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**MEDICAL BIOLOGY PRACTICALS. GENETICS.**

## Practical 5. Sex determination and sex linkage.

*By Boris M.Sharga, Diana B. Pylypiv, Volodymir P.Feketa*

The temperature was regarded as factor of human sex determination (SD) since ancient times. Particularly, Aristotle (335 B.C.E.) naively proposed that the heat of the male partner during intercourse determines the gender of child [13].

Temperature sex determination (TSD) was found in reptiles (crocodiles and turtles) and in fishes [14, 30]. The nest temperature (not male temperature) has effect on SD. For example, nearly all eggs of *Alligator mississippiensis* incubated at 33°C, produce males. The development at 30°C resulted in nearly all hatching as females [10]. TSD occurs in species with undifferentiated chromosome (ch) Y.

The developing gonads in vertebrate have the bipotential genital ridges: the cortex and the medulla. Ovaries develop from growing cortex, while testes develop from the medulla with an antagonism between two alternative processes [28].

Aromatase regulating gonadal estrogen level is proposed as main target of a putative thermosensitive factor in TSD. The estrogen levels may influence SD. Yolk steroids and steroids from embryonic nervous system are sources of hormones for TSD. The TSD animals have different SD modes. They have thermosensitive genes: in *Emydidae—sox9*, in *Testudinae— sox9*, *sf1*, *wt1*, and in *Emydidae—dax1*. In TSD a genes chain *amh-sox9* affects the appearance of testes. The chain *sry-sox9-amh* is used for genetic sex determination (GSD) in mammals [28, 49].

*Teleost* fishes (>30 000 species) are variable in sexuality: *gonochorism*, *synchronous/sequential hermaphrodite*, or *unisexual* reproduction. Fishes have GSD or environmental SD [19]. The amazon mollies (*Poecilia formosa*) is a unisexual fish.

In *protandrous hermaphroditic* clownfish (*Amphiprion* genus) the males can turn into females due to behavioral changes after *α*-female death. Both clownfish sexes are of same karyotype. The aggressiveness of *α*-female suppresses an area of the brain in the other clownfish that is responsible for female hormones production. This prevents the formation of other females. When *α*-female dies estradiol level in the *α*-male is increased and testosterone is decreased. The female organs grow and the male genitalia degenerate. The *α*-male fish becomes *α*-female [47]. If a clownfish is left in an aquarium alone (no suppression) it will develop as female directly.

There are fish species with XX/XY and ZW/ZZ (most common) SD systems; the swordtail has WXZ system [19]. About 10% of fish species have heteromorphic sex chs, but most of them are at an early stage of differentiation.

Birds and mammals have GSD *only* by distinct sex chs [13]. In ZW system of birds, insects and fishes, the male is ZZ (homogametic) and female is ZW (heterogametic) sex.

McClung C. had discovered the “accessory chromosome” in grasshoppers [26]. He theorized that female in grasshoppers is induced by the presence of two X chs (XX), while male is determined by the absence of a second X ch (XO). This helped to prove that chromosomes carry genetic information that determines phenotype.

Insects vary in SD [40]. The majority of them have dimorphic sex chs, but in some species, e. g., grasshoppers, the male is X0, and the female have XX chs. In moths and butterflies (*Lepidoptera*) females are X0, and males have X chs pair (XX).

US biologist, T.H.Morgan explained XY system of SD. He was awarded by Nobel Prize in Physiology or Medicine (1933) for his discoveries concerning the role played by the chromosome in heredity.

White eyes gene in *Drosophila melanogaster* fruit fly [29] and "lacticolor" gene in moth *Abraxas grossulariata* [8] were the first sex-linked recessive genes found.

To illustrate the X-linked inheritance of white-eyes in fruit fly, T.H.Morgan performed experiment in reciprocal crosses [29]. These are crosses in which the sexes and phenotypes of parents are reversed. Difference in reciprocal crosses prooved the X-linkage of white eye gene (Table 1).

**Table 1. Reciprocal crosses performed by T.H.Morgan**

| |
|---|
| ***Fist cross:*** Parents, P: Red-eyed female ♀ $X^{w+}X^{w+}$ × ♂ $X^{w}Y$ White eyed male<br>Gametes, G: $X^{w+}$ $X^{w}$, Y<br>Offspring, F1: All red eyed ♀ $X^{w+}X^{w}$ × ♂ $X^{w+}Y$<br>Gametes, G: $X^{w+}$,$X^{w}$ $X^{w+}$,Y<br>Offspring, F2: $X^{w+}X^{w+}$; $X^{w+}X^{w}$; $X^{w+}Y$; $X^{w}Y$<br>***Result:*** All females are red eyed. Red eyed males : white eyed males, 1 : 1 |
| ***Second cross:*** Parents, P: White eyed female ♀ $X^{w}X^{w}$ × ♂ $X^{w+}Y$ Red-eyed male<br>Gametes, G: $X^{w}$ $X^{w+}$,Y<br>Offspring, F1: Red-eyed female ♀ $X^{w+}X^{w}$ × ♂ $X^{w}Y$ White eyed male<br>Gametes, G: $X^{w+}$, $X^{w}$ $X^{w}$,Y<br>Offspring, F2: $X^{w+}X^{w}$; $X^{w}X^{w}$; $X^{w+}Y$; $X^{w}Y$<br>***Result:*** Red eyed females : white eyed females, 1 : 1.<br>Red eyed males : white eyed males, 1 : 1. |

The *Hymenoptera* (ants, bees, wasps and sawflies) are lack of sex chs, as do thrips and some smaller clades. Many of them have **haplodiploid system** of SD in which haploid males develop from unfertilized eggs and diploid females develop from fertilized eggs [4]. In honeybees, e.g., females, the worker and queen, are grown from fertilized (2n=32) eggs. The drones are produced from unfertilized haploid (n=16) eggs.

**Paternal genome elimination** was found in *Liposcelis* booklice and some other insects [4, 16]. Both sexes start from fertilized 2n eggs. The paternal chs are eliminated early during development in males. Females transmit a recombined genome to offspring, but males pass only the maternal copy.

In *D. melanogaster*, the male is XY and the female is XX. Unlike in mammals, the Y in the fruit fly does not determine maleness (Table 2). The ratio *X chs : number of autosomal sets (X : A)* provides SD. If a fly has 1 X and is diploid for the autosomes (2*n*), the *X:A* ratio is 1:2 = 0.5, this means that fly is male. The males are XX/4n also. To be a female, 2n fly should have 2 X chs, the *X:A*= 2:2 = 1.0.

Metafemale genetic constitutions is XXX/2n, (*X:A* > 1.0). The metamales appear at combination XY/3n and X0/3n (*X:A* < 0.5). The latter is sterile. The combinations of XX/3n, XXX/4n provide intersex fly (0.5< *X:A* < 1.0).

**Table 2. Chromosomal sex determination in fruit fly and humans**

| Chromosomes | | Gender phenotype | |
|---|---|---|---|
| **Sex** | **Autosomal** | ***D. melanogaster*** | **Humans** |
| XX | 2 n | Female (*X:A* = 1.0) | Female |
| XY | 2 n | Male (*X:A* = 0.5) | Male |
| XO | 2 n | Male, sterile (*X:A* = 0.5) | Female, Turner syndrome |
| XXY | 2 n | Female (*X:A* = 1.0) | Male (Klinefelter syndrome) |
| XYY | 2 n | Male (*X:A* = 0.5) | Male |
| XXYY | 2 n | Female (*X:A* = 1.0) | Male (Klinefelter syndrome) |
| XXX | 2 n | Metafemale (*X:A* >1.0) | Female (triple-X syndrome) |

In mammals, e.g., humans, females, usually, have 2 X chs and produce one type of gametes (*homogametic sex*), while males have XY and produce gametes of two types (*heterogametic sex*). The *SRY* gene on Y ch causes maleness by activating and regulating an autosomal gene *Sox9*. If the *Sox9* becomes active in an XX embryo, it produces male gonads, no ovaries, and it develops into an anatomical male. If the *Sox9* does not turn on in an XY embryo, the ovaries develop, and the individual becomes an anatomical female. This happens for up to 1 in 20 000 XY embryos [44]. After transgenosis *Sox9* induces testis formation in XX mice [50] also.

R-spondins are a family of growth factors. The R-spondin 1 (*RSPO1*) gene disruption (recessive mutation) results in XX sex reversal, palmoplantar hyperkeratosis and predisposition to skin squamous cell carcinoma. The mutation leads to complete female-to-male sex change in the absence of the testis-determining gene, *Sry* [35]. As a rule, in females *Sox9* is switched off by *RSPO1*, which, via other genes in the cascade, leads to ovaries production. The mutated *RSPO1* is unable to switch-off, leaving *Sox9* on and leading to male development in XX humans [34]. XX mice with their *Sox9* expressed, turn back on form testes [50].

Some species have sex chs series, e.g., the platyrus karyotype (2 n = 52) consists of 21 autosomes and 10 sex chs (5X and 5Y chs in male and 5 X-pairs in female) [12].

The majority of plants are *hermaphroditic*, i.e., have both sex organs on the same flower (e.g., *Rosaceae*), other are *monoecious* as they have them in separate flowers on the same plant (e.g., corn). The *dioecious* species (~ 6% of flowering species) [51] have sexex on separate plants, bearing flowers containing only anthers or ovaries, e.g., hollies, ginkgo (Fig.1). SD is mostly genetic and morphologically distinct sex chs have only few species, e.g., ginkgo [21], liverwort [33], sorrel and white campion [51]. Of these, heteromorphic sex chs have been best studied in two model species - white campion (*Silene latifolia*) and sorrel (*Rumex acetosa*) [51].

During meiosis in males some parts of X and Y chs (*homologous regions*) are paired and recombined and other parts are non-pairing, non-recombining [44] or *differential regions*. They were indicated by observing where chs synapsed during

meiosis and where they did not. The X and Y chs contain short regions of homology with same genes, the *pseudoautosomal genes*, e.g., *Mic2* gene, encoding a cell surface antigen, is found on short arms of both the X and Y chs. It has *pseudoautosomal inheritance*. Genes in *differential regions* are called *hemizygous* in males. The genes in differential regions of X or Y chs are said to be *X-linked* or *Y-linked (holandric)* genes. The genes in homology regions are *X-and-Y linked*. The genes on X and Y chs in general are *sex-linked* [11]. Evolutionary suppression of recombination between Y and X chs resulted in their current different gene numbers [39], ~1 100 and <200 genes on the human X and Y chs, respectively [39, 44]. Since the genes are more numerous on X ch, the X-linked traits are more common.

**Fig. 1.The holly (*Ilex aquifolium* L.), left, Maidenhair tree (*Ginkgo biloba* L.), right.**
*By Diana B. Pylypiv.*

***X-linked recessive inheritance*** is concluded from pedigree by next clues: 1) more males, than females affected 2) none of the offspring of an affected male is affected, all his daughters are carriers 3) 50% of sons from these daughters are affected 4) sons of an affected male are free of the mutated allele.

X-linked recessive trait is expressed in all males and in homozygous for trait allele females. The incidence of recessive X-linked phenotypes in females is the square of that in males: e. g., if 1 in 30 males is affected, then expected females with condition are: $^1/_{30} \times {}^1/_{30} = {}^1/_{900}$. X-linked recessive trait is inherited from carrier mother or from an affected father. Each son born to a carrier mother has a 50% probability of inheriting the trait. The daughter born to an affected father and a non-carrier mother will be a carrier (Fig. 2).

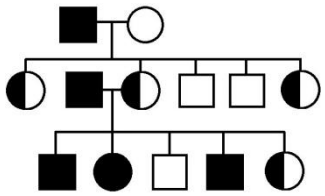

**Fig. 2. X-linked recessive trait pedigree.**
*By Diana B. Pylypiv.*

There are many *X-linked recessive* disorders in human, such as adrenoleuko-dystrophy, Becker's muscular dystrophy, creatine transported defect, Duchenne muscular dystrophy, endocardial fibroelastosis, Fabry disease, hemophilia, spinal and bulbar muscular atrophy, lysosomal storage disease, Menkes disease, Norrie disease, ocular albinism, ocular albinism type 1, ornithine transcarbamylase deficiency, Pelizaeus-Merzbacher disease, X-linked agammaglobulinemia, X-linked dystonia parkinsonism, X-linked intellectual disability, X-linked recessive chondrodysplasia punctata, X-linked spinal muscular atrophy type 2, XMEN disease and syndromes, such as of occipital horn, MASA, FG, McLeod, nasodigitoacoustic,

oculocerebrorenal, Renpenning's, Say-Meyer, Simpson-Golabi-Behmel, Smith-Fineman-Myers, Wieacker and others.

Let us regard some examples. *Hemophilia*, the life threatening inability of blood to clot, is more common in males than in females, as males are hemizygous and express 1 mutant allele. To be hemophilic, a female must inherit 2 mutant alleles, a less frequent event since the mutant allele is rare in human population. The hemophilia has X-linked recessive patern of inheritance (Table. 3).

**Table 3. Inheritance of hemophilia, *X*-linked recessive disease**

| |
|---|
| Parents, P: mother, carrier ♀$X^hX$ × ♂$XY$, father, non-carrier, healthy |
| Gametes, G: $X^h$, $X$ $X$, $Y$ |
| Children, F: daughters $X^hX$, $XX$, sons $X^hY$, $XY$ |
| Daughters are healthy, 50% of them are healthy carriers, 50% of sons are diseased |

Once, the allele of the disease appeared as mutation in the reproductive cells of Queen Victoria or one of her parents. This hemophilia allele was passed to her son Leopold and, by intermarriage through two of her daughters, Alice and Beatrice, to many royals in Europe [39].

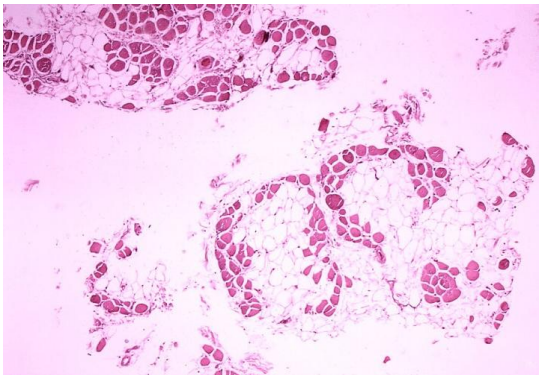

**Fig. 3. Cross section of gastrocnemius muscle in patient, who died of pseudohypertrophic DMD: extensive replacement of muscle fibers by adipose cells.** *By Dr. Edwin P. Ewing, Jr*. [18].

*Duchenne muscular dystrophy* (DMD) was first described by G. Duchenne in the 1860s. Diseased people may show muscle weakness as early as 3 years of life. The DMD gradually weakens the skeletal muscles and eventually affects the myocard and breathing muscles. Patients rarely survive beyond early 30s. These are due to recessive mutation in gene of dystrophin, a protein needed as structural support into myocytes for anchoring elements of the internal cytoskeleton to the plasma membrane. Without dystrophin, the plasma membrane becomes permeable and may rupture. In pseudohypertrophic DMD the damaged myocytes are gradually substituted by adipose cells (Fig. 3).

**Table 4. Muscular dystrophy inheritance in dog**

| | |
|---|---|
| 1) | P: diseased female $X^dX^d$ × $X^DY$ healthy male |
| | G: $X^d$ $X^D$, $Y$ |
| | F: healthy females $X^DX^d$, $X^dY$ diseased males |
| | 50% carriers : 50% diseased, 1:1 by sex |
| 2) | P: healthy females $X^DX^D$ × $X^dY$ diseased males |
| | G: $X^D$ $X^d$,$Y$ |
| | F: healthy females $X^DX^d$, $X^DY$ healthy male |
| | 100% are healthy, 1:1 by sex |

Similar to DMD X-linked muscular dystrophy is found among dogs [1, 2, 3, 42]. Like in humans, the mutation in the dystrophin gene resulting in devastating muscle atrophy. It starts at about 6 to 8 weeks of age. Ill dogs usually die within the 1st year of age, however, some can reach age 3 to 5 and mate. Using these dogs example (Table 4), we can see again, how reciprocal crosses are performed to test the

the trait for X-linkage. As the outcome of the reciprocal crosses yielded different results, we can conclude inheritance of X-linked gene.

***X-linked dominant inheritance*** is recognized in pedigrees through the following clues: 1) condition is passed from father to daughters only 2) females married to unaffected males pass the trait to half of their sons and daughters.

Each child of a mother affected with an X-linked dominant trait has a 50% chance of inheriting the trait and being affected with the disorder. If only the father is affected, 100% of the daughters will be affected, since they inherit their father's X ch, and 0% of the sons will be affected, since they inherit their father's Y ch (Fig. 4).

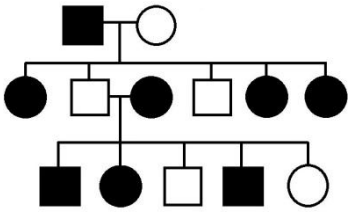

**Fig. 4. X-linked dominant trait pedigree.** *By Diana B. Pylypiv.*

Males are normally hemizygous for the X ch, having only one copy of mutated gene. As a result, X-linked dominant disorders usually show higher expressivity in males than females. Among X-linked dominant human disorders are: idiopathic hypoparathyroidism, incontinentia pigmenti, ornithine carbamoiltransferase deficiency, vitamin D-resistant rickets (XLH) and syndromes: Alport's, Aarskog-Scott, Rett, Coffin-Lowry, fragile X.

*X-linked Vitamin D-resistant rickets (syn. X-linked hypophosphatemia (XLH), X-linked dominant hypophosphatemic rickets)* is a form of osteomalacia due to ineffective D vitamin ingestion associated with a *PHEX* gene mutation resulting in PHEX protein inactivity [41]. It leads to bone deformity, short stature and *genu varum* (bow leggedness) (Fig. 5). The latter can be treated with Ilizarov frames and by surgery. The disease prevalence is 1 : 20 000 [7]. The PHEX protein regulates protein FGF23, a fibroblast growth factor 23 coded by *FGF23* gene. FGF23 inhibits the kidneys' ability to reabsorb phosphate into the bloodstream. Mutated *PHEX* regulates FGF23 incorrectly. The resulting overactivity of FGF-23 reduces vitamin D 1α-hydroxylation and phosphate reabsorption by the kidneys, leading to hypophosphatemia and to the symptoms of hypophosphatemic rickets. Also in the disease, where PHEX enzymatic activity is absent or reduced, osteopontin, a mineralization-inhibiting secreted substrate protein found in the extracellular matrix of bone, accumulates in bones, e.g., teeth, and contributes to the osteomalacia (odontomalacia)[5]. Biochemically disease is recognized by *hypophosphatemia* and low level of calcitriol ($1,25\text{-}(OH)_2$ vitamin $D_3$).

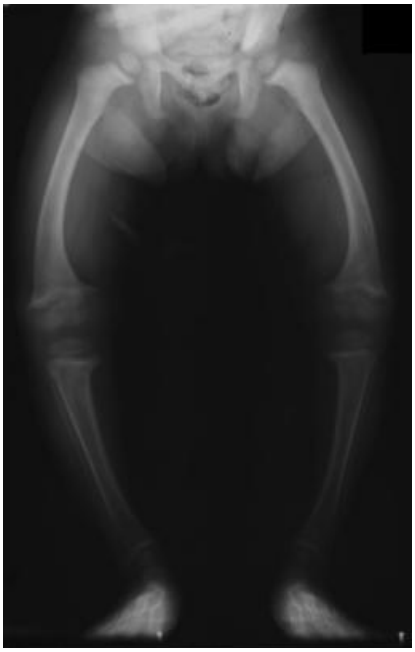

**Fig. 5. Anteroposterior view of the 2 y.o. rickets child legs.** *By M.L.Richardson* [17].

***Y-Linked inheritance*** or ***holandric inheritance*** is observed for genes located on the Y ch; these are inherited by sons from their father (Fig. 6).

The Y linkage has 3 clues: 1) the trait occurs in males only 2) it is passed to all sons of affected males 3) daughters of affected males are not only phenotypically normal but also do not have affected offspring.

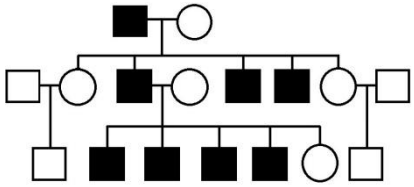

**Fig. 6. Y-linked trait pedigree.**
*By Diana B. Pylypiv.*

Stern C. (1957) suggested Y-linkage for several genes [45]. In the 1950-60s using human pedigrees, many genes were recognized as Y-linked. New advanced techniques and statistical analysis showed that this was done incorrectly for many of them, particularly, for hairy ear rims trait [20, 34].

In guppies, Y-linked genes help determine sex selection. This is done indirectly by traits that allow the male fish to appear more attractive to a prospective mate. These traits were shown to be Y-linked [37]. Four measures of sexual activity in guppies are Y-linked also [9].

The Y ch has been almost entirely mapped. The mapping proves the Y-linkage for many important genes, e. g., *ASMTY* (acetylserotonin methyltransferase), *TSPY* (testis specific protein), IL3RAY (interleukin 3 receptor), *SRY* (sex-determining region), *TDF* (testis determining factor), *ZFY* (zinc finger protein), *PRKY* (protein kinase, Y-linked), *AMGL* (amelogenin), *CSF2RY* (granulocyte-macrophage, colony stimulating factor receptor, alpha subunit of Y ch), *ANT3Y* (adenine nucleotide translocator-3 on the Y, *SOX21*(cause of baldness), *AZF2* (azoospermia factor 2), *BPY2* (basic protein on the Y ch), *AZF1* (azoospermia factor 1), *DAZ* (Spermatogenes is deleted in azoospermia), *RBM1* (RNA binding motif protein, Y ch, family1, member A1), *RBM2* (RNA binding motif protein 2), *UTY* (ubiquitously transcribed TPR gene on Y ch), *USP9Y* and *AMELY*.

Y ch deletions are frequent cause of male infertility.

**Dosage compensation** (DC) is the phenomenon in which the level of expression of many genes on the sex chs (e.g., the X ch) is similar in both sexes, even though males and females have a different complement of sex chs. This term was suggested by H.Muller in 1932 [31] to explain the effects of eye color mutations in *Drosophila*. He observed that 1 apricot eye color allele in male produces the same effect as 2 of these alleles in female. The female with deletion of 1 of 2 alleles on X chs has eyes of paler color, i.e. 1 allele in female is not equivalent to 1 copy of the allele in the male. The difference is in the gene dosage: 2 copies in females *versus* 1 copy in males is being DC at the level of gene expression.

In *Drosophila*, the male doubles the expression of most genes on the X ch. To equalize the XX in hermaphrodite with X0 in male the XX *Caenorhabditis elegans* decreases both X chs genes expression to ~ 50%. In birds, males are ZZ and females are ZW. Only some Z-linked genes may be in DC, but many of them are not. In 1961, M.Lyon found that DC in mammals occurs by inactivation of one of two X chs in female [24].

K.Patau with co-workers identified and studied the X ch inactivation centre (*Xic*) [46]. The counting of X chs by human cell is done by estimation of the *Xic*s number. If 1 of the 2 X chs in a female is missing its *Xic* due to mutation, a cell counts only one *Xic* and X inactivation not happens. This leads to embryo death.

The specific *Xist* (X-inactive specific transcript) gene expression within the *Xic* is needed for the X ch compaction into a Barr body (Bb) [6]. While most other genes on the inactivated X ch are silenced, the *Xist* gene is expressed in *Xist* RNA which coats and inactivates the X ch. After coating, proteins associate with the *Xist* RNA and promote chromosomal compaction into a Bb.

The process of X inactivation can be divided into 3 phases: *initiation, spreading,* and *maintenance*. During initiation one of the X chs is chosen. During the spreading, this ch is inactivated. X chs that lack the *Xist* gene cannot be inactivated [36]. The transfer and expressing the *Xist* gene on another ch leads to its silencing [15, 23]. Prior to inactivation, both X chs weakly express *Xist* RNA from the *Xist* gene. Then, active X ch ceases *Xist* expression, whereas the future inactive X ch highly increases it. The *Xist* RNA coats the future inactive X ch only and recruits compaction proteins [32]. The inactivation spreads from *Xic* in both directions on the X ch [15]. The silencing of genes on the inactivating ch occurs soon after coating. *Xist* RNA is involved in Bb movement to the nuclear periphery. *Xist* initiates X inactivation X genes and maintains it by methylation. The *maintenance* phase continues from the embryonic stage through adulthood. When cell divide, the Bb is replicated, and both copies remain compacted. Some genes are expressed in Bb of adult female, e.g., *Xist*. In humans, up to 25% of the genes on the X ch may escape inactivation. Many of them occur in clusters, e.g., *pseudoautosomal* genes. Their inactivation is not necessary as they are located on both the X and Y chs.

In mice, the paternal X ch is silenced. In rabbits, maternal or paternal selection occurs downstream of *Xist* expression.

The *Tsix* RNA is the antisense to *Xist*. The *Tsix* gene overlaps the *Xist* gene and is transcribed on the opposite strand of the *Xist* gene DNA [22]. *Tsix* is a negative regulator of *Xist*; X chs without *Tsix* expression (high levels of *Xist* transcription) are inactivated much more frequently than active chs. Like *Xist*, prior to inactivation, both X chs weakly express *Tsix* gene. At start of X-inactivation, the future inactive X ch ceases to express *Tsix* RNA (and increases *Xist* expression), whereas active X ch continues to express *Tsix* for several days.

*Rep* A is another long non coding RNA working with *Xist* RNA in X inactivation. *Rep A* inhibits *Tsix* and eliminates expression of *Xite*. *Rep A* promotes *Tsix* region methylation by attracting PRC2, i.e., inactivation of one of the X chs [27].

Thus, X-linked long non-coding RNAs are key players in X ch inactivation [25].

Another form of X inactivation occurs only in male meiotic spermatogenesis, *meiotic sex chromosome inactivation* (MSCI). MSCI is the process of transcriptional silencing of the X and Y chs [48].

## Solved problems

**Problem 1.** Wife is red colour blindness carrier, husband is healthy. What proportion of their female and male progeny will show the trait? What are the genotypes of parents and progeny?

| | |
|---|---|
| Solution: P: wife, carrier, $X^rX \times XY$, husband<br>G: $X^r$, X; XY<br>F: girls - $X^rX$, XX; boys - $X^rY$, XY | Answer: The trait ratio 1 : 1 in sons and daughters. The parents' genotypes $X^rX$; XY. |

**Problem 2.** A bent tail in mice is caused by mutant allele. Six pairs of mice were crossed. Their phenotypes and those of their progeny are given below [11]. *N* is normal, *B* is bent phenotype. Estimate the inheritance way of this phenomenon.

| Parents | | Progeny | | Solution: | Answer: |
|---|---|---|---|---|---|
| females | males | females | males | | |
| N | B | All B | All N | $X^NX^N \times X^BY \rightarrow X^NX^B; X^NY.$ | The genetic basis of these results is X-linked dominant mutation. |
| B | N | 1/2B, 1/2N | 1/2B, 1/2N | $X^NX^B \times X^NY \rightarrow X^NX^B; X^NX^N; X^BY; X^NY.$ | |
| B | N | All B | All B | $X^BX^B \times X^NY \rightarrow X^NX^B; X^BY.$ | |
| N | N | All N | All N | $X^NX^N \times X^NY \rightarrow X^NX^N; X^NY.$ | |
| B | B | All B | All B | $X^BX^B \times X^BY \rightarrow X^BX^B; X^BY.$ | |
| B | B | All B | 1/2B, 1/2N | $X^NX^B \times X^BY \rightarrow X^BX^B; X^NX^B; X^BY; X^NY.$ | |

**Problem 3**. Who of any female's grandparents can't contribute any of X-linked genes to her genotype?

| Solution: | Mother side: | Father side: | Answer: The grandfather from her father side can't contribute X-linked genes. |
|---|---|---|---|
| Grandparents: | XX × XY | XX × XY | |
| Parents: | XX | × XY | |
| Female: | XX | | |

**Problem 4**. How many Barr bodies form in human somatic cells with next compositions of sex chs: 1) X0 2) XXX 3) XYY 4) XXY?

Solution: The number of Bar bodies is estimated from equation: *Bb number = Number of X – 1*. Answer 1) 0 2) 2 3) 0 4) 1.

**Problem 5**. A man with hemophilia and healthy woman have a son and daughter with hemophilia. What are the genotypes of this couple?

Solution: h-hemophilia allele. Mother must be heterozygouse carrier if daugterhave have disease. Answer: $\male X^hY \times \female X^hX$.

## Problems for individual work of students

**Problem 1**. A man is heterozygous *Aa* for one autosomal gene, and he carries a recessive X-linked allele *d.* What proportion of his sperm will be *ad?*

**Problem 2**. Deduce the inheritance patern for trait in pedigree on Fig.7.

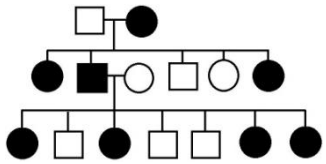

**Fig. 7.**

*By Diana B. Pylypiv.*

**Problem 3**. Select correct answer. In order to be a male a human: 1) must have oneX chromosome 2) must have two X chromosomes 3) must have at least one Y chromosome 4) can't have any of X chromosomes.

**Problem 4.** Human and *Drosophila* both have X and Y chromosomes, however, SD differs in these species. How?

**Problem 5.** Describe the phenotype of XY person with *SRY* gene deletion.

**Problem 6.** Explain, why heterozygotic female may have Hunter syndrome?

**Problem 7.** *Case study*. A baby with fuzzy, sparse hair, fair complexion, chubby cheeks and irritability was subjected to X-rays examination, which demonstrated abnormal skull and skeleton bones development. Microscopic examination of hair revealed classical sign of pili torti. The urine homovanillic acid/vanillylmandelic acid

ratio is 56.1. Molecular biology analysis revealed ATP7A gene mutation. Estimate the diagnosis and explaine the inheritance of the disease.

**Problem 8.** A blood smear of Tunisian lady showed half RBC number parasitazed by *Plasmodium*. These cells have normal activity of G6PD. The rest of cells have weak activity of the enzyme, however, resistant to parasite. Explain, why?

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