

# Organizzazione del genoma umano

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## 99.9995 % genoma nucleare

contiene la stragrande maggioranza delle informazioni

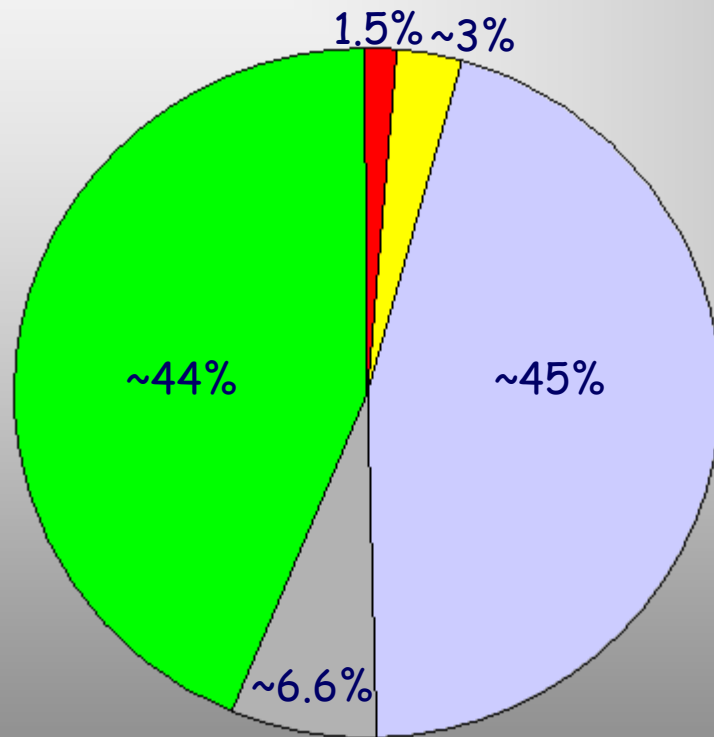
è stato stimato contenere 20.000-25.000 geni

## 0,0005 % genoma mitocondriale

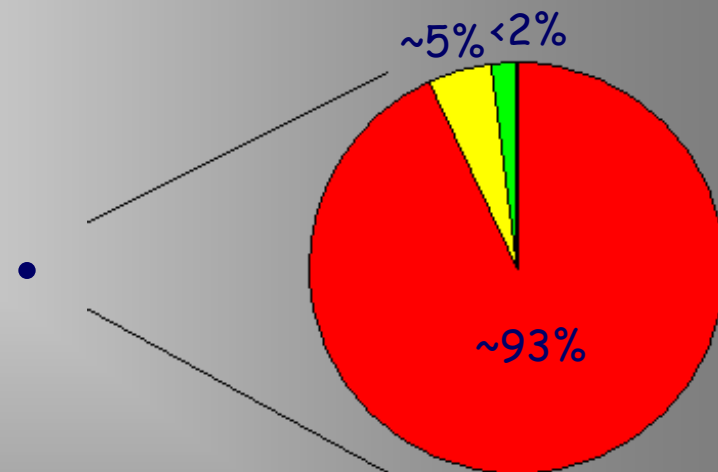
contiene i geni ribosomali e alcuni geni che producono mRNA

tradotti nel mitocondrio stesso (in totale 37)

## Genoma nucleare



## Genoma mitocondriale



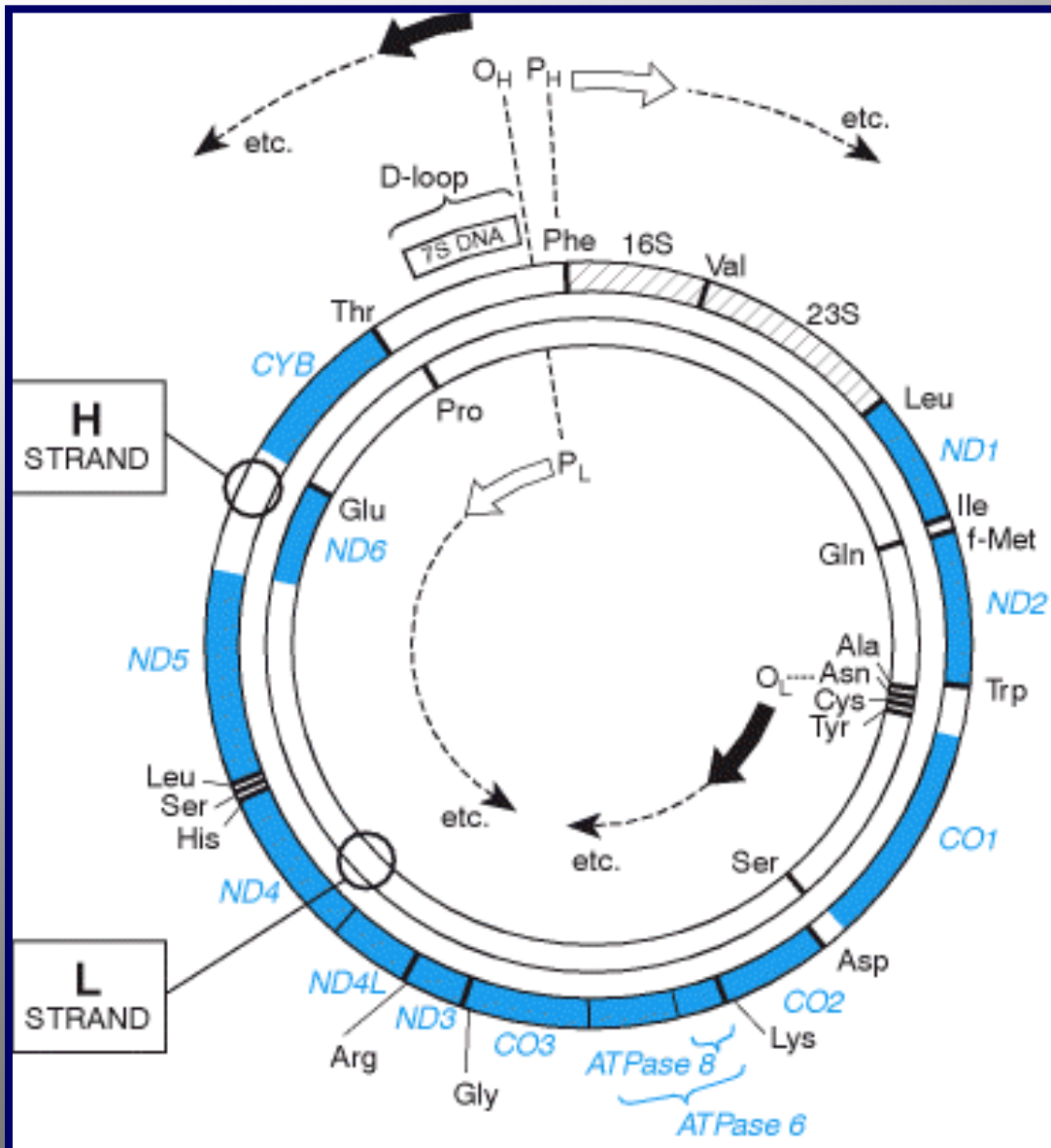
- Altamente conservato, codificante
- Altamente conservato, altro
- Ripetizioni derivanti da trasposizione
- Eterocromatina
- Altro non conservato

# 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 |
| 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  |

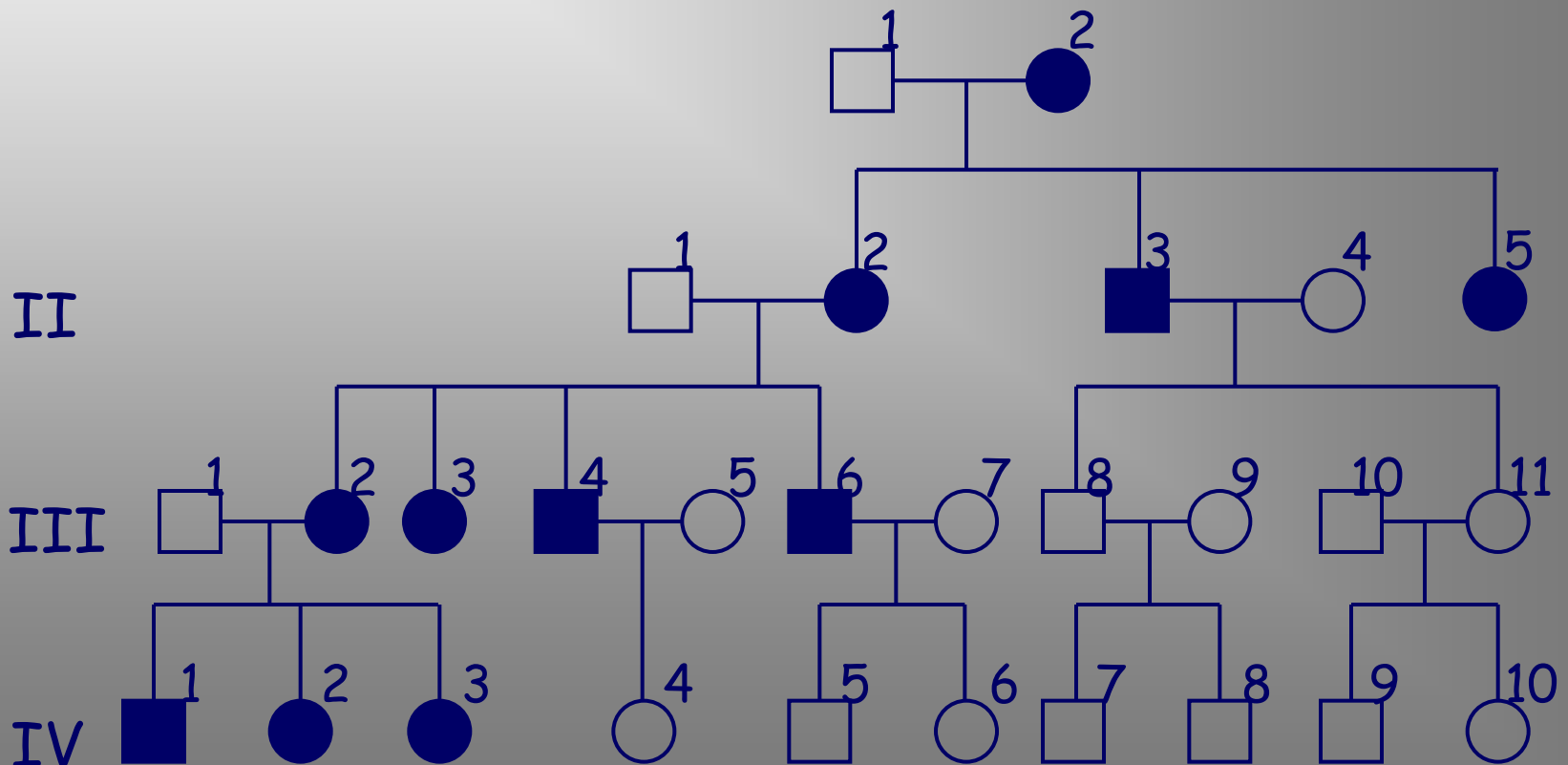
## I tre aspetti più importanti della Genetica Mitocondriale

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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

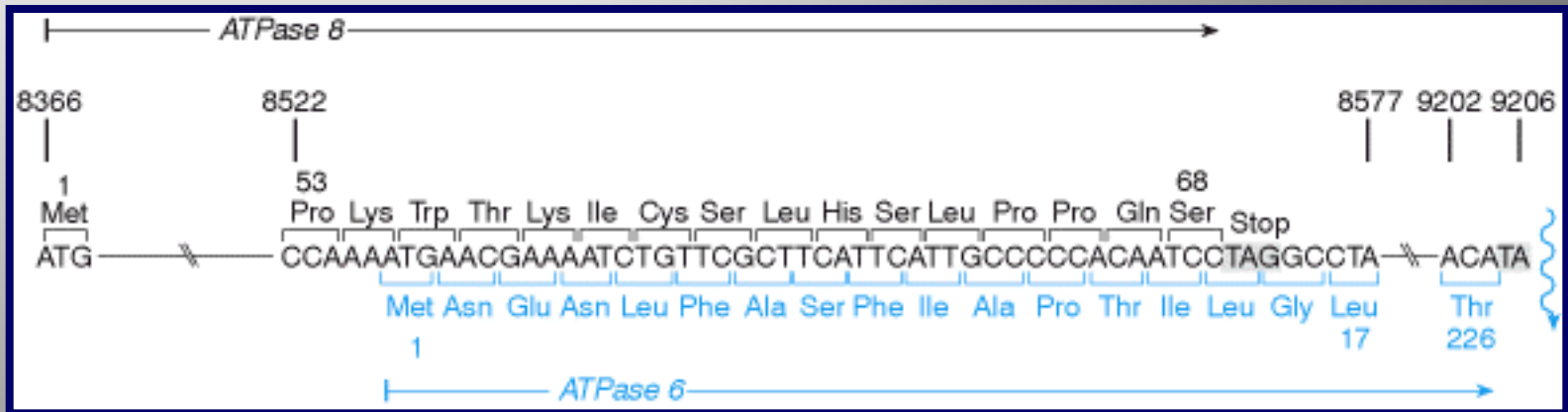
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1. Eredità materna. Alla fecondazione, tutti i mitocondri (e tutti i mtDNA) dello zigote derivano dall'ovocita.
- 2a. Eteroplasmia. Si ha quando un individuo possiede due popolazioni di mtDNA: normale (wild type) e mutante.
- 2b. Effetto soglia. Il 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:

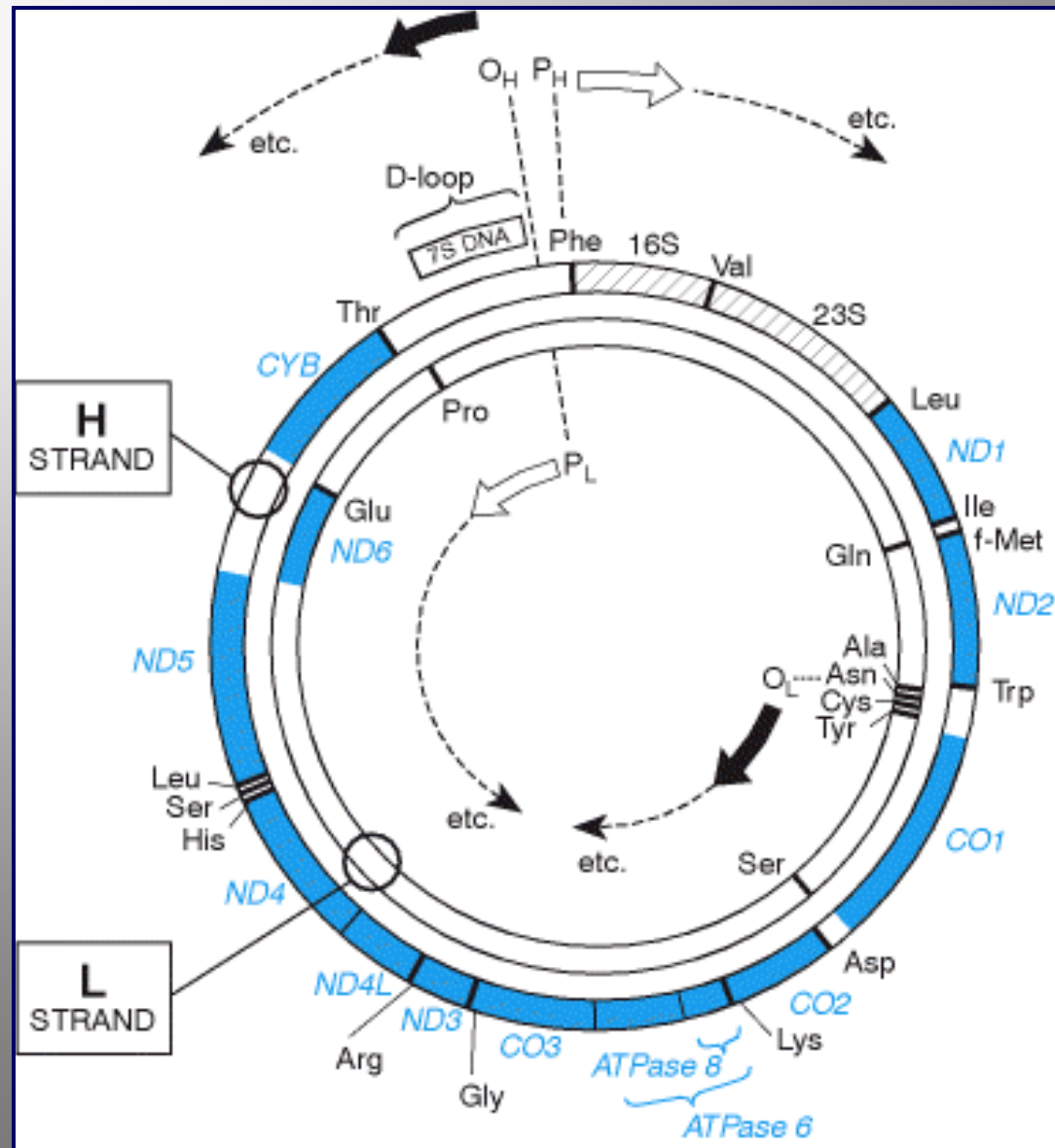
## I 37 geni non possiedono introni

## Alcuni presentano zone di sovrapposizione

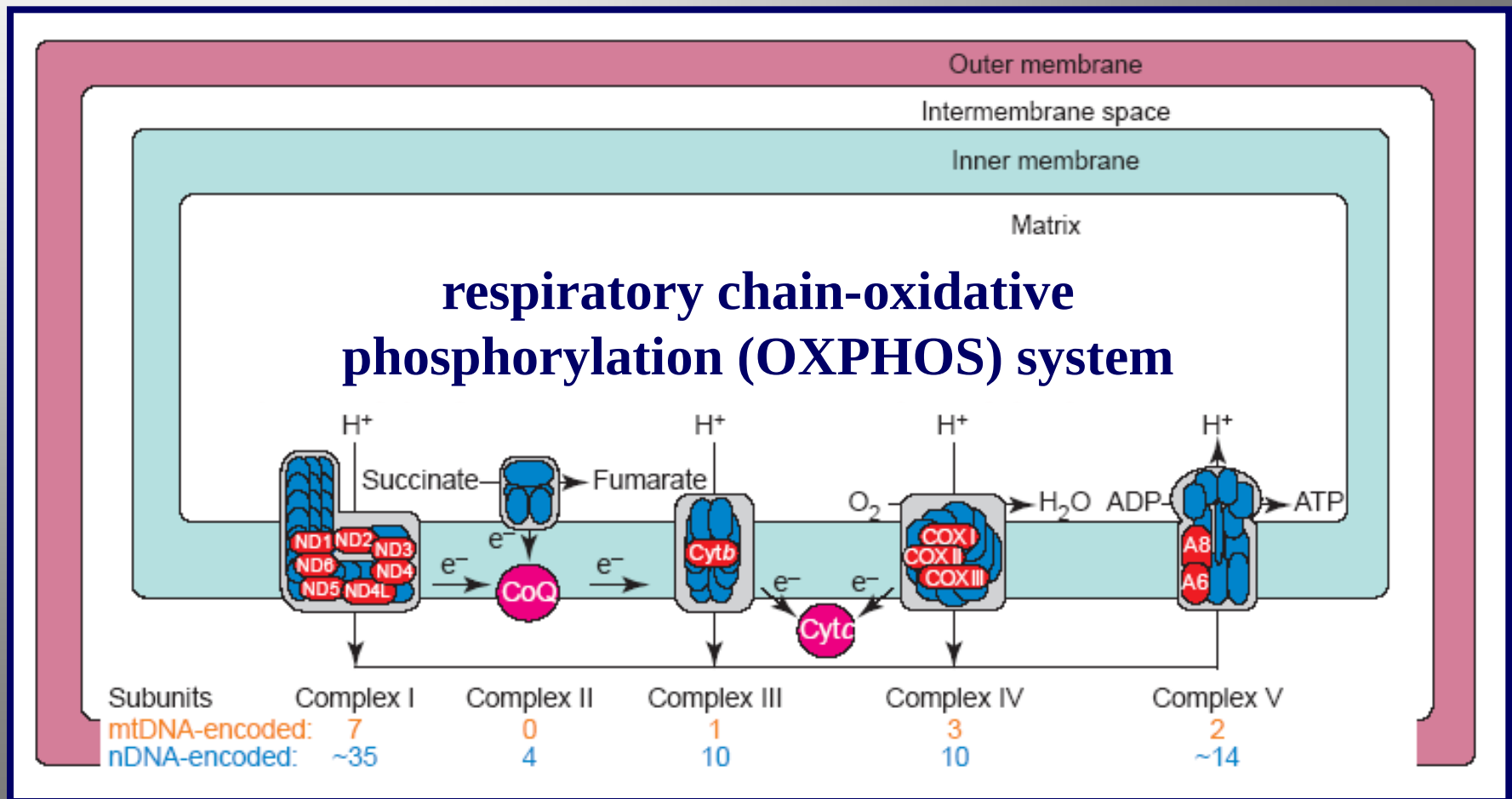


**Alcuni sono contigui o separati da uno o due codoni**

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**

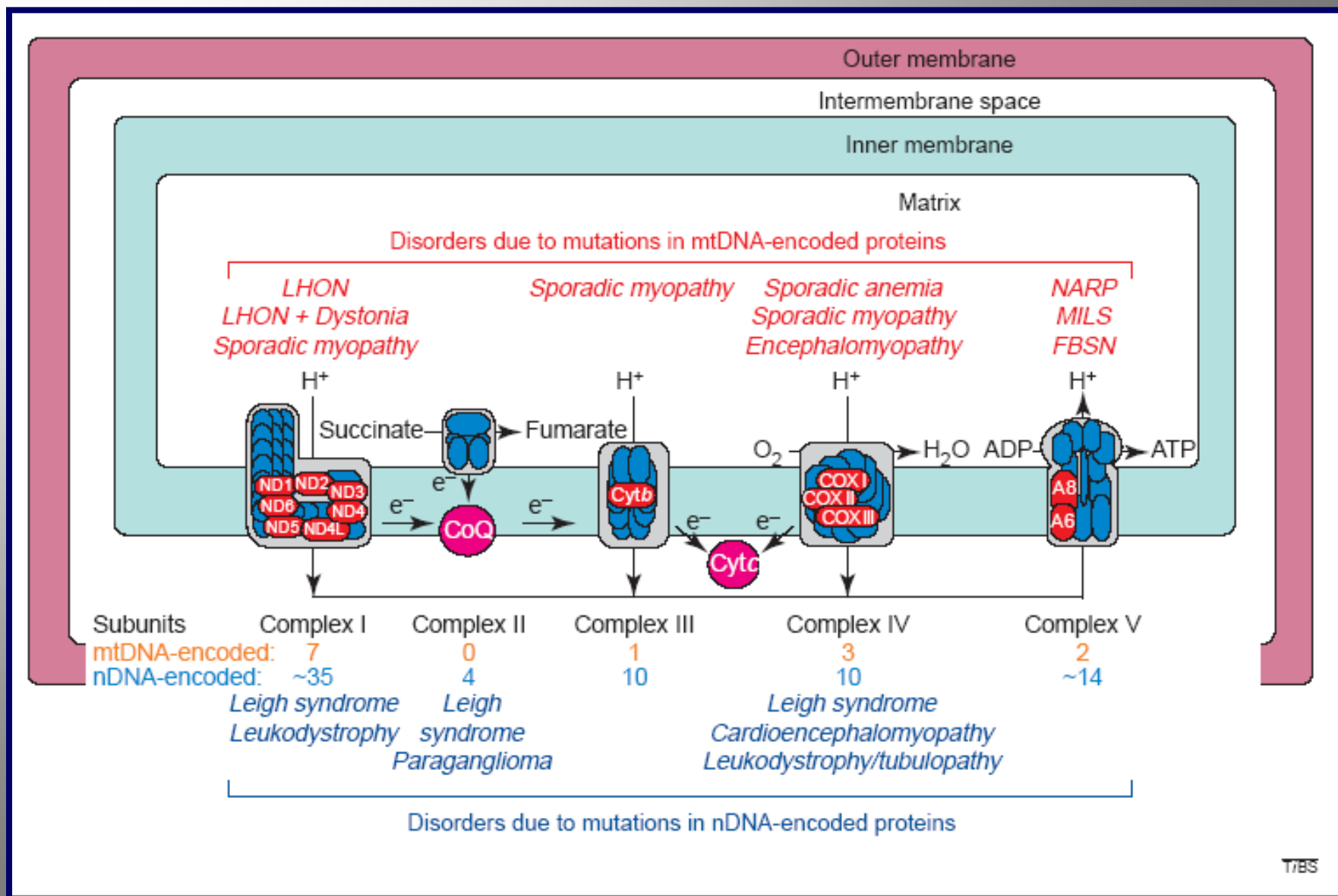


I 13 geni che codificano per proteine codificano tutti per componenti del sistema della catena respiratoria

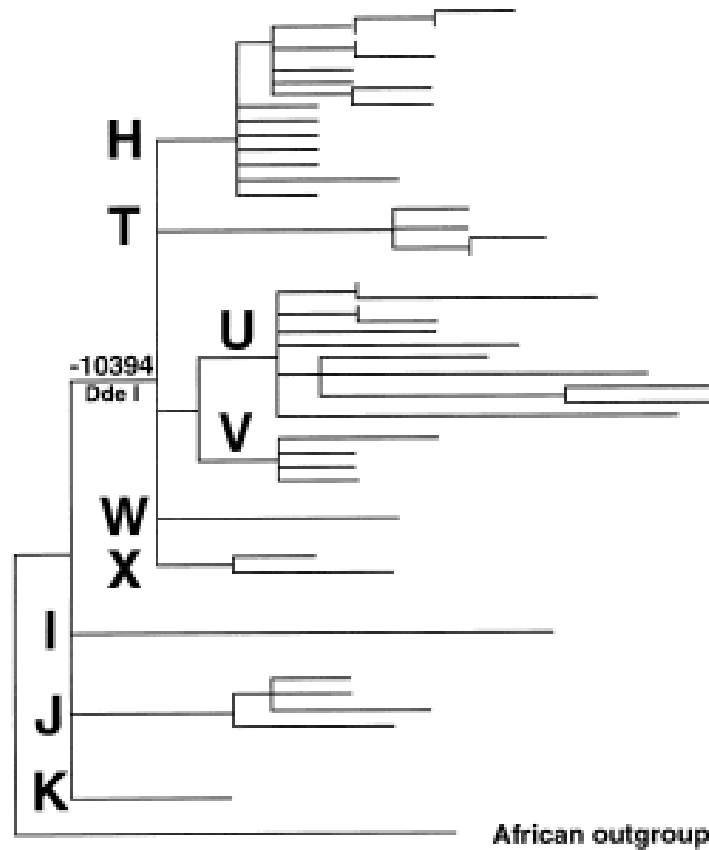


### Point mutations in tRNAs and rRNAs

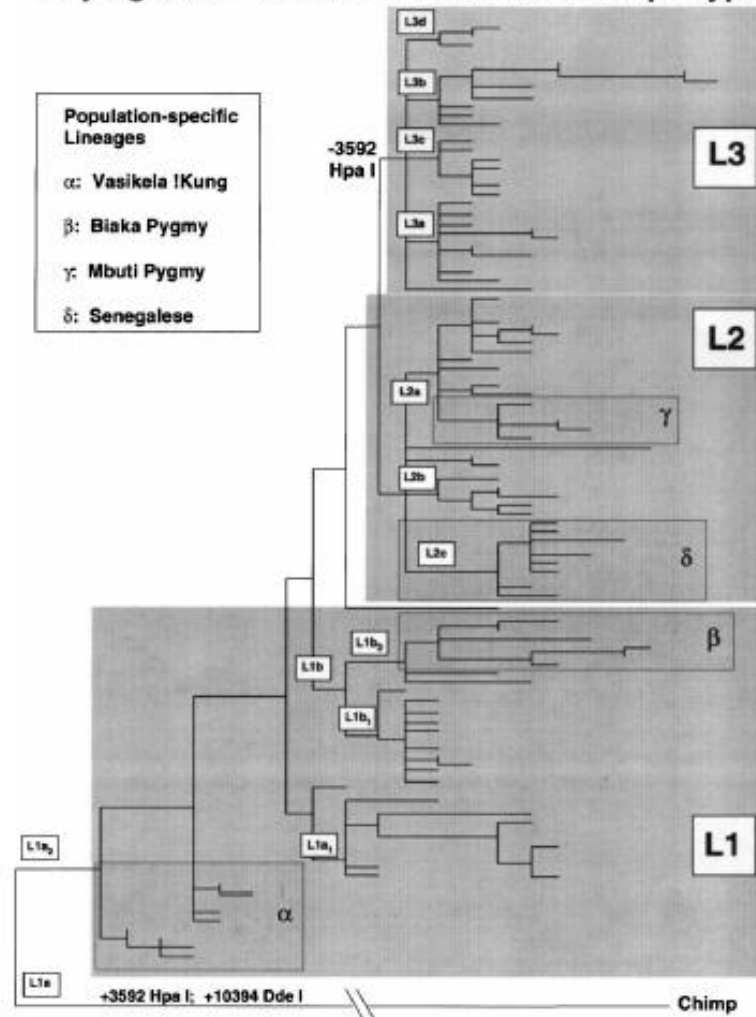
| Disorder                            | No. of mutations | Genes                          |
|-------------------------------------|------------------|--------------------------------|
| Cardiomyopathy                      | 19               | 12S, 16S, A, D, E, G, I, L1, T |
| Deafness                            | 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                              |



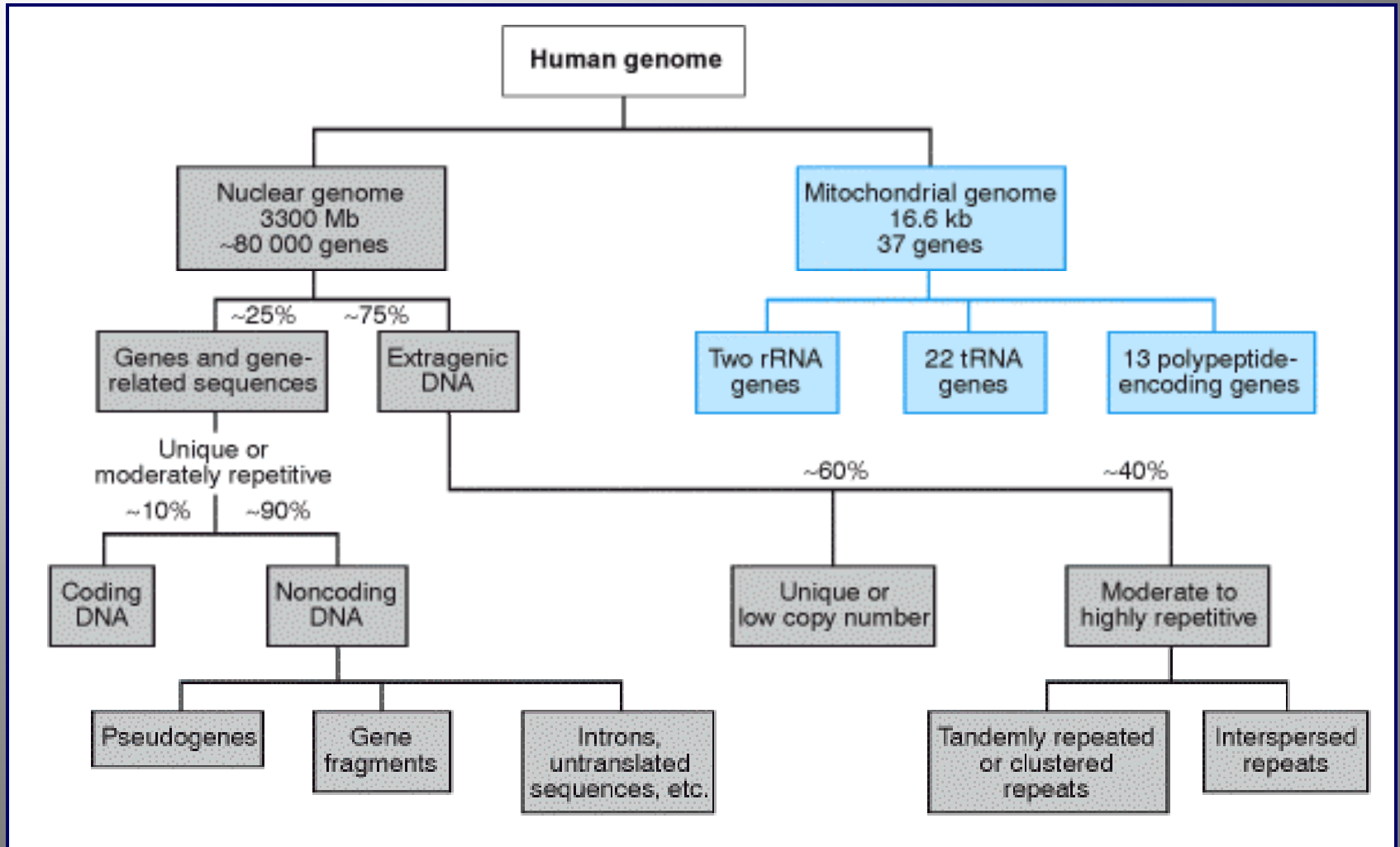
## Phylogenetic Tree of European mtDNA Haplotypes



## Phylogenetic Tree of African mtDNA Haplotypes



# Organizzazione del DNA nucleare

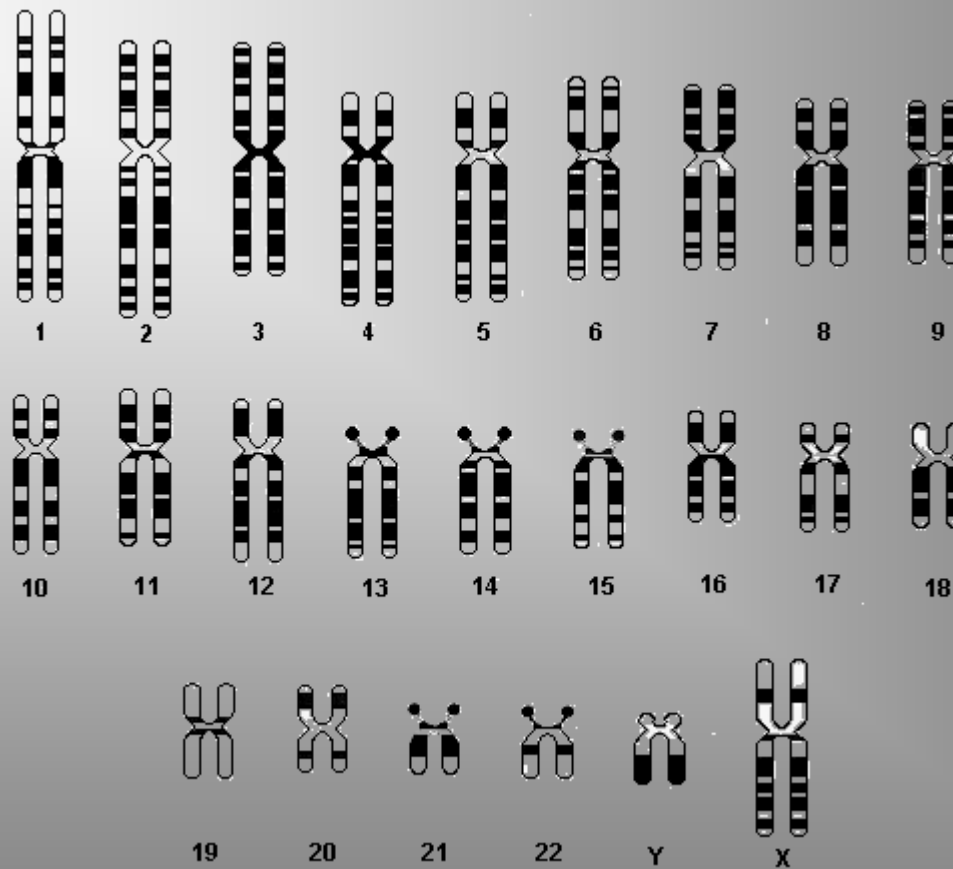


**Table 7.2. DNA content of human chromosomes <sup>a</sup>**

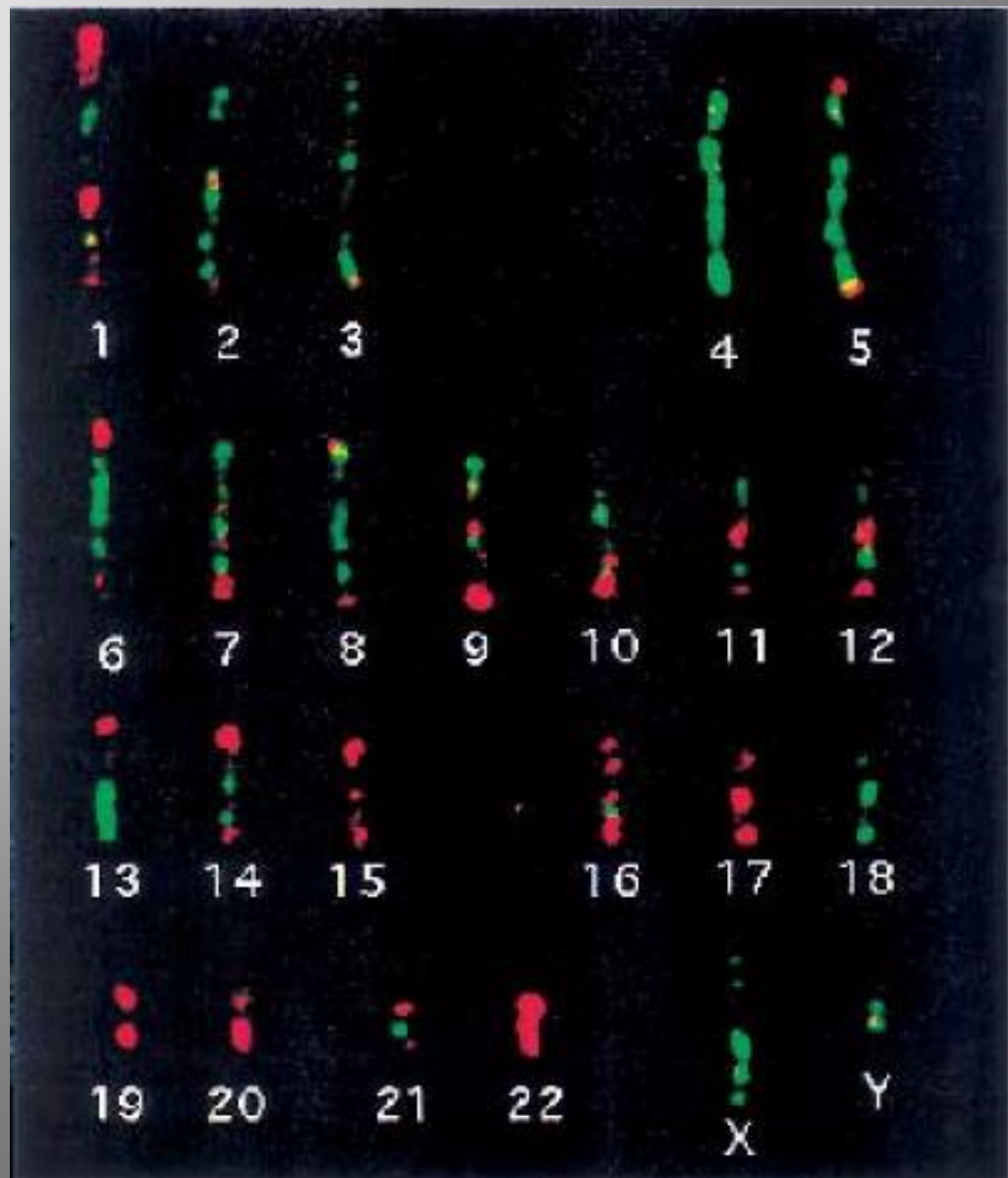
| Chromosome | Amount of DNA (Mb) | Chromosome | Amount of DNA (Mb) |
|------------|--------------------|------------|--------------------|
| 1          | 263                | 13         | 114                |
| 2          | 255                | 14         | 109                |
| 3          | 214                | 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                 |

<sup>a</sup> 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](#).



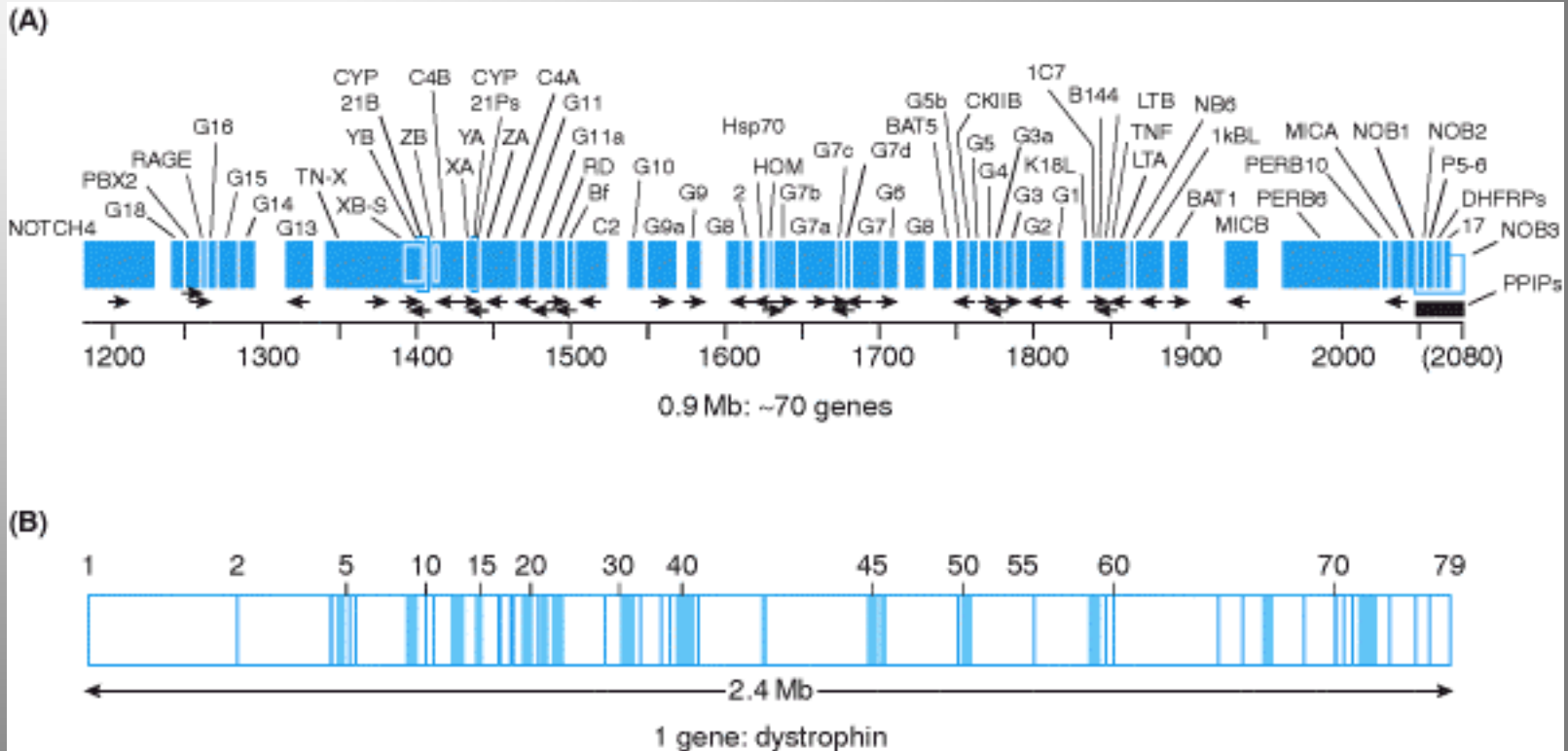


## GpG islands

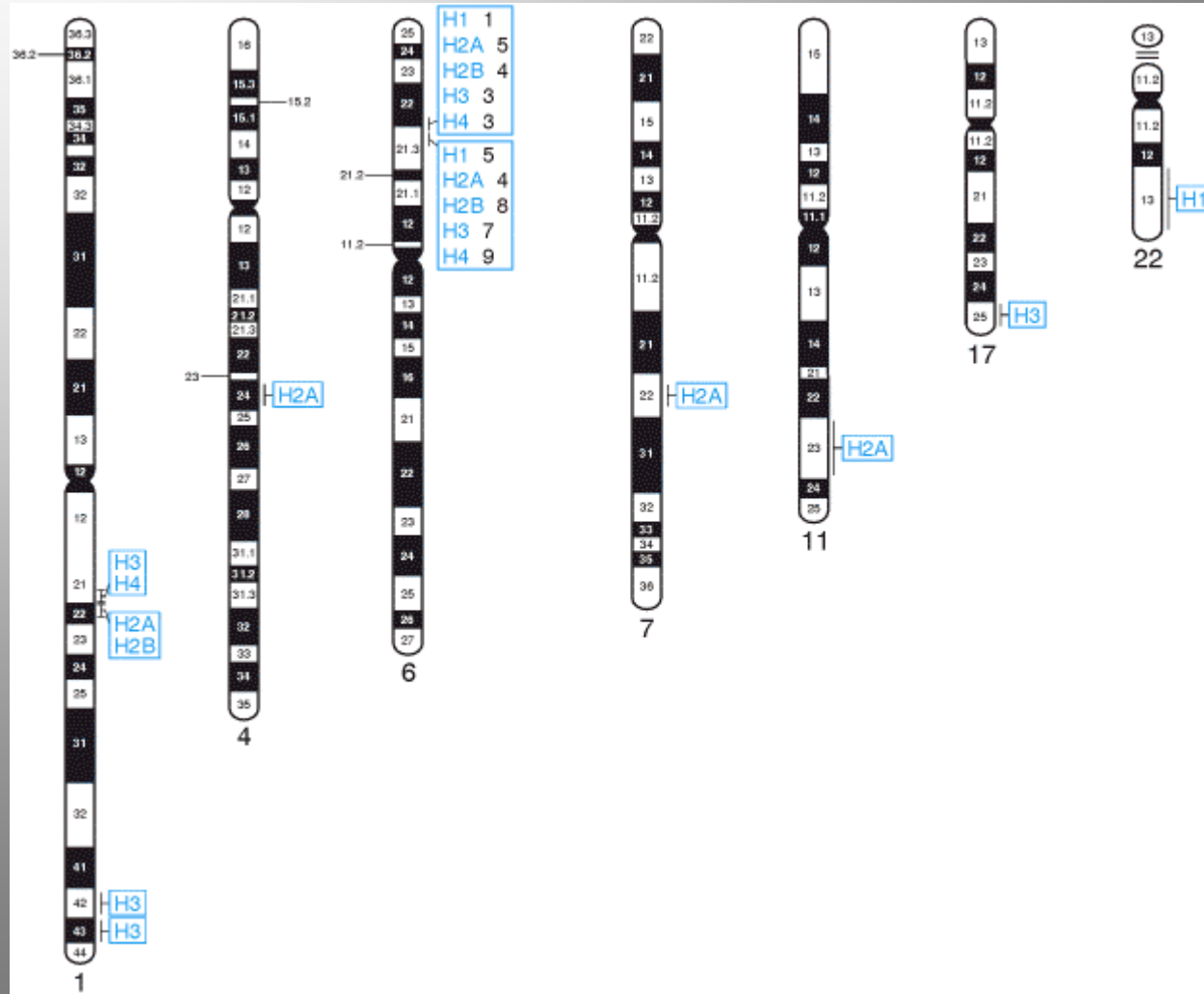


| Nuclear genome                      |                                                                         |
|-------------------------------------|-------------------------------------------------------------------------|
| Size                                | 3300 Mb                                                                 |
| No. of different DNA molecules      | 23 (in XX) 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                     | <b>20-25.000</b>                                                        |
| 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 |

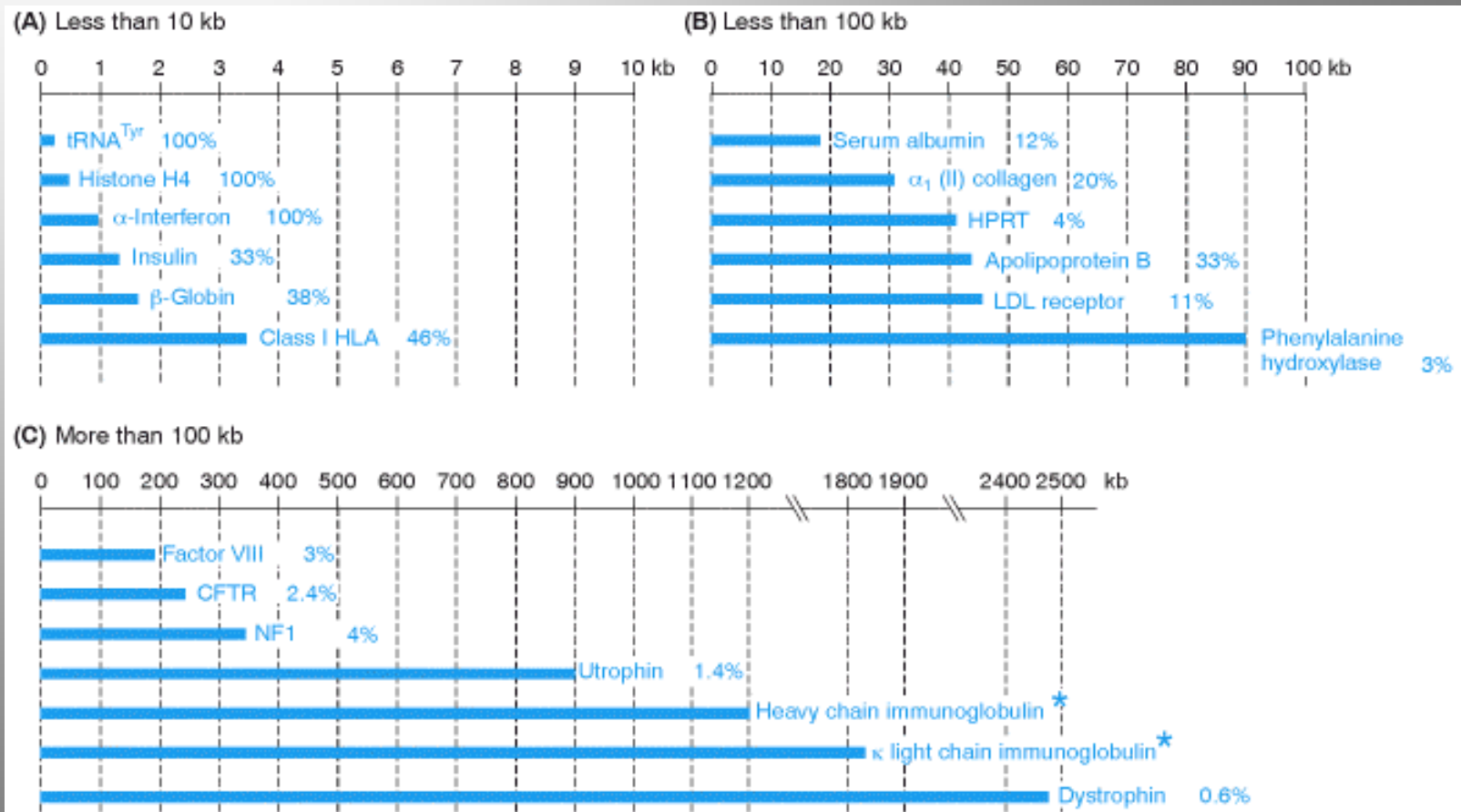
## Confronto tra la regione dell'HLA (classe III) e regione della DMD



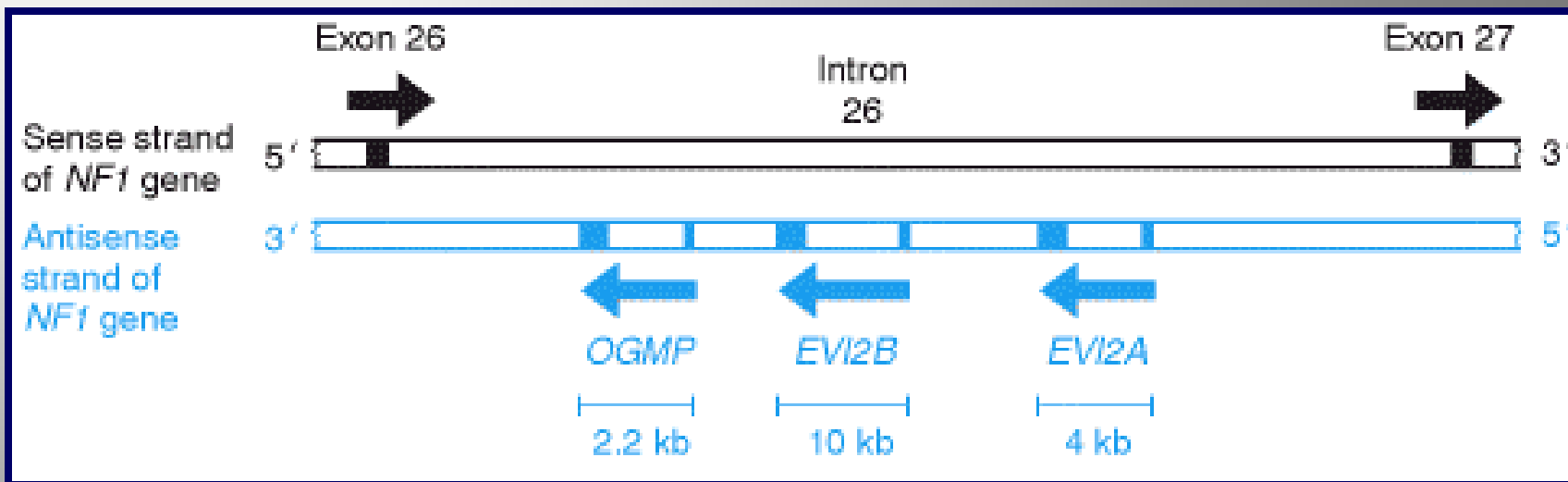
## Distribuzione dei geni per gli istoni



## Variabilità per numero e contenuto degli esoni

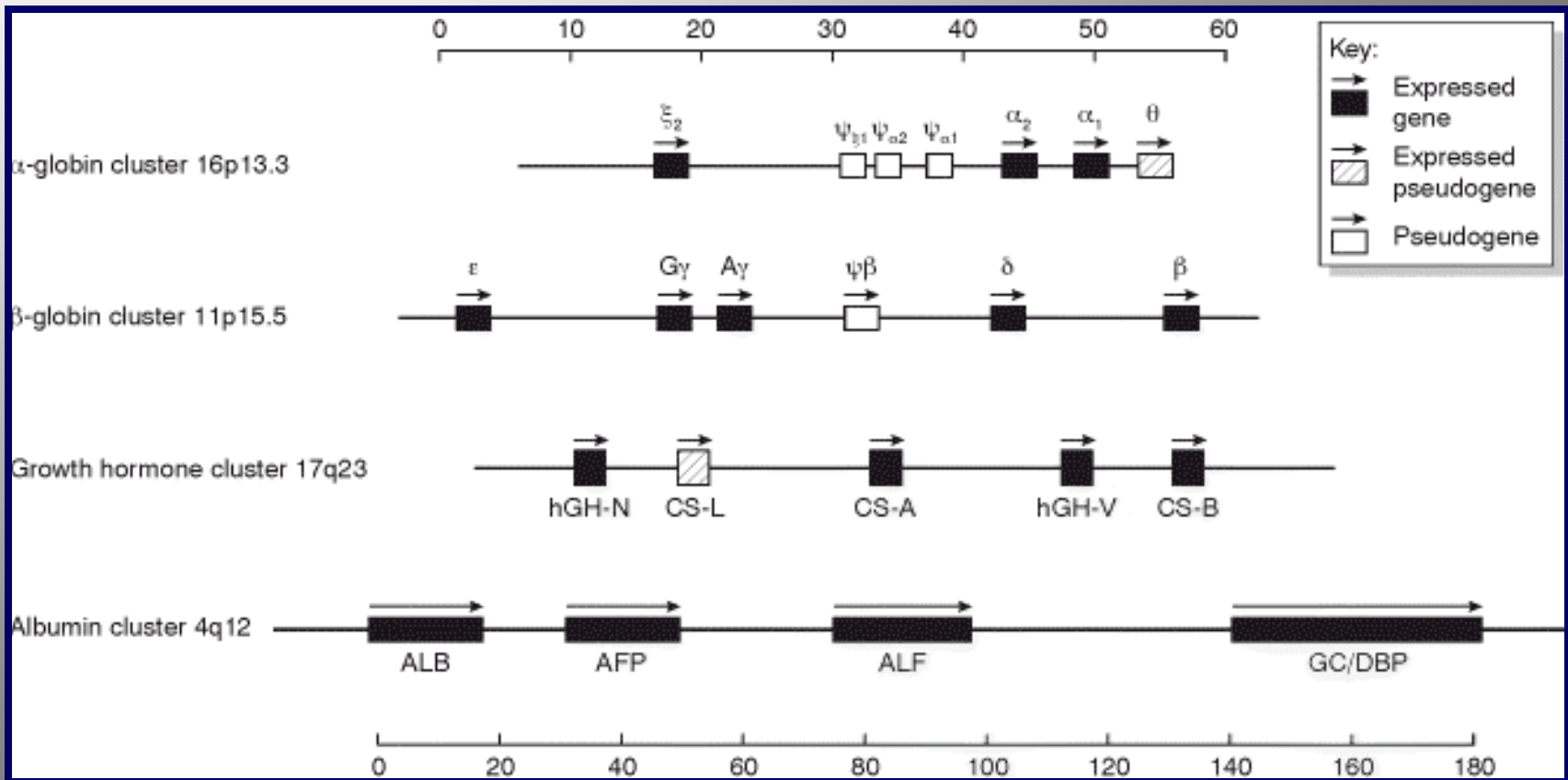


## Geni dentro altri geni



- 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



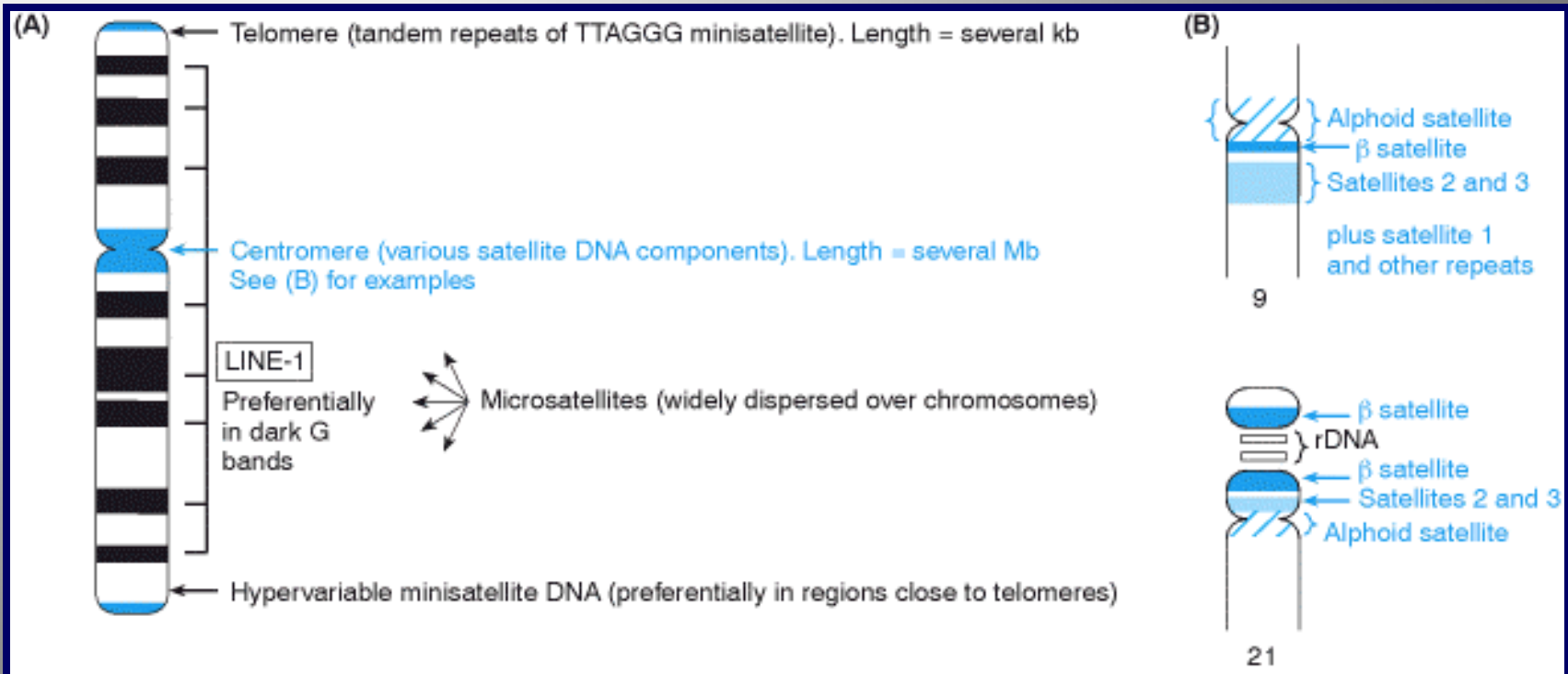
**Table 7.9. Examples of clustered and interspersed multigene families**

| Family                                   | Copy no. | Organization location                                                         | Chromosome                        |
|------------------------------------------|----------|-------------------------------------------------------------------------------|-----------------------------------|
| <b>A. Clustered gene families</b>        |          |                                                                               |                                   |
| <i>Single cluster gene families</i>      |          |                                                                               |                                   |
| Growth hormone gene cluster              | 5        | Clustered within 67 kb; one conventional pseudogene                           | 17q22-24                          |
| $\alpha$ -Globin gene cluster            | 7        | Clustered over ~50 kb (see <a href="#">Figure 8.23</a> )                      |                                   |
| Class I HLA heavy chain genes            | ~20      | Clustered over 2 Mb (see <a href="#">Figure 8.4</a> )                         |                                   |
| <i>Multiple cluster gene families</i>    |          |                                                                               |                                   |
| HOX genes                                | 38       | Organized in four clusters ( <a href="#">Figure 9.5</a> )                     | 2p, 7, 12, 17                     |
| Histone gene family                      | 61       | Modest-sized clusters at a few locations; two large clusters on chromosome 6  | (see <a href="#">Figure 7.6</a> ) |
| Olfactory receptor gene family           | ~1000    | About 25 large clusters scattered throughout the genome                       | Many                              |
| <b>B. Interspersed gene families</b>     |          |                                                                               |                                   |
| 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)                                                     |
|-------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------|
| <b>'Megasatellite' DNA</b> (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                                                    |
| <b>Satellite DNA</b> (blocks often from 100 kb to several Mb in length) |                |                                                                                   |
| $\alpha$ (alphoid DNA)                                                  | 171 bp         | Centromeric heterochromatin of all chromosomes                                    |
| $\beta$ ( <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                                                   |
| <b>Minisatellite DNA</b> (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                                             |
| <b>Microsatellite DNA</b> (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 <sup>a</sup> | Family <sup>a</sup>      | 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%                |

<sup>a</sup> See text.