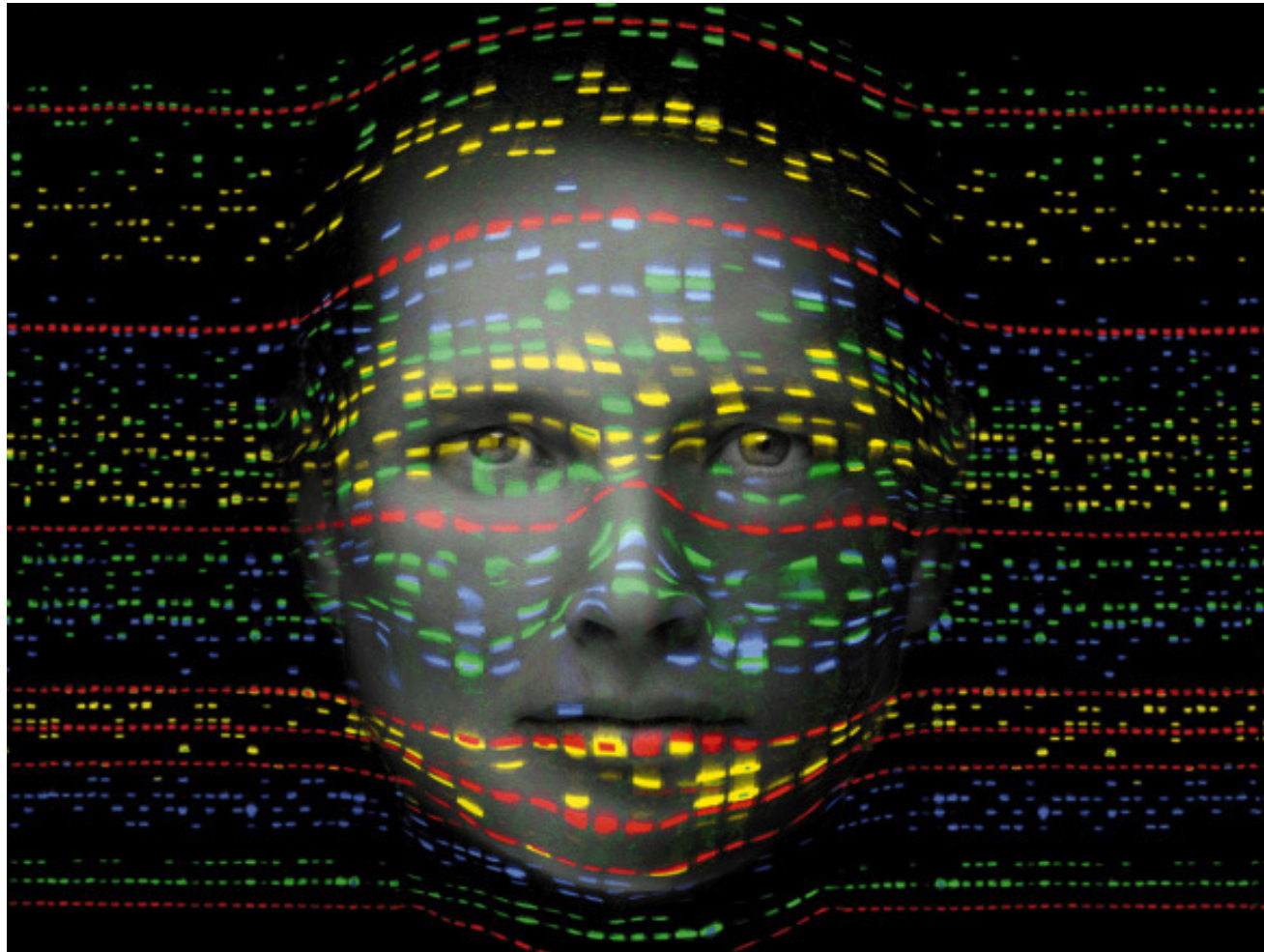


GENOMIKA

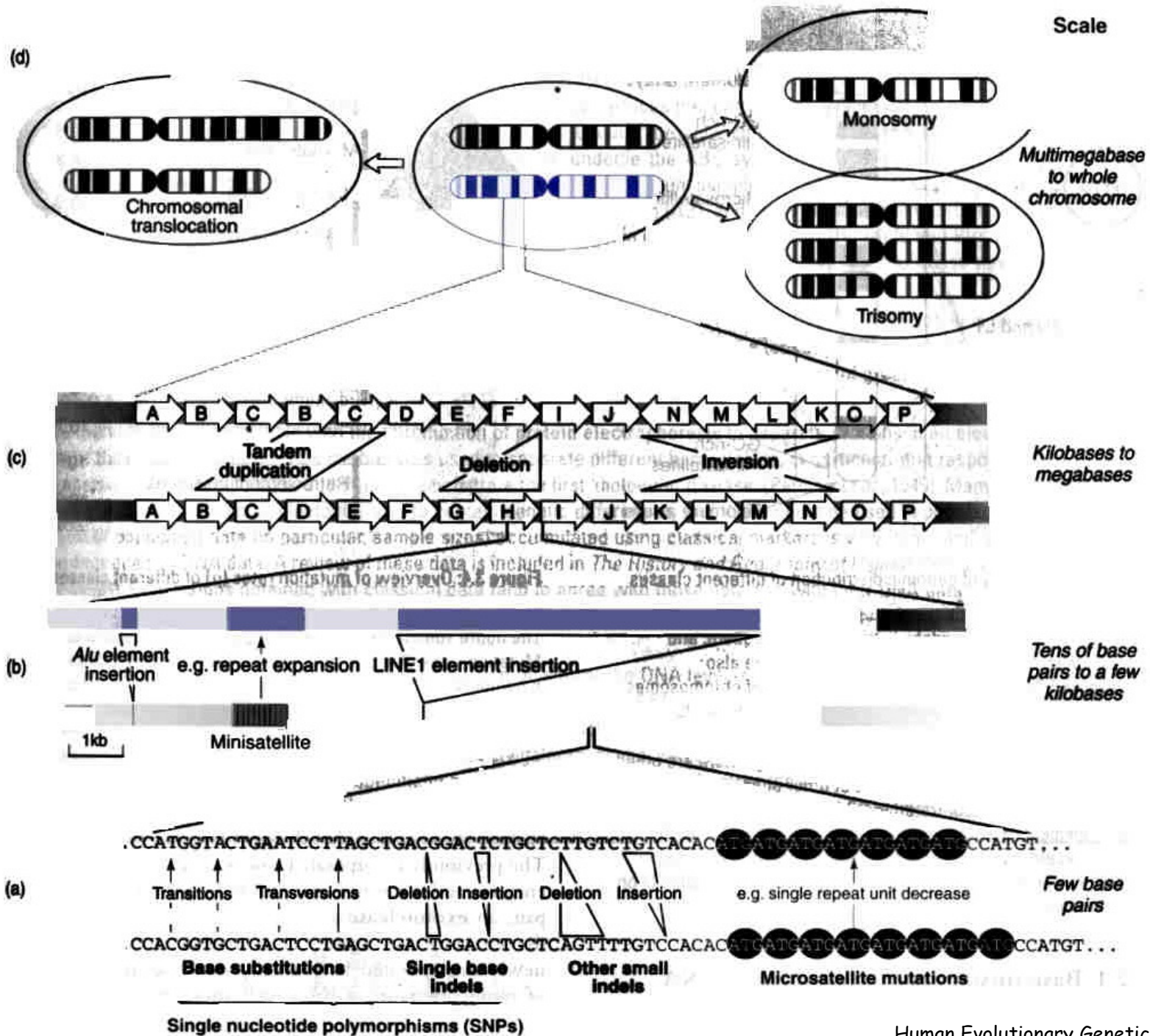
Genetikai polimorfizmusok



ELTE TTK Genetikai Tanszék

A humán genom projekt eredményei

- Előzetes publikálás 2001-ben (Science, Nature)
- Az eddig leírt legnagyobb méretű teljes genom (~ 2900 Mb)
- Az eukarióta genomra jellemző szerkezeti és szerveződési tulajdonságok (modellszervezetek)
- Meglepően alacsony a fehérje kódoló gének száma (22000 - 24000)
- RNS gének növekvő száma (tRNA, snRNA, miRNA, stb.)
- Orphan gének: nincs homológja, humán gének ~ 1/3-a
- Nem kódoló, repetitív szekvenciák túlnyomó aránya



DNS molekula szekvenciális változása: polimorfizmusok

(A) Pontmutációk: szubsztitúció, inzerció/delécio → szekvencia polimorfizmus → single nucleotide polymorphism

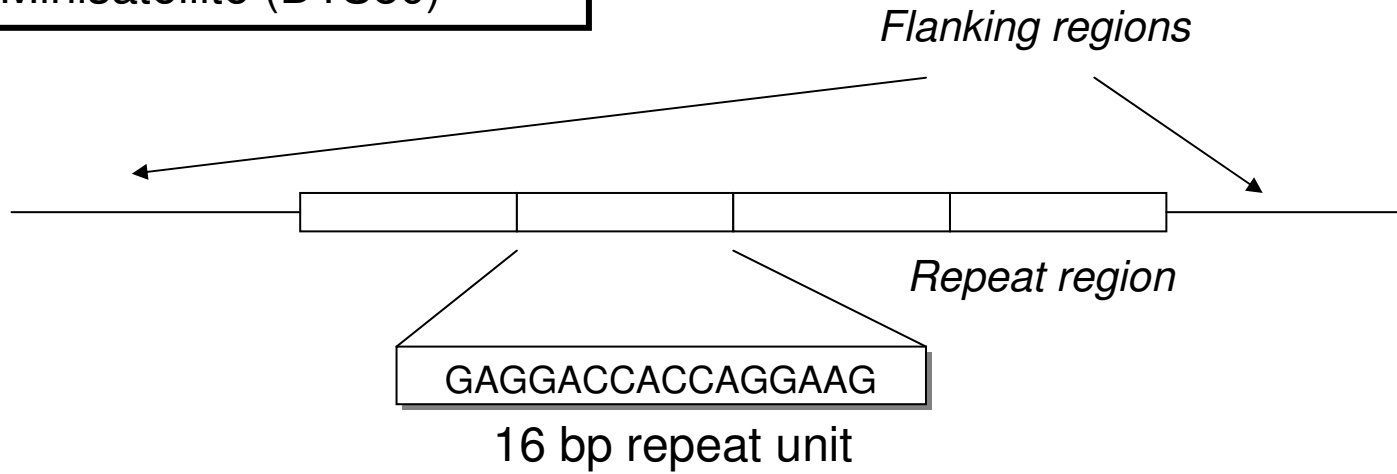
-----AGACTAGACATT-----
-----AGATTAG_CATT-----
SNPs

(B) Szekvencia ismétlődések: szatellit DNS, repetitív szekvenciák → hosszpolimorfizmus → short tandem repeats

-----(AATG)(AATG)(AATG)-----
-----(AATG)(AATG)-----
STRs

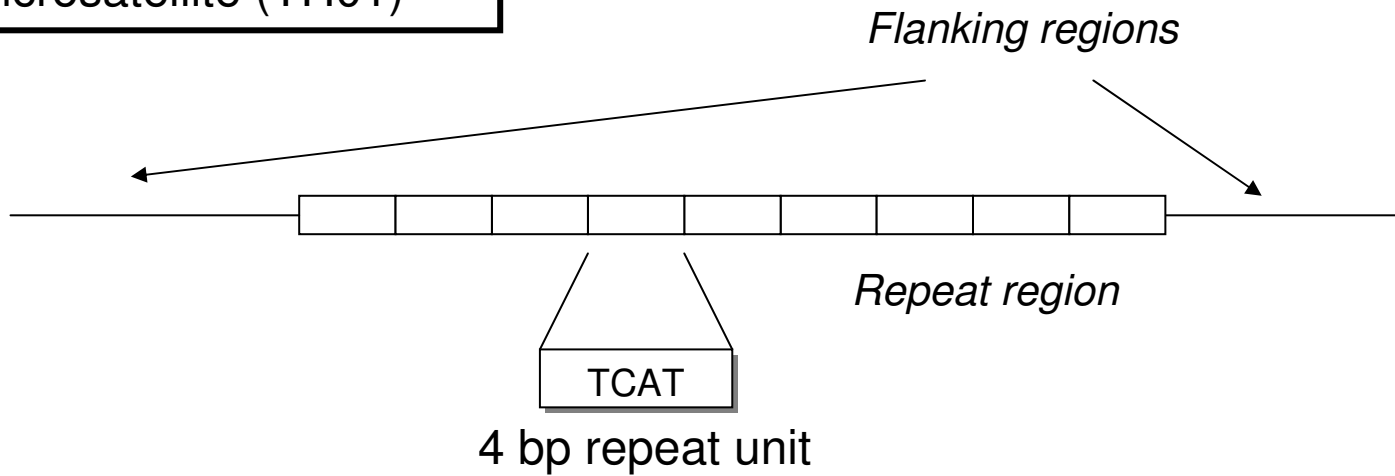
Minisatellite (D1S80)

VNTRs

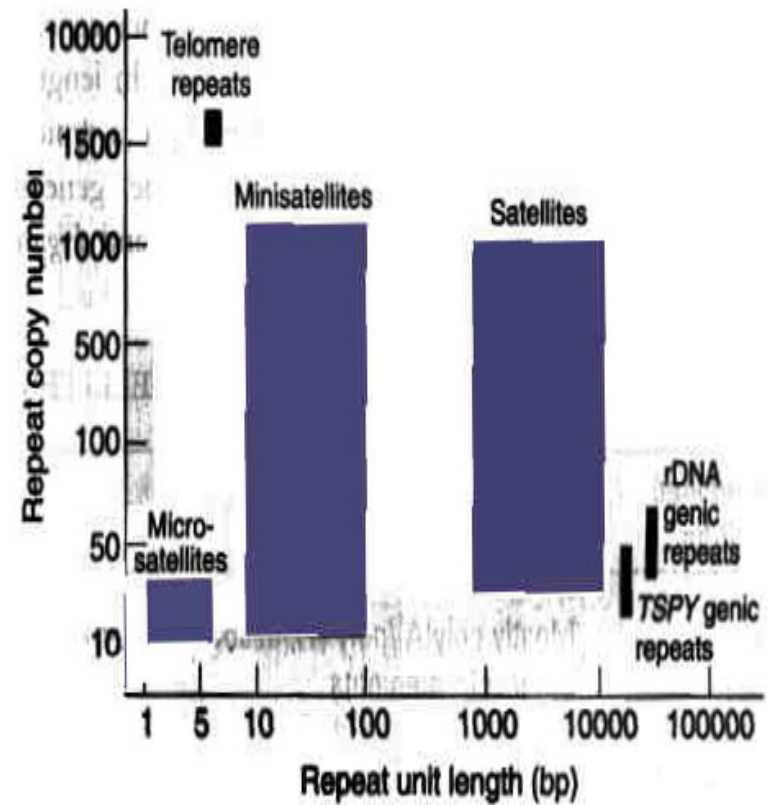
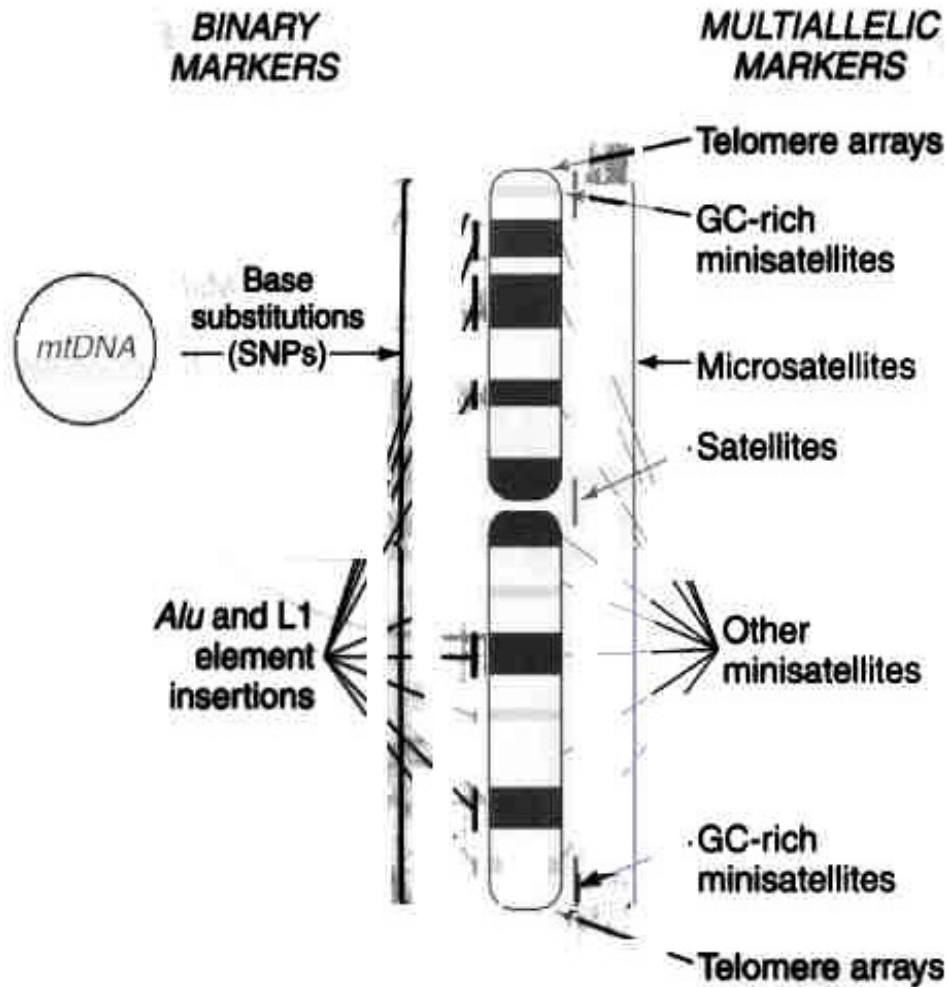


STRs (SSRs)

Microsatellite (TH01)

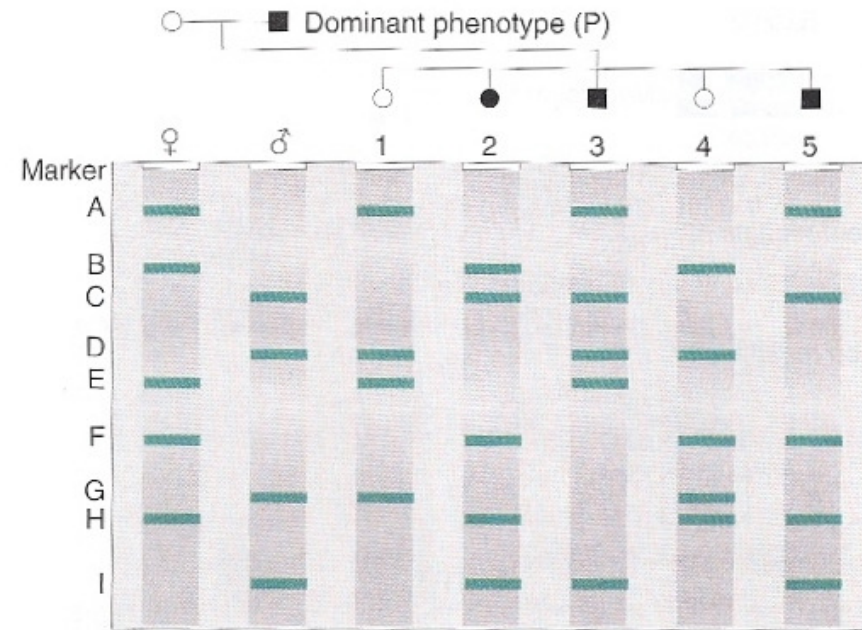
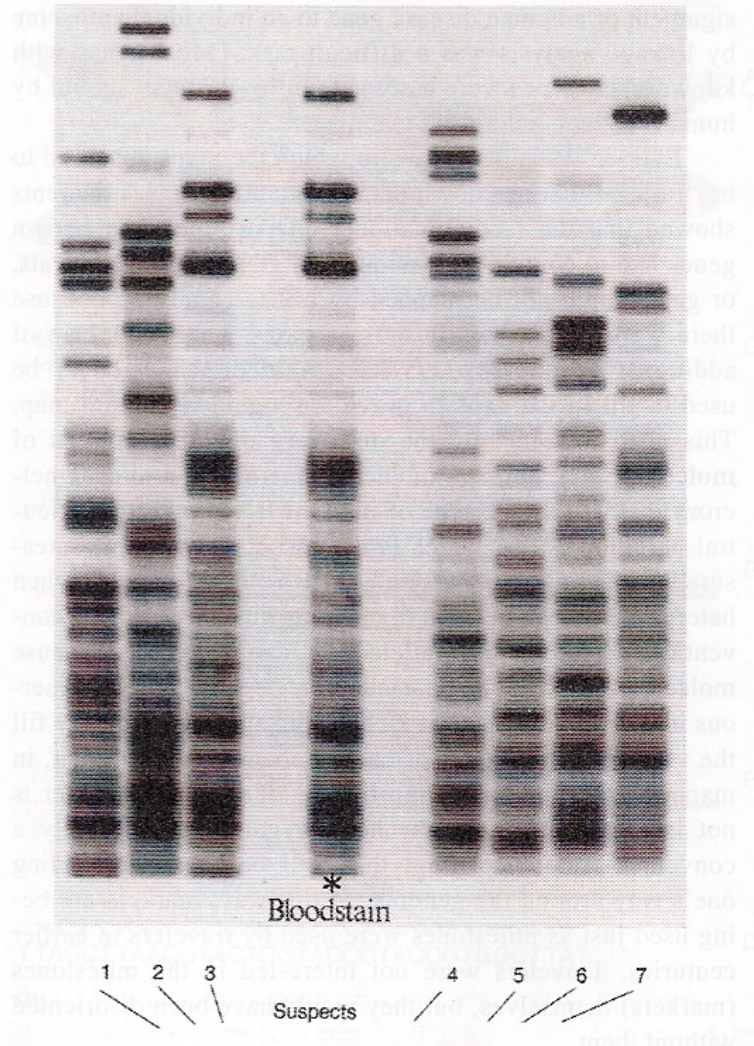


Polimorf markerek eloszlása a genomban



Multi-locus VNTR assay

1985 - Alec Jeffreys



ANALYSIS EXAMPLES

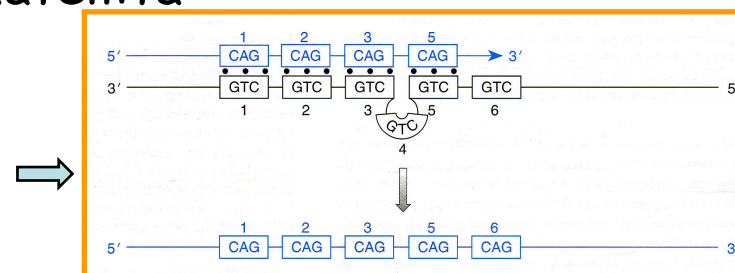
- F and H Always inherited together — linked?
- A and B In progeny, always *either* A or B — "allelic"?
- A and D Four combinations; A and D, A, D, or neither — unlinked?
- F, H, and E Always *either* F and H or E — closely linked in trans?
- Allele P Possibly linked to I and C.

Genetikai térképezés

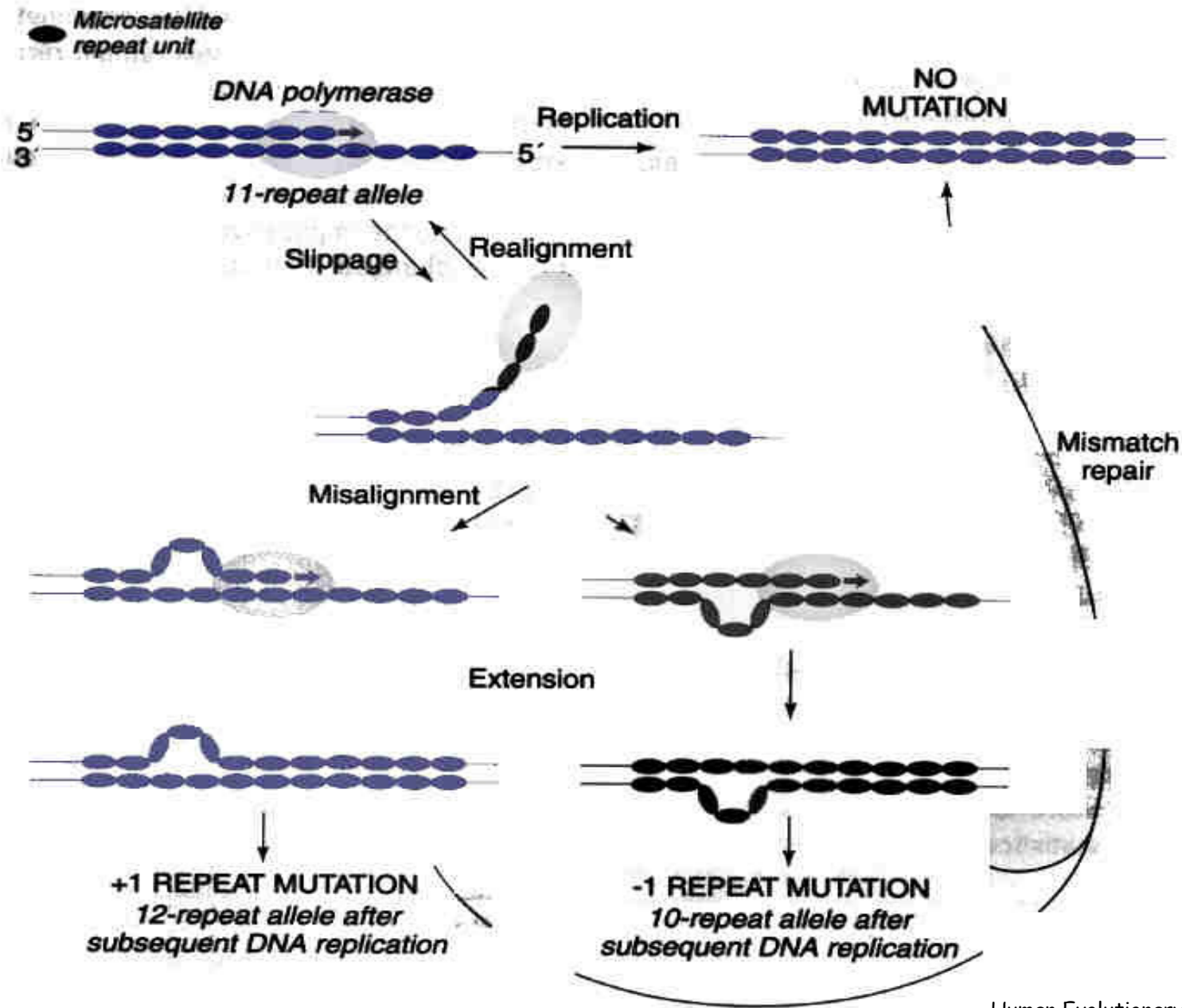
Year	Forensic DNA Science & Application	Parallel Developments in Biotechnology	Microsoft Corporation Chronology
1985	Alec Jeffreys develops multi-locus RFLP probes	PCR process first described	First version of Windows shipped
1986	DNA testing goes public with Cellmark and Lifecodes in United States	Automated DNA sequencing with 4-colors first described	Microsoft goes public
1988	FBI begins DNA casework with single-locus RFLP probes		
1989	TWGDAM established; NY v. Castro case raises issues over quality assurance of laboratories	DNA detection by gel silver-staining, slot blot, and reverse dot blots first described	
1990	Population statistics used with RFLP methods are questioned; PCR methods start with DQA1	Human Genome Project begins with goal to map all human genes	Windows 3.0 released (quality problems); exceeds \$1 billion in sales
1991	Fluorescent STR markers first described; Chelex extraction		Windows 3.1 released
1992	NRC I Report; FBI starts casework with PCR-DQA1	Capillary arrays first described	
1993	First STR kit available; sex-typing (amelogenin) developed	First STR results with CE	
1994	Congress authorizes money for upgrading state forensic labs; 'DNA wars' declared over; FBI starts casework with PCR-PM	Hitachi FMBIO and Molecular Dynamics gel scanners; first DNA results on microchip CE	

Mikroszatellita (STR) mint DNS marker

- 1980 – első humán RFLP marker: D14S1 – miniszatellita
- 1991 – első humán STR markerek (SSRs)
- 2-6 bázispárból álló szakaszok tandem ismétlődése: di-, tri-, tetra-, penta-, hexamer repeatek: egyszerű, összetett és komplex repeatek
- A humán genomban több ezer mikroszatellita
- Nagyfokú polimorfizmus:
 - pontmutációk
 - inszerciók/deléciónok: slippage
- Igazságügyi és egészségügyi alkalmazás: DNS-profil, genetic mapping, genetic disorders
 - 6-100 allél/lókuszt a humán népességben
 - allélnevezéktan az ismétlődő szakaszok száma szerint
 - a bűnügyi DNS nyilvántartások alapja

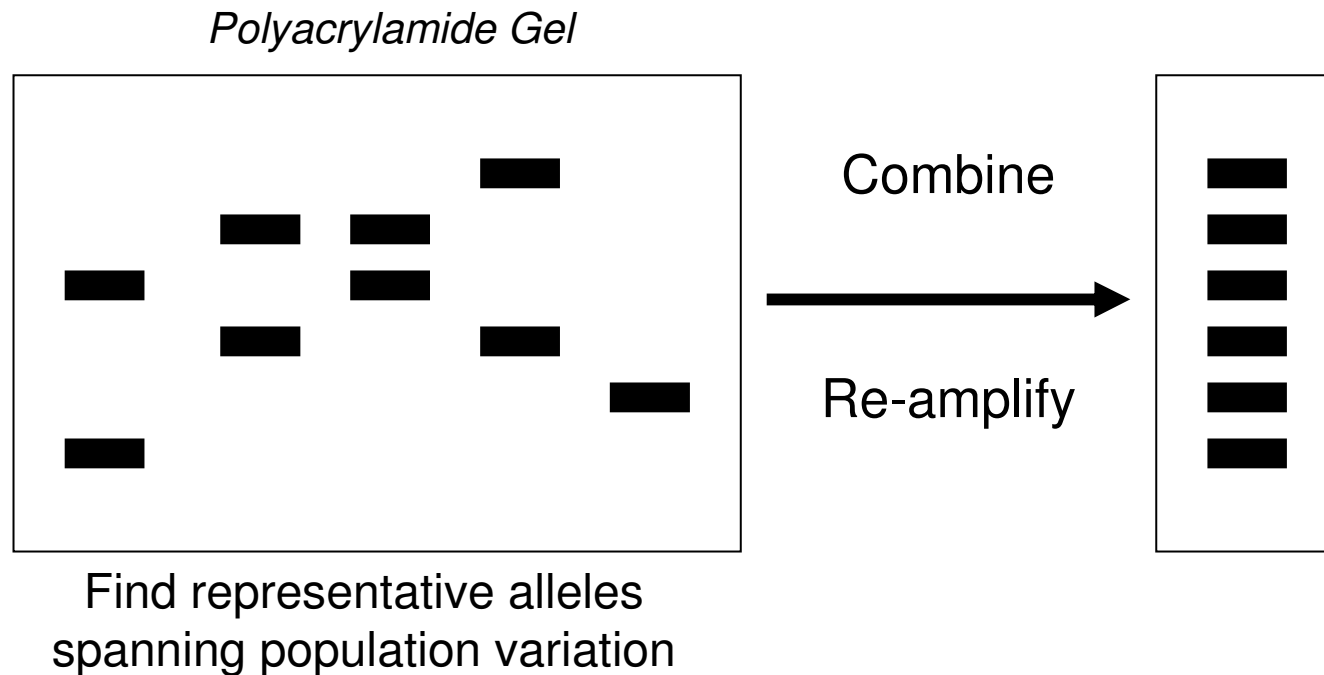


„Slipped Strand Mispairing” - Mikrosatellita polimorfizmus



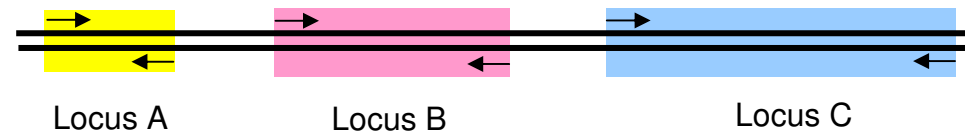
STR allélek genotipizálása, alléllétra

Separate PCR products from various samples amplified with primers targeted to a particular STR locus

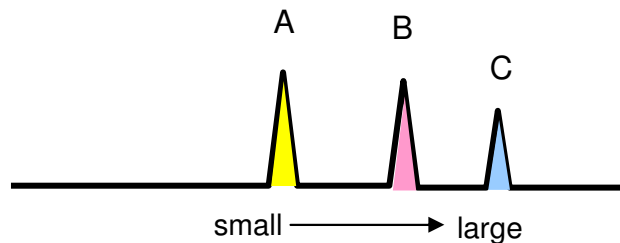


Multiplex - PCR

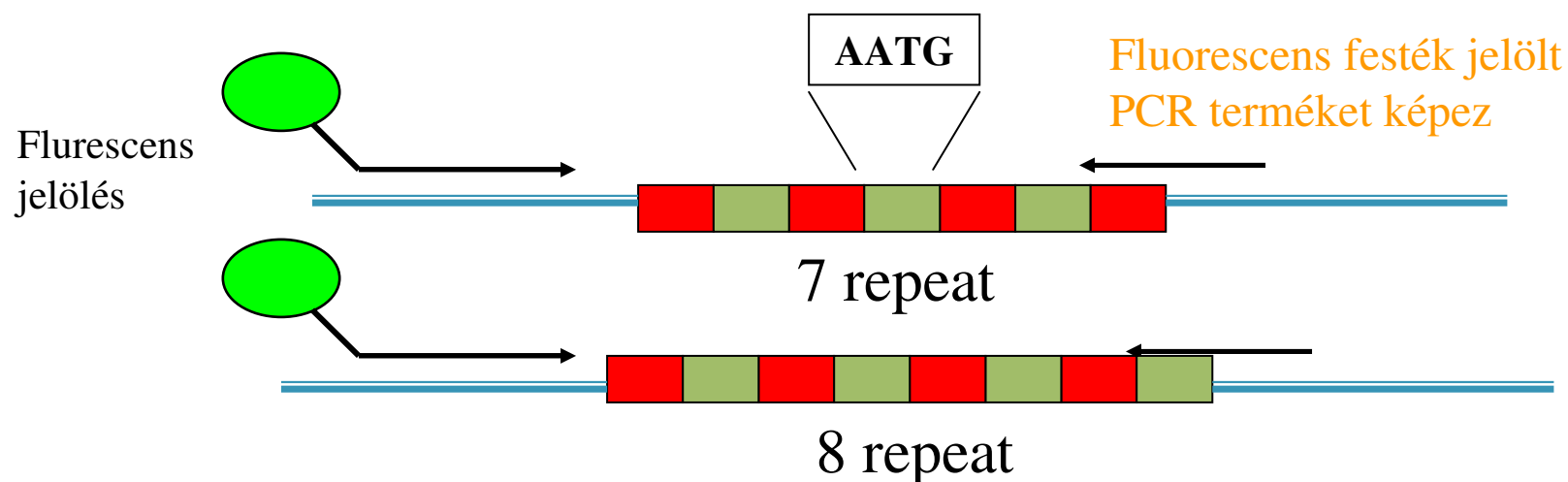
(A) Három lokusz szimultán amplifikálása egy reakcióban



(B) PCR termékek elválasztása fragmens méret alapján



Mikroszatellita - STR - markerek (Short Tandem Repeat)



a repeat régió variábilis az egyes minták között míg a flanking régió ahol a PCR primerek tapadnak állandó

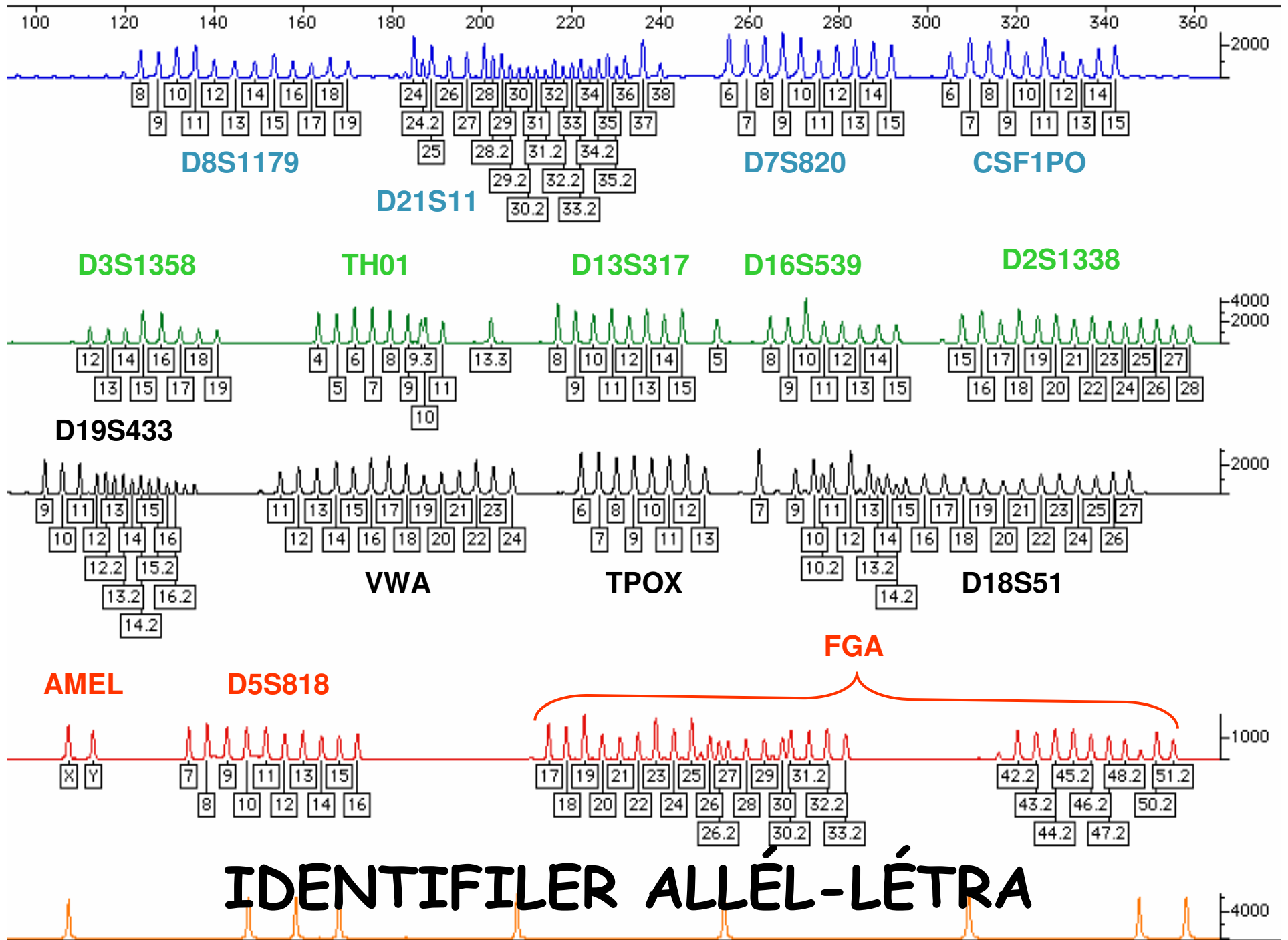
Homozigóta = a két allél megegyezik

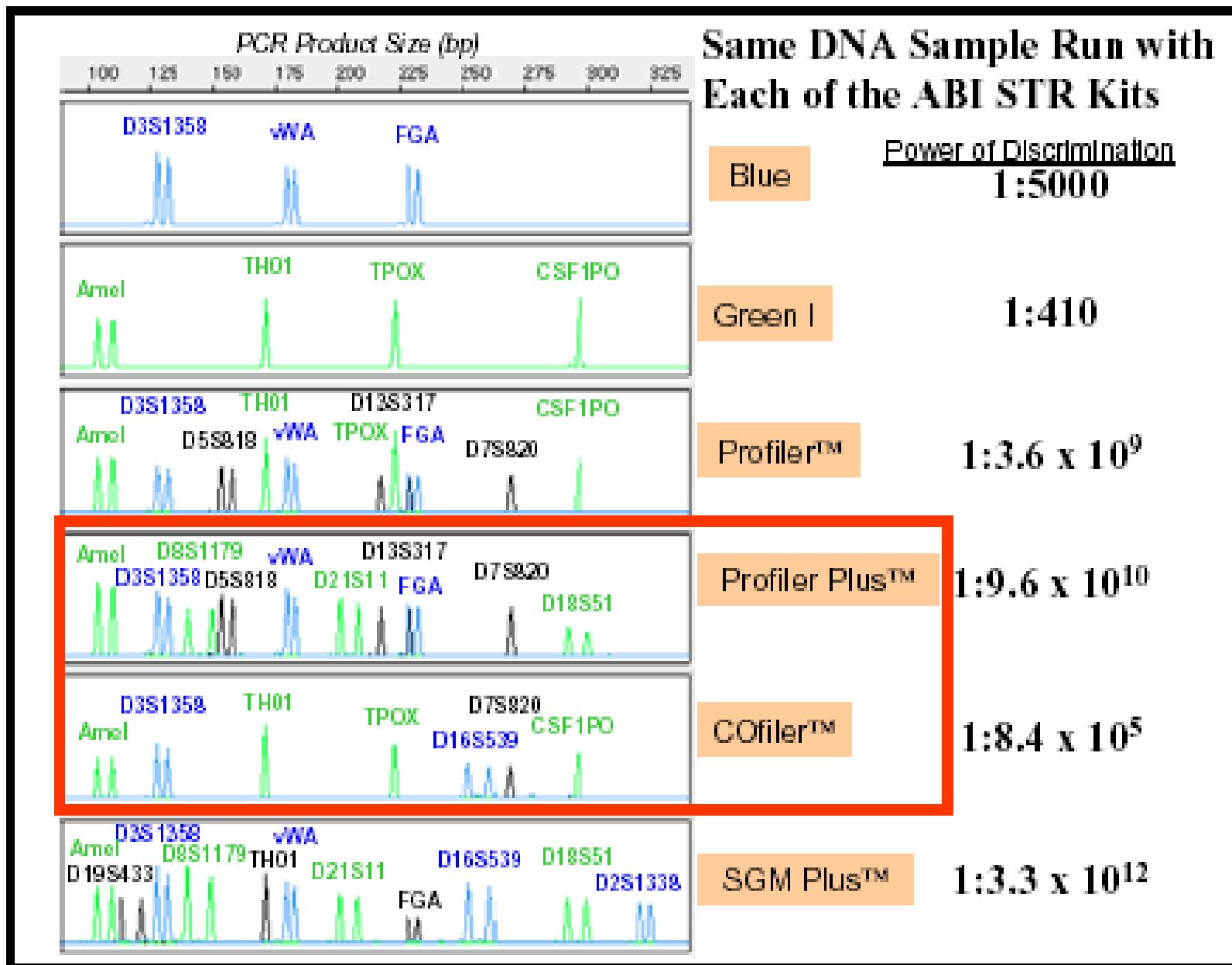
Heterozigóta = allélek különbözők és egymástól elválaszthatók

A primerek kötési helye meghatározza a PCR termék méretét!



ABI PRISM
3100 Capillary Array
36 cm Part No. 4315931
Serial No. 33D01257





Mikroszatellita pontmutációk

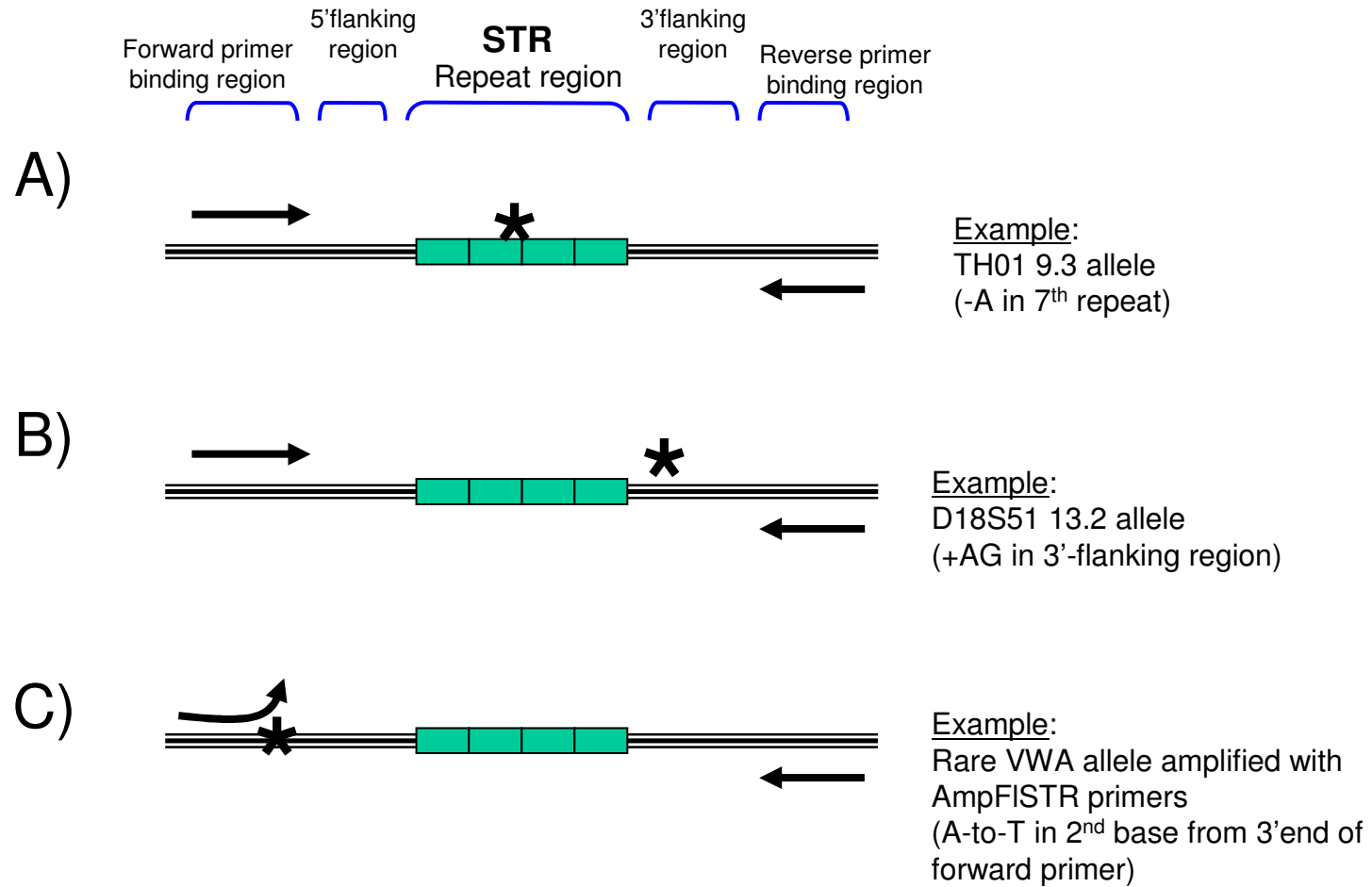
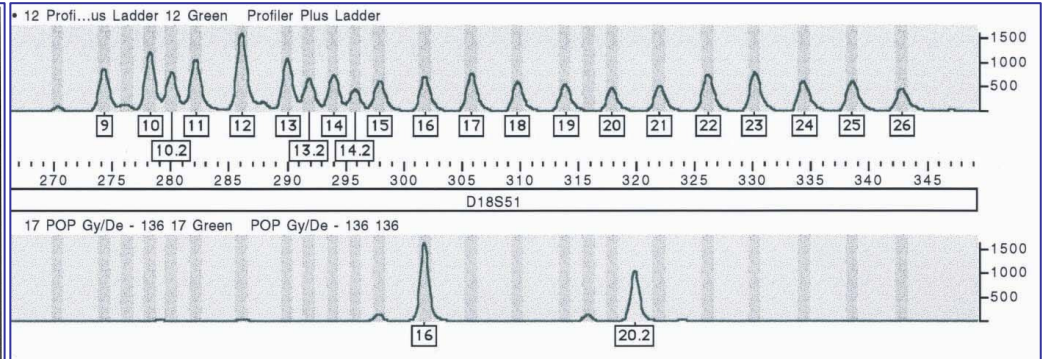
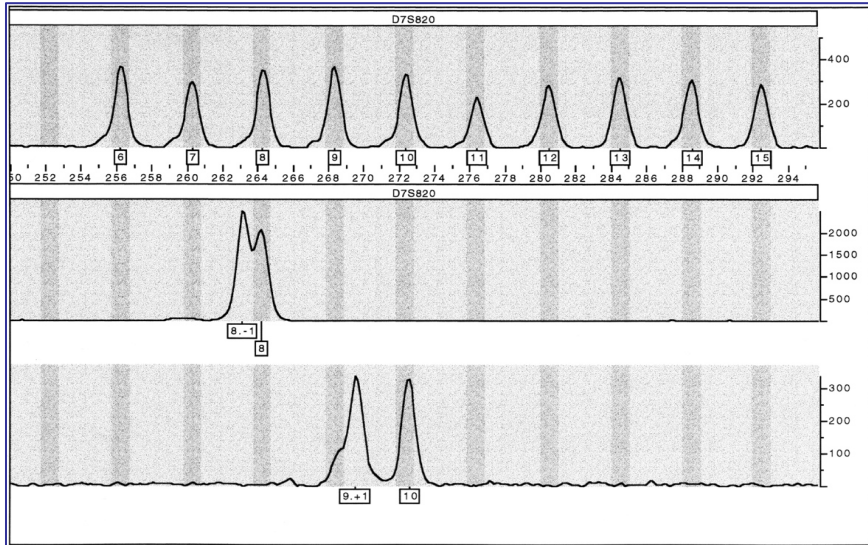


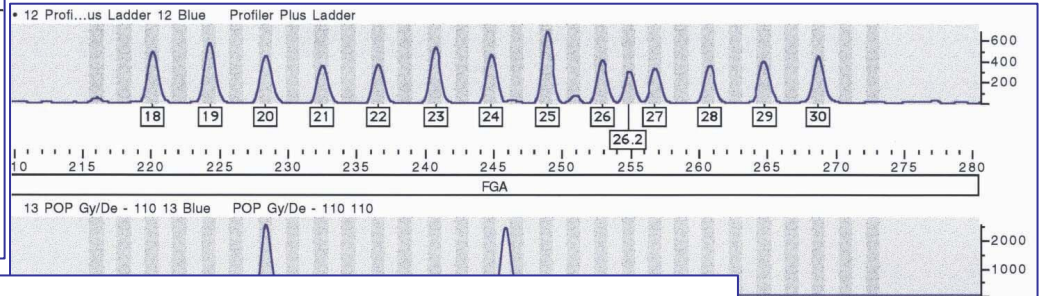
Figure 6.8, J.M. Butler (2005) *Forensic DNA Typing*, 2nd Edition © 2005 Elsevier Academic Press

Mikrovariáns mikroszatellita allélek



Allél	Fragmenthossz	5' flanking régió	Repeat régió	3' flanking régió
16	299 bp	██████████	- (AGAA) ₁₆ -	ΔΔAG AGAGAG - ██████████
20.2	317 bp	██████████	- (AGAA) ₂₁ -	AG AGAGAG - ██████████
15*	295 bp	██████████	- (ATAG) ₁₅ -	AAAG AGAGAG - ██████████

Allél	Fragsmens méret	5' Flanking régió	Repeat régió	3' Flanking régió
8.-1	205 bp	██████████	-(GATA) ₈ -	██████████ - (T) ₈ ATCT -
9.+1	211 bp	██████████	-(GATA) ₉ -	██████████ - (T) ₁₀ ATCT -
10	214 bp	██████████	-(GATA) ₁₀ -	██████████ - (T) ₈ AATCT -
12 (ref.)	222 bp	██████████	-(GATA) ₁₂ -	██████████ - (T) ₉ ATCT -
		24 bp		13 bp 124 bp

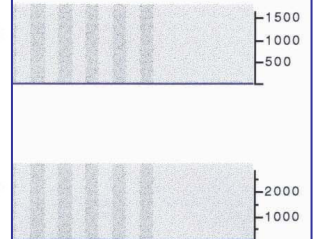


D13S317 allele 12

5'-gggttgctggacatggtatcACAGAAGTCTGGGATGTGGA---N82---(ATCT)₁₂ATCAATC(ATCT)₃TTCTGTCTGTCTTTTTGGGC---N36---gaccaacaattcaagctctc-3'

D13S317 allele 7 (variant)

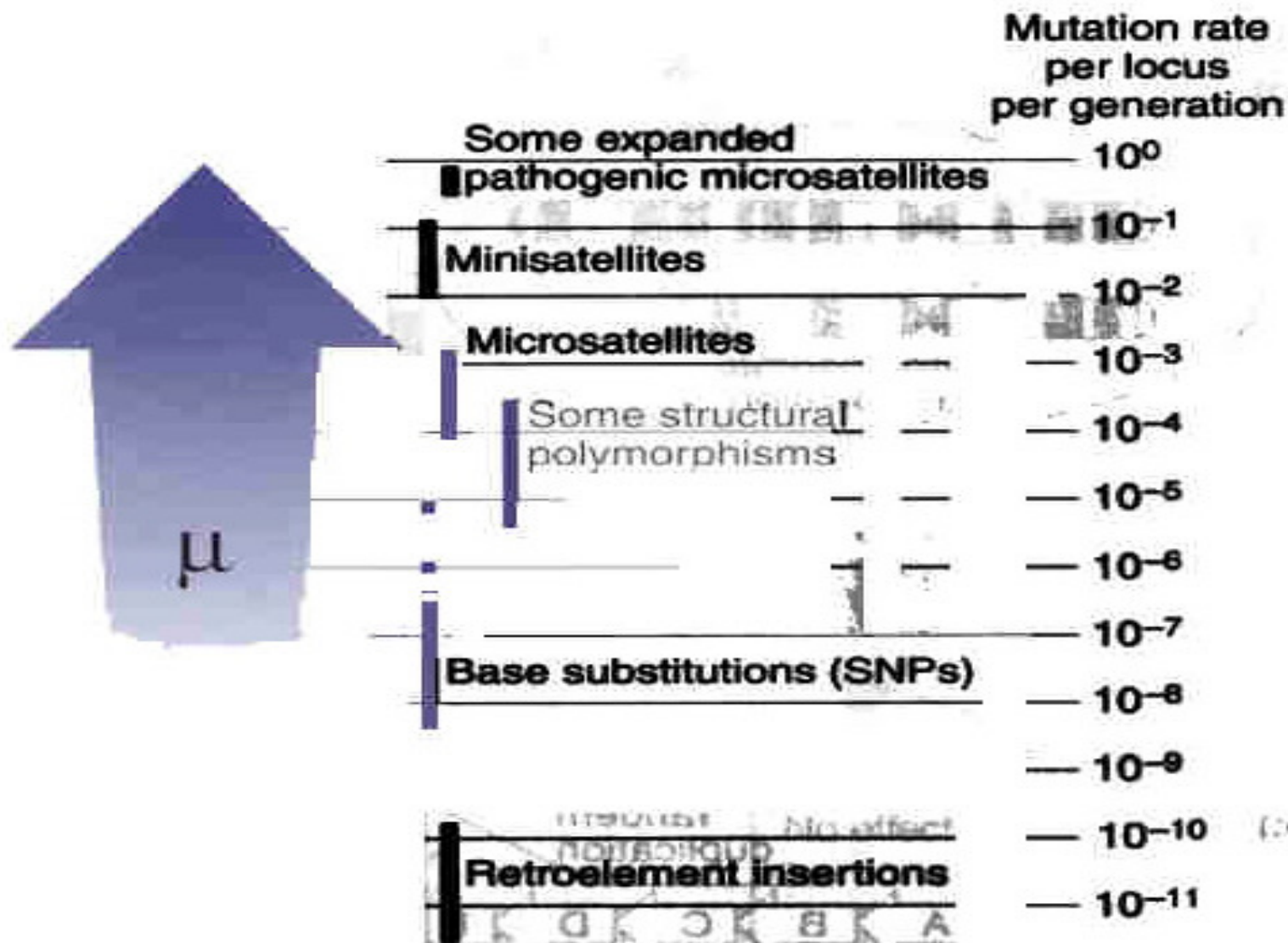
5'-gggttgctggacatggtatcACAGAAGTCTGGGATGTGGA---N82---(ATCT)₇ATCAATCAATC(ATCT)₃TTCTGTCTTTTTGGGC---N36---gaccaacaattcaagctctc-3'



STR System	Maternal Meioses (%)	Paternal Meioses (%)	Number from either	Total Number of Mutations	Mutation Rate
CSF1PO	95/304,307 (0.03)	982/643,118 (0.15)	410	1,487/947,425	0.16%
FGA	205/408,230 (0.05)	2,210/692,776 (0.32)	710	3,125/1,101,006	0.28%
TH01	31/327,172 (0.009)	41/452,382 (0.009)	28	100/779,554	0.01%
TPOX	18/400,061 (0.004)	54/457,420 (0.012)	28	100/857,481	0.01%
VWA	184/564,398 (0.03)	1,482/873,547 (0.17)	814	2,480/1,437,945	0.17%
D3S1358	60/405,452 (0.015)	713/558,836 (0.13)	379	1,152/964,288	0.12%
D5S818	111/451,736 (0.025)	763/655,603 (0.12)	385	1,259/1,107,339	0.11%
D7S820	59/440,562 (0.013)	745/644,743 (0.12)	285	1,089/1,085,305	0.10%
D8S1179	96/409,869 (0.02)	779/489,968 (0.16)	364	1,239/899,837	0.14%
D13S317	192/482,136 (0.04)	881/621,146 (0.14)	485	1,558/1,103,282	0.14%
D16S539	129/467,774 (0.03)	540/494,465 (0.11)	372	1,041/962,239	0.11%
D18S51	186/296,244 (0.06)	1,094/494,098 (0.22)	466	1,746/790,342	0.22%
D21S11	464/435,388 (0.11)	772/526,708 (0.15)	580	1,816/962,096	0.19%
Penta D	12/18,701 (0.06)	21/22,501 (0.09)	24	57/41,202	0.14%
Penta E	29/44,311 (0.065)	75/55,719 (0.135)	59	163/100,030	0.16%
D2S1338	15/72,830 (0.021)	157/152,310 (0.10)	90	262/225,140	0.12%
D19S433	38/70,001 (0.05)	78/103,489 (0.075)	71	187/173,490	0.11%
SE33 (ACTBP2)	0/330 (<0.30)	330/51,610 (0.64)	None reported	330/51,940	0.64%

STR lókuszok mutációs rátája: 10^{-3} - 10^{-4} / meiózis

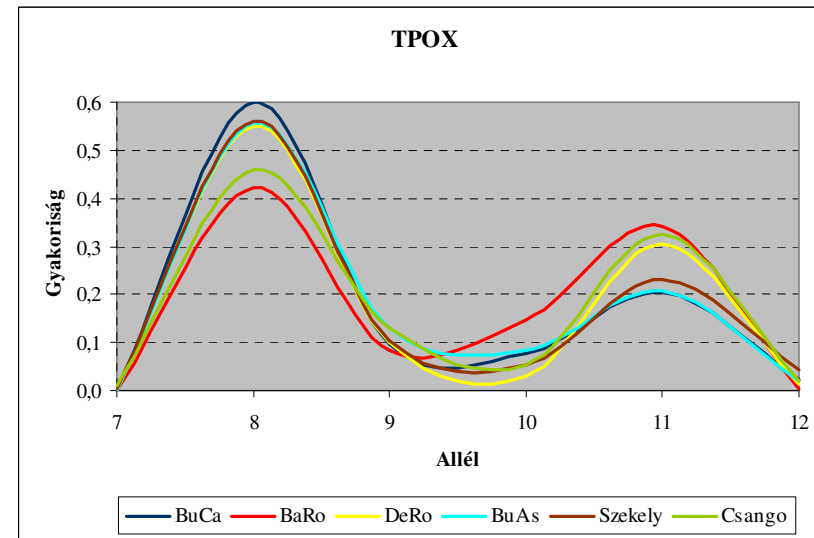
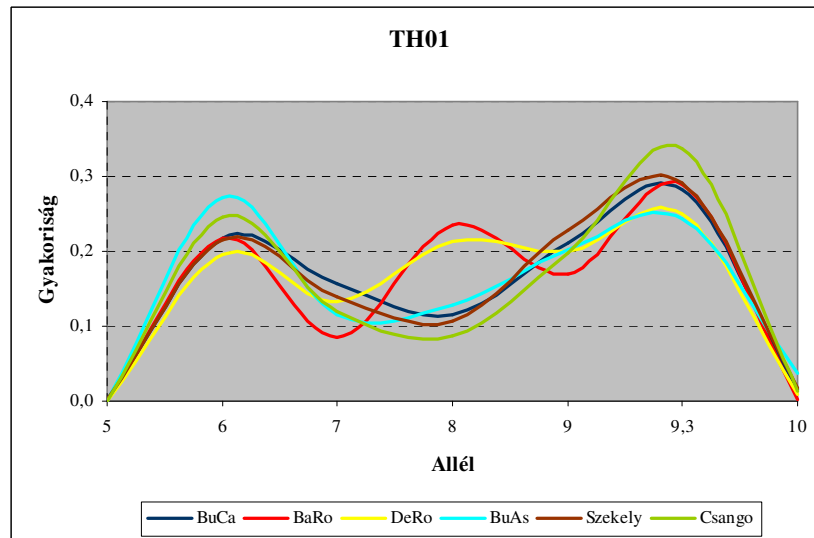
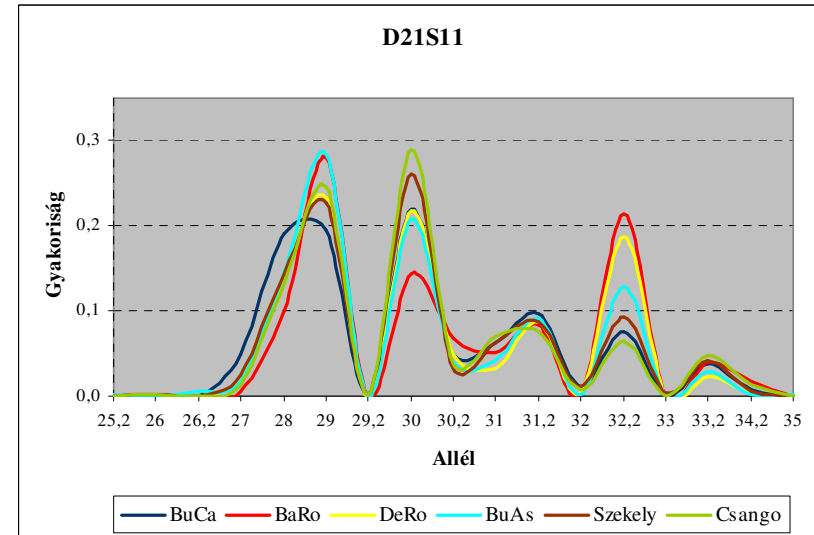
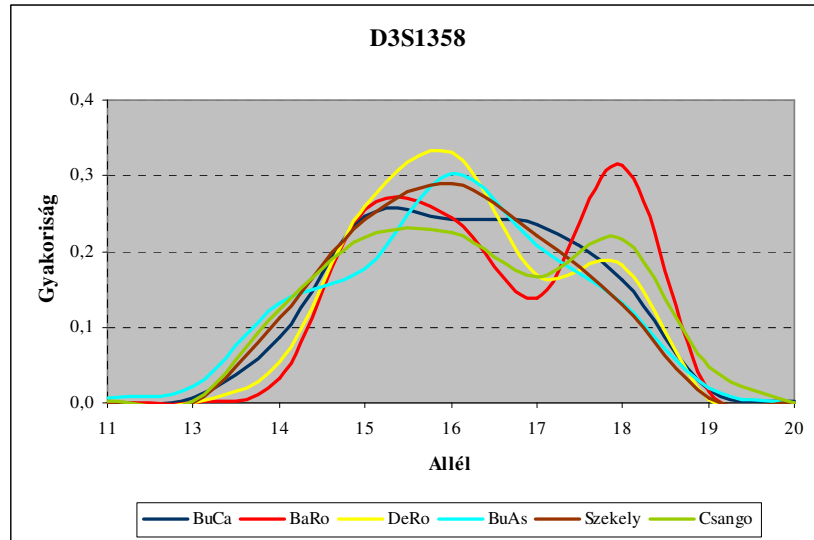
Polimorf szekvenciák mutációs rátája (μ)



Genotípus gyakoriságok statisztikai interpretálása

- **Allél-gyakorisági adatok** generálása a vizsgált populációban gyűjtött minták sorozatából (általában 100-200 nem rokon egyed / populáció autoszóma STR lókuszok esetén)
- **Allél-gyakorisági értékek meghatározása** minden lókuszon és az összes megfigyelt allélra
- Allél-gyakorisági értékek felhasználásával **a kérdéses DNS-profil előfordulási gyakoriságának kiszámolása**
 - Homozigóta (p^2), Heterozigóta ($2pq$)
 - Product rule: független lókuszok genotípus gyakoriságának multiplikálhatósága $PM = (P1)(P2)\dots(Pn)$

Mikroszatellita allélgyakoriság diagramok



STR Locus	Profile Computed	Number of Populations Used	Cumulative Profile Frequency Range (1 in ...)	Cumulative Profile Frequency against U.S. Caucasians (Appendix II)
D3S1358	16,17	166	5.24 to 62.6	9.19
VWA	17,18	166	37.6 to 1080	81.8
FGA	21,22	166	737 to 119 000	1010
D8S1179	12,14	166	8980 to 5 430 000	16 400
D21S11	28,30	166	165 000 to 248 000 000	186 000
D18S51	14,16	166	3.85×10^6 to 2.68×10^{10}	4.88×10^6
D5S818	12,13	166	2.28×10^7 to 4.22×10^{11}	4.51×10^7
D13S317	11,14	166	4.32×10^8 to 1.69×10^{13}	1.38×10^9
D7S820	9,9	166	1.17×10^{10} to 2.98×10^{16}	4.22×10^{10}
D16S539	9,11	97	4.06×10^{11} to 1.11×10^{18}	5.82×10^{11}
TH01	6,6	97	9.30×10^{12} to 1.45×10^{19}	1.05×10^{13}
TPOX	8,8	97	3.33×10^{13} to 1.54×10^{20}	3.63×10^{13}
CSF1PO	10,10	97	3.43×10^{14} to 2.65×10^{21}	7.43×10^{14}

Genetic Structure (AMOVA)

a,

F_{ST}	P	BuCa															BaRo															DeRo															BuAs														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
BuCa																																																													
BaRo																																																													
DeRo																																																													
BuAs																																																													

b,

Φ_{ST}	P	BuCa															BaRo															DeRo															BuAs														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
BuCa																																																													
BaRo																																																													
DeRo																																																													
BuAs																																																													

a, Jelölések: $(F_{ST}, \Phi_{ST}) > 0,02; P < 0,1$ $0,02 > (F_{ST}, \Phi_{ST}) > 0,01; 0,01 < P < 0,05$ $(F_{ST}, \Phi_{ST}) < 0,01; P > 0,05$

F_{ST}	P	BuCa																	Szekely																	Csango																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
BuCa																																																				
Szekely																																																				
Csango																																																				

b,

Φ_{ST}	P	BuCa																	Szekely																	Csango																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
BuCa																																																				
Szekely																																																				
Csango																																																				

Jelölések: $(F_{ST}, \Phi_{ST}) > 0,02; P < 0,1$ $0,02 > (F_{ST}, \Phi_{ST}) > 0,01; 0,01 < P < 0,05$ $(F_{ST}, \Phi_{ST}) < 0,01; P > 0,05$

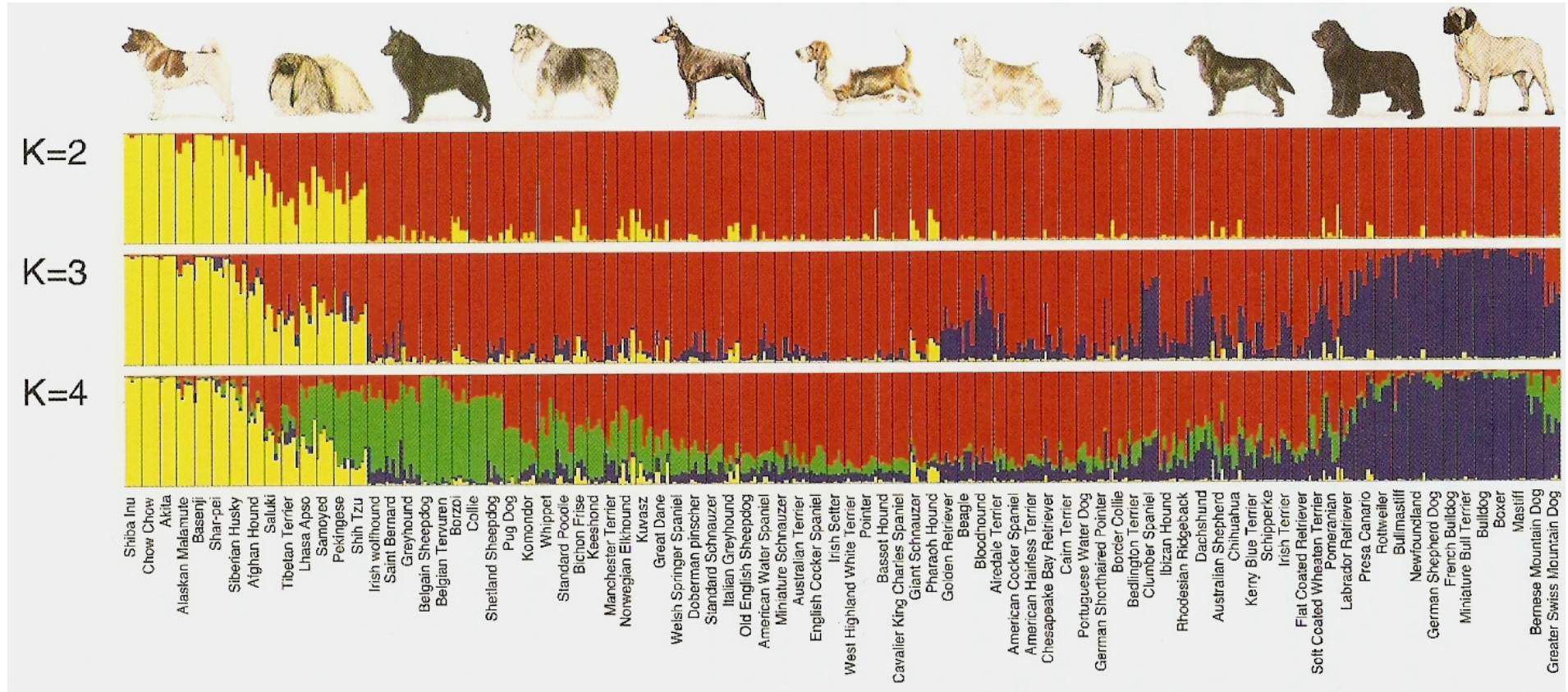
Fajtaazonosítás?... Populációs vizsgálatok!!!

1. Ősi

2. Terelő

3. Vadász

4. Védő



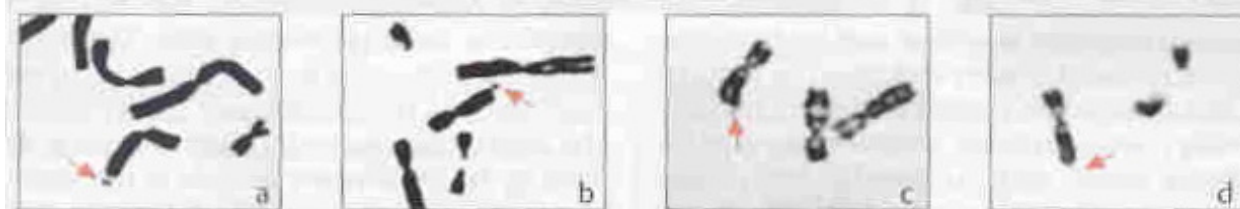
- 85 fajta (n=414)
- 95 mikroszatellita marker (dinukleotid repeat)
- 99%-ban helyes besorolás

Repeat expanziók okozta defektusok

Disease (Examples)	Gene	Frequency	Tri-nucleotide	Normal Number	Mutant Allele	Chromosome
Huntington disease	<i>HD</i>	1:10 000	(CAG) _n	0–26	36–121	4p16.3
Fragile X syndrome	<i>FMRI</i>	1:5 000	(CGG) _n	6–50	52–500	Xq27.3
Myotonic dystrophy	<i>DMPK</i>	1:8 000	(CTG) _n	5–37	50–500	19q13.2
Spinal-bulbar muscular atrophy (Kennedy)	<i>SBMA</i>	<1:50 000	(CAG) _n	11–31	36–65	Xq11-12



A. Phenotype



B. Fragile site Xq27.3

Fragilis X
 Huntington disease
 Myotonic dystrophy
 Friedrich ataxia
 stb.

Y-kromoszóma mikroszatellita markerek

Female-Male Mixture Performance with Autosomal vs. Y-Chromosome DNA Markers

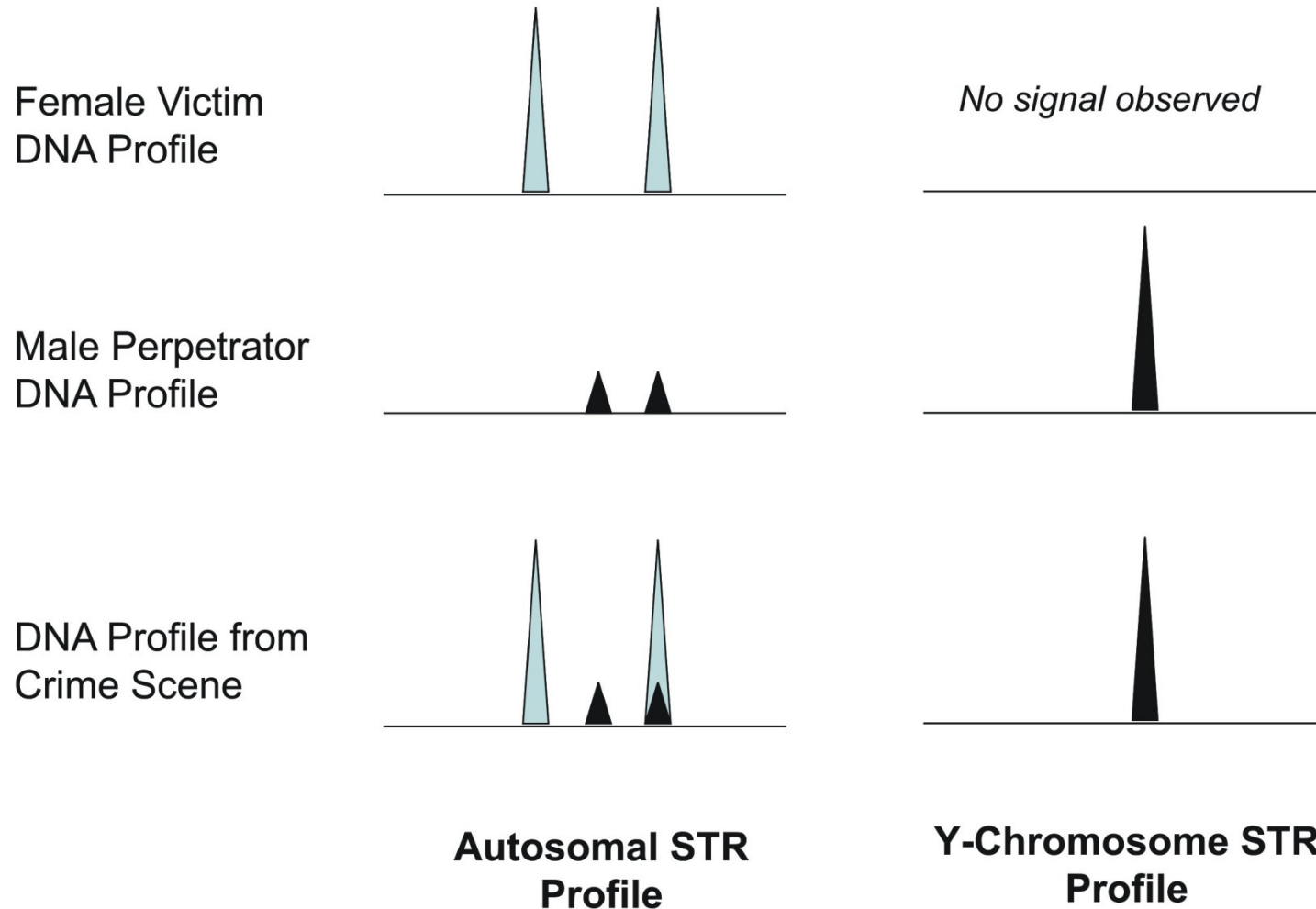
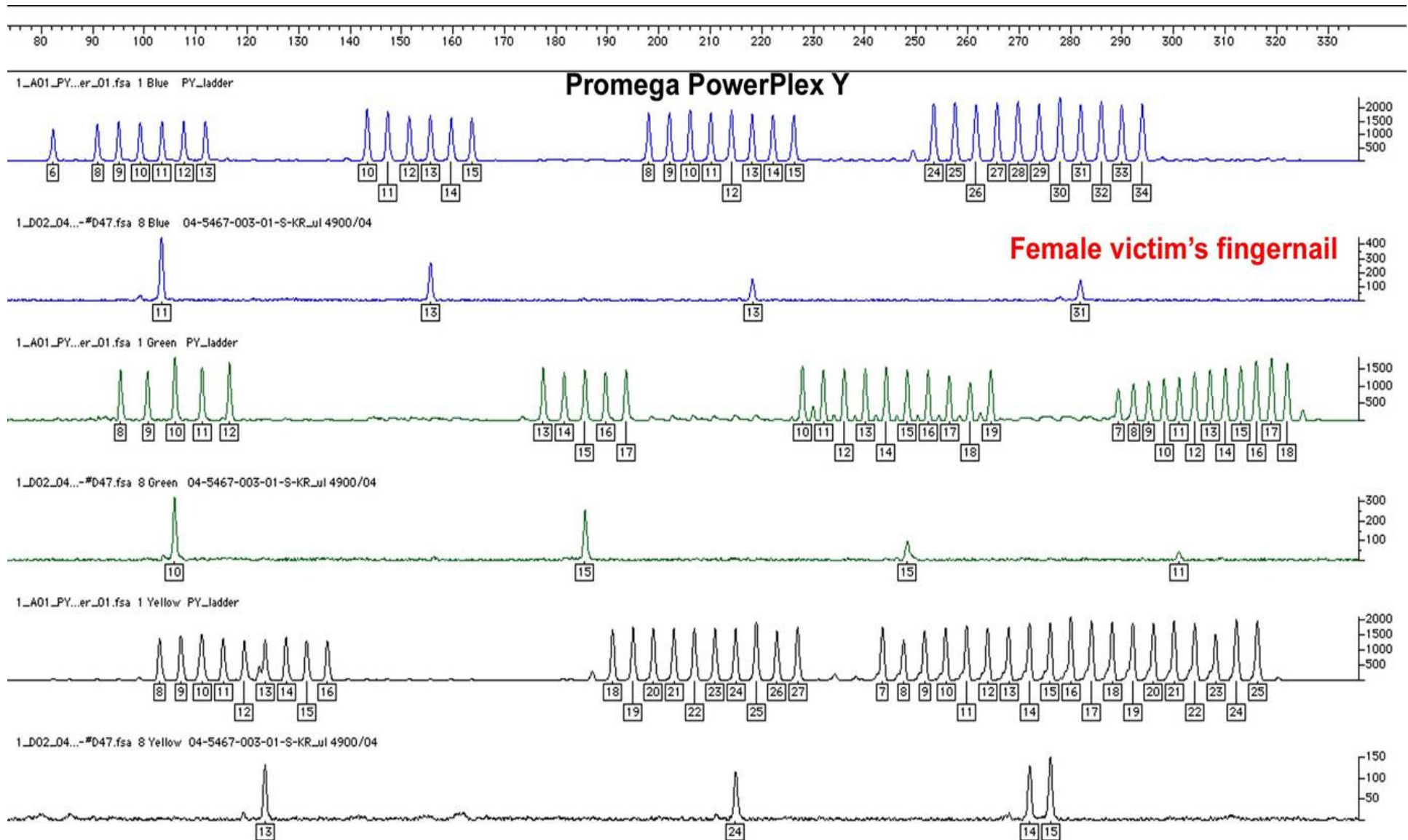
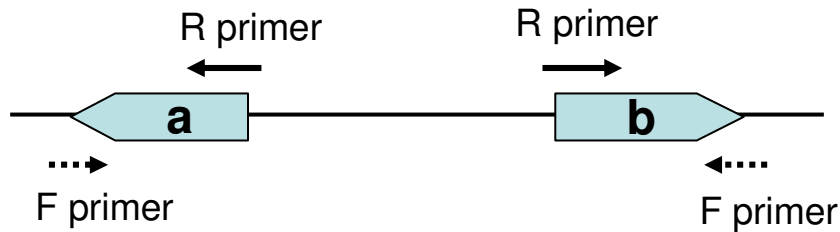


Figure 9.2, J.M. Butler (2005) *Forensic DNA Typing*, 2nd Edition © 2005 Elsevier Academic Press

Y kromoszómás mikroszatelliták kevert DNS mintákból

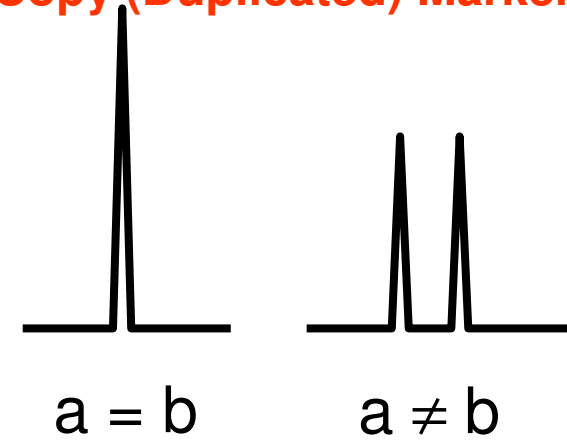


(A) DYS385 a/b

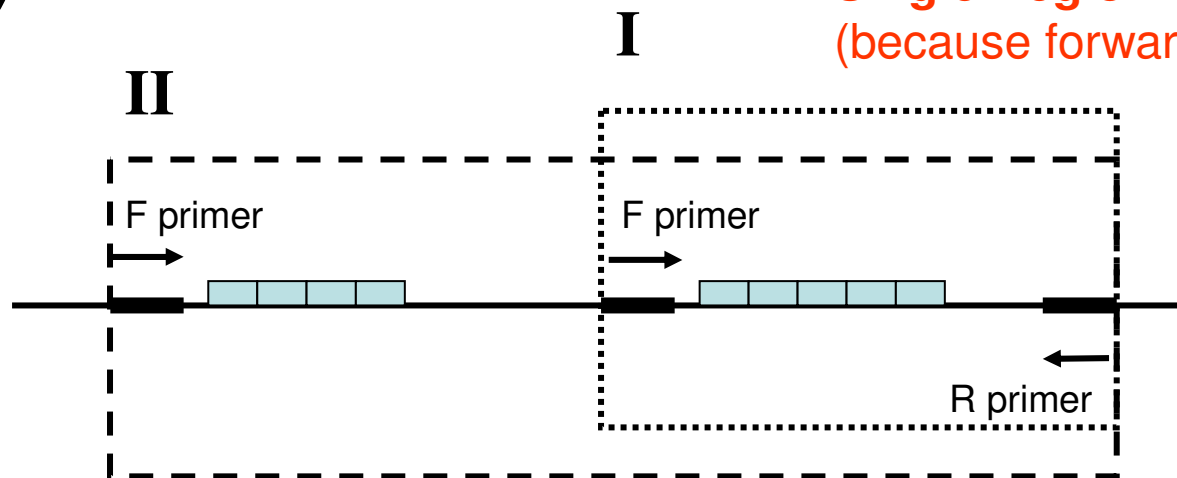


Duplicated regions are 40,775 bp apart and facing away from each other

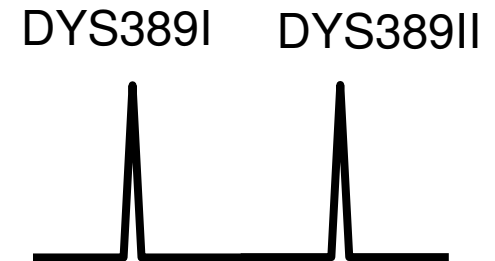
Multi-Copy (Duplicated) Marker



(B) DYS389 I/II



Single Region but Two PCR Products (because forward primers bind twice)



Modern Use of Y-STR Testing

Captured December 13, 2003



**Matching Y-STR
Haplotype Used to
Confirm Identity**



(along with allele sharing
from autosomal STRs)

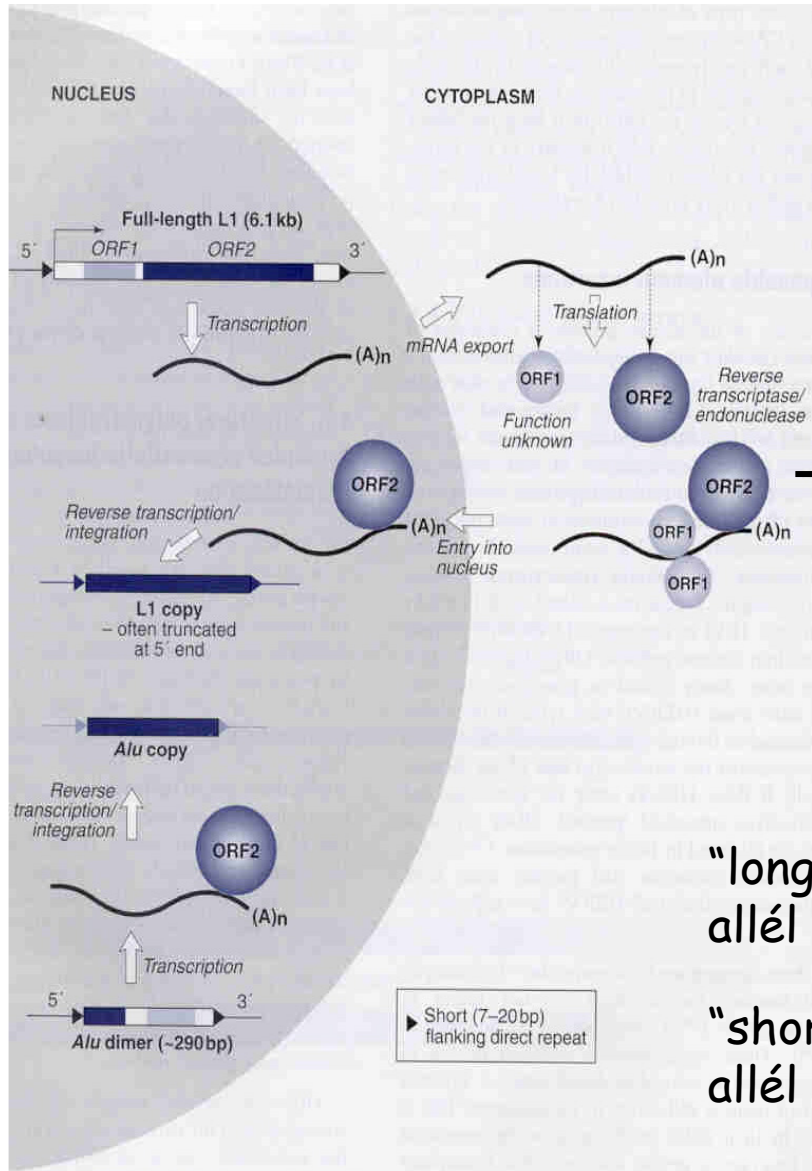


Uday and Qusay Hussein

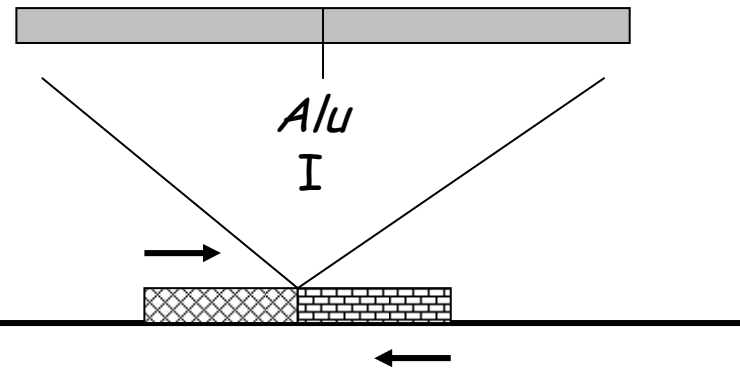
Killed July 22, 2003

**Is this man really
Sadaam Hussein?**

Mobilis elemek: biallélikus hossz-polimorfizmus



Human *Alu* Repeat (~300 bp)



Kétféle alléltípus

"long" (+)
allél



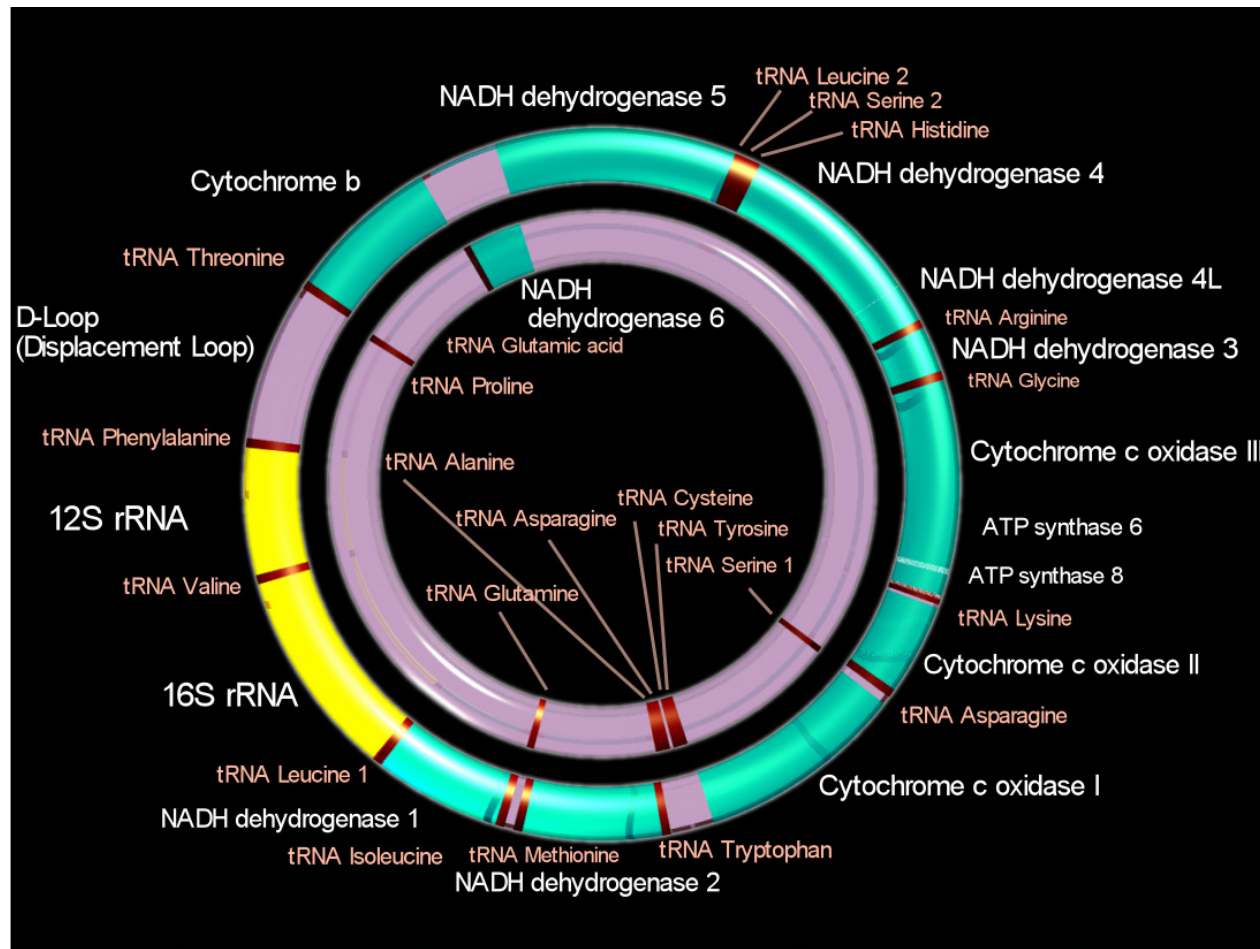
400
bp

"short" (-)
allél



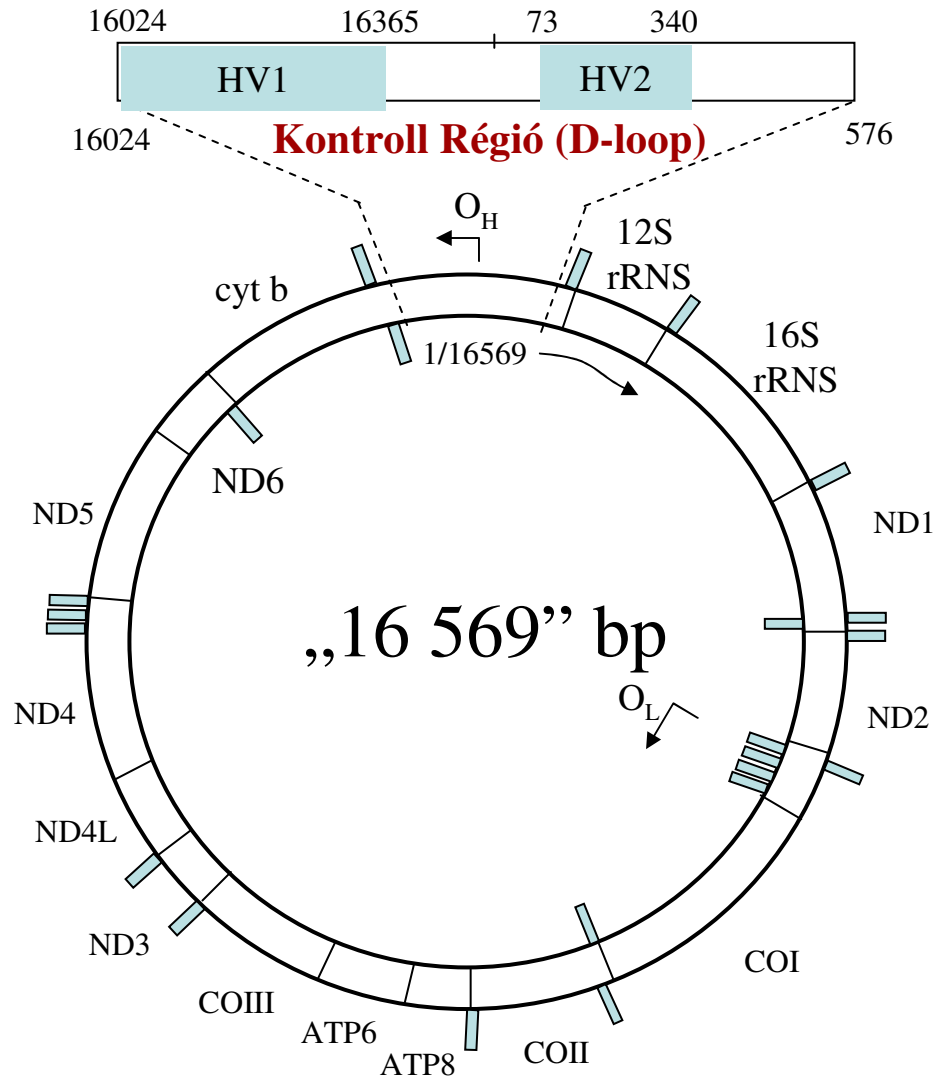
100
bp

A mitokondriális genom



- kódoló régió: 37 gén
 - 2 rRNA
 - 22 tRNA
 - 13 polipeptid (belső membrán)
- 13 polipeptid
 - a mitokondriális NADH dehidrogenáz 7 alegysége
 - cytochrome c 3 alegysége
 - ATP szintáz 2 alegysége
 - cytochrome b
- nukleáris gének által kódolt proteinek
 - cytochrome c, RNS és DNS polimerázok a citoszolból
- kisebb mutációs ráta
 - szinonim mutációk
- haplotípusok szekvenciális variációja
 - betegségek, fenotípusos expresszió
 - genetikai drift
 - faj azonosítása
 - filogenetikai vizsgálatok

A humán mitokondriális DNS



Sejten belüli nagy kópiaszám (~1000)

Maternális öröklésmenet:

nincs rekombináció!

Nagy mutációs ráta: DNA repair?

Kódoló Régió: 37 gén

Kontroll Régió v. D-loop (~1120 bp):

Hipervariábilis szakaszok (HV1, HV2)

Cambridge referencia szekvencia

Heteroplazmia, mutációs hot-spots

Szekvencia adatbázisok: EMPOP

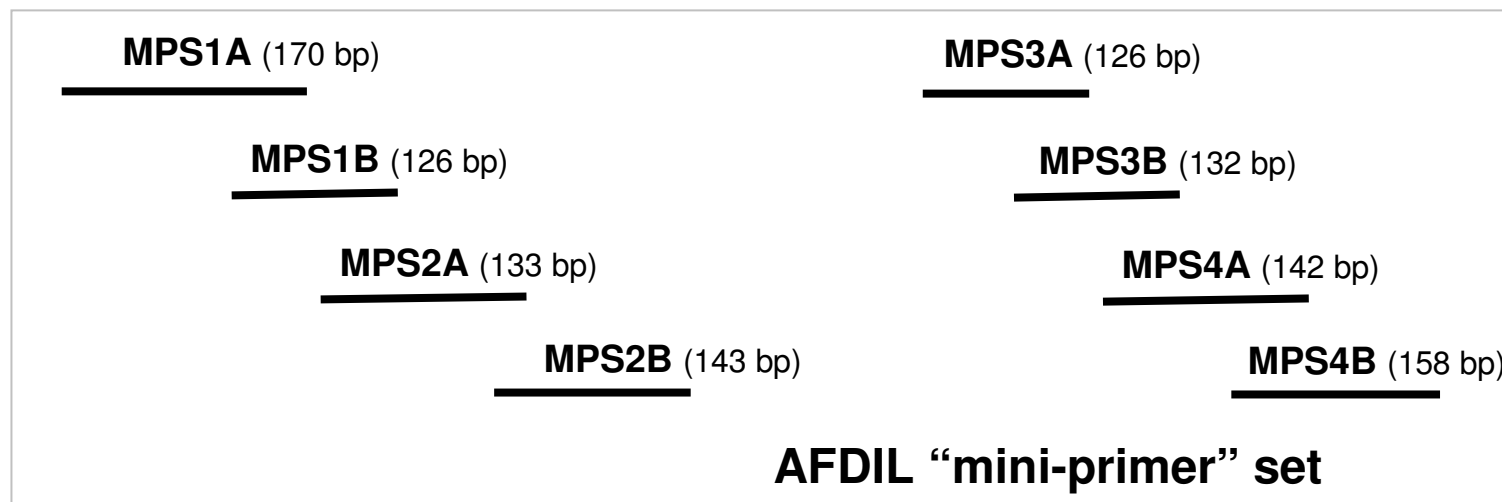
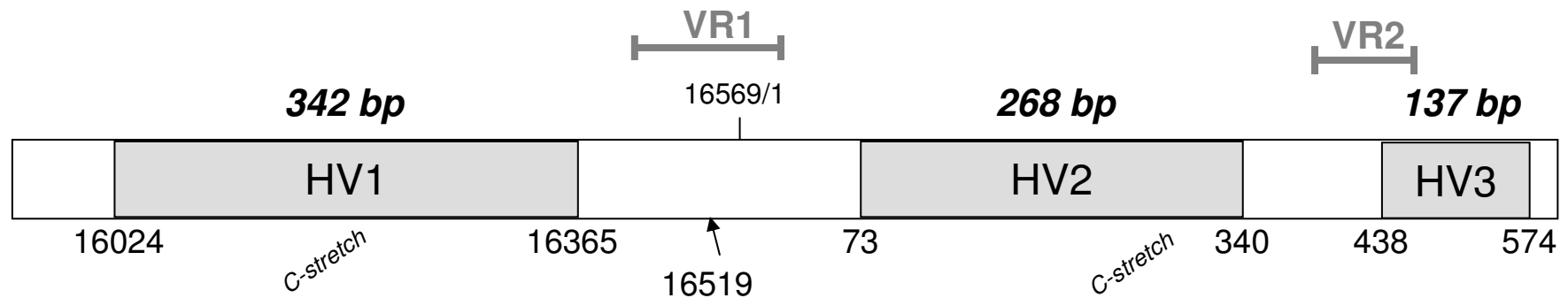


Figure 10.3, J.M. Butler (2005) *Forensic DNA Typing*, 2nd Edition © 2005 Elsevier Academic Press

Mitokondriális DNS d-loop diverzitási paraméterek a magyar népességben

Paraméter (1121 bp)	BuCa (n=211)	BaRo (n=205)	Székely (n=178)	Csángó (n=182)
Polimorf pontok	183	109	176	123
Tranzíciók	158	96	152	104
Transzverziók	12	3	11	7
Megfigyelt haplotípusok	180 (167 egyedi)	57 (33 egyedi)	135 (105 egyedi)	84 (59 egyedi)
Véletlen egyezési valószínűség (RMP)	1,00%	8,97%	1,04%	5,55%
Haplotípus-párok átlagos eltérése	9,5	9,8	10,8	10,7
Genetikai diverzitás	0,995	0,915	0,995	0,949

* A policitozin szálak C inzercióit a 16193, 309 és 573 nukleotid pozíciókban kihagyva a számításokból

mt DNS haplotípusok - haplocsoportok

Budapesti Referencia: 263G-315.1C-16519C (H1; 6.6 %)

Baranyai Romák:

1. 73G-263G-315.1C-489C-524.1A-524.2C-16129A-16223T-16291T-16298C-16519C (M5a; 16.1 %)
2. 73G-263G-315.1C-489C-524.1A-524.2C-524.3N-524.4N-16129A-16223T-16291T-16298C-16519C (M5a; 7.8 %)

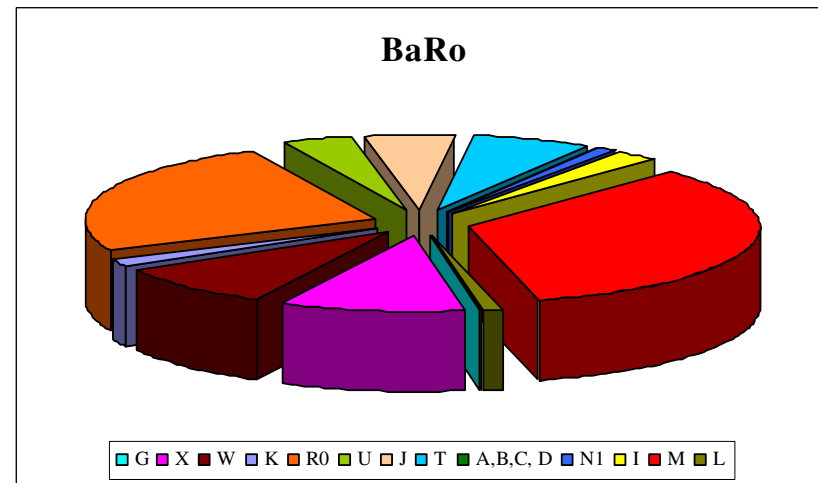
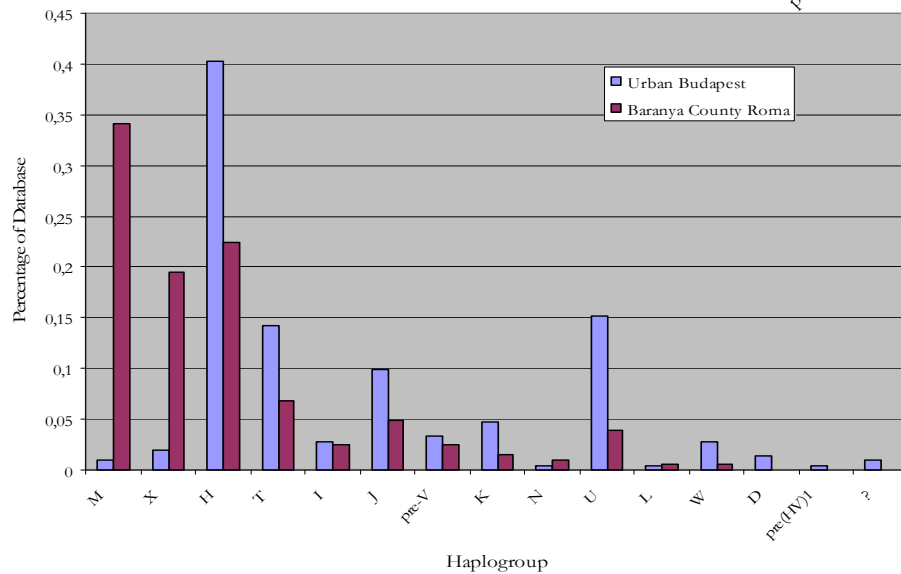
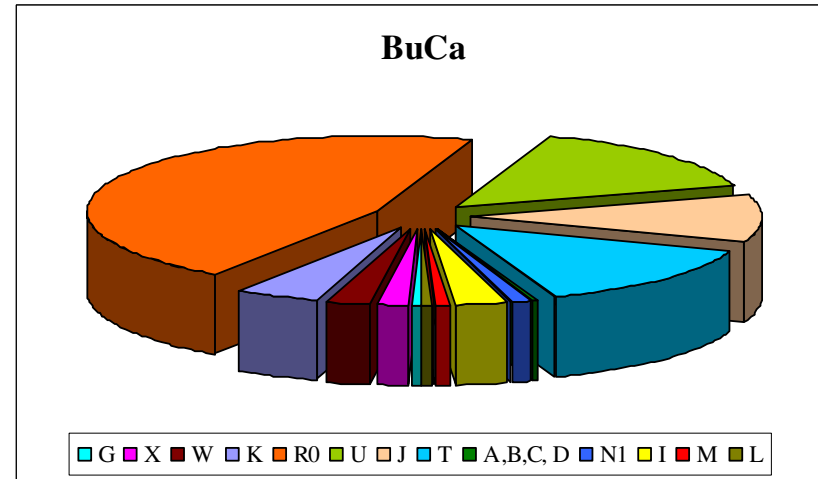
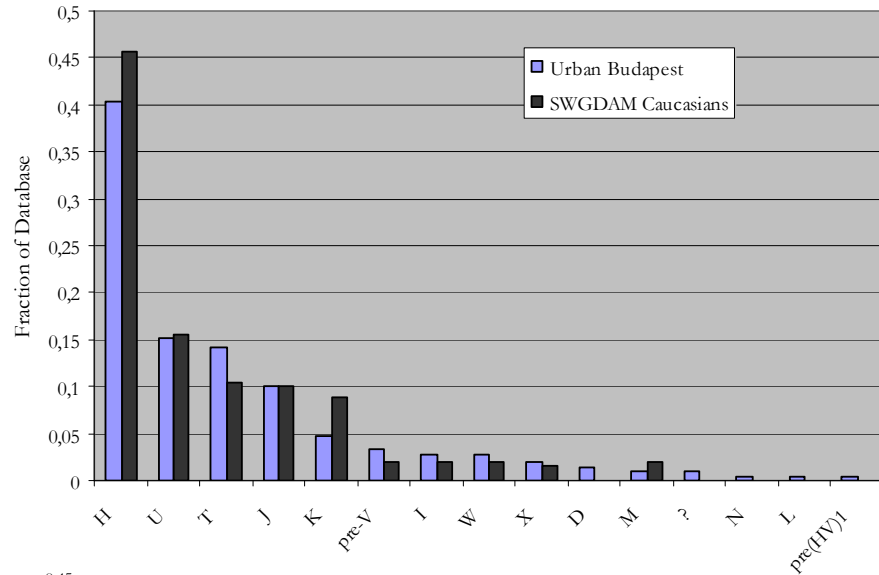
Csíkszeredai Székelyek:

1. 263G-315.1C-16519C (H1; 3.9 %)
2. 263G-315.1C-16172C-16173T-16519C (H*; 3.9 %)

Gyimesi Csángók:

1. 73G-146C-152C-263G-315.1C-498del-16224C-16311C-16519C (K1c; 19.2 %)
2. 73G-185A-189G-263G-295T-315.1C-462T-489C-16069T-16126C (J1; 8.2 %)

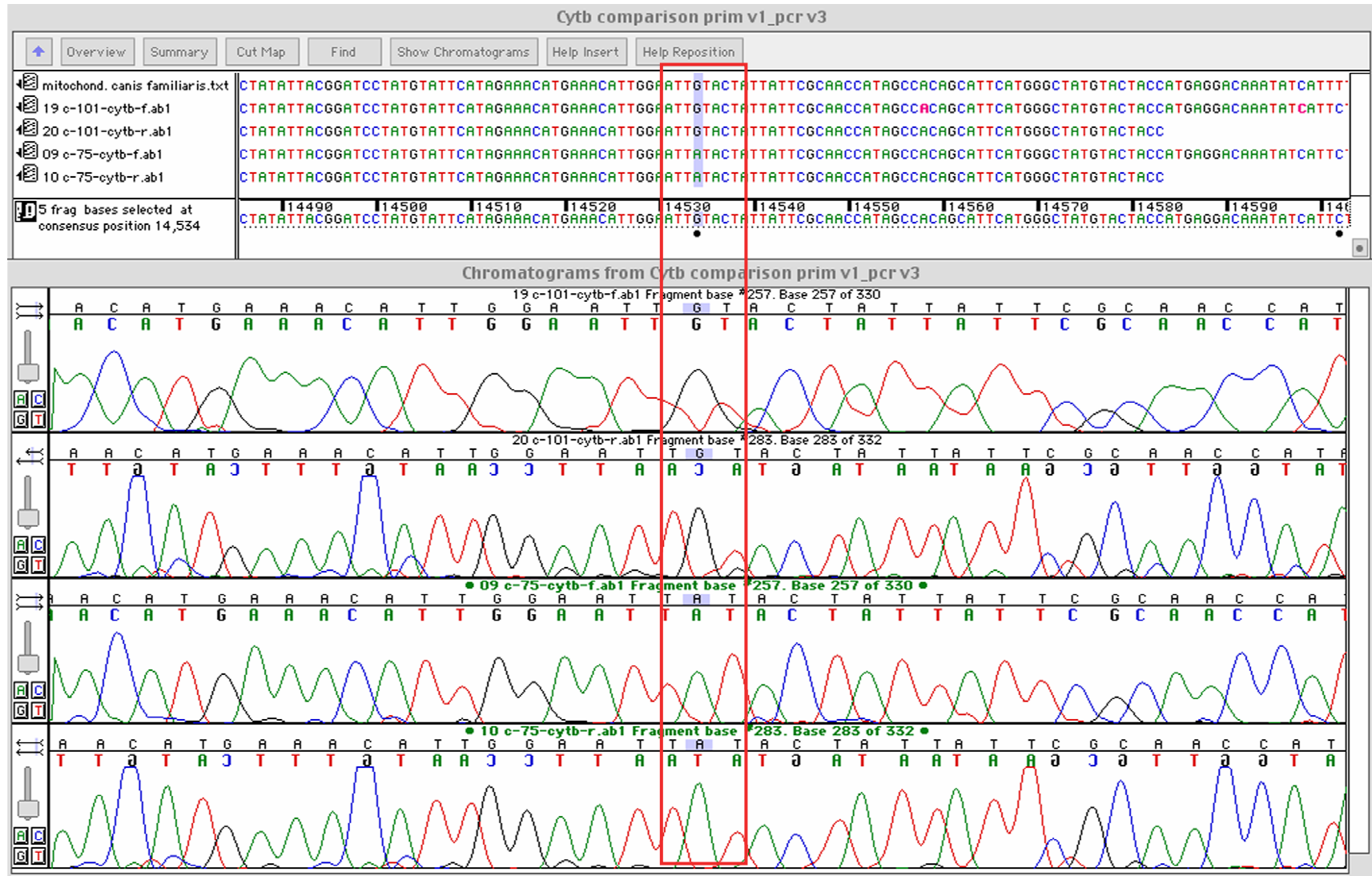
Mitokondriális DNS haplocsoport eloszlások



Egynukleotid polimorfizmusok (SNPs)

- Biallélikus markerek (6 lehetőség)
 - (A / G, C / T, A / T, C / G, T / G, A / C)
- Több millió SNP a genomban
 - kb. 500-1000 bázispáronként
 - pontmutációk génekben és/vagy regulátor régiókban
- Fenotípus kapcsolatok
 - pigmentáció, testalkat, ...
- Leszármazási vonalak (Y-SNP's)
- Diagnosztika
 - multifaktoriális poligénes betegségek

SNPs a *cytochrome b* génben (Canis f.)





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Forensic Science International: Genetics 1 (2007) 100–104



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Review

Finding genes that underlie physical traits of forensic interest using genetic tools

Hannah Pulker^a, María Victoria Lareu^a, Christopher Phillips^b, Angel Carracedo^{a,b,*}

^a*Institute of Legal Medicine, University of Santiago de Compostela, Spain*

^b*National Genotyping Centre-USC Node, Hospital Clinico Universitario, Santiago de Compostela, Spain*

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Int J Legal Med (2009) 123:315–325

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ORIGINAL ARTICLE

Pigment phenotype and biogeographical ancestry from ancient skeletal remains: inferences from multiplexed autosomal SNP analysis

Caroline Bouakaze • Christine Keyser • Eric Crubézy • Daniel Montagnon • Bertrand Ludes



Available online at www.sciencedirect.com



Forensic Science International: Genetics 1 (2007) 105–110



www.elsevier.com/locate/fsig

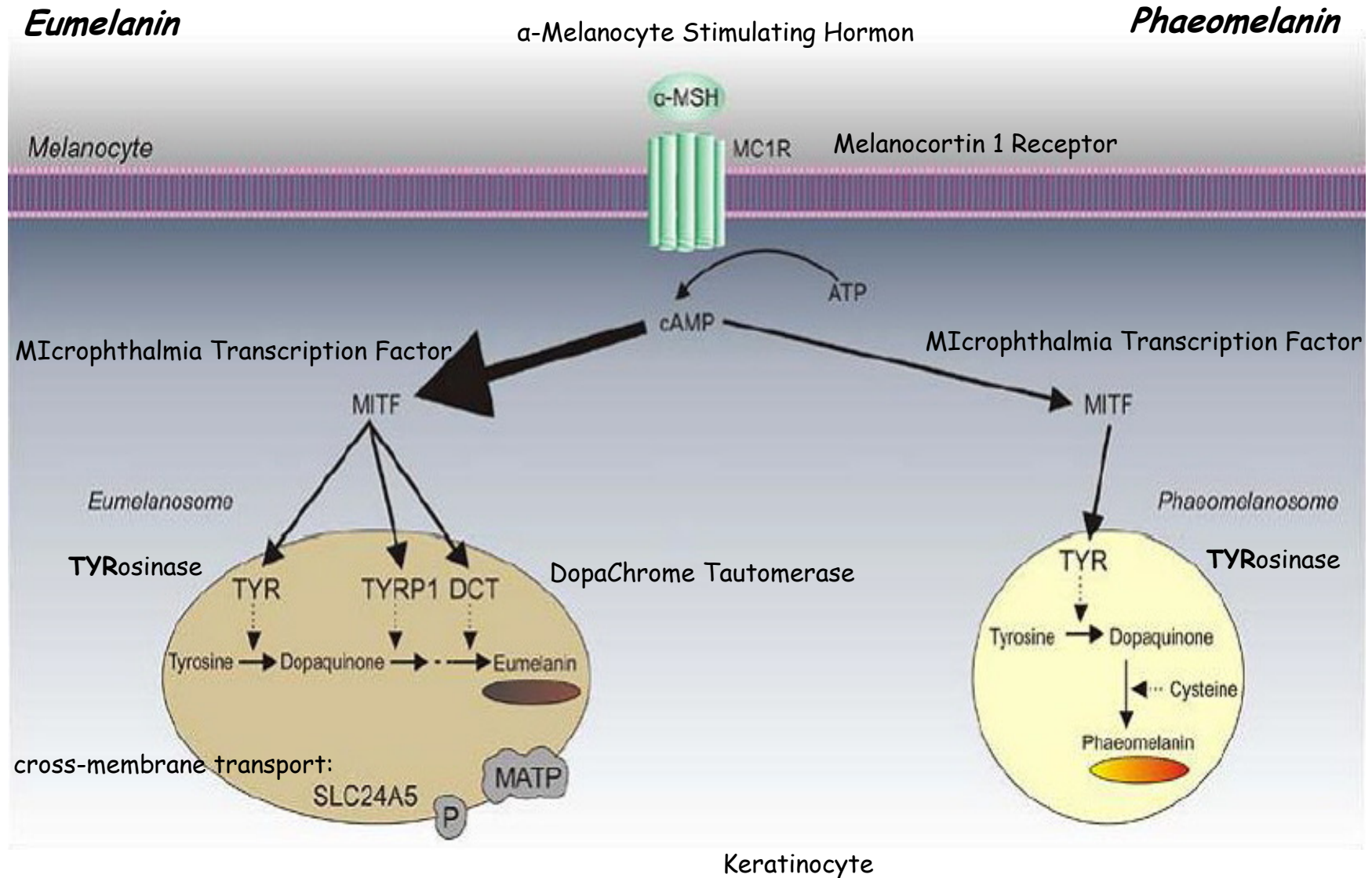
Genotype versus phenotype: Human pigmentation

Gillian Tully^{*}

The Forensic Science Service Ltd., Trident Court, Solihull Parkway, Birmingham B37 7YN, United Kingdom

Received 24 January 2007; accepted 27 January 2007

A humán melanogenezis



A humán pigmentáció genetikai szabályozása

- Melanoszóma: eumelanin v. phaeomelanin útvonal
- 127 pigmentációs gén az egér genomban
- Emberben ebből eddig 12 gént azonosítottak
- SNPs: fenotípus asszociált, ancestry-informative (AIMs)
- MC1R allélek aktivitása: RHC fenotípus, szeplősödés

Humán bőrpigmentáció gének

Principal skin pigmentation candidate genes

Locus	Chromosome	Protein	Mut phenotype	Function
Melanosome proteins				
TYR	11q14-11q21	Tyrosinase	OCA1	Oxidation of tyrosine
TYRP1	9p23	Gp75, TRYP1	OCA3	DHICA-oxidase, TYR stabilisation
DCT	13q32	DCT, TRYP2		Dopachrome tautomerase
OCA2	15q11.2-15q12	P-protein	OCA2 (eye)	pH of melanosome
SLC45A2	5p14.3-5q12.3	MATP, AIM-1	OCA4 (skin)	Melansome maturation
SLC24A5	15q21.1	Cation exchanger		Melanosome precursor
Signal proteins				
ASIP	20q11.2-20q12	Agouti signal protein		MC1R antagonist
MC1R	16q24.3	MSH receptor	Red hair (skin)	G-protein coupled receptor
POMC	16q24.3	MSH receptor	Red hair	MC1R antagonist
OA1	Xp22.3	OA1 protein	OA1	G-protein coupled receptor
MITF	3p12.3-3p14.1	MITF	Waardenburg	Transcription factor
Proteins involved in melanosome transport or uptake by keratinocytes				
MYO5A	15q21	MyosinVa	Griscelli	Motor protein
RAB27A	15q15-15q21.1	Rab27a	Griscelli	RAS family protein
HPS1	10q23.1-10q23.3	HPS1	Hermansky-Pudlak	Organelle biogenesis and size
HPS6	10q24.32	HPS6	Hermansky-Pudlak	Organelle biogenesis

ACTH: adrenocorticotrophin hormone; DCT: dopachrome tautomerase; DHICA: 5,6-dihydroxyindole-2-carboxylic acid; MATP: membrane-associated transporter protein; MC1R: melanocortin-1 receptor; MITF: microphthalmia-associated transcription factor; MSH: melanocyte stimulating hormone; OCA: oculocutaneous albinism; POMC: pro-opiomelanocortin; TYRP1: tyrosinase-related protein 1.

SNPs a pigmentációs génekben

- *ASIP* (aguti): 3'UTR 8818A - MSH antagonista - phaetomelanin termelés
- *MATP*: melanoszóma pH reguláció, 374Leu allél - sötét szín, albinizmus
- *SLC24A5*: „arany” gén, zebrafish, Ala111Thr allél, világos árnyalat, europid rasszban fixált, szelekciós nyomás?
- *OCA2*: albinizmus gén, 305 Arg/Trp, Afrika / Európa

Gene	Location	Protein	Reference SNP ID (rs#) ^a	Alleles	Variation type
<i>MC1R</i>	16q24.3	MC1R: melanocortin 1 receptor	rs1805007 rs1805008	C/T C/T	ns coding, c.451C>T, p.R151C ns coding, c.478C>T, p.R160W
<i>HERC2</i>	15q13	Unknown	rs12913832	A/G	Non-coding, intron 86
<i>OCA2</i>	15q11.2-15q12	P-protein: NA ⁺ /H ⁺ antiporter or glutamate transporter	rs7495174 rs6497268 or rs4778241 rs11855019 or rs4778138 rs1545397	T/C G/T T/C G/A	Non-coding, intron 1 Non-coding intronic
<i>SLC45A2</i>	5p13.3	MATP: membrane-associated transporter protein	rs16891982	C/G	ns coding, c.1122C>G, p.F374L
<i>SLC24A5</i>	15q21.1	SLC24A5 (or NCKX5): solute carrier family 24, member 5; potassium-dependent sodium- calcium ion exchanger	rs1426654	G/A	ns coding, p.A111T
<i>DCT</i>	13q32	DCT or TYRP2/TRP-2: dopachrome tautomerase or tyrosinase-related protein-2	rs2031526	G/A	Non-coding, intronic

ns non-synonymous

^a Reference SNP ID refer to the reference sequence identifier given to the SNP in the dbSNP database

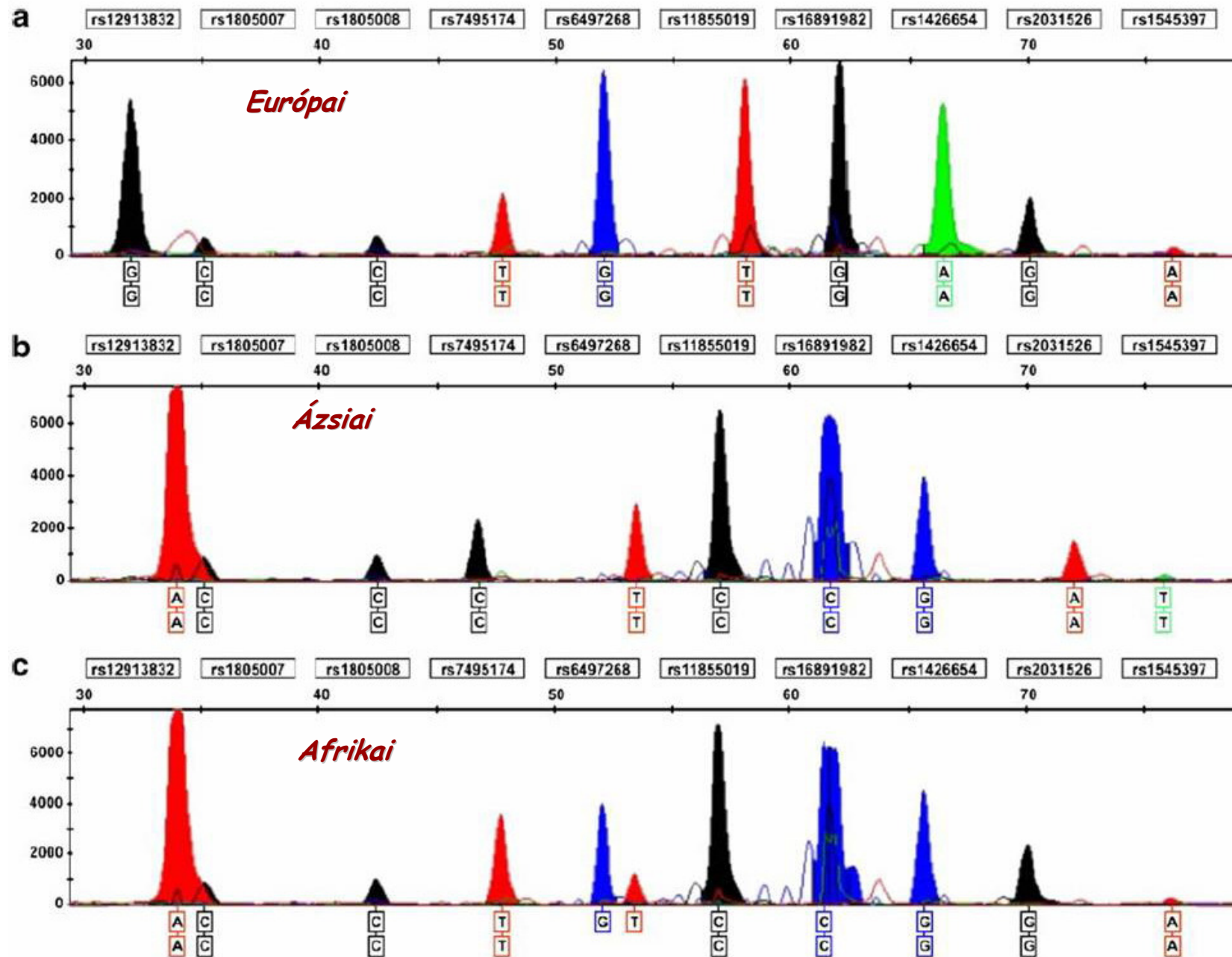
MC1R gén mutációk

Mutations in the MC1R gene, their penetrance and functional significance (where known)

Mutation	Type	Designation	Penetrance (odds ratio)	Functional significance	References (for functional significance and penetrance)
R151C	Mis-sense	R	63.3	Altered cellular location	[16,26]
R160W	Mis-sense	R	63.3	Altered cellular location	[16,26]
D294H	Mis-sense	R	63.3	Impaired G coupling ability	[26,27]
D84E	Mis-sense	R	63.3	Altered cellular location	[16,26]
I155T	Mis-sense	Lack of statistical data—strong familial association		Altered cellular location	[16,26]
V92M	Mis-sense	r	5.1	Reduced α -MSH binding	[26,28,29]
V60L	Mis-sense	r	5.1		[26]
R163Q	Mis-sense	r	5.1	Slightly reduced α -MSH binding	[26,29]
R142H	Mis-sense	Lack of statistical data—strong familial association			[26]

- MC1R allélváltozatok különböző aktivitással rendelkeznek.
- 317 AS, 7 transzmembrán domén,
- SNPs, RHC fenotípus,
- neandervölgyi pigmentáció
- genetikai tesztek, fenotípus predikció

10 pigmentációs gén SNPs genotipizálás (SNaPshot)



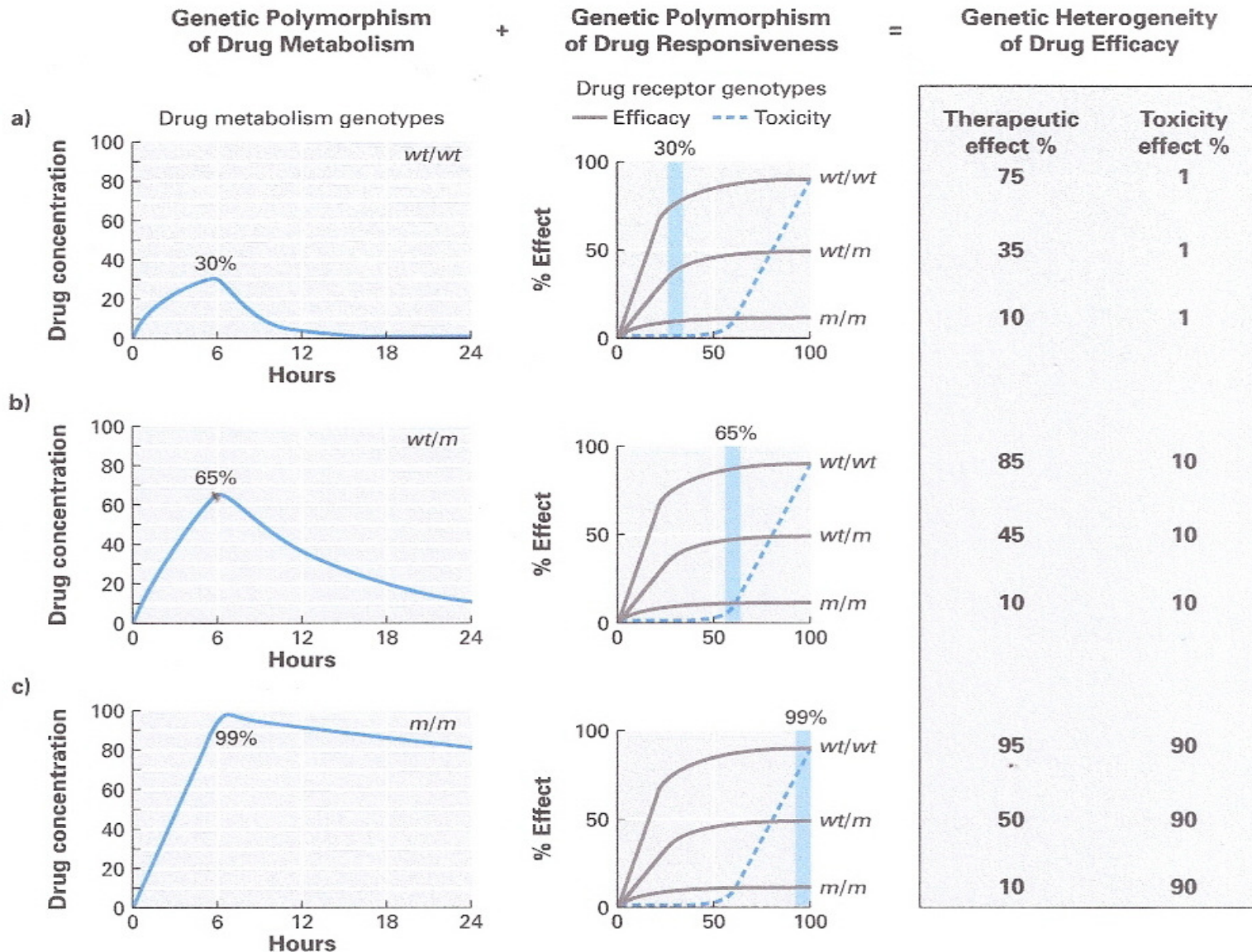
Sample	Self-reported pigmentary traits			rs12913832 HERC2	rs1805007 MC1R	rs1805008 MC1R	OCA2 diplotype ^a	rs16891982 SLC24A2	rs1426654 SLC24A5	rs2031526 DCT	rs1545397 OCA2	Inferred ancestry of individuals ^b		
	Eye color	Hair color	Skin color									European	Asian	African
E1	Blue	Red	Fair	<u>G/G</u>	C/C	C/T	<u>TGT/TGT</u>	G/G	A/A	G/G	A/A	0.963	0.012	0.024
E2	Green	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.954	0.021	0.025
E3	Blue	Blond	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.954	0.024	0.022
E4	Blue	Blond	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.960	0.020	0.020
E5	Blue/gray	Auburn	Fair	<u>G/G</u>	C/T	C/C	<u>TGT/TGT</u>	G/G	A/A	G/G	A/A	0.961	0.013	0.026
E6	Green/gray	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	C/G	A/A	G/G	A/A	0.787	0.038	0.175
E7	Green/hazel	Light brown	Fair	A/G	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.955	0.022	0.024
E8	Green/hazel	Dark brown	Fair	A/A	C/C	C/C	TGT/CTC	G/G	A/A	G/G	A/A	0.961	0.013	0.027
E9	Green/hazel	Dark brown	Fair	A/A	C/C	C/C	TTT/CTC	G/G	A/A	G/G	A/A	0.963	0.013	0.024
E10	Blue	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	C/G	A/A	G/G	A/A	0.789	0.049	0.163
E11	Green	Auburn	Fair	<u>G/G</u>	C/T	C/C	TGT/TGC	G/G	A/A	G/G	A/A	0.958	0.014	0.028
E12	Blue/hazel	Light brown	Fair	A/G	C/C	C/C	TGT/TTT	G/G	A/A	G/G	A/A	0.962	0.012	0.026
E13	Blue/hazel	Light brown	Fair	A/G	C/C	C/C	TGT/TTT	G/G	A/A	G/G	A/A	0.965	0.013	0.022
E14	Green	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	C/G	A/A	G/G	A/T	0.763	0.165	0.073
E15	Brown	Dark brown	Fair	A/G	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.957	0.022	0.021
E16	Brown	Dark brown	Fair	A/A	C/C	C/C	TGT/CTC	C/G	A/A	A/G	A/T	0.669	0.283	0.048
E17	Green/hazel	Dark brown	Medium	A/G	C/C	C/C	TGT/TTT	C/G	A/A	G/G	A/T	0.755	0.170	0.076
E18	Blue	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	G/G	A/T	0.935	0.045	0.021
E19	Brown	Red	Fair	A/G	C/T	C/C	<u>TGT/TGT</u>	G/G	A/A	G/G	A/A	0.964	0.013	0.022
E20	Green	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	C/G	A/A	G/G	A/A	0.792	0.047	0.161
E21	Green/gray	Blond	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.957	0.022	0.021
E22	Blue	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	G/G	A/A	0.959	0.014	0.026
E23	Green/hazel	Light brown	Fair	A/G	C/C	C/C	TGT/TTT	G/G	A/A	A/G	A/A	0.957	0.020	0.022
E24	Green	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	C/G	A/A	G/G	A/A	0.786	0.049	0.166
E25	Brown	Red	Fair	A/G	C/C	T/T	TGT/TGC	G/G	A/A	G/G	A/A	0.963	0.014	0.023
E26	Blue	Light brown	Fair	<u>G/G</u>	C/C	C/C	<u>TGT/TGT</u>	G/G	A/A	A/G	A/A	0.954	0.021	0.025
E27	Blue	Red	Fair	<u>G/G</u>	C/C	C/T	<u>TGT/TGT</u>	G/G	A/A	G/G	A/A	0.958	0.014	0.028
Af1	Brown	Black	Dark	A/A	C/C	C/C	TGC/TTC	C/C	G/G	A/G	A/A	0.028	0.094	0.878
Af2	Brown	Black	Dark	A/A	C/C	C/C	TGC/TTC	C/C	G/G	G/G	A/A	0.023	0.031	0.946
Af3	Brown	Black	Dark	A/A	C/C	C/C	TGC/TTC	C/C	A/G	G/G	A/A	0.164	0.041	0.795
As1	-	-	-	A/A	C/C	C/C	TTT/CTC	C/C	G/G	A/G	A/T	0.042	0.649	0.308
As2	-	-	-	A/A	C/C	C/C	CTC/CTC	C/C	G/G	A/G	T/T	0.020	0.921	0.060
As3	-	-	-	A/A	C/C	C/C	CTC/CTC	C/C	G/G	A/A	T/T	0.013	0.964	0.023
As4	-	-	-	A/G	C/C	C/C	TTT/CGC	C/C	A/G	A/A	A/T	0.212	0.708	0.080
As5	-	-	-	A/A	C/C	C/C	TTC/CGC	C/C	G/G	A/G	T/T	0.019	0.922	0.059
As6	-	-	-	A/A	C/C	C/C	CTC/CTC	C/G	G/G	A/A	T/T	0.119	0.858	0.023

E European modern sample, Af African modern sample, As Asian modern sample

^a OCA2 diplotype correspond to markers rs7495174/rs6497268/rs11855019. OCA2 diplotype and rs12913832 genotype predictive of blue eye color phenotype are underlined

^b Probability of being from European/Asian/African population determined using the STRUCTURE program. The greatest probability, most likely estimate of ancestry, is indicated in bold

Farmakogenomika



Farmakogenomika

SNPs: genotípus specifikus gyógyítás

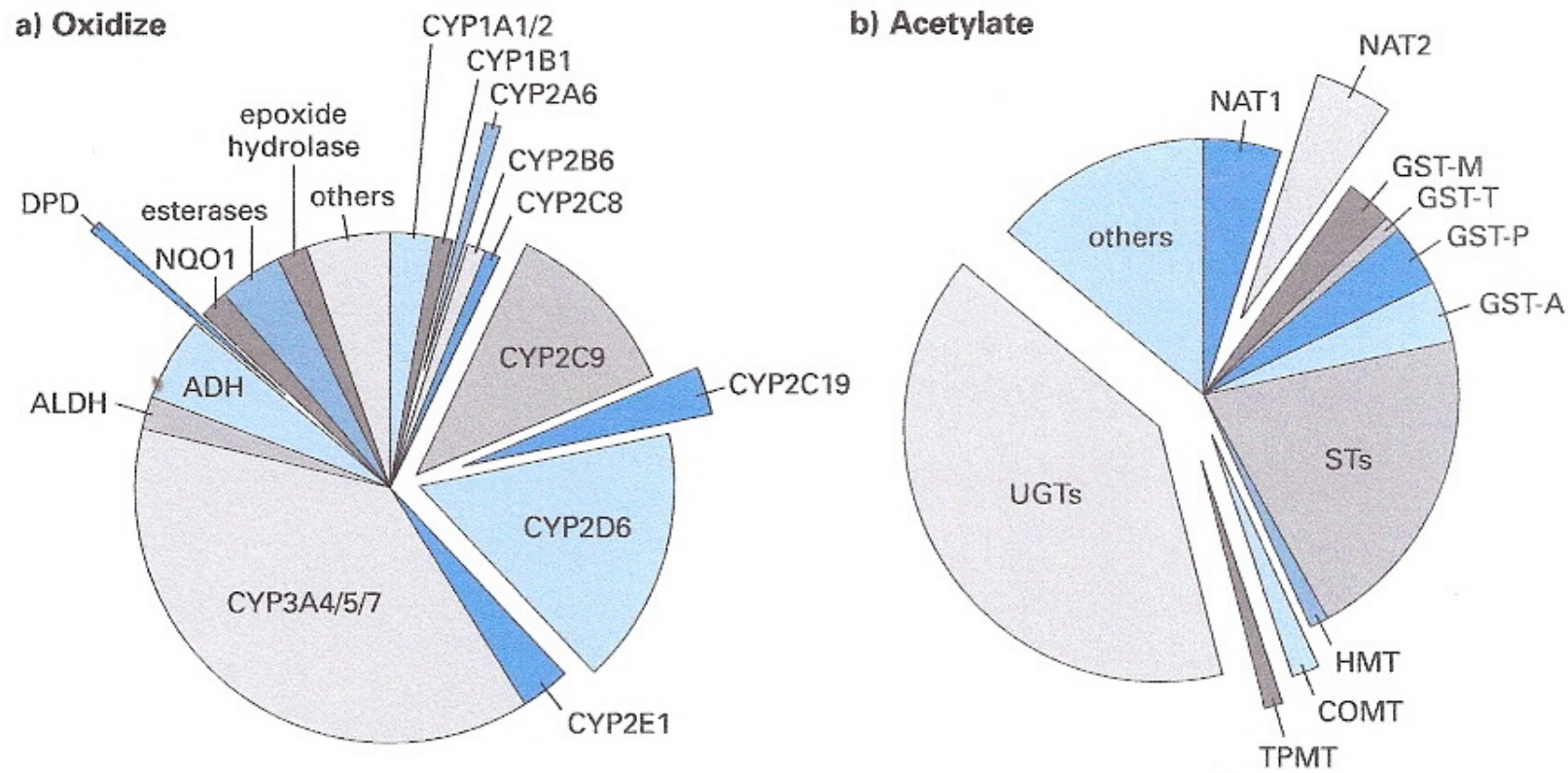


FIGURE 3.9 • Polymorphic drug metabolizing enzymes. **a)** Some enzymes oxidize drugs and make them more reactive. **b)** Other enzymes add acetyl groups onto the most reactive portion of drugs and typically inactivate them. The percentage of oxidation and acetylation of drugs that each enzyme contributes is estimated by the relative size of each section of the corresponding chart.

CYP2D6: 22 kr., 9 exon,
12 SNPs: alternatív splicing

Farmakogenomika

- Farmakogenomika: személyre szabott gyógyítás?
- Genetikai tanácsadás, felvilágosítás
- Etikai kérdések, személyes adatok

