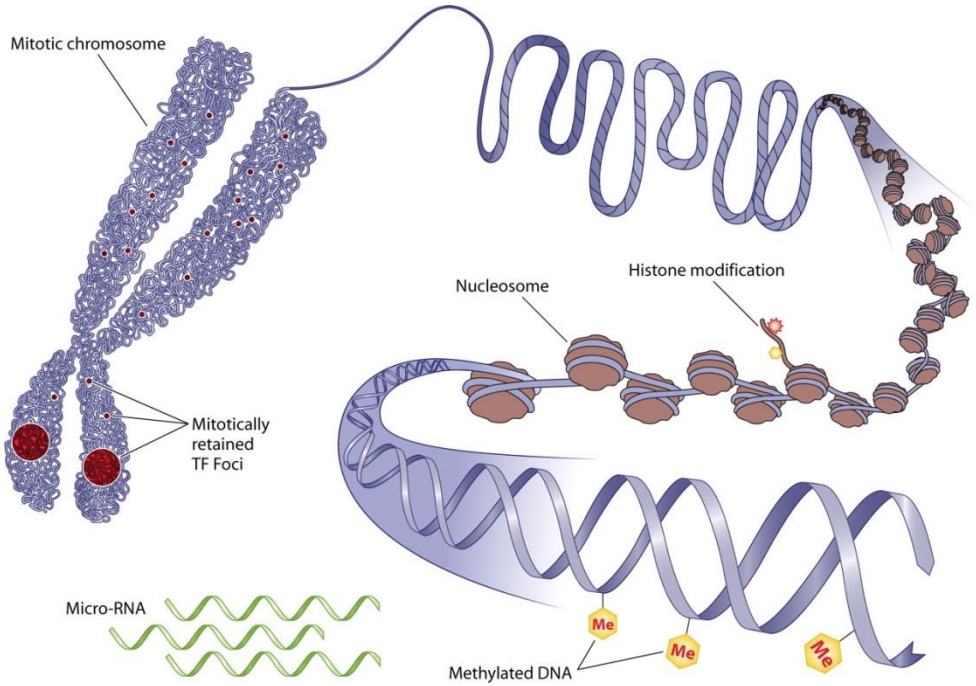
- *Genomics* is the scientific study of a genome or genomes.
- A *genome* is the complete DNA sequence, referring to the entire genetic information of a gamete, an individual, a population, or a species.

Genetics or Genomics

- "Genomics" gave birth to a series of other "-omics" that refer to the comprehensive study of the full complement of genome products
  - proteins (hence, *proteomics*),
  - transcripts (*transcriptomics*), or
  - metabolites (*metabolomics*).

Genetics or Genomics

- By analogy with genetics and genomics, *epigenetics* and *epigenomics* refer to the study of factors that affect gene (or, more globally, genome) function, but without an accompanying change in genes or the genome.



Genetics or Genomics

- *Genomic Medicine* refers to the use of large-scale genomic information and to consideration of the full extent of an individual's genome and other "omes" in the practice of medicine and medical decision making.

Genetics or Genomics

Examples:

- **gene expression profiling** to characterize tumors or to define prognosis in cancer
- **genotyping variants** in the set of genes involved in drug metabolism or action to determine an individual's correct therapeutic dosage

Genetics or Genomics

Examples:

- **scanning the entire genome** for millions of variants that influence one's susceptibility to disease
- analyzing multiple protein or RNA **biomarkers** to detect exposure to potential pathogens

Genetics or Genomics

Examples:

- Monitor therapy
- predictive information in presymptomatic individuals

Characteristics of the Reference Human Genome

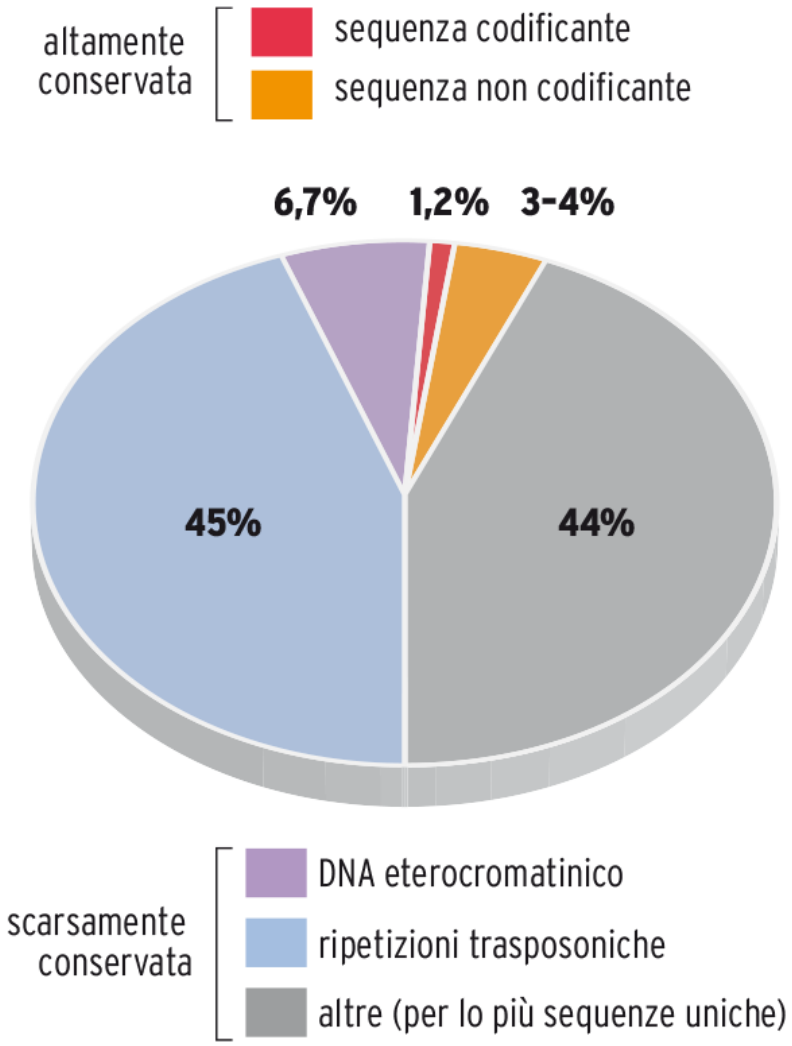
- The typical human genome consists of approximately 3 billion (3×10^9) base pairs of DNA,
- 24 types of nuclear chromosomes (22 autosomes, plus the sex chromosomes, X and Y)
- the smaller mitochondrial chromosome

Characteristics of the Reference Human Genome

Length of the human genome (base pairs)	3,096,649,726
Number of known protein-coding genes	20,441
Average gene density (number of genes/Mb)	6.6
Number of ncRNA genes	22,219
Number of known short sequence variants	156,148,362
Number of known structural variants	4,485,861

From Ensembl, database GRCh38, version 85.38 (accessed August 2016).

Organizzazione del genoma umano



How much of our genome is functionally significant?

- There seemed to be pervasive transcription of the genome, and 80.4% of the human genome was claimed (ENCODE data) to participate in at least one RNA-associated or chromatin-structure-associated event in at least one cell type.

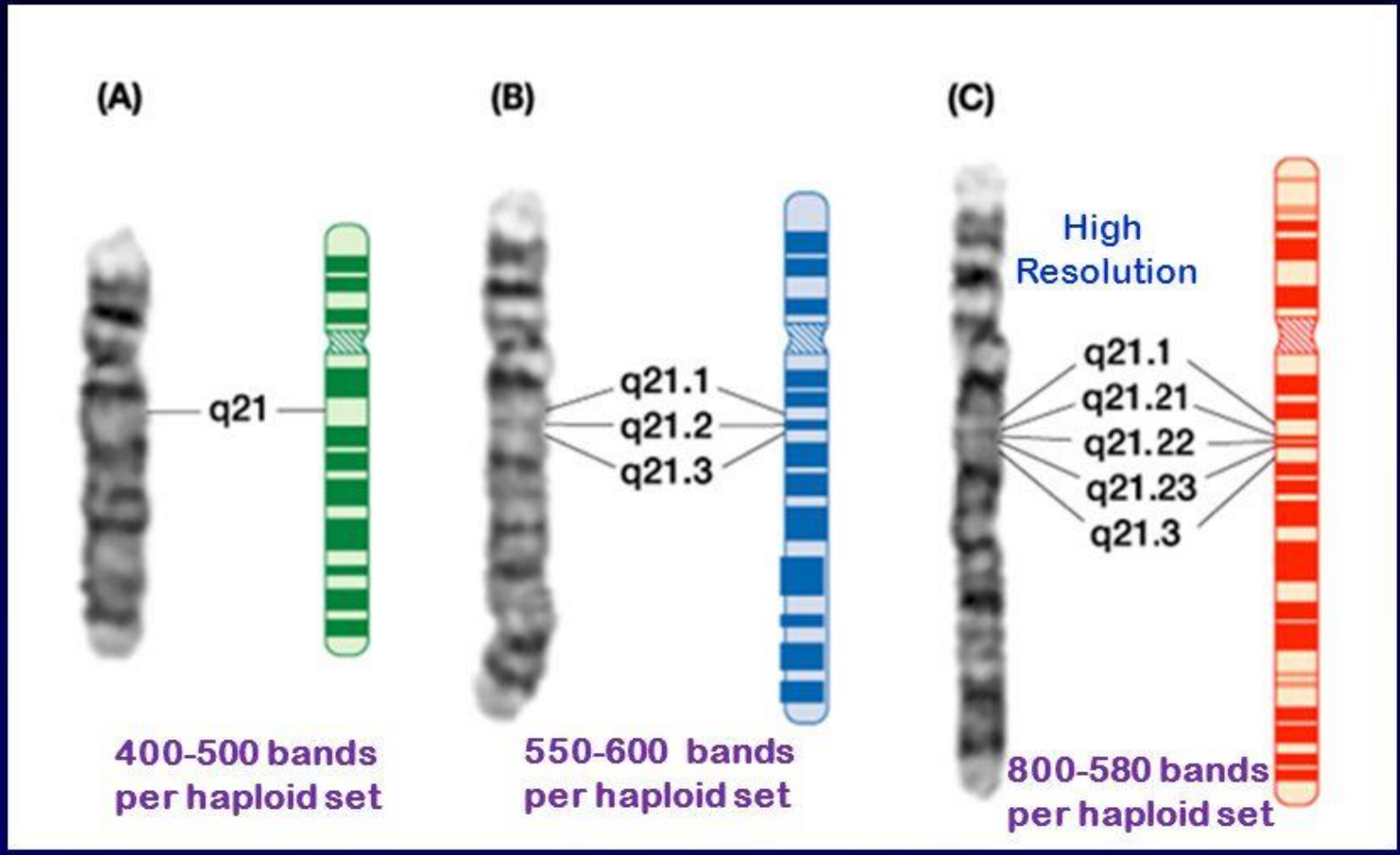
- However, the possible conclusion that much of our genome might be functionally significant has been strongly resisted by many evolutionary biologists.

- Part of the difficulty in interpreting the ENCODE data is that much of the 80.4% figure comes from the observed representation of RNA transcripts, but many RNAs are produced at such low levels that they might alternatively represent transcriptional background ‘noise.’

Spectrum of resolution

- Individual chromosomes can best be visualized and studied at metaphase in dividing cells, and **karyotyping of patient chromosomes has been a valuable and routine clinical laboratory procedure for a half century,** albeit at levels of resolution that fall well short of most pathologic DNA variants

High Resolution G banding

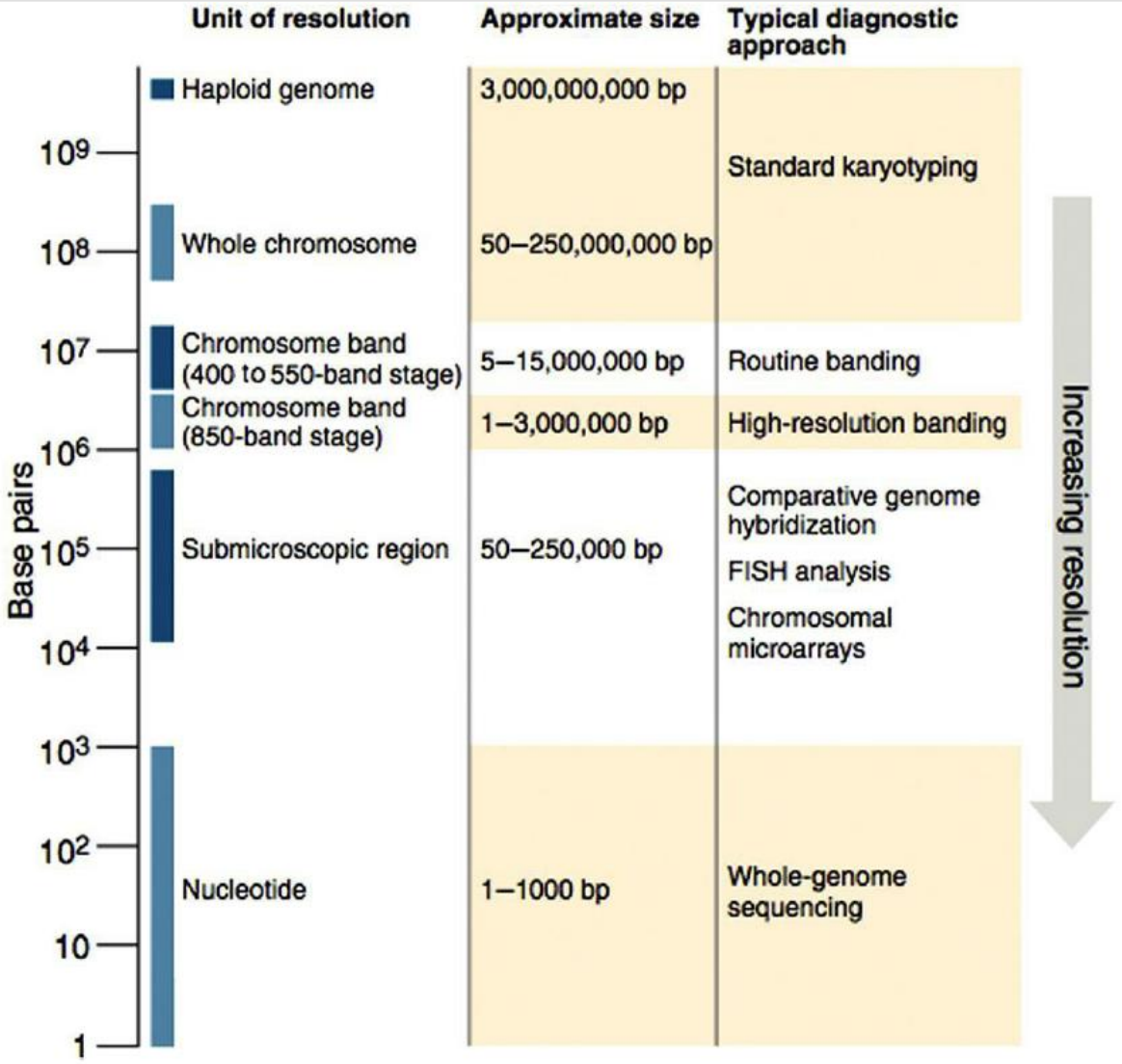


- Human chromosome 4 at varying resolutions due to exact mitotic stage, (or degrees of spreading - squashing - stretching)
- Each band corresponds to about 5000-10000 kb

Spectrum of resolution

- The ultimate resolution comes from direct sequence analysis, and an increasing number of new technologies have facilitated **comparisons of individual genomes** with the reference human genome sequence

Spectrum of resolution in chromosome and genome analysis



Genes in the Human Genome

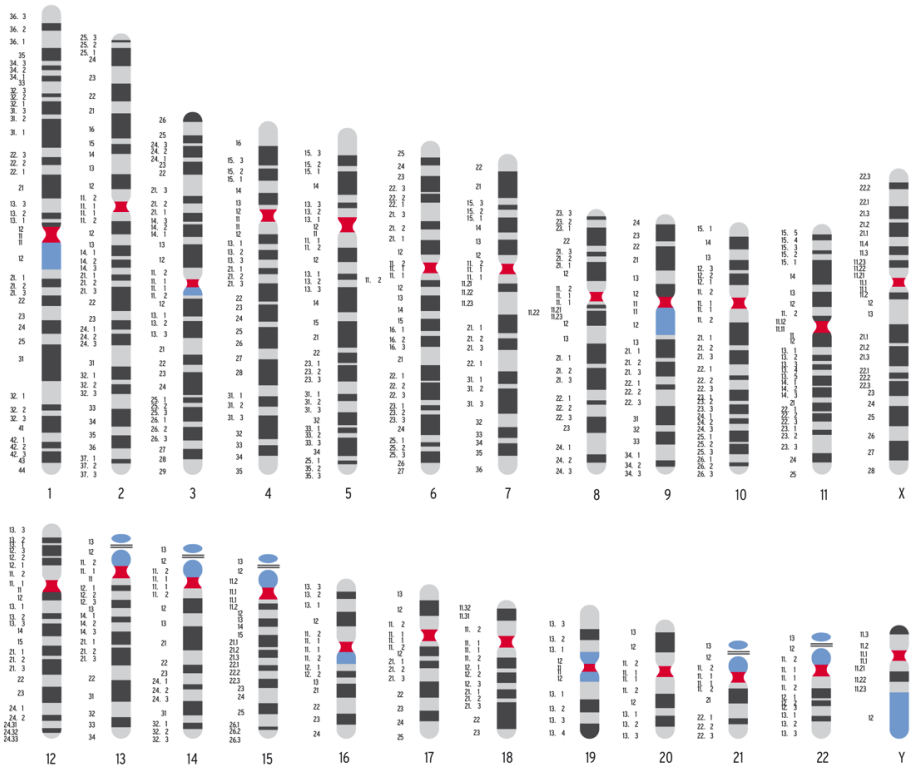
- the human genome contains an estimated 20,000 protein-coding genes
- there are some genes, including clinically relevant genes, that are currently undetected

Genes in the Human Genome

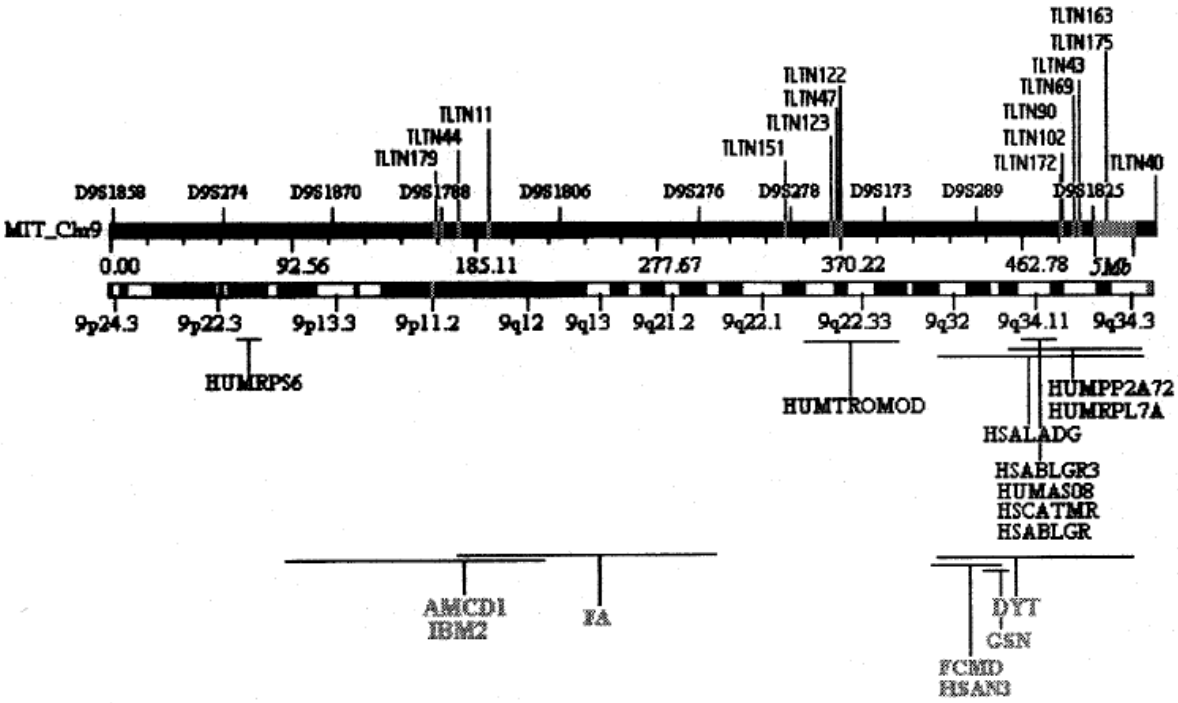
- In addition to being relatively sparse in the genome, genes are distributed quite nonrandomly along the different human chromosomes.
- Some chromosomes are relatively gene-rich, while others are quite gene-poor, ranging from approximately 3 genes/Mb of DNA to more than 20 genes/Mb

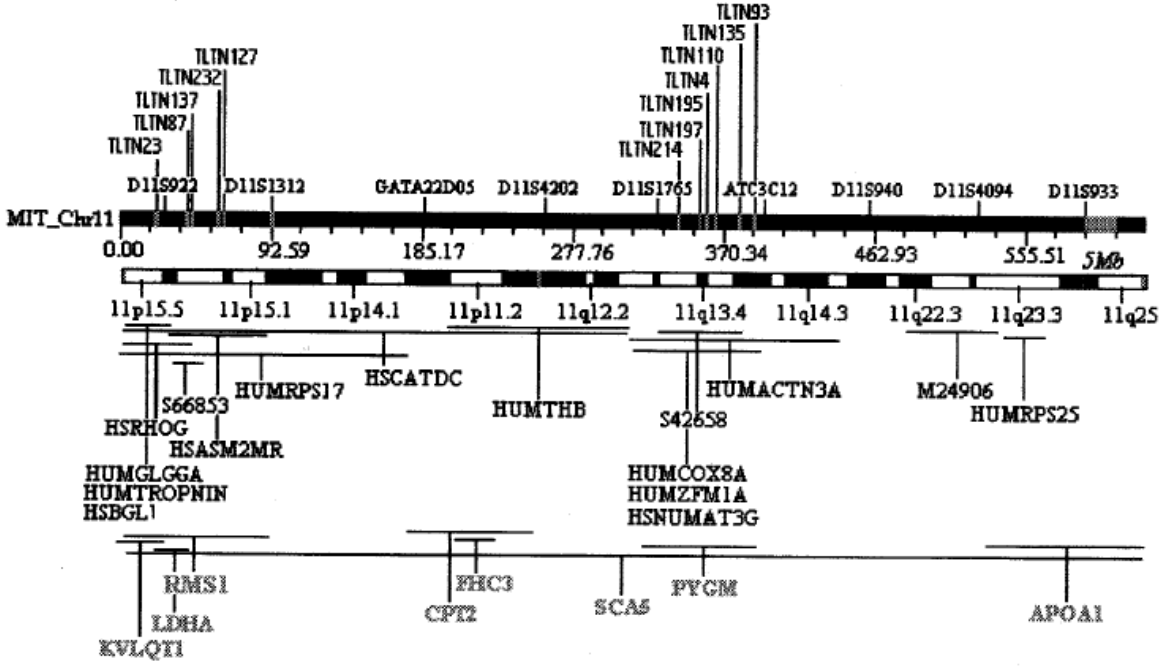
Gene distribution in the human genome

- Close to 7% of the nuclear genome is located in constitutive heterochromatin that remains highly condensed throughout the cell cycle



- Genome sequencing showed that gene and exon density in the euchromatic regions can vary enormously.
- Some chromosomes are gene-rich, such as chromosomes 19 and 22; others are gene-poor, notably the Y chromosome (which makes only 31 different proteins that mostly function in male determination).
- Within a chromosome, the pattern of alternating dark and light bands reflects


TLTN163
TLTN175
TLTN43
TLTN69
TLTN90
TLTN102
TLTN172
TLTN40
TLTN122
TLTN47
TLTN123
TLTN151
TLTN11
TLTN44
TLTN179
D9S1858
D9S274
D9S1870
D9S1788
D9S1806
D9S276
D9S278
D9S173
D9S289
D9S1825
MIT_Chr9
0.00
92.56
185.11
277.67
370.22
462.78
5Mb
9p24.3
9p22.3
9p13.3
9p11.2
9q12
9q13
9q21.2
9q22.1
9q22.33
9q32
9q34.11
9q34.3
HUMRPS6
HUMTROMOD
HUMPP2A72
HUMRPL7A
HSALADG
HSABLGR3
HUMAS08
HSCATMR
HSABLGR
AMCD1
IBM2
FA
DYT
CSN
FCMD
HSAN3


TLTN93
TLTN135
TLTN110
TLTN4
TLTN195
TLTN197
TLTN214
TLTN127
TLTN232
TLTN137
TLTN87
TLTN23
D11S922
D11S1312
GATA22D05
D11S4202
D11S1765
ATC3C12
D11S940
D11S4094
D11S933
MIT_Chr11
0.00
92.59
185.17
277.76
370.34
462.93
555.51
5Mb
11p15.5
11p15.1
11p14.1
11p11.2
11q12.2
11q13.4
11q14.3
11q22.3
11q23.3
11q25
HSCATDC
HUMRPS17
S66853
HSRHOG
HSASM2MR
HUMTHB
HUMACTN3A
S42658
M24906
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HUMGLGGA
HUMTROPNIN
HSBGL1
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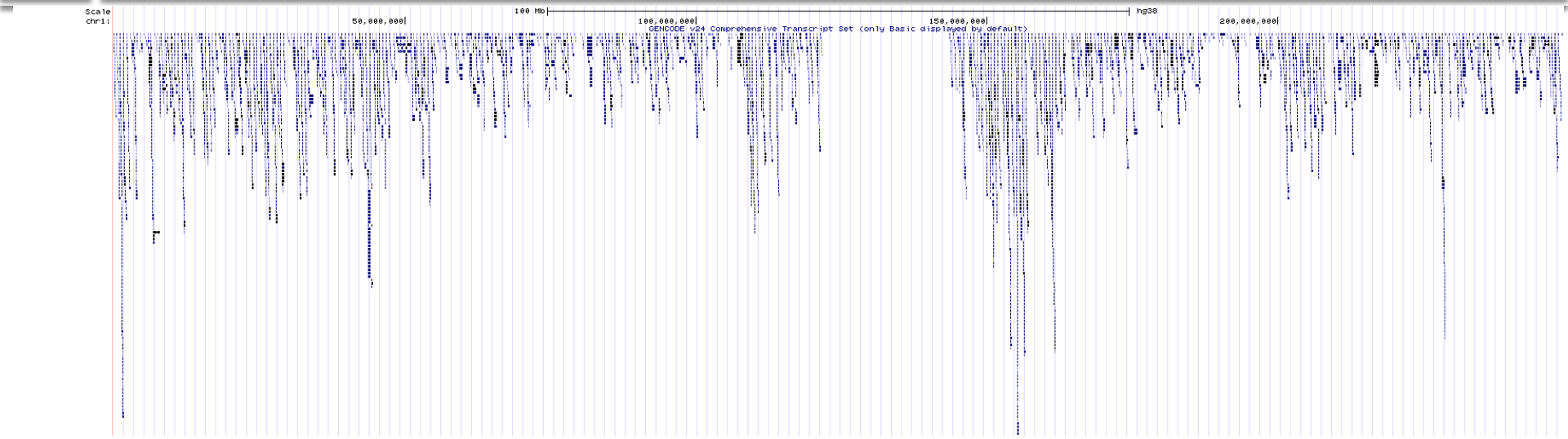
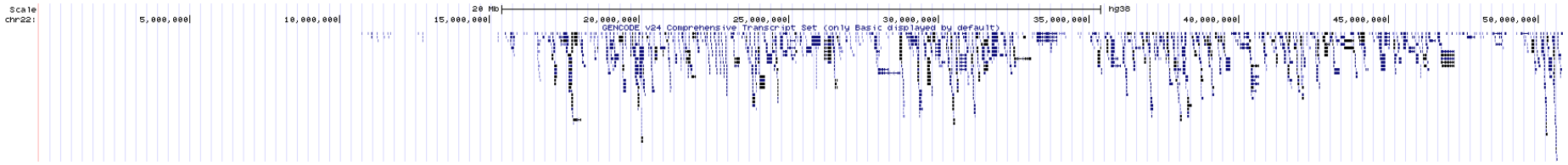
KVLQT1
FHC3
CPT2
SCA5
PYGM
APOA1


Scale
chr1:
50,000,000
100 Mb
100,000,000
150,000,000
hg38
200,000,000
GENCODE v24 Comprehensive Transcript Set (only Basic displayed by default)

- Chr1
- Chr22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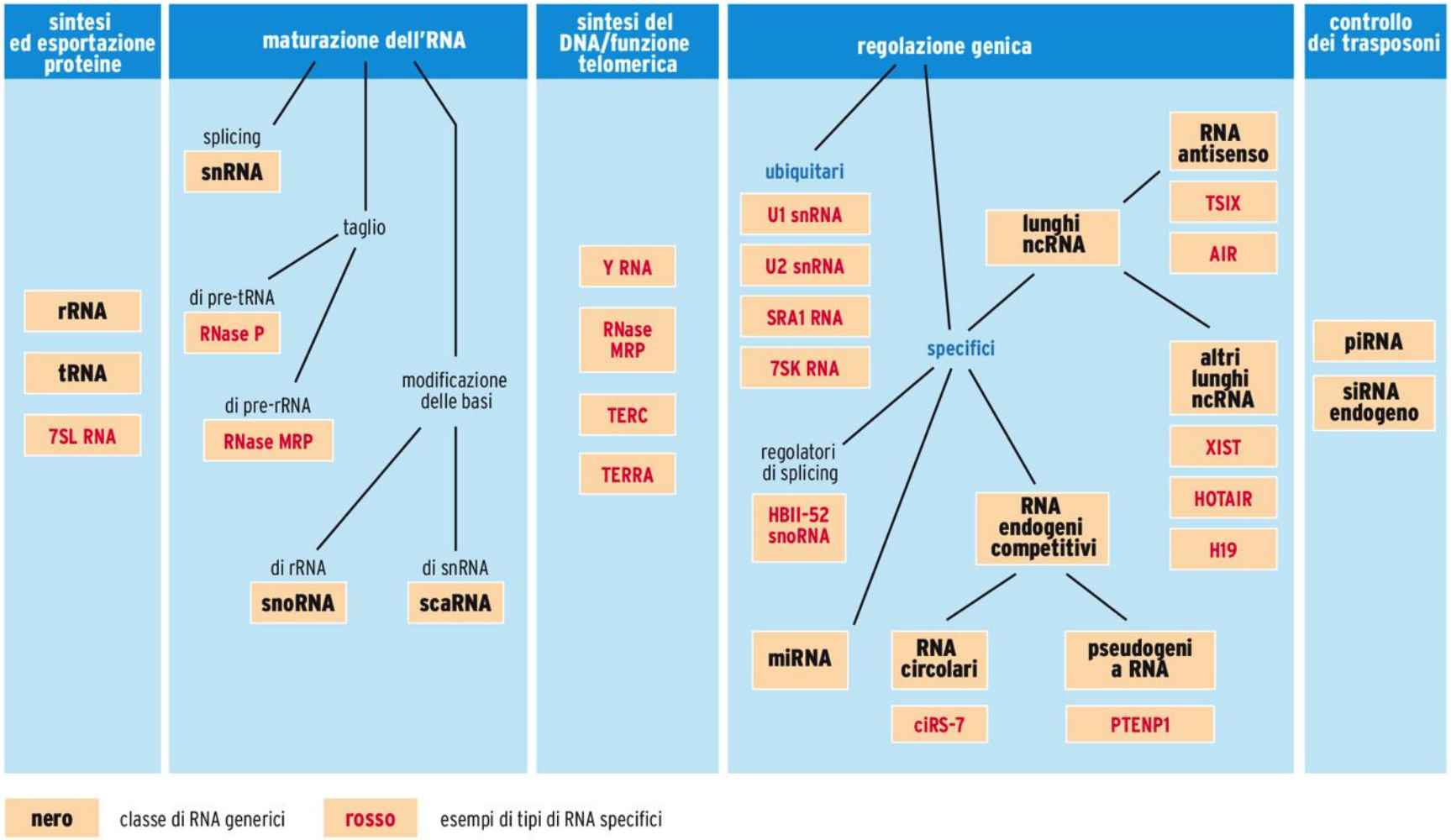
GENCODE v24 Comprehensive Transcript Set (only Basic displayed by default)

Coding and Noncoding Genes

- There are a number of different types of gene in the human genome.
  - Most genes known or thought to be clinically relevant are protein coding
  - additional genes whose functional product appears to be the RNA itself

ncRNA


sintesi ed esportazione proteine
rRNA
tRNA
7SL RNA
maturazione dell'RNA
splicing
snRNA
taglio
di pre-tRNA
RNase P
di pre-rRNA
RNase MRP
modificazione delle basi
di rRNA
snoRNA
di snRNA
scaRNA
sintesi del DNA/funzione telomerica
Y RNA
RNase MRP
TERC
TERRA
regolazione genica
ubiquitari
U1 snRNA
U2 snRNA
SRA1 RNA
7SK RNA
specifici
regolatori di splicing
HBII-52 snoRNA
miRNA
RNA circolari
ciRS-7
RNA endogeni competitivi
pseudogeni a RNA
PTENP1
lunghi ncRNA
RNA antisenso
TSIX
AIR
altri lunghi ncRNA
XIST
HOTAIR
H19
controllo dei trasposoni
piRNA
siRNA endogeno
nero
classe di RNA generici
rosso
esempi di tipi di RNA specifici

Variation in the Human Genome

- Any given individual carries **4–5 million sequence variants** that are known to exist in multiple forms (i.e., are polymorphic) in our species.

- each and every base pair in the human genome is expected to vary in someone somewhere around the globe.

Variation in the Human Genome

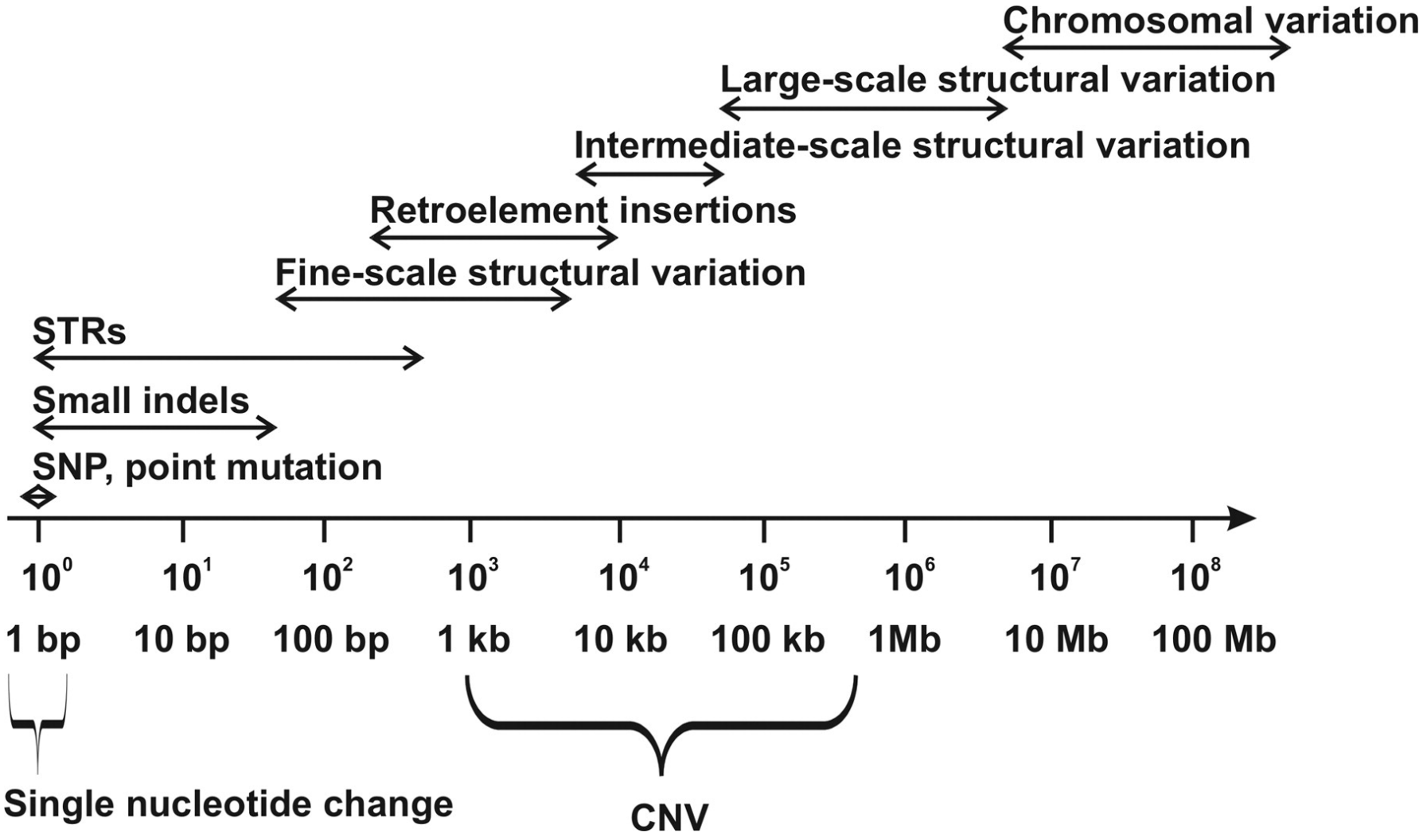
- **Types of Variation**
  - any two randomly selected individuals have sequences that are 99.9% identical

- The majority of these differences involve simply a single unit in the DNA code and are referred to as single-nucleotide polymorphisms (SNPs)

Variation in the Human Genome

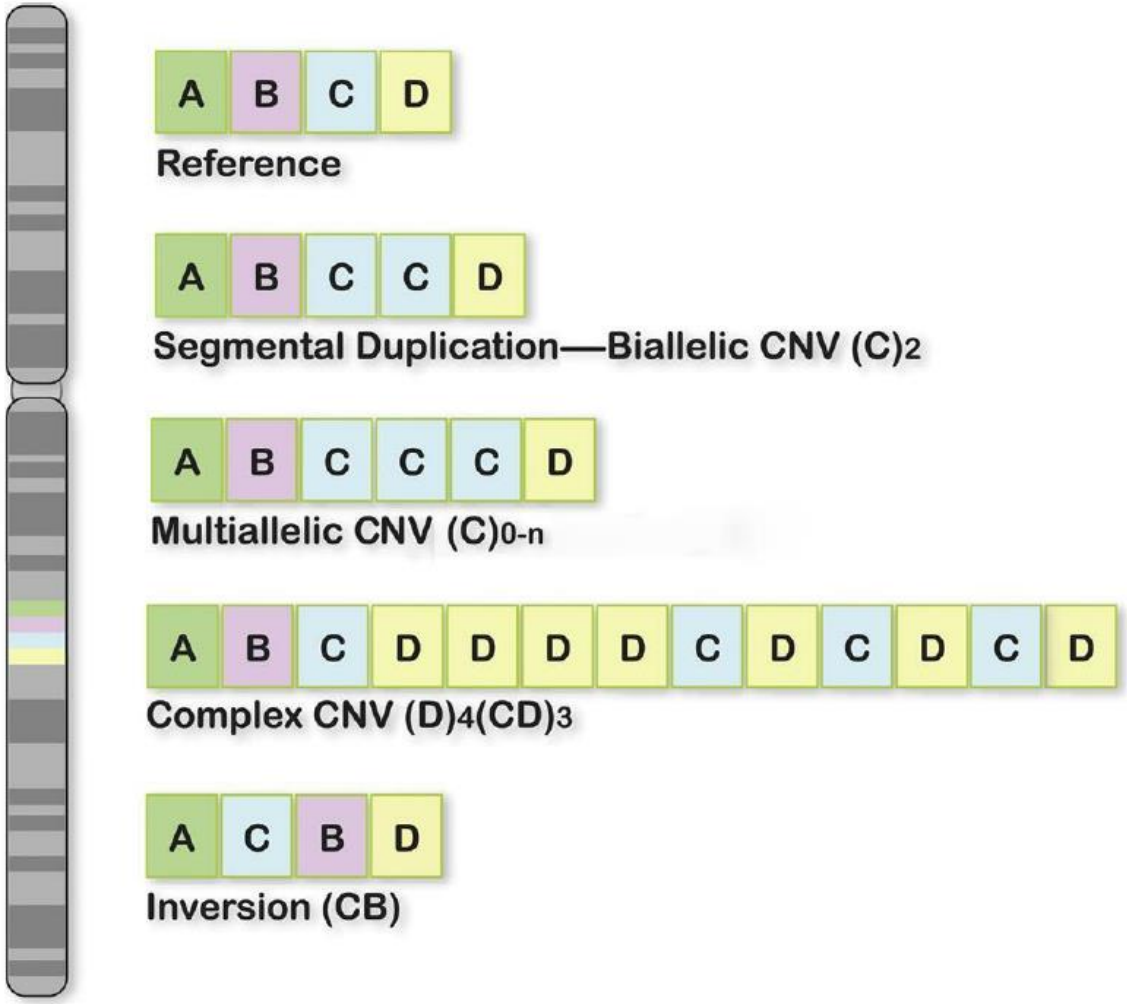
- The remaining variation consists of insertions or deletions (**in/dels**) of (usually) short sequence stretches, variation in the number of copies of repeated elements or inversions in the order of sequences at a particular locus in the genome

Variation in the Human Genome



Variation in the Human Genome

- Schematic representation of different types of structural polymorphism in the human genome, leading to deletions, duplications, inversions, and CNV changes relative to the reference arrangement.



Common Variation in the Human Genome

Type of Variation	Size Range (approx.)[a]	Effect(s) in Biology and Medicine
Single-nucleotide polymorphisms	1 bp	Nonsynonymous → functional change in encoded protein?
		Others → potential regulatory variants?
		Most → no effect? ("neutral")
Copy number variants (CNVs)	10 kb to 1 Mb	Gene dosage variation → functional consequences?Most → no effect or uncertain effect
Insertion/deletion polymorphisms (in/dels)	1 bp to 1 Mb	In coding sequence: frameshift mutation? → functional change
		Most → uncertain effects
Inversions	Few bp to 100 kb	? break in gene sequence
		? long-range effect on gene expression
		? indirect effects on reproductive fitness
		Most → no effect? ("neutral")
Segmental duplications	10 kb to >1 Mb	Hotspots for recombination → polymorphism (CNVs)

Variation in the Human Genome

- http://www.internationalgenome.org/about/

Populations: ● - African; ● - American; ● - East Asian; ● - European; ● - South Asian;

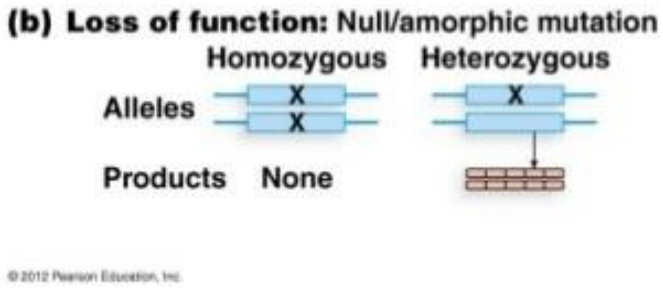
Variation in Individual Genomes

the 1000 Genomes Project concluded that each genome carries

- 100 or more likely loss-of-function mutations
- 10,000 nonsynonymous changes
- 500,000 variants that overlap known gene regulatory regions.

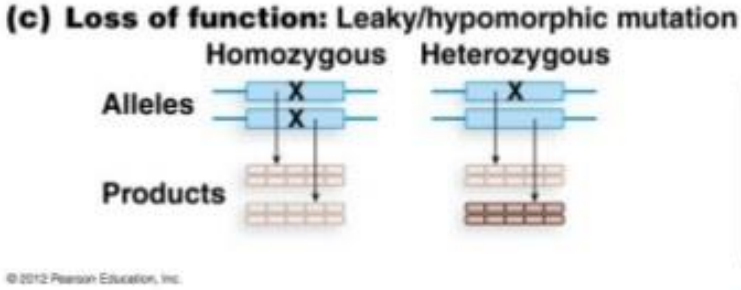
Variation in Individual Genomes

thousands of genes in the human genome are highly tolerant to many mutations that appear likely to result in a loss of function



Null alleles produce no functional product. Homozygous null organisms have mutant (amorphic) phenotype due to absence of the gene product. Heterozygous organisms produce less functional gene product than homozygous wild-type organisms and may have mutant phenotype. See text for discussion of dominant versus recessive mutations.

Amorphic = no function



Leaky mutant alleles produce a small amount of wild-type gene product. Homozygous organisms have a mutant (hypomorphic) phenotype. Heterozygous organisms may also be mutant.

Hypomorphic = less function

De *NOVO* MUTATION

- studies have shown that any individual carries an estimated 30–70 new mutations per genome that were not present in the genomes of his or her parents.
- generation of a new length variant depends on recombination, rather than on errors in DNA synthesis to generate a new base pair
- the measured rate of formation of new CNVs is orders of magnitude higher than that of base substitutions

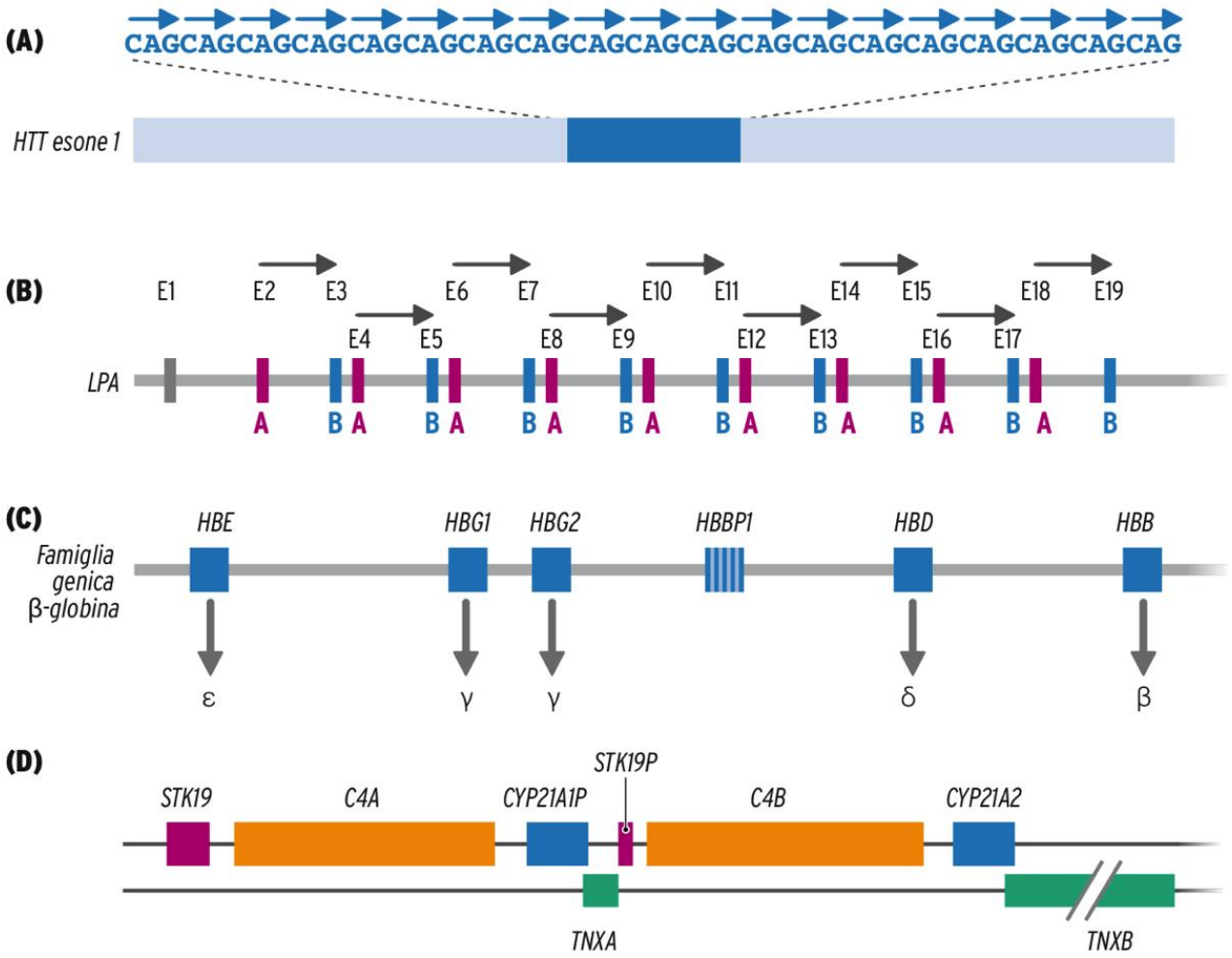
Variation in Individual Genomes

the number of SNPs described for our species is still incomplete

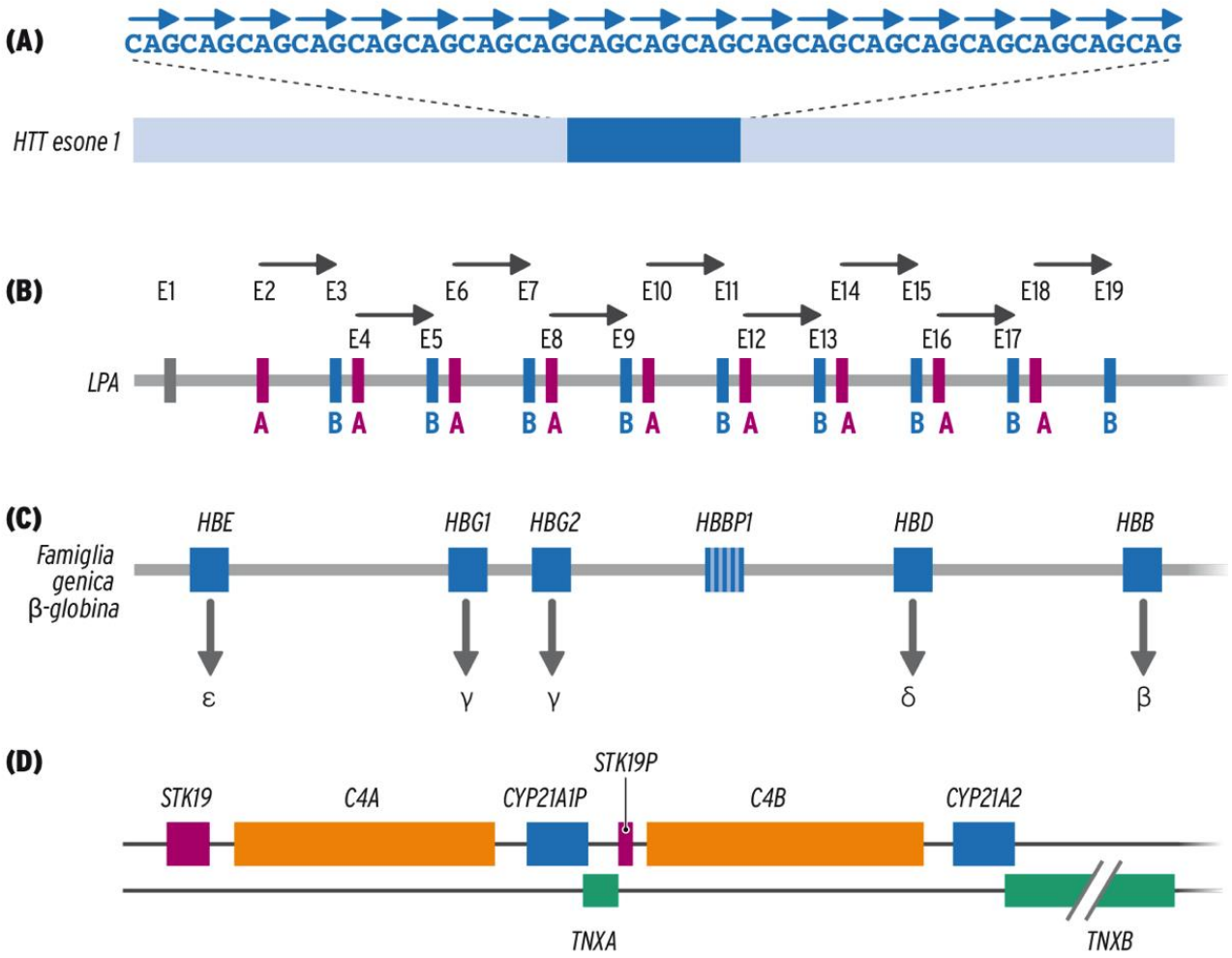
each genome carries thousands of nonsynonymous SNPs

These measurements underscore the potential impact of gene and genome variation on human biology and on medicine.

Examples of tandemly repetitive coding DNA and clustered gene families.



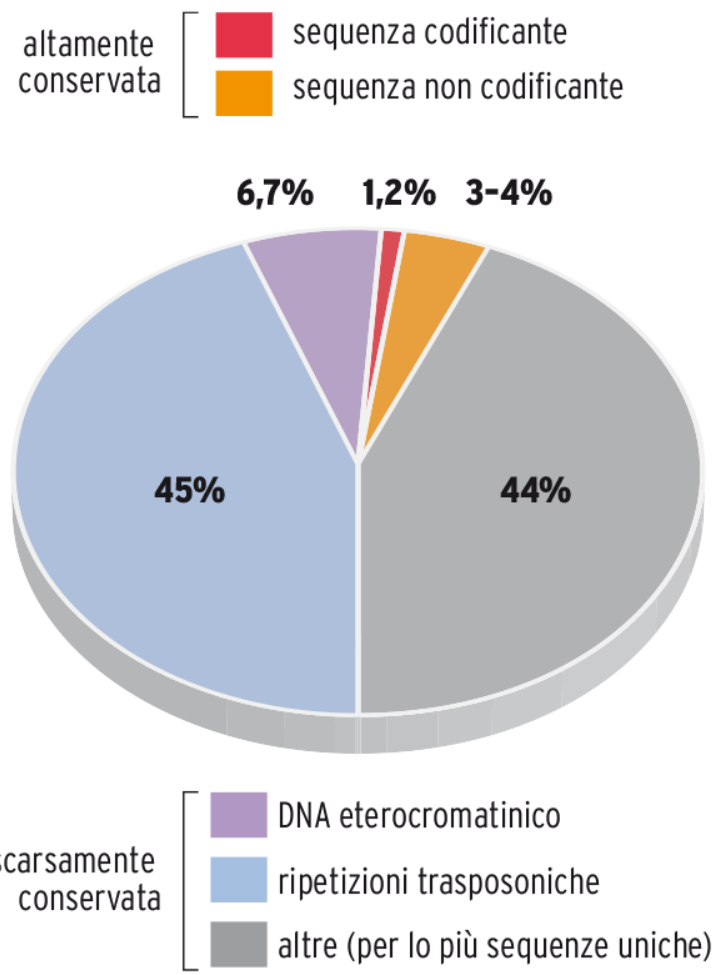
Examples of tandemly repetitive coding DNA and clustered gene families.



Our large nuclear genome is the outcome of periodic changes that have occurred over very long timescales during evolution:

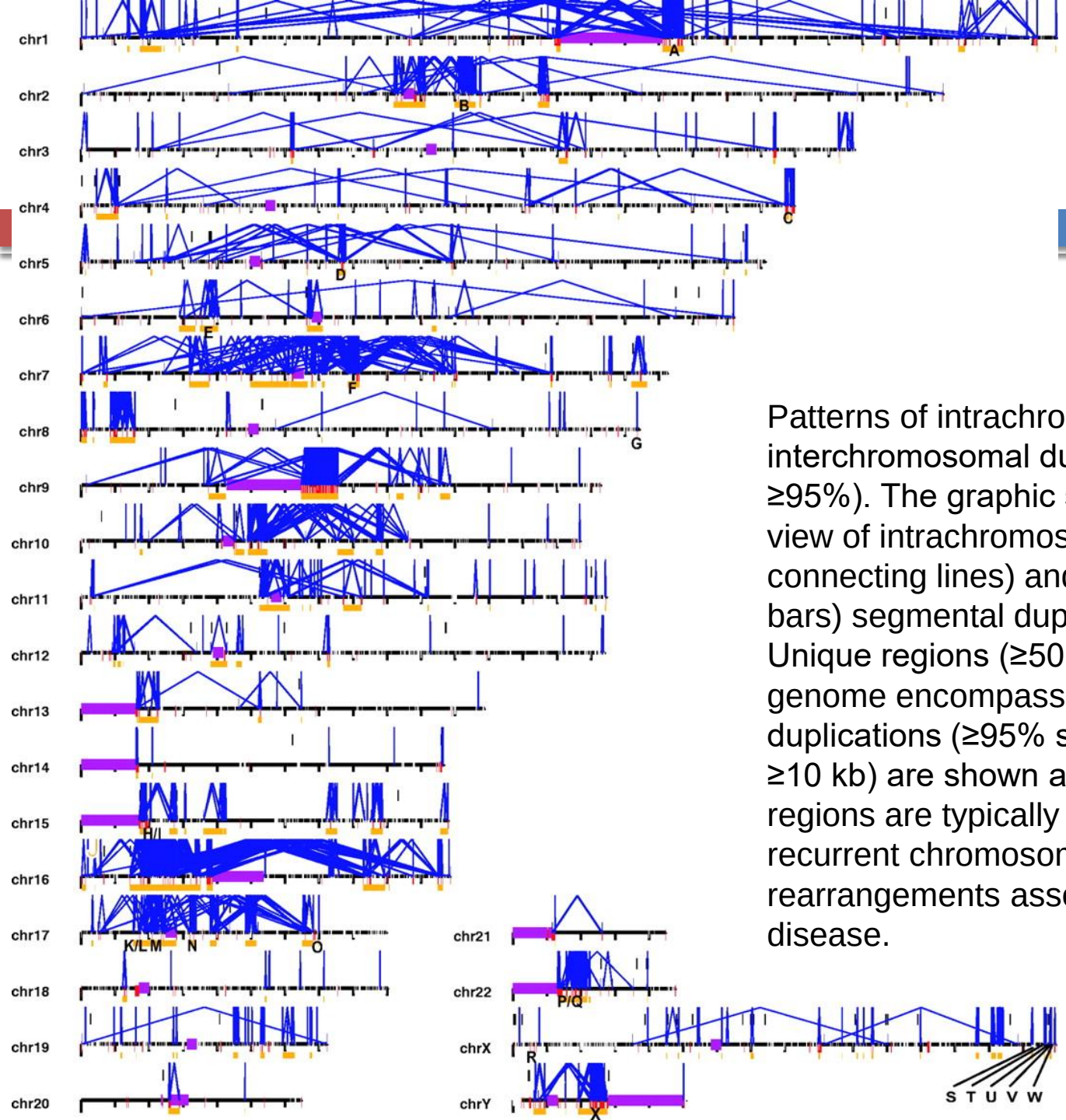
- rare whole-genome duplication
- intermittent chromosome rearrangements,
- localized DNA duplications,
- DNA duplication followed bydispersal to other genome locations, and loss of DNA sequences.

- Nevertheless, highly repetitive DNA sequences that are derived from transposons (mobile DNA elements; see below) plus the repetitive DNA families found in heterochromatin account for more than 50% of our genome



Segmental duplications

- about 5% of our euchromatin DNA consists of neighboring duplicated segments that are more than 1 kb long and show more than 90% sequence identity.



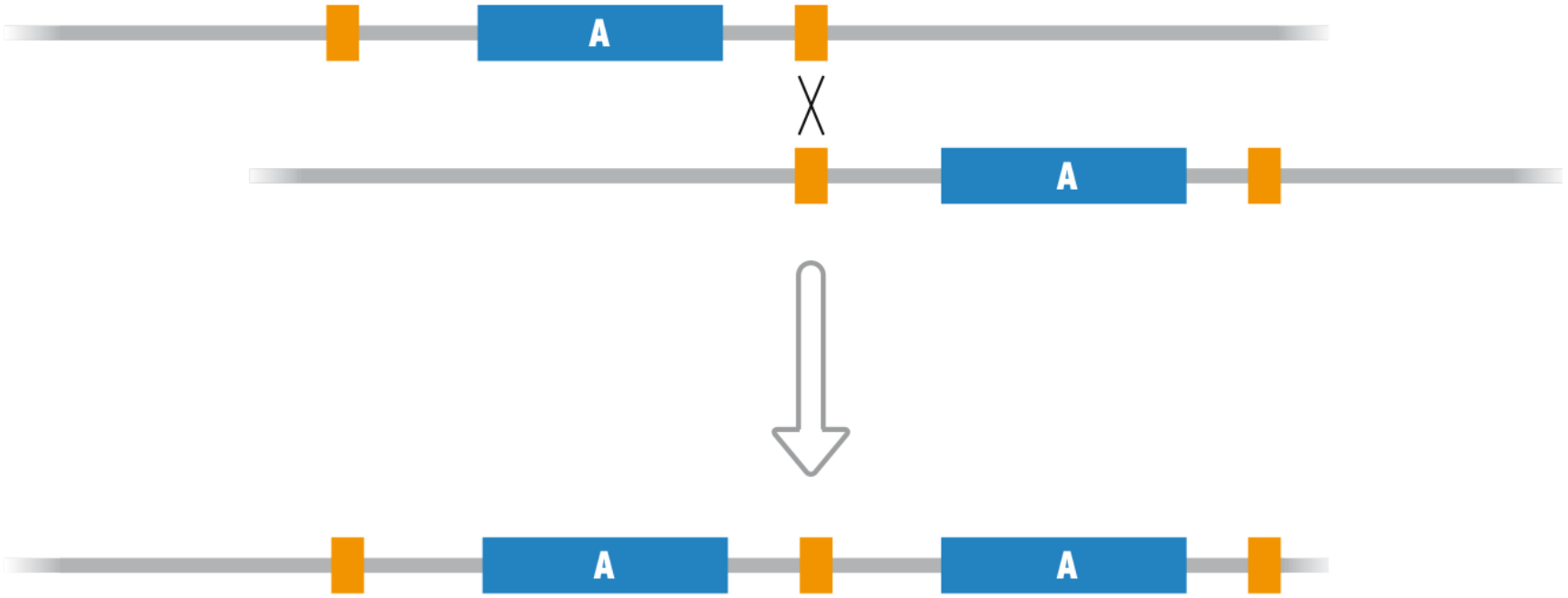
Patterns of intrachromosomal and interchromosomal duplication (≥10 kb; ≥95%). The graphic shows a genome-wide view of intrachromosomal (blue, with connecting lines) and interchromosomal (red bars) segmental duplications.
Unique regions (≥50 kb and <10 Mb) of the genome encompassed by intrachromosomal duplications (≥95% sequence identity and ≥10 kb) are shown as gold bars. Such regions are typically associated with recurrent chromosomal structural rearrangements associated with genetic disease.

- Twenty-four of these regions (labeled A to X) correspond to known genomic disorders: (A) Gaucher disease, (B) familial juvenile nephronophthisis, (C) fascioscapulo- humeral muscular dystrophy, (D) spinal muscular atrophy, (E) congenital adrenal hyperplasia III, (F) Williams-Beuren syndrome, (G) glucocorticoid-remediable aldosteronism, (H) Prader-Willi syndrome, (I) Angelman syndrome, (J) polycystic kidney disease, (K) Charcot-Marie-Tooth disease type 1A, (L) hereditary neuropathy with liability to pressure palsies, (M) Smith-Magenis syndrome, (N) neurofibromatosis, (O) pituitary dwarfism, (P) cat eye syndrome, (Q) DiGeorge/velocardiofacial syndrome, (R) ichthyosis, (S) Hunter syndrome (mucopolysaccharidosis type II), (T) red-green color blindness, (U) Emery-Dreifuss muscular dystrophy, (V) incontinentia pigmenti, (W) hemophilia A, and (X) azoospermia (AZFc region).

Examples of multi-gene families in the human genome.

GENE FAMILY	COPY NUMBER	GENOME ORGANIZATION
β-Globin	6 (includes one pseudogene)	clustered within 50 kb at chromosome 11p15 (see Figure 2.12C)
Class I human leukocyte antigen (HLA)	17 (includes many pseudogenes and gene fragments)	clustered over 2 Mb at 6p21.3
Neurofibromatosis type I	1 functional gene; 8 unprocessed pseudogenes	functional gene, *NF1*, at 17q11.2; pseudogenes dispersed to pericentromeric regions on several other chromosomes
Ferritin heavy chain	1 functional gene; 27 processed pseudogenes[a]	functional gene, *FTH1*, at 11q13; pseudogenes dispersed over multiple chromosome locations
U6 snRNA	49 genes; 800 processed pseudogenes[a]	scattered on many chromosomes

Variation in Individual Genomes



Tandem gene duplication.

The significance of gene duplication and repetitive coding DNA

Dosage

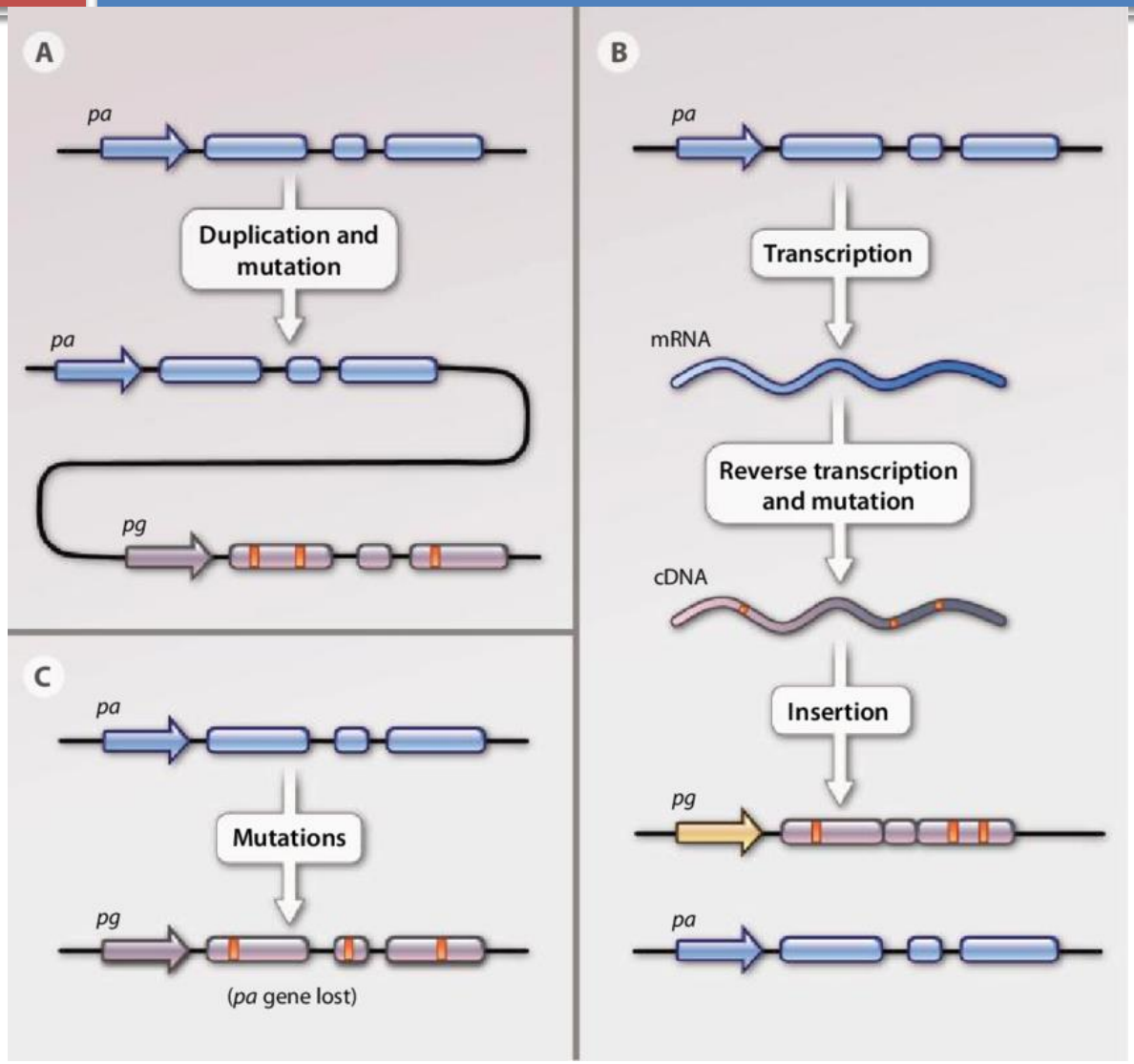
Duplication of genes can be advantageous simply because it allows more gene product to be made. Increased gene dosage is an advantage for genes that make products needed in large amounts in cells—we have hundreds of virtually identical copies of genes that make individual ribosomal RNAs and individual histone proteins, for example.

The significance of gene duplication and repetitive coding DNA

Novel genetic variants

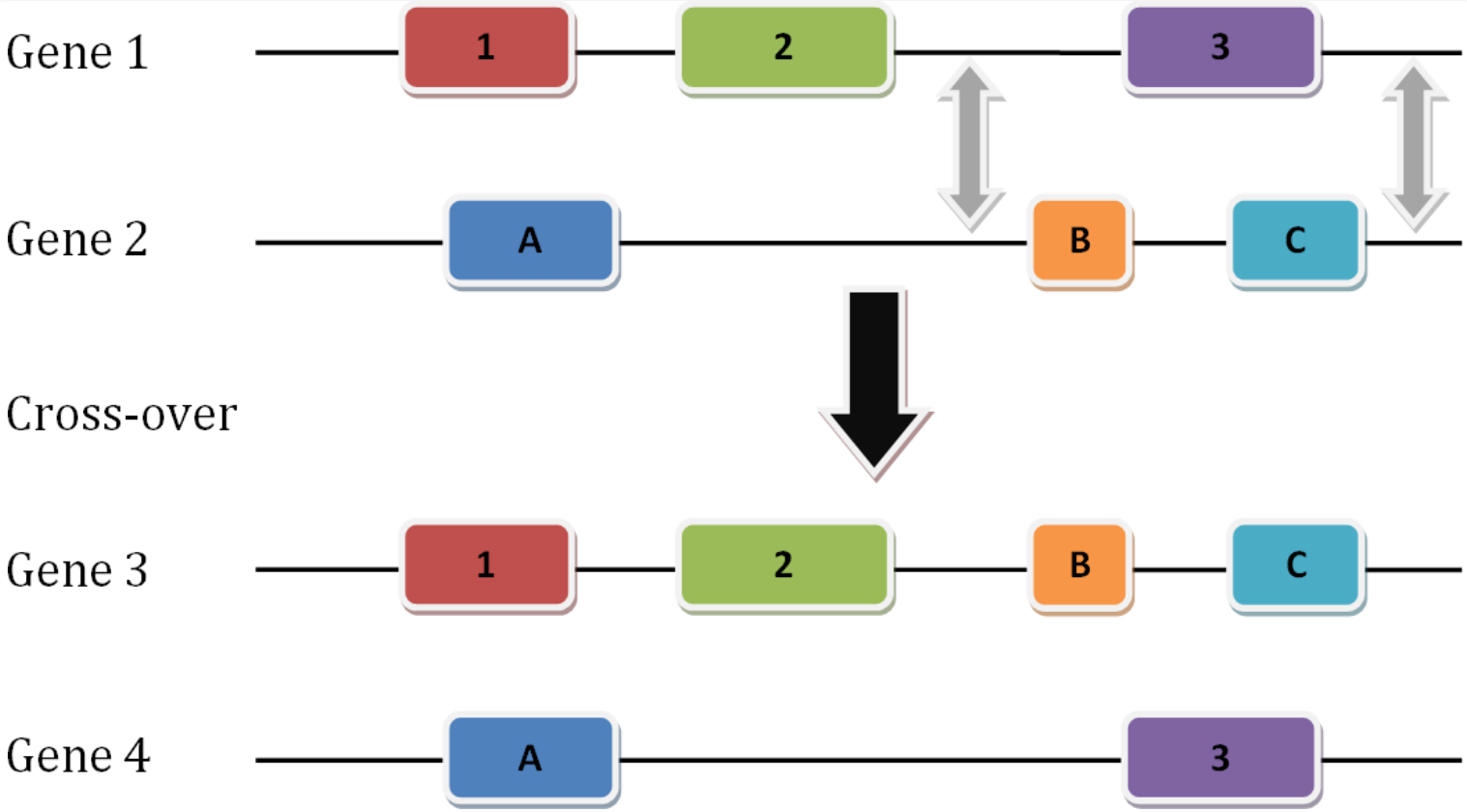
Once a gene or exon has duplicated, there are initially two copies with identical sequences. When that happens, the constraints on changing the sequence imposed by Darwinian natural selection may be applied to one of the two sequences only. The other sequence is free from normal constraints to maintainthe original function; it can diverge in sequence over many millions of years to produce a different but related genetic variant.

Pseudogenes



(A) Nonprocessed pseudogenes derive from gene duplication and are located on the same chromosome as the parental gene from which they are derived . (B) Processed pseudogenes arise by retrotransposition and are located on a different chromosome than the parental gene. (C) Unitary pseudogenes derive from mutations of the parental gene, which is in turn lost. Blue boxes and lines, parental (pa) gene and mRNA; gray boxes and lines, pseudogene (pg) gene and RNA; orange dots and boxes, mutations; yellow arrow, unrelated promoter.

Exon shuffling



Transposon-based repeats in the human genome

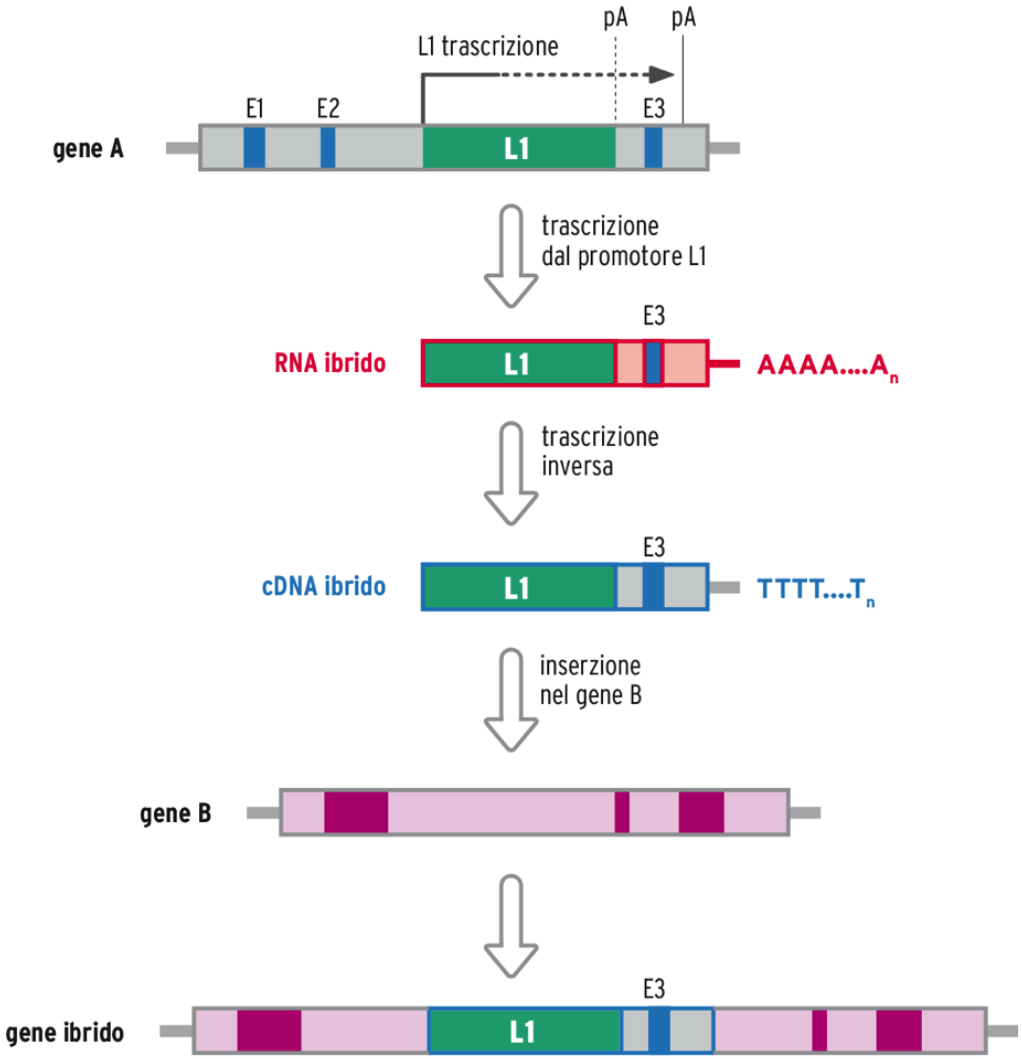
ripetizioni retrotrasposoniche		lunghezza complessiva	effettua il jumping?	numero nel genoma	frazione del genoma
LINEs		6-8 kb	sì	850 000	21%
SINEs		100-300 bp	no	1.5 million	13%
elementi retrovirali-simili		6-11 kb	sì	450 000	8%
		1.5-3 kb	no		
ripetizioni trasposoniche del DNA		2-3 kb	sì	300 000	3%
		80-3000 bp	no		

- LINES (long interspersed nuclear elements). Full-length LINES are 6–8 kb long and can encode a reverse transcriptase, but many LINE repeats are truncated and the average size is close to 1 kb. There are three distantly related LINE families in the human genome, of which the most numerous is the LINE-1 (also called L1) family. The only human LINE elements that are currently capable of transposition are a small subset (about 80–100 copies) of the full-length LINE-1 repeats.

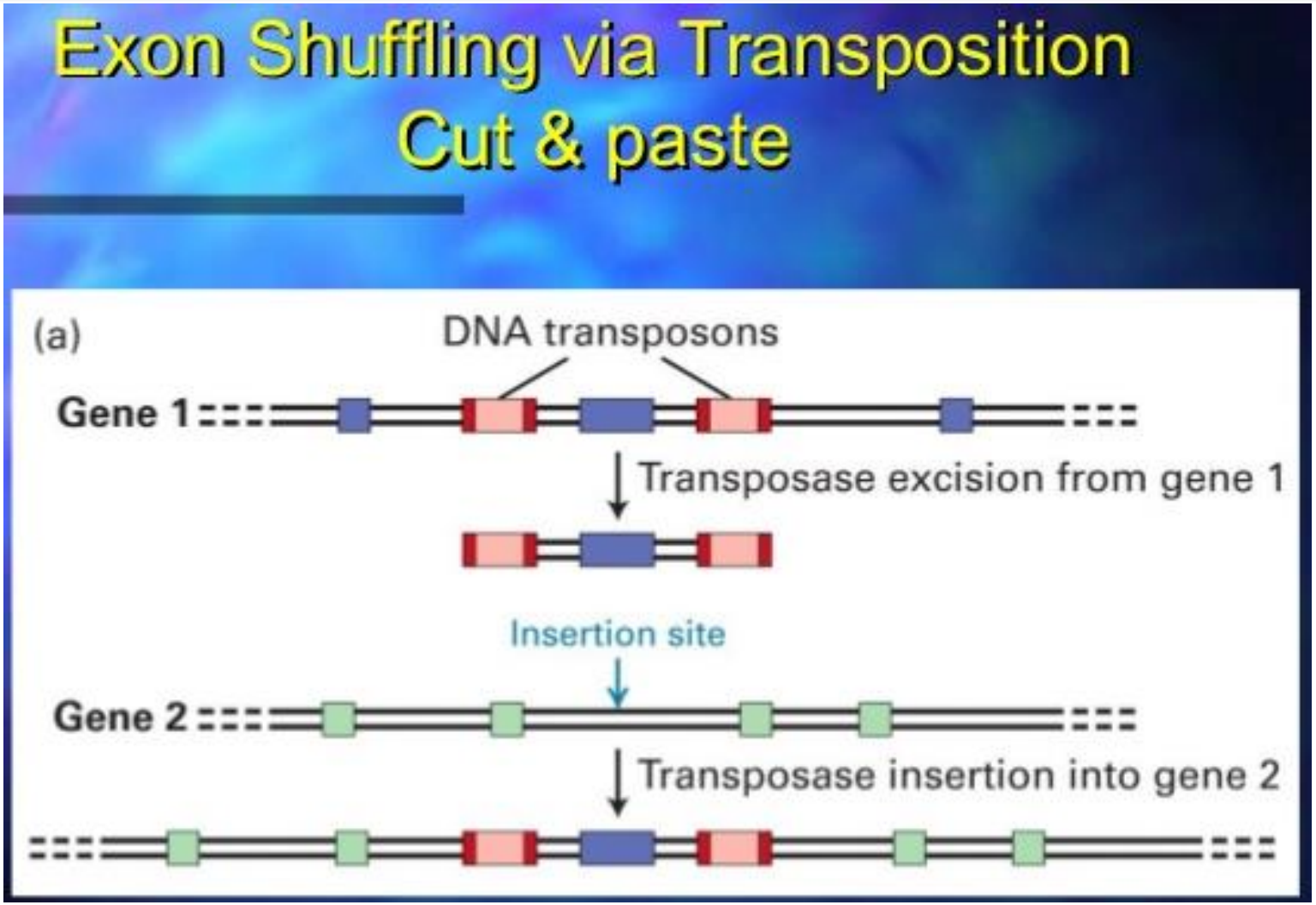
- SINES (short interspersed nuclear elements). Full-length SINEs range from 100 to 300 bp in length. About 70% of SINES belong to the Alu repeat family, which has close to 1.5 million copies.
- The Alu repeats are primate-specific and seem to have evolved from cDNA copies of 7SL RNA (a component of the signal recognition particle), which has an internal promoter sequence. Alu sequences are often transcribed (by adjacent promoters) but cannot make proteins. Nevertheless, some Alu repeats can transpose and rely on neighboring elements, such as LINE elements, to produce the reverse transciptase required for making cDNA copies.

- Retrovirus-like LTR elements. Full-length retrovirus-like elements (sometimes called human endogenous retroviruses or HERVs) are 6–11 kb long. In addition to containing long terminal repeats (LTRs) they may contain sequences resembling the key retroviral genes, including the pol gene that encodes reverse transcriptase, but there is little evidence of actively transposing human HERVs.

Retrotransposons can mediate exon shuffling.



Variation in Individual Genomes



Copy Number Variation

Over the past decade, a number of important studies have focused on the prevalence of structural variants in the genome,

collectively account for far more variation in genome sequence (expressed in terms of the amount of genomic DNA affected) than do SNPs

Copy number variation

Global variation in copy number in the human genome

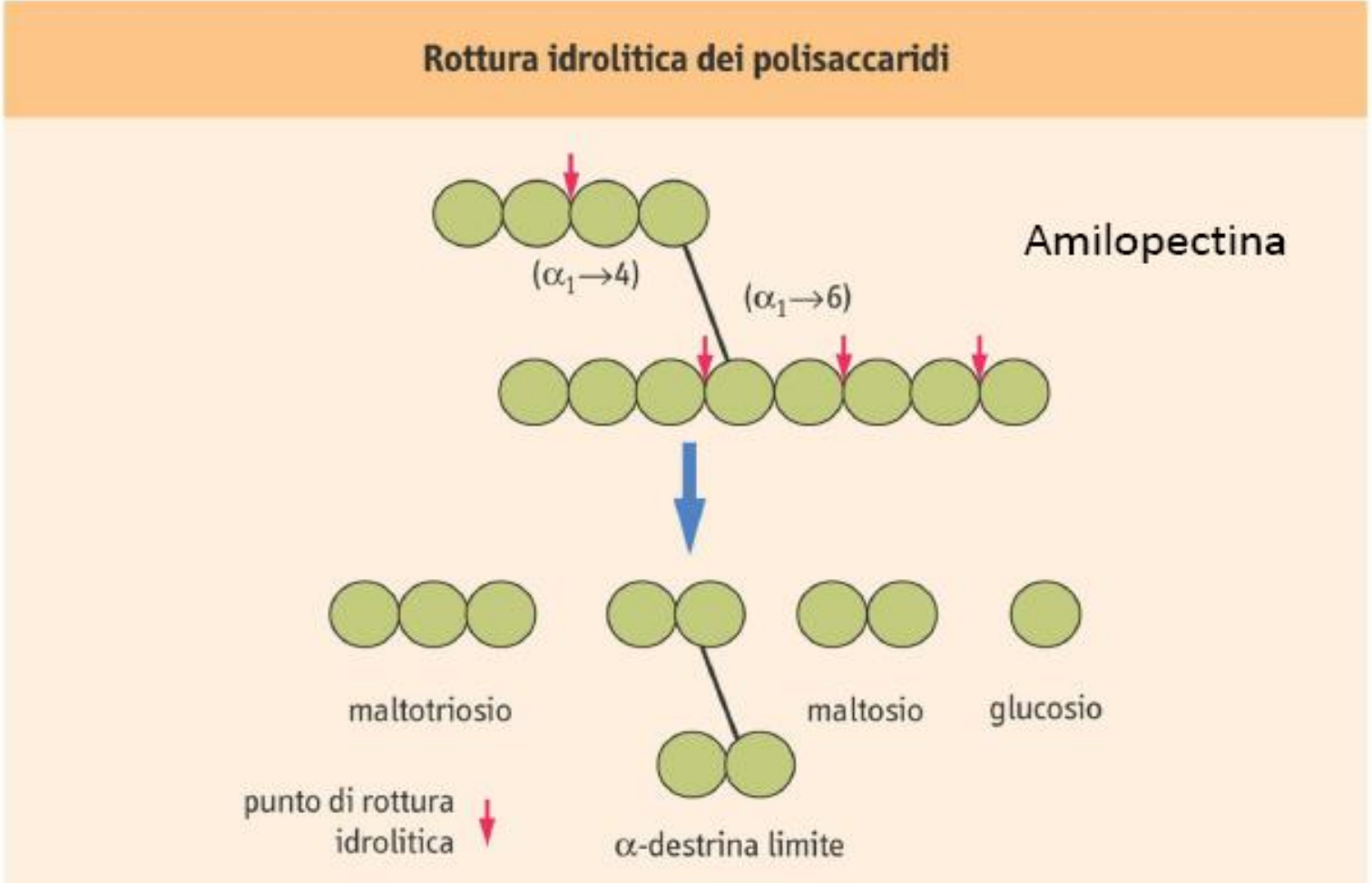
Richard Redon[1], Shumpei Ishikawa[2,3], Karen R. Fitch[4], Lars Feuk[5,6], George H. Perry[7], T. Daniel Andrews[1], Heike Fiegler[1], Michael H. Shapero[4], Andrew R. Carson[5,6], Wenwei Chen[4], Eun Kyung Cho[7], Stephanie Dallaire[7], Jennifer L. Freeman[7], Juan R. González[8], Mònica Gratacòs[8], Jing Huang[4], Dimitrios Kalaitzopoulos[1], Daisuke Komura[3], Jeffrey R. MacDonald[5], Christian R. Marshall[5,6], Rui Mei[4], Lyndal Montgomery[1], Kunihiro Nishimura[2], Kohji Okamura[5,6], Fan Shen[4], Martin J. Somerville[9], Joelle Tchinda[7], Armand Valsesia[1], Cara Woodwark[1], Fengtang Yang[1], Junjun Zhang[5], Tatiana Zerjal[1], Jane Zhang[4], Lluis Armengol[8], Donald F. Conrad[10], Xavier Estivill[8,11], Chris Tyler-Smith[1], Nigel P. Carter[1], Hiroyuki Aburatani[2,12], Charles Lee[7,13], Keith W. Jones[4], Stephen W. Scherer[5,6] & Matthew E. Hurles[1]

Copy number variation (CNV) of DNA sequences is functionally significant but has yet to be fully ascertained. We have constructed a first-generation CNV map of the human genome through the study of 270 individuals from four populations with ancestry in Europe, Africa or Asia (the HapMap collection). DNA from these individuals was screened for CNV using two complementary technologies: single-nucleotide polymorphism (SNP) genotyping arrays, and clone-based comparative genomic hybridization. A total of 1,447 copy number variable regions (CNVRs), which can encompass overlapping or adjacent gains or losses, covering 360 megabases (12% of the genome) were identified in these populations. These CNVRs contained hundreds of genes, disease loci, functional elements and segmental duplications. Notably, the CNVRs encompassed more nucleotide content per genome than SNPs, underscoring the importance of CNV in genetic diversity and evolution. The data obtained delineate linkage disequilibrium patterns for many CNVs, and reveal marked variation in copy number among populations. We also demonstrate the utility of this resource for genetic disease studies.

http://www.nature.com/nature/journal/v444/n7118/abs/nature05329.html

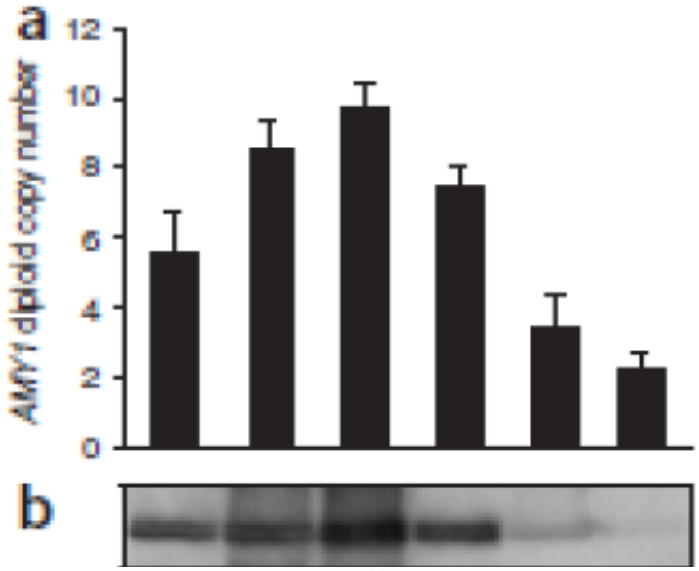
Amilasi

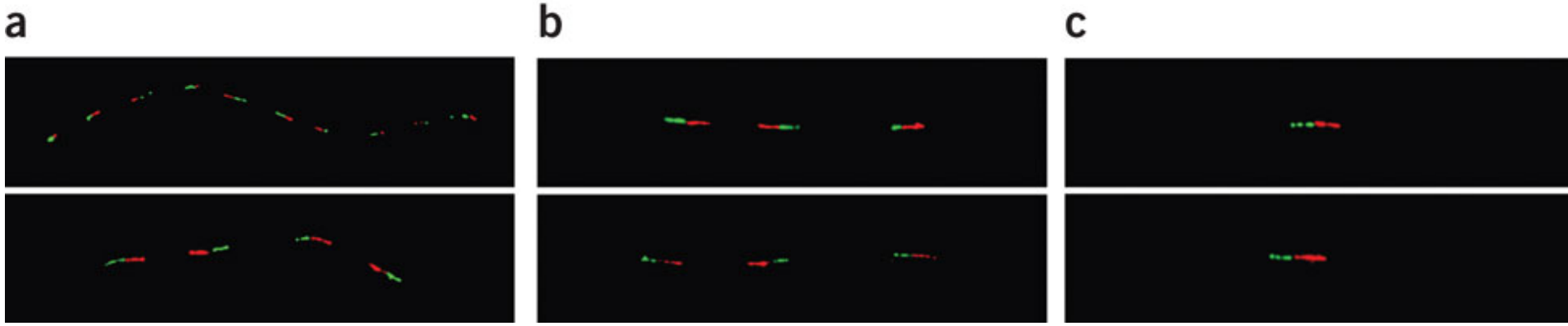
2 forme isoenzimatiche
alfa-amilasi salivare o ptialina
alfa-amilasi pancreatica



•Il gene per l'amilasi salivare *AMY1* è presente in copia multipla nel genoma
• il numero di copie varia tra gli individui e tra le popolazioni
e corrisponde all'espressione della proteina nella saliva

a) Numero di copie del gene in diversi individui





http://www.nature.com/ng/journal/v39/n10/abs/ng2123.html