Androloji kongresi 2007

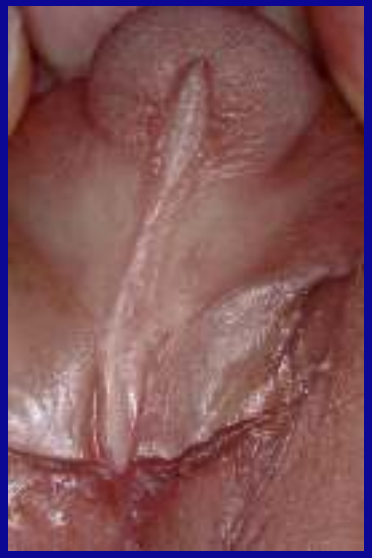
Doç. Dr. Selçuk Yücel

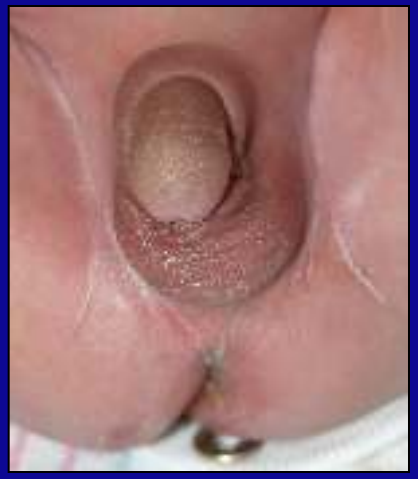
Akdeniz Üniversitesi Tıp Fakültesi
Üroloji Anabilim Dalı

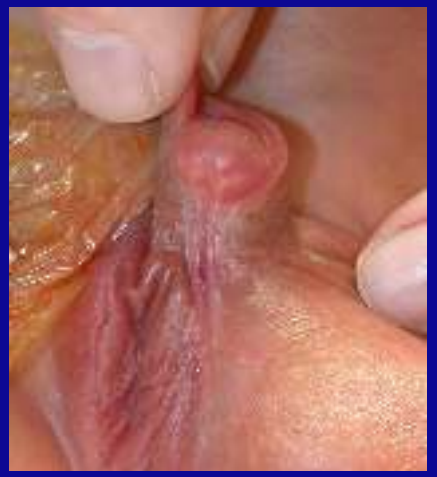
Antalya

Ürolojide Güncel Yaklaşımlar, 2008
Ankara

Hangi Cinsiyet?







Ürolojide Güncel Yaklaşımlar, 2008
Ankara

International Intersex Consensus Conference, 2006

- Cinsiyet Gelişim Bozuklukları

  Disorders of Sex Development (DSD)

- Her türlü doğumsal kromozomal, gonadal veya anatomik cinsiyet atipik gelişimi

International Intersex Consensus Conference, 2006

Doğum sonrası erken dönem

- Genital tanımsızlık
  - Dişi Tip Belirgin

    (Klitoromegali, Posterior labial füzyon, İnguinal/Labial kitle)
  - Erkek Tip Belirgin

    (Palpe edilemeyen testisler, Mikropenis, Perineal hipospadias, palpe edilemeyen testis ile beraber hipospadias)
- Ailede DSD öyküsü
- Genital ve karyotipik uyumsuzluk

International Intersex Consensus Conference, 2006

İleri Yaşlarda

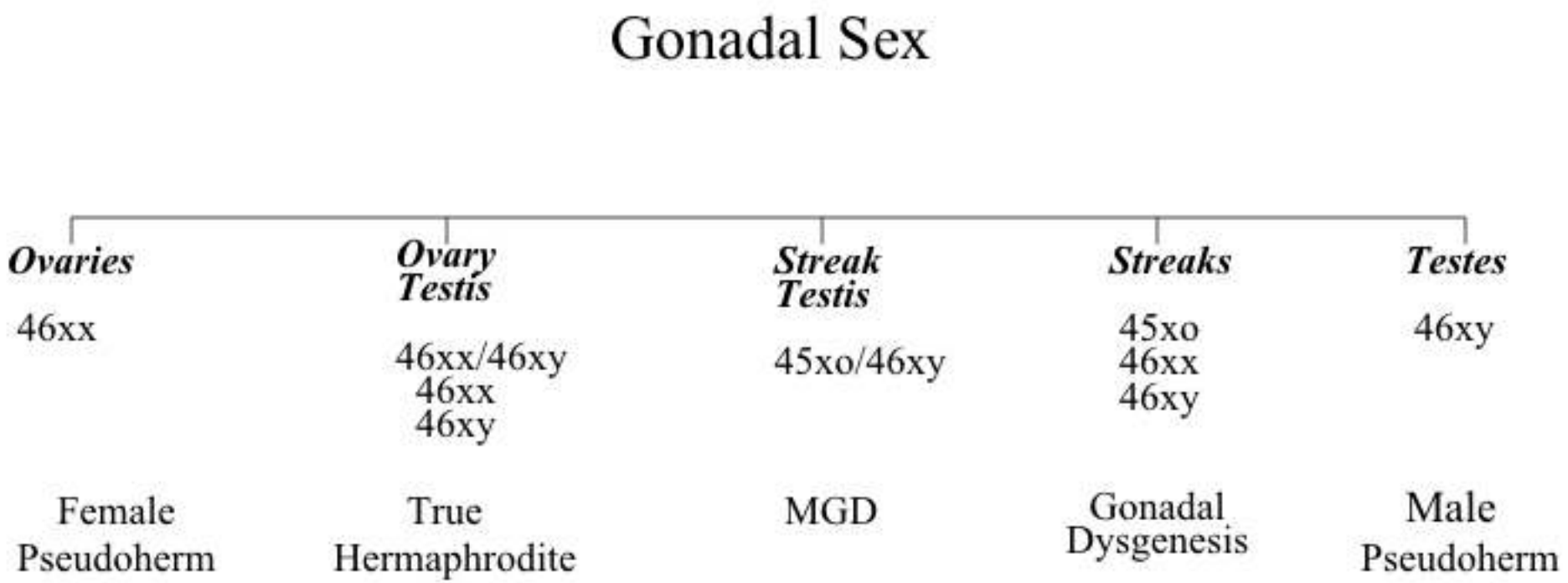
- Geç farkına varılmış genital tanımsızlık
- Kızda inguinal herni
- Gecikmiş / Eksik puberte
- Kızda virilizasyon
- Primer amenore
- Oğlanda meme gelişimi
- Oğlanda gros hematüri

International Intersex Consensus Conference, 2006

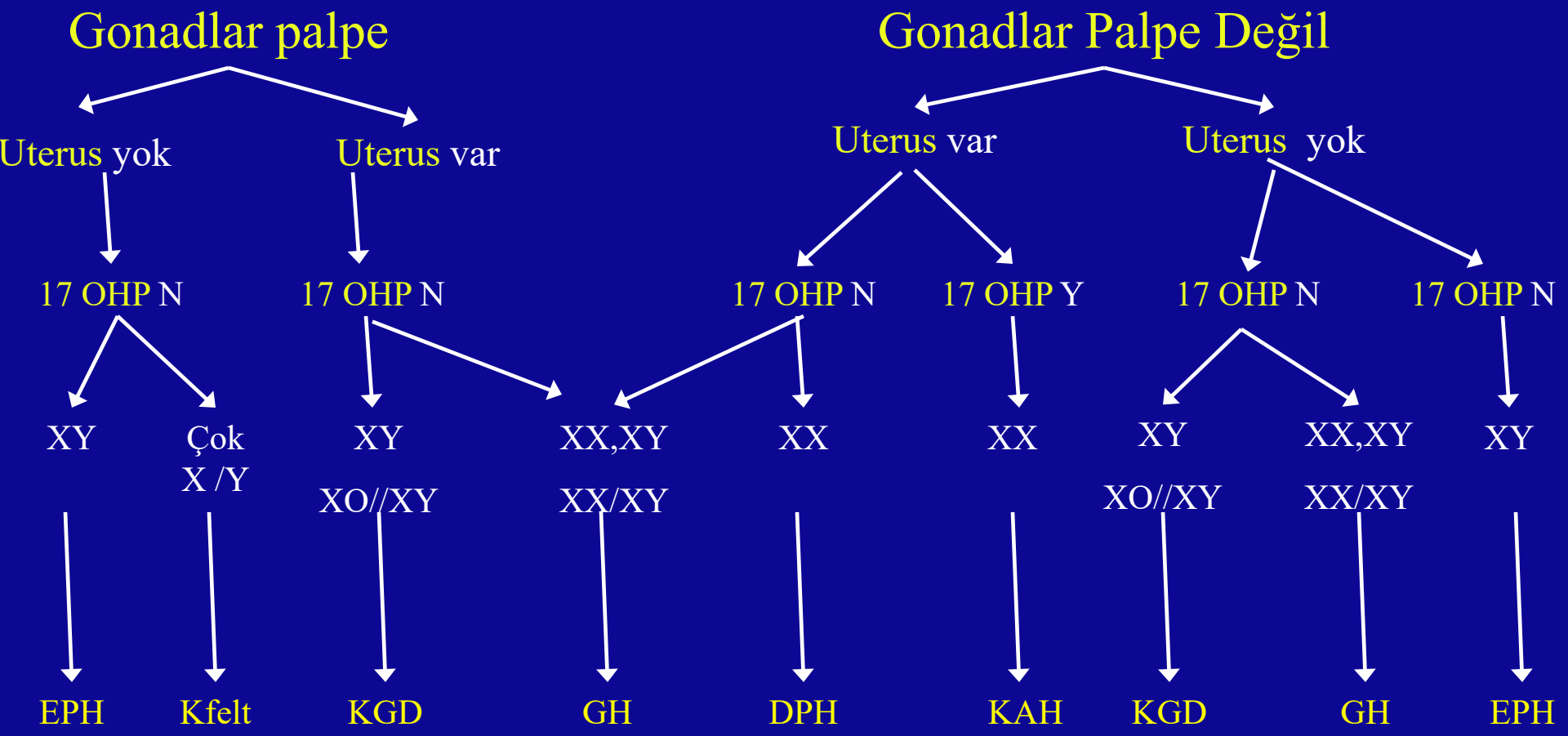
Yenidoğan taraması ilk basamak

- SRY odaklı karyotipleme
- Görüntüleme
- 17-OH Progestrone (Plasma)
- Testosterone
- Gonadotropinler
- Anti-Müllerian Hormon
- Elektrolitler
- 48 saat Içinde sonuç !!!!

Allen sınıflandırması (Gonadal histoloji)



Tanımlanamayan genitalya



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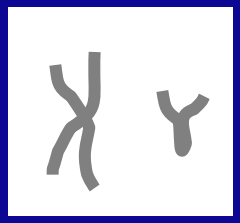
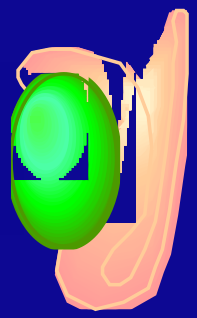
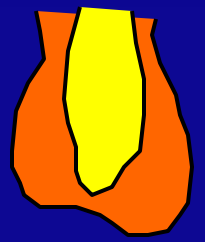
Kromosomal seks

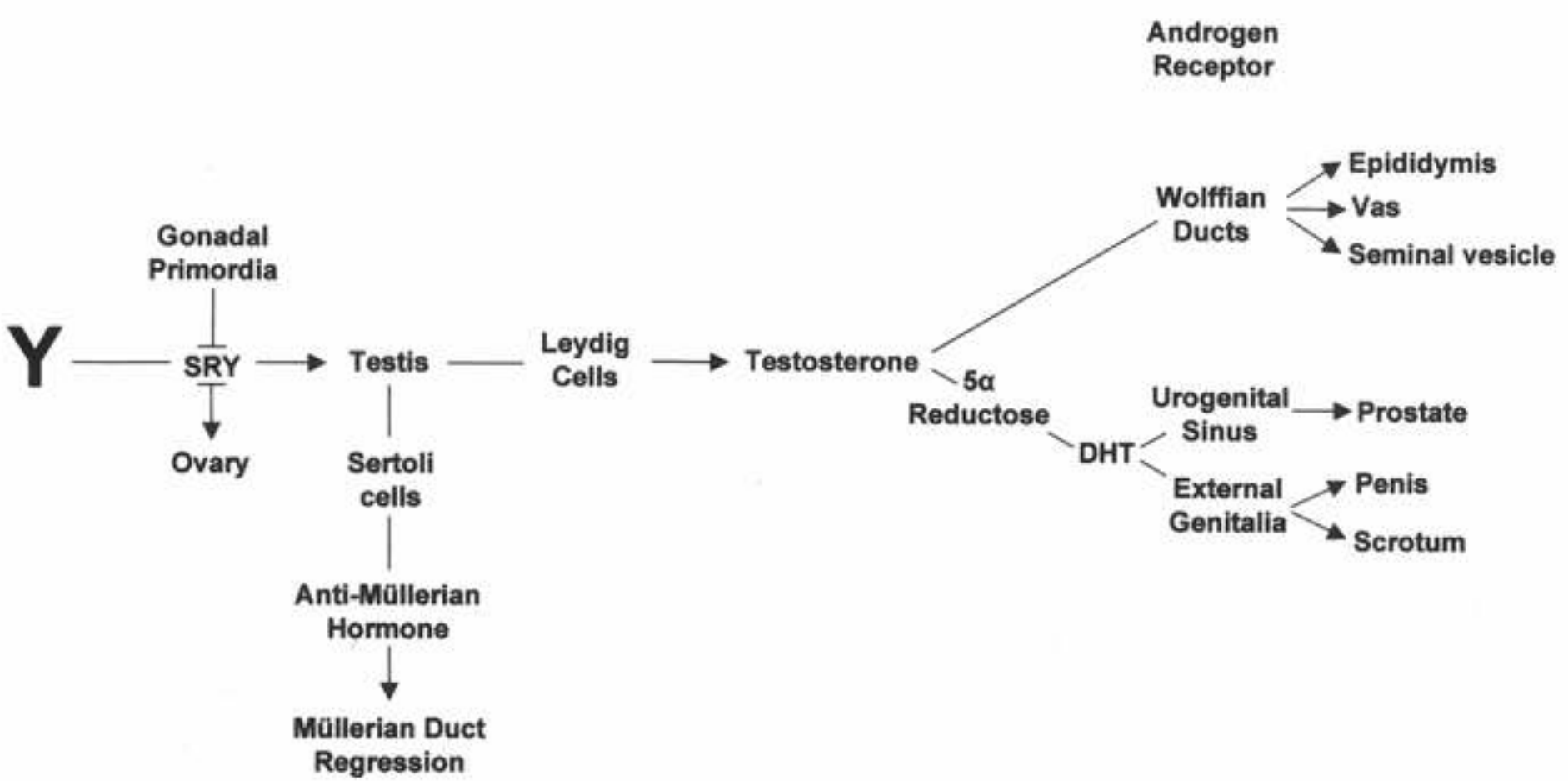


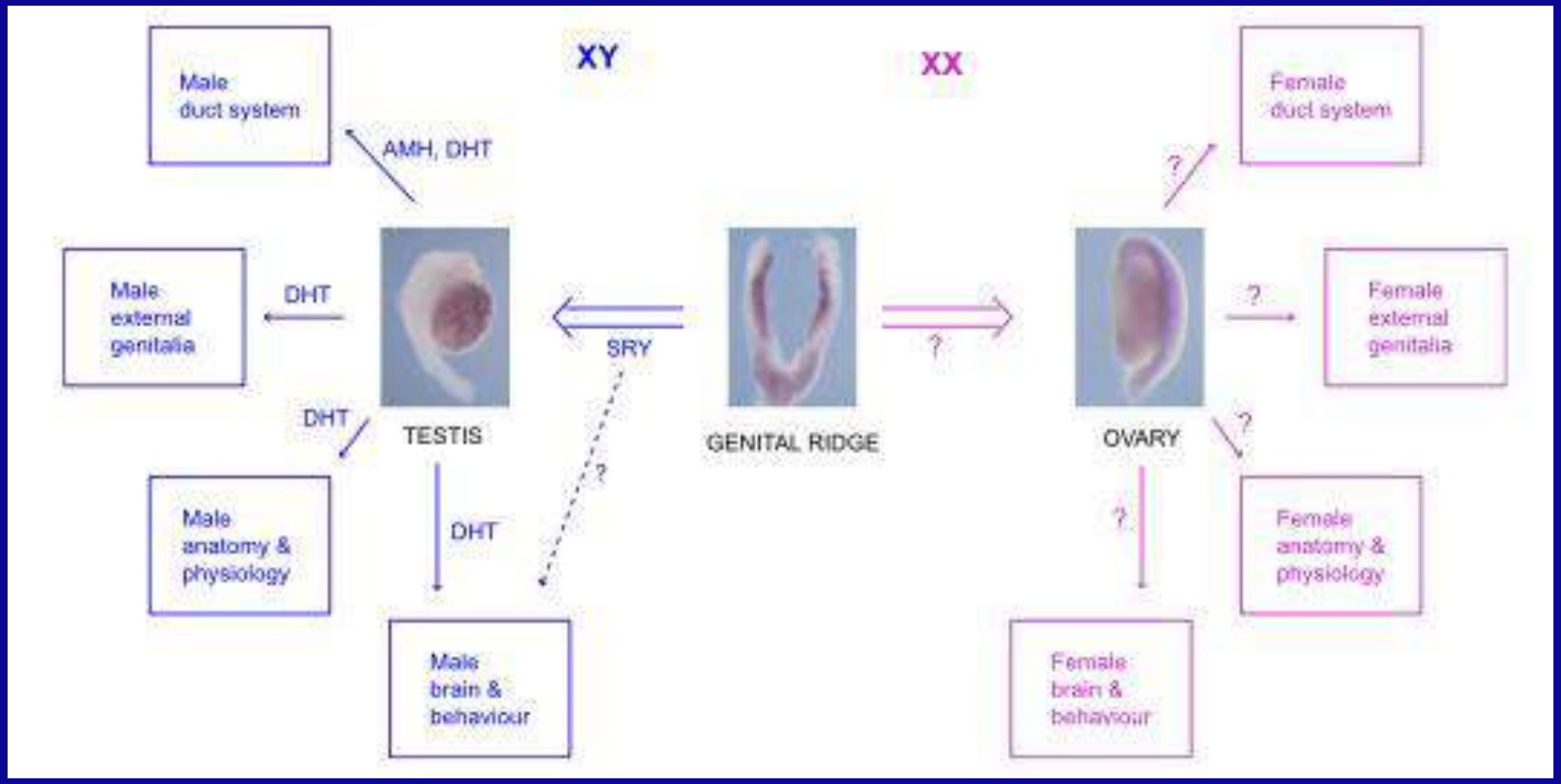
Gonadal seks



Fenotipik seks




Androgen
Receptor
Gonadal
Primordia
Y
SRY
Ovary
Testis
Sertoli
cells
Anti-Müllerian
Hormone
Müllerian Duct
Regression
Leydig
Cells
Testosterone
Wolffian
Ducts
Epididymis
Vas
Seminal vesicle
5α
Reductose
DHT
Urogenital
Sinus
Prostate
External
Genitalia
Penis
Scrotum



Ürolojide Güncel Yaklaşımlar, 2008
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Lhx9	Transcription factor	Blockage in genital ridge development	*
Emx2	Transcription factor	Blockage in genital ridge development	*
M33	Transcription factor	Gonadal dysgenesis	*
		Testis-determining pathway	
Gata4/ Fog2	Transcription/cofactor	Reduced *Sry* levels, XY sex reversal	*
Sry	Transcription factor	XY sex reversal	XY sex reversal (LOF); XX sex reversal (GOF)
Sox9	Transcription factor	XY sex reversal	Campomelic dysplasia, XX sex reversal (GOF)
Sox8	Transcription factor	XY sex reversal in combination with partial loss of *Sox9* function	*
Fgf9	Signaling molecule	XY sex reversal	*
Dax1	Nuclear receptor	Impaired testis cord formation and spermatogenesis	Hypogonadism
Pod1	Transcription factor	XY sex reversal	*
Dhh	Signaling molecule	Impaired differentiation of Leydig and PM cells	XY gonadal dysgenesis
Pgdra	Receptor	Reduction in mesonephric cell migration	*
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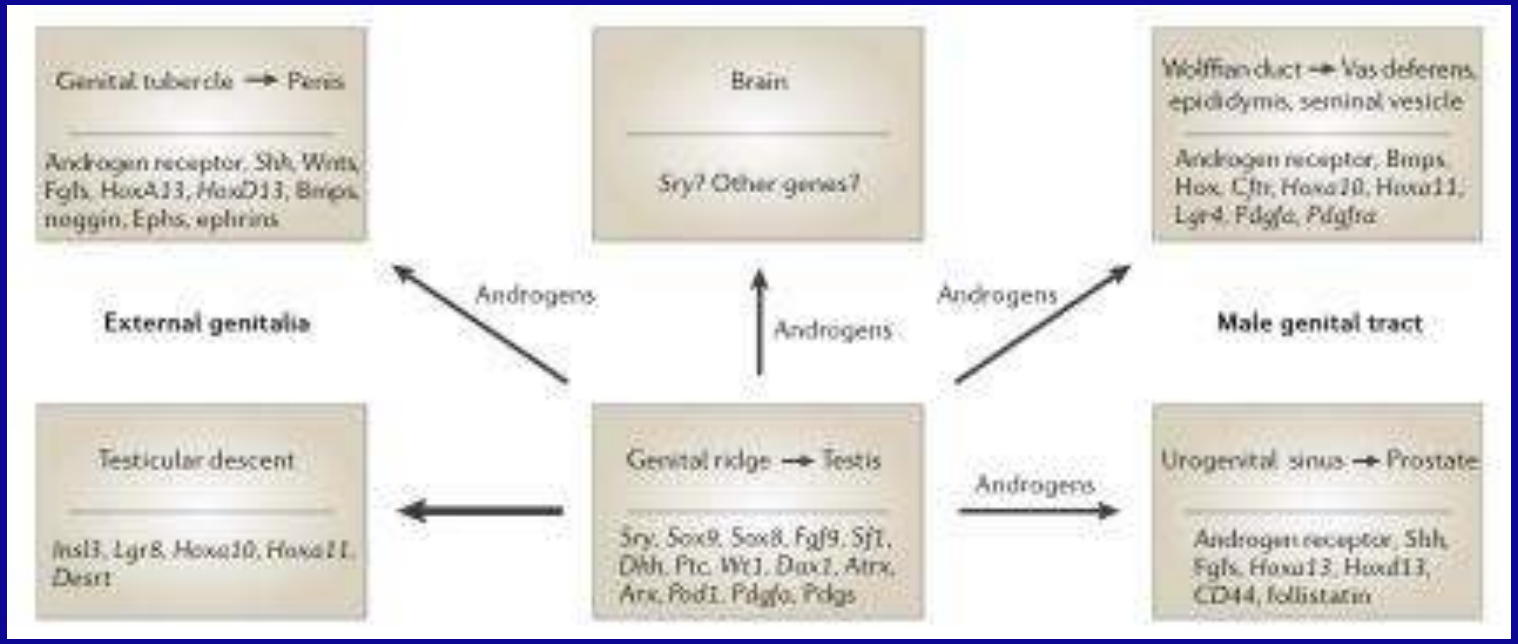

Ürolojide Güncel Yaklaşımlar, 2008
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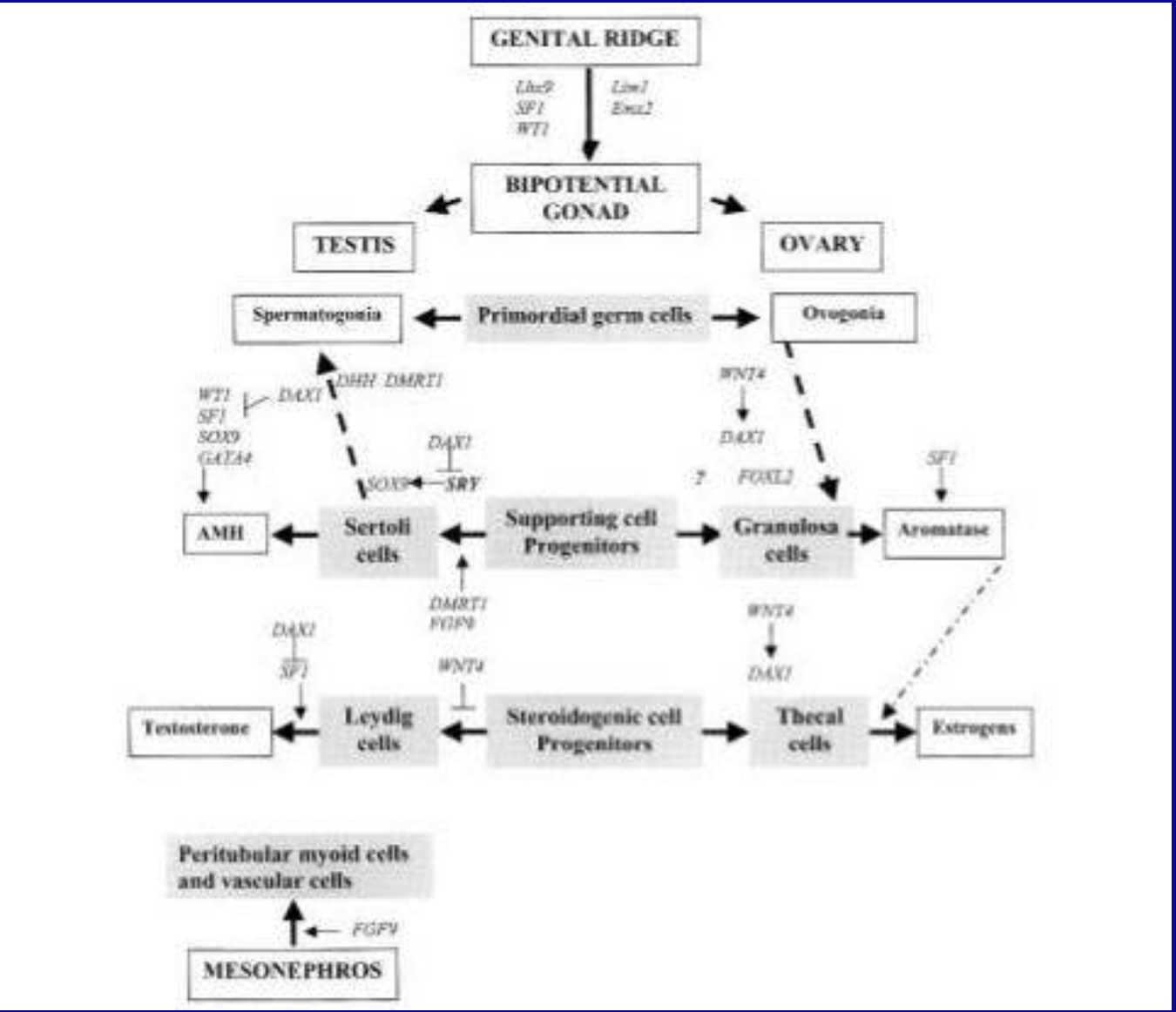
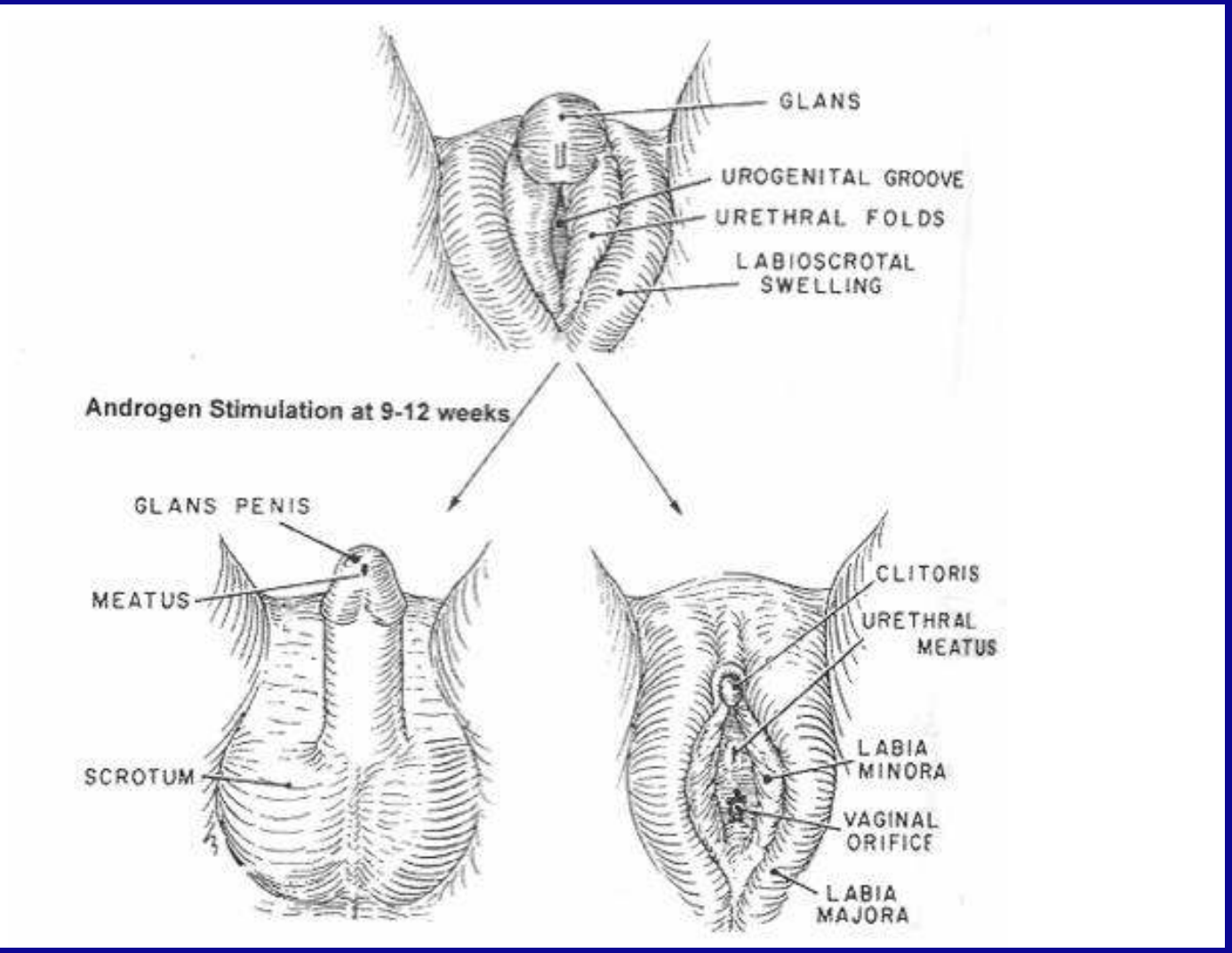


Ürolojide Güncel Yaklaşımlar, 2008
Ankara

8 haftalık fetüste başkalaşmamış cinsiyet



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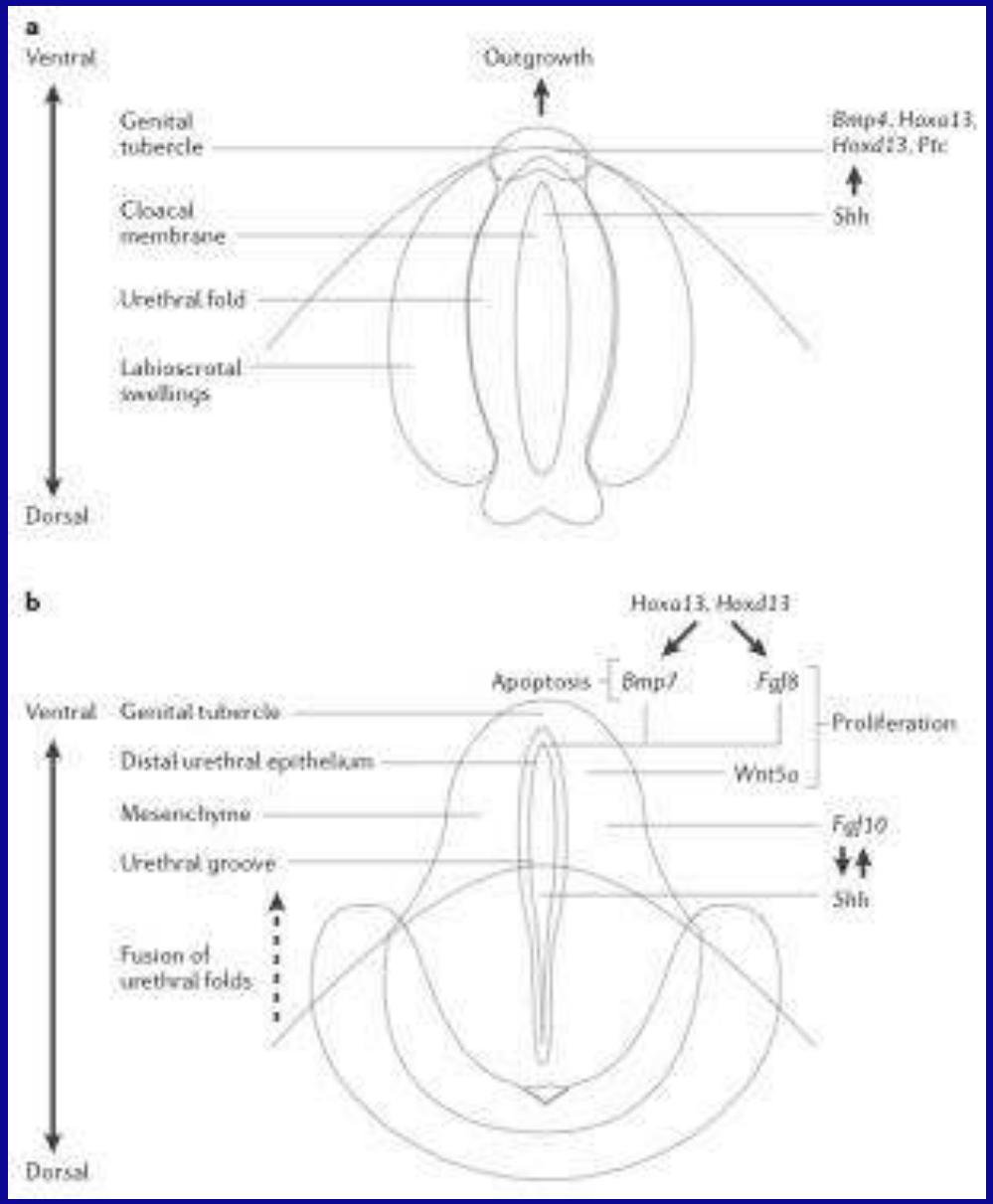

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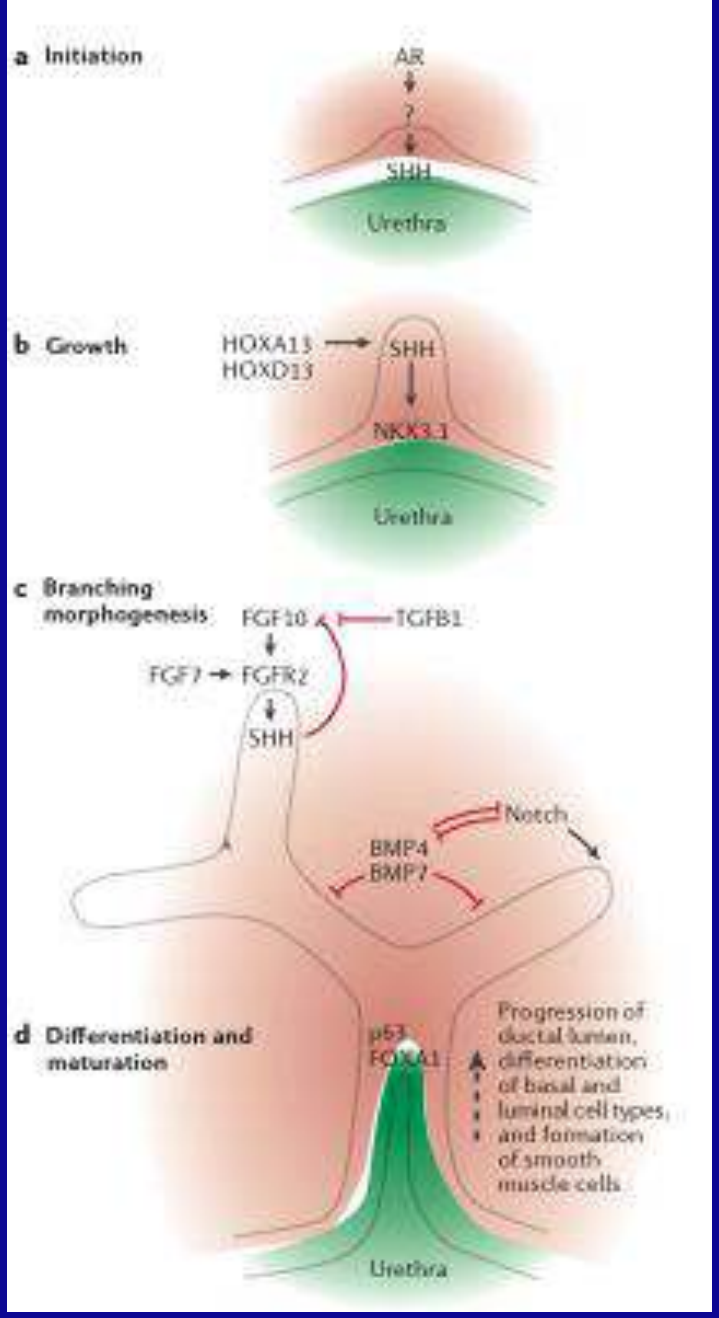
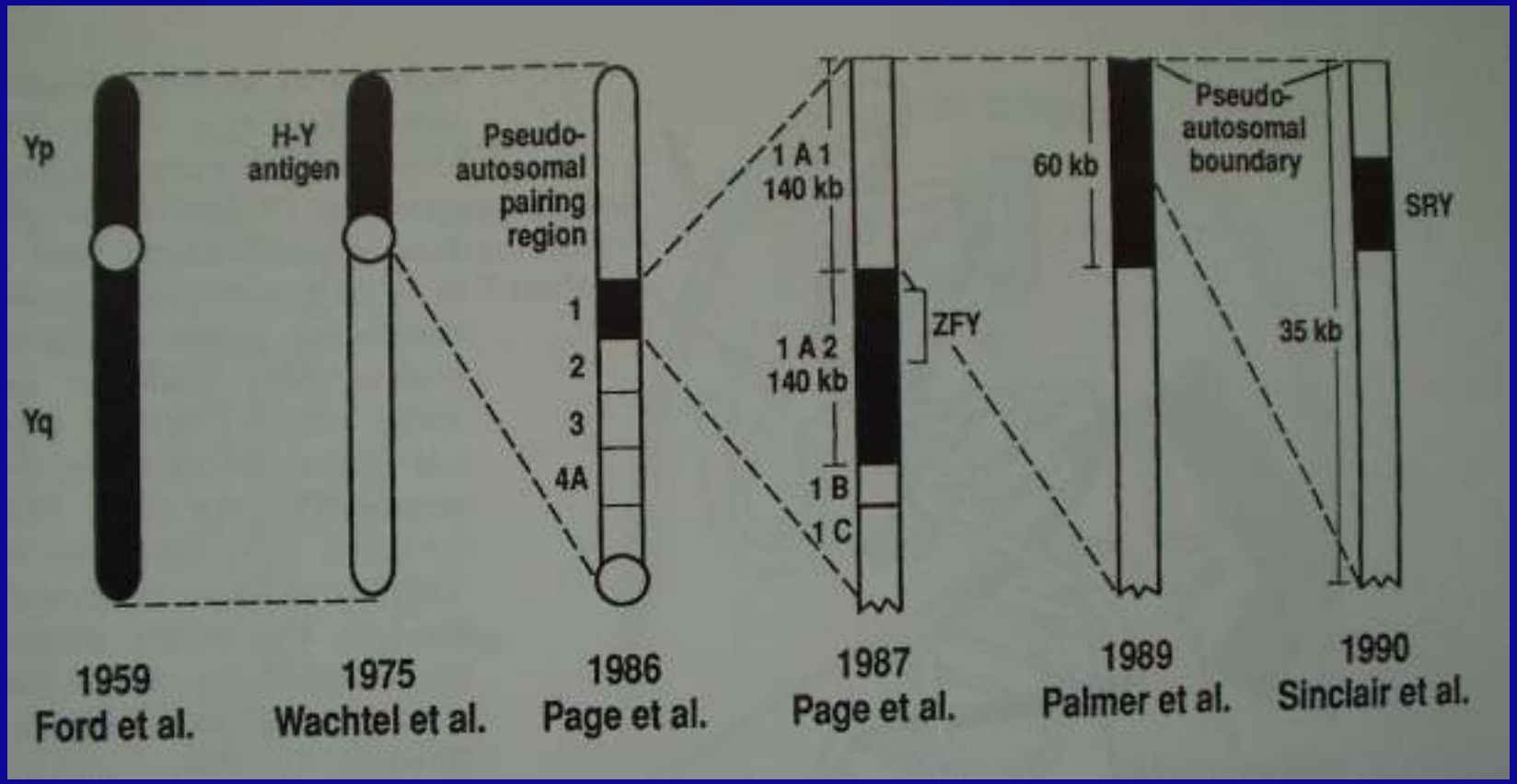
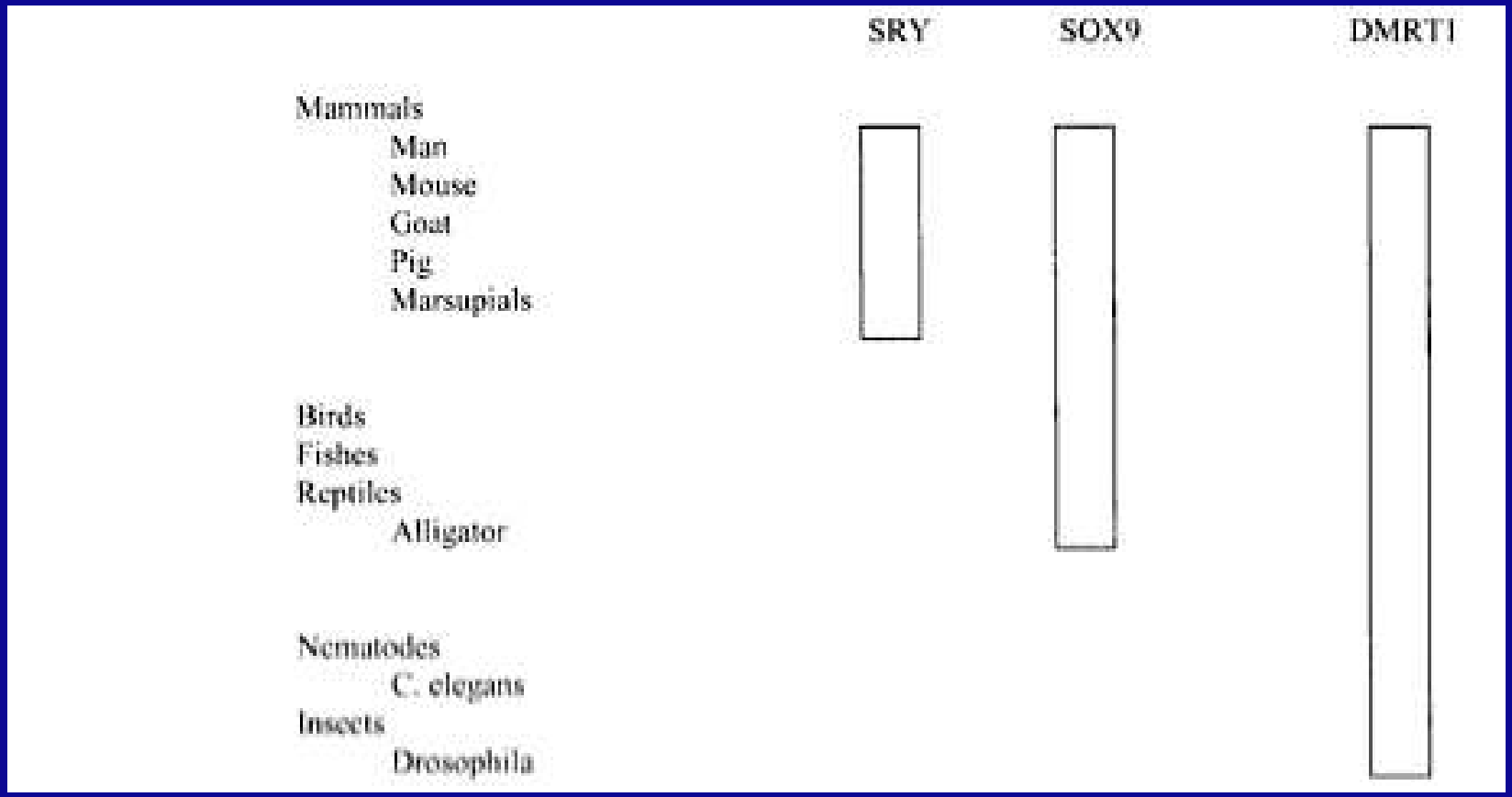


Ürolojide Güncel Yaklaşımlar, 2008
Ankara

Gonadal Başkalaşım Bozuklukları

- Seminifer Tübül Disgenezi (Klinefelter sendromu ve benz)
- 46,XX erkek veya 46,XY kadın (Ters Cinsiyet)
- Gonadal Disgenez Sendromları
  - Turner Sendromu
  - Saf Gonadal Disgenez
  - Karışık Gonadal Disgenez
  - Disgenetik Erkek PH
  - Testiküler Regresyon Sendromu
- Gerçek HM


Yp
Yq
H-Y antigen
Pseudo-autosomal pairing region
1
2
3
4A
1 A 1 140 kb
1 A 2 140 kb
1 B
1 C
ZFY
60 kb
Pseudo-autosomal boundary
35 kb
SRY
1959 Ford et al.
1975 Wachtel et al.
1986 Page et al.
1987 Page et al.
1989 Palmer et al.
1990 Sinclair et al.



Ürolojide Güncel Yaklaşımlar, 2008
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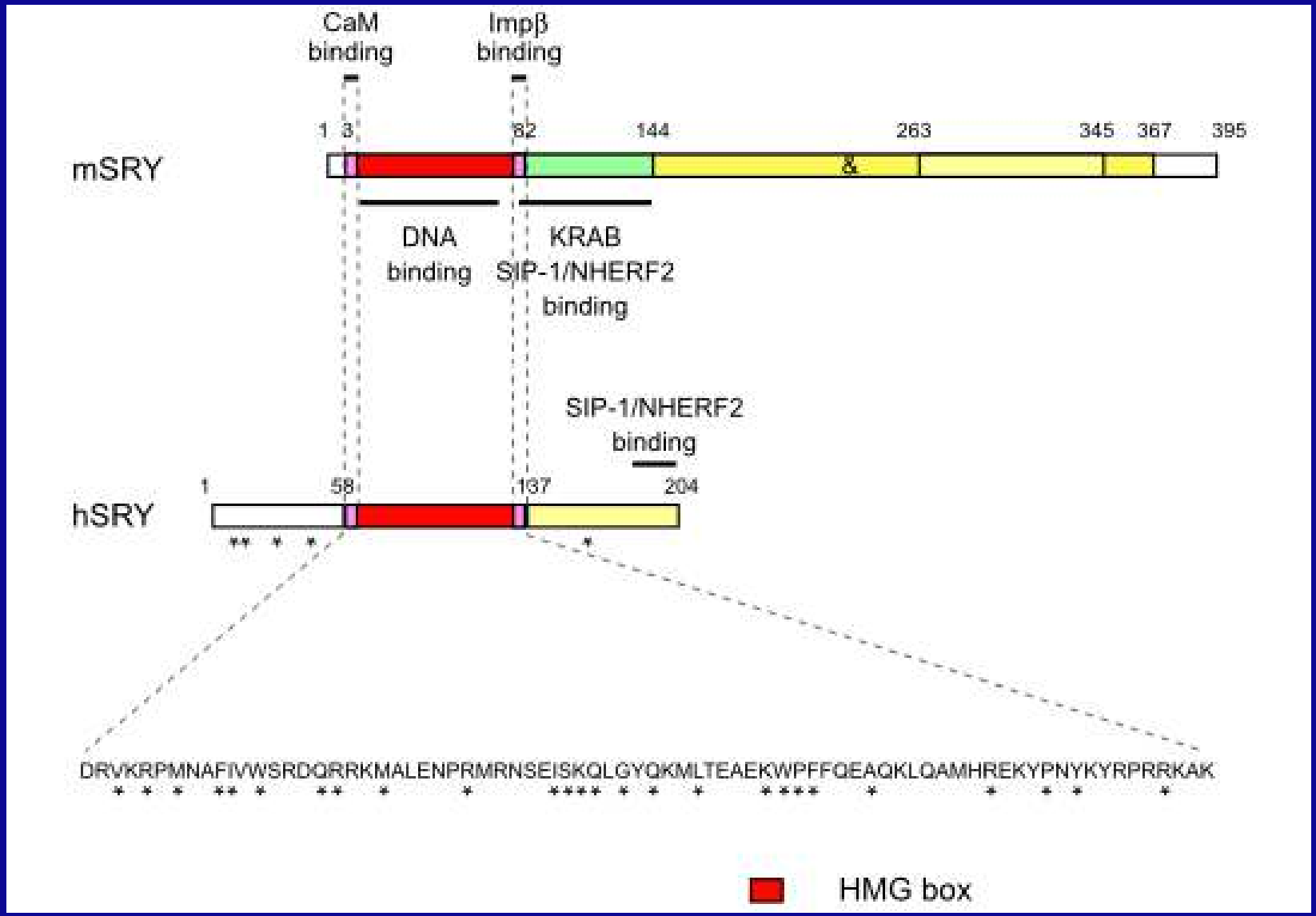

CaM binding
Impβ binding
1
3
82
144
263
345
367
395
mSRY
&
DNA binding
KRAB
SIP-1/NHERF2 binding
SIP-1/NHERF2 binding
1
58
137
204
hSRY
DRVKRPMNAFIVWSRDQRRKMALENPRMRNSEISKQLGYQKMLTEAEKWPFFQEAQKLQAMHREKYPNYKYRPRRKAK
HMG box

Gonadal Başkalaşım Bozuklukları

- Seminifer Tübül Disgenezi
  (Klinefelter sendromu ve benz)

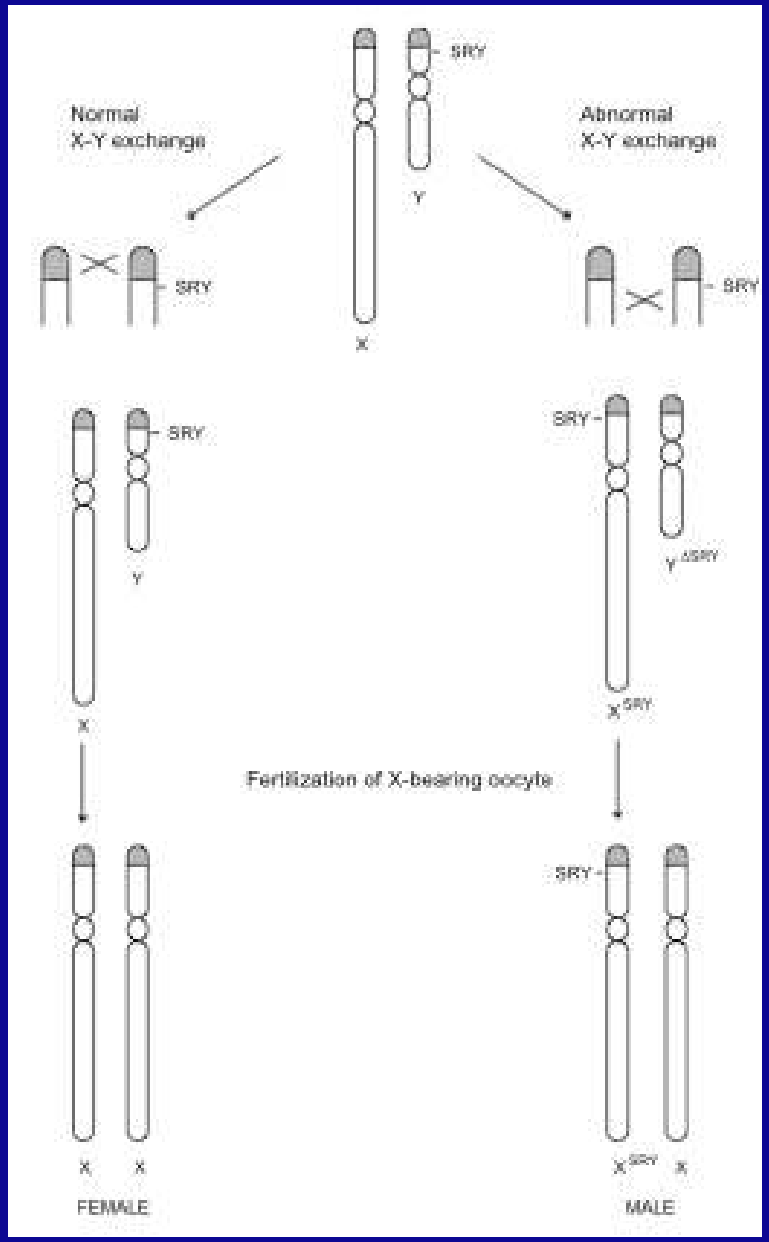
- En sık gonadal anomali (1:1000)
- En az 1 Y Kromozomu ve En az 2 X Kromozomu
  - 47, XXY, 48, XXXY, 48, XXYY, 49, XXXXYY
  - Sperm varsa, 46,XY/47,XXY
- T D/N, GT Y, E N/Y

Gonadal Başkalaşım Bozuklukları

- Ters Cinsiyet

- 1:20.000
- SRY geninin X krz yada otozomal krz translokasyonu
- SRY geninin fonksiyon kaybedici mutasyonu (LOF)
- Başka bir genin SRY fonksiyonu kazanıcı mutasyonu (GOF)
- SRY bağımlı ya da bağımsız başka genlerin mutasyonu

- T D/N, GT Y, E N/Y



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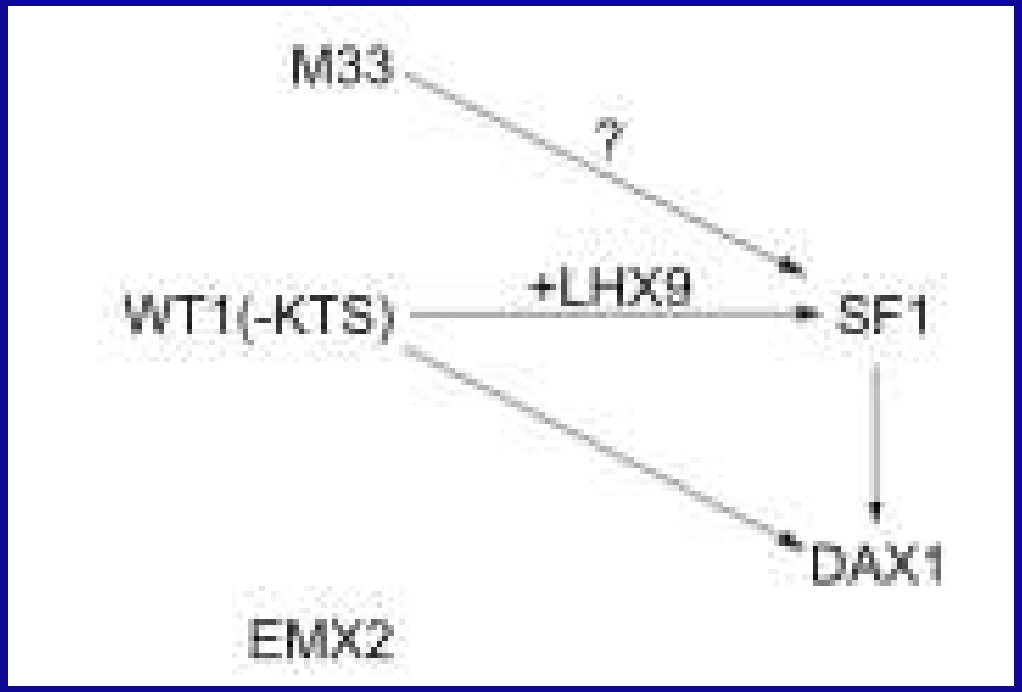

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Gonadal Başkalaşım Bozuklukları

- Turner Sendromu

- 1:2500
- Tek X Krz (45, X0)
- Y krz ? Gonadoblastoma
- Oosit hiç yok (Çizgi gonad)
- T D, GT Y, E D

Gonadal Başkalaşım Bozuklukları

- Saf Gonadal Disgenez

- 46, XX
- Oosit hiç yok (Çizgi gonad)

- T D, GT Y, E D

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Gonadal Başkalaşım Bozuklukları

- Karışık Gonadal Disgenez

- İkinci en sık tanımlanamayan genital nedeni
- Tek taraf testis diğer taraf çizgi gonad ve persistan Müllerian kanal
- 45,XO/46,XY
- Disgenetik testis tarafı Wollfiyan kanal

- HCG stim pozitif yanıt ve AMH mevcut

Ürolojide Güncel Yaklaşımlar, 2008 Ankara

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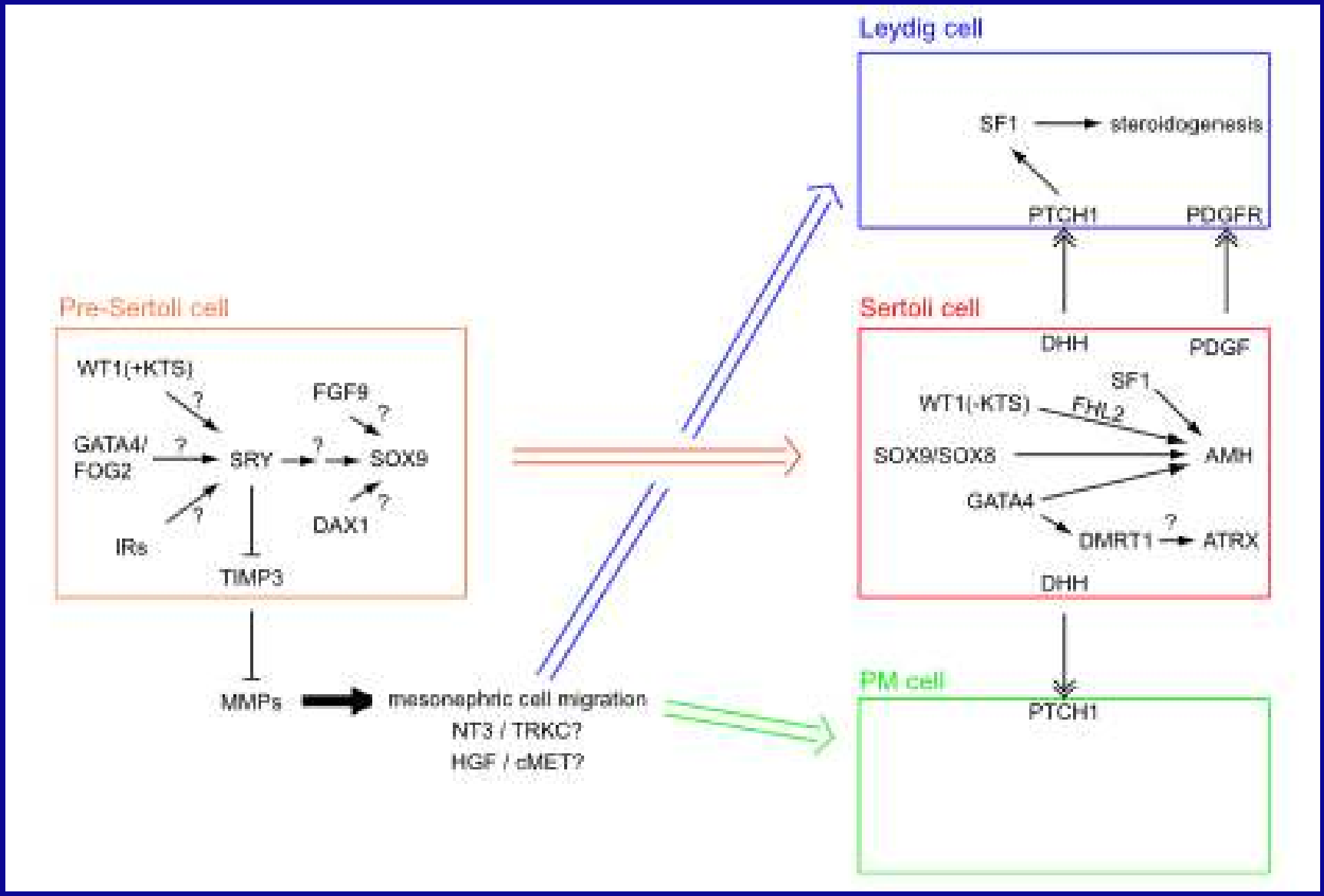
Gonadal Başkalaşım Bozuklukları

- Disgenetik Erkek Psödohermafroditizm

- Çift taraflı disgenetik testis
- 45,XO/46,XY veya 46,XY
- Disgenetik testis tarafı Wollfiyan kanal

- Değişken HCG stim yanıt ve AMH seviyesi mevcut



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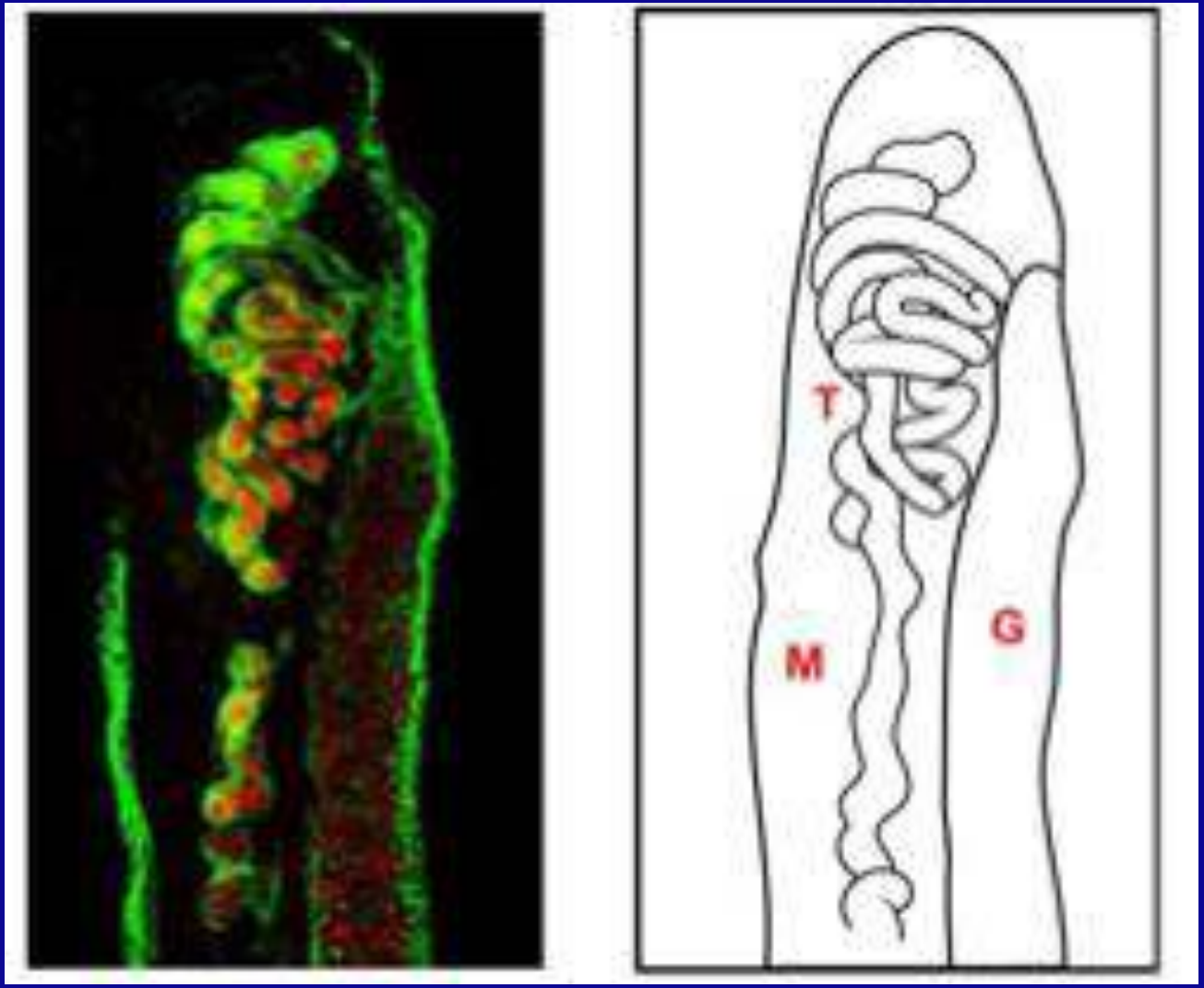
Gonadal Başkalaşım Bozuklukları

- Testiküler Regresyon Sendromu

- Çift taraflı testis yokluğu
- 46,XY

- Negatif HCG stim yanıt ve negatif AMH seviyesi
- T D, GT Y



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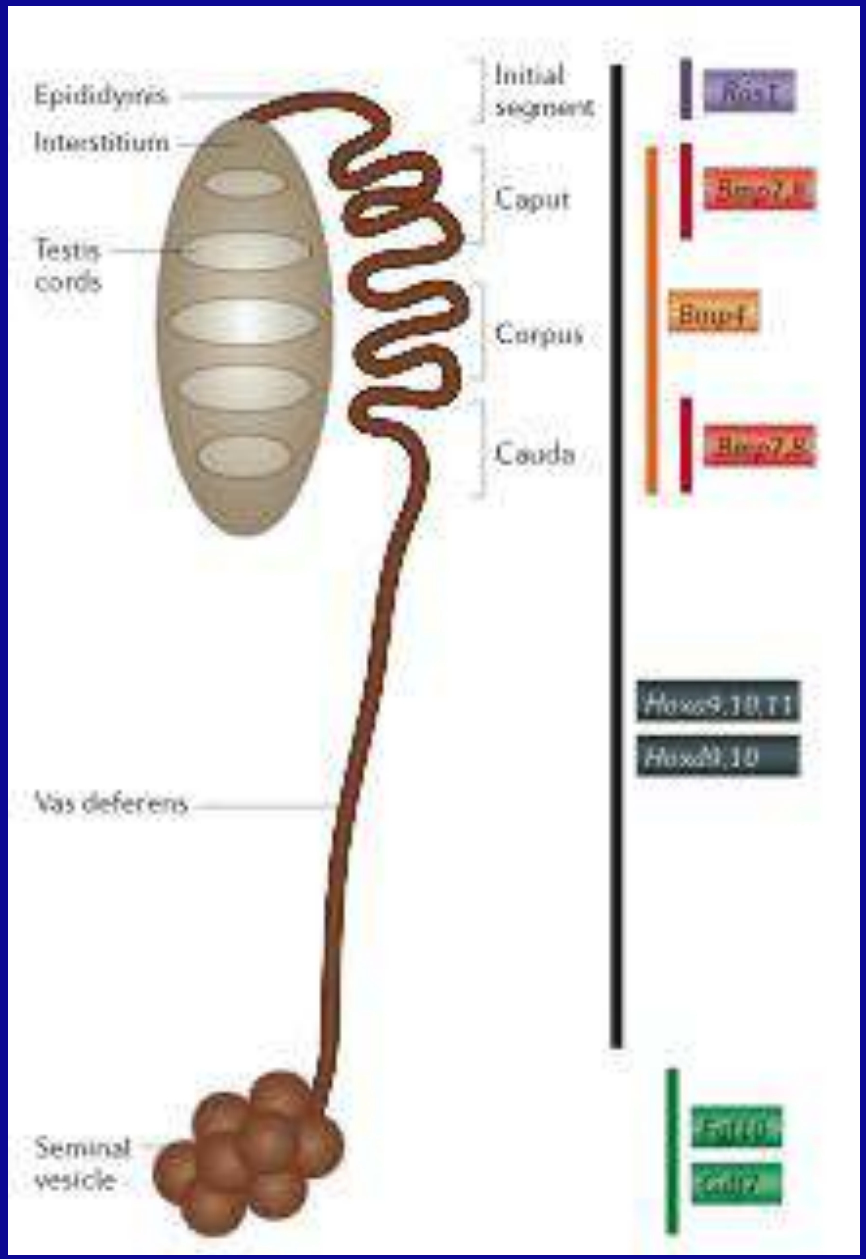

Ürolojide Güncel Yaklaşımlar, 2008
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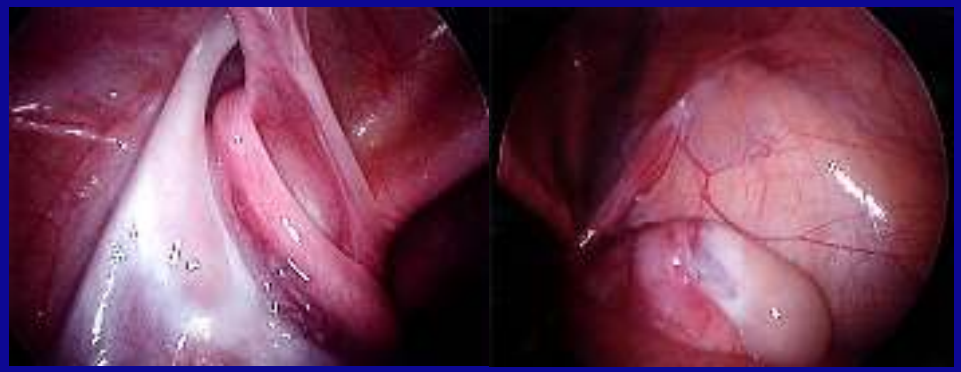
Gonadal Başkalaşım Bozuklukları

- Gerçek Hermafroditizm

- Over ve testisin aynı anda olması
- 46,XX (olguların 2/3 ü) herhangi bir krz SRY etkisi
- 46,XY SRY nin tam çalışmaması
- 46,XX/46,XY kimerizm



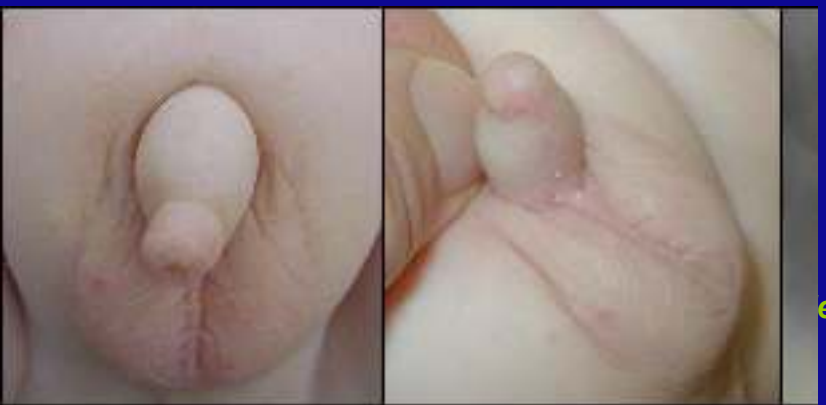
Dişi Psödohermafrotidizm

- Konjenital Adrenal Hiperplazi
  - 21-OHlase eksikliği
  - 11B-OHlase eksikliği
  - 3B OHst D eksikliği
- Maternal Androjenler

Dişi Psödohermafrotidizm

- 21 Hidroksilaz eksikliği

- En sık genital tanımsızlık nedeni (1:5000-15.000)
  - Yüksek plazma 17 OH progesteron ve progesteron seviyesi
  - Yüksek 17-ketost ve pregnanetriol
  - Kortizol eksikliği
    - 2/3 olgu tuz kaybedici (aldosteron eksikliği)
    - 1/3 olgu sadece virilizan
    - Nadiren non-klasik form - HLA bağıntılı CYP-21 inaktivasyon düzeyi



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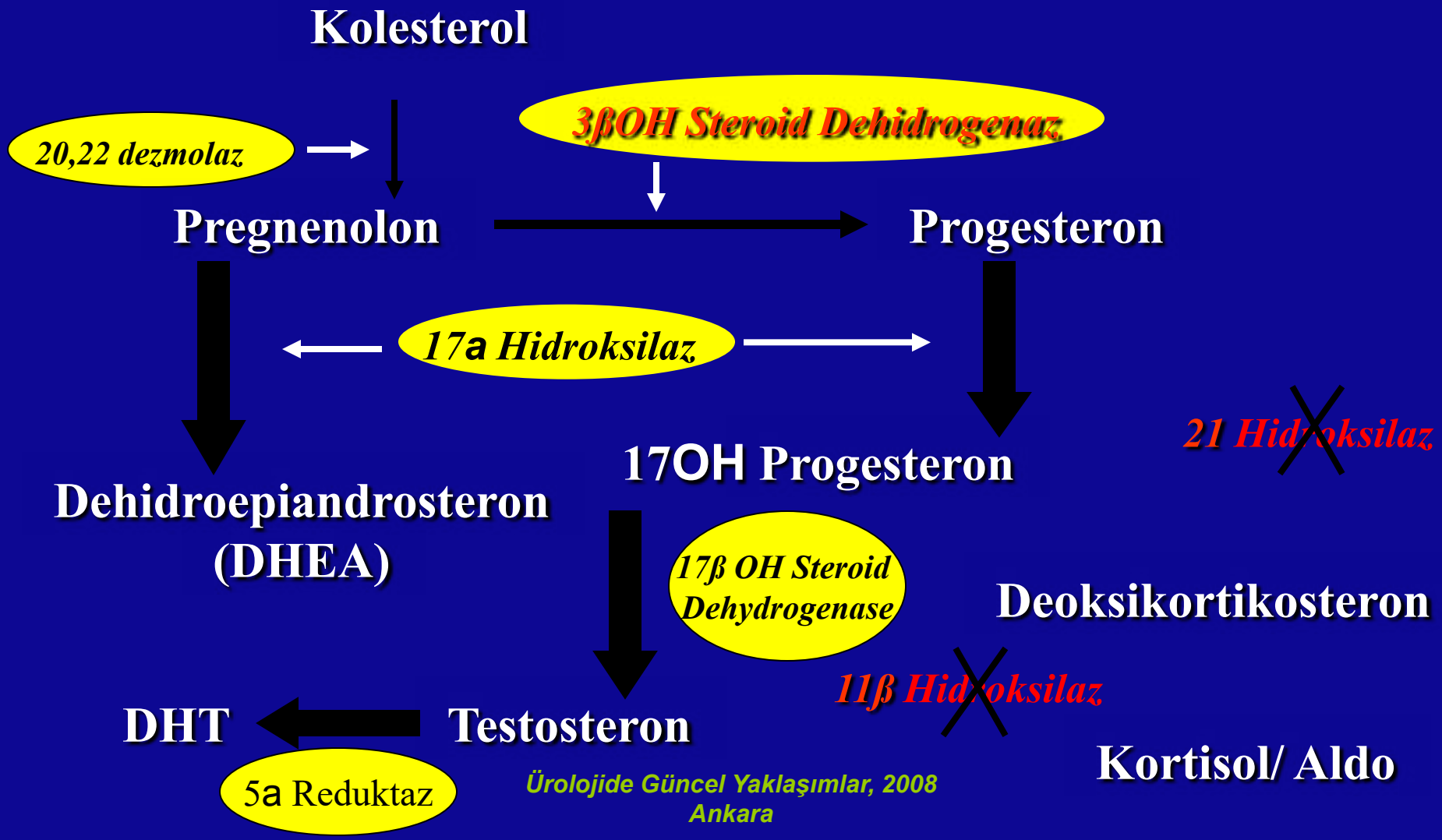
Dişi Psödohermaphroditizmde Enzimatik Blok



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Dişi Psödohermafrotidizm

- 11 Beta Hidroksilaz eksikliği

- KAH de %5
  - Yüksek plazma 11-deoksikortikosterol ve 11-deoksikortikosteron seviyesi
  - Yüksek 17-ketost ve 17-hidroksikortikosteroid
  - Yüksek deoksikortikosteron varlığı (Hipertansiyon sık)
    - Klasik tip
    - Hafif ve geç farkedilen tip- CYP-11B1 gen mutasyonu derecesine bağlı HLA bağıntısız

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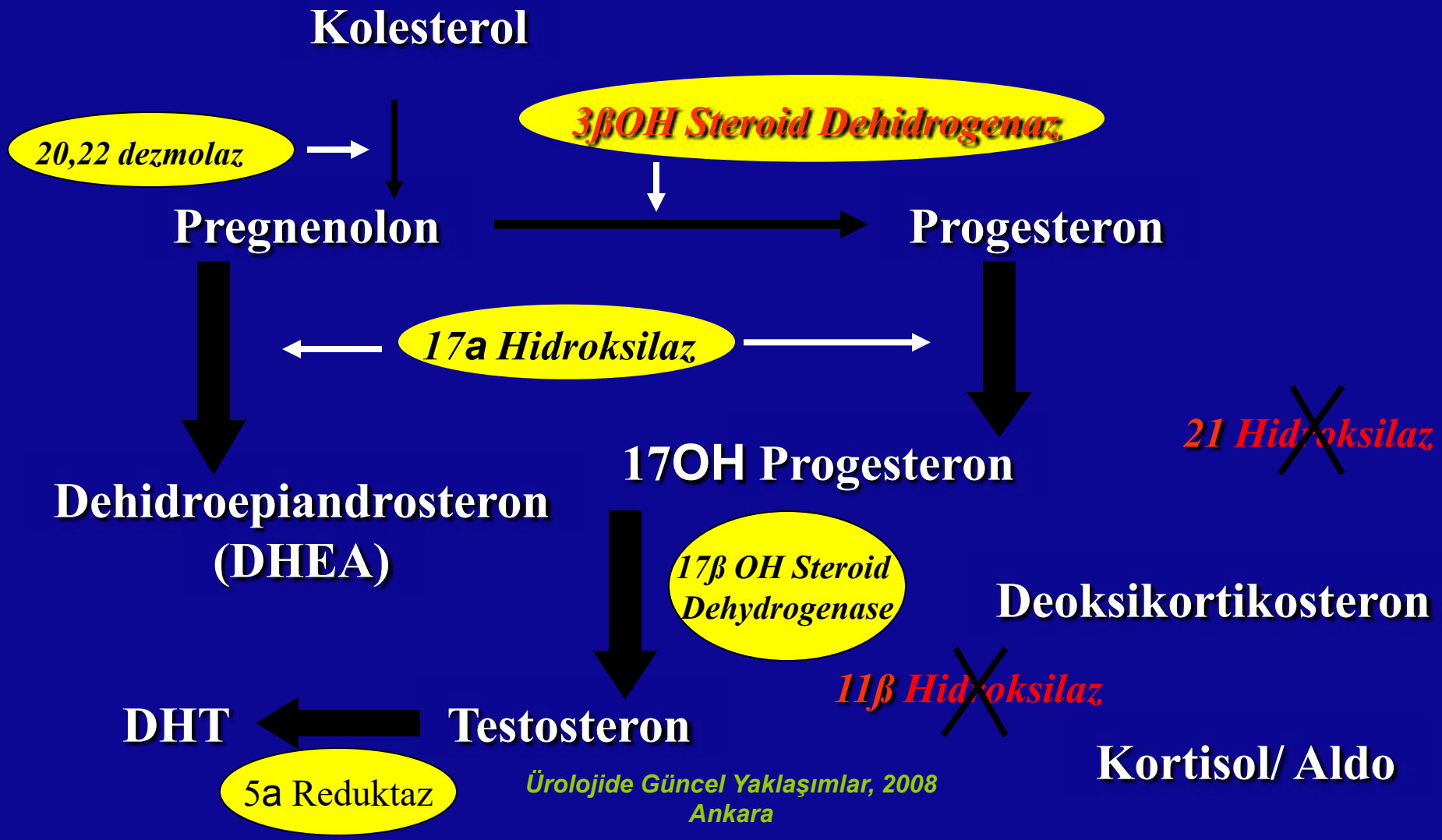
Dişi Psödohermaphroditizmde Enzimatik Blok



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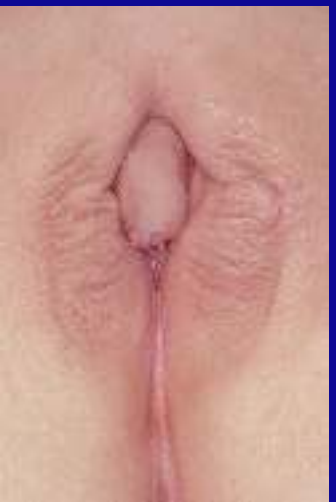
Dişi Psödohermafrotidizm

- 3 Beta Hidroksisteroid Dehidrogenaz eksikliği

- KAH de <%1
  - Yüksek plazma 17 hidroksipregnenelon ve dehidroepiandrestron
  - Otozomal ressessif ve hafif virilizan tipte
  - Erkeklerde de virilizasyonda azalma nedeni



Ürolojide Güncel Yaklaşımlar, 2008
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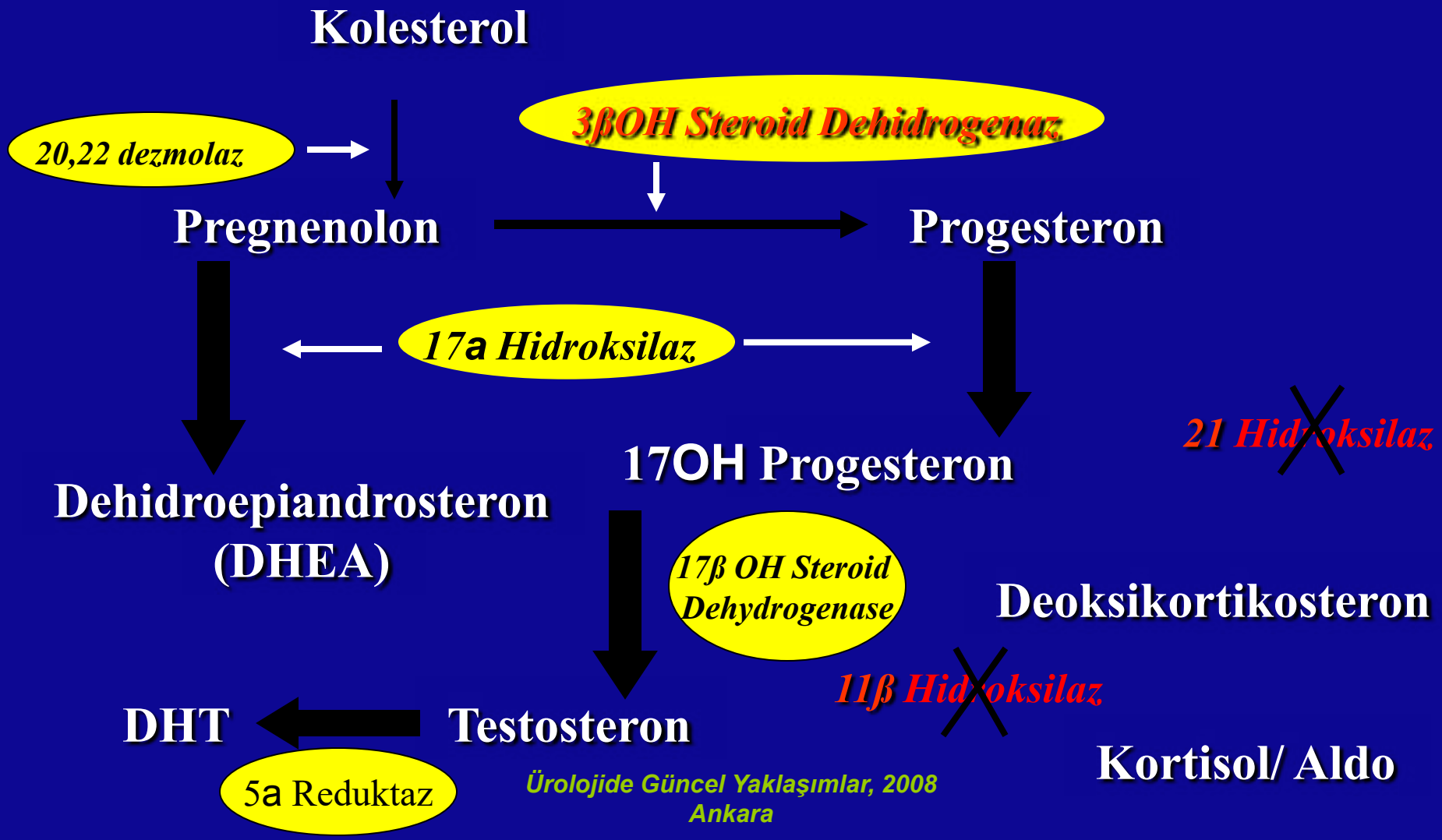


Ürolojide Güncel Yaklaşımlar, 2008
Ankara

Gen (Locus)	Protein	Fenotip
HSD17B3 (9q22)	17BOHStDH, 17ketoSt Red 3	MPH
CYP17 (10q24-25)	17 Ohlase: 20-22 lyase	MPH
CYP21 (6q21.3)	21 OHlase	FPH
HSD3B2 (1p13.1)	3B OHSt D t2	FPH
CYP11B1 (8q24)	11 B OHlase	FPH
StAR (8p11.2)	Stgenic reg pr	FPH

Erkek Psödohermafrotidizm

- Leydig Hücre Agenezi
- Testosterone Biyosentez Bozuklukları
  - Konjenital Adrenal Hiperplazi
    - Konjenital Lipoid Adrenal Hiperplazi
    - 3 B OH St D eksikliği
    - 17 A OHlase eksikliği
    - 17-20 Lyase eksikliği
    - 17 B OHst Oksidoredüktase eksikliği
- Androjene Bağımlı Hedef Organ Bozukluğu
  - Androjen Reseptör Hatası
  - Tam Testiküler Feminizasyon
  - Kısmi Androjen Yanıtsızlığı
  - İnfertil Erkeklerde Androjen Yanıtsızlığı
- Çevre Dokularda Androjen Metabolizması Hatası
  - 5 A redüktaz eksikliği
- AMH Bozukluğu
  - Persistan Müllerian Kanal Sendromu

Erkek Psödohermafrotidizm

- Leydig Hücre Aplazisi (LH Reseptör Anomalisi)

- Çok nadir
- TF dan farkı T D ve LH Y
- HCG stim negatif ama AMH mevcut
- AR doğal

Erkek Psödohermafrotidizm

- Kolestrol Yan Zincir Ayırımı Eksikliği

  Steroidogenic Acute Regulatory Protein (StAR)
- Nonvirilize dişi genitali olan ciddi hiponatremi, hiperkalemi ve metabolik asidozlu bebeklerde
- StAR taraması (20,22 Desmolase)
- Kolestrol mitokondrinin dış membranından Iç membranına taşınmaz

Erkek Psödohermafrotidizm

- 17 alfa Hidroksilaz Eksikliği
- Yüksek 18-hidroksikortikosteron, kortikosteron ve deoksikortikosteron
- Düşük Kortizol ve Yüksek ACTH

Erkek Psödohermafrotidizm

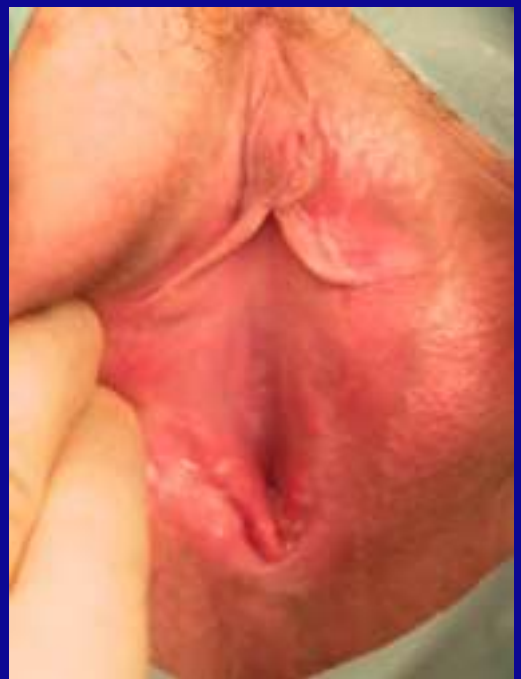
- 17, 20 Liyaz Eksikliği
- Normal Kortizol, Aldosteron ve ACTH
- Sadece Testosteron Düşük

Erkek Psödohermafrotidizm

- 17 Beta Hidroksisteroid Oksiredüktase Eksikliği
- Testosteron sentezinde son basamak hatası
- Pubertede Androstenedion aşırı artar ve virilizasyon başlar
- T D, LH Y
- AHM mevcut

Erkek Psödohermafrotidizm

- Tam Androjen Duyarsızlığı(Testiküler Feminizasyon)
- X kromozomunda AR
- Tek kopya olduğu için nokta mutasyon bile etkili
- Sadece normal AR %1 in altına düşünce tam TF
  - N T/DHT oranı
  - AR miktar tespiti
  - AR kalite tespiti (Hücre kültüründe)



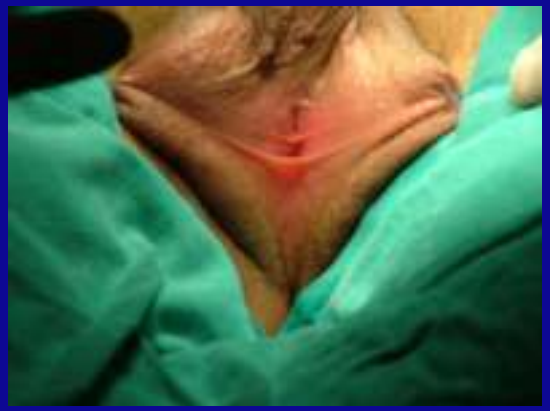
Ürolojide Güncel Yaklaşımlar, 2008 Ankara

Erkek Psödohermafrotidizm

- Kısmi Androjen Duyarsızlığı(Reifenstein Sendromu)
- X kromozomunda AR
- Tek kopya olduğu için nokta mutasyon bile etkili
- AR sayısı ve kalitesi kısmen bozuk
- Eksternal genital daha az tanımlanabilecek düzeyde
- N T/DHT oranı, Hücre kültüründe AR fonks testi

Erkek Psödohermafrotidizm

- 5 Alfa Redüktaz Eksikliği
- Tip 2 genindeki mutasyon
- Doğumdaki ciddi hipospadiak görünüm pubertede belirgin virilizasyon ile karakterize
- T/DHT Y
- Hücre kültüründe 5aR aktivitesi düşüklüğü



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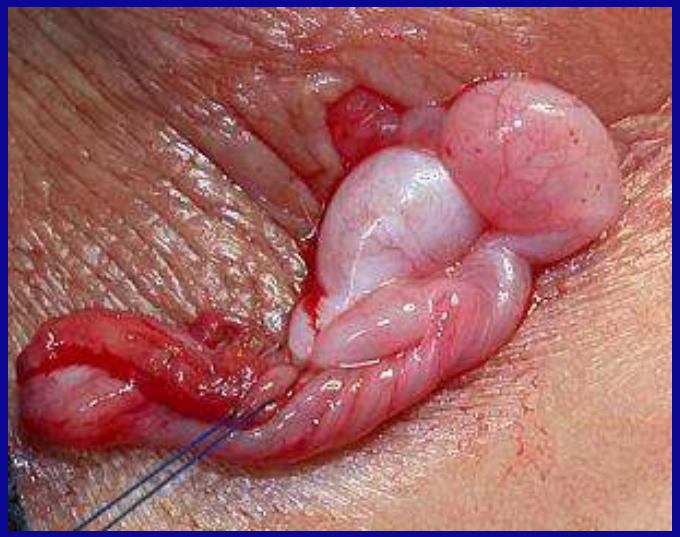
Ankara

Erkek Psödohermafrotidizm

- Persistan Müllerian Kanal Sendromu
- İnmemiş testiste müllerian derivativlerin kalması
- AMH eksikliği veya kalite bozukluğu



Ürolojide Güncel Yaklaşımlar, 2008
Ankara

Gen (Locus)		Protein	Fenotip
AMH tip 2 res	(12q12-13)	Serine threonine kinase res	PMDS
AMH	(19q13)	protein	PMDS
AR	(Xq11-12)	Ligand trskrip faktör	Andr İnsenst
SRD5A2	(5p15)	5a redüktase tip 2	MPH

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