

BIO-373
Genetics & Genomics

Sex determination and X-linked heredity

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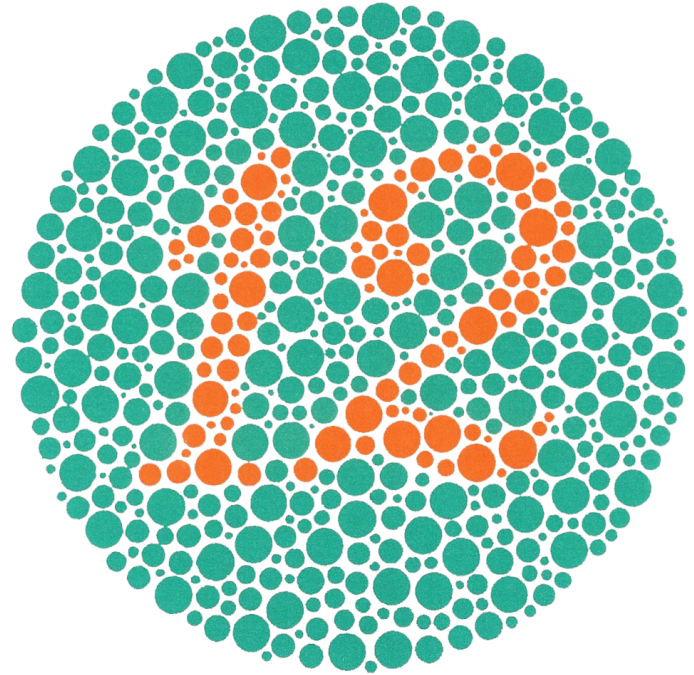
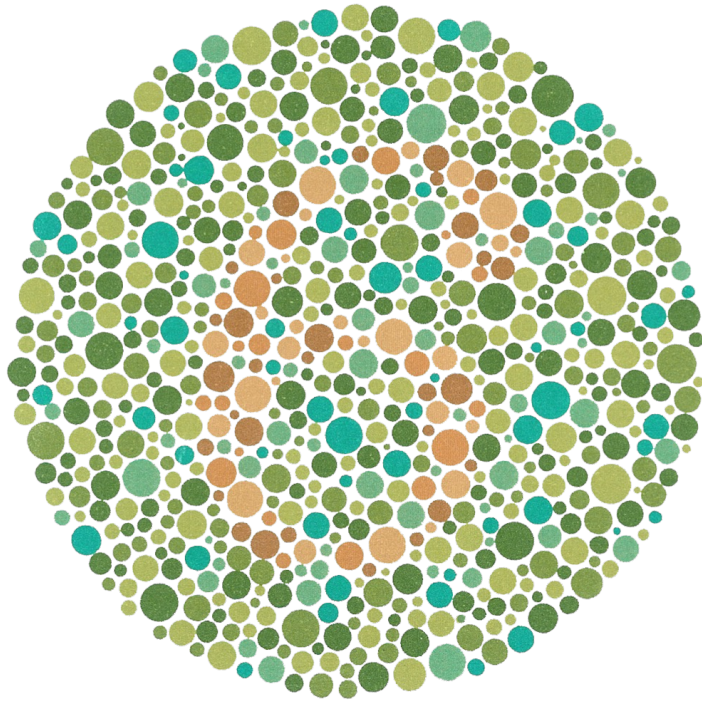
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Plan

1. X-linked inheritance
 2. Sex-limited and sex-influenced inheritance
 3. Sexual differentiation
 4. Sex determination
 5. Sex ratio
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1. X-linked inheritance

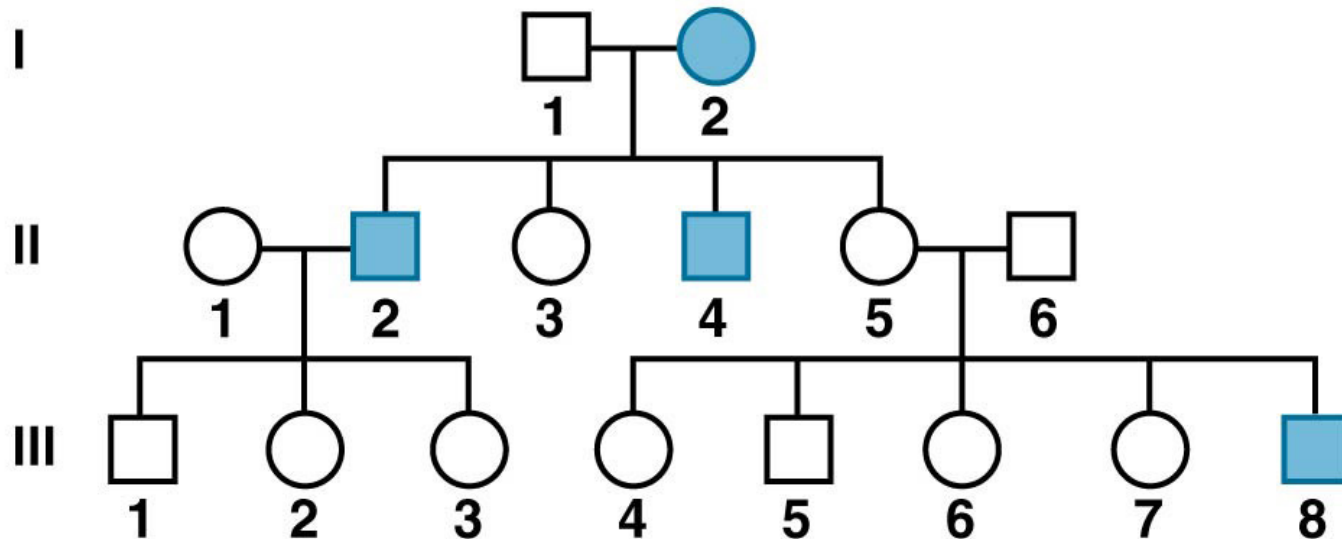
X-linked heredity in humans



X-linked heredity in humans

■ Color blindness (daltonism)

- Most common form = deuteranopia: absence of green photoreceptors (M cones) in retina
- Red/green color blindness
- 8% of men, 0.5% of women



X-linked diseases

- Observed only in males
 - Females can almost exclusively be **heterozygous carriers** who do not develop the disorders
 - Example: **Duchenne muscular dystrophy**
 - Mutation in DMD gene on X chromosome
 - DMD encodes **dystrophin**, which is part of a protein complex that connects the cytoskeleton of a muscle fiber to the extracellular matrix through the cell membrane
 - Often lethal around age 20-30
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TABLE 4.2 Human X-Linked Traits

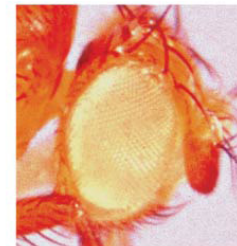
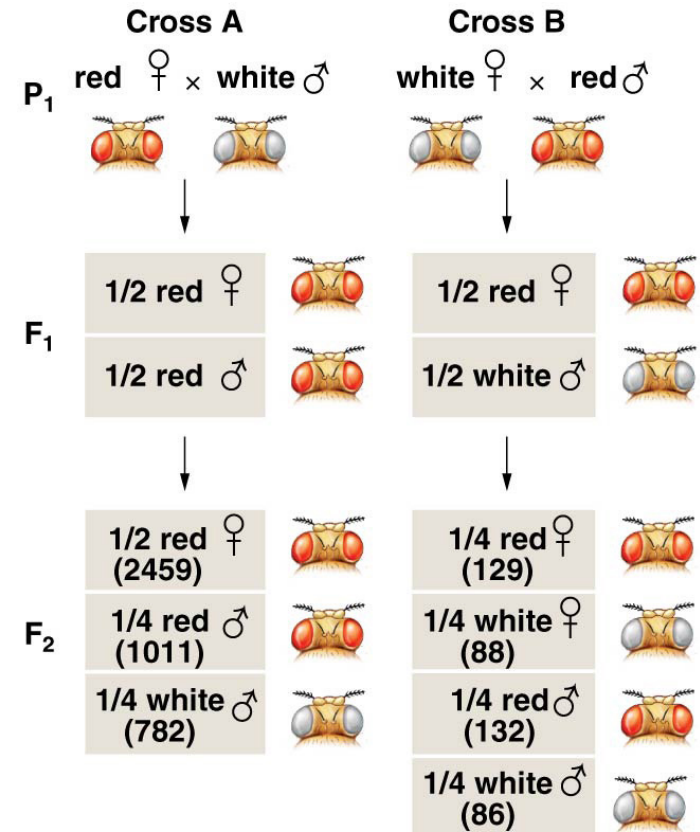
Condition	Characteristics
Color blindness, deutan type	Insensitivity to green light
Color blindness, protan type	Insensitivity to red light
Fabry's disease	Deficiency of galactosidase A; heart and kidney defects, early death
G-6-PD deficiency	Deficiency of glucose-6-phosphate dehydrogenase; severe anemic reaction following intake of primaquines in drugs and certain foods, including fava beans
Hemophilia A	Classic form of clotting deficiency; deficiency of clotting factor VIII
Hemophilia B	Christmas disease; deficiency of clotting factor IX
Hunter syndrome	Mucopolysaccharide storage disease resulting from iduronate sulfatase enzyme deficiency; short stature, claw-like fingers, coarse facial features, slow mental deterioration, and deafness
Ichthyosis	Deficiency of steroid sulfatase enzyme; scaly dry skin, particularly on extremities
Lesch-Nyhan syndrome	Deficiency of hypoxanthine-guanine phosphoribosyltransferase enzyme (HPRT) leading to motor and mental retardation, self-mutilation, and early death
Duchenne muscular dystrophy	Progressive, life-shortening disorder characterized by muscle degeneration and weakness; sometimes associated with mental retardation; deficiency of the protein dystrophin

How was X-linked heredity demonstrated?

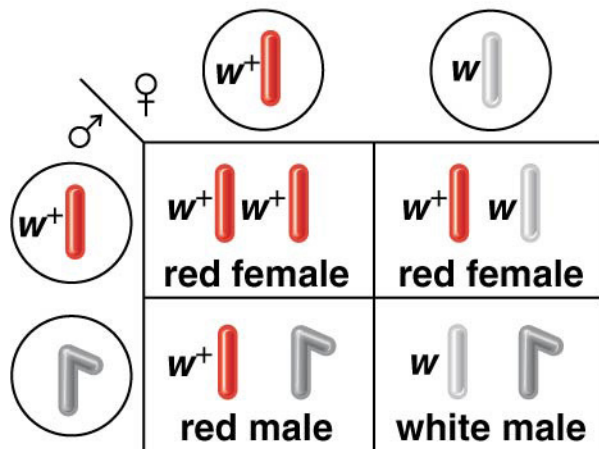
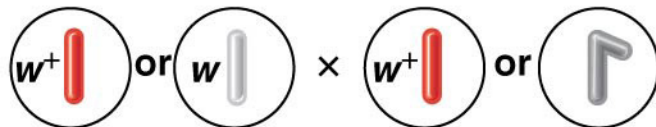
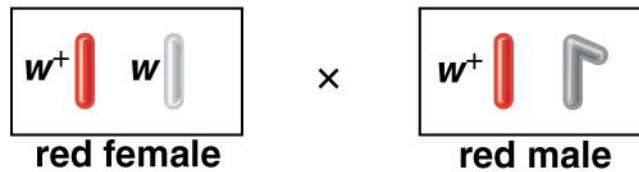
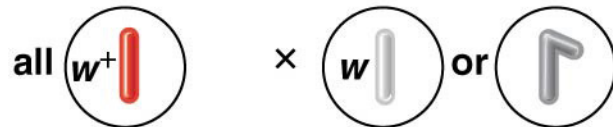
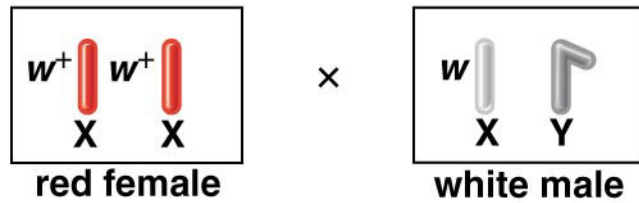
X-linkage in *Drosophila*

(T.H. Morgan)

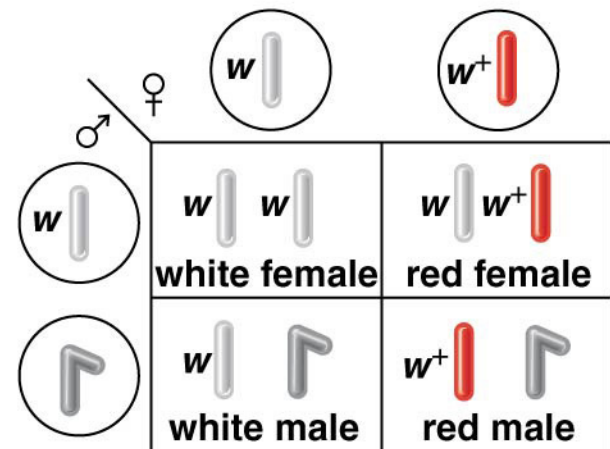
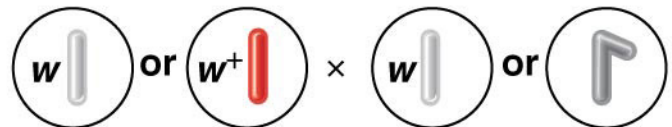
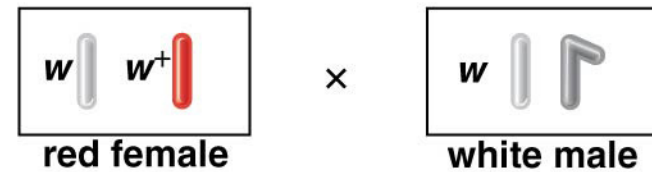
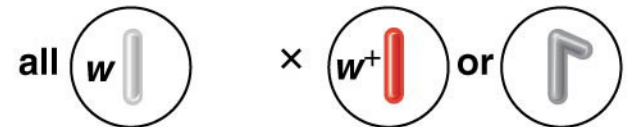
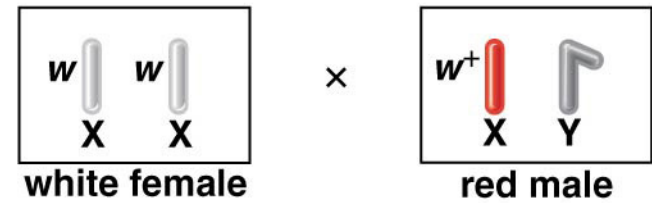
- Reciprocal crosses between white- and red-eyed flies → different results
- *White* eye variant (w^+/w)
 - Red eye color is dominant to white
 - Inheritance pattern of white eye related to sex of parent
- Conclusion: *White* locus is on the X chromosome



Cross A



Cross B



2. Sex-limited and sex-influenced inheritance

Sex vs. gender

- Sex: biological definition
 - Man = person assigned male at birth (AMAB)
 - Woman = person assigned female at birth (AFAB)
- Gender: social construct / personal identification

The distinction between sex and gender differentiates a person's sex (the anatomy of an individual's reproductive system, and secondary sex characteristics) from that person's gender, which can refer to either social roles based on the sex of the person (gender role) or personal identification of one's own gender based on an internal awareness (gender identity).

Sex influences phenotype

- **Sex-limited inheritance**
 - Expression of a phenotype is absolutely limited to one sex
- **Sex-influenced inheritance**
 - Expression of a phenotype is influenced by sex

In both cases, autosomal genes are responsible for the phenotypes, it's only their expression that depends on sex (mostly on hormonal factors).



Feather plumage in chickens

- Encoded by an autosomal gene
- Hen-feathering controlled by dominant allele expressed in both sexes
- Rooster-feathering controlled by recessive allele only expressed in males
- Expression is controlled by sex hormones

Genotype	Phenotype	
	♀	♂
<i>HH</i>	Hen-feathered	Hen-feathered
<i>Hh</i>	Hen-feathered	Hen-feathered
<i>hh</i>	Hen-feathered	Cock-feathered



Male pattern baldness

- The responsible allele B is dominant in males and recessive in females
- In BB genotype in females, phenotype is less pronounced

Genotype	Phenotype	
	♀	♂
BB	Bald	Bald
Bb	Not bald	Bald
bb	Not bald	Not bald

3. Sexual differentiation

Sexual differentiation

- Organisms using sexual reproduction have two types of sexual differentiation
 - **Primary sexual differentiation**
 - Involves only gonads where gametes are produced
 - **Secondary sexual differentiation**
 - Changes in the overall appearance of organism, including the formation of external sexual organs
-

Unisexual vs. hermaphroditic organisms

- Diversity of sexual differentiation between individuals in many plant or animal species
 - **Unisexual = dioecious = gonochoric**
 - Have **only** male or female reproductive organs
 - **Bisexual = monoecious = hermaphroditic**
 - Have **both** male and female reproductive organs
 - Can produce fertile gametes of both sexes (egg and sperm)
-

Caenorhabditis elegans

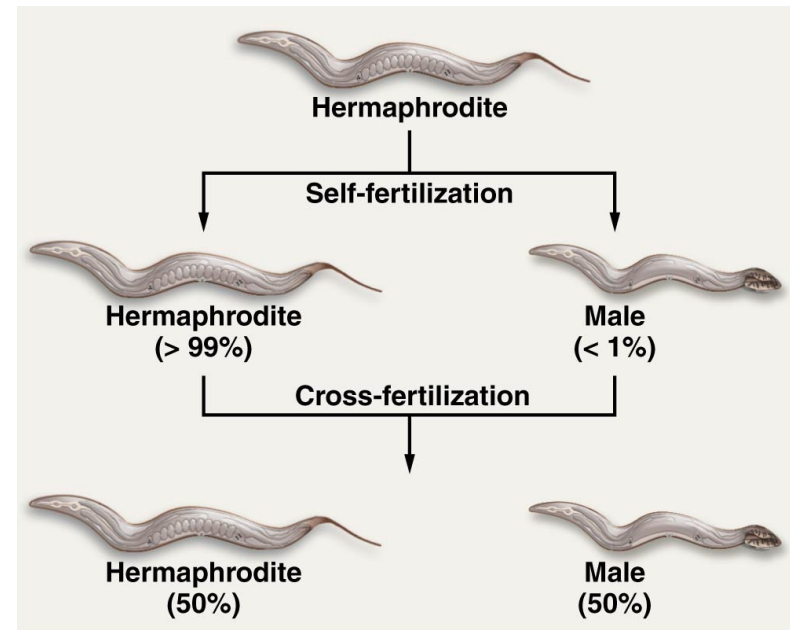
- Major model organism
- Nematode worm made, at adult stage, of 959 cells
- Two sexual phenotypes
 - Males have only testes
 - Hermaphrodites have both testes and ovaries



Caenorhabditis elegans

Two reproduction strategies

- Self-fertilization (very frequent)
 - Eggs are fertilized by stored sperm
 - The vast majority of descendants are hermaphrodites, with $<1\%$ of males
- Cross-fertilization (rare)
 - Mating between male and hermaphrodite
 - 50% male and 50% hermaphrodite offspring



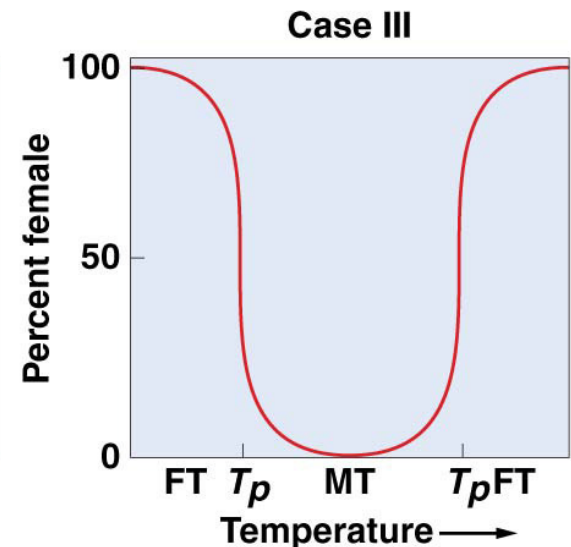
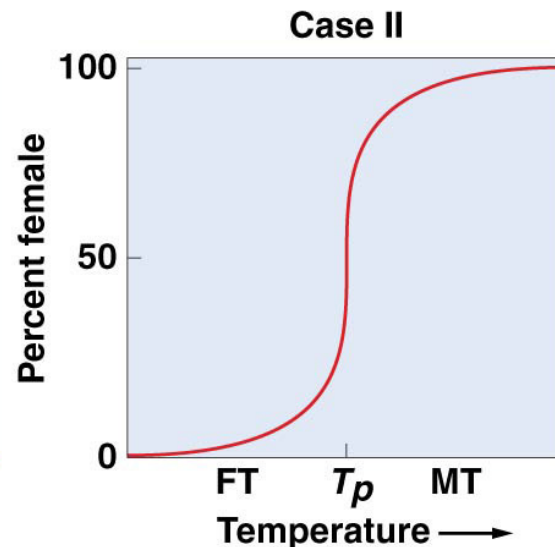
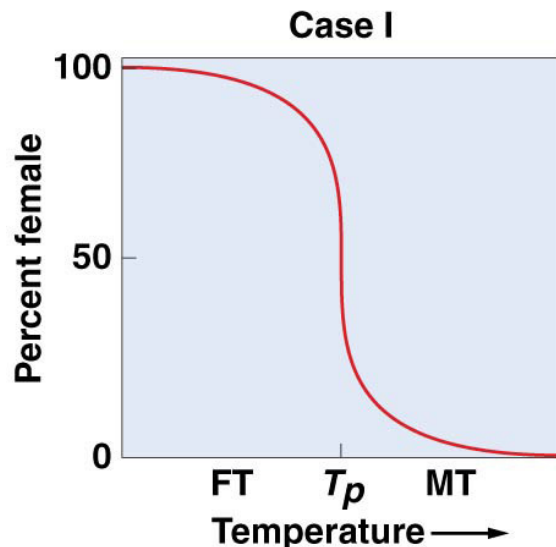
4. Sex determination

Sex determination

- Depends on **sexual chromosomes** in most diploid animals
 - Depends on **temperature** in some reptile
-

Temperature-dependent sex determination

- Three different patterns of temperature sex determination in crocodiles, most turtles, and some lizards
- Incubation temperature of eggs during embryonic development determines sex
- Dependent on steroid hormones, notably estrogens



Sex determination by sexual chromosomes

■ *Protenor* mode

- **XX/XO**
- Depends on random distribution of X chromosome into half of male gametes
- Presence of **two X** chromosomes in zygote → female offspring
- Presence of **one X** chromosome in zygote → male offspring



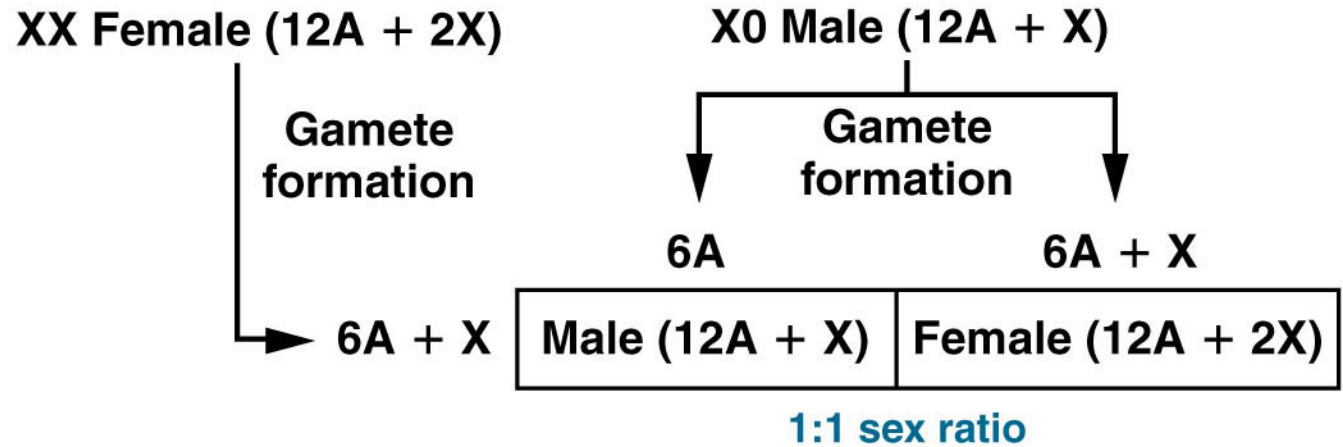
Sex determination by sexual chromosomes

- ***Lygaeus* mode**
 - **XX/XY**
 - Female gametes have one X chromosome
 - Male gametes have either an X or Y chromosome



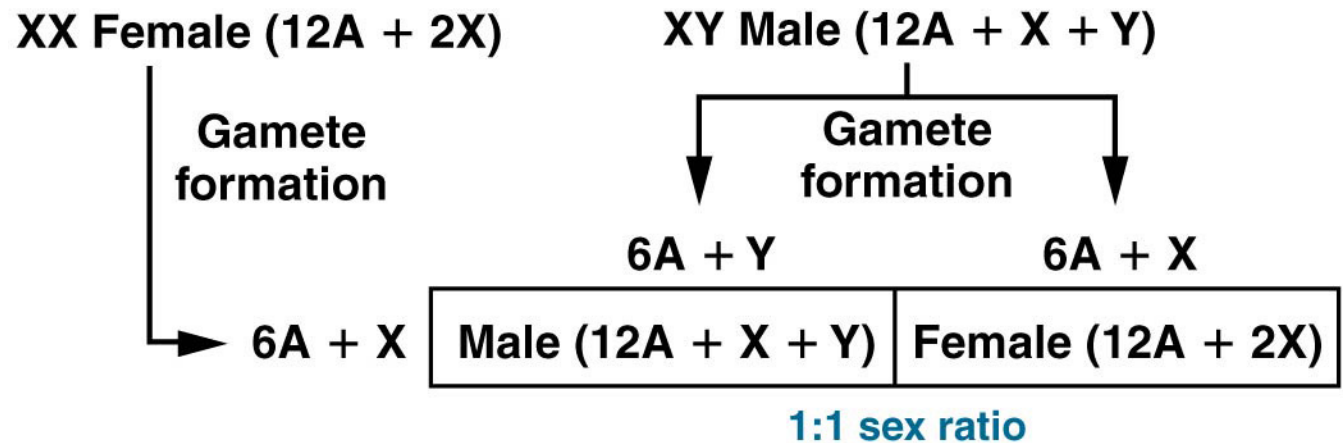
Protenor

(a)

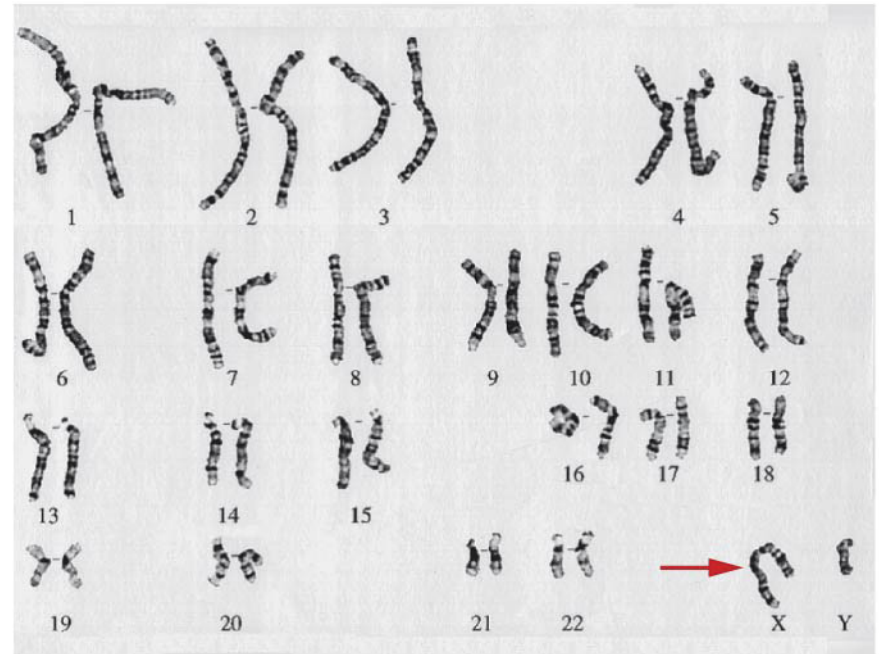
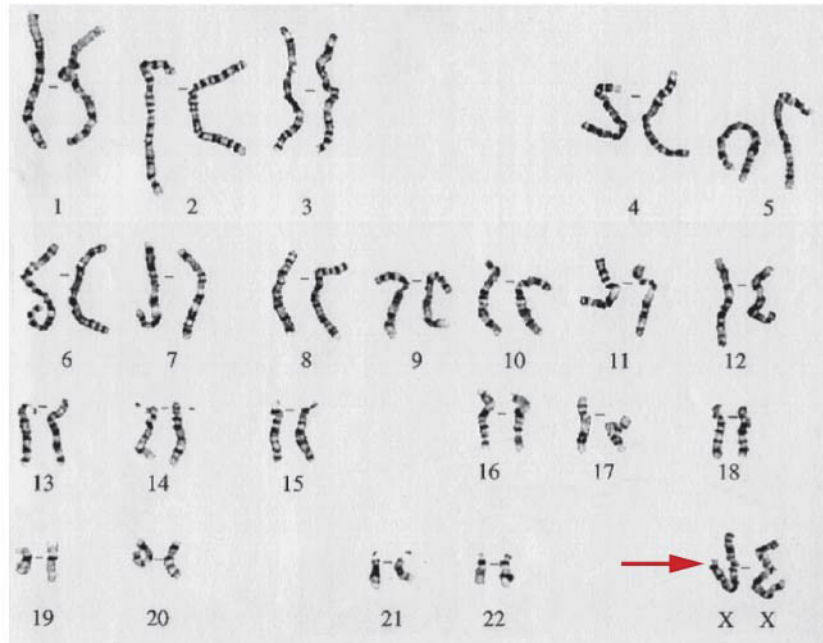


Lygaeus

(b)

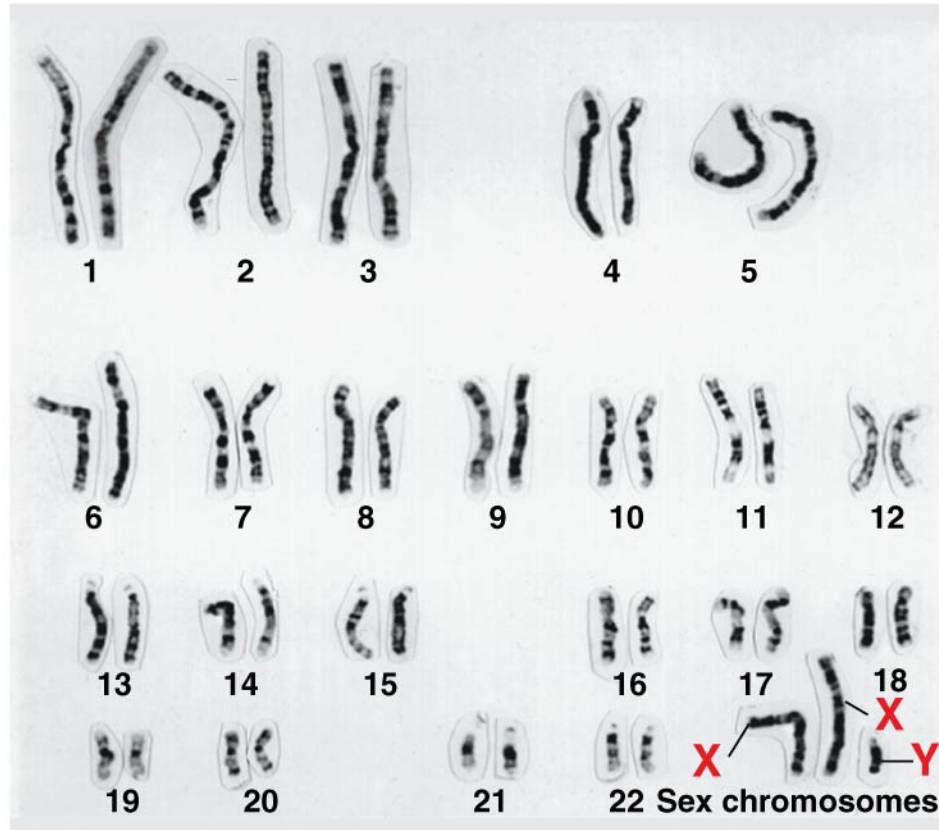


Sex determination in humans



Klinefelter and Turner syndromes

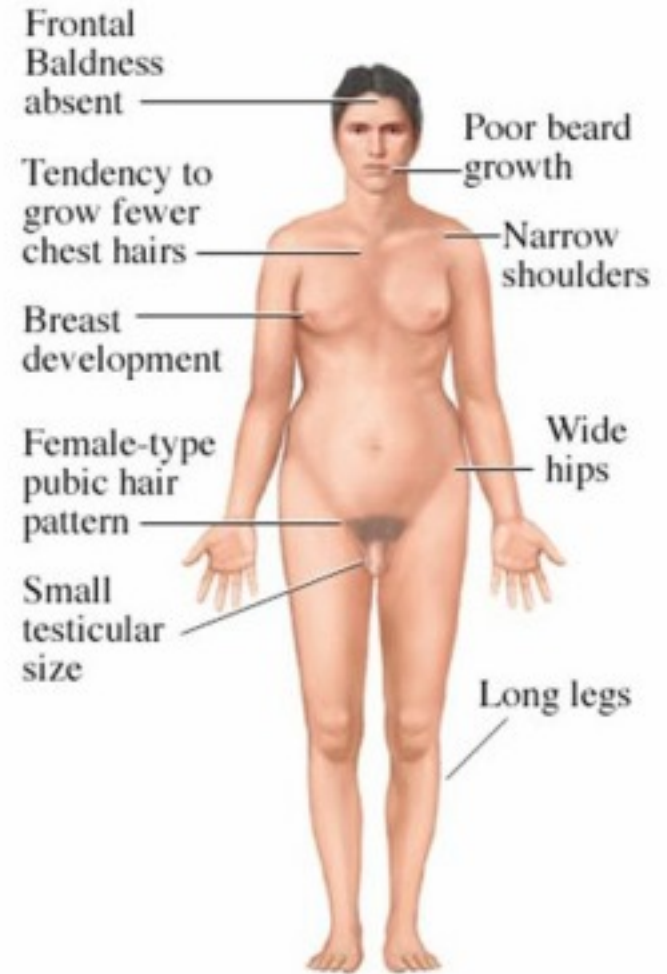
- Anomalies in the number of sexual chromosomes
 - Characterized by aberrant sexual development
 - Both syndromes result from nondisjunction, i.e. failure of X chromosomes to segregate during meiosis
-

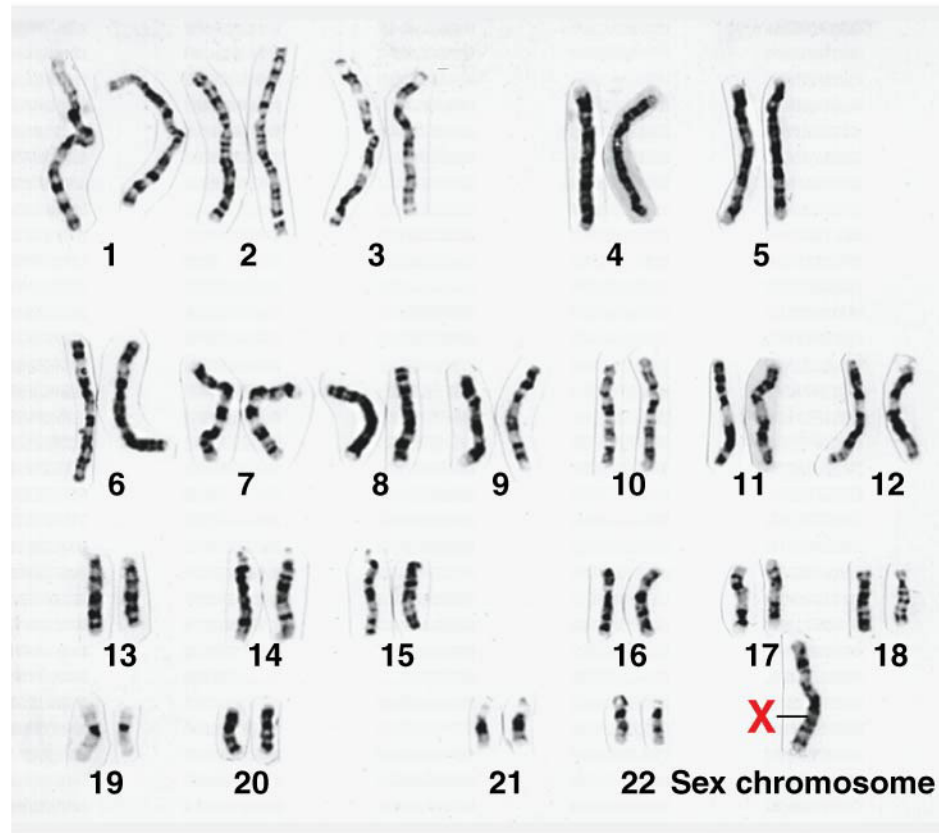


Klinefelter syndrome

■ 47,XXY

- Tall, long arms and legs, large hands and feet
- Internal ducts are male, rudimentary testes fail to produce sperm
- Some feminine traits present: enlarged breasts, rounded hips
- Sometimes 48,XXXY, 48, XXYY or even 49 XXXXY
- 2/1000 births in boys

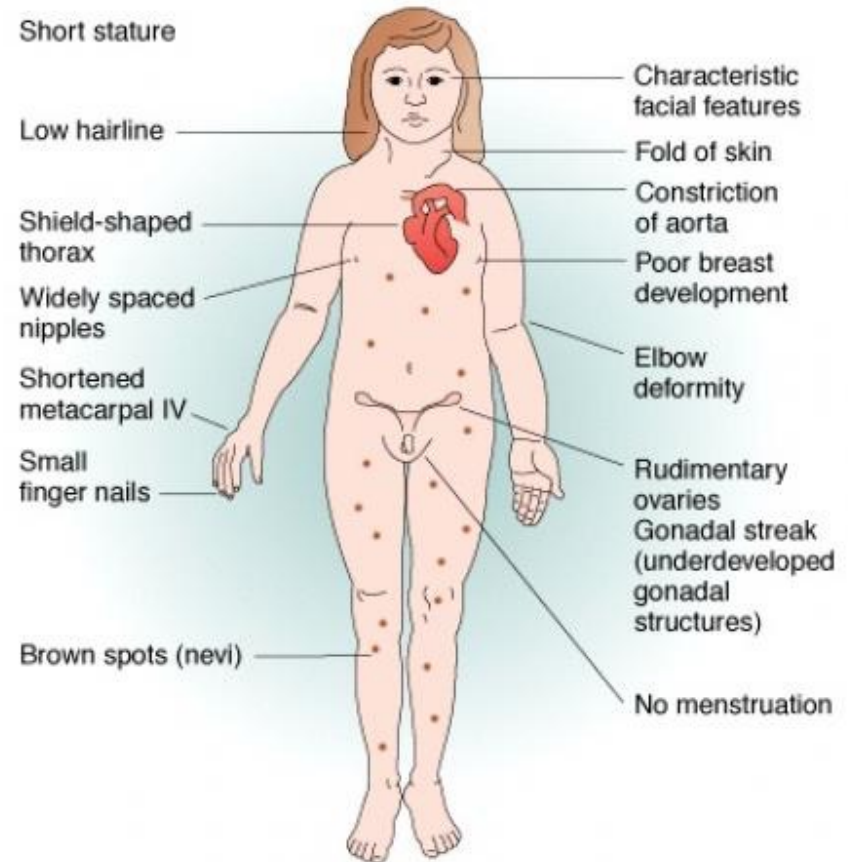




Tuner Syndrome

■ 45,X

- Phenotypically female
 - Female external genitalia and internal ducts
 - Ovaries are rudimentary
 - Underdeveloped breasts
- Short stature
- Often sterility
- 1/2000 births in girls



Other anomalies of sex chromosome numbers

■ 47,XXX (triple-X)

- Three X chromosomes
- Normal set of autosomes
- Results in female differentiation
- Sometimes women are perfectly normal
- Sometimes underdeveloped secondary sex characteristics (sterility and mental retardation) occur

■ 47,XYY

- Male differentiation
- Tall
- Subnormal intelligence
- Personality disorders?

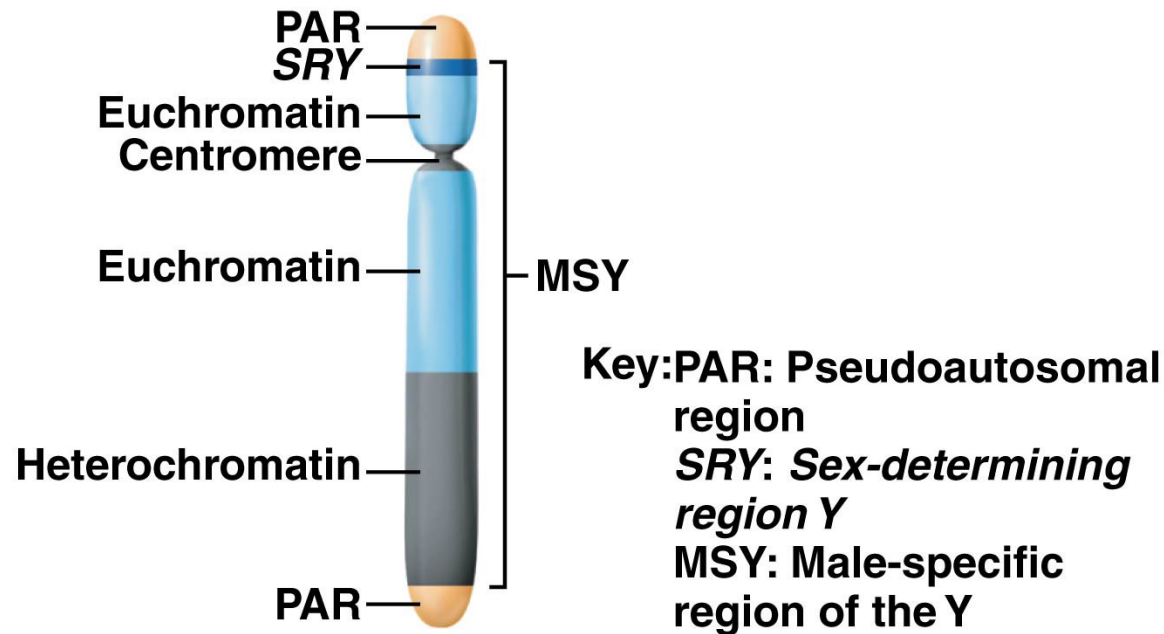
TABLE 7.1 Frequency of XYY Individuals in Various Settings

Setting	Restriction	Number Studied	Number XYY	Frequency XYY
Control population	Newborns	28,366	29	0.10%
Mental-penal	No height restriction	4,239	82	1.93
Penal	No height restriction	5,805	26	0.44
Mental	No height restriction	2,562	8	0.31
Mental-penal	Height restriction	1,048	48	4.61
Penal	Height restriction	1,683	31	1.84
Mental	Height restriction	649	9	1.38

Source: Compiled from data presented in Hook, 1973, Tables 1-8. Copyright 1973 by the American Association for the Advancement of Science.

<https://www.vox.com/2015/2/25/8103965/genetics-crime-xyy>

Y chromosome



NATURE | SCIENTIFIC AMERICAN

Reprieve for men: Y chromosome is not vanishing

The sex chromosome has been shrinking throughout mammalian evolution, but many of its remaining genes play crucial roles beyond sex determination.

Particular regions of Y chromosome

- **PARs: Pseudoautosomal regions**
 - Present on both ends of Y chromosome
 - Share homology with regions on X chromosome
 - Allow recombination events with X during meiosis, and are essential for segregation of X and Y chromosomes
 - **MSY: Male-specific region of the Y**
 - Nonrecombining region of Y chromosome
 - ***SRY*: Sex-determining region Y**
 - Located adjacent to PAR of the short arm of Y chromosome
 - Contains the *SRY* gene, which controls male development
-

Testis-determining factor (TDF)

- The *SRY* gene encodes the TDF protein
 - It becomes active in XY embryos at 6–8 weeks of development
 - TDF a transcription factor which triggers the transformation of non-differentiated gonads into testes
-

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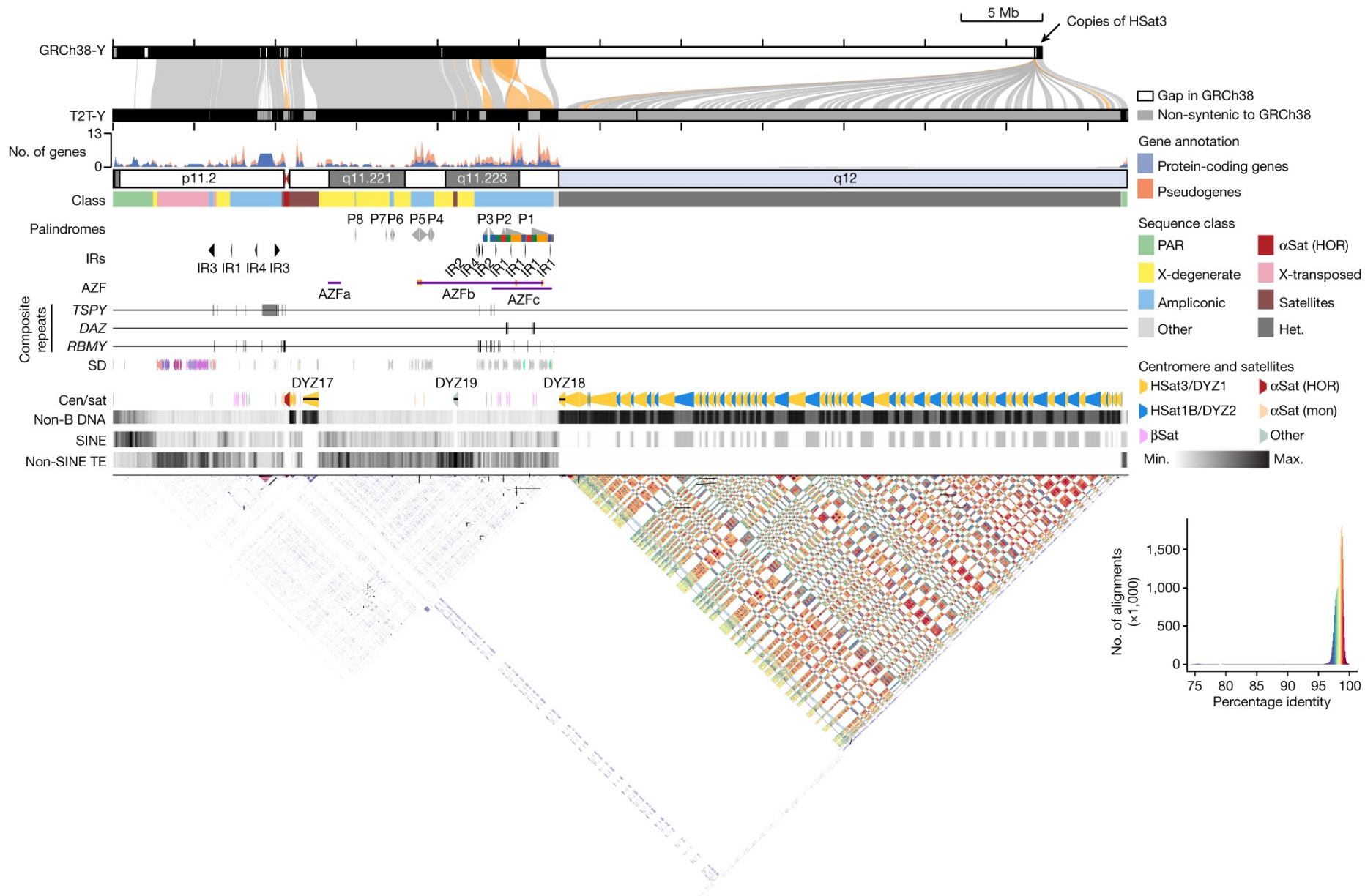
The complete sequence of a human Y chromosome

[Arang Rhie](#), [Sergey Nurk](#), [Monika Cechova](#), [Savannah J. Hoyt](#), [Dylan J. Taylor](#), [Nicolas Altemose](#), [Paul W. Hook](#), [Sergey Koren](#), [Mikko Rautiainen](#), [Ivan A. Alexandrov](#), [Jamie Allen](#), [Mobin Asri](#), [Andrey V. Bzikadze](#), [Nae-Chyun Chen](#), [Chen-Shan Chin](#), [Mark Diekhans](#), [Paul Flicek](#), [Giulio Formenti](#), [Arkarachai Fungtammasan](#), [Carlos Garcia Giron](#), [Erik Garrison](#), [Ariel Gershman](#), [Jennifer L. Gerton](#), [Patrick G. S. Grady](#), ... [Adam M. Phillippy](#) 

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Y chromosome



5. Sex ratio

Sex ratio

- **Sex ratio**
 - Actual proportion of male to female offspring
 - **Primary sex ratio**
 - Reflects proportion of males to females conceived in population
 - **Secondary sex ratio**
 - Reflects proportion of each sex at birth
-

Sex ratio in humans

- Primary sex ratio should be one if the following conditions are met:
 - Males produce equal numbers of X- and Y-bearing sperm
 - Each type of sperm has equivalent viability and motility in female reproductive tract
 - Egg surface equally receptive to both X- and Y-bearing sperm
-

Sex ratio in humans

- **1969 worldwide census data, secondary sex ratio observed in multiple populations:**
 - Whites in U.S.: 106 males to 100 females (1.06)
 - African American population: 1.025
 - Korea: 1.15
 - Suggests that more males are conceived than females
-

PMC full text: [Proc Natl Acad Sci U S A. 2006 Sep 5; 103\(36\): 13271–13275.](#)
Published online 2006 Aug 28. doi: [10.1073/pnas.0602203103](#)
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Table 1.

Numbers of missing females for selected Asian countries, 2001

Country	Calculated no. of missing females, in millions ^{–*}
Afghanistan	0.5–1
Bangladesh	1.8–3.7
China	34–41
India	27–39
South Korea	0.2–0.3
Pakistan	2.6–4.9
Taiwan	0.4–0.6
Iran	0.8–1.2

*Adapted from refs. [28](#) and [45](#).