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Uzhhorod National University
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MEDICAL BIOLOGY PRACTICALS. GENETICS.

Practical 4. Genes interaction. Modifier genes. Epistasis. Complementation.
Suppressor and Duplicate genes. Polygenic inheritance.

Compiled by *B.M.Sharga, D.B.Pylypiv, V.P.Feketa*

Complex interactions of genes are indicated by the modified Mendelian ratios.

Mammalian coat color is produced by a set of interacting genes coding pigment type, its distribution in the individual hairs and on the body, and pigment presence/absence [5]. The hair color inheritance was best studied on mice [18]. At least 5 major genes interact in mice color production: **A**, **B**, **C**, **D** and **S** [5, 18].

The A gene is for distribution of pigment in the hair. The wild **A** gives a wild ‘agouti’ phenotype, the gray “salt-and-pepper” color, due to yellow band on dark hair shaft. The **a** allele codes for dark hair with no band. The lethal **A^Y** allele is for yellow hair shaft. The **a^l** allele in mice causes a yellow belly and dark rest of the body.

The B gene determines the agouti color and together with **A** but gives solid black with **aa**. The genotype **A_{bb}** gives a streaked brown color, a *cinnamon*, and **aabb** provides solid brown (Fig. 1). Domestic horses, in contrast to wild, have no **A** allele. The brown color in horse (chestnut) is recessive to black [5].

AABB (agouti) × aabb (brown) or	
AAbb (cinnamon) × aaBB (black)	
F1: all AaBb (agouti)	
AaBb (agouti) × AaBb (agouti)	
F2: 9 A- B- (agouti) 9	
3 A- bb (cinnamon)	3
3 aaB- (black)	3
1 aabb (brown)	1

Fig.1. A and B genes inheritance

Modifier gene D (MG) is for pigment intensity in mice. The genotypes **DD** and **Dd** give full color, but **dd** “dilutes” black, cinnamon and agouti fur to “milky” due to an uneven distribution of pigment in the hair shaft [5, 17]. If both parents are **aaCC**, we can write the crosses as in Fig. 2. The MGs modulate the phenotype of individuals with monogenic and multigenic traits. One class of MGs acts as

protective alleles suppressing disease in otherwise susceptible individuals [16].

The S gene. The **S** controls the spots presence/absence. The **S** results in no spots, and **ss** produces a *piebald* spotting in animals. The spotting is can be visible

P: BBDD (black) × bbdd (dilute brown)	
or BBdd (dilute black) × bbDD (brown)	
F1: BbDd × BbDd (black all)	
F2: 9 B-D- (black) 9	
3 B-dd (dilute black)	3
3 bbD- (brown)	3
1 bbdd (dilute brown)	1

Fig. 2. Modifier gene action

on any of the colored coats. The human piebaldism is a result of *kit* gene mutations [20]. This is rare autosomal dominant disorder of melanocyte development resulting in congenital white forelock and, usually, multiple symmetrical depigmented or hypopigmented macules.

Brown, blond and black hair in human is due to black and brown eumelanins, the hair pigments, produced from pheomelanin under the MC1R gene control. The recessive mutant MC1R gene codes for altered version of the MC1R protein resulting in red hair in individuals with 2 alleles of this gene [19].

The Fischer–Saller scale determine 8 main shades of human hair: A (very light blond), B to E (light blond), F to L (blond), M to O (dark blond), P to T (light brown to brown), U to Y (dark brown/black), I to IV (red) and V to VI (red blond) [13].

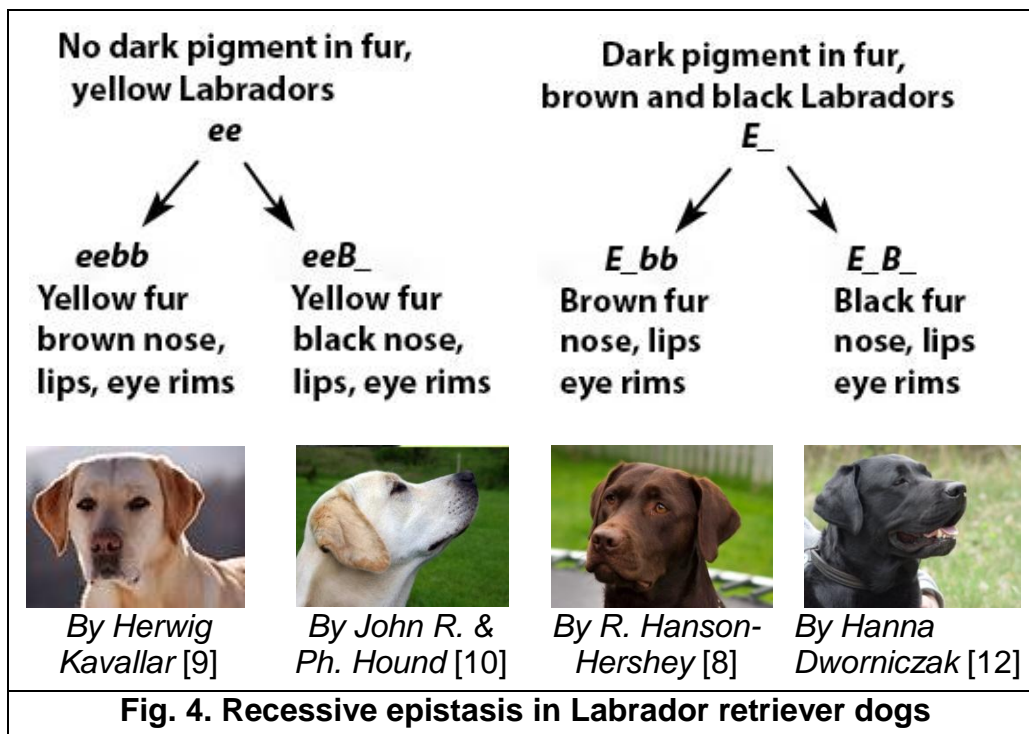
Epistasis (E) (= Greek "standing over") is non-allelic genes interaction in their effects on a trait [1]. Generally, E means any type of interaction, when the genotype at one locus affects the expression of the genotype at another locus. In a strict sense, E refers to a situation in which the genotype at one locus determines the phenotype in such a way as to mask the effect of other locus genotype. The *epistatic gene* disallows the phenotypical manifestation of *hypostatic gene* [7]. For example, the human baldness gene is epistatic to genes for blond or red hairs [15]. The E is found among the genes of ontogenesis and genes regulating immunity. The E complicates the identification of risk loci for complex disorders. Localization of these interacting loci requires DNA sampling from many of families with 2 or more disorder cases.

Recessive epistasis (RE). The wild-type allele *C* allows coat coloring, and allele *c* in homozygote (*cc*) prevents it resulting in 9:3:4 phenotype ratio (Fig.3). RE

<i>BB CC</i> (black) × <i>bbcc</i> (albino) or <i>BBcc</i> (albino) × <i>bbCC</i> (brown)	
F1: all <i>BbCc</i> (black)	
<i>BbCc</i> (black) × <i>BbCc</i> (black)	
F2: 9 <i>B_C_</i> (black)	9
3 <i>bbC_</i> (brown)	3
3 <i>B_cc</i> (albino)	
1 <i>bbcc</i> (albino)	4

Fig. 3. Recessive epistasis

governs the colors of Labrador dogs also. As in mice, the alleles *B* and *bb* code for black and brown color, respectively. The homozygote *ee* shows RE upon the *B*- and *bb* combinations, providing golden fur (Fig.4). The black and brown dogs have the allele *E*. Whether a golden dog is *B_* or *bb* is estimated by nose, lips and eye rims color, as **RE** acts mainly in the dog coat



with tissue-specific expression of genes [5]. The *E* allele is necessary for coat coloring. The *e* is an inactive form of *E*, and *B* or *bb* alleles are black and brown color determinants. In homozygote *ee* no pigment is produced. Thus, in RE,

the inhibition occurs only in recessive homozygote.

Dominant epistasis (DE). In fox gloves (*Digitalis purpurea*) gene *M* stands for ability and *m* is for inability of anthocyanin synthesis. In cross between the




MMDDww and *MMddWW* genotypes the 1st parent is dark reddish, due to *D* modifier allele allowing of anthocyanin large levels deposition. The *d* is for anthocyanin small levels accumulation. The 2nd is white with reddish spots as plant synthesizes pigment due to allele *M*, however, *W* allele prevents deposition except in the flower throat spots. The 12:3:1 phenotypic ratio is produced (Fig. 5). The allele *W* in F2 eliminates the alternatives coded by *D_* or *dd*, dark or light reddish, and replaces

P: (MM) <i>DDww</i> × (MM) <i>ddWW</i>	
(dark reddish) (white with reddish spots)	
F1: <i>DdWw</i> × <i>DdWw</i> (white with reddish spots)	
F2:	
9 <i>D_ W_</i> (white with reddish spots)	12
3 <i>ddW_</i> (white with reddish spots)	
3 <i>D_ ww</i> (dark reddish)	3
1 <i>dd ww</i> (light reddish)	1
Fig. 5. Dominant epistasis in fox gloves	

them by white with reddish spots phenotype. In *DE*, the epistatic allele is the dominant allele. The inhibition occurs in homozygote *WW* and heterozygote *Ww* (Fig. 5).

In melon white color allele *W* suppresses the effect of yellow *Y* and green color alleles *yy*.

Recessive combination *ww* allows the expression of *Y_* and *yy* coded skin colors and *W* allele is epistatic over these alleles (Fig. 6).

P: white <i>WWyy</i> × <i>wwYY</i> yellow		
F1: white all <i>WwYy</i> × <i>WwYy</i>		
F2:	White :	Yellow : Green
9 <i>W_ Y_</i> + 3 <i>yy</i> = 12	3 <i>wwY_</i>	1 <i>wwyy</i>
		
Fig. 6. Dominant epistasis in melon By Diana B. Pylypiv		

Always in *E* one gene is “upstream,” in the chain of commands and it has effect on the genes lower in the hierarchy of command [5].

Complementation (*C*) is a phenomenon in which 2 recessive mutations of with similar phenotypes in 2 pure lines result in a wild phenotype when both are combined in F1 genotype. *C* means that the mutations are in different, *complementary* genes. If 2 genotypes coding similar recessive phenotypes fail to complement, they are alleles of the same gene [5; 7]. For

example, 2 specific white-flowered pure lines of peas are crossed and F1 have purple flowers. The F2 from F1 selfing have purple and white plants in ratio 9:7. Here 2 different genes have similar effects on petal color. Let's represent the alleles of these genes by *A*, *a*, *B*, and *b* (Fig. 7).

Homozygosity for the recessive allele of *either* results in white petals. To have

White line 1 <i>AAbb</i> × <i>aaBB</i> White line 2
F1: <i>AaBb</i> all are purple
<i>AaBb</i> (purple) × <i>AaBb</i> (purple)
F2: 9 <i>A_ B_</i> (purple) 9
3 <i>A_ bb</i> (white)
3 <i>aaB_</i> (white) } 7
1 <i>aabb</i> (white)
Fig. 7. Complementation of genes

the purple flowers, at least 1 dominant allele of *both* genes needed. When we have 2 white lines, it is necessary to know, if these variants appear due to recessive alleles of the same gene or not. The complementation test is an effective test of allelism. If the 2 recessive phenotypes producing wild-type phenotype in F1, the parental genotypes have complemented each other, i. e.,

recessive alleles are of different genes. If the F1 and the F2 all albino, the recessive alleles are of the same gene [5].

The Suppressor gene (SG). Malvidin synthesis in *Primula* plant is determined

<i>KKdd</i> malvidin × <i>kkDD</i> no malvidin
F1: all <i>KkDd</i> no malvidin
<i>KkDd</i> × <i>KkDd</i>
F2: 9 <i>K_D_</i> no malvidin
3 <i>kkD_</i> no malvidin 13
1 <i>kkdd</i> no malvidin
3 <i>K_dd</i> malvidin 3
Fig. 8. The suppressor gene effect

by a dominant allele *K* which may be suppressed by a separate dominant suppressor gene *D* (Fig. 8). A **SG** may have an associated phenotype or it may, as in the malvidin example, have no detectable phenotypic effect other than the suppression of the phenotypic expression of another gene.

Duplicate genes (DG). The gene copies may be present in the genome. DG control fruit shapes (“heart” or “narrow”) in 2

<i>A₁ A₁ A₂ A₂</i> × <i>a₁ a₁ a₂ a₂</i>
“heart” “narrow”
F1: <i>A₁ a₁ A₂ a₂</i> “heart”
F2: 9 <i>A₁_ A₂_</i> “heart”
3 <i>A₁_ a₂ a₂</i> “heart”
3 <i>a₁ a₁ A₂_</i> “heart”
1 <i>a₁ a₁ a₂ a₂</i> “narrow”
15 “heart” : 1 “narrow”
Fig. 9. Duplicate genes

lines of *Capsella bursa – pastoris* plant (Fig. 9). Both: *A₁* or *A₂* alleles code for “heart” fruit. A cross of 2 lines resulted in F1 with “heart” fruits. The F₂ shows a 15:1 ratio of “heart” to “narrow”. “Heart” fruits result from the presence of at least 1 dominant allele of either gene, which are identical in function.

Polygenic inheritance (PI) is controlled by 2 or more genes. For example, human eye color, which was thought of as a single gene trait, has PI. At least 3 genes (BEY1, BEY2 and GEY) with complicated patterns of expression are determining eye color. The genes BEY1, BEY2 as dominant provide brown color to the iris and as recessive allele code for blue eyes. The GEY gene as dominant determines green eye color and as recessive conditioning blue eyes. The green allele is dominant to blue alleles, but it is recessive to all brown alleles (brown>green>blue). These genes do not code for all eye color variations, e.g., changes in eye color over time, the continuous range of eye colors, and patterns of colors in iris. Still undiscovered genes affect eye color. PI can cause a trait to have continuous gradual variation between two extremes. The human body weight and height, cleft lip, schizophrenia, diabetes mellitus, myopia have PI also.

Baldness genes are situated on X and 20th chromosomes [15]. Testosterone and other androgens can bind onto hair follicle cells and affect when, where, and how much a person’s hair grows [15]. The androgene receptor gene is located on the X chromosome, which means that, for males, it was inherited from their mother. The male pattern baldness has PI with many genetic variants involved [6]. Beside human, the PI is observed in animals, plants and other living things.

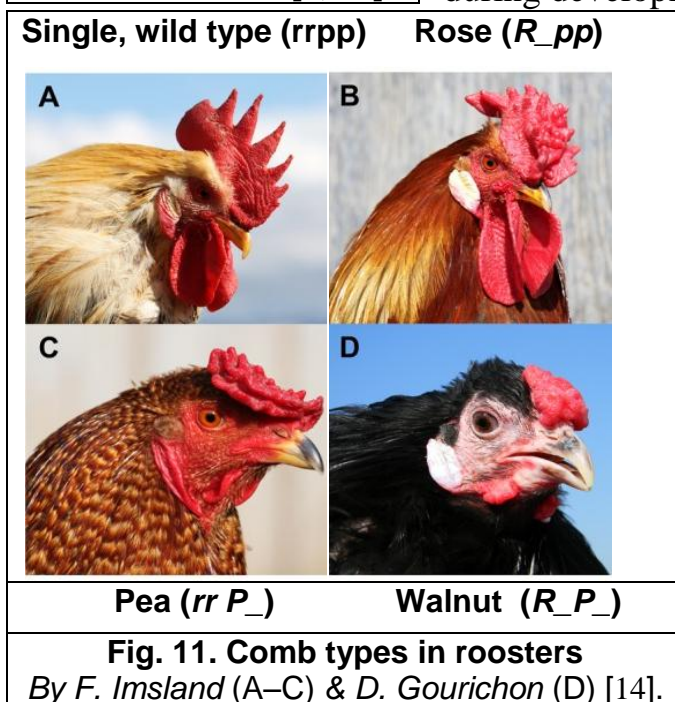
According to many textbooks, the human main skin color types are the result of at least 3-4 genes interaction. Each skin color gene has 2 forms: dominant and recessive, coding for high and low levels of melanin production, respectively. Melanin is a brown pigment that protects skin from harmful UV rays: the darker skin, the better protection. The skin color genes exhibit incomplete dominance, i.e., recessive homozygote *aabbcc*, dominant homozygote *AABBCC* and heterozygote *AaBbCc* for 3 skin colour genes have 0, 6 and 3 units of pigment, respectively. Based on these 3 genes, 7 shades of darkness in people can be determined. Of course,

should be more genes and skin types. Felix von Luschan's chromatic scale of not tanned human skin comprised of 36 colors [4, 11] (Fig.10).

	1	10			19	28	
	2	11			20	29	
	3	12			21	30	
	4	13			22	31	
	5	14			23	32	
	6	15			24	33	
	7	16			25	34	
	8	17			26	35	
	9	18			27	36	

Fig. 10. F. Luschan's skin color scale [4, 11]

The comb types in rooster are another example of **PI** (Fig.11). Rose-comb inheritance was first described W. Bateson [1]. The rose-comb and pea-comb mutated alleles are coding together for walnut-comb phenotype [2] (Fig.11). When 1 of dominant genes **P** or **R** is present, pea or rose comb is produced. The single comb is in recessive homozygotes. Extensive Rose-comb phenotypic variability [17] indicates that its morphogenesis is influenced by several genes and represents a good model to study of genes interactions during development [14]. Homozygotes **RR** (mutation



R of wild type with an inversion and disruption of the *CCDC108* gene) show poor sperm motility. *CCDC108* is conserved in chicken and human, suggesting *CCDC108* as a candidate gene for sperm motility disorders in man [14]. Heterozygotes **Rr** have good fertility and transmit **R** and **r** to progeny equally [3].

To find **a**, the number of pairs of alleles involved in **PI** by using the number of phenotypic forms **p** of the trait they condition, the formula $a = \frac{p-1}{2}$ is used. However, due to multigenic nature of **PI** strict **p** estimation is often impossible, as the

variation of phenotypes shows a continuum or the trait is affected by environment.

Solution of problems

Problem 1. The allele **A** (non-lethal in homozygote) causes yellow coats in rats. The allele **R** of other gene that assort independently results in black fur. Together, **A** and **R** produce a gray, whereas **a** and **r** produce a white coat. A gray male is crossed with a yellow female, and the **F1** is 3/8 yellow, 3/8 gray, 1/8 black and 1/8 white. Estimate the genotypes of the parents and inheritance pattern [5].

Solution: **A**-yellow coat; **R**- black coat; **A_R_** - gray coat; **aarr** – white coat

♀ **Aarr** × ♂ **AaRr**

♂ G:	AR	Ar	aR	ar
♀ G:				
Ar	AARr , gray	AArr , yellow	AaRr , gray	Aarr , yellow
ar	AaRr , gray	Aarr , yellow	aaRr , black	Aarr , white

Answer: Parents genotypes are **Aarr**, **AaRr**. Genetic basis is **CG** interaction.

Problem 2. The interferon production in human is conditioned by complementary interaction of 2 dominant genes: **A** and **B**, localized onto separate chromosomes (**A** on 2nd and **B** on 5th). Regard 2 situations: 1) The couple has both genes in heterozygotic state. Estimate the probability of children birth with normal interferon production 2) Husband has suppressed ability to produce the interferon as gene **B** absent. The wife and all her relatives are homozygotic for **A** and **B** genes.

Solution: 1) **P:** ♀ **AaBb** × ♂ **AaBb**

♂G:	AB	Ab	aB	ab
♀G:				
AB	AABB*	AABb*	AaBB*	AaBb*
Ab	AABb*	Aabb	AaBb*	Aabb
aB	AaBB*	AaBb*	aaBB	aaBb
ab	AaBb*	Aabb	aaBb	aabb
Note: *normal interferon production				

Answer: 1) Probability of children with interferon production is $9/16 \times 100 = 56.25\%$. 2) All children are normal in interferon production. The genetic basis of these results is complementation:

P: ♀ **AABB** × ♂ **Aabb**

G: **AB** **Ab, ab**

F1: **AABb***; **AaBb***

Problem 3. The pedigree brown and white dogs were continuously mated and all the F1 young are white. The F₂ progeny from F1 × F1 crosses are: 125 white, 34 black, and 8 brown. Estimate the genetic basis for these results.

Solution: It is necessary to calculate the ratio of white, black and brown animals in F₂. Because here is dihybrid cross, we should regard the total number in F₂ (125+34+8=167) as a multiple of 16. So, young white (125×16):167 = 11,98; for black (34×16):167 = 3,26; and for brown (8×16):167 = 0,73. The true ratio is: 12 white: 3 black: 1 brown as in DE.

Regard **W** allele as epistatic over black **B** and brown **bb** alleles, and **w** as recessive allele allowing color manifestation. Than the combinations of the alleles **W_B_** and **W_bb** code for white, **ww_B** for black, **wwbb** for brown dogs:

P: white ♀ WWBB × ♂ wwbb brown F1: white ♀ WwBb × ♂ WwBb white F2: 9 W_B_ white, 3 ww_B black, 3 W_bb white, 1 wwbb brown	<u>Answer:</u> The DE of W upon B and b genes is a basis of the results.
--	---

Problem 4. Yellow Labrador dog was mated with black Labrador. The F1 pups were as follows: 4 yellow, 2 black and 2 brown. Determine the genotypes of the parents and young and genetic basis of the results.

Solution: Here **E_** alleles allows to manifest color and **ee** prevent it.

P: yellow ♀ eebb × ♂ EeBb black G: eb EB, Eb, eB, eb F1: black EeBb , brown Eebb , yellow eeBb and eebb	<u>Answer:</u> The basis of the results is RE of ee upon B and b genes.
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Problem 5. Two *Primula* plants unable to produce the malvidin were crossed and the F1 was evaluated for this chemical production. The malvidin synthesis was detected in 10 of 80 F1 plants. Estimate all genotypes and genetic interaction mode.

Solution: ***K_*** – malvidin production, ***kk*** – no malvidin production, ***D*** – suppressor gene, ***dd*** – no suppression of malvidin production.

♀ ***kkDd*** × ♂ ***KkDd***

♂ G: / ♀ G:	<i>KD</i>	<i>Kd</i>	<i>kD</i>	<i>kd</i>	<u>Answer:</u> The basis of the results is dominant SG effect.
<i>kD</i>	<i>KkDD</i> no malvidin	<i>KkDd</i> no malvidin	<i>kkDD</i> no malvidin	<i>kkDd</i> no malvidin	
<i>kd</i>	<i>KkDd</i> no malvidin	<i>Kkdd</i> <i>malvidin</i>	<i>kkDd</i> no malvidin	<i>kkdd</i> no malvidin	

Problem 6. What comb types will appear in the F1, F2 and in what proportion if single-combed birds are crossed with birds of a pure-breeding walnut strain?

- a) What are the genotypes of the parents in a walnut × rose mating from which the progeny are 3/8 rose, 3/8 walnut, 1/8 pea, and 1/8 single? b) Write the genotypes of the parents in a walnut × rose cross from which all the progeny are walnut? c) How many genotypes produce the walnut, rose and pea phenotype [5]?

Solution: a) **P:** ♀ ***rrpp*** × ♂ ***RRPP***

G: ***rp*** ***RP***

F1: ♀ ***RrPp*** × ♂ ***RrPp***

F2: 9 ***R_P_*** walnut comb, 3 ***rr_P*** pea comb,

3 ***R_pp*** rose comb, 1 ***rrpp*** single comb

♀ / ♂	<i>RP</i>	<i>rP</i>	<i>Rp</i>	<i>rp</i>
<i>RP</i>	<i>RRPP</i> walnut comb	<i>RrPP</i> walnut comb	<i>RRPp</i> walnut comb	<i>RrPp</i> walnut comb
<i>rP</i>	<i>RrPP</i> walnut comb	<i>rrPP</i> pea comb	<i>RrPp</i> walnut comb	<i>rrPp</i> pea comb
<i>Rp</i>	<i>RRPp</i> walnut comb	<i>RrPp</i> walnut comb	<i>RRpp</i> rose comb	<i>Rrpp</i> rose comb
<i>rp</i>	<i>RrPp</i> walnut comb	<i>rrPp</i> pea comb	<i>Rrpp</i> rose comb	<i>rrpp</i> single comb

- b) ***RRPP*** × ***R_pp*** c) 4 genotypes for walnut comb ***RRPP***, ***RrPP***, ***RRPp***, ***RrPp***; 2 genotypes for rose comb ***RRpp***, ***Rrpp***; 2 genotypes for pea comb ***PPrr***, ***Pprr***.

Problem 7. The man with extremely dark skin has a wife with extremely light skin. What kind of skin they may expect in children?

Solution: The extremely dark skin is due to ***A***, ***B***, ***C*** alleles in homozygotic state. The ***a***, ***b*** and ***c*** alleles in homozygotes code for extremely white skin.

For this couple cross is:
P: ♀ ***aabbcc*** × ♂ ***AABBCC***
G: ***abc*** ***ABC***
F: ***AaBbCc***

Answer: The expected skin color in children is intermediate.

Problems for individual work of students

Problem 1. Two strains of *Drosophila* flies are white eyed due to autosomal recessive mutations. How to test if these mutations interrupt different steps in a single red pigment-producing metabolic pathway or they are mutants of one gene?

Problem 2. The human height is determined at least by 3 pairs of not linked genes. Each dominant allele adds about 5 cm of height. The recessive homozygotes' height is \approx 150 cm. The man with height of 180 cm has a wife with height of 150 cm. Predict the height of their future children.

Problem 3. Two rose combed roosters were crossed with single combed hens. One male has low sperm motility and another is normal by this trait. Write the genotypes of all these birds. What comb types is expected in young?

Problem 4. There are many variations in hue of blue and brown eye color in human. What kind of inheritance may be involved in the eye color production?

Problem 5. Two agouti mice are crossed several times. The phenotypes of young are: 48 agouti, 18 black, and 25 albino. What genotypes and kind of inheritance are in action here?

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