

Haplotip ve Baęlantı Analizi

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Linkage= Baęlantı
Association= İlişkilendirme

Linkage
Linkage disequilibrium

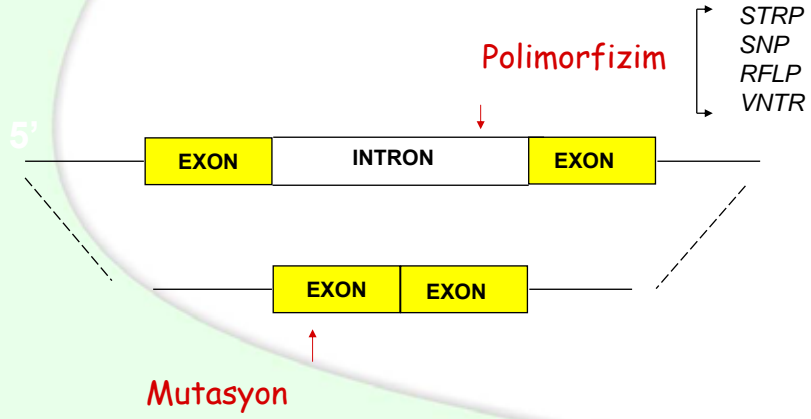
Polimorfizm

Mayozda parça
deęişimi



Adım 1

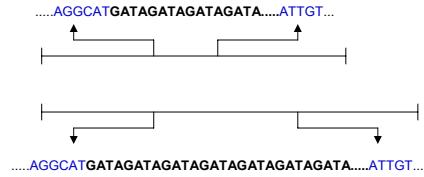
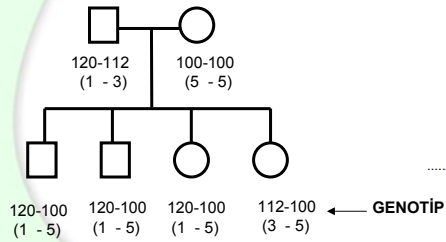
Polimorfizim kavramını çok iyi anla



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STRP

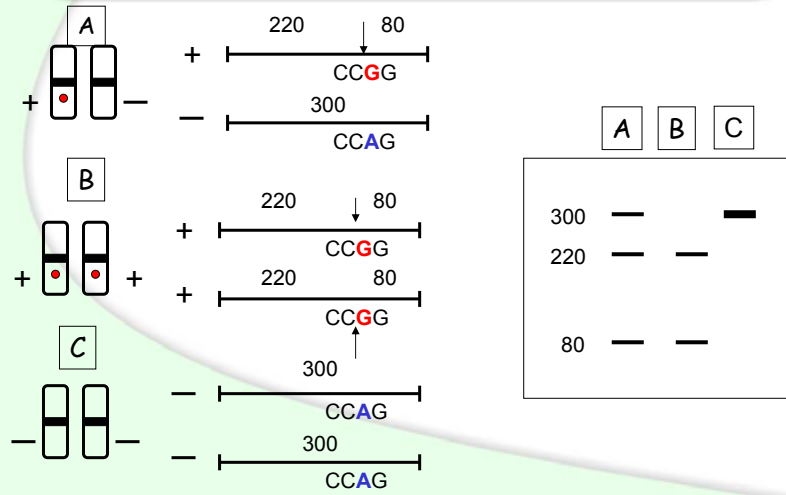


Size	Baba	Anne	Ç-1	Ç-2	Ç-3	Ç-4
120	—	—	—	—	—	—
110	—	—	—	—	—	—
100	—	—	—	—	—	—



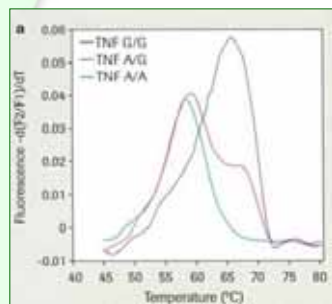
3

RFLP

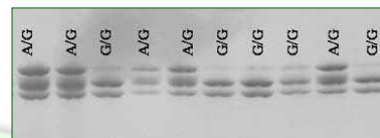
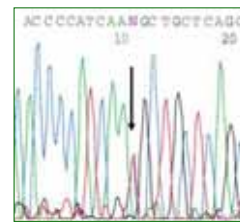


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SNP



Otomatik yöntemler



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FARMAKOGENETİK

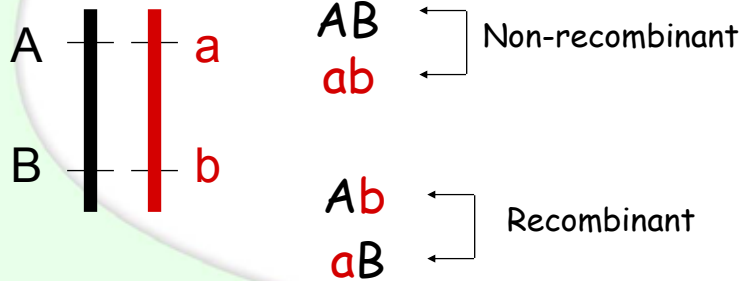
- İlaç nasıl metabolize oluyor?
- Enzim polimorfizimi metabolizmayı değiştiriyor mu? (FARMAKOKİNETİK ETKİ)
- Enzim polimorfizimi ilaca yanıtı değiştiriyor mu? (FARMAKODİNAMİK ETKİ)
- Genetik kimliğe göre ilaç dozu ayarlanabilir mi?
- İlacın birey için güven aralığı tanımlanabilir mi?
- İlaç kombinasyonları olayı nasıl değiştirir?

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Hacettepe Üniversitesi

Adım 2

Mayozda parça değişimini anla

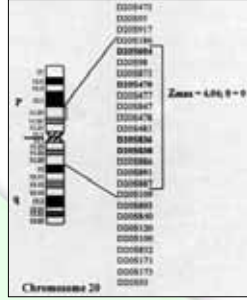


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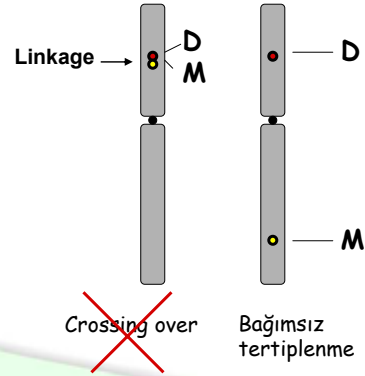
Bağlantı (Linkage) hastalık ile markır alel arasında tam segregasyondur

Polimorfik DNA markırları
Pozisyonu biliniyor



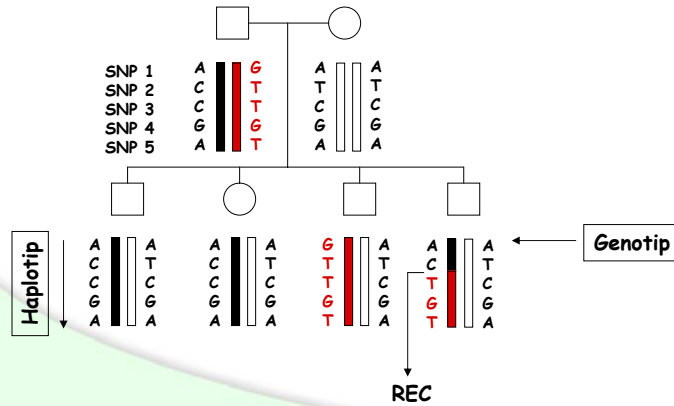
<http://research.marshfieldclinic.org/genetics/>

Hastalık
Pozisyonu bilinmiyor



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Mayozda parça değişimi (Crossing Over)



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Adım 3

Genetik modeli belirle

Kalıtım kalıbı

Nuclear

☐ Tek gen

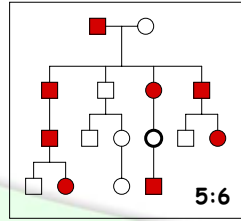
☐ Diğer

- ✓ Gen + çevre
- ✓ Oligo/poligen
- ✓ Imprinting
- ✓ Penetrans
- ✓ Sex limited
- ✓ Sex influenced
- ✓ Kriptik mutationlar

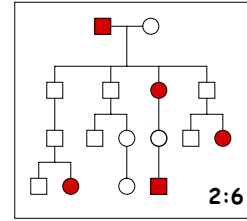
Otozom

Gonozom

Mitokondri



OD-%90 penetrance



OD-%30 penetrance

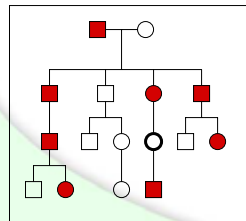
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Adım 4

Analiz stratejisini belirle

Model bağımlı

Parametric (Linkage)



GAW: Genetic analysis workshop

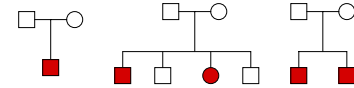
Modelden bağımsız

Non-parametric (Association)

☐ Toplum tabanlı



☐ Aile tabanlı



Ana-baba
çocuk

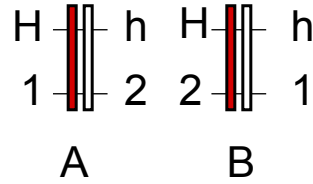
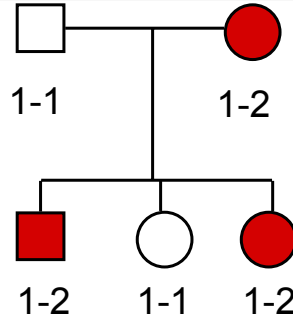
Farklı
kardeşler

Kardeş
çiftleri

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Linkage

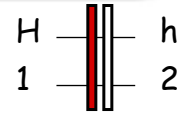
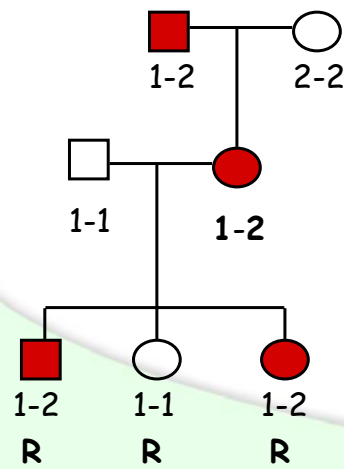


A durumu	R	R	R
B durumu	NR	NR	NR

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Linkage



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Hacettepe

Adım 7

Linkage hesapla

Doğrudan tahmin

$$\ominus = \frac{\text{Rekombinant}}{\text{Rec} + \text{Nonrec}} \quad \text{cM}$$

$\frac{50}{100} \quad \% 50 \text{ (No linkage)}$

$\frac{1}{100} \quad \% 1 \text{ (LINKAGE)}$

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LOD SCORE

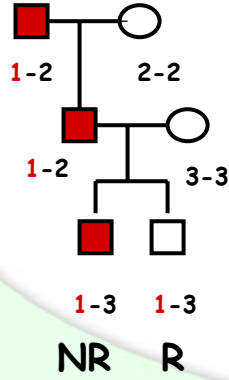
Dolaylı tahmin

$$Z = \log_{10} \frac{\text{(Likelihood of linkage)}}{\text{(Likelihood of no linkage)}}$$

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LOD SCORE **Dolaylı tahmin** Logarithm of Odds Ratio



Pedigrinin olasılık dağılım fonksiyonunu yaz

$$L = (1-\theta) \theta$$

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Hacettepe



LOD SCORE

(Farklı θ fraksiyonlarında lod score hesapla)

$$Z = \log_{10} \frac{\text{(Likelihood of linkage)}}{\text{(Likelihood of no linkage)}}$$

$$Z = \log_{10} \frac{(1-\theta) \theta}{(1-\theta) \theta} = \frac{(1-0.01) 0.01}{(1-0.5) 0.5} \leftarrow$$

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Hacettepe Üniversitesi

Lod skor tablosu oluřtur

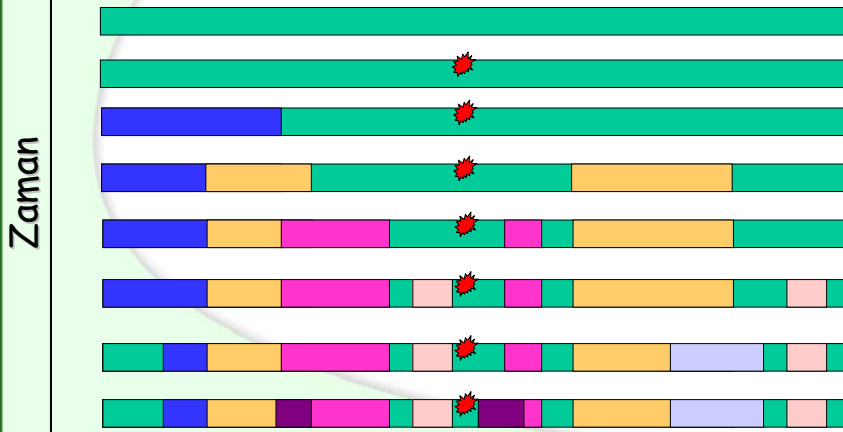
FAM No	Recombination fraction (θ)					LOD Scores
	0.05	0.10	0.20	0.30	0.40	
1	0.95	1.08	1.03	0.80	0.45	
2	-0.16	0.07	0.21	0.22	0.14	
3	0.26	0.22	0.13	0.06	0.02	
4	-0.35	0.08	0.33	0.28	0.12	
5	0.12	0.32	0.42	0.36	0.22	
6	0.65	0.78	0.72	0.50	0.19	
Total	1.46	2.56	2.85	2.23	1.14	

$Z \geq 3 = 10^{-3}$ Linkage

$Z \leq -2 = 10^{-2}$ No linkage

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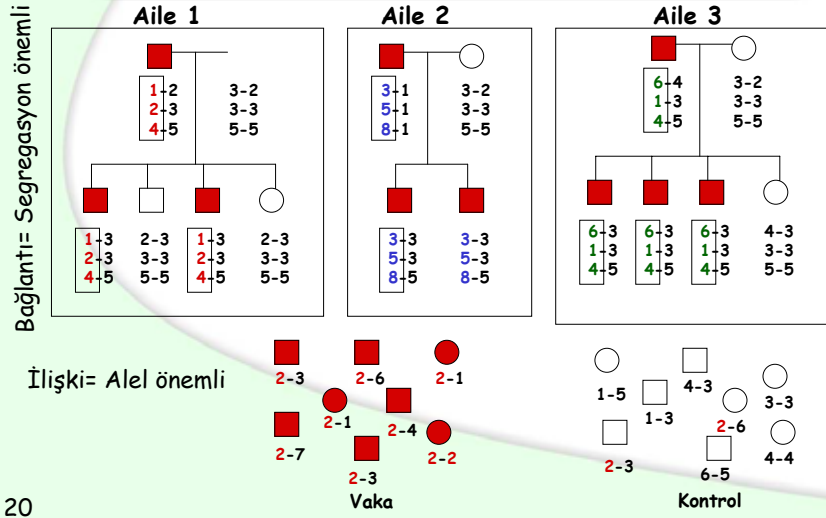
İliřki (association)



Eski mutasyonlar, küçük LD alanı, kuvvetli iliřki

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Bağlantı / İlişki



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b

Kontrol grubu Hardy-Weinberg denkleğine uyuyor mu?

$$(p + q)^2 = p^2 + 2pq + q^2$$

Vaka: AA → 166 ; AG → 416 ; GG → 241
Toplam: 823

Genotip	Alel-A	Alel-G	Toplam
A-A	332	0	332
A-G	416	416	832
G-G	0	482	482
Toplam	748	892	1646

Kontrol: AA → 102; AG → 307; GG → 246
Toplam: 655

Genotip	Alel-A	Alel-G	Toplam
A-A	204	0	332
A-G	307	307	832
G-G	0	492	482
Toplam	511	799	1310

p (A aleli frekansı) = 511/1310 = 0.39
q (G aleli frekansı) = 799/1310 = 0.61

Beklenen genotip frekansları

AA: $(0.39)^2 = 0.152 \times 655 = 100$ (102)

AG: $2 \times (0.39 \times 0.61) = 0.475 \times 655 = 312$ (307)

GG: $(0.61)^2 = 0.372 \times 655 = 243$ (246)

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Linkage Disequilibrium

İki alleli sistem a1 a2
b1 b2

	a1 (p)	a2 (1-p)	
b1 (q)	pq	(1-p)q	Beklenen frekanslar
b2 (1-q)	p(1-q)	(1-p)(1-q)	

D = gözlenen frekans - beklenen frekans

D=0 → equilibrium

D>0 → a1 ve b1 associate

D<0 → a2 ve b2 associate

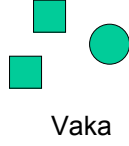
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Linkage Disequilibrium

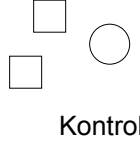
- ❑ Mutasyon
- ❑ İki farklı popülasyonun karışımı
- ❑ Seleksiyon
- ❑ Drift

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Toplum tabanlı çalışmalar



Vaka



Kontrol

Hardy-Weinberg denkliği
 $(p + q)^2 = p^2 + 2pq + q^2$

} Alel ilişkisi

Anne

(112), (212)

M1

(1-2)

M2

(1-1)

M3

(2-2)

Baba

(212), (211)

(112), (122),
(212), (222)

(1-2)

(1-2)

(2-2)

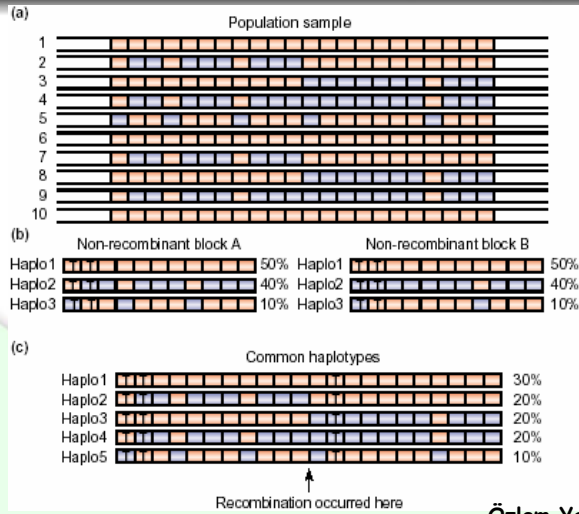
(222), (221),
(212), (211)

} Haplotip ilişkisi

EM Algoritmi

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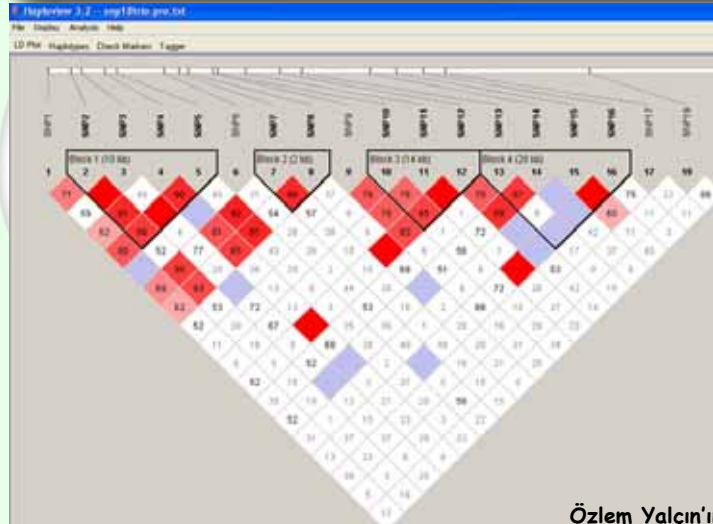
HAPMAP HAPLOTİP BLOKLARI



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Özlem Yalçın'ın izni ile

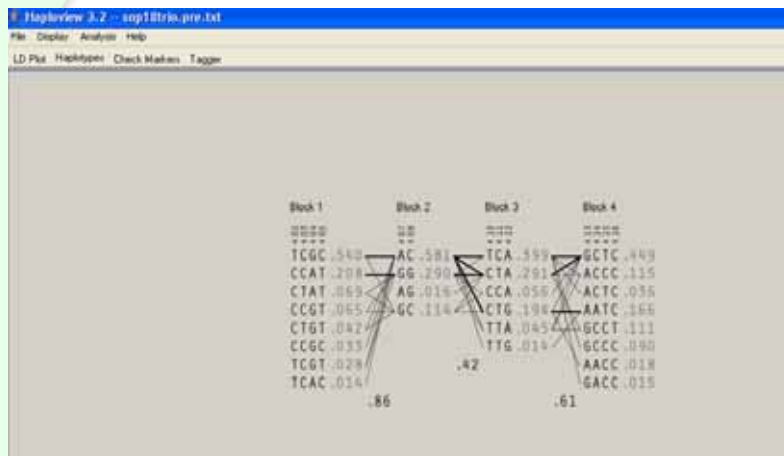
HAPLOVIEW



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Özlem Yalçın'ın izni ile

HAPLOVIEW



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Özlem Yalçın'ın izni ile

ÖZET-Parametrik

- ❑ Pedigri bul
- ❑ Genetik modeli belirle
- ❑ Simulation yap (SLINK)
- ❑ Genotiple (Aday gen/Genom- boyu analiz)
- ❑ Linkage hesapla (Pairwise or multipoint)
LINKAGE
GENE-HUNTER
MERLIN
ALLEGRO
- ❑ Sensitivite analizi

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ÖZET-Parametre bağımsız

- ❑ Fonksiyonel SNP olduğu düşünülüyorsa
Tek SNP-ilişki analizi
Hardy-Weinberg denkliği
- ❑ SNP'ler kullanılarak olası gen bulunmak isteniyorsa
Aday gende bir dizi SNP ile Haplotip analizi
Markırlar ve haplotip-nitelik arası LD
Haplotip fazı tahmin
Covariate- regresyon analizleri
HAPLOVIEW
PHASE
PBAT
- ❑ Deney desenini değiştir (TDT, sTDT vs.)

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