

Genoma Umano e Malattie Genetiche

Strachan, Read - Genetica Molecolare Umana - UTET
(possibilmente 3 Edizione)

Organizzazione del genoma umano

99.9995 % genoma nucleare

contiene la stragrande maggioranza delle informazioni

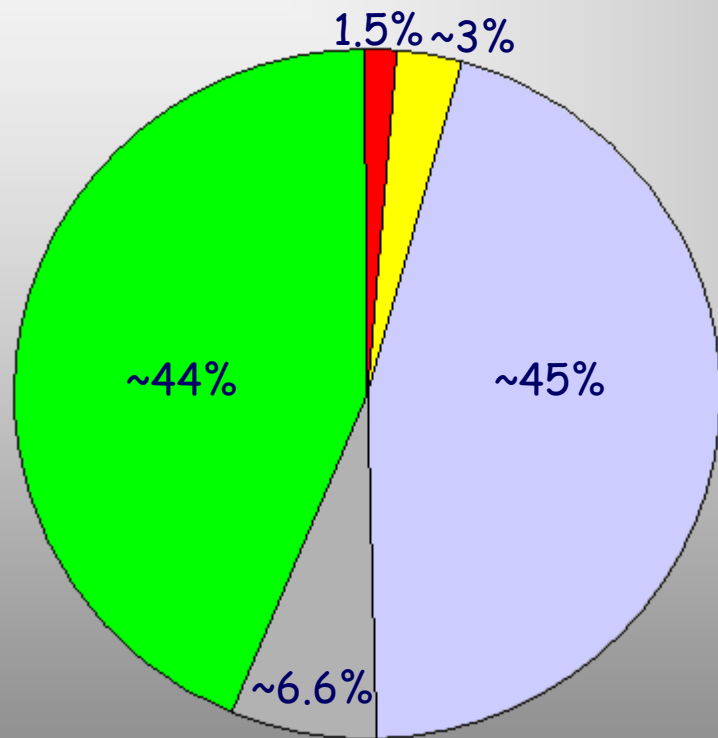
è stato stimato contenere 20.000-25.000 geni

0,0005 % genoma mitocondriale

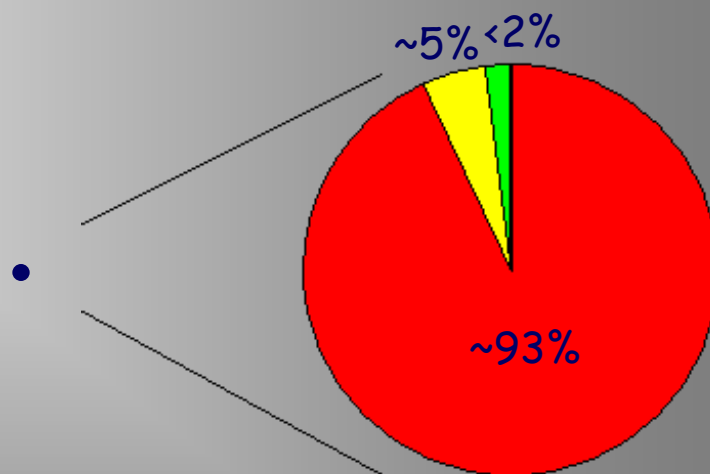
contiene i geni ribosomali e alcuni geni che producono mRNA

tradotti nel mitocondrio stesso (in totale 37)

Genoma nucleare



Genoma mitocondriale



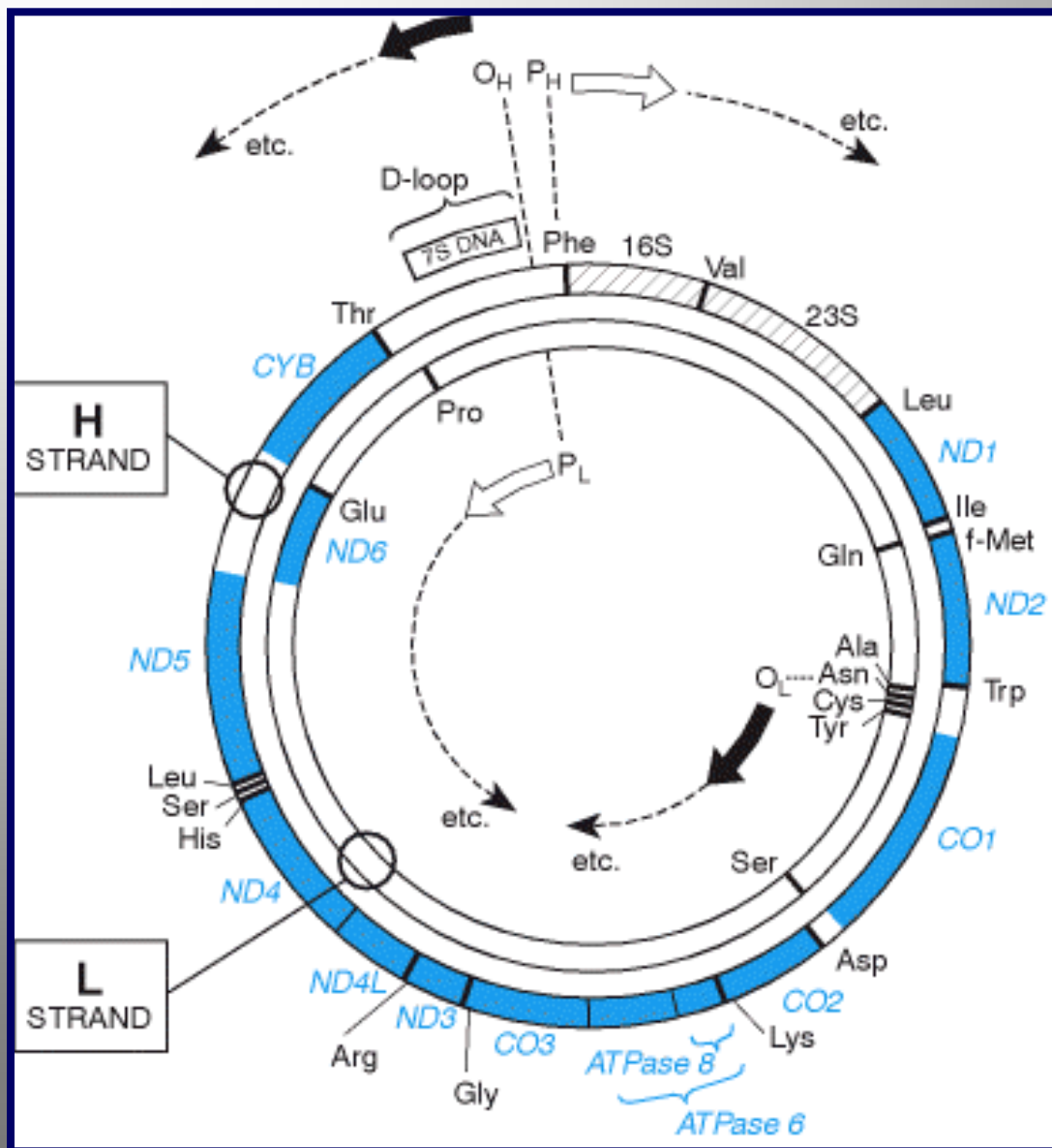
- Altamente conservato, codificante
- Altamente conservato, altro
- Ripetizioni derivanti da trasposizione
- Eterocromatina
- Altro non conservato

Differenze tra DNA mitocondriale e nucleare

Table 7.1. The human nuclear and mitochondrial genomes

	Nuclear genome	Mitochondrial genome
Size	3300 Mb	16.6 kb
No. of different DNA molecules	23 (in XX) or 24 (in XY) cells, all linear	One circular DNA molecule
Total no. of DNA molecules per cell	23 in haploid cells; 46 in diploid cells	Several thousand
Associated protein	Several classes of histone and nonhistone protein	Largely free of protein
Number of genes	~20.000	37
Gene density	~1/40 kb ?	1/0.45 kb
Repetitive DNA	Large fraction,	Very little
Transcription	The great bulk of genes are transcribed individually	Continuous transcription of multiple genes
Introns	Found in most genes	Absent
% of coding DNA	~3%	~93%
Recombination	At least once for each pair of homologs at meiosis	Not evident
Inheritance	Mendelian for sequences on X and autosomes; paternal for sequences on Y	Exclusively maternal

Organizzazione del DNA mitocondriale



H strand is rich in
guanines

L strand is rich in
cytosines

7S DNA = triple strand
DNA

Key:

→ O_H, O_L origin and direction
of synthesis of heavy and
light strands

→ P_H, P_L origin and direction
of transcription of heavy and
light strands

▨ rRNA genes (2)

| tRNA genes (22)

■ Genes encoding
proteins (13)

Organizzazione del DNA mitocondriale (codice genetico)

AAA } Lys	CAA } Gln	GAA } Glu	UAA } STOP
AAG } Lys	CAG } Gln	GAG } Glu	UAG } STOP
AAC } Asn	CAC } His	GAC } Asp	UAC } Tyr
AAU } Asn	CAU } His	GAU } Asp	UAU } Tyr
ACA } Thr	CCA } Pro	GCA } Ala	UCA } Ser
ACG } Thr	CCG } Pro	GCG } Ala	UCG } Ser
ACC } Thr	CCC } Pro	GCC } Ala	UCC } Ser
ACU } Thr	CCU } Pro	GCU } Ala	UCU } Ser
AGA } Arg	CGA } Arg	GGA } Gly	UGA } STOP
AGG } STOP	CGG } Arg	GGG } Gly	UGG } Trp
AGC } Ser	CGC } Arg	GGC } Gly	UGC } Cys
AGU } Ser	CGU } Arg	GGU } Gly	UGU } Cys
AUA } Ile	CUA } Leu	GUA } Val	UUA } Leu
AUG } Met	CUG } Leu	GUG } Val	UUG } Leu
AUC } Ile	CUC } Leu	GUC } Val	UUC } Phe
AUU } Ile	CUU } Leu	GUU } Val	UUU } Phe

RICAPITOLANDO:

60 CODONI riconosciuti da tRNA (+ 4 codoni di stop)

22 GENI CHE CODIFICANO PER tRNA

?

THIRD BASE WOBBLE

8 dei 22 tRNA riconoscono famiglie di 4 codoni che differiscono solo per la terza base

14 dei 22 tRNA riconoscono coppie di codoni che sono identiche per le prime due basi e che condividono purine o pirimidine in terza posizione

Organizzazione del DNA mitocondriale (codice genetico)

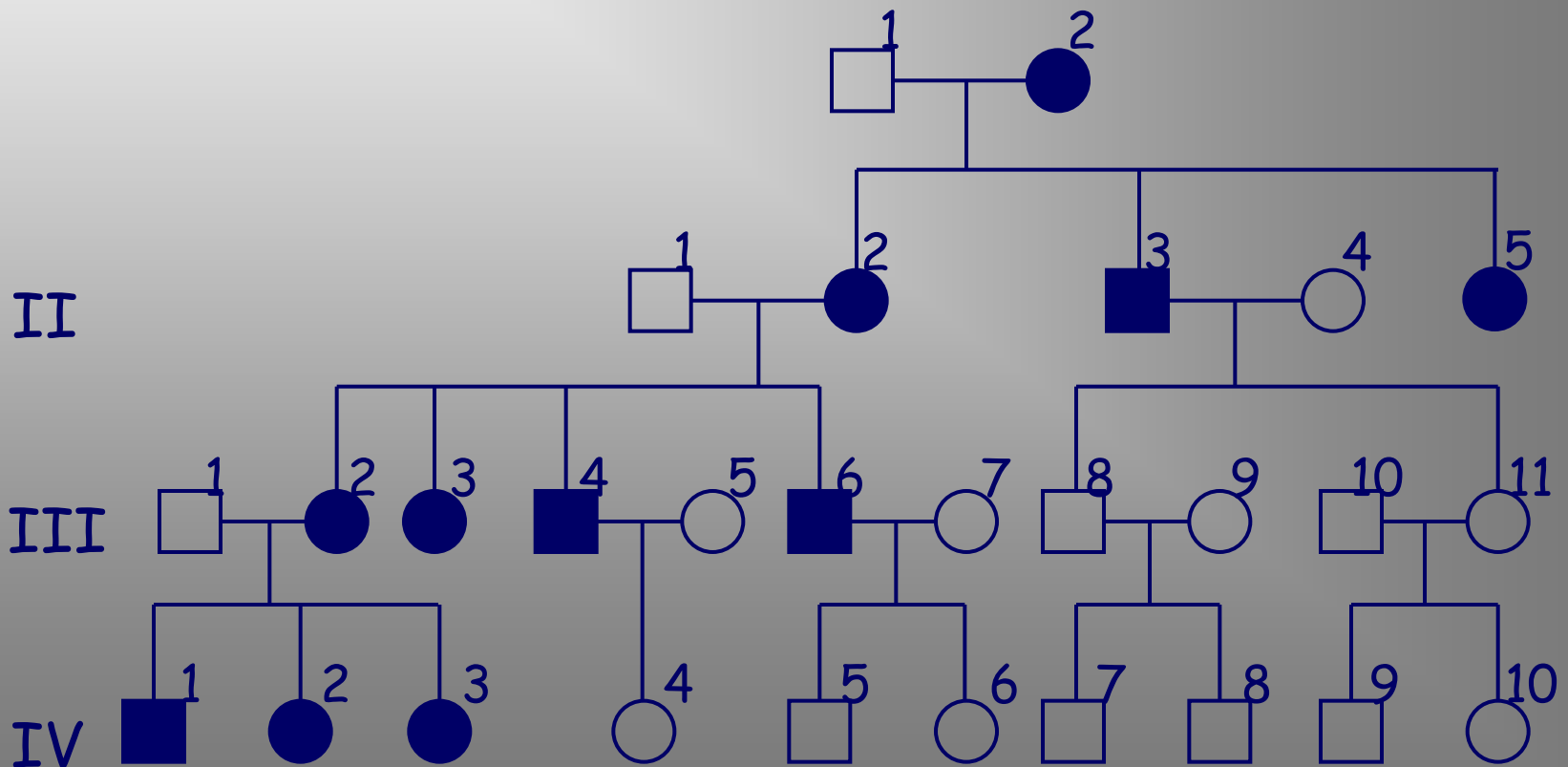
AAA } Lys	CAA } Gln	GAA } Glu	UAA } STOP
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AUC } Ile	CUC } Leu	GUC } Val	UUC } Phe
AUU } Ile	CUU } Leu	GUU } Val	UUU } Phe

I tre aspetti più importanti della Genetica Mitocondriale

1. Eredità materna. Alla fecondazione, tutti i mitocondri (e tutti i mtDNA) dello zigote derivano dall'oocita.

Si prenda come esempio la sindrome MELAS.

L'acronimo MELAS deriva dalla dizione inglese della patologia: Encefalomiopatia Mitocondriale con Acidosi Lattica ed Episodi di Ictus. I sintomi clinici insorgono durante l'infanzia o nell'adulto prima dei 40 anni.



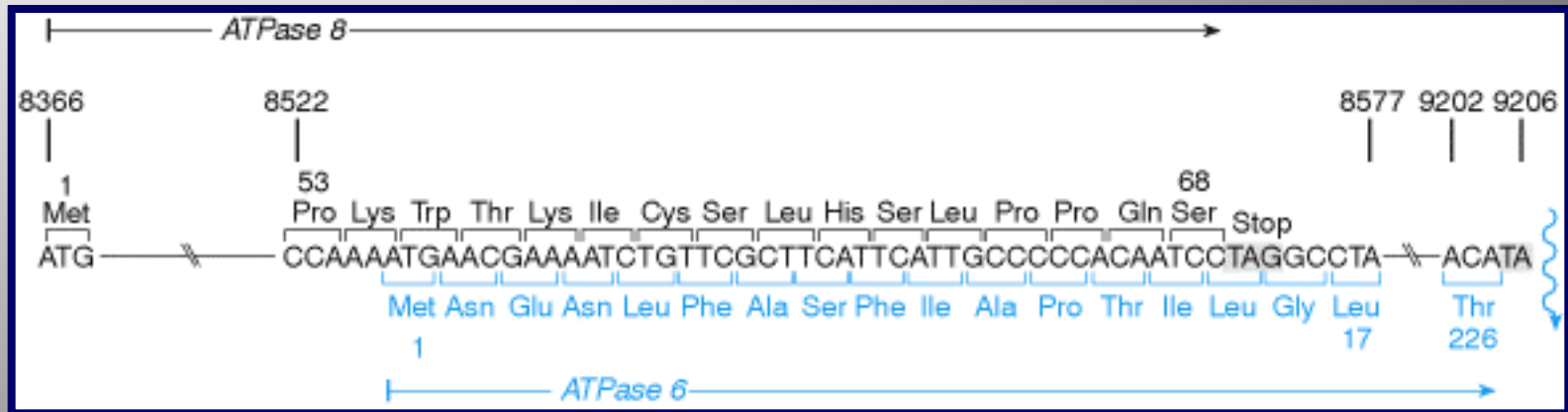
I tre aspetti più importanti della Genetica Mitocondriale

1. Eredità materna. Alla fecondazione, tutti i mitocondri (e tutti i mtDNA) dello zigote derivano dall'ovocita.
- 2a. Eteroplasmia. Si ha quando un individuo possiede due popolazioni di mtDNA: normale (wild type) e mutante.
- 2b. Effetto soglia. Il numero minimo critico di molecole di mtDNA mutante che deve essere presente perché una malattia si manifesti. La proporzione di molecole mutate influisce sulla gravità del difetto biochimico, ma non necessariamente con relazione lineare.
3. Segregazione mitotica. Alla divisione cellulare, la proporzione di mtDNA mutanti che si ritrovano nelle cellule figlie può essere molto diversa da quella della cellula madre. Il motivo risiede nel fatto che la replicazione e l'ereditarietà delle linee cellulari somatiche sono soggetti ad eventi stocastici.

La regione codificante del mtDNA (93%) è estremamente compatta:

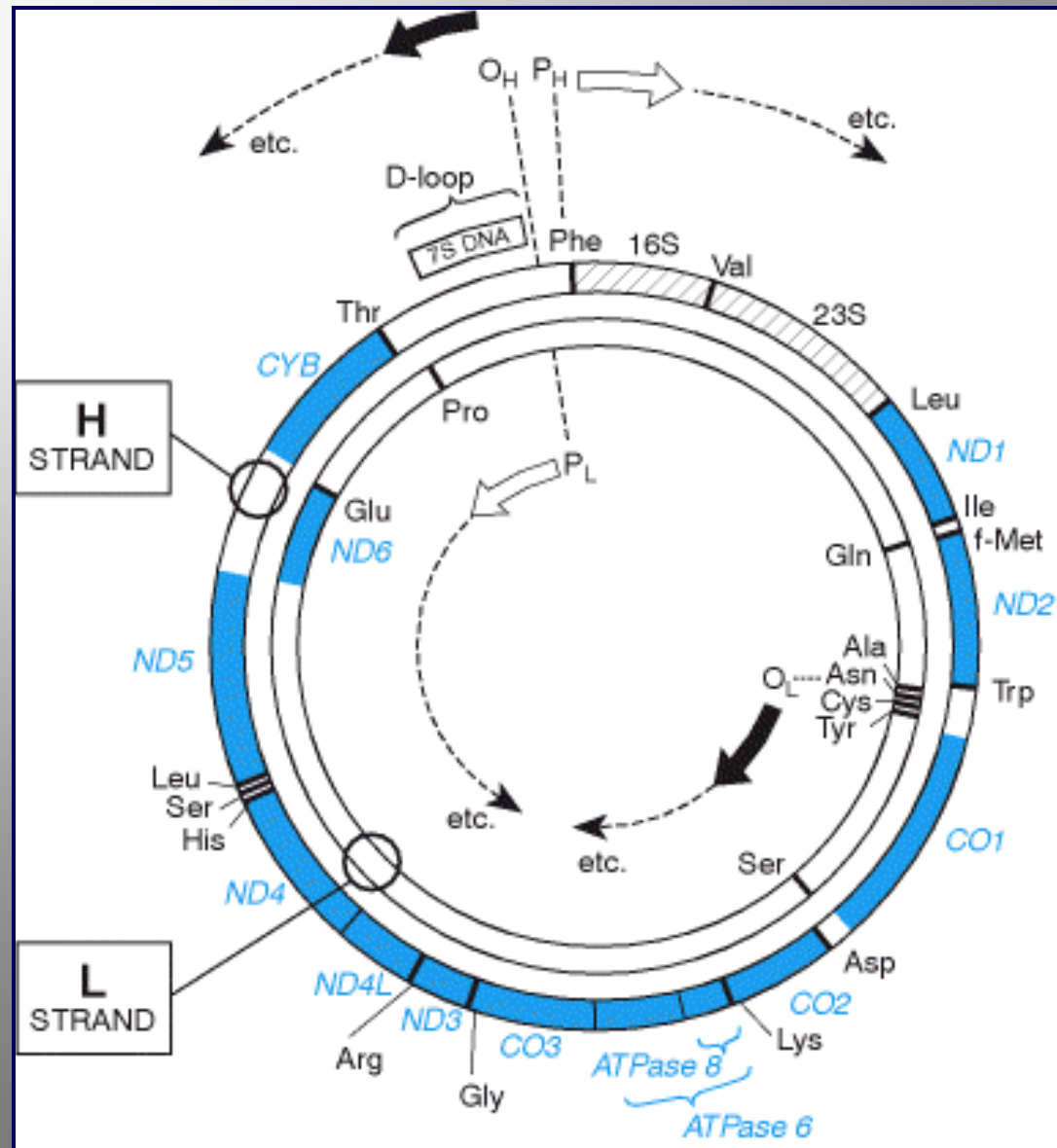
I 37 geni non possiedono introni

Alcuni presentano zone di sovrapposizione

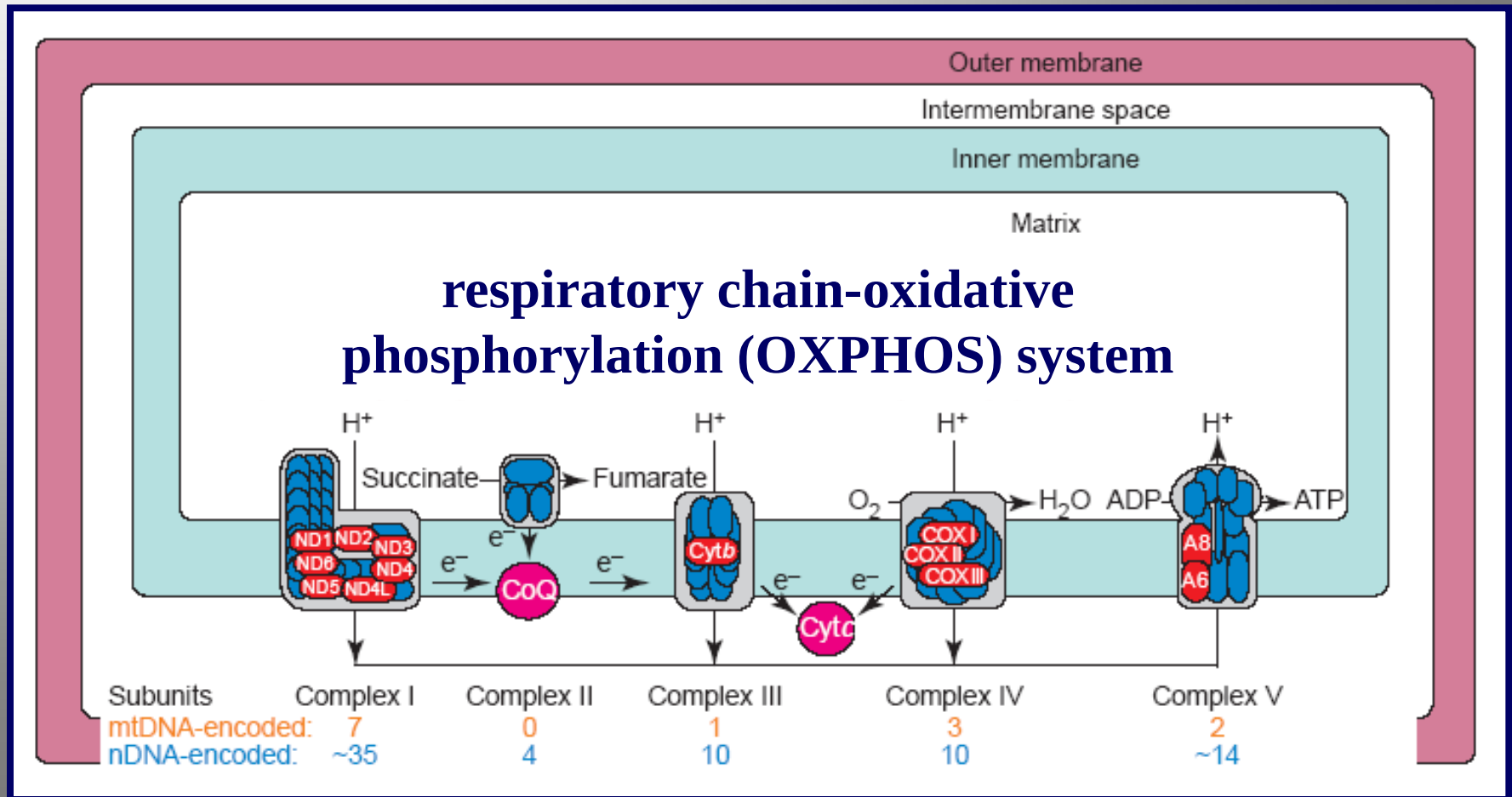


Alcuni sono contigui o separati da uno o due codoni

L'unica regione significativamente libera da regioni codificanti è il D-loop. Una regione a triplo filamento dovuto alla sintesi in duplicato della catena H, chiamata **7S DNA**

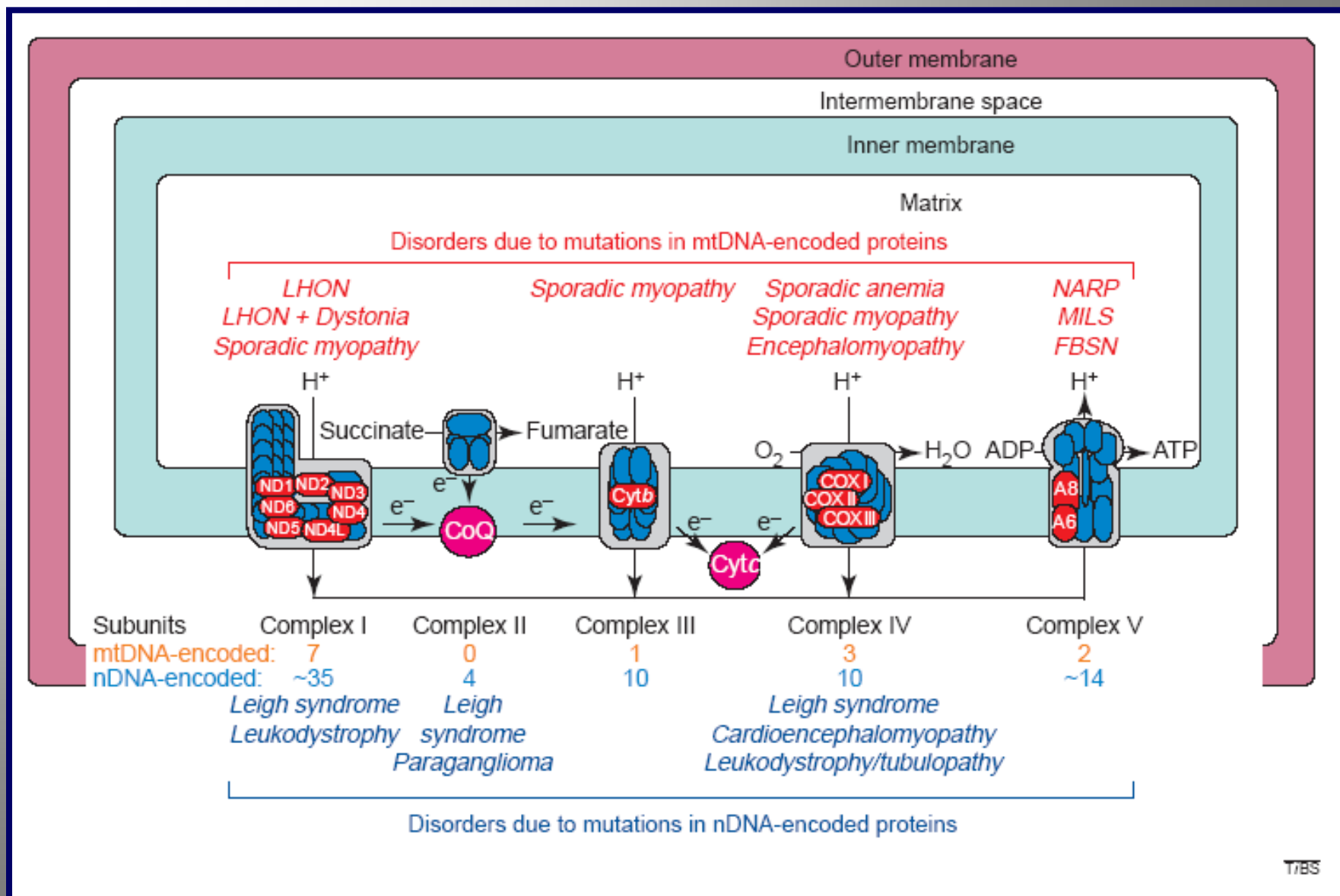


I 13 geni che codificano per proteine codificano tutti per componenti del sistema della catena respiratoria

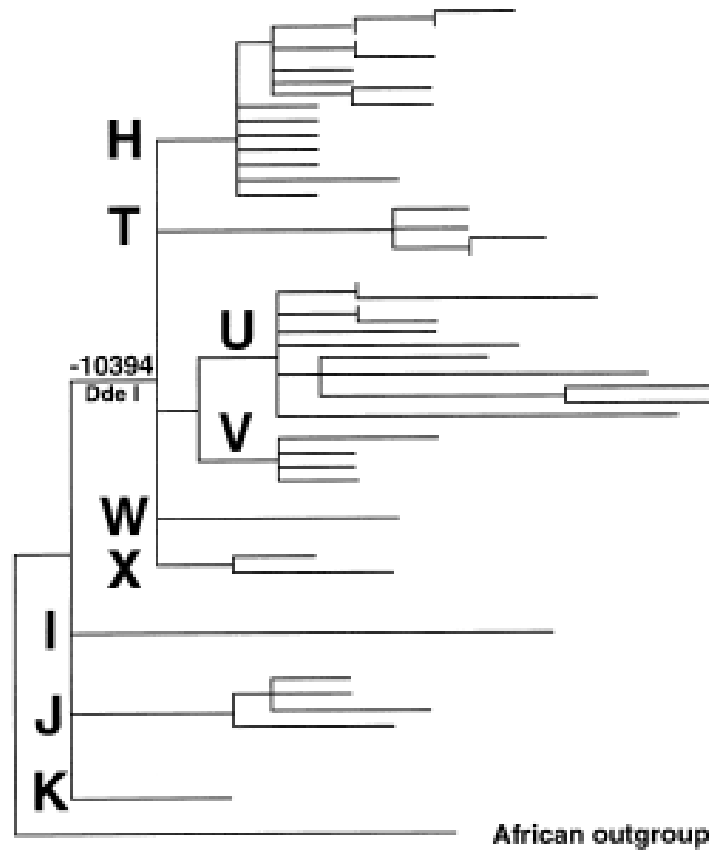


Point mutations in tRNAs and rRNAs

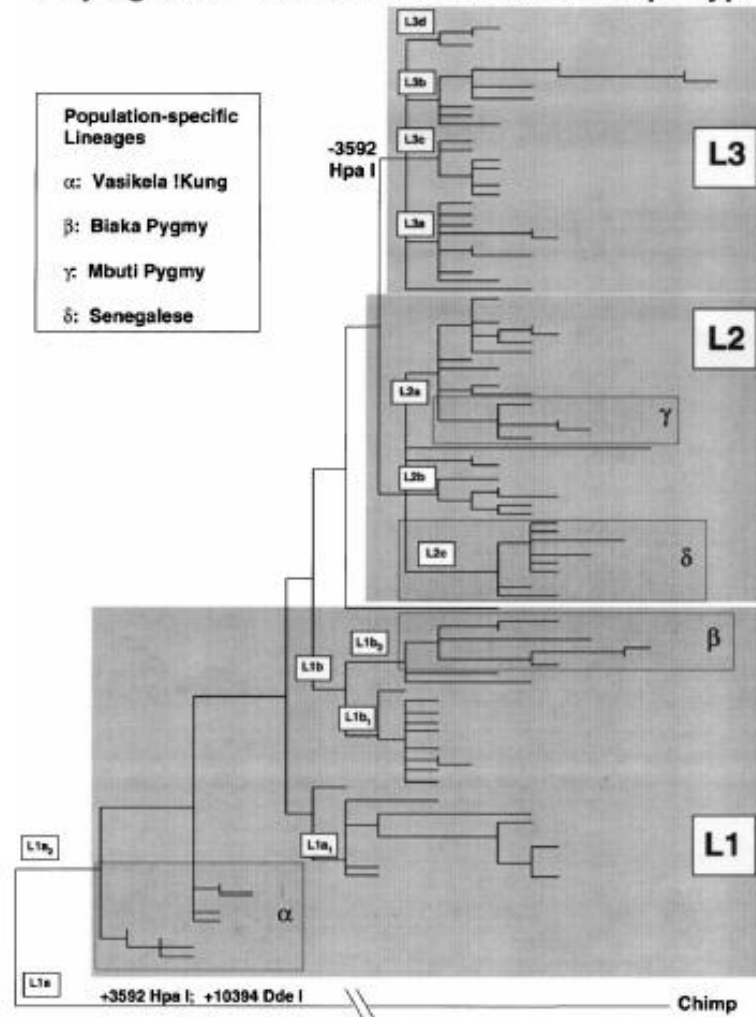
Disorder	No. of mutations	Genes
Cardiomyopathy	19	12S, 16S, A, D, E, G, I, L1, T
Deafness	4	12S, S1
Diabetes	3	L1, K, S2
Encephalomyopathy	7	E, L1, L2, K, T, W
Encephalopathy	2	C, K
Epilepsy	1	S2
Fatal infantile respiratory defects	1	T
Leigh syndrome	2	V, W
MELAS	6	F, L1, V
MERRF	3	K
Multisystem	3	G, L1, V
Myoclonus	1	D
Myoglobinuria	1	F
Myopathy	9	F, L1, L2, M, N, P, W
PEO	8	I, K, L1, L2, Y
Sideroblastic anemia	1	L2
Spinocerebellar ataxia	1	W
Splenic lymphoma	1	M



Phylogenetic Tree of European mtDNA Haplotypes



Phylogenetic Tree of African mtDNA Haplotypes



Organizzazione del DNA nucleare

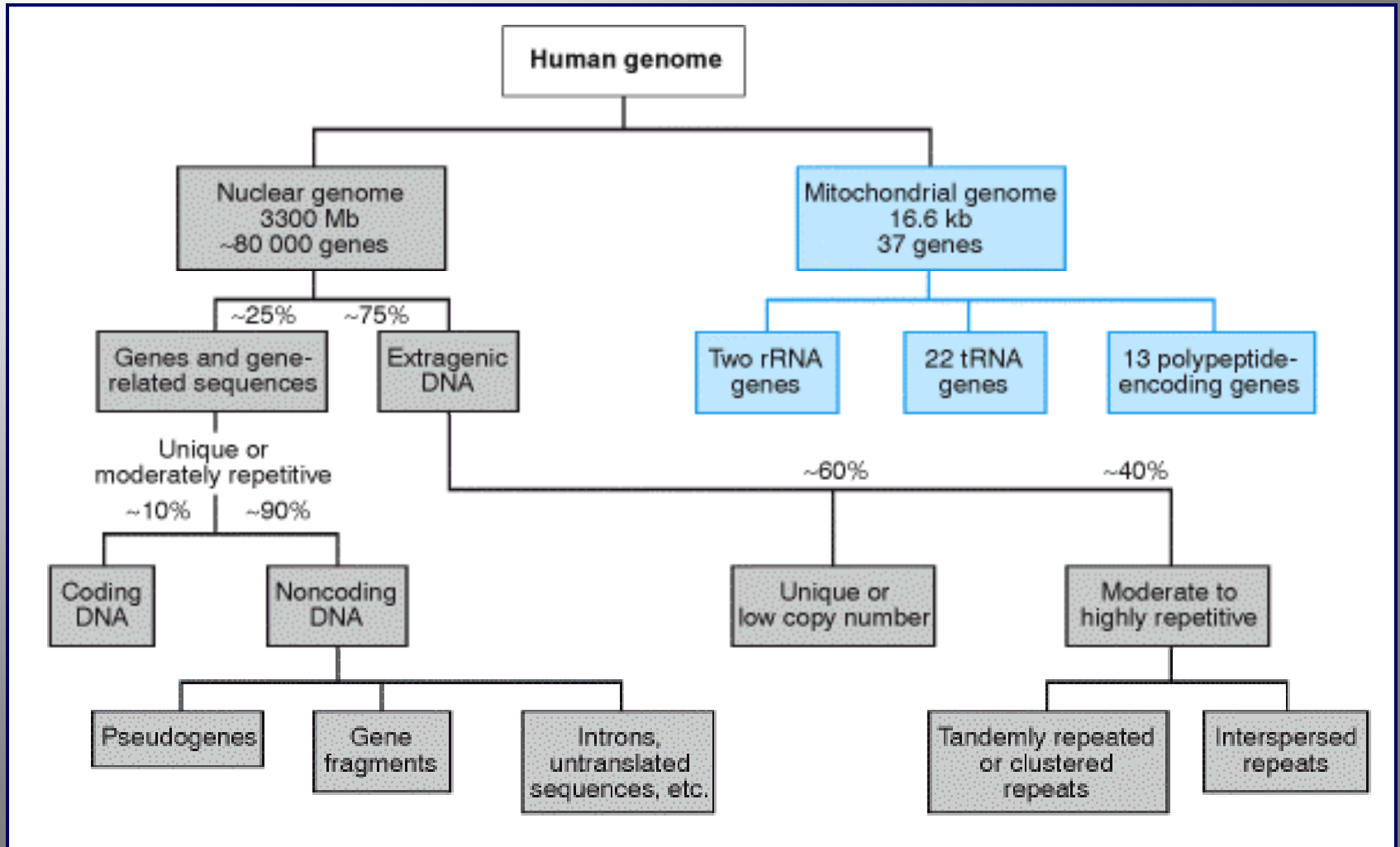
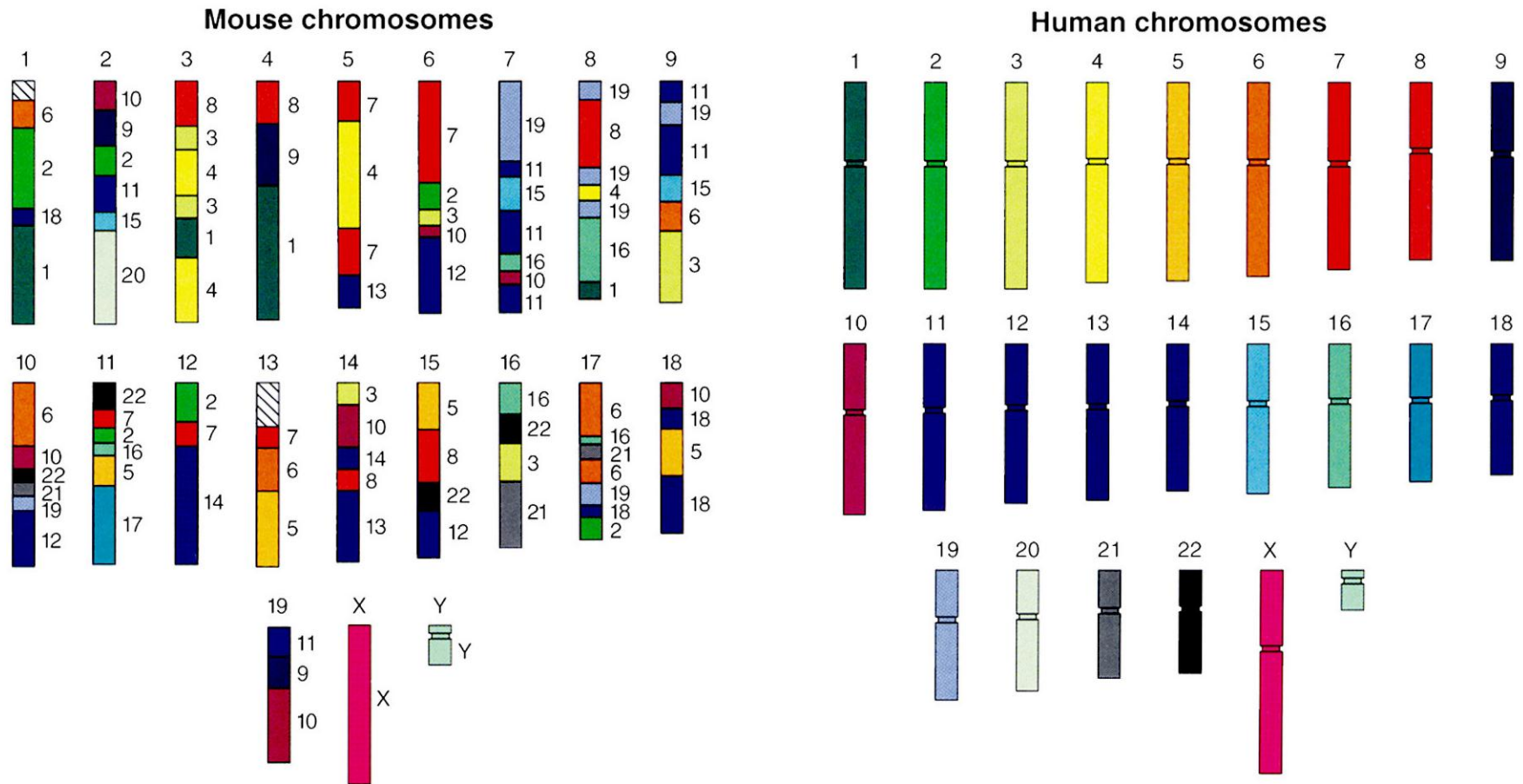


Table 7.2. DNA content of human chromosomes ^a

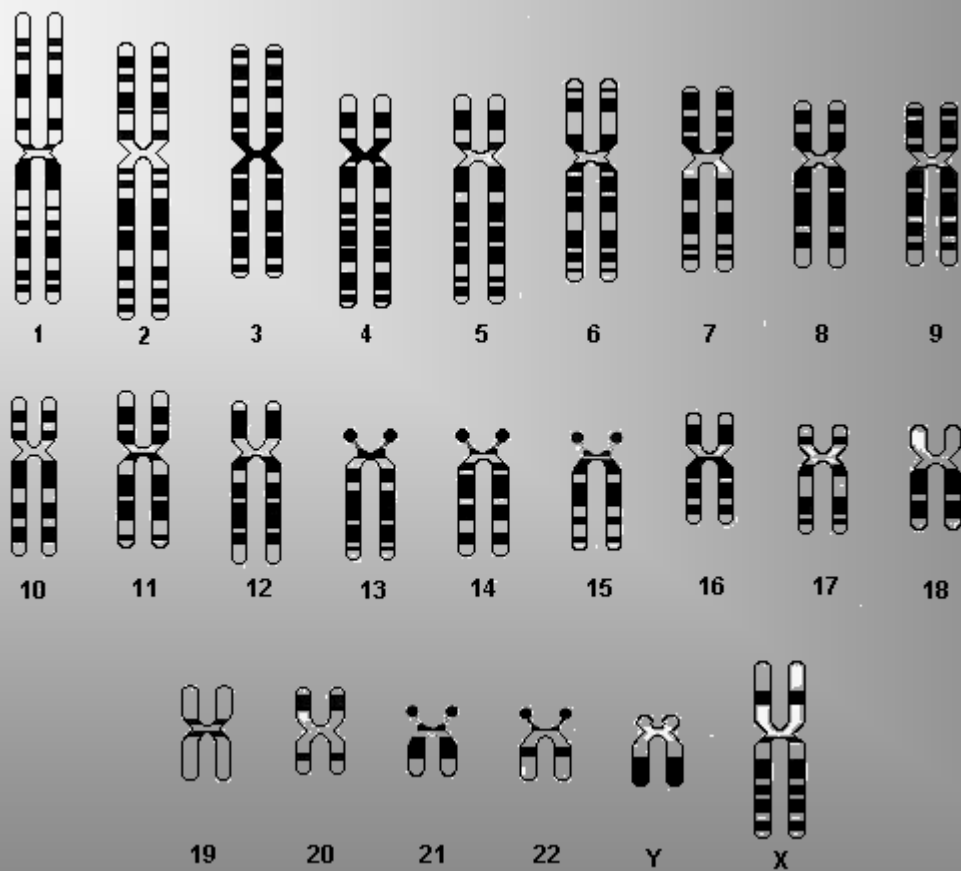
Chromosome	Amount of DNA (Mb)	Chromosome	Amount of DNA (Mb)
1	263	13	114
2	255	14	109
3	214	15	106
4	203	16	98
5	194	17	92
6	183	18	85
7	171	19	67
8	155	20	72
9	145	21	50
10	144	22	56
11	144	X	164
12	143	Y	59

^a The DNA content is given for chromosomes prior to entering the S (DNA replication) phase of cell division (see [Figure 2.2](#)). Data abstracted from [electronic reference 1](#).

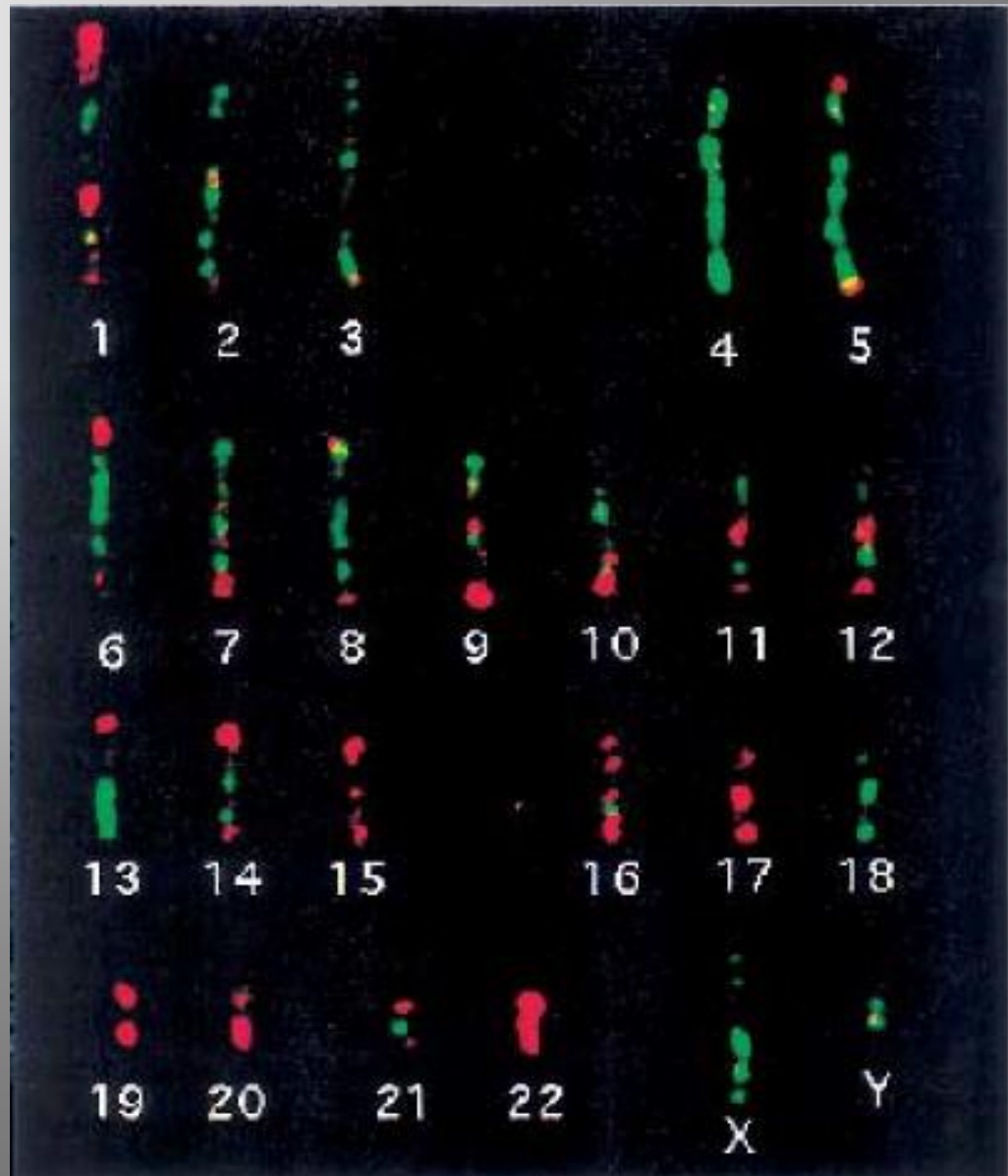
Mouse and Human Genetic Similarities



Courtesy Lisa Stubbs
Oak Ridge National Laboratory

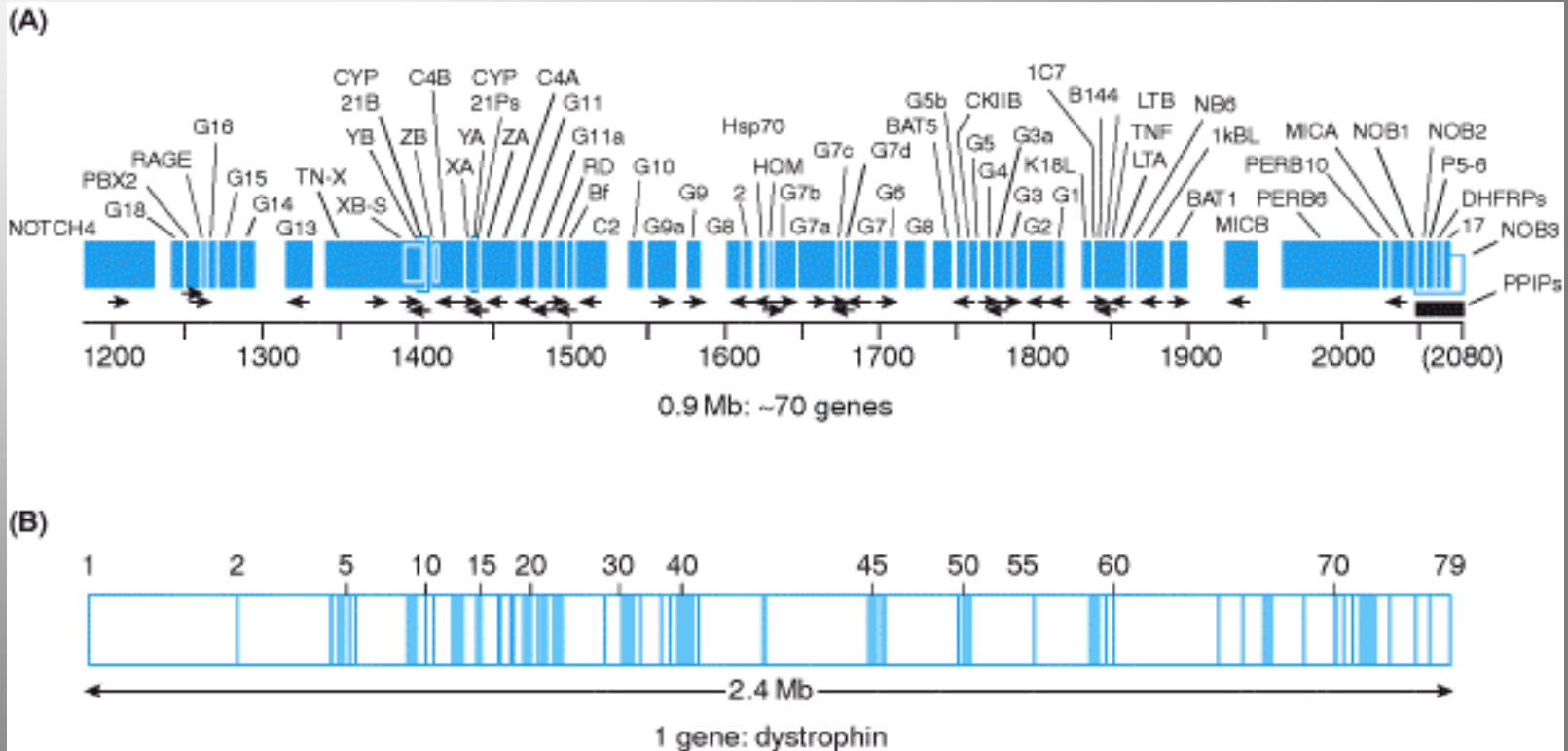


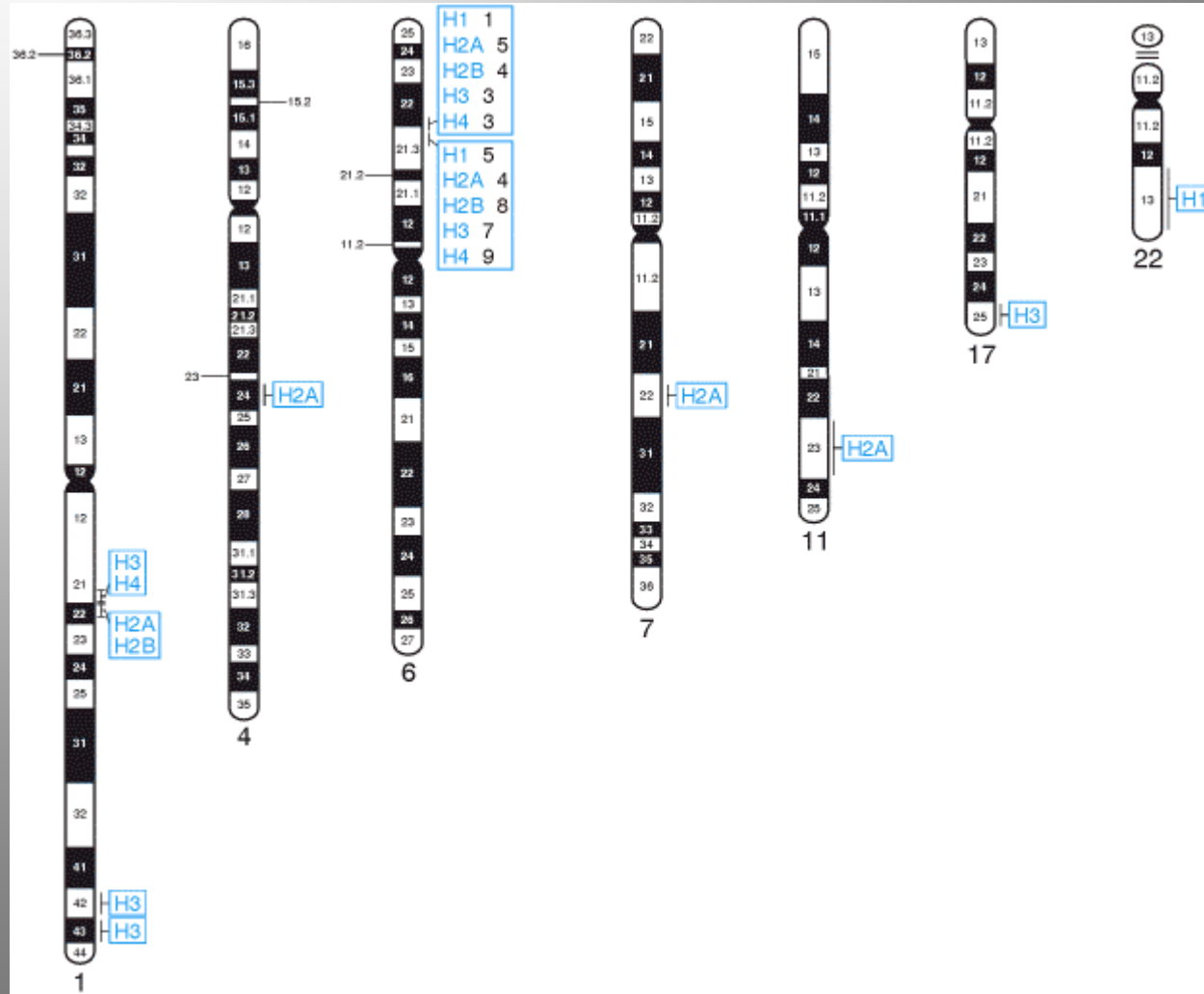
GpG islands



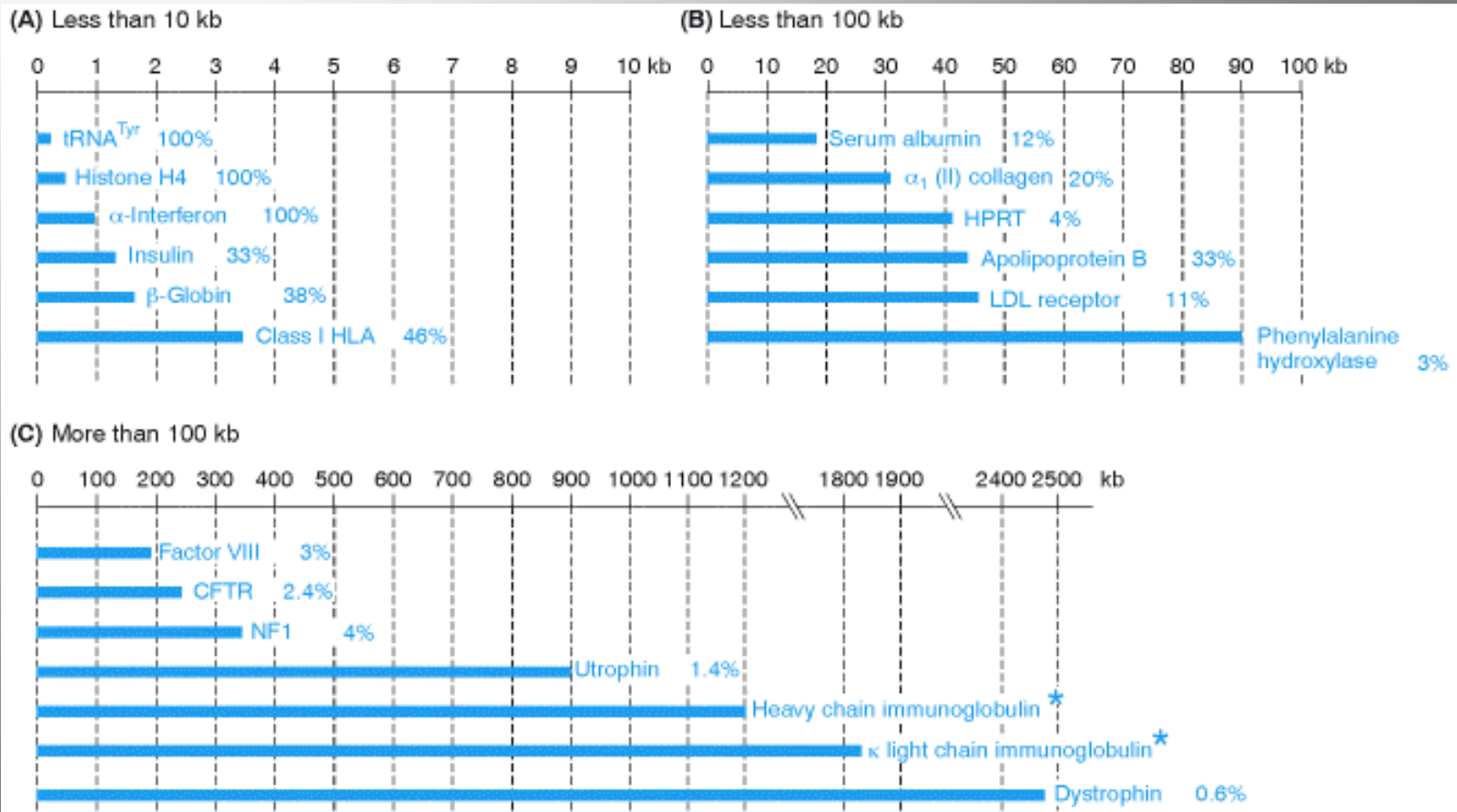
Nuclear genome	
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No. of different DNA molecules	23 (in XXX) or 24 (in XY) cells, all linear
Total no. of DNA molecules per cell	23 in haploid cells; 46 in diploid cells
Associated protein	Several classes of histone and nonhistone protein
Number of genes	20-25.000
Gene density	~1/40 kb ?
Repetitive DNA	Large fraction, :
Transcription	The great bulk of genes are transcribed individually
Introns	Found in most genes
% of coding DNA	~3%
Recombination	At least once for each pair of homologs at meiosis
Inheritance	Mendelian for sequences on X and autosomes; paternal for sequences on Y

Confronto tra la regione dell'HLA (classe III) e regione della DMD

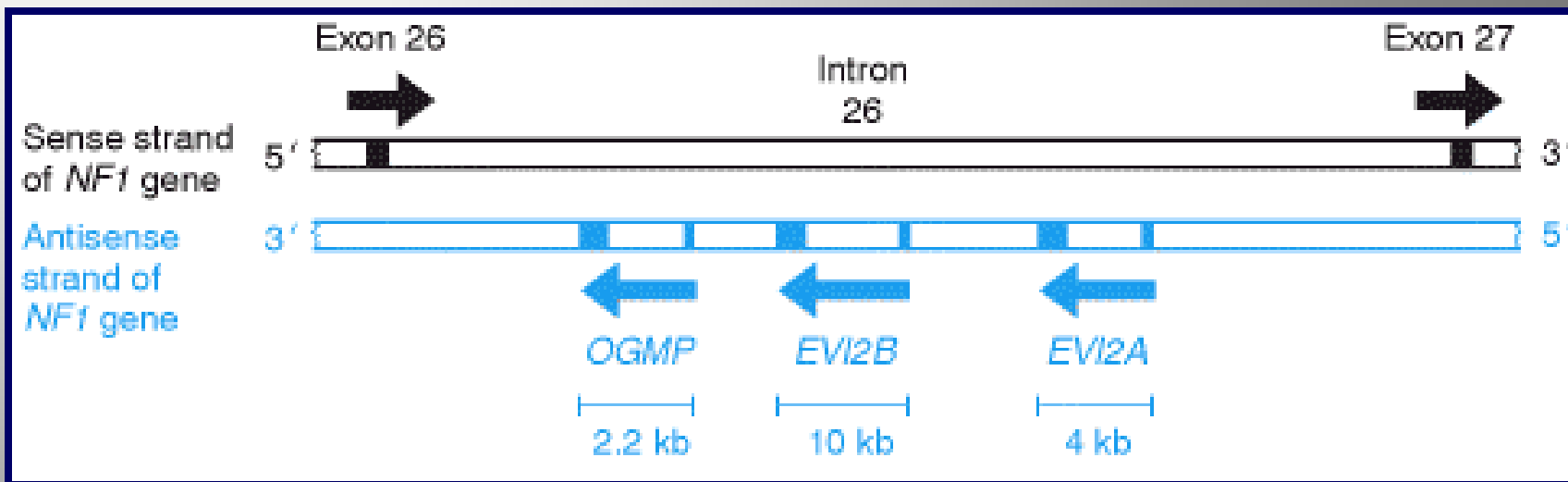




Variabilità per numero e contenuto degli esoni



Geni dentro altri geni



- NF1 = neurofibromatosi di tipo 1
 OGMP = glicoproteina mielinica olidentrocitica
 EVI2A e EVI2B = omologhi umani di geni murini coinvolti nella genesi della leucemia. Localizzati in siti di integrazione virale ecotropici

Famiglie geniche raggruppate nella stessa regione cromosomica

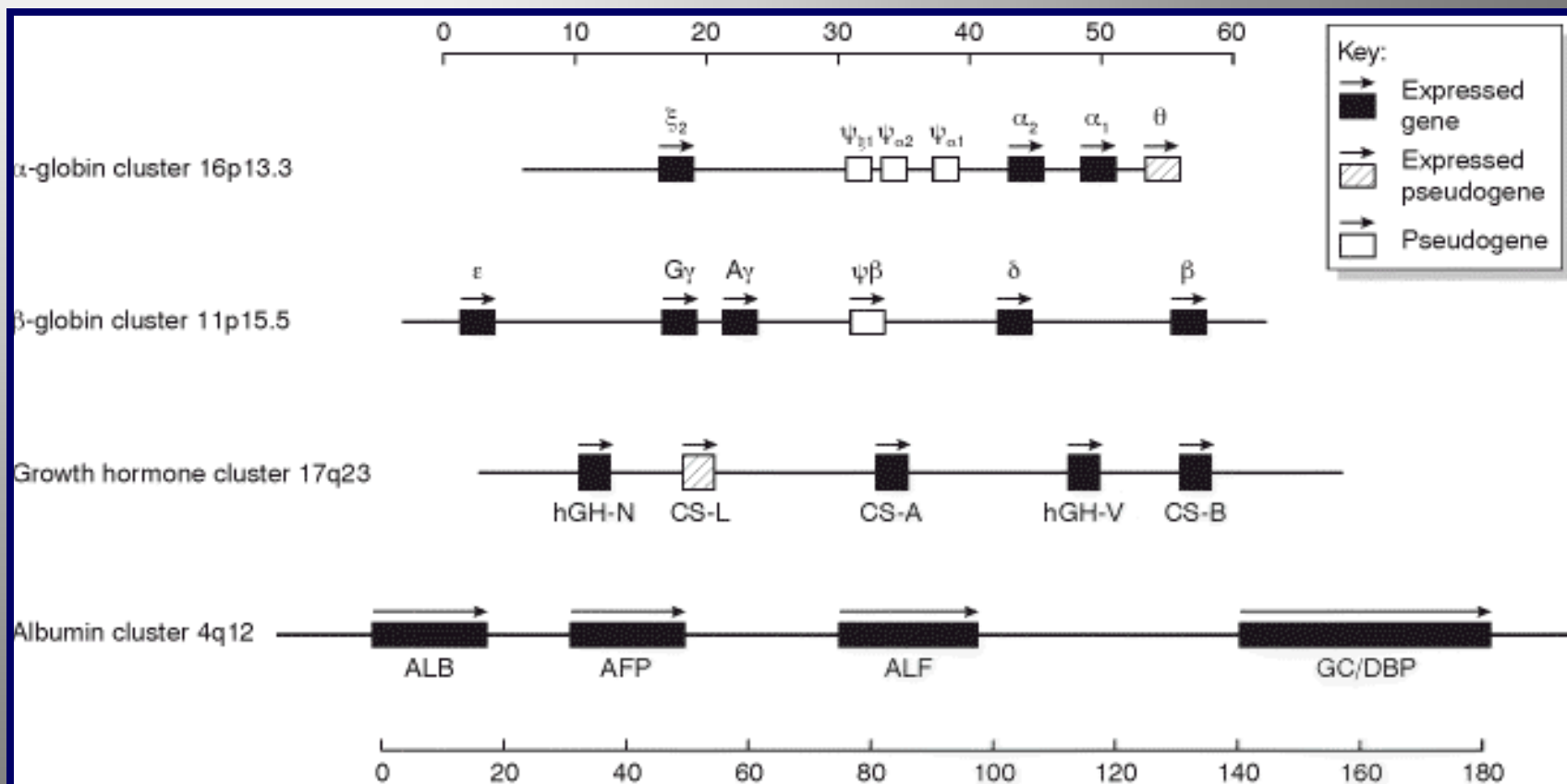


Table 7.9. Examples of clustered and interspersed multigene families

Family	Copy no.	Organization location	Chromosome
A. Clustered gene families			
<i>Single cluster gene families</i>			
Growth hormone gene cluster	5	Clustered within 67 kb; one conventional pseudogene	17q22-24
α -Globin gene cluster	7	Clustered over ~50 kb (see Figure 8.23)	
Class I HLA heavy chain genes	~20	Clustered over 2 Mb (see Figure 8.4)	
<i>Multiple cluster gene families</i>			
HOX genes	38	Organized in four clusters (Figure 9.5)	2p, 7, 12, 17
Histone gene family	61	Modest-sized clusters at a few locations; two large clusters on chromosome 6	(see Figure 7.6)
Olfactory receptor gene family	~1000	About 25 large clusters scattered throughout the genome	Many
B. Interspersed gene families			
Aldolase	5	Three functional genes and two pseudogenes on five different chromosomes	Many
PAX	9	All nine genes are expressed	Many
NFI (Neurofibromatosis type I)	>12	One functional gene at 17q11.2; others are defective non-processed DNA copies	Mostly pericentromeric
Ferritin heavy chain	>15	One functional gene known on chromosome 11; most are processed pseudogenes	Many
Glyceraldehyde 3-phosphate dehydrogenase	>18	One functional gene on 12p; many processed pseudogenes	Many
Actin	>20	Four functional genes and many processed pseudogenes	Many

Table 7.11. Major classes of tandemly repeated human DNA

Class	Size of repeat	Major chromosomal location(s)
'Megasatellite' DNA (blocks of hundreds of kb in some cases)		
RS447	4.7 kb	~50–70 copies on 4p15 plus several copies on distal 8p
untitled	2.5 kb	~400 copies on 4q31 and 19q13
untitled	3.0 kb	~50 copies on the X chromosome
Satellite DNA (blocks often from 100 kb to several Mb in length)		
α (alphoid DNA)	171 bp	Centromeric heterochromatin of all chromosomes
β (<i>Sau3</i> A family)	68 bp	Centromeric heterochromatin of 1, 9, 13, 14, 15, 21, 22 and Y
Satellite 1 (AT-rich)	25–48 bp	Centromeric heterochromatin of most chromosomes and other heterochromatic regions
Satellites 2 and 3	5 bp	Most, possibly all, chromosomes
Minisatellite DNA (blocks often within the 0.1–20 kb range)		
telomeric family	6 bp	All telomeres
hypervariable family	9–64 bp	All chromosomes, often near telomeres
Microsatellite DNA (blocks often less than 150 bp)		
	1–4 bp	Dispersed throughout all chromosomes

Localizzazione cromosomale delle maggiori classi di DNA ripetitivo

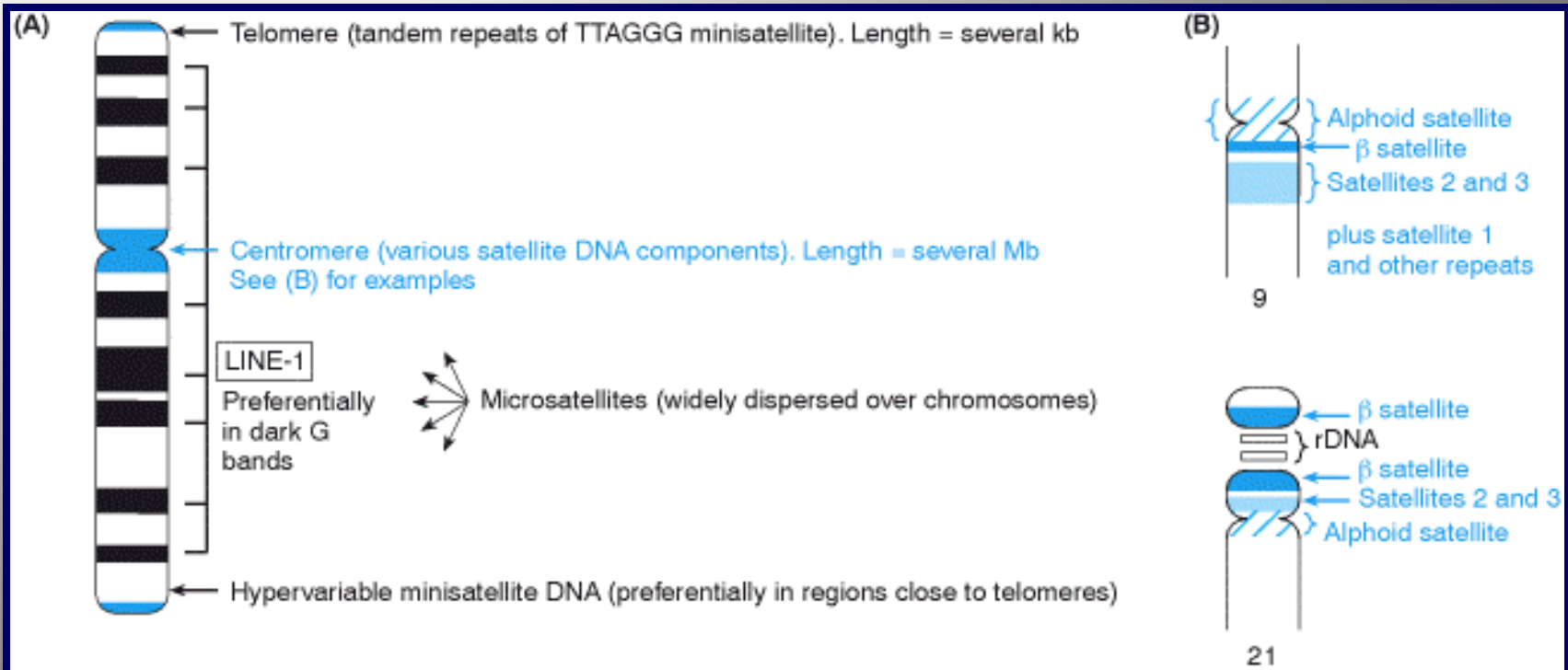


Table 7.12. Major classes and families of interspersed human repetitive DNA (adapted from Smit, 1996)

Class ^a	Family ^a	Size of repeat unit	No. of copies	Percentage of genome
SINE	<i>Alu</i> family	Full length ~0.3 kb	~1 000 000	~ 7.0%
	MIR families	Average size ~0.13 kb	~400 000	~1.7%
LINE	LINE-1 (Kpn) family	Full length is 6.1 kb, but average size ~0.8 kb	~200 000–500 000	~5–12%
	LINE-2 family	Average size ~0.25 kb	~270 000	~2.1%
LTR	HERV	Average size ~1.3 kb	~50 000	~1.3%
	Others	Average size ~0.5 kb	~200 000	~3.3%
DNA transposon	Mariner & other families	Varies; perhaps average size = 0.25 kb	~200 000	~1.6%
Others	Various	Perhaps average size of about 0.4 kb	~60 000	~0.8%

^a See text.