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Department of Fundamental Medical Disciplines

MEDICAL BIOLOGY PRACTICALS. GENETICS.

Practical 1. Solution of problems in Medical Genetics. Mendelian inheritance of human traits. Monohybrid Genetics.

Compiled by B.M. Sharga, Y.P. Sanislo, D.B. Pilipiv, V.P. Feketa

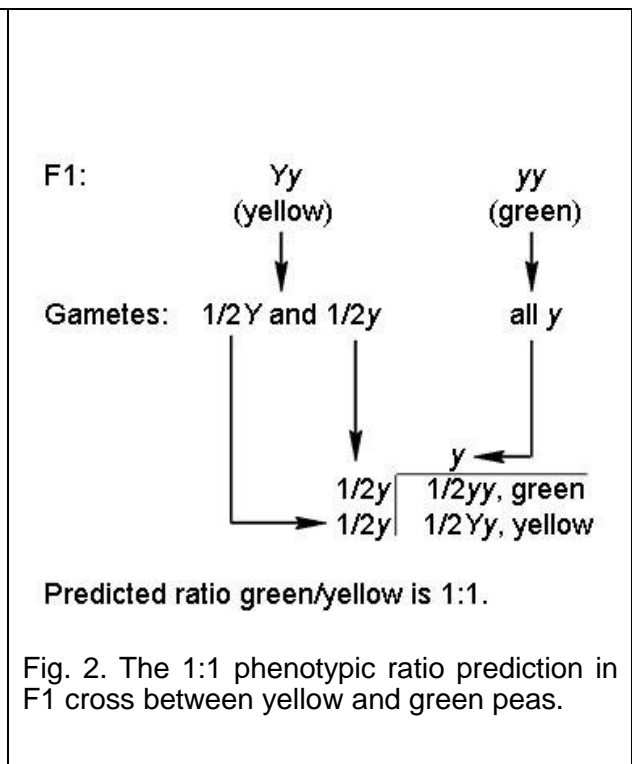
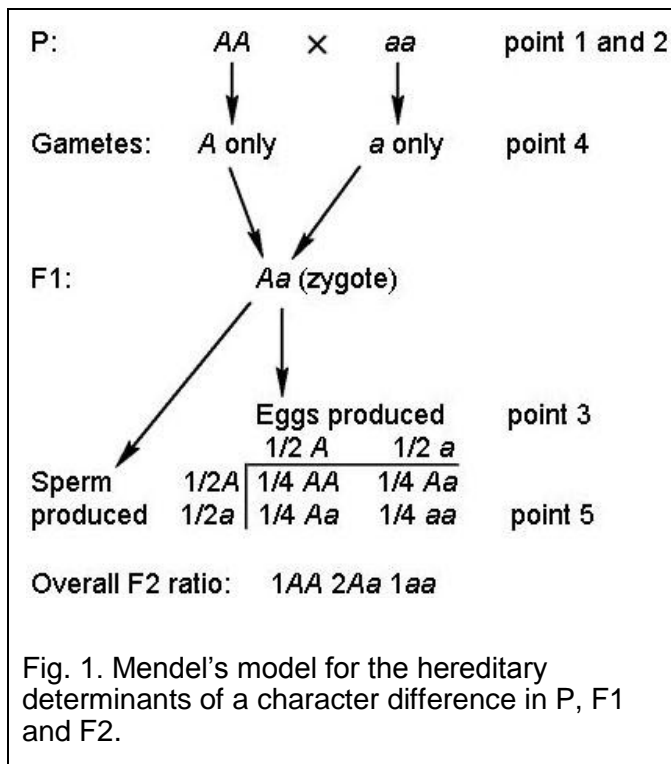
Human Genetics is among most interesting fields of Medical Biology. However, before starting to solve the problems, we need to refresh our knowledge of some categories and to get understanding of Mendelian Genetics principles, which form a basis for Human Genetics also.

The Gregor Mendel started his studies of heredity in 1843. He knew nothing about chromosomes or nature of genes at that time. Nevertheless, his studies of garden pea traits inheritance allowed him to open very important laws and to introduce quantitative approach into its evaluation. He predicted the existence of genes by observing precise mathematical ratios in the descendants of two genetically different parental plants.

When he crossed pure (homozygous) lines of garden pea, round × wrinkled seeds, yellow × green seeds, purple × white petals, inflated × pinched pods, green × yellow pods, axial × terminal flowers, long × short stems, he received in first generation (F1) all plants of one parental phenotype in each cross: round, yellow, purple, inflated pods, green pods, axial flowers, long stems, respectively. However, in F2 obtained from self-pollination of the F1, he discovered the segregation by phenotypes round: wrinkled seeds, yellow: green seeds, purple: white petals, inflated: pinched pods, green: yellow pods, axial: terminal flowers, long: short stems as 3:1. The study of next generation F3 revealed, that 3:1 phenotypes ratio is corresponded to 1:2:1 genotypic ratio and this was true for each of 7 characters. For example, for stem size we can write: $\frac{3}{4}$ long stem ($\frac{1}{4}$ pure-breeding long + $\frac{2}{4}$ “impure” long) and $\frac{1}{4}$ pure-breeding short. Gregor Mendel explained these 1:2:1 ratio by next ideas [1]:

1. Mendel saw no blending of phenotypes, so he made conclusion about existence of hereditary determinants. We now call them genes.
2. Each pea plant has 2 determinants (now genes) — a determinant pair (now gene pair) — in each cell for each character studied. Mendel’s reasoning here is obvious: the F1 plants, for example, must have had one gene for the dominant phenotype and another gene for the recessive phenotype, which showed up only in later generations.
3. The determinant pairs (gene pairs) segregate equally into the gametes or eggs and sperm.
4. Consequently, each gamete carries only one member of each determinant pair (gene pair).
5. The union of one gamete from each parent to form the first cell (or zygote) of a new progeny individual is random — that is, gametes combine without regard to which member of a determinant pair (gene pair) is carried [1].

Using *A* for gene representing dominant phenotype and *a* for recessive phenotype gene, Mendel illustrates these points diagrammatically (Fig.1). To test his model G. Mendel, for instance, crossed F1 plant grown from a yellow seed with F1 plant grown from the green seed. Next generation ratio 1:1 was predicted. This Mendel’s prediction is pictured in Fig. 2, where *Y* stand for the gene that determine dominant phenotype (yellow seeds) and *y* stands for the gene that codes for recessive phenotype (green seeds). From this cross he gathered 52 green (*yy*) and 58 yellow (*Yy*) seeds, enough close approximation to the predicted 1:1 ratio. This also confirmed the concept of *Y* and *y* **equal segregation** in F1 plant.



The concept was recognized as **Mendel's First Law**: *The two members of a gene pair segregate from each other into the gametes, so that one-half of the gametes carry one member of the pair and the other one-half of the gametes carry the other member of the pair.*


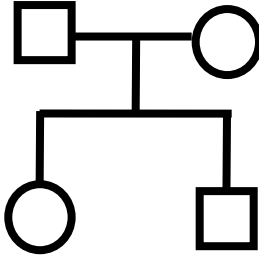
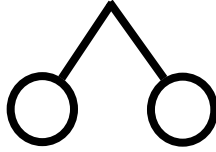
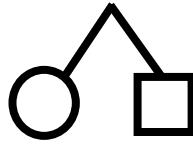



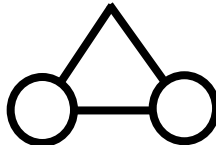


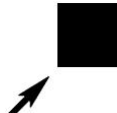





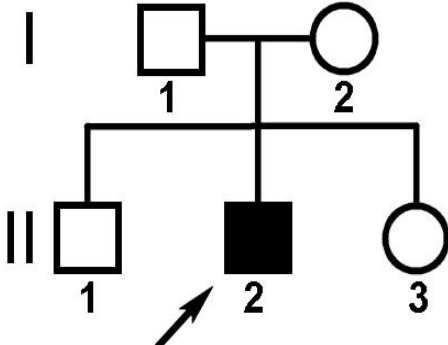
The individuals represented by Yy , Aa or Bb are called **heterozygotes** or **hybrids**, while the yy , aa or bb represent the pure line or **homozygotes** ("hetero-" for "different" and "homo" for "same"). Thus, an AA organism is **homozygous dominant** and aa is **homozygous** for the **recessive** gene, or **homozygous recessive**. The designated genetic constitution of the character(s) under study is called the **genotype**. Thus, YY and Yy , for example, are different genotypes coding for same phenotype of the seeds (yellow). The underlying the 3:1 phenotypic ratio in the F2 there is a 1:2:1 genotypic ratio of $YY : Yy : yy$. The dominant phenotype is established in analysis by the appearance of F1. Mendel showed that the dominance of one phenotype over another is in fact due to the dominance of one member of a gene pair over the other.

Mendel developed an analytic scheme for the identification of genes regulating any biological character or function. For example, in petal color character (purple/white) Mendel showed, that the difference was determined by one gene pair. Actually, Mendel managed with gene of petal color. The gene exists in two alternative forms: one is dominant for purple color (C) and another is recessive (c) for white color of the petals. The pea plants have one of gene pairs CC , Cc or cc . Both members of the pair affect the same character, the petal color. The alleles C and c on molecular level may differ only at one or few nucleotides and they are versions of one basic gene. The gene pair consists of identical alleles in homozygote (CC or cc) and of different alleles in heterozygote (Cc).

To estimate the heterozygote, it is necessary to cross an organism (suspected heterozygote, for example, Cc) with a monozygotic individual (cc). If segregation $Cc : cc$ (1:1) is observed in offspring, the organism is heterozygote.

The controlled mating for genetic analysis in human cannot be made. The pedigree or family tree analysis, a record of mating within the families is made instead of that. The first member of family with an unusual trait or mutation is called **propositus**. The geneticists draw the family tree with use of special symbols (Table.1) and tracing the propositus character within the family history.

Table 1. Current symbols for human pedigree analysis

Mating  Male Female		Parents and children: 1 girl, 1 boy, (in order of birth) 	Dizygotic (non-identical) female twins 	Dizygotic male and female twins 
Consanguineous marriage 				
Dizygotic (non-identical) male twins 		Monozygotic (identical) male twins 	Monozygotic (identical) female twins 	Carrier of sex-linked recessive 
Death 	Propositus 	Affected individuals 		
Abortion of stillbirth (sex unspecified) 		Heterozygotes for autosomal recessive 		
Number of children of sex indicated 		Sex unspecified 		
Identifying persons in a pedigree: the propositus is child 2 in generation II 				

Many of human traits are inherited as contrasting *alleles* (alternative states of the gene) in the way of simple Mendelian genetics. The family tree analysis can reveal the inheritance patterns of many human disorders. The condition of recessive trait (e.g., albinism, cystic fibrosis or phenylketonuria) is determined by recessive allele and alternative unaffected phenotype is coded by dominant allele (Table 2). The dominant allele is usually marked in capitals (*A*, *B* or *C*, etc.) and recessive allele is written as (*a*, *b* or *c*, etc.).

The Mendelian ratios are rarely observed in families, because the sample size (children number) is too small [1]. The pedigree of recessive trait is usually with few shaded symbols only within groups of affected siblings. Their grandparents, parents and later generations tend not to be with this particular trait. Usually, people who have disease-coding recessive allele are heterozygous and dominant gene diminishes the effect of recessive allele. This not allows manifest the latter. In pedigrees recessive trait is revealed by the appearance of a recessive disorder in male and female progeny of unaffected parents.

Table 2. Disorder prevalence (approximate), autosomal recessive (Wikipedia data)

Sickle cell anaemia	1 in 625
Cystic fibrosis	1 in 2,000
Tay-Sachs disease	1 in 3,000
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses	1 in 25,000
Lysosomal acid lipase deficiency	1 in 40,000
Glycogen storage diseases	1 in 50,000
Galactosemia	1 in 57,000

disease is $q^2 = (1/50)^2 = 1/2500$, and the frequency of heterozygotes is $2pq = 2 \times 49/50 \times 1/50 \approx 1/25$. Thus, for this example the heterozygotes are 100 times more frequent, than diseased people.



Fig. 1. Autosomal recessive disorder

The square totally shaded in red is affected male, red-blue figures are heterozygous for autosomal recessive allele. Adopted from

https://en.wikipedia.org/wiki/File:Autosomal_recessive.png

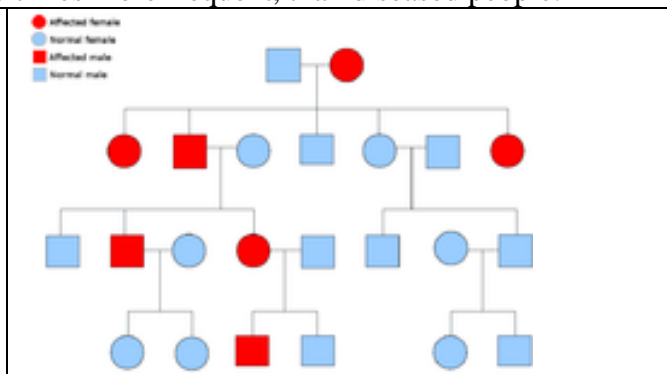


Fig. 2. Autosomal dominant disorder

The squares (males) and cycles (females) totally shaded in red are affected individuals

Adopted from

https://en.wikipedia.org/wiki/File:Autosomal_dominant.png

The birth of the diseased individual usually depends on the chance of marriage of unrelated heterozygotes. The mating between relatives (inbreeding) is allowed for cousins in some countries. This increases the chance of heterozygotes mating, and thus, increases the risk of recessive homozygotes production with the disease.

The dominant characters are usually betrayed in every generation of pedigree and affected fathers and mothers transmit the disease (or other trait) to their daughters and sons. Achondroplasia (a kind of dwarfism) is an example of dominant disorder with Mendelian inheritance. Achondroplastic homozygotes are not surviving, all achondroplastics are heterozygotes.

Abnormal alleles appear *de novo* due to mutations (genetic changes). These are rare events, however possible.

Huntington's disease (Table 3) is another example of profound disorder, which is inherited in dominant manner [4]. The symptoms are neural degeneration, leading to convulsion and premature death. It has late onset. Usually, the disease is not appearing until the reproductive age. The children of carrier have 50% probability of the dominant allele and disease inheritance. Modern molecular diagnostic techniques allow identify the dominant allele carriers before they experience the disease onset. Genetic consulting of young couples is also important for prediction of abnormal allele possibility.

Some other rare dominant traits in human are polydactyly (extra fingers and toes) and brachydactyly (short digits) and piebald spotting, found in domestic animals also.

Table 3. Disorder prevalence (approximate), autosomal dominant (Wikipedia data)

Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Neurofibromatosis type I	1 in 2,500
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000 [3]
Huntington's disease	1 in 15,000 [4]

Polymorphism is a set of 2 or more common, normal, alternative, phenotypes (*morphs*). For example, the earlobes are dimorphic with attached and free as the 2 major morphs. The morphs and polymorphism are often determined by the alleles of one gene, inherited in the simple Mendelian manner. The polymorphism is observed on all levels of life

organization, down to the level of DNA.

Let us solve problems in Human Genetics inherited in a simple Mendelian manner. Most of them were adopted from [2].

Problem 1. The man with blue eyes, both parents of which was gasel eyed, married gasel eyed woman, father of which was gasel eyed and mother was blue-eyed. From this marriage one boy was born with blue eyes. Determine the genotype of each of mentioned persons. Build a pedigree.

Solution: The blue eyes are less spread in human population, than dark eyes. Child is blue eyed, and this means that blue eyes is recessive trait.

B- gasel eyes- dominant; b-blue eyes – recessive character.

Grand Parents: female ♀bb × ♂B male ♂Bb × ♀Bb

Parents: wife ♀Bb × husband ♂bb

Son: ♂bb

Problem 2. The man with freckles had married woman without this trait. All 3 daughters of this couple have freckles. One of them had married the man without it. What children they can produce? Determine if freckles are inherited as dominant or recessive allele.

Solution: F – freckles-dominant, f - no freckles-recessive trait,

Parents: ♀ff × ♂F₋

Children: all three ♀ Ff, one married ♂ff :

Parents: ♀ Ff × ♂ff

Gametes: F, f f

Children: Ff, ff 1:1, 50% : 50%

Problem 3. Bright-haired young man, both parents of which were dark-haired, had married dark-haired girl. The father of latter was blond, and mother was dark-haired. They have baby with dark hair. They like to receive the consulting about the probability of blond child in next birth.

Solution: D - dark hair, d- bright hair

Grand Parents: ♀Dd × ♂Dd ♀D₋ × ♂dd

Parents: young man ♂dd × ♀ Dd young woman

Probability of blond child: Dd 50% dark dd50% blond

Problem 4. Red hair is recessive trait, non-red is dominant character. At which marriages we can expect 100% probability of red-haired children birth? When we can expect 50% and 25% probabilities of red-haired children?

Solution: R- non-red, r- red hair

	Probability 100%	Probability 50%	Probability 25%
Parents, P:	♀rr × ♂ rr	♀Rr × ♂ rr	♀Rr × ♂ Rr
Gametes, G	r, r r, r	R, r r, r	R, r R, r
Children, F	rr	Rr : rr, 1:1	RR, Rr, Rr, rr, 1:1:1:1

Problem 5. Albinism is inherited as autosomal recessive trait. The one partner in the couple is albino. The one of the twins from this couple is albino, and another is normal by this character. What is the probability of the albino in next child birth?

Solution: C – normal; c – albino,

Parents: ♀Cc × ♂cc

Gametes: C,c and c

Children : 50% Cc 50% cc

Probability of albino child is 50%

Problem 6. The children's form of Tay-Sach's idiotism is inherited as autosomal recessive trait. It has fatal end at the children age about 4-5 years of life. The first child is died at the time, when wife was pregnant with another one. What is the probability of this disease in the next child?

Solution: T – normal; t – Tay-Sach's disease, recessive.

Parents should be heterozygous as they reached the reproductive age and were without disease.

Parents: ♀Tt × ♂Tt,

Gametes: T, t and T, t

Children : TT25% Tt50% tt 25%

Probability of Tay-Sach's disease in next child is 25%.

Problem 7. The dark-haired man has married dark-haired woman. The child born is red-haired. What are the parents' genotypes if dark color is dominant trait?

Solution: ♀Dd × ♂Dd

Problem 8. The tall man has tall father and small mother. He married woman with high height. Her parents were low in height. The young family has the tall child. Determine the genotypes of the child's parents and grandparents. It is known, that high height is recessive character and low height is dominant trait.

Solution: H –low height; h – high height

Parents of wife: ♀Hh × ♂Hh; of tall man: ♀Hh × ♂hh;

Genotypes of the child's parents: ♀hh × ♂hh

Child: hh

Problem 9. Aniridia is a dominant trait causing blindness. It is inherited as autosomal dominant trait. What is the probability of healthy child birth, if one of the parents suffers from the disease. Only the father of ill person (husband) is also ill with this disease.

Solution: A- disease; a – normalcy. If only the father of husband is ill it means that husband is heterozygous.

Couple genotypes: ♀aa × ♂Aa. Children: 50% Aa and 50% aa. Answer: 50 %.

Problem 10. Achondroplasia is inherited as dominant autosomal trait. Both parents are suffering from the disease, however their child is healthy. What is the probability of healthy next child?

Solution: A- disease; a – normalcy

Couple genotypes: ♀Aa × ♂Aa.

Gametes: A,a and A,a.

Children: AA25% Aa 50% and 25% aa. Answer: 25%.

Problem 11. Hypertonic woman married a healthy man. All their children are hypertonics. Their son married a healthy woman and daughter has hypertonic husband. What about possibility to have hypertonic grandchildren?

Solution: From our life experience we can conclude that the hypertonia is not spread in many people of the population. Because woman married a healthy man and all their children are hypertonics the disease is controlled by recessive allele of the gene. Thus, a- disease; A – no disease; woman is homozygote (aa) and her husband is heterozygote (Aa) and children are aa. As her daughter had married hypertonic man all grandchildren from daughter must be hypertonic:

Daughter's family: P: ♀aa × ♂aa (no chance to have healthy child)

In son's family we do not know if healthy wife heterozygote AA or Aa, which can be with 50:50% probability 1/2 : P ♀A_ × ♂aa. If this woman is AA, all her children should be healthy

(100% healthy). However, question is about probability of hypertonics in her family. It could happen if woman has Aa genotype. With such genotype the 50% probability of ill children exists:

P: ♀ Aa × ♂ aa

G: A, a a

F: $\frac{1}{2}$ Aa : $\frac{1}{2}$ aa

Healthy : ill

So, the probability of ill grandchildren from son's family is a probability of happening of two events (heterozygote wife in son's family and ill children) at one time: $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4} = 25\%$.

Do solve the problems alone:

Problem 12. The Wilson's disease is inherited as recessive autosomal trait. What is the probability of ill children, if wife suffering from the disease and husband is healthy? His parents, sister and brother are healthy also.

Problem 13. The allergy is hypersensitivity to different irritants. The allergic girl had married a healthy man, whose father was allergic also. What about inheritance of the allergy by their children? Is it dominant or recessive trait? What are the genotypes of all these persons?

Problem 14. The *xeroderma pigmentosum* is inherited as autosomal recessive trait. The mother of girl is healthy and her father have this cancer problem. The girl had married a young healthy man, the carrier of this recessive gene. What about disease probability in their children and grandchildren?

Problem 15. Afibrinogenemia (absence of fibrinogen in blood plasma) often lead to death because of complications with bleeding. It is inherited as recessive autosomal trait. Healthy parents have ill child. What is the probability of next babe with this disease?

Problem 16. Galactosemia is autosomal recessive trait. What is the probability of this disease in children if husband is homozygote and mother is heterozygote by this allele?

Problem 17. One of the form of cystinuria is inherited as autosomal recessive trait. In heterozygotes an elevated level of cystine is observed only, while homozygotes are suffer from cystine stones in kidneys. Determine the probability of the cystinuria in grandchildren if both grandmothers were healthy and both grandfathers were with cystinuria.

Problem 18. Rare gene *a* is coding for anophthalmia, the eyes absence. The dominant gen A determines the normal eye ball development. The eye balls of heterozygotes are smaller than in average of people without this allele. Both parents are heterozygotes by the allele. What is the genotype and phenotype of their children?

Problem 19. The talasemia is inherited as not completely dominant trait. In 90-95% of homozygotic organisms it leads to death, however, it is in moderate non-clinical form in heterozygotes. What is the probability of this disease in children, if both parents have moderate non-clinical form of the disease?

Problem 20. The man with short lashes had married the woman with long lashes and their baby is with long lashes. The father and brother of wife have short and her mother have long lashes. Long lashes is dominant trait, short is recessive. Determine the genotypes of all persons. What is a probability of babe with short lashes?

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