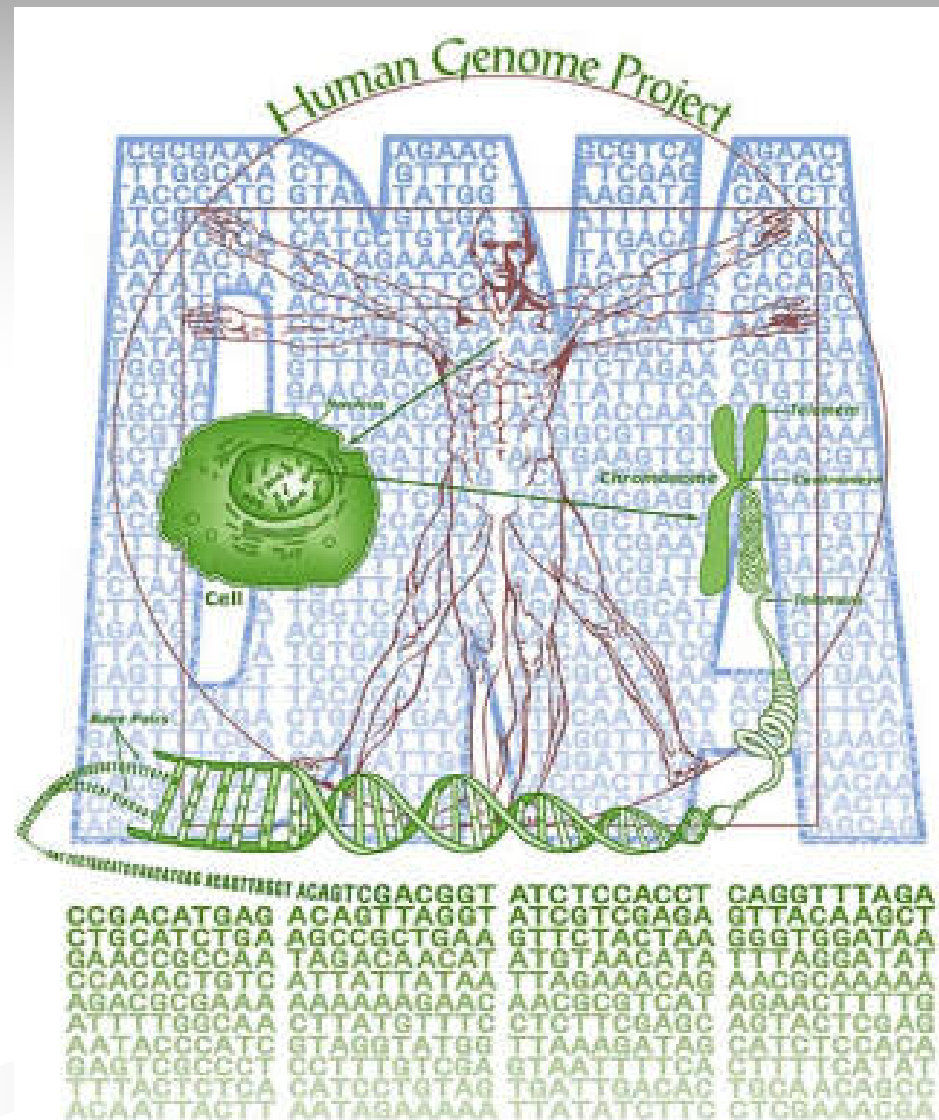


# Projekt ľudského genómu

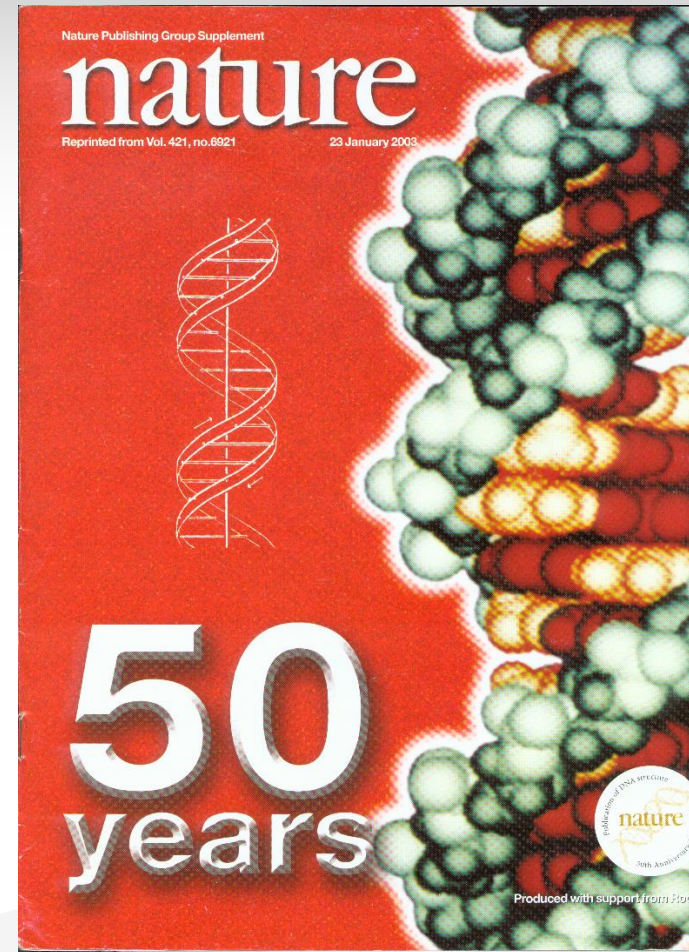
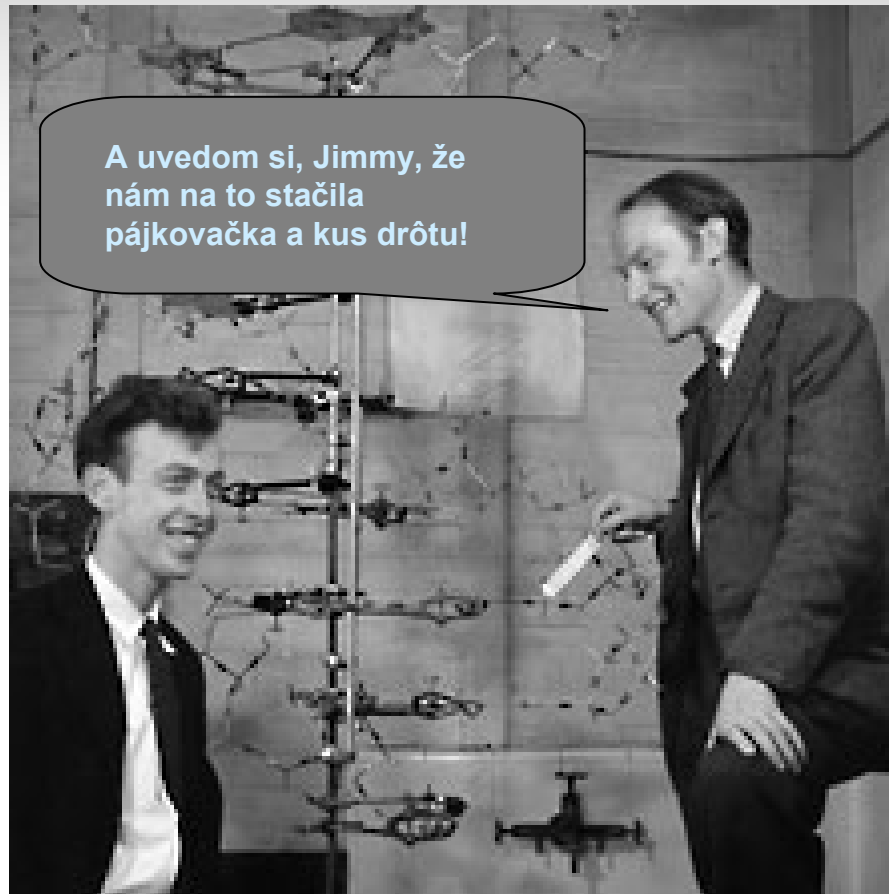
- Prehistória
- História
- Ciele
- Metódy
- Priebeh
- Výsledky
- Využitie
- Perspektívy

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základná www stránka:

[www.doegenomes.org](http://www.doegenomes.org)



# Prehistória: Watson a Crick 1953



# A STRUCTURE FOR DEOXYRIBOSE NUCLEIC ACID

**J.D.Watson**

**F.H.C.Crick**

**Nature, April 25, 1953**

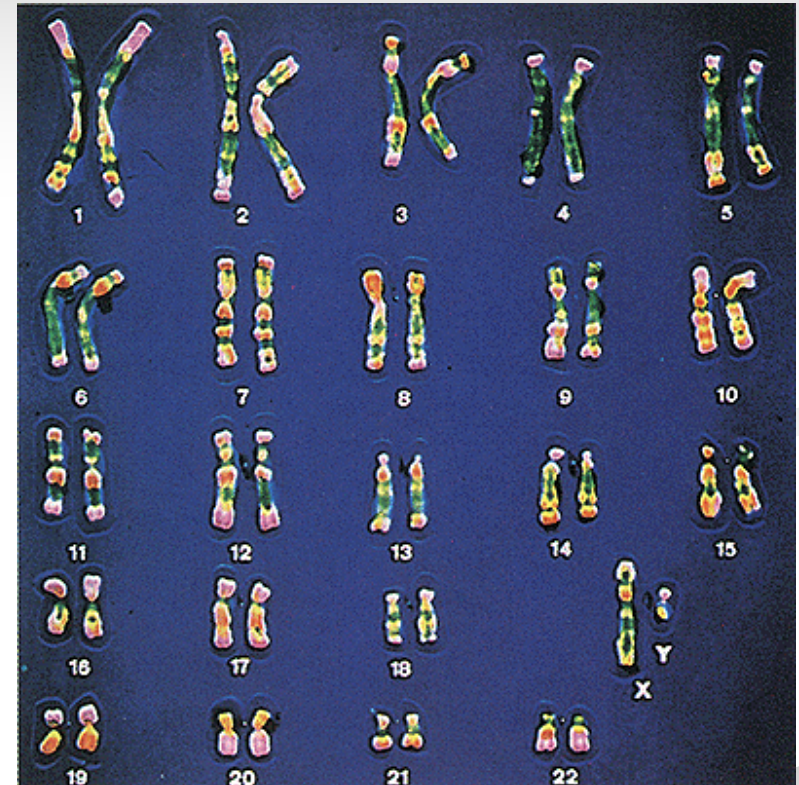
„It has not escaped our notice that  
the specific pairing we have  
postulated immediately suggests  
a possible copying mechanism for  
the **genetic material**“

# Genetika človeka v r. 1953

- hodnotenie rodokmeňov
- štúdium dvojčiat
- cca 50 monogénných ochorení
- 5 monogénných znakov (ABO, Rh...)
- 48 chromozómov
- 5 miliónov génov
- žiadna DNA (podľa učebníc)

# 60-te roky: cytogenetika človeka

- 1956: 46 chromozómov
- 1959: chromozómové aberácie a choroby
- 1960: nomenklatúra a metodika
- chromozómy a nádory
- chromozómy: „orgán“ lekárskej genetiky
- Ľudských génov jeden milión, o DNA stále ani zmienka...



# 70-te roky: žeby DNA?

- polymorfizmy (sérové skupiny, izoenzýmy...)
- väzba a chrom. lokalizácia
- bunkové hybridy
- biochemická genetika

Ale už aj:

- **prvé RFLP** v ľudskej DNA (1978)
- **DNA diagnostika** chorôb (1979)
- **100 000 génov**

# Human Genome Project: história

- 1986: Santa Fe - DoE Intl. Meeting
- **James Watson**: „vystúpiť na cestu od dvojitej závitnice k 3 miliardám schodov ľudského genómu“
- 1988: Kongres USA schválil 15 ročný projekt a dotáciu 3 mld USD
- **1990: začiatok projektu**
- 2005: predpokladané ukončenie

Koordinácia:

1988: **HUGO** (Human Genome Organization)

HUGO Europe – Americas - Pacific

# HGP: rozsah

- $3\,200 \times 10^6$  bp (dĺžka Dunaja v mm !)
- dovtedy najdlhší sekvenovaný úsek: ľudská mtDNA (16 500 bp, 1981)
- vtedajšia rýchlosť: 100 bp / osoba / deň
- cena: 5 - 10 USD/bp

## Oficiálny začiatok HGP: 1990

- 20 pracovísk zo 6 štátov
- 3 mld USD
- cca 15 rokov práce (t.j. do r. 2005)



# História sekvenovania DNA

bp/osoba/rok	rok	udalost'
1	1965	<i>Holley</i> sekv. alanyl tRNA <i>S. cerev.</i>
15	1970	<i>Wu</i> sekvenoval 12 bp lambda fága
150	1977	<i>Sanger</i> dideoxy, <i>Gilbert</i> chem. sekv.
1 500	1978	<i>Sanger</i> sekv. phi-x174 (5375 bp)
15 000	1980	<i>Messing</i> vyvinul M13 vektor
25 000	1986	<i>Hood</i> – čiastočne automat. sekv.
1,000 000	1995	<i>Venter</i> – autom. fluoresc. sekv.
150, 000 000	1999	Perkin-Elmer 96 kapilárny sekv.
? 000, 000 000	2004	každý kto má vybavenie

# HGP: ciele

- Triangulovať genóm pomocou DNA markerov
- Identifikovať a mapovať gény, určiť ich štruktúru a funkciu v zdraví aj v patológii
- Identifikovať dôležité mimogénové sekvencie
- Určiť úplnú sekvenciu genómu (3,2 Gb)
- Všetky dáta uložiť vo verejne prístupných databázach
- Sekvenovať genómy modelových organizmov (drozofila, myš, *C. elegans*, *A. thaliana* a i.)
- Skúmať etické, legálne a sociálne aspekty

# Metódy mapovania

## *Genetické mapovanie*

- rodokmeňová analýza (rekombinácia)
- triangulácia pomocou markerov

## *Fyzické mapovanie*

### - **nízke rozlíšenie:**

- hybridizácia somat. buniek
- in situ hybridizácia (FISH)

### **vysoké rozlíšenie:**

restrikčné mapovanie  
STS mapovanie  
EST mapovanie  
sekvenovanie

# Triangulácia ľudského genómu

## Genetické markery: história

1900	krvné skupiny	cca 20
1960	sérové proteíny a izoenzýmy	$10^2$
1980	DNA RFLP	$10^3$
1985	minisatelity	$10^4$
1990	mikrosatelity	$10^5$
1995	SNP (single nt polymorphisms)	$10^6$

## Triangulácia genómu: genetické mapy

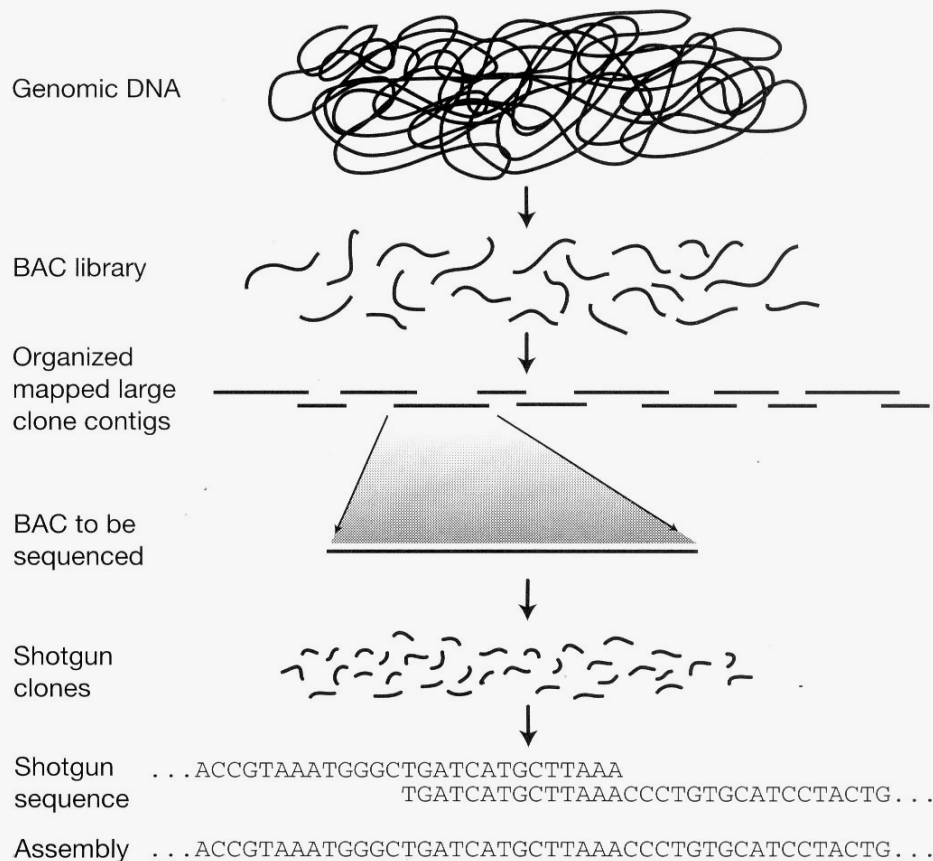
1987	RFLP	402	nad 10 cM
1992	STR	813	cca 5 cM
1996	STR	5262	1,6 cM
1997	integrovaná	6800	0,7 cM

podrobnejšia triangulácia nie je potrebná  
(v súčasnosti cca  $2 \times 10^6$  mapovaných SNP)

# International Human Genome Sequencing Consortium

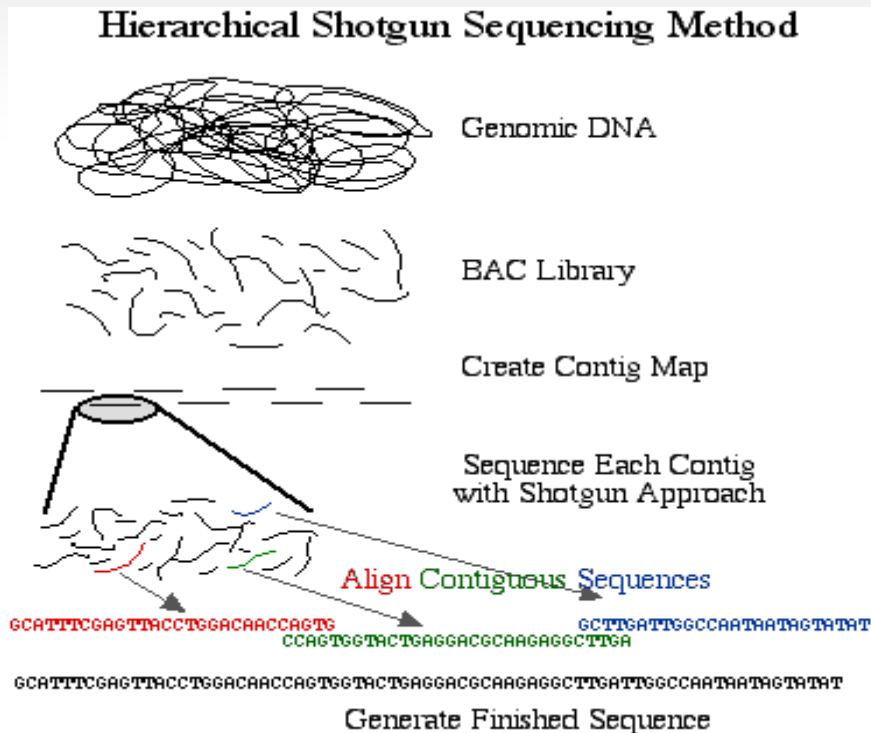
## Hierarchická metóda (clone-by-clone):

Hierarchical shotgun sequencing



- Triangulácia genómu pomocou STR markerov
- 100 až 200 kb dlhé BAC klony, mapovanie týchto klonov do STR mapy
- Zostrojiť kontigy
- Štiepiť BACy na náhodné („shotgun“) fragmenty
- Sekvenovať fragmenty
- Zoradiť do sekvencie

# HGP: hierarchická stratégia sekvenovania („clone-by-clone“)



- triangulovať genóm pomocou STR
- zostrojiť BAC-knižnice
- mapovať klony do STR mapy
- utvoriť BAC kontigy
- štiepiť BAC-y náhodne na sekvenovateľné fragmenty
- sekvenovať fragmenty
- zoradiť do konečnej sekvencie klonu
- zoradiť sekvencie klonov do definitívnej sekvencie
- anotovať sekvenciu

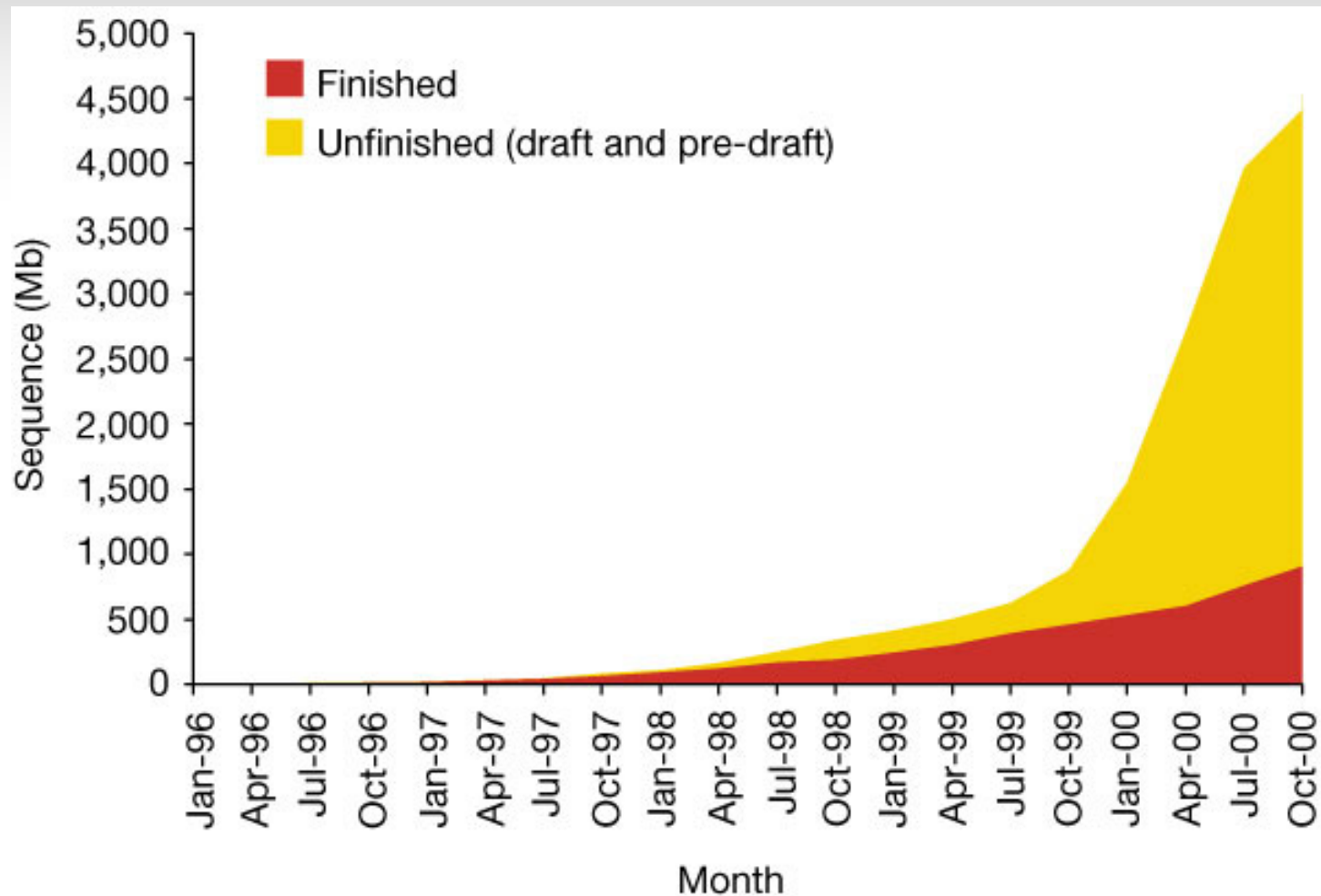
# HGP: Francis Collins a Eric Lander







# Nárast údajov o sekvencii 1996-2001

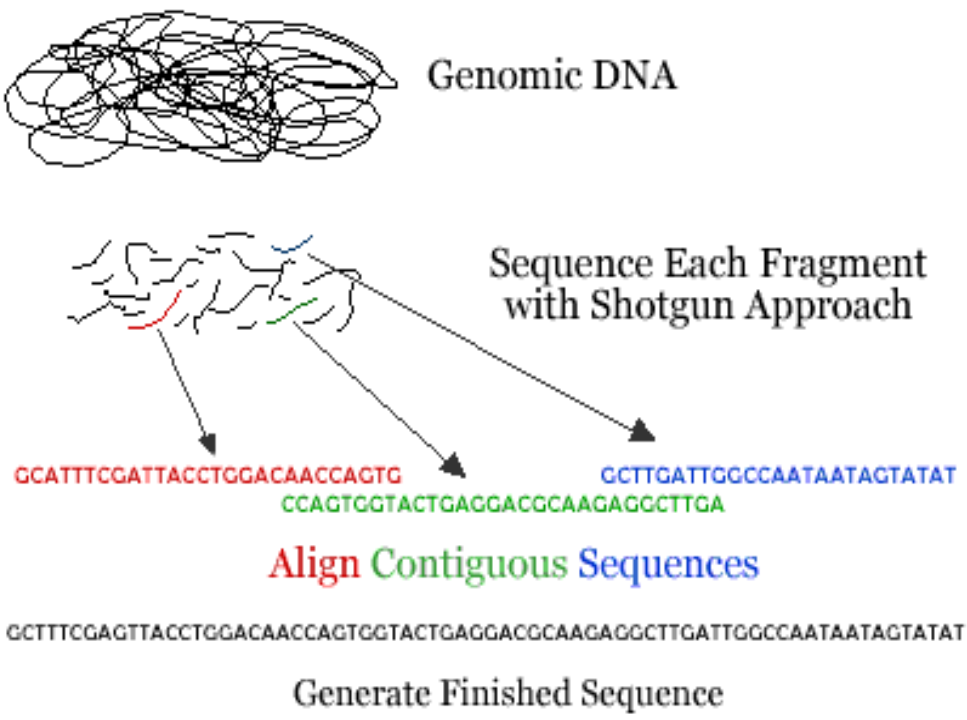


# Craig J. Venter a Celera Genomics



# Stratégia sekvenovania: Celera Genomics

## Whole Genome Shotgun Sequencing Method



- Celogenómová shotgun stratégia sekvenovania
- Skombinovanie s dátami HGP
- Utvorenie knižníc s definovanými dĺžkami (2, 10, 50 kb)

15 February 2001

# nature

ISSN 0950-0804 PUBLISHED WEEKLY

[www.nature.com](http://www.nature.com)

the  
**human**  
genome



**articles**


# Initial sequencing and analysis of the human genome

**International Human Genome Sequencing Consortium\***

*\* A partial list of authors appears on the opposite page. Affiliations are listed at the end of the paper.*

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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.



# The Sequence of the Human Genome

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# HGP v Bielom Dome, jún 2001





# F. Collins a C. J. Venter 2001



# Sekvenované eukaryo genómy

organizmus	rok	Mb	%	% eu	gény	g./Mb
<i>S.cerevisiae</i>	1996	12	93	100	5 800	483
<i>C. elegans</i>	1998	97	99	100	19 099	197
<i>Drozofila</i>	2000	116	64	97	13 601	117
<i>Arabidopsis</i>	2000	115	92	100	25 498	221
H.s. chr. 21	2000	34	75	100	225	7
H.s. chr. 22	1999	34	70	97	545	16
<b>H.s. HGP</b>	<b>2001</b>	<b>2 693</b>	<b>84</b>	<b>90</b>	<b>31 780</b>	<b>12</b>
H.s. Celera	2001	2 654	83	88-93	39 114	15

# Prehľad ľudského genómu: Celera

■ Dĺžka sekvencie	2,91 Gb
■ Podiel GC párov	38 %
■ Podiel repetitívnej DNA	35 %
■ Počet anotovaných génov	26 383
■ Celkový počet génov (odhad)	39 114
■ Priemerná dĺžka génu	27 kb
■ Najviac génov v chromozóme	19 (23g./Mb)
■ Najmenej génov v chromozóme	13 a Y (5/Mb)
■ Gény tvoria	25,5-37,8 %
■ Exóny tvoria	1,1 – 1,4 %
■ Výskyt SNP	1 : 1250 bp

*Nature* 431, 931 - 945 (21 October 2004); doi:10.1038/nature03001

# Finishing the euchromatic sequence of the human genome

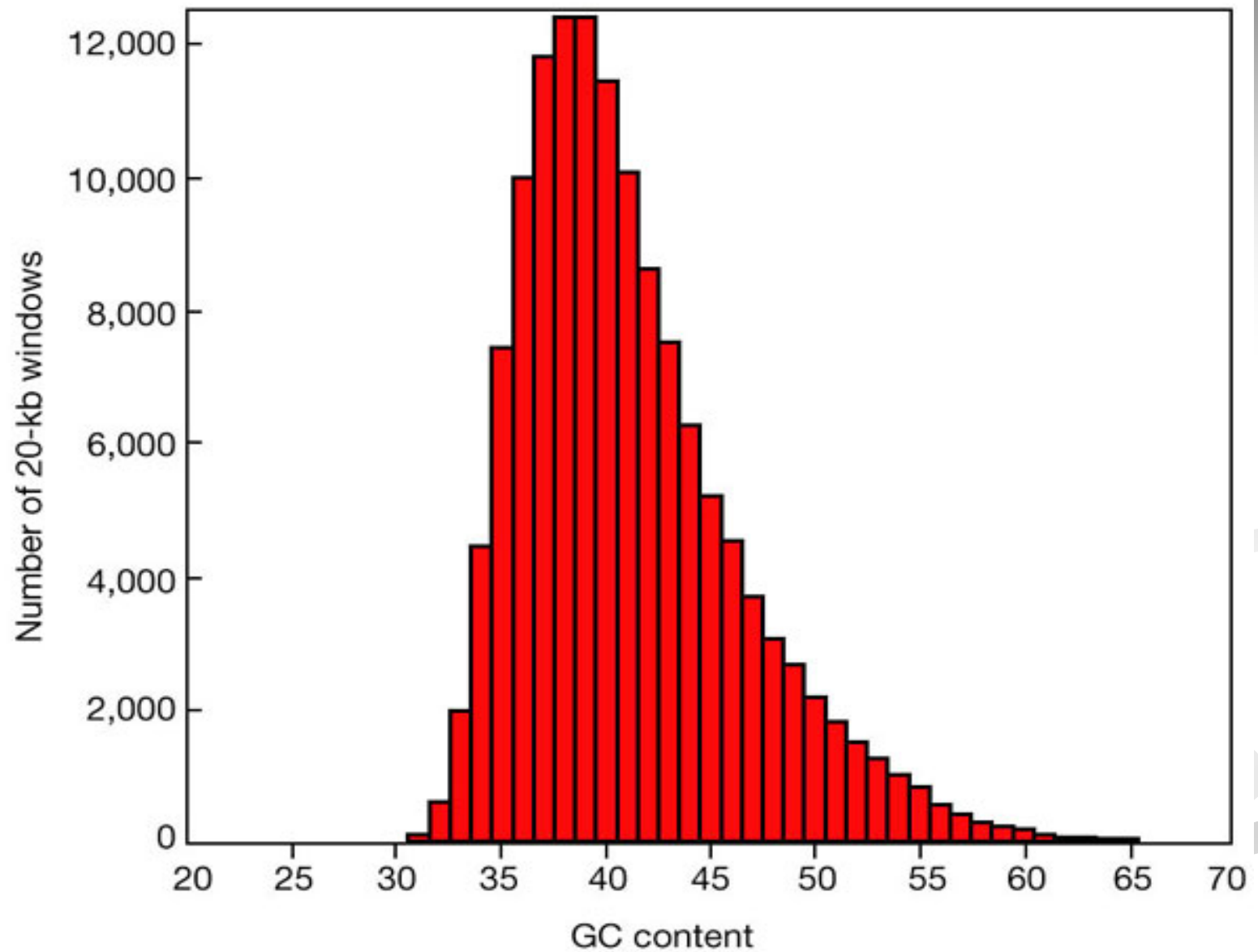
INTERNATIONAL HUMAN GENOME SEQUENCING CONSORTIUM

[http://vega.sanger.ac.uk/Homo\\_sapiens/](http://vega.sanger.ac.uk/Homo_sapiens/)  
[www.ensembl.org](http://www.ensembl.org)

# Dokončená sekvencia (2004): základné údaje







- pokrýva 2,85 Gb; **celý genóm má 3,08 Gb**
- pokrýva > 99% euchromat. genómu
- sekvenačné chyby zriedkavejšie ako 1 : 100 000, priemerné pokrytie 11-násobné
- len <350 medzier (väčšinou heterochrom. úseky a vysoko repetitívne sekvencie)
- **20 000 – 25 000 proteíny kódujúcich génov** (22 287)
- priemerne 9 génov na Mb; veľká variabilita
- 232 000 exónov; v priemere 10,4 exónu na gén; **exóny tvoria len 1,2% dĺžky sekvencie**
- identifikovaných **cca 20 000 pseudogénov**, asi ich je viac ako génov
- segmentové duplikácie tvoria 5,3% euchromatickej sekvencie („evolutionary gene nurseries“)
- ale pozor: anotácia sekvencie stále ešte nie je dokončená!

# Obsah GC párov v ľudskom genóme: 20 Mb okná



# Zastúpenie rozličných typov rozptýlených repetícií

Classes of interspersed repeat in the human genome

			Length	Copy number	Fraction of genome
LINEs	<b>Autonomous</b>		6–8 kb	850,000	21%
	<b>Non-autonomous</b>		100–300 bp		
Retrovirus-like elements	<b>Autonomous</b>		6–11 kb	450,000	8%
	<b>Non-autonomous</b>		1.5–3 kb		
DNA transposon fossils	<b>Autonomous</b>		2–3 kb	300,000	3%
	<b>Non-autonomous</b>		80–3,000 bp		

# Triedy rozptýlených repetícií

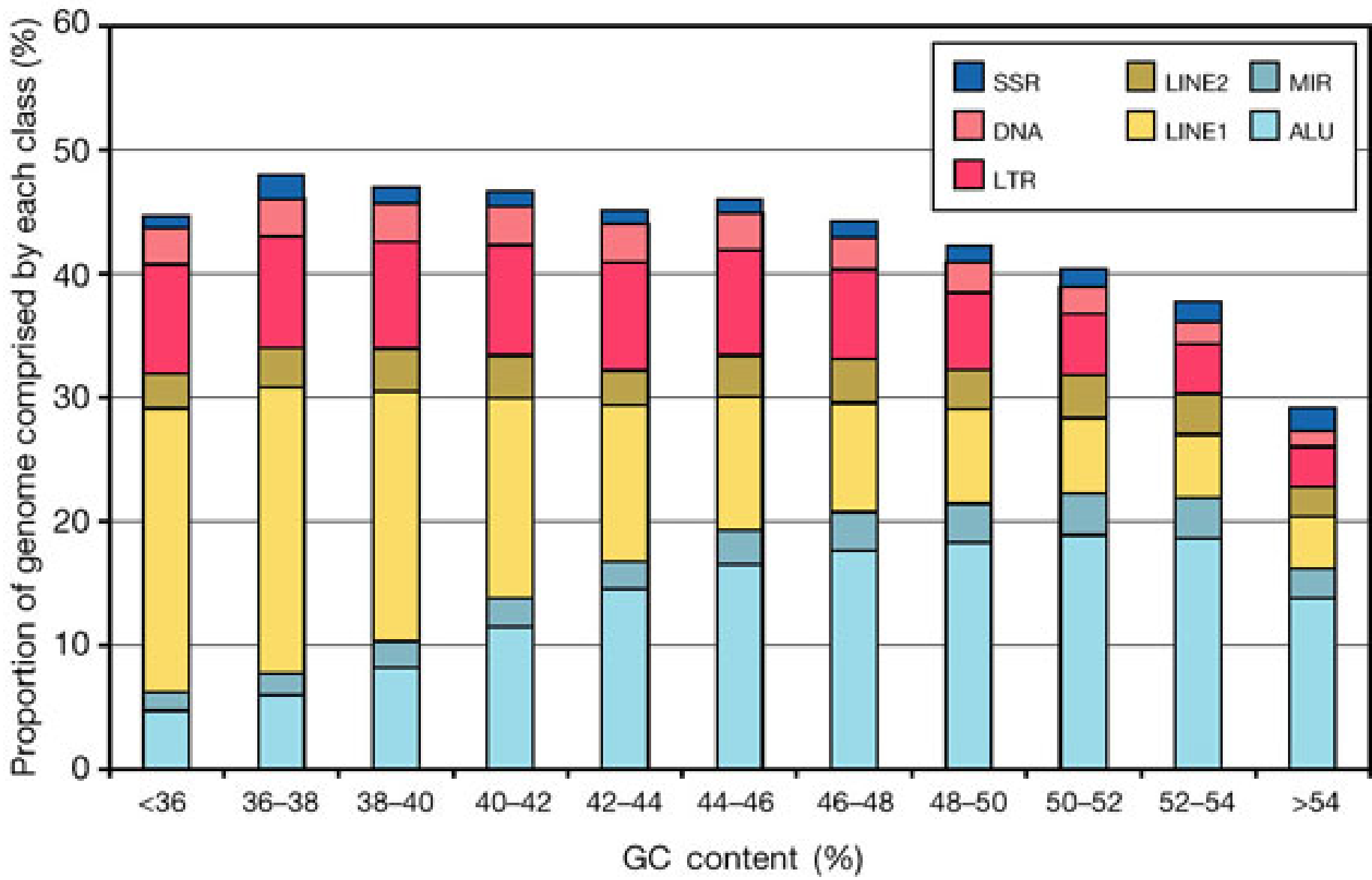
**Table 11 Number of copies and fraction of genome for classes of interspersed repeat**

	Number of copies (× 1,000)	Total number of bases in the draft genome sequence (Mb)	Fraction of the draft genome sequence (%)	Number of families (subfamilies)
SINEs	1,558	359.6	13.14	
Alu	1,090	290.1	10.60	1 (~20)
MIR	393	60.1	2.20	1 (1)
MIR3	75	9.3	0.34	1 (1)
LINEs	868	558.8	20.42	
LINE1	516	462.1	16.89	1 (~55)
LINE2	315	88.2	3.22	1 (2)
LINE3	37	8.4	0.31	1 (2)
LTR elements	443	227.0	8.29	
ERV-class I	112	79.2	2.89	72 (132)
ERV(K)-class II	8	8.5	0.31	10 (20)
ERV (L)-class III	83	39.5	1.44	21 (42)
MaLR	240	99.8	3.65	1 (31)
DNA elements	294	77.6	2.84	
hAT group				
MER1-Charlie	182	38.1	1.39	25 (50)
Zaphod	13	4.3	0.16	4 (10)
Tc-1 group				
MER2-Tigger	57	28.0	1.02	12 (28)
Tc2	4	0.9	0.03	1 (5)
Mariner	14	2.6	0.10	4 (5)
PiggyBac-like	2	0.5	0.02	10 (20)
Unclassified	22	3.2	0.12	7 (7)
Unclassified	3	3.8	0.14	3 (4)
Total interspersed repeats		1,226.8	44.83	

.....  
 The number of copies and base pair contributions of the major classes and subclasses of

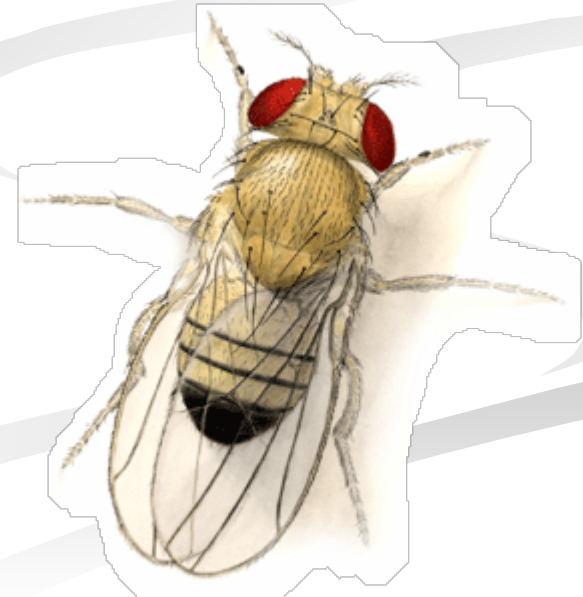
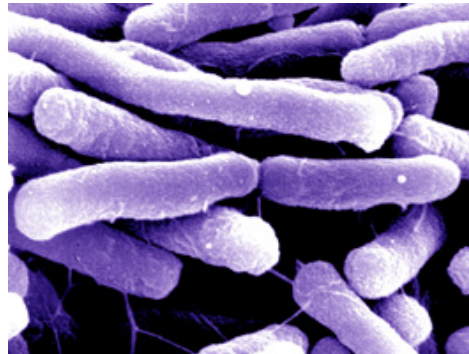
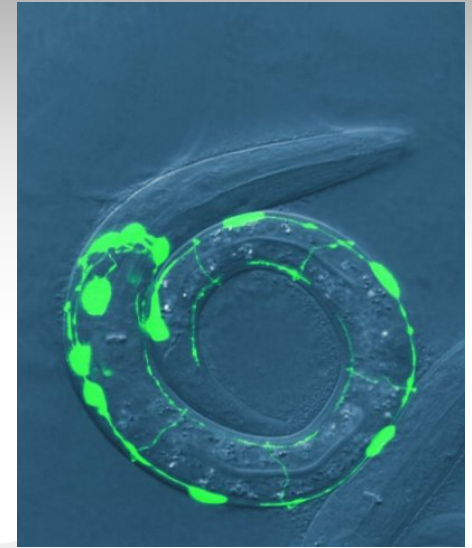


# Hustota hlavných tried repetícií ako funkcia obsahu GC párov



# Počet g3nov u rozli3n3ch organizm3v

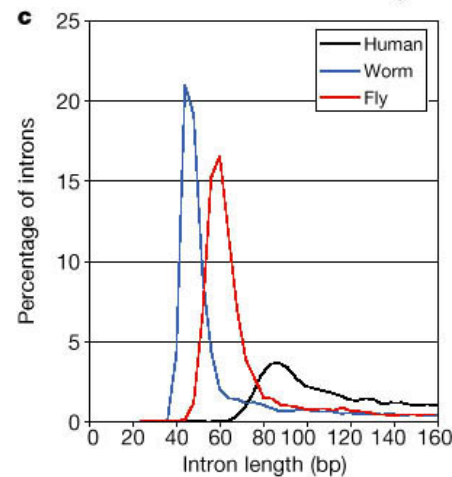
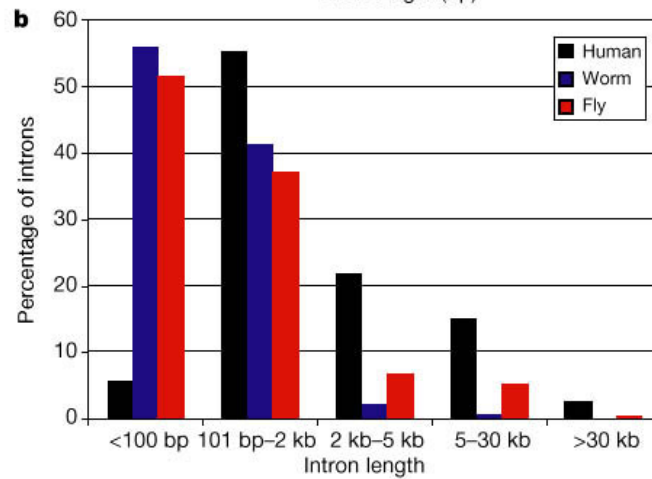
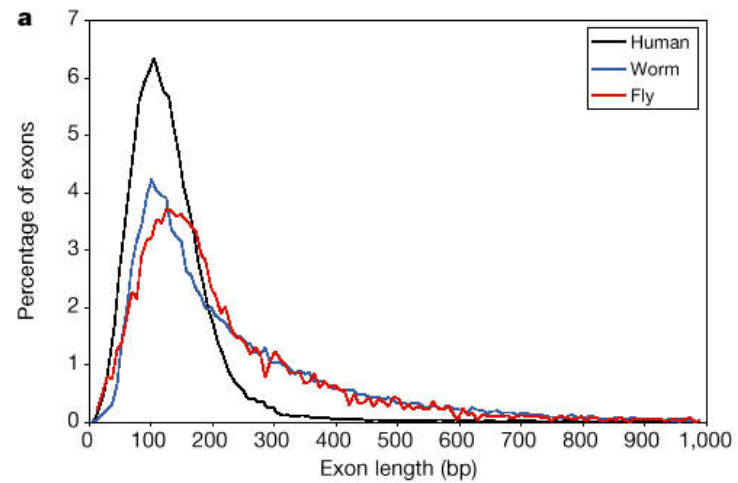
- **3lovek**  
okolo 25 000
- ***Caenorhabditis elegans***  
okolo 20 000
- ***Drosophila melanogaster***  
14 000
- ***E. coli***  
okolo 6000



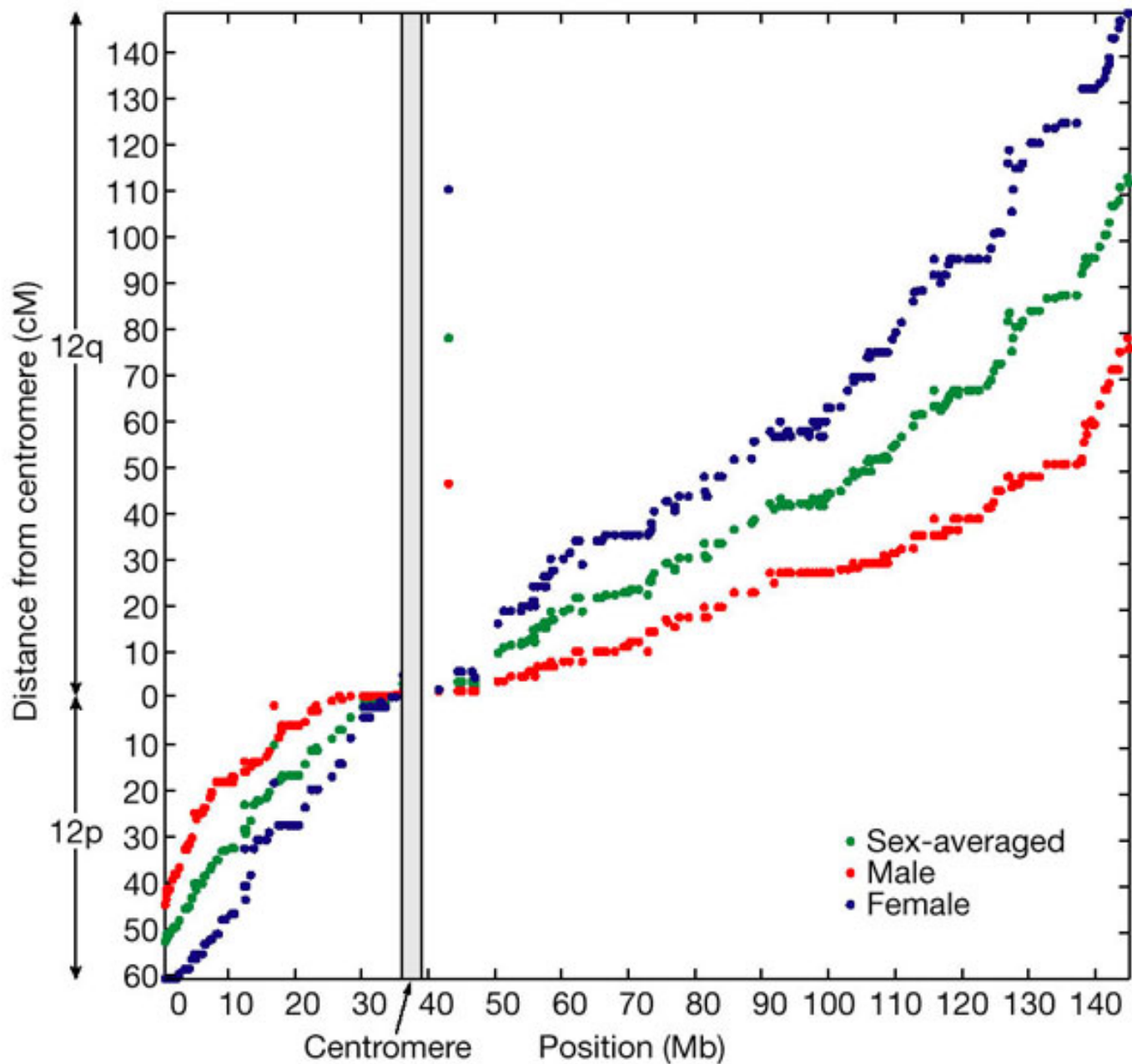
# Dížková distribúcia (človek, drozofila, C. e.):

exónov:

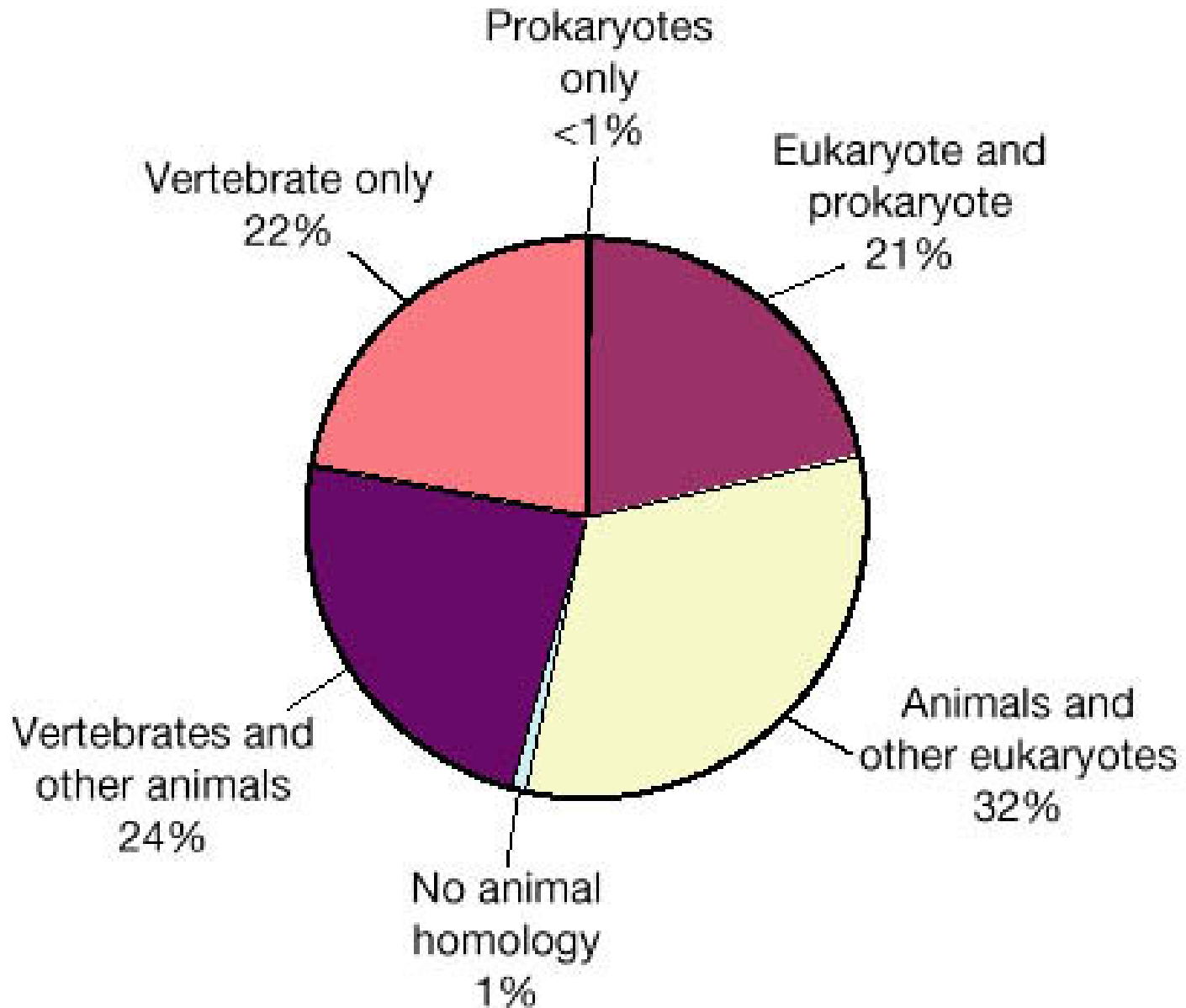
intrónov:



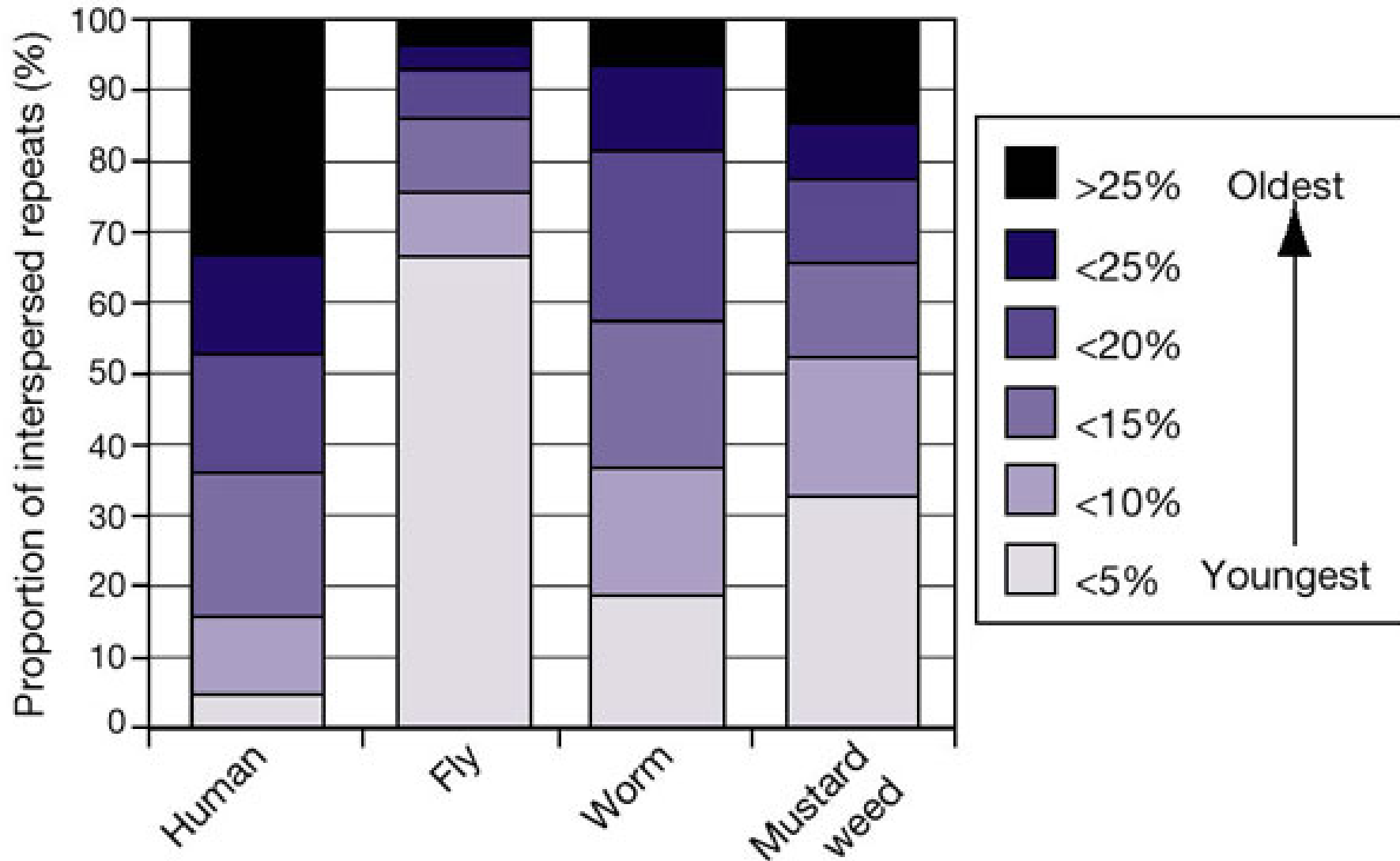
# Chromozóm 12: Mb / cM



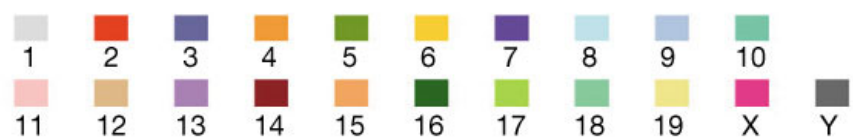
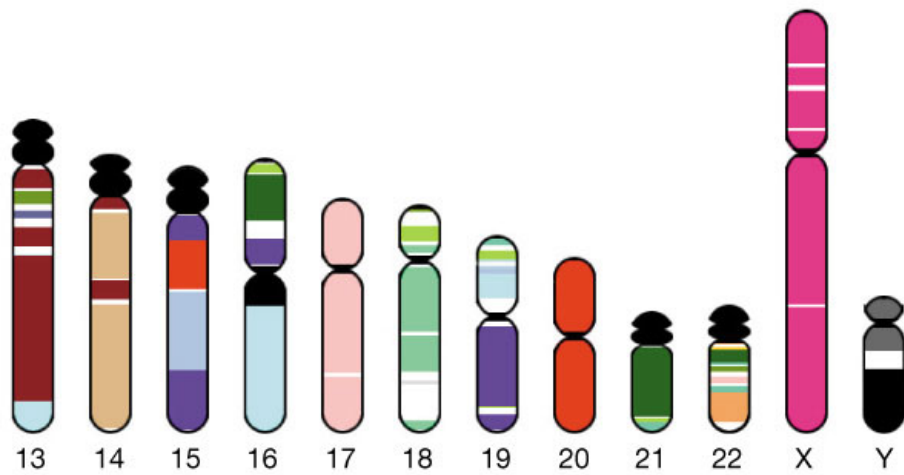
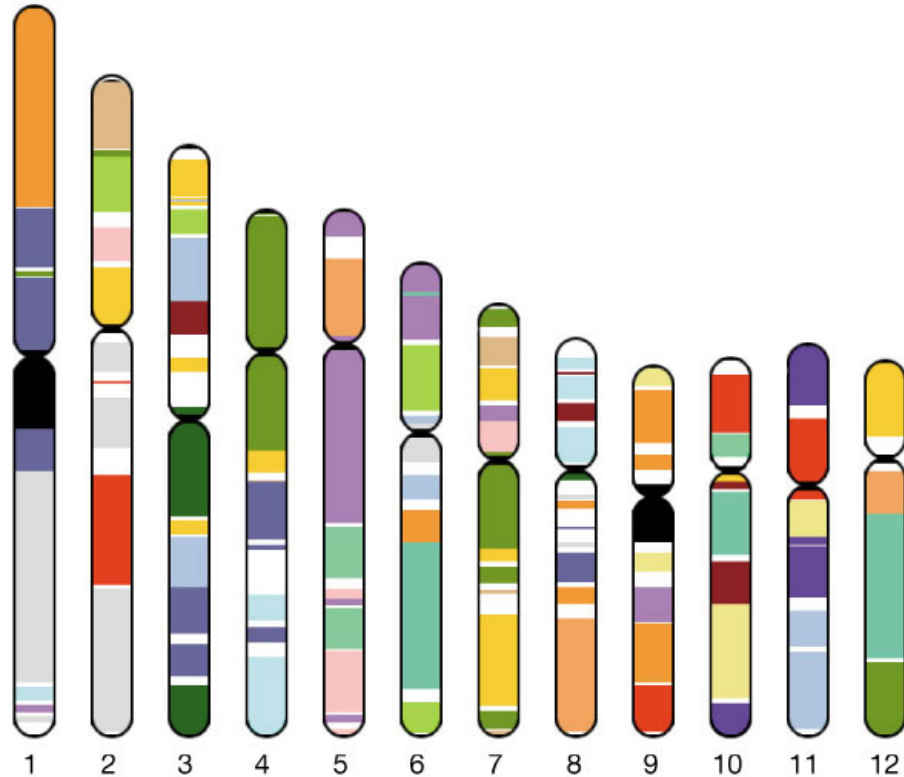
# Distribúcia homológov ľudských proteínov



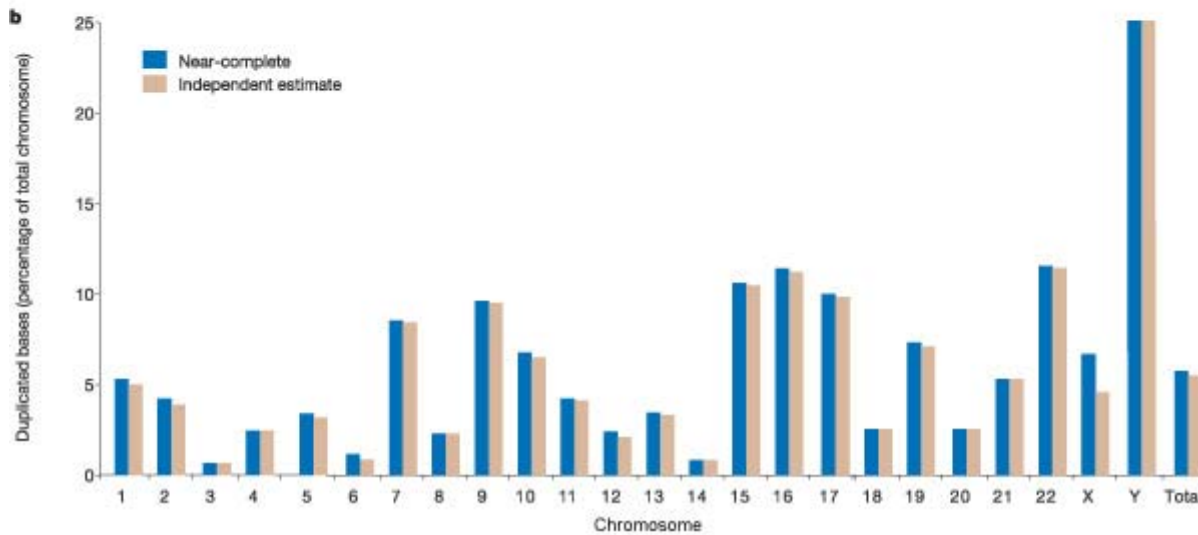
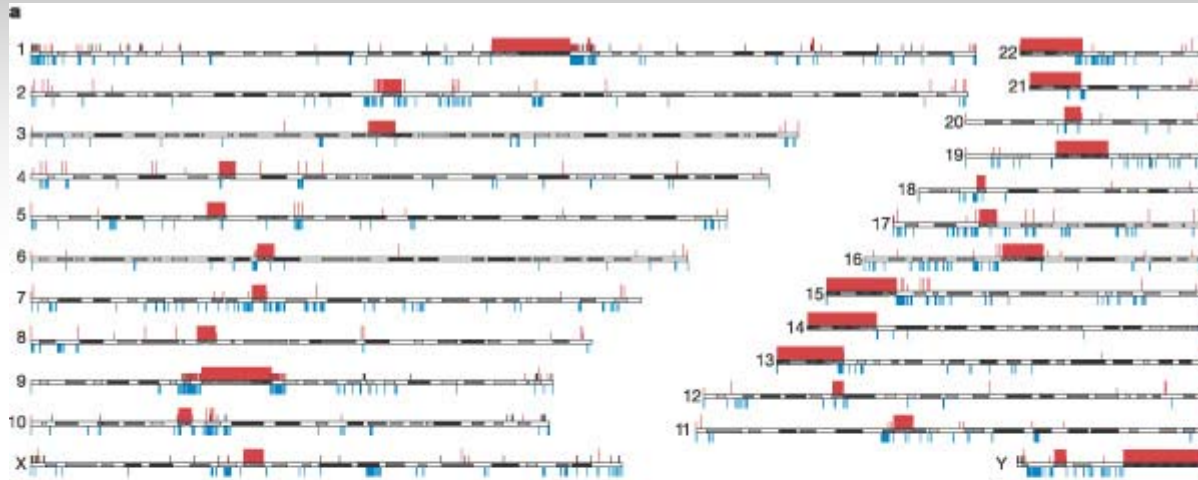
# Evolučný vek rozptýlených repetícií v eukaryo- genóмоch



# Konzervované segmenty ľudského a myšieho genómu



# Segmentové duplikácie v ľudskom genóme





# Pozične klonované gény s využitím HGP sekvencie

**Table 26 Disease genes positionally cloned using the draft genome sequence**

Locus	Disorder	Reference(s)
<i>BRCA2</i>	Breast cancer susceptibility	55
<i>AIRE</i>	Autoimmune polyglandular syndrome type 1 (APS1 or APECED)	389
<i>PEX1</i>	Peroxisome biogenesis disorder	390, 391
<i>PDS</i>	Pendred syndrome	392
<i>XLP</i>	X-linked lymphoproliferative disease	393
<i>DFNA5</i>	Nonsyndromic deafness	394
<i>ATP2A2</i>	Darier's disease	395
<i>SEDL</i>	X-linked spondyloepiphyseal dysplasia tarda	396
<i>WISP3</i>	Progressive pseudorheumatoid dysplasia	397
<i>CCM1</i>	Cerebral cavernous malformations	398, 399
<i>COL11A2/DFNA13</i>	Nonsyndromic deafness	400
<i>LGMD 2G</i>	Limb-girdle muscular dystrophy	401
<i>EVC</i>	Ellis-Van Creveld syndrome, Weyer's acrodistal dysostosis	402
<i>ACTN4</i>	Familial focal segmental glomerulosclerosis	403
<i>SCN1A</i>	Generalized epilepsy with febrile seizures plus type 2	404
<i>AASS</i>	Familial hyperlysinaemia	405
<i>NDRG1</i>	Hereditary motor and sensory neuropathy-Lom	406
<i>CNGB3</i>	Total colour-blindness	407, 408
<i>MUL</i>	Mulibrey nanism	409
<i>USH1C</i>	Usher type 1C	410, 411
<i>MYH9</i>	May-Hegglin anomaly	412, 413
<i>PRKAR1A</i>	Carney's complex	414
<i>MYH9</i>	Nonsyndromic hereditary deafness DFNA17	415
<i>SCA10</i>	Spinocerebellar ataxia type 10	416
<i>OPA1</i>	Optic atrophy	417
<i>XLCSNB</i>	X-linked congenital stationary night blindness	418
<i>FGF23</i>	Hypophosphataemic rickets	419
<i>GAN</i>	Giant axonal neuropathy	420
<i>AAAS</i>	Triple-A syndrome	421
<i>HSPG2</i>	Schwartz-Jampel syndrome	422

# HGP: možnosti využitia

- Etiológia genetických a nádorových ochorení
- Diagnostika monogénnych a nádorových ochorení
- Diagnostika multifaktoriálnych ochorení
- Génová terapia (genetických a nádorových ochorení)
- Cielená liečba („molekulárna farmakológia“)
- Štúdium biologických funkcií na molekulárnej úrovni (diferenciácia, starnutie ...)
- Evolúcia človeka a pôvod ľudských populácií
- **Nosce te ipsum:** podstatný krok k poznaniu biológie nášho druhu
- Podstatná časť práce je ešte len pred nami