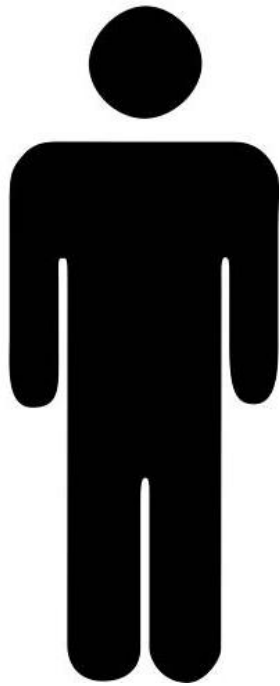


Geschlechts-Determination /-Entwicklung und Infertilität



Geschlechts-Festlegung

- chromosomal
- gonadal
- somatisch
- psychol./ sozial

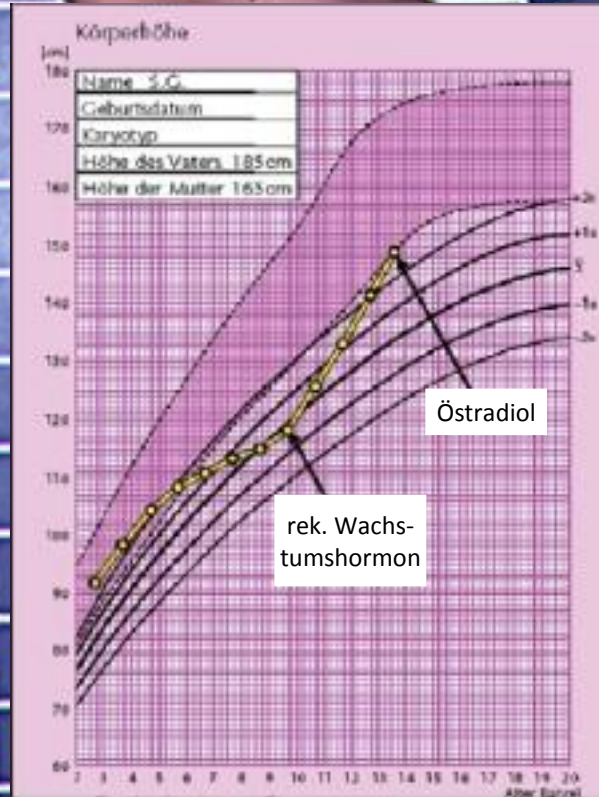
Geschlechts-Bestimmung / -Entwicklung

- Geschlechtsentwicklung
- Rolle des Y-Chromosoms
- Y-chromosomale Gene
- Kaskade der Geschlechtsbestimmung
/ -Entwicklung + Störungen

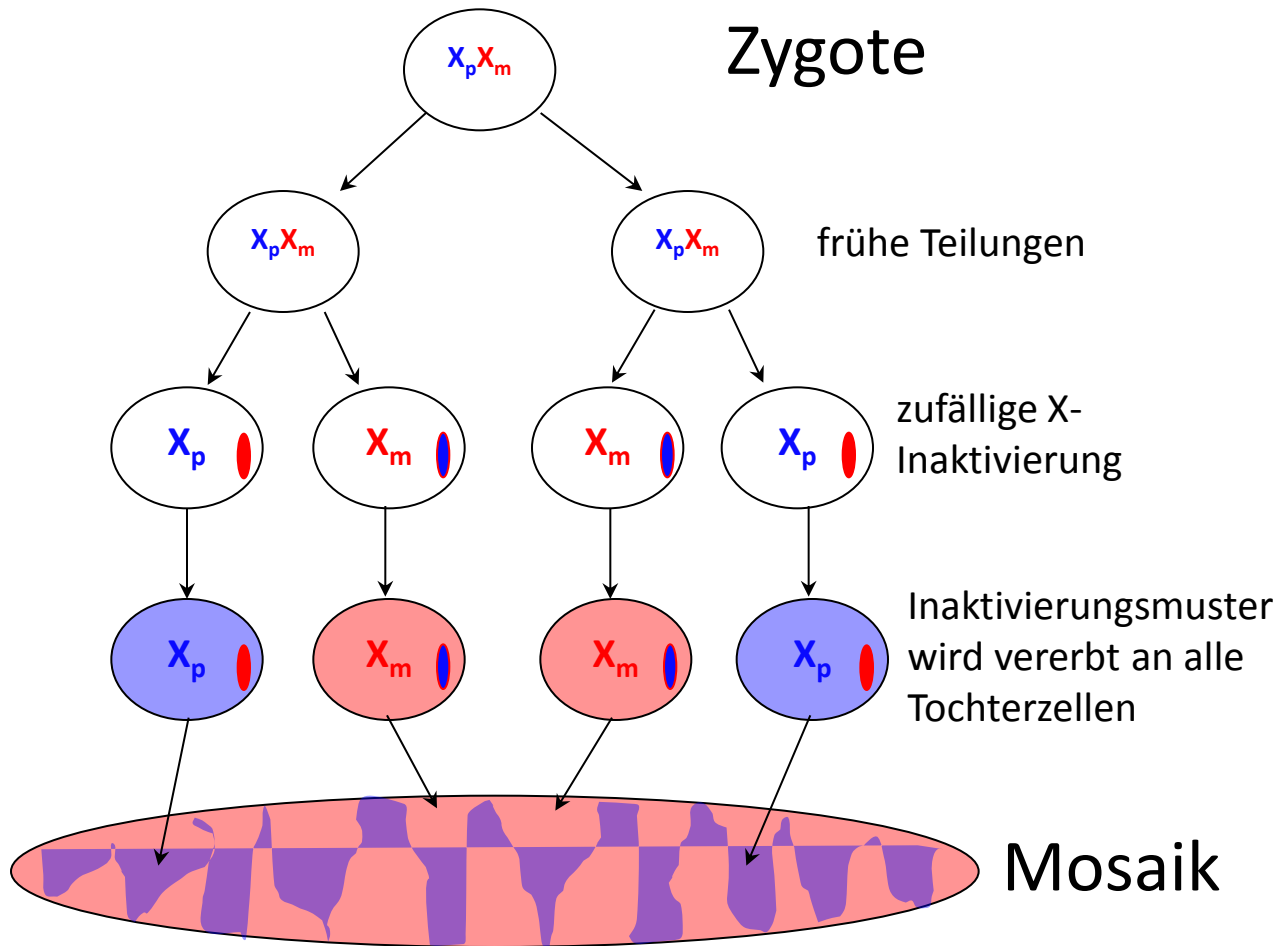
fetales Turner-Syndrom

>95% Abortrate; 1:2000 Neugeborene

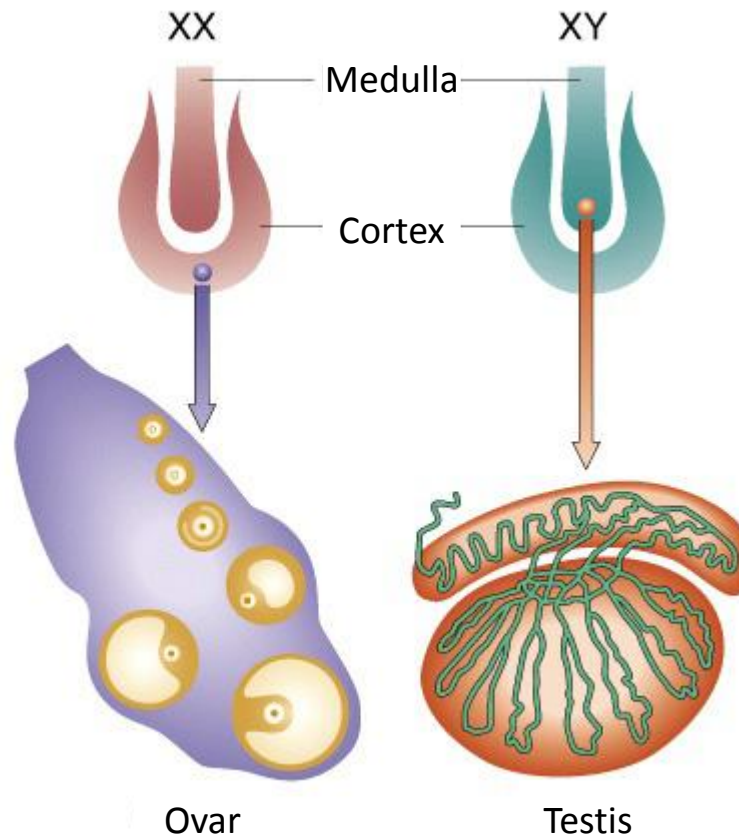




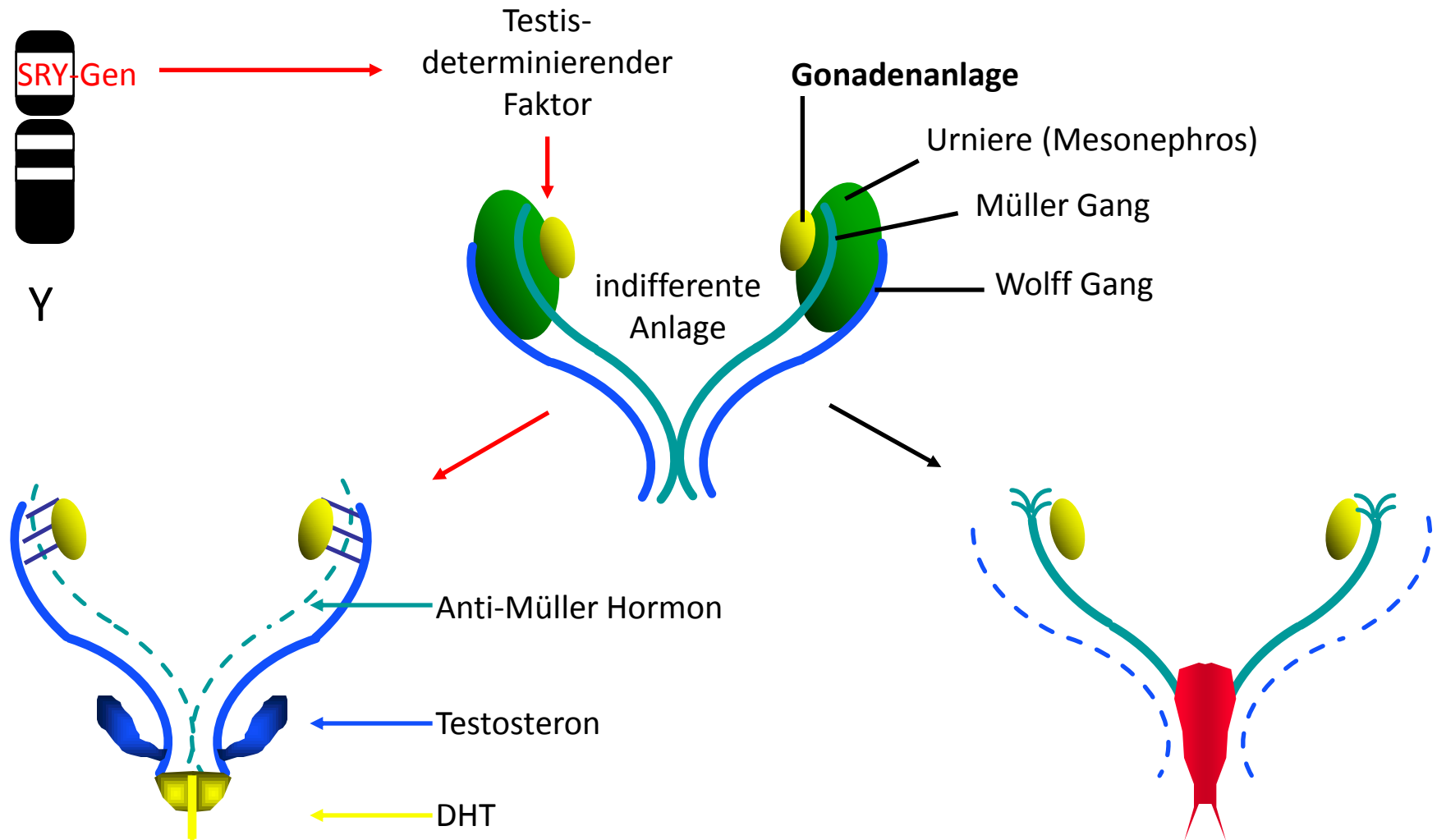
X-Chromosomen Inaktivierung



normale Entwicklung der Sexualorgane

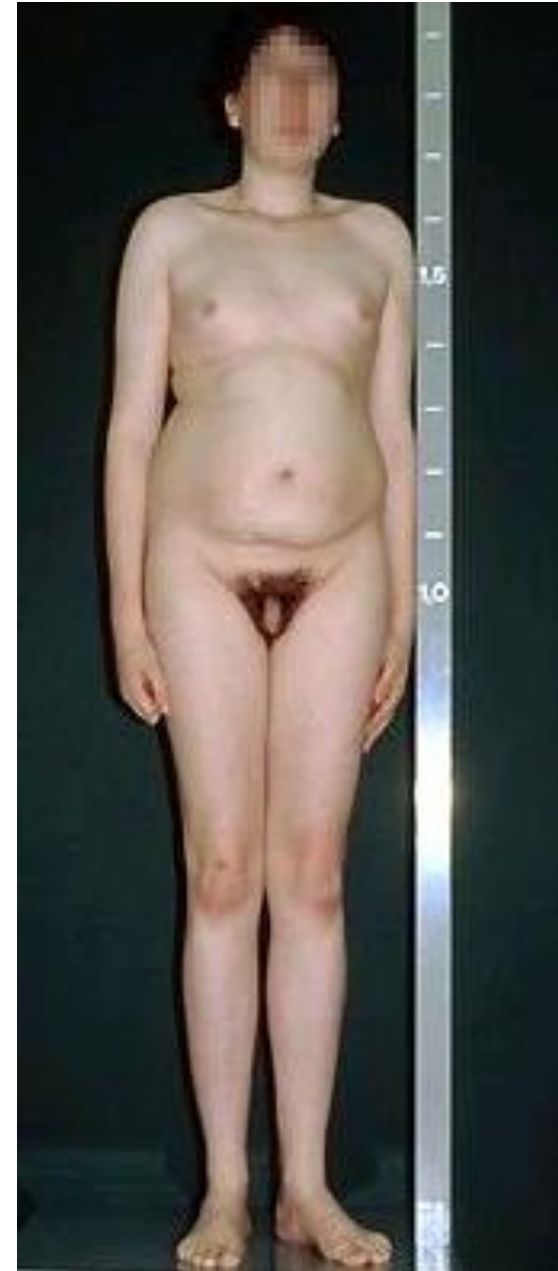


embryonale Geschlechtsdifferenzierung

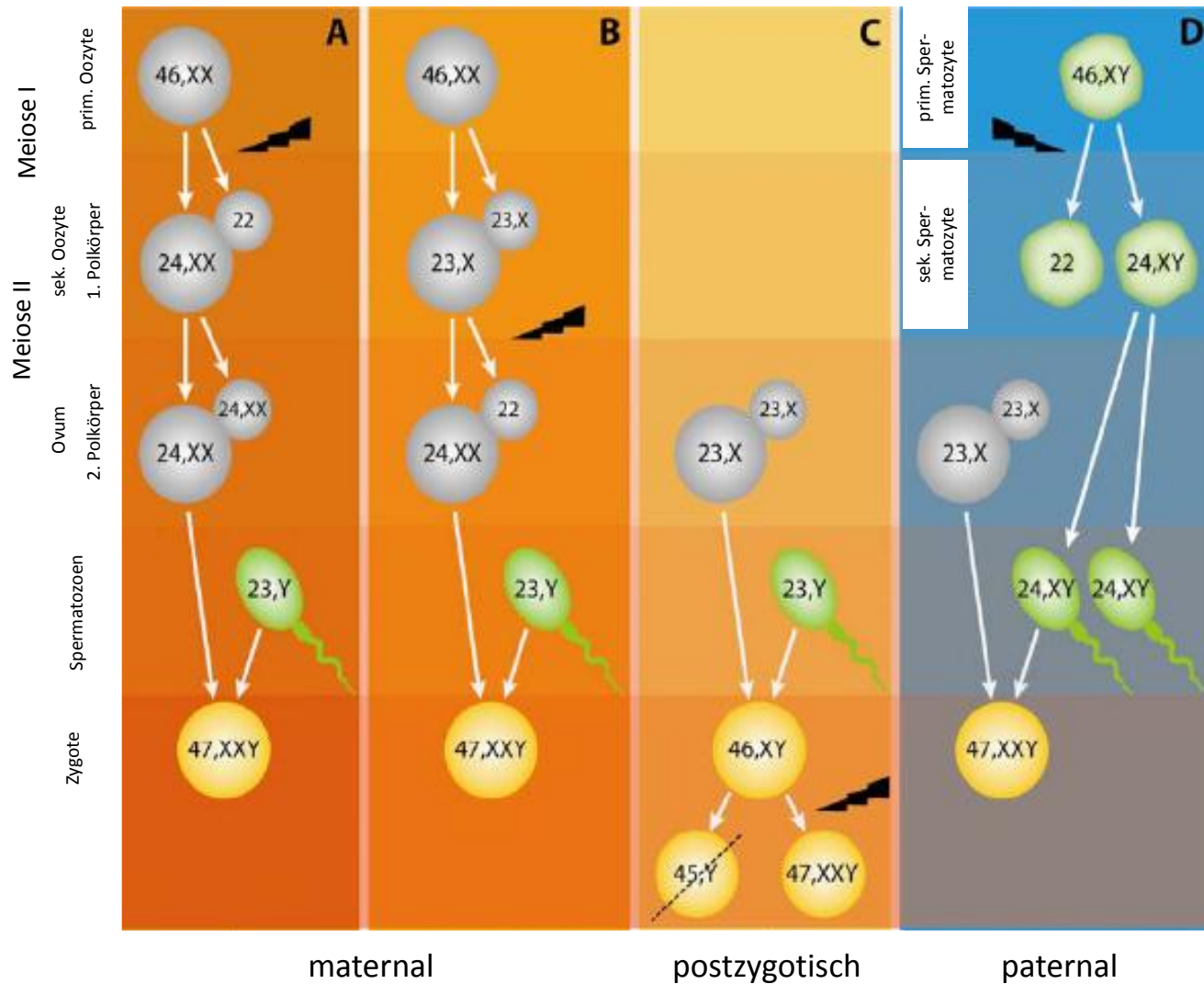


Klinefelter-Syndrom

- Karyotyp 47,XXY
- Hodengröße bei Geburt o.B
- Pubertät oft verspätet
- ausbleibendes Hodenwachstum, Hodenatrophie
- “eunuchoider” Hochwuchs, Körperbehaarung “weiblich”
(→ Testosteron-Substit. ab ~12. LJ)
- Intelligenz o.B. (∅ 10 Punkte ↓ vIQ)



47,XXY-Syndrom: Ursachen

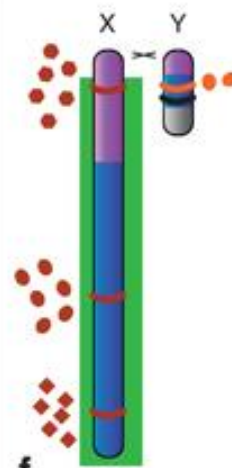
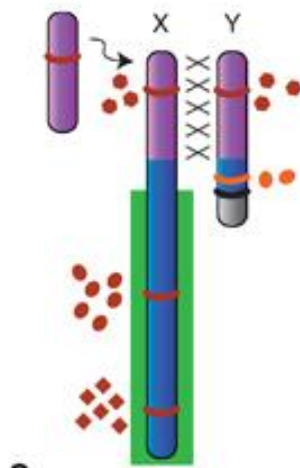
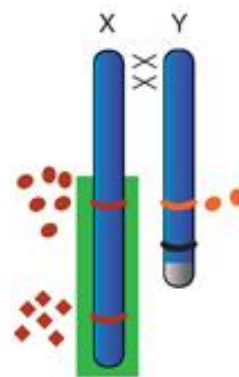
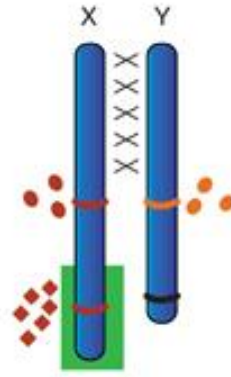
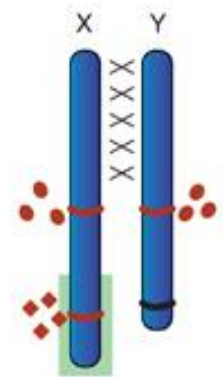
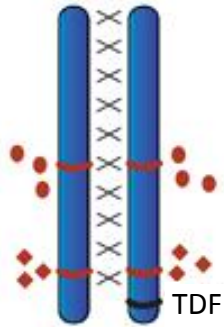


Y-Chromosom und Geschlechtsbestimmung

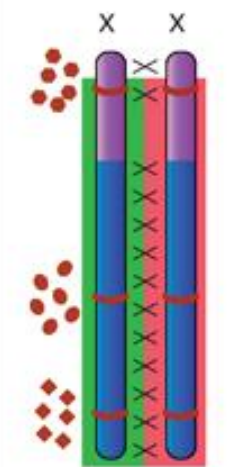
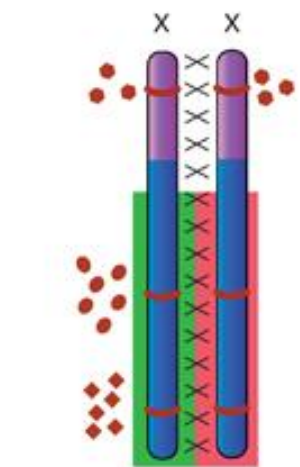
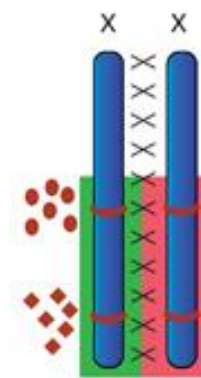
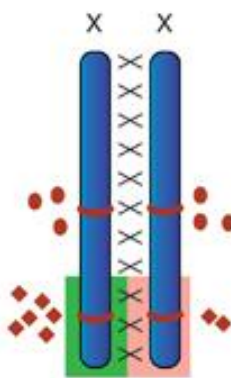
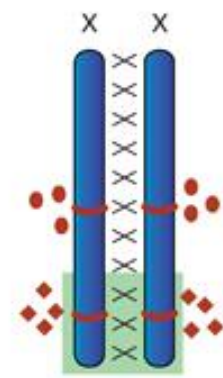
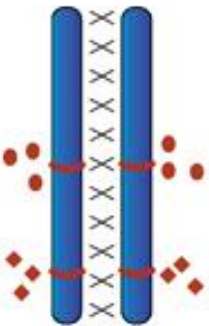
Das Y-Chromosom ist normalerweise
notwendig aber nicht hinreichend für
die Entwicklung von Testes
(Phänotyp)

Geschlechtschromosomen-Evolution

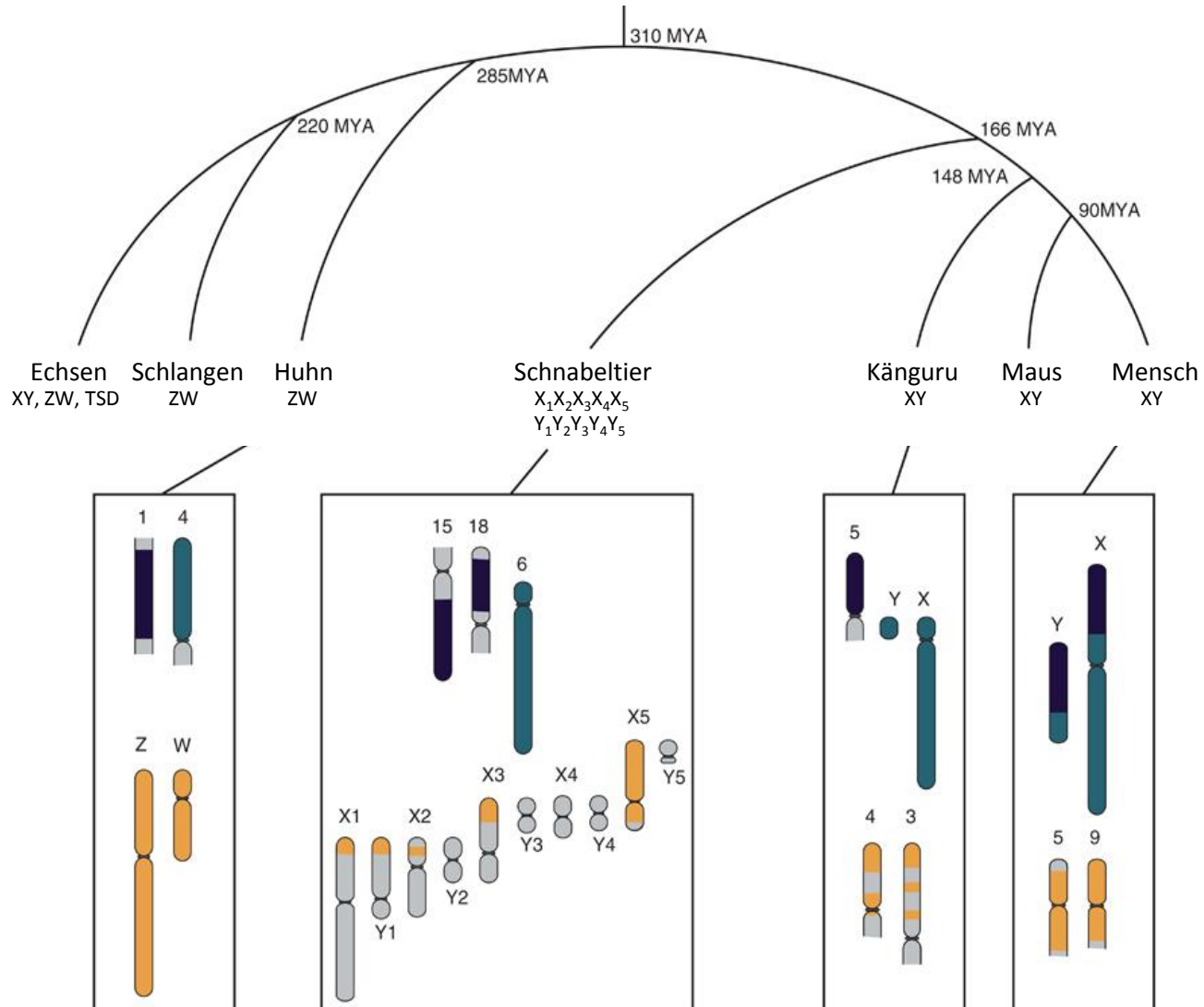
Proto X Proto Y

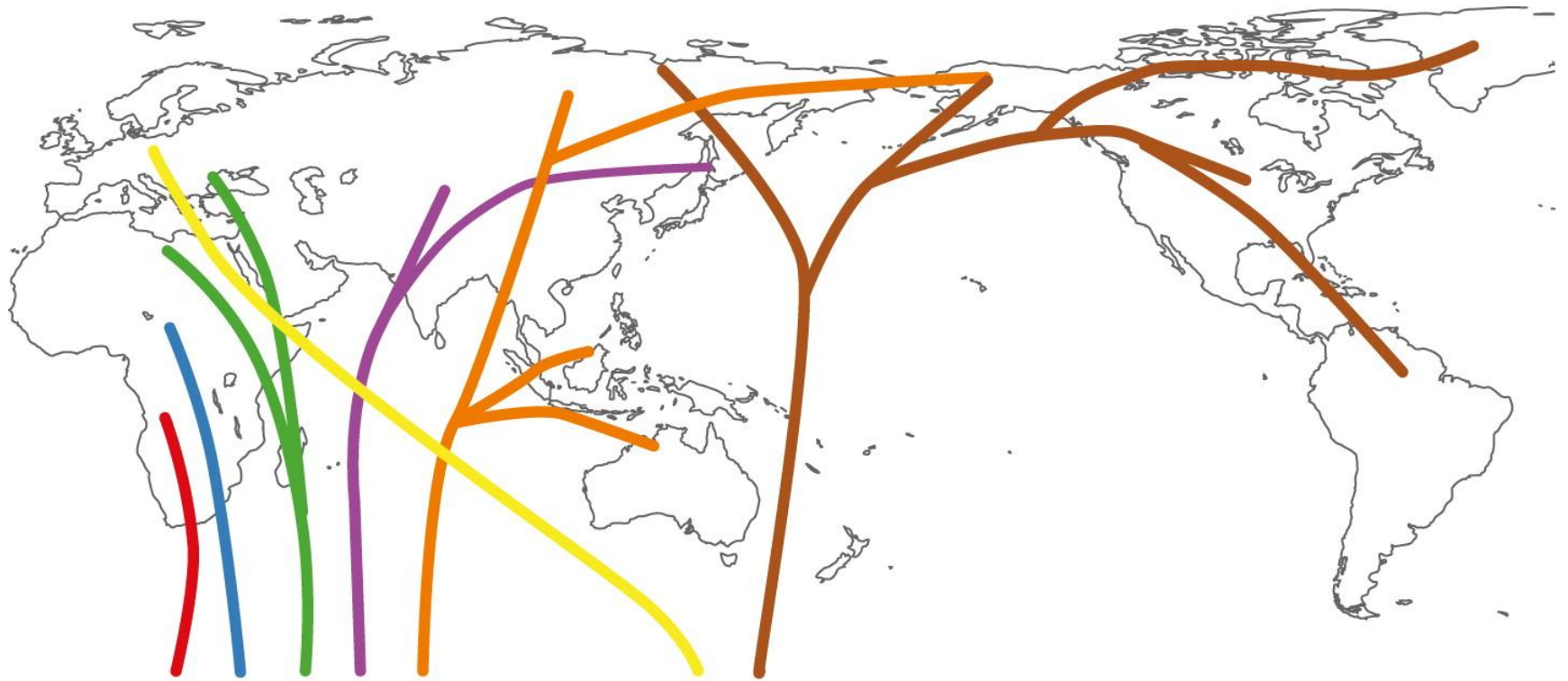


Proto x Proto x

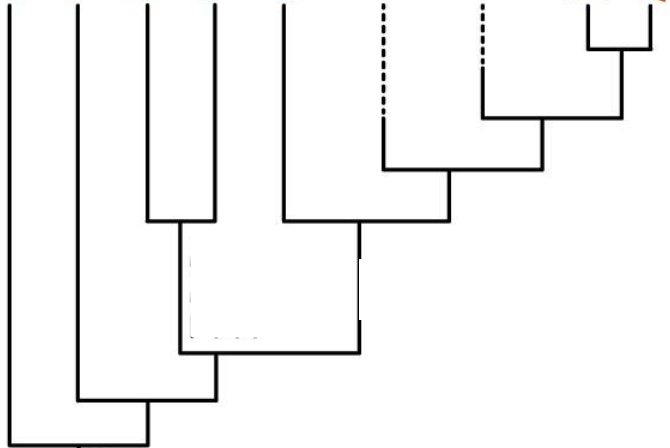


Geschlechtschromosomen-Evolution





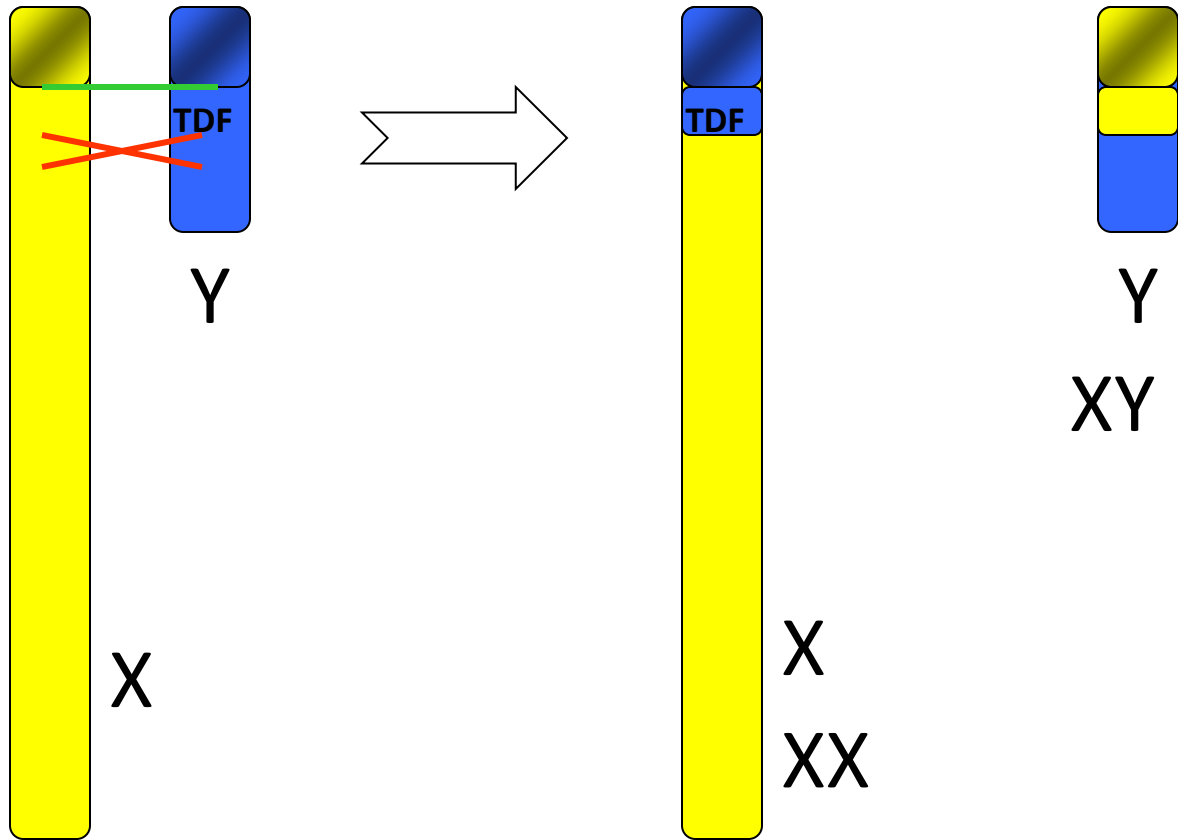
A B E D C R Q



„Adams Y“

Y-Chromosomen Verbreitung

XX- und XY-



OMIM-Statistik 13.7.2013

	X	Y
Gene mit bekannter Sequenz	661	48
Gene mit bekannter Sequenz und Phänotyp	4	0
Phänotyp Beschreibung, molek. Basis bekannt	277	4
Mendel-Phänotyp / Locus, molek. Basis unbek.	132	5
Andere, haupts. Phänotypen mit vermut. Mendel-Basis	122	2
Σ	1196	59



400042. SPERMATOGENIC FAILURE, Y-LINKED, 1; SPGFY1 SERTOLI CELL-ONLY SYNDROME, TYPE II, INCLUDED; Yq11

400044. 46,XY SEX REVERSAL 1; SRXY1 46,XY TRUE HERMAPHRODITISM, SRY-RELATED, INCLUDED; Yp11.31

400045. 46,XX SEX REVERSAL 1; SRXX1 46,XX TRUE HERMAPHRODITISM, SRY-POSITIVE, INCLUDED; Yp11.31

415000. SPERMATOGENIC FAILURE, Y-LINKED, 2; SPGFY2 AZOOSPERMIA FACTOR REGIONS, INCLUDED; Yq11.21

425500 HAIRY EARS, Y-LINKED: Gene map Yq

The trait consists of long hairs growing from the helix of the pinna; see Dronamraju (1964) and Stern et al. (1964). Controversy has prevailed as to whether it is **Y**-linked or autosomal (see 139500), or perhaps both (in different families). Rao (1970, 1972) proposed that hairy ears result from the interaction of 2 loci, 1 on the homologous segment of the X and **Y** and 1 on the nonhomologous segment of the **Y**.

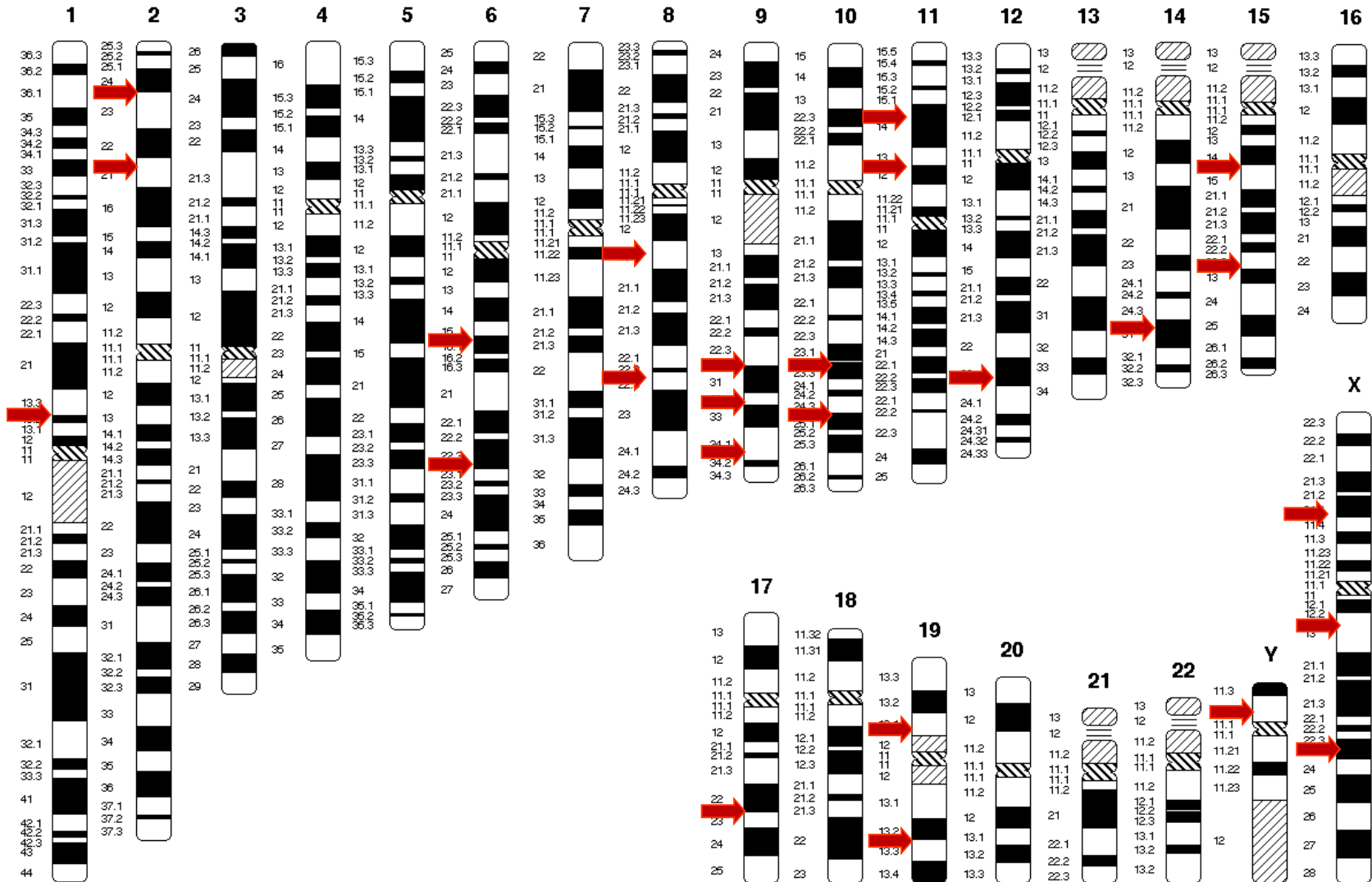
Using **Y**-chromosomal DNA binary-marker haplotyping, Lee et al. (2004) demonstrated that a cohort of southern Indian hairy-eared males carried **Y** chromosomes from many haplogroups of the **Y**-phylogeny, which, under a hypothesis of **Y** linkage, would require multiple independent mutations within a single population. There was no significant difference between the **Y**-haplogroup frequencies of hairy-eared males and those of a geographically matched control sample of unaffected males. Lee et al. (2004) concluded that the trait is not **Y**-linked in southern India and that, by extension, it is unlikely to be so in any population.

Dronamraju, K. R. **Y**-linkage in man. *Nature* 201: 424-425, 1964.

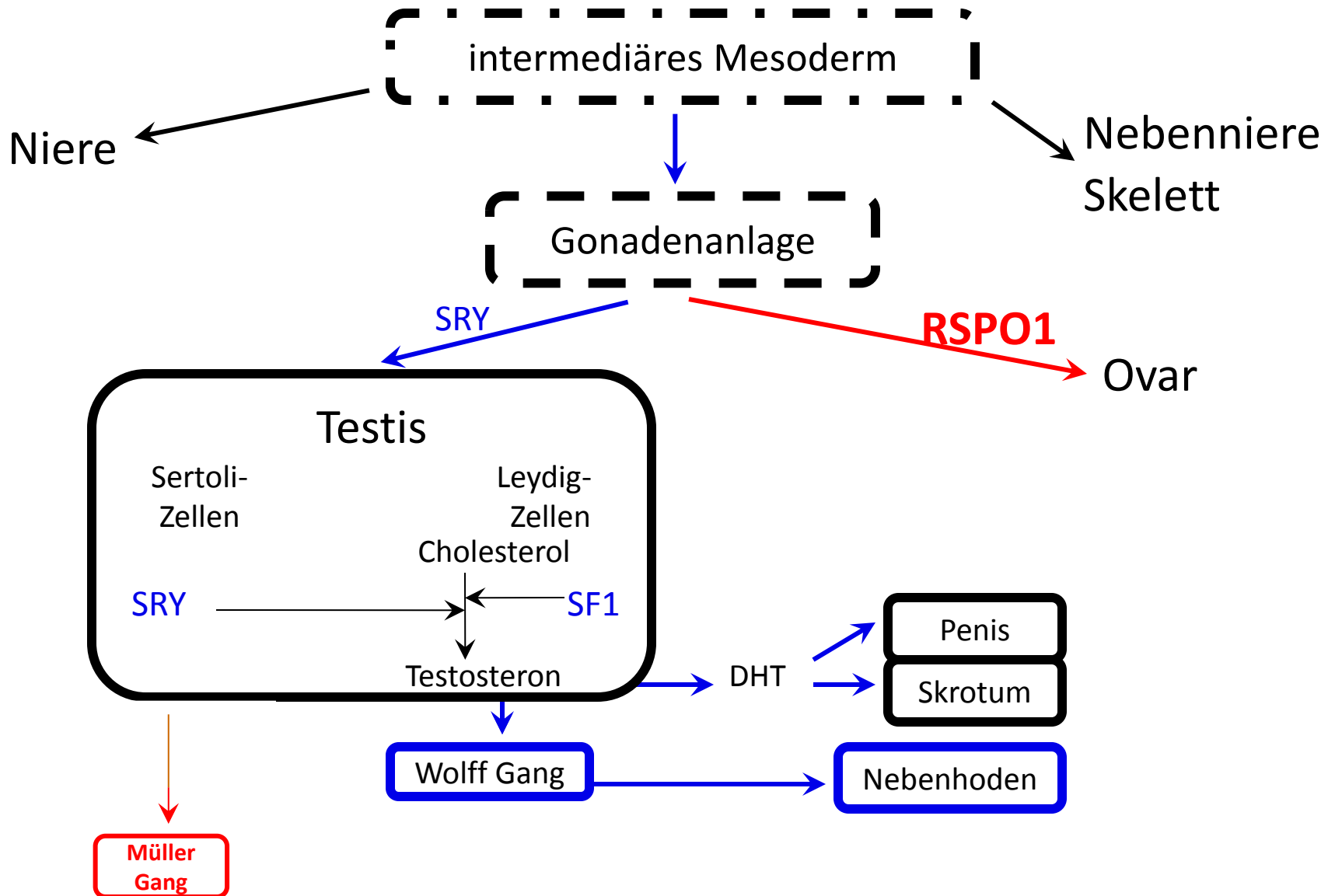


Figure 1 | Fire ants and queen. Wang and colleagues' genetic analysis¹ of the fire ant *Solenopsis invicta* has revealed a pair of 'social chromosomes' containing a non-recombining region that is expected to encode many of the behavioural traits that define these ants' social structures. The similarity between these chromosomes and sex chromosomes may help our understanding of how Y chromosomes evolve.

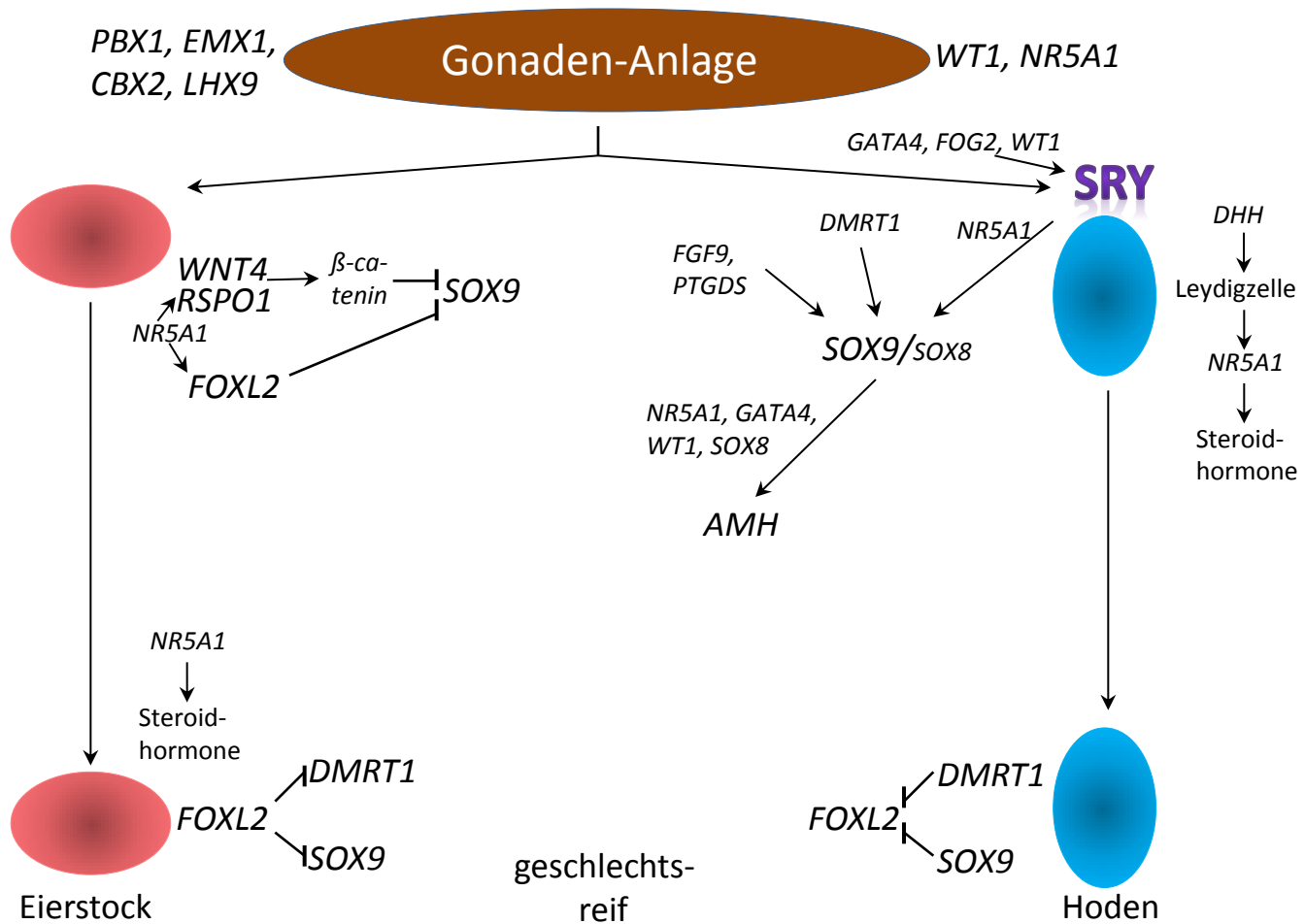
Gene f. Geschlechtsbestimmung und -Entwicklung



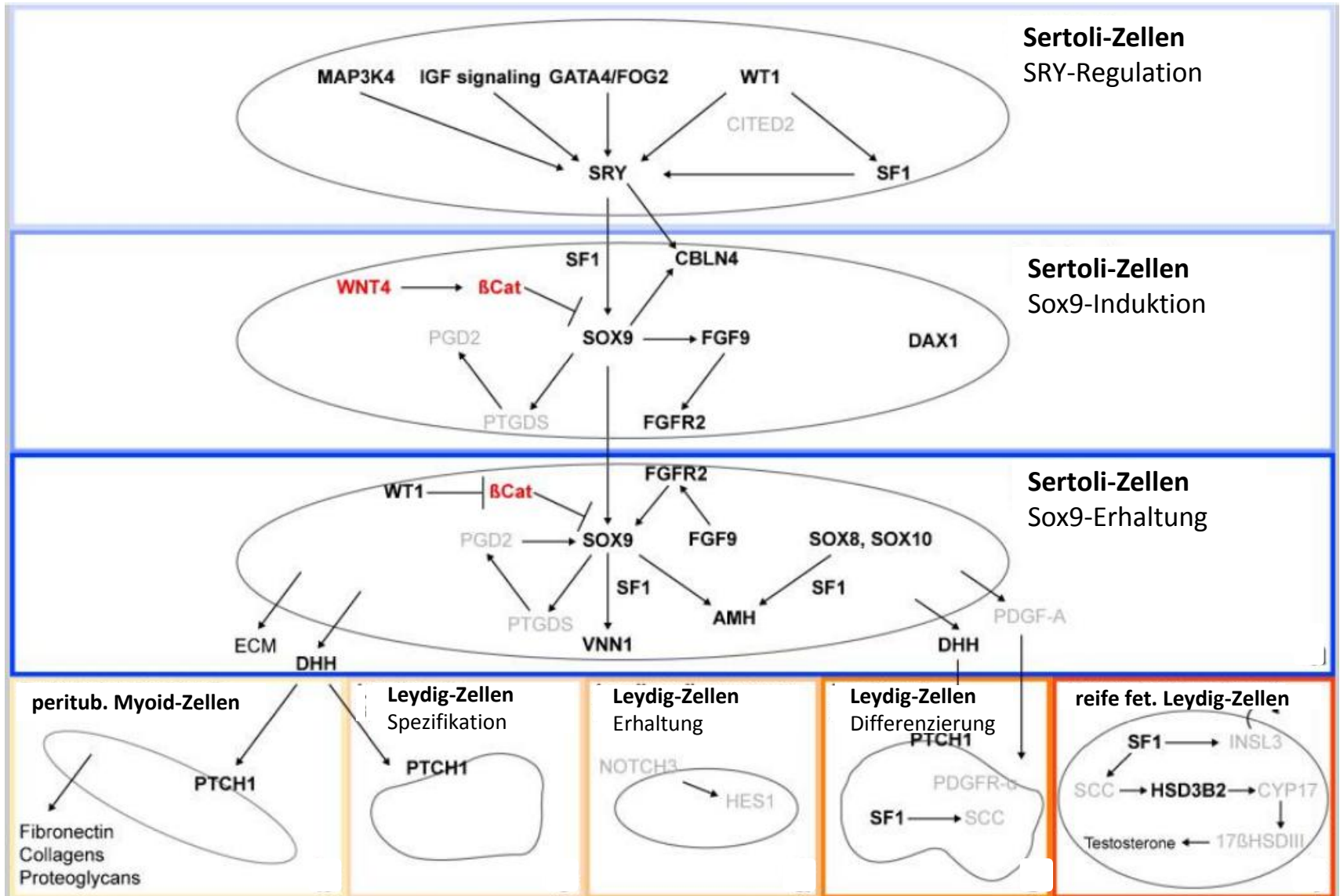
Entwicklung Geschlechtsorgane



Geschlechtsbestimmung

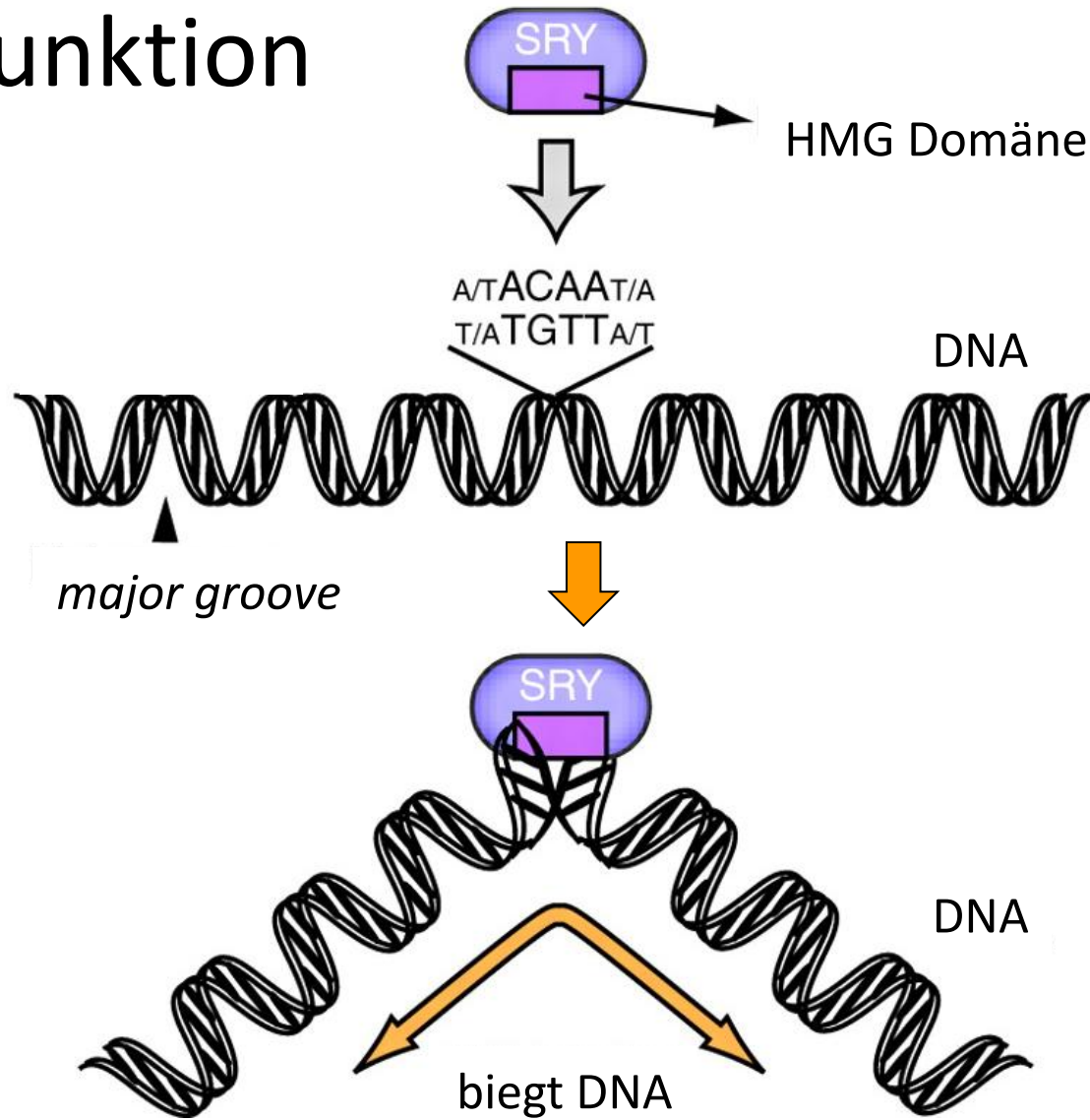


Regulation in Hoden-Zellen



[Ypter-p11.2](#) ASMTY Acetylserotonin methyltransferase (Y chromosome) [402500](#) pseudoautosomal
[Ypter-p11.2](#) ASMTLY Acetylserotonin methyltransferase-like, Y-linked [400011](#)
[Ypter-p11.2](#) MIC2Y Antigen identified by monoclonal 12E7, Y homolog [450000](#) pseudoautosomal
[Ypter-p11.2](#) SHOXY Short stature homeo box Y [400020](#) Short stature, idiop. familial [300582](#); Leri-Weill dyschondrosteosis [127300](#); Langer mesomelic dysplasia [249700](#) pseudoautosomal
[Ypter-p11.2](#) SFRS17A, XE7Y Splicing factor, arginine/serine rich, 17A [465000](#)
[Ypter-p11.2](#) TSPY Testis-specific protein, Y-linked [480100](#)
[Yp11.3](#) CRLF2Y Cytokine receptor-like factor 2, Y-linked [400023](#) pseudoautosomal
[Yp11.3](#) IL3RA, IL3RY, IL3RAY Interleukin-3 receptor (Y chromosome) [430000](#) 308385 = X homolog; pseudoautosomal
[Yp11.3](#) RPS4Y1 Ribosomal protein S4, Y-linked, 1 [470000](#)
[Yp11.3](#) SRY, TDF, TDY Sex-determining region Y (testis determining factor) [480000](#) 46XY complete gonadal dysgenesis, [400044](#); 46XX true hermaphroditism, [400045](#)
[Yp\(Tdy, Sry\)](#) [Yp11.3](#) ZFY Zinc finger protein, Y-linked [490000](#)
[Yp11.2](#) PCDH11Y, PCDH22, PCDHY Protocadherin 22 [400022](#)
[Yp11.2](#) PRKY Protein kinase, Y-linked [400008](#)
[Yp11.2](#) TBL1Y Transducin-beta-like 1, Y-linked [400033](#)
[Yp11.2](#) TGIF2LY, TGIFLY Transforming growth factor-beta-induced factor 2-like, Y-linked [400025](#)
[Yp11](#) AMELY, AMGL Amelogenin (Y chromosome) [410000](#) 301200 = X homolog D
[Yp11](#) CSF2RY Granulocyte-macrophage colony-stimulating factor receptor, alpha subunit (Y chromosome) [425000](#) 306250 = X homolog; distal to MIC2Ya
[Yp11](#) XGR XG regulator [489500](#) in pseudoautosomal region
[Yp](#) ANT3Y Adenine nucleotide translocator-3 (Y chromosome) [403000](#) 300151 = X homolog; proximal to CSF2RY
[Yq](#) BPY2 Basic protein on Y chromosome, 2 [400013](#)
[Yq](#) HEY Hairy ears, Y-linked [425500](#) ?Hairy ears, Y-linked
[Yq11](#) DAZ Deleted in azoospermia [400003](#) ?Sertoli-cell-only syndrome (1) ?same as AZF D [17\(dazla\)](#)
[Yq11](#) DDX3Y, DBY DEAD/H box-3, Y-linked [400010](#)
[Yq11](#) KDM5D, JARID1D, SMCY, HYA Lysine-specific demethylase 5D [426000](#) encodes H-Y epitope in mouse [Yp\(Smcy\)](#)
[Yq11](#) RBMY1A1, RBM1, YRRM1, RBM2 RNA binding motif protein, Y chromosome, family 1, member A1 [400006](#) [Y\(Rbmy\)](#)
[Yq11](#) UTY Ubiquitously transcribed TPR gene on Y chromosome [400009](#)
[Yq11.2](#) DAZ2 Deleted in azoospermia 2 [400026](#)
[Yq11.2](#) DAZ3 Deleted in azoospermia 3 [400027](#)
[Yq11.2](#) CYorf15A Chromosome Y open reading frame 15A [400031](#)
[Yq11.2](#) HSFY Heat shock transcription factor, Y-linked [400029](#)
[Yq11.2](#) RPS4Y2 Ribosomal protein S4, Y-linked [400030](#)
[Yq11.2](#) CYorf15B Chromosome Y open reading frame 15B [400032](#)
[Yq11.2](#) NLGN4Y, KIAA0951 Neuroligin 4, Y-linked [400028](#)
[Yq11.2](#) PRY2 PTPBL-related gene on Y, 2 [400041](#)
[Yq11.2](#) USP9Y, DFFRY Ubiquitin-specific protease-9, Y chromosome (Drosophila fat facets related, Y-linked) [400005](#) Azoospermia, [415000](#)
[Yq11.221](#) CDY2 Chromodomain protein, Y chromosome, 2 [400018](#)
[Yq11.221](#) TMSB4Y Thymosin, beta-4, Y chromosome [400017](#)
[Yq11.221](#) VCY, BPY1 Variably charged, Y chromosome [400012](#)
[Yq11.222](#) XKRY XK-related protein on Y chromosome [400015](#)
[Yq11.223](#) EIF1AY Eukaryotic translation initiation factor 1A, Y isoform [400014](#)
[Yq11.223](#) PRY PTPN13-like, Y-linked [400019](#)
[Yq11.23](#) CDY1, CDY Chromodomain protein, Y chromosome [400016](#)
[Y\(Cdy1\)](#) [Yq12](#) GCY, TSY, STA Growth control, Y-chromosome influenced [475000](#)
[Chr.Y](#) DFNY1 Deafness, Y-linked 1 [400043](#) Deafness, Y-linked 1
[Chr.Y](#) RPY Retinitis pigmentosa, Y-linked [400004](#) Retinitis pigmentosa, Y-linked

SRY-Funktion



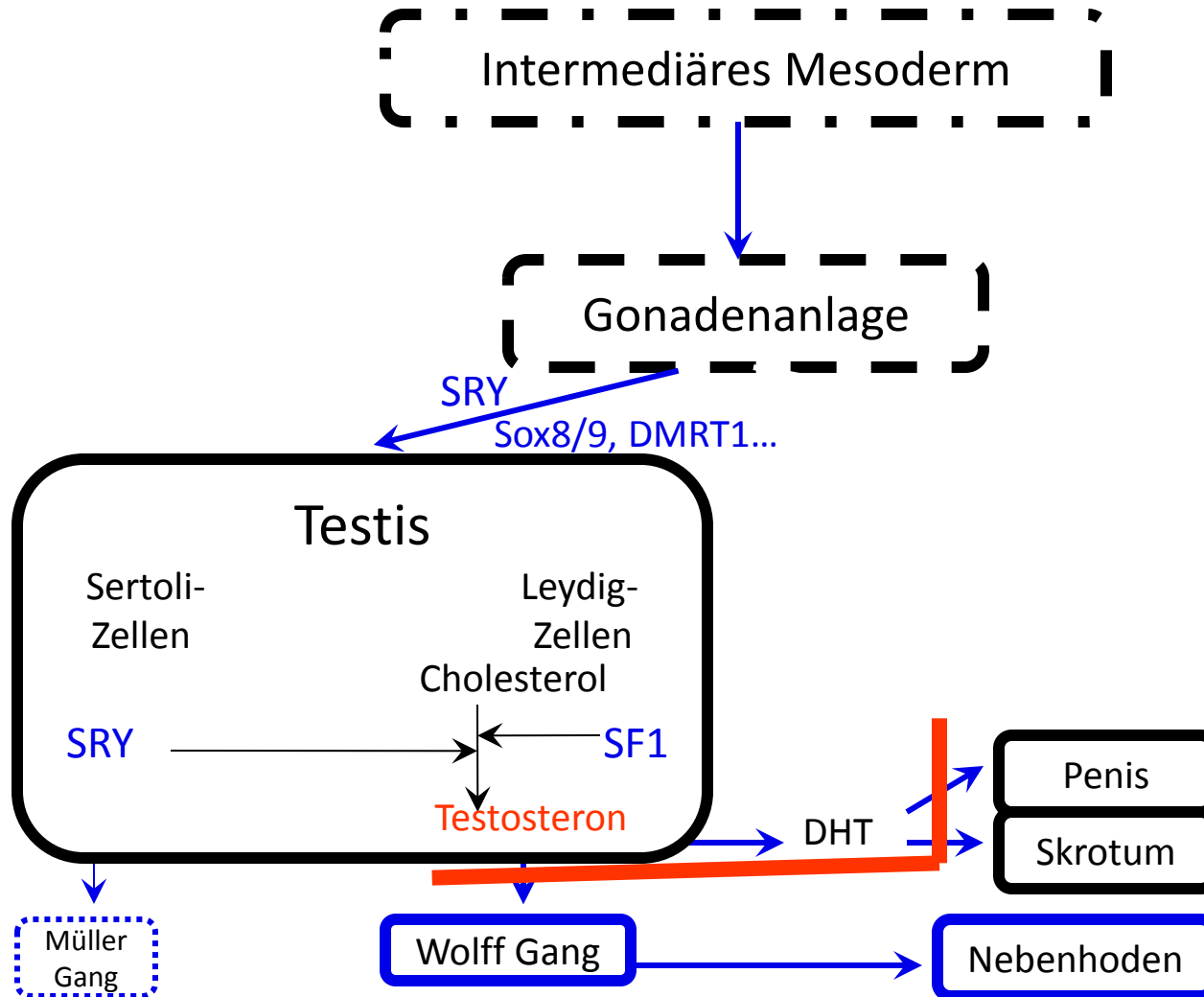
Mutationen im *SRY*-Gen



HMG box

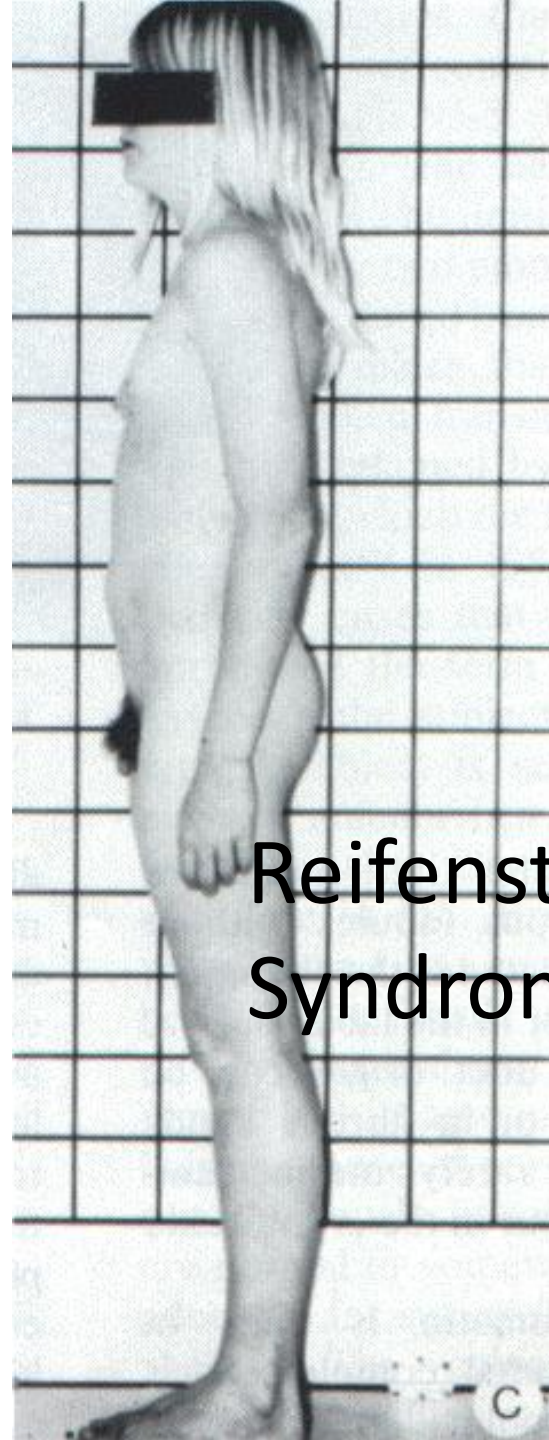
▼ INSERTION ● MISSENSE
▲ DELETION ● NONSENSE

Fehl-Entwicklung Geschlechtsorgane



Komplette
testikuläre
Femini-
sierung

Komplette
testiku-
läre
Femini-
sierung

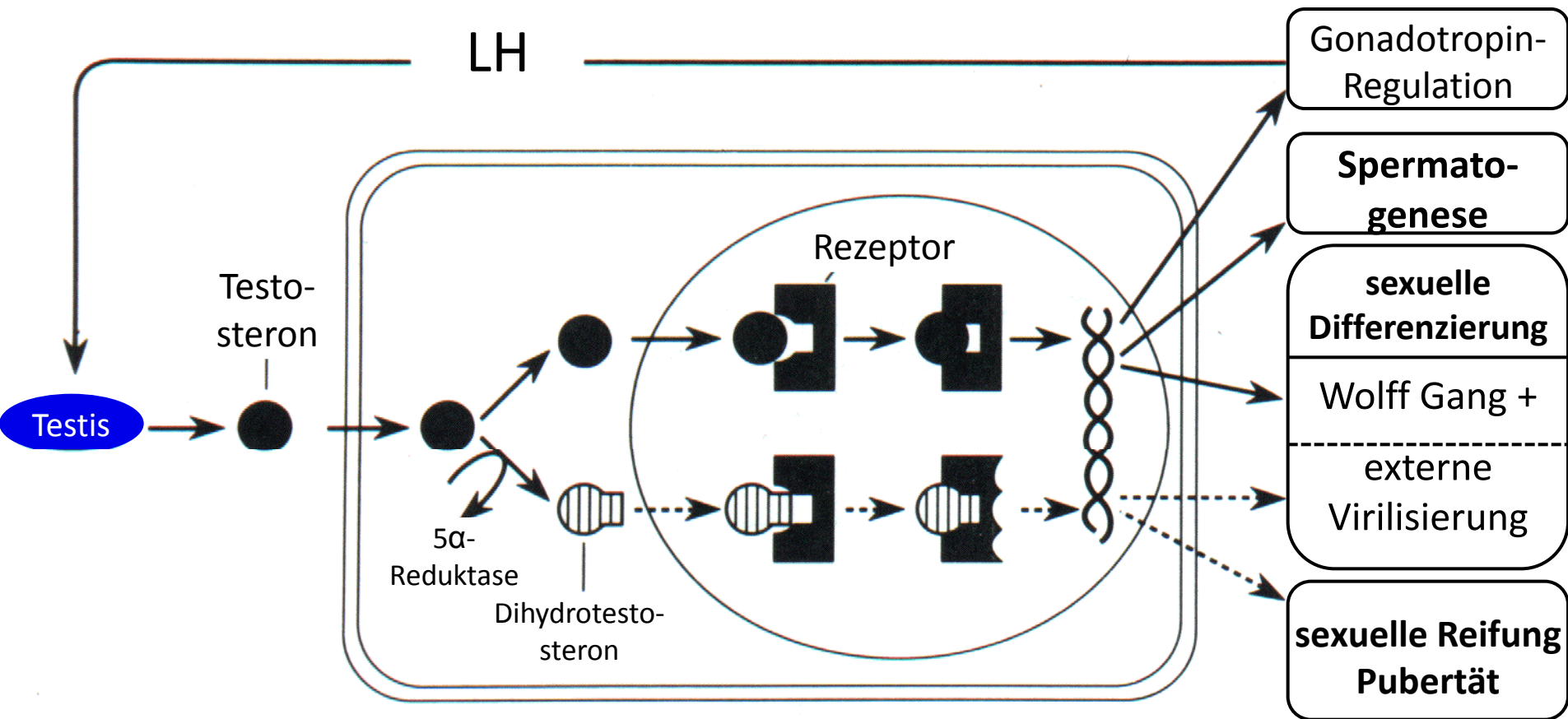


Reifenstein-
Syndrom

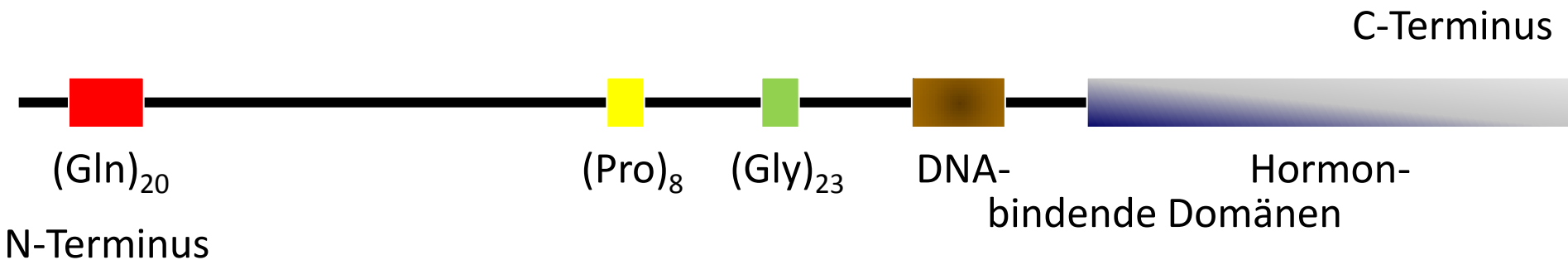
Androgen-Insensitivität: Phänotypen

Typ	äußere Genitalien (Synonym)	Befunde
CAIS	(testikuläre Feminisierung)	<p>∅ oder rudimentäre Wolff' Gang-Derivative Epididymis und <i>vas deferens</i> + / - inguinale / labiale Testes; kurze blind endende Vagina praktisch ∅ Scham- und/oder Achselbehaarung</p>
PAIS	<p>prädominant (inkomplettes AIS)</p> <p>“nicht eindeutig” /</p> <p>prädominant</p>	<p>inguinale oder labiale Testes <i>Clitoromegalie</i> + labiale Fusion distinkte urethrale + vaginale Öffn. / Urogenital-Sinus <i>Microphallus</i> (<1 cm) mit Clitoris-artiger Glans; <i>labia majora</i>-artiges Bifid-Skrotum descendierte / maldescendierte Testes Perineoscrotal-Hypospadie oder Urogenital-Sinus Gynäkomastie in Pubertät</p> <p>simple (glanduläre / penile) or schwere (perineale) “isolierte” Hypospadie mit normalem Penis + descendierte Testes oder schwere Hypospadie mit Micropenis, Bifid-Skrotum, + descendierte / maldescendierte Testes Gynäkomastie in Pubertät</p>
MAIS	(<i>undervirilized syndrome</i>)	<p>gestörte Spermatogenese und/oder unvollständige pubertäre Virilisierung, Gynäkomastie in Pubertät</p>

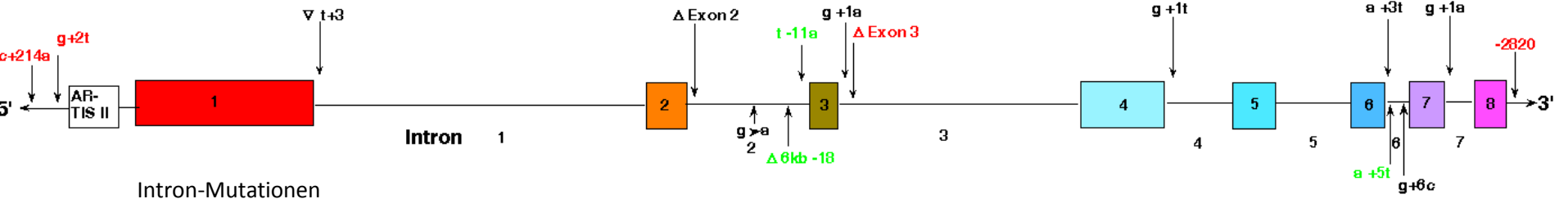
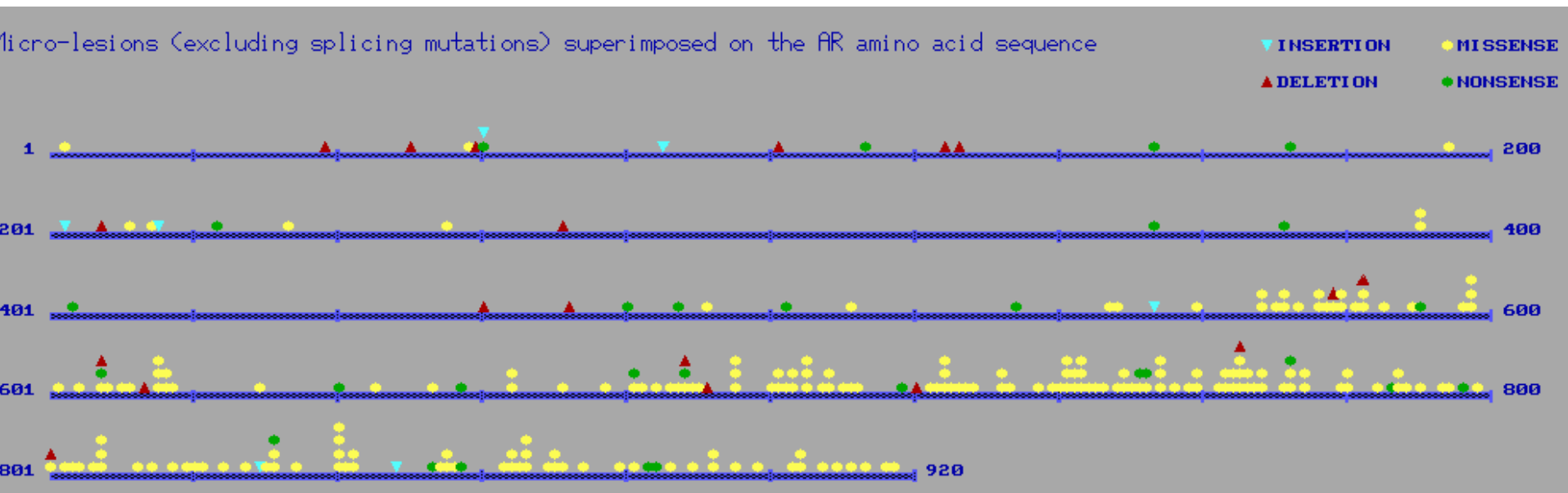
physiologische Androgen-Wirkung



Androgen-Rezeptor



Androgen-Rezeptor Mutationen



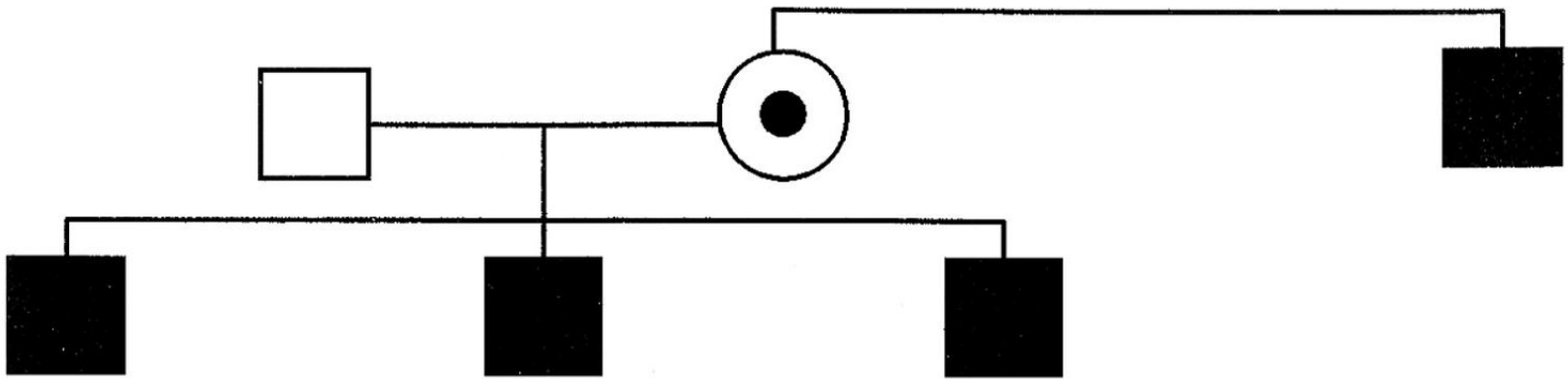
Androgenresistenz

Tabelle 1		
Phänotypische Klassifikation bei Virilisierungsstörungen*		
Typ	Phänotyp	Phänotyp/Funktion
1	männlich	gestörte Spermatogenese und/oder gestörte Virilisierung in der Pubertät
2	vorwiegend männlich	isolierte Hypospadie und/oder Mikropenis und höhergradige Hypospadie, Skrotum bipartitum
3	ambivalent	klitorisähnlicher Mikrophallus, labienähnliches bipartiertes Skrotum, perineoskrotale Hypospadie oder Sinus urogenitalis mit kurzer, blind endender Vagina
4	vorwiegend weiblich	Klitorishypertrophie und/oder labiale Fusion, Sinus urogenitalis mit kurzer, blind endender Vagina
5	weiblich	präpuberal keine Virilisierungszeichen, in der Pubertät Virilisierung bei 5α -Reduktase-Defekt, Feminisierung bei Androgenrezeptordefekt

*nach Sinnecker et al., 1996, 1997

Hiort et al, Ärzteblatt 1999

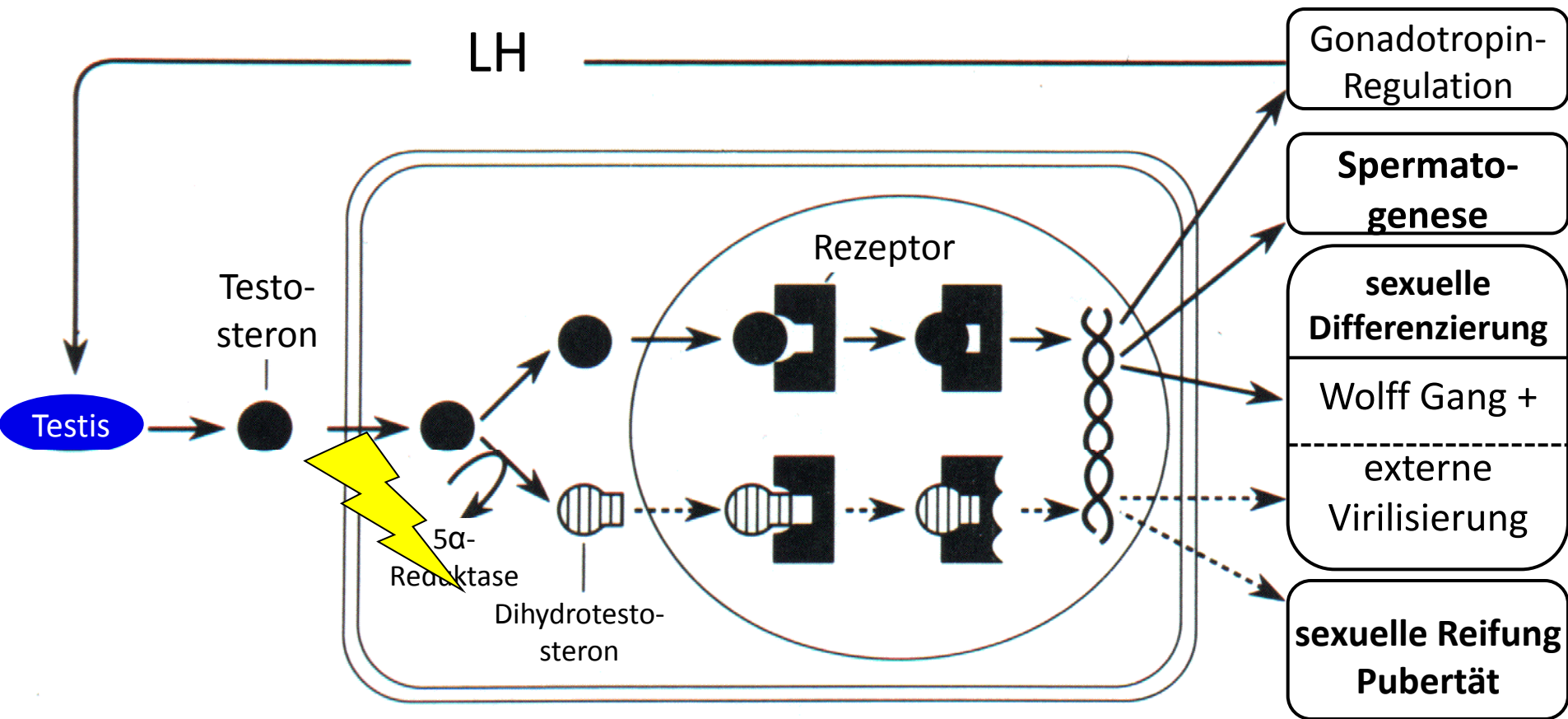
Androgen-Resistenz



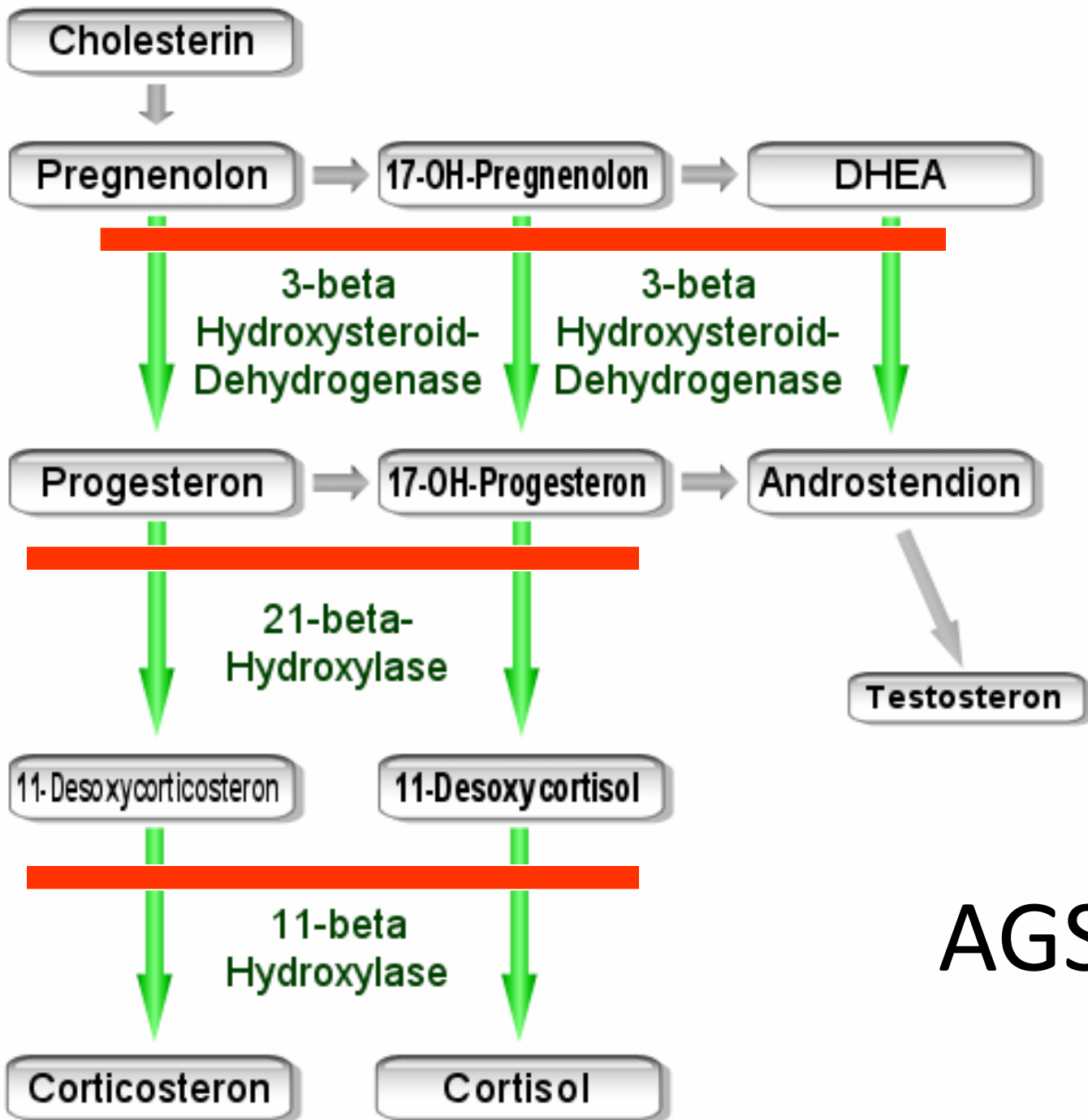
Androgen-Rezeptormutation in 46,XY mit Keimzelltumor



physiologische Androgen-Wirkung



Steroid 5 α -
Reduktase
Defizienz
>50 Mutationen



AGS

Adrenogenitales Syndrom (AGS)

- Enzymdefekt in Cortisol-Synthese (Nebenniere)
Feedback: ACTH-Ausschüttung ↑
- häufig: 21-Hydroxylase-Defekt (~150 Mutationen)
Virilisierung äußeres Genitale
Pubertas praecox
- pädiatrischer Notfall: 3β-Hydroxylase-Defekt
Salzverlust (auch Aldosteron-Synthese betroffen)

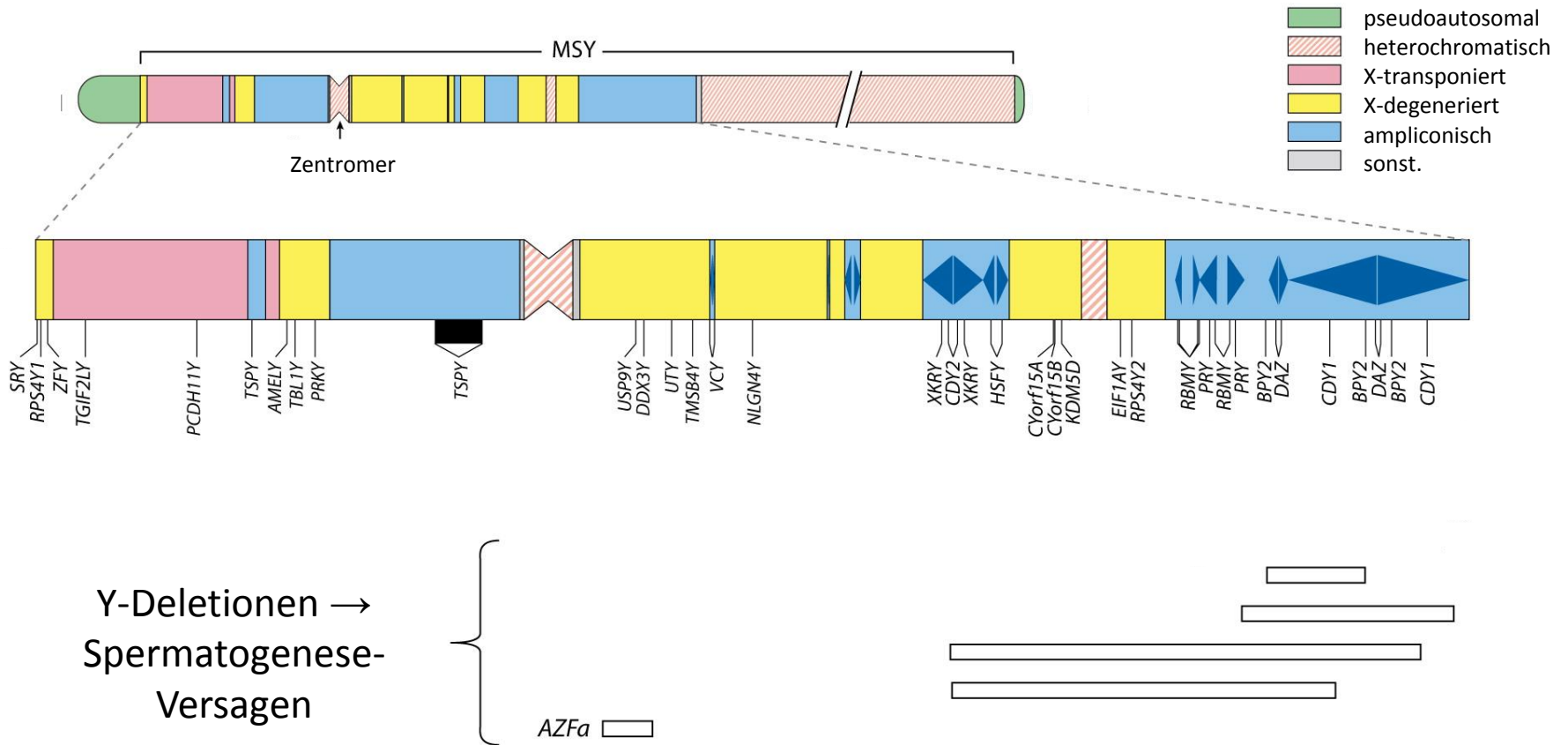
Infertilität

- 15% der Paare; >20% der Infertilität genet. bedingt
- Chromosomen: Y (AZFa, -b, -c), Autosomen, X, mito

Prävalenz/Phänotypen von häufigen Chromosomen-Aberrationen bei Infertilität

genetische Aberration	Phänotyp	Prävalenz (%)
chromosomale Aberrationen	Azoo- bis Normozoospermie	5 (Σ infertile Population); 15 (Azoosp.)
47,XXY	Azoo- bis schwere Oligozoosp.	5 (schwere Oligozoosp.); 10 (Azoosp.)
Robertson-Translokation	Azoo- bis Normozoospermie	0.8 (Σ infertile Population); 1.6 (Oligozoosp.); 0.1 (Azoospermie)
Y-Mikrodeletionen	Azoo- bis Oligozoospermie	10–15 (Azoosp.); 5–10 (Oligozoosp.)
AZFa Deletion	Azoosp., Sertoli cell-only Synd.	0.5–1.0
AZFb Deletion	Azoosp., spermatogener Arrest	0.5–1.0
AZFc Deletion	schwere Oligozoo- bis non-obstructive Azoospermie	6–12
part. AZF-c Deletionen	Azoo- bis Normozoospermie	3–5

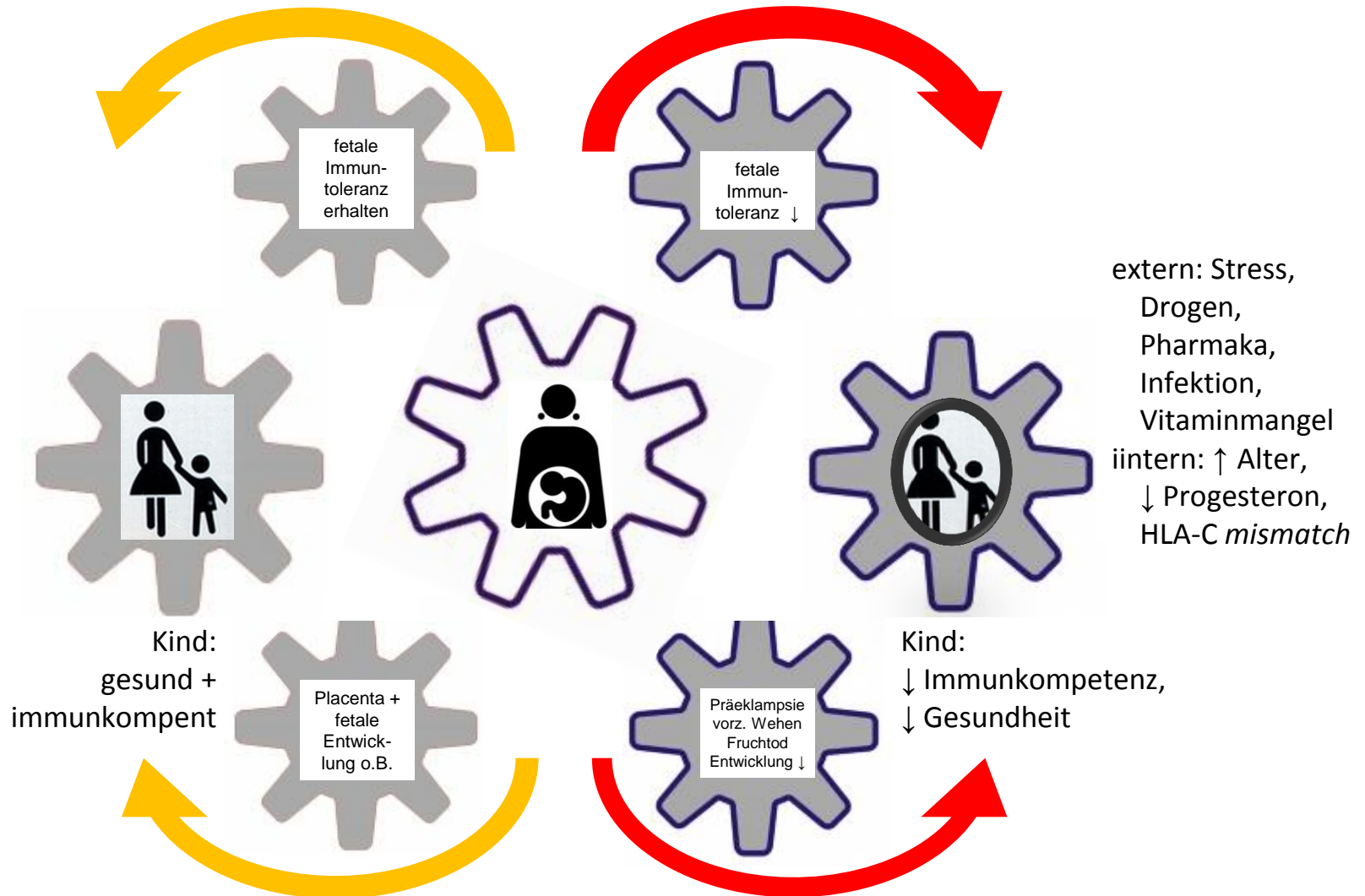
Infertilität



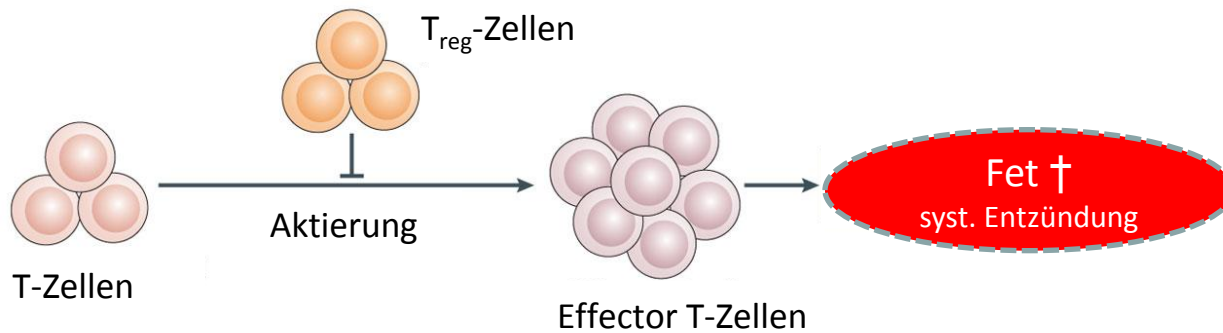
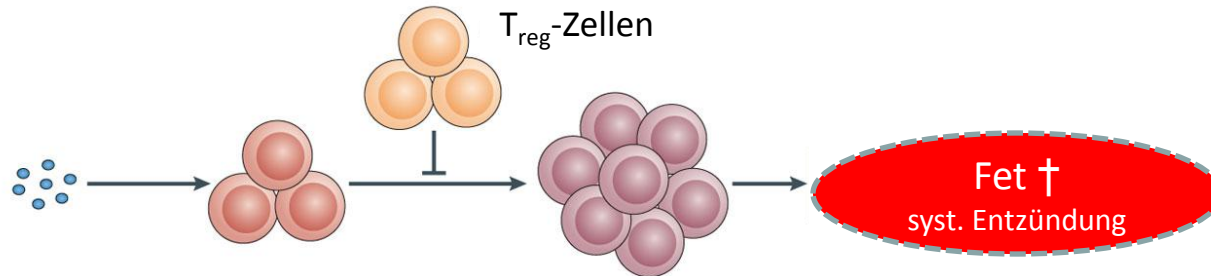
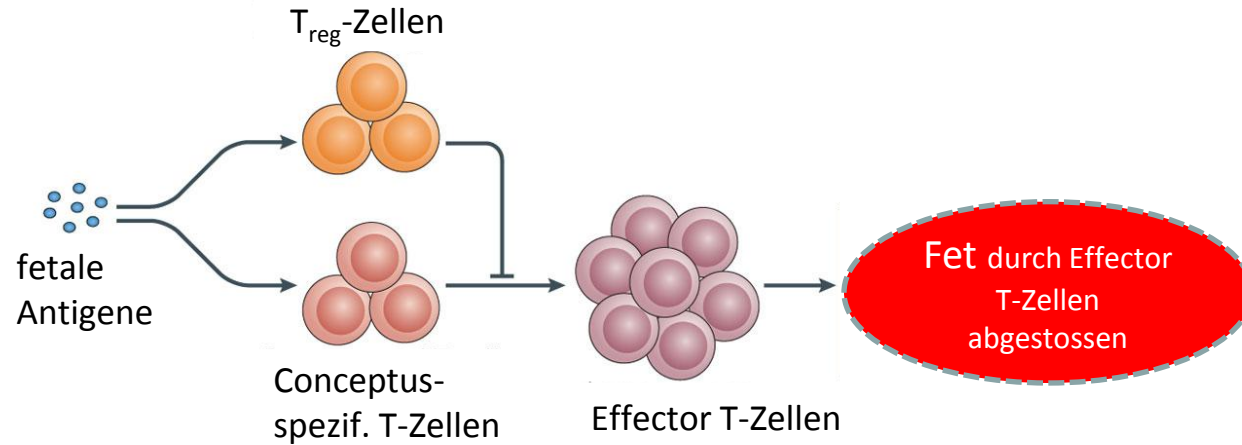
Infertilität

- 15% der Paare
- Chromosomen: 5% auffälliger Karyotyp
 - Störungen (Tumore) der Genitalorgane
(PCOS, Verklebungen, Endometriose)
 - hormonelle Störungen
 - Infektionen
 - Stoffwechselstörungen
 - Umwelt

normale Schwangerschaft + potentielle Anpassungsprobleme



ad immunologisch bedingte Infertilität



Zusammenfassung

- chromosomale, gonadal-hormonale und somatische Geschlechtsbestimmung auch in vielen Details verstanden
- Geschlechtsidentität ?