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Biology

8. Basics of genetics

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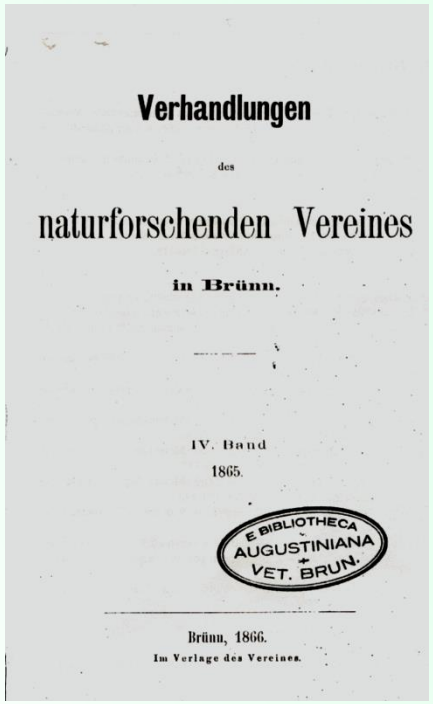
History of genetics


Verhandlungen

des

naturforschenden Vereines

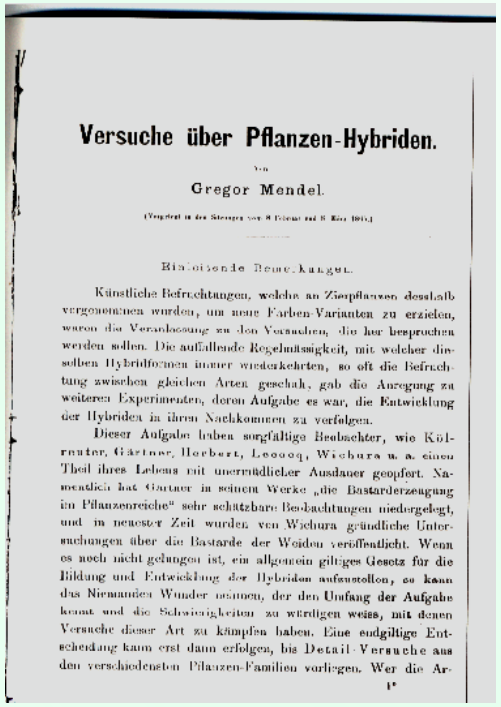
in Brünn.

IV. Band

1865.

Brünn, 1866.

Im Verlage des Vereines.


Versuche über Pflanzen-Hybriden.

von

Gregor Mendel.

Künstliche Befruchtungen, welche an Ziergewächsen deshalb vorgenommen wurden, um neue Farben-Varianten zu erzielen, waren die Veranlassung zu den Versuchen, die hier besprochen werden sollen. Die auffallende Regelmässigkeit, mit welcher dieselben Hybridformen immer wiederkehrten, so oft die Befruchtung zwischen gleichen Arten geschah, gab die Anregung zu weiteren Experimenten, deren Aufgabe es war, die Entwicklung der Hybriden in ihren Nachkommen zu verfolgen.

Dieser Aufgabe haben sorgfältige Beobachter, wie Kölreuter, Gärtner, Herbert, Lecoq, Wichura u. a. einen Theil ihres Lebens mit unermüdlicher Ausdauer geopfert. Namentlich hat Gärtner in seinem Werke „die Bastarderzeugung im Pflanzenreiche" sehr schätzbare Beobachtungen niedergelegt, und in neuester Zeit wurden von Wichura gründliche Untersuchungen über die Bastarde der Weiden veröffentlicht. Wenn es noch nicht gelungen ist, ein allgemein giltiges Gesetz für die Bildung und Entwicklung der Hybriden aufzustellen, so kann das Niemanden Wunder nehmen, der den Umfang der Aufgabe kennt und die Schwierigkeiten zu würdigen weiss, mit denen Versuche dieser Art zu kämpfen haben. Eine endgiltige Entscheidung kann erst dann erfolgen, bis Detail-Versuche aus den verschiedensten Pflanzen-Familien vorliegen. Wer die Ar-

1*

10 000 BC.

- neolithic revolution - the emergence of agriculture
- selection of the most suitable individuals for further breeding/cultivation

460-370 BC.

- Hippokrates
- „If a phlegmatic person is born a phlegmatic person, a choleric person is born a choleric person, an epileptic person is certainly born from epileptic parents…"

1820

- C.F. Nasse
- described the inheritance of hemophilia - sex-linked

1822-1884

- Johann Gregor Mendel
- The foundations of genetics are laid

1900

- **de Vries, Tschermak a Correns**
- the rediscovery of Mendel's laws

1906

- **William Bateson**
- used the term **genetics**, heterozygote and homozygote, F1 and F2 etc.

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History of genetics

- **Wilhelm Johannsen -** introduces the terms gene, genotype and phenotype

- **Thomas Hunt Morgan -** work on chromosomes (Chromosomes and heredity)
  - the model organism used friut fly (*Drosophila melanogaster*)
  - new knowledge about genes and gene linkage
  - In 1933 he became the first geneticist to win the Nobel Prize
  - genes are always stored in a linear sequence on the chromosome
  - the genes of one chromosome form a linkage group
  - gene exchange can take place between the genes of a homologous pair of chromosomes through crossing-over. The frequency of crossing-over is proportional to the distance of the genes

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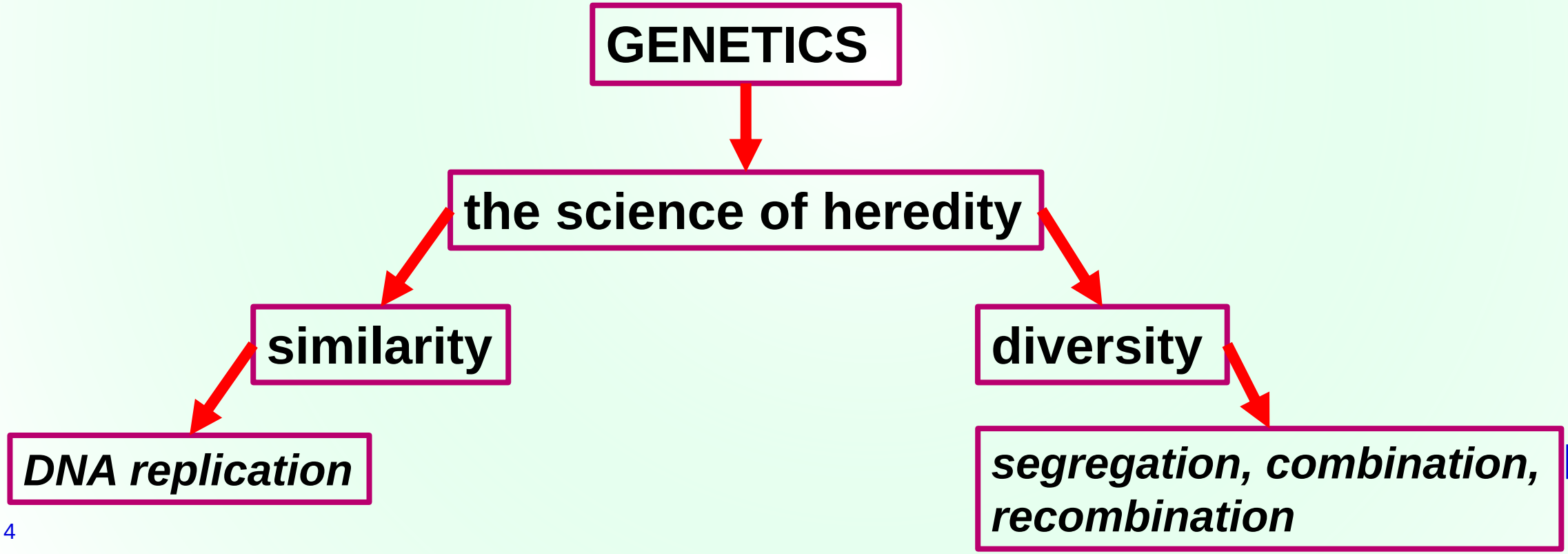
Genetics

- is a science dealing with the heredity and variability of living systems (and their causes)
- monitors the variability, differences and transmission of genetic and hereditary traits between parents and offspring and also between offsprings themselves



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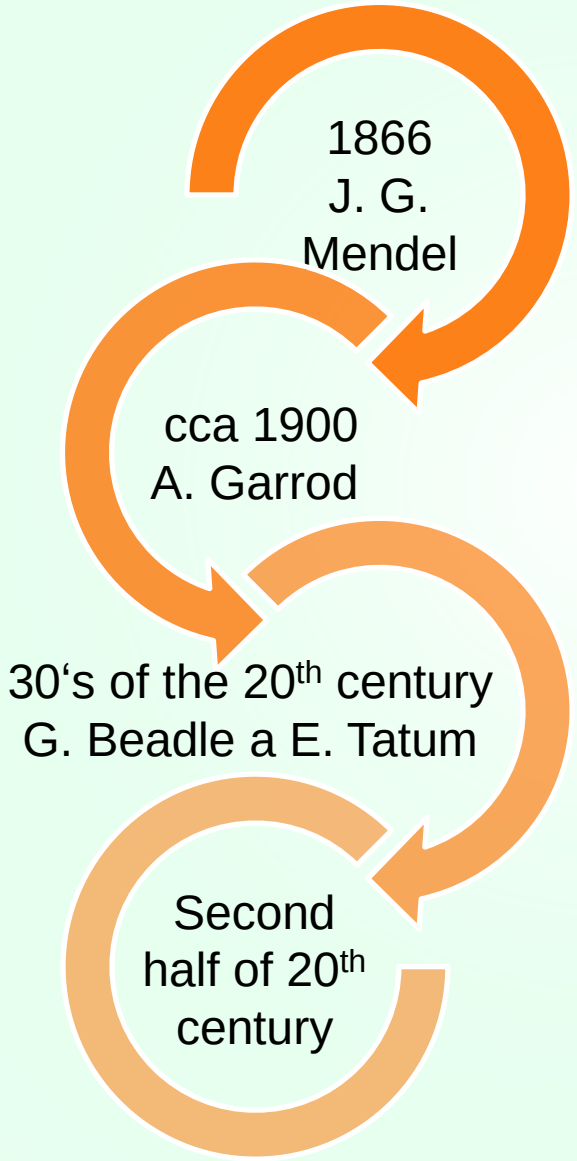
What is a "gene" in functional terms?



- Genes (factors, traits) = constant factors controlling phenotypic traits
- "One mutant gene = one metabolic block"
- "One gene = one enzyme"
- "One gene = one polypeptide"

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A bit of terminology

- **gene** – a section of DNA that codes for one functional transcript (mRNA, rRNA, tRNA, siRNA, lncRNA,...)
- **allele** – a specific form of a gene

- **genotype** – a set of specific genes (alleles) of an organism
- **phenotype** - manifestation of characters

Genes → genotype → phenotype → traits

environmental influence

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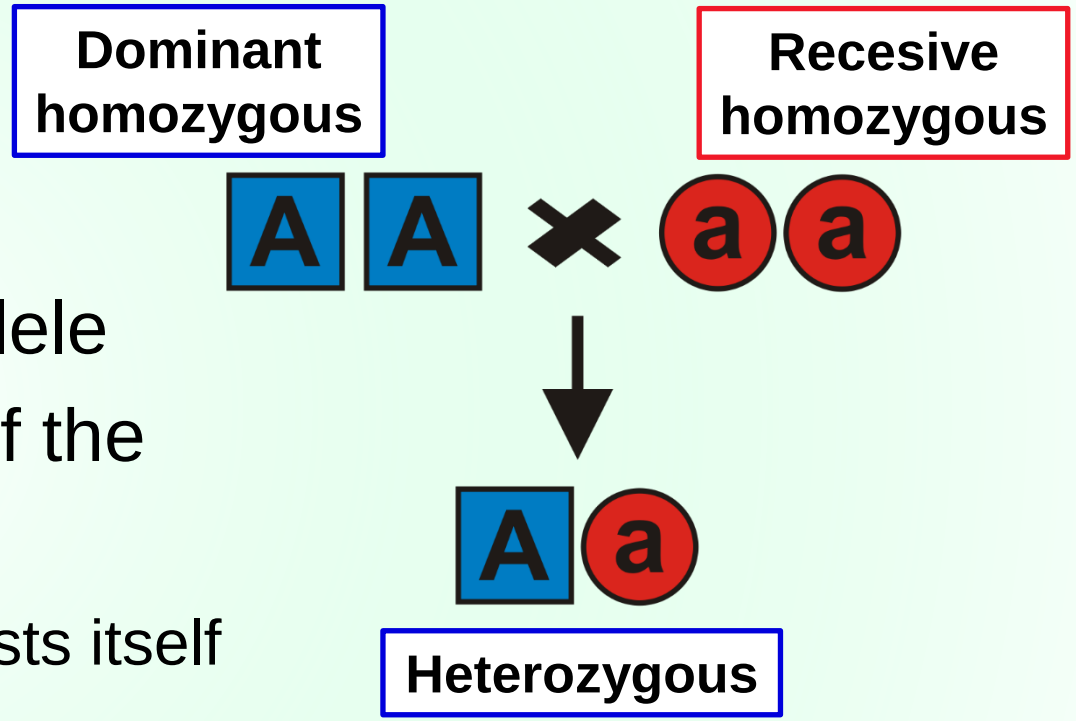
„Classic“ (mendelian) heredity

- Heredity of qualitative traits



Inter-allelic relationships I.

- **complete dominance** - the dominant allele completely suppresses the expression of the recessive allele
  - a dominant allele is therefore one that manifests itself even in a heterozygous combination
- **incomplete dominance** - the dominant allele does not suppress the recessive allele completely, the recessive allele is also partially expressed

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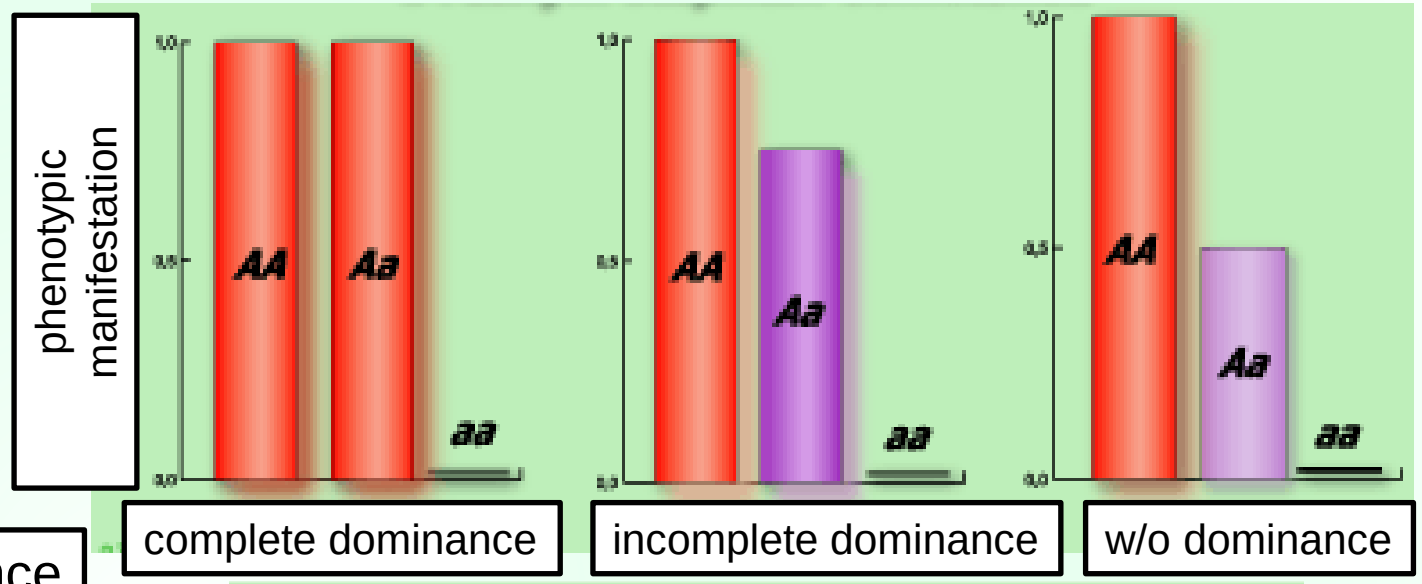
Inter-allelic relationships I.

https://user.mendelu.cz/urban/vsg1/mendel/klas_interakce1.html

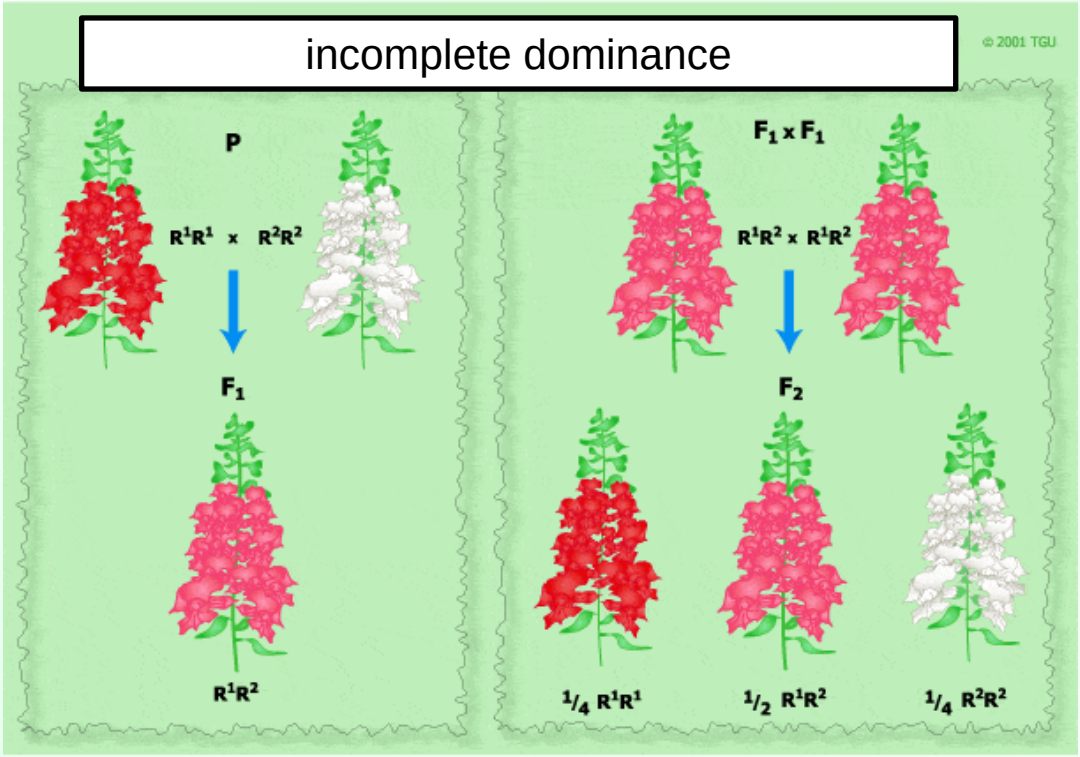


complete dominance

Genotype	Phenotype
AA	
Aa	
aa	

incomplete dominance

Genotype	Phenotype
AA	
Aa	
aa	



This Meme Made Possible By Incomplete Dominance

Non-Mendelian Inheritance

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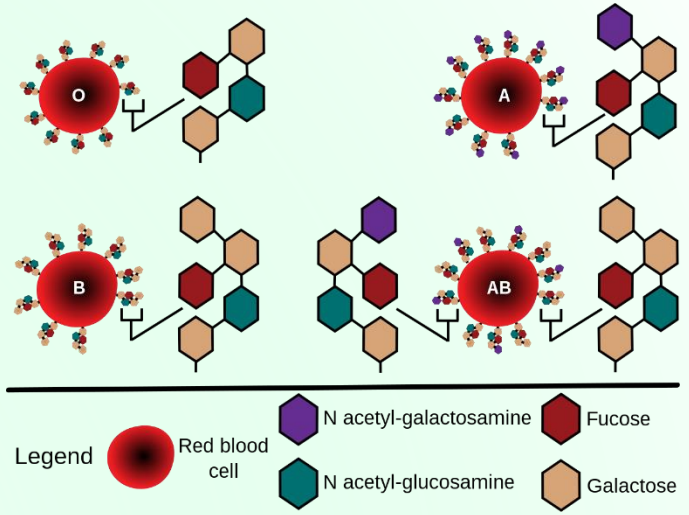
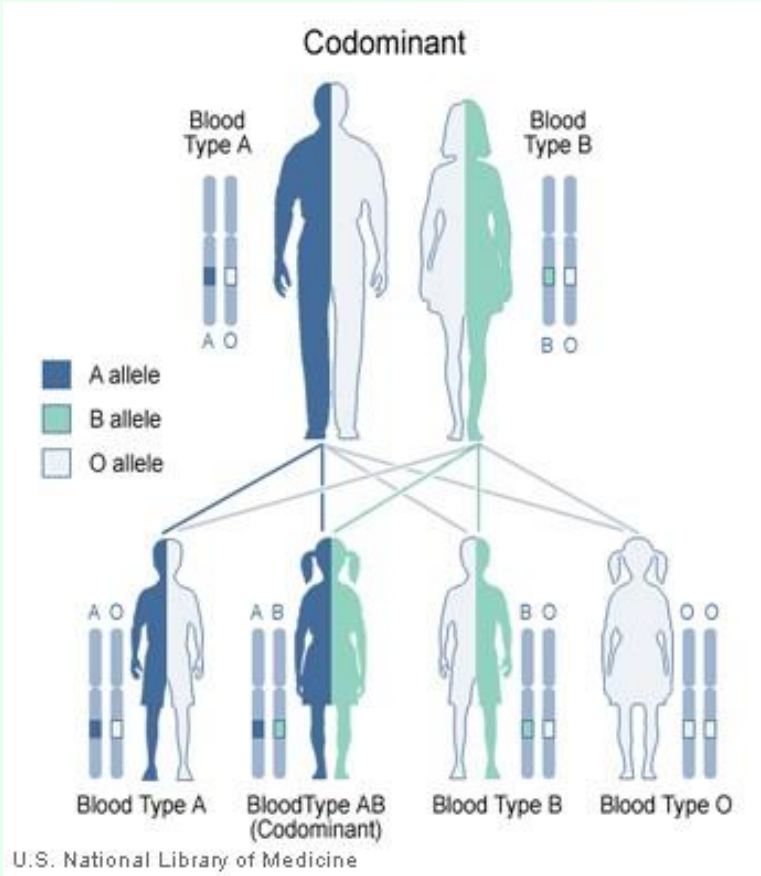
Inter-allelic relationships II.

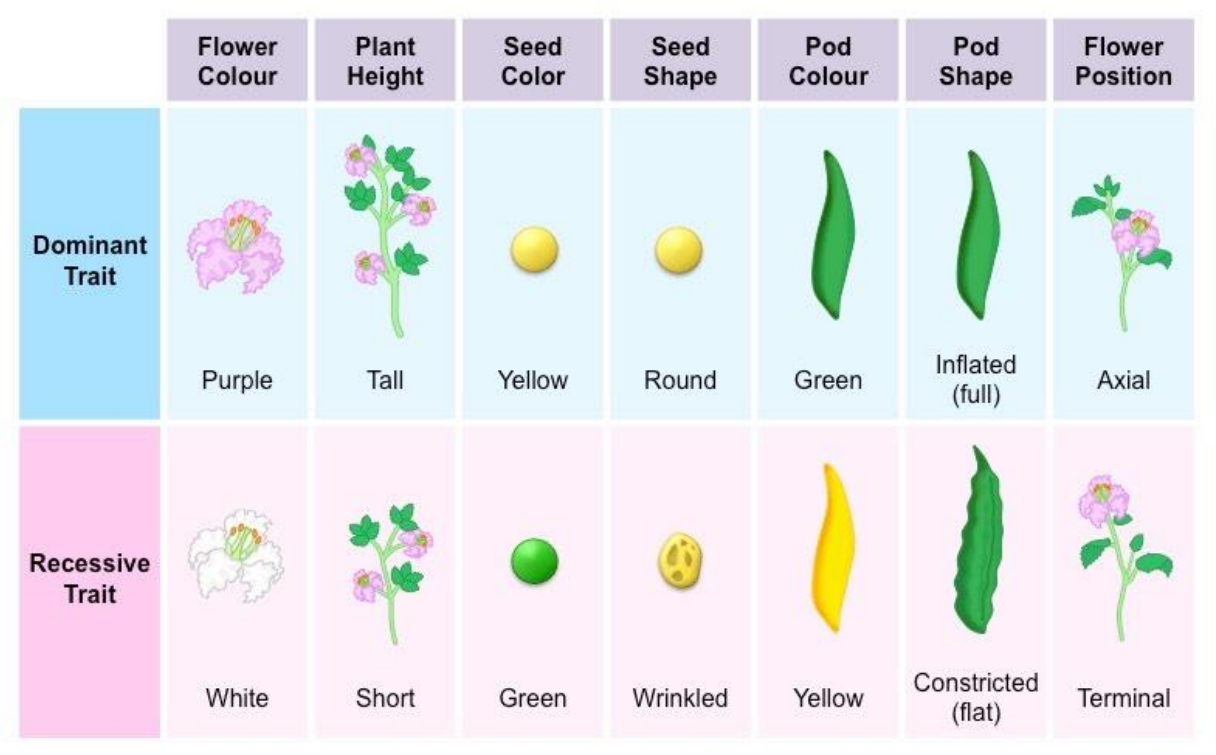
- **Codominance** - both present alleles are fully expressed in the heterozygote and do not affect each other
- **Superdominance** - a heterozygote (Aa) shows a stronger form of the trait than both types of homozygotes (aa, AA)
  - **Heterosis effect** - mainly used in agriculture (*e.g.* F1 tomato hybrids)
  - The heterozygous effect is caused by the accumulation of dominant heterozygous genes from both parents in the offspring (F1). For example, one parent has AABBccdd, the other parent has aabbCCDD, an offspring with a heterozygous effect has AaBbCcDd. Dominance theory assumes that dominant alleles are better than recessive ones. Those who have more genes with dominant alleles have better results.





Mendel's laws of heredity

- First experiments on pea (*Pisum sativum*) = suitable experimental model
- worked with pure parental lines (homozygotes)
- monohybridisms
- applications of **mathematics and statistics**



https://ib.bioninja.com.au/standard-level/topic-3-genetics/34-inheritance/mendels-laws.html

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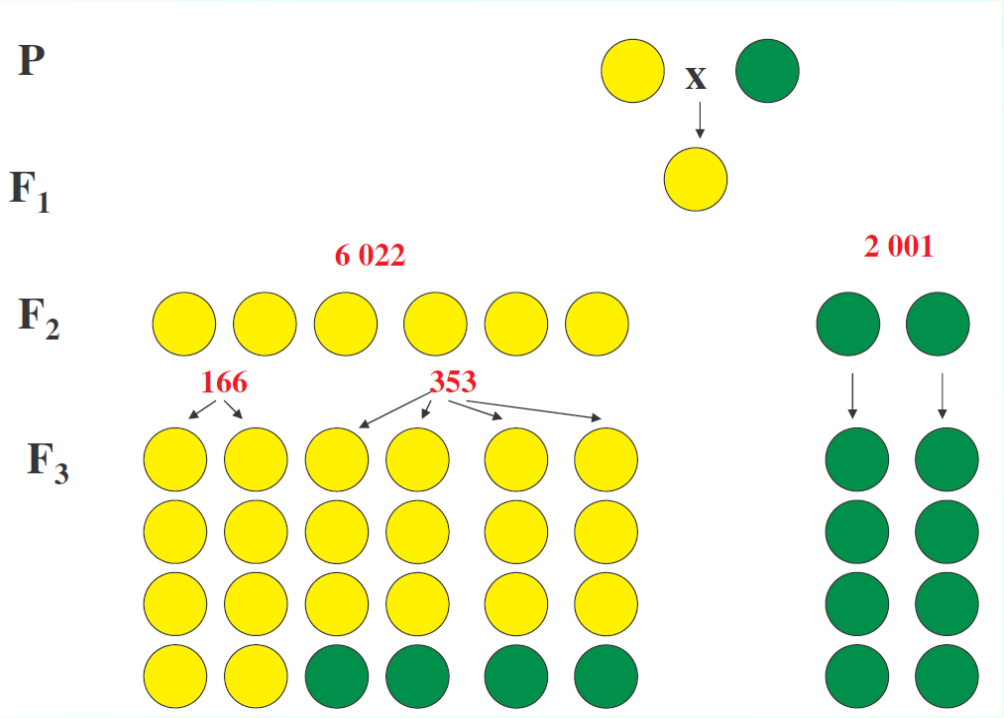
Mendel‘s experiments



Pea trait	Dominant trait		Recessive trait		Numbers in second generation (F2)	Ratio
Seeds						
Seed shape	Round		Wrinkled		5474:1850	2.96:1
Seed colour	Yellow		Green		6002:2001	2.99:1
Whole plants						
Flower colour	Purple		White		705:224	3.15:1
Flower position	Axial		Terminal		651:207	3.14:1
Plant height	Tall		Short		787:277	2.84:1
Pod shape	Inflated		Constricted		882:299	2.95:1
Pod colour	Green		Yellow		428:152	2.82:1

https://www.sciencelearn.org.nz/images/2478-pea-traits-studied-by-mendel

1st law on the uniformity of F1 hybrids

- If we cross **two homozygotes**, their offspring of the F1 generation are all the same in the observed trait. Reciprocal crosses with any individuals of the F1 generation give identical results.

2nd law of splitting in the offspring of hybrids

- When **heterozygotes are crossed**, the genotypes and phenotypes of the resulting individuals can be expressed as a ratio of small whole numbers. A genotypic and phenotypic split ratio is created. The offspring will show a recessive trait.

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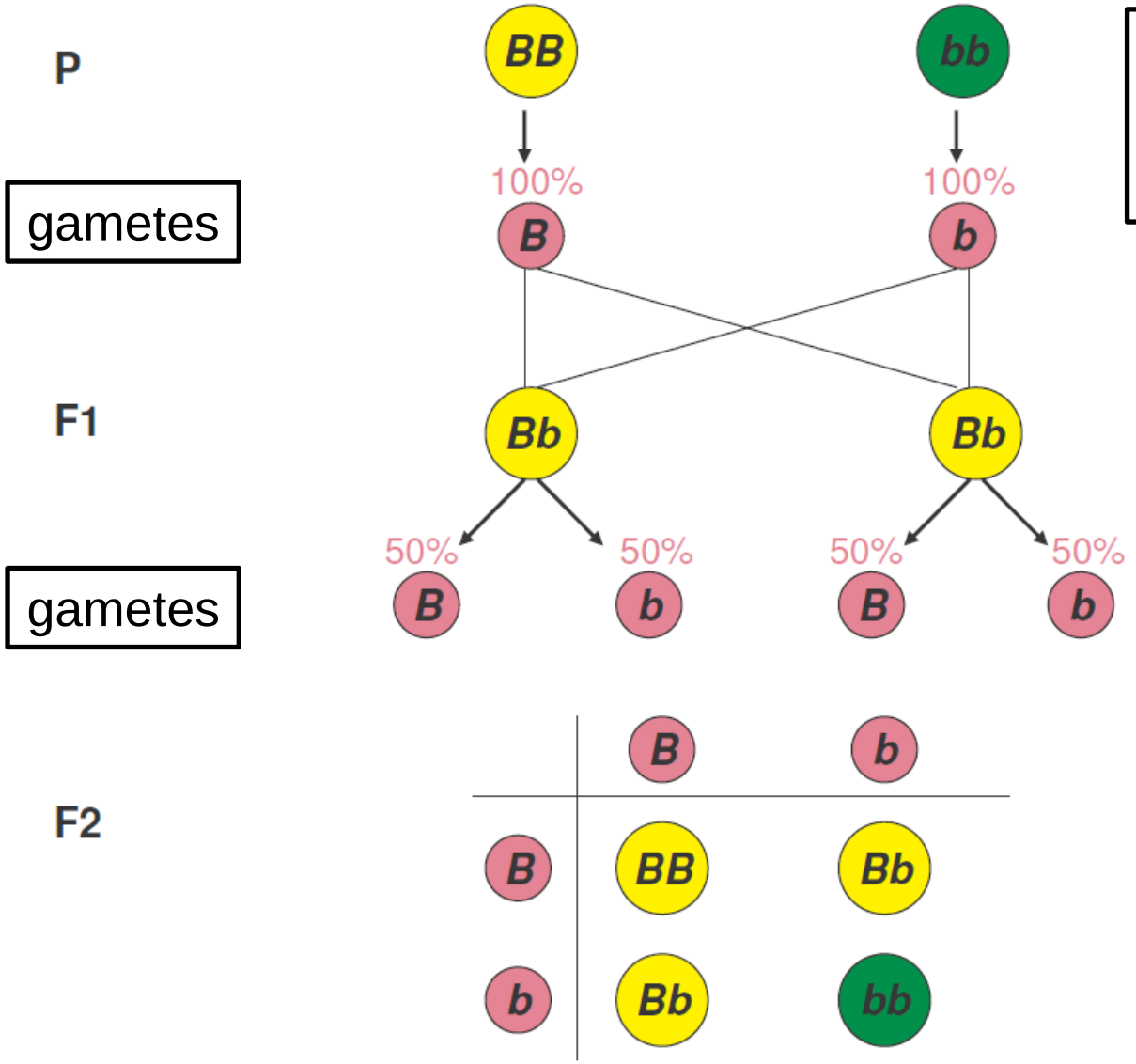
Punnett square

B – dominant allele for yellow color
b – recesive allele for green color



♂/♀	A	A
A	AA	AA
A	AA	AA

♂/♀	a	a
a	aa	aa
a	aa	aa

♂/♀	A	A
a	Aa	Aa
a	Aa	Aa

3rd law of independence of alleles

- A genotype is a set of individual genes that determine traits. Each trait is determined by a pair of separate alleles

4th law of segregation of alleles

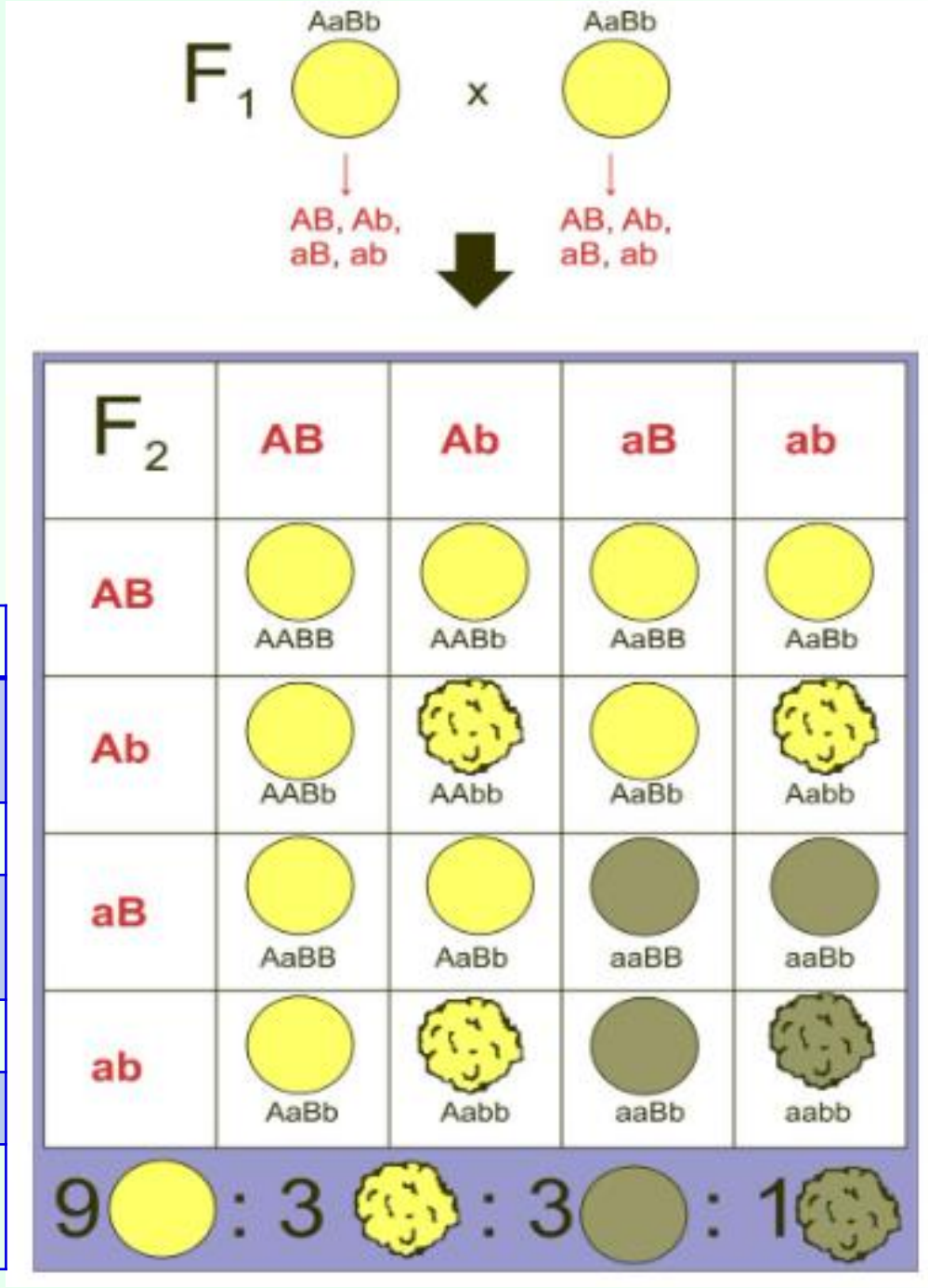
- Pairs of separate alleles diverge during maturation, and one of the two alleles passes into each gamete

5th law of independent choice

- includes **more characters** → alleles do not influence each other, so a spectrum of different combinations is created

Generalization for n- hybridism

	n = 1	n = 2	generally
number of gamete types of the hybrid	$2 = 2^1$	$4 = 2^2$	2^n
number of zygote types	$3 = 3^1$	$9 = 3^2$	3^n
number of different homozygouts in both allele pairs	$2 = 2^1$	$4 = 2^2$	2^n
number of breeding novelties	$0 = 2^1-2$	$2 = 2^2-2$	2^n-2
genotype ratio in F2	$(1:2:1)^1$	$(1:2:1)^2$	$(1:2:1)^n$
phenotype ratio in F2 under full dominance in all allele pairs	$(3:1)^1$	$(3:1)^2$	$(3:1)^n$



Deviations from Mendelian cleavage ratios

- a situation where Mendel's laws do not fully apply
- deviations from Mendelian rules (referred to the genetics of the human individual):

  - Reduced vitality (lethality) of gametes and zygotes
  - Gene linkage
  - Gene interaction
  - Linked to gender
  - Extranuclear inheritance
  - Polygenic inheritance
  - Variable expression

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Reduced vitality (lethality) of gametes and zygotes

gametes - haplontic selection **zygotes - diplontic selection**

vital > subvital > semilethal > lethal

recessive lethality	**AA**	**Aa**	
recessive lethality of the dominant allele		**Aa**	**aa**
dominant lethality			**aa**

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Recessive lethality of the dominant allele

- Manx cat

- MM – lethal
- Mm – without tail
- mm – normal

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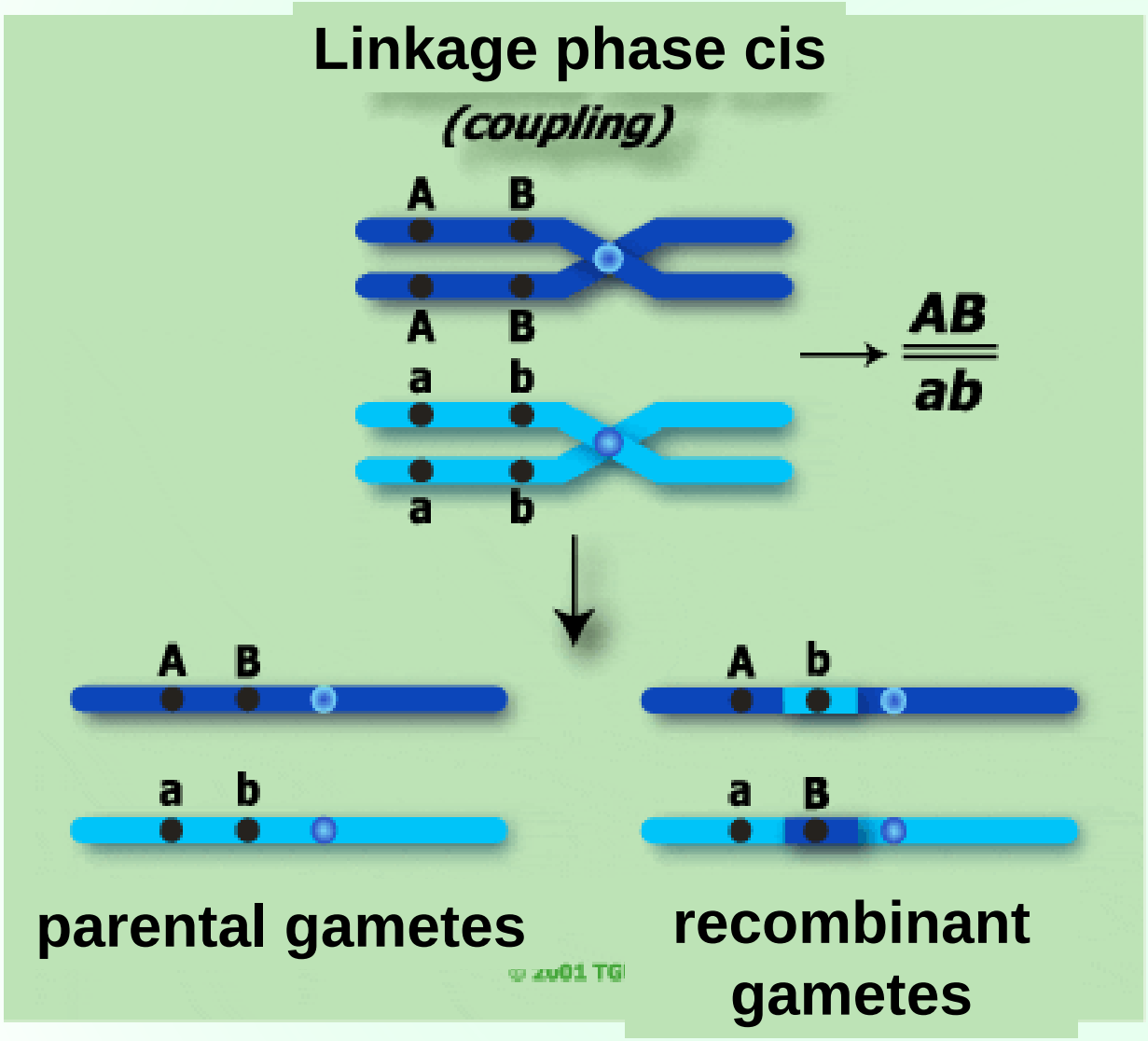
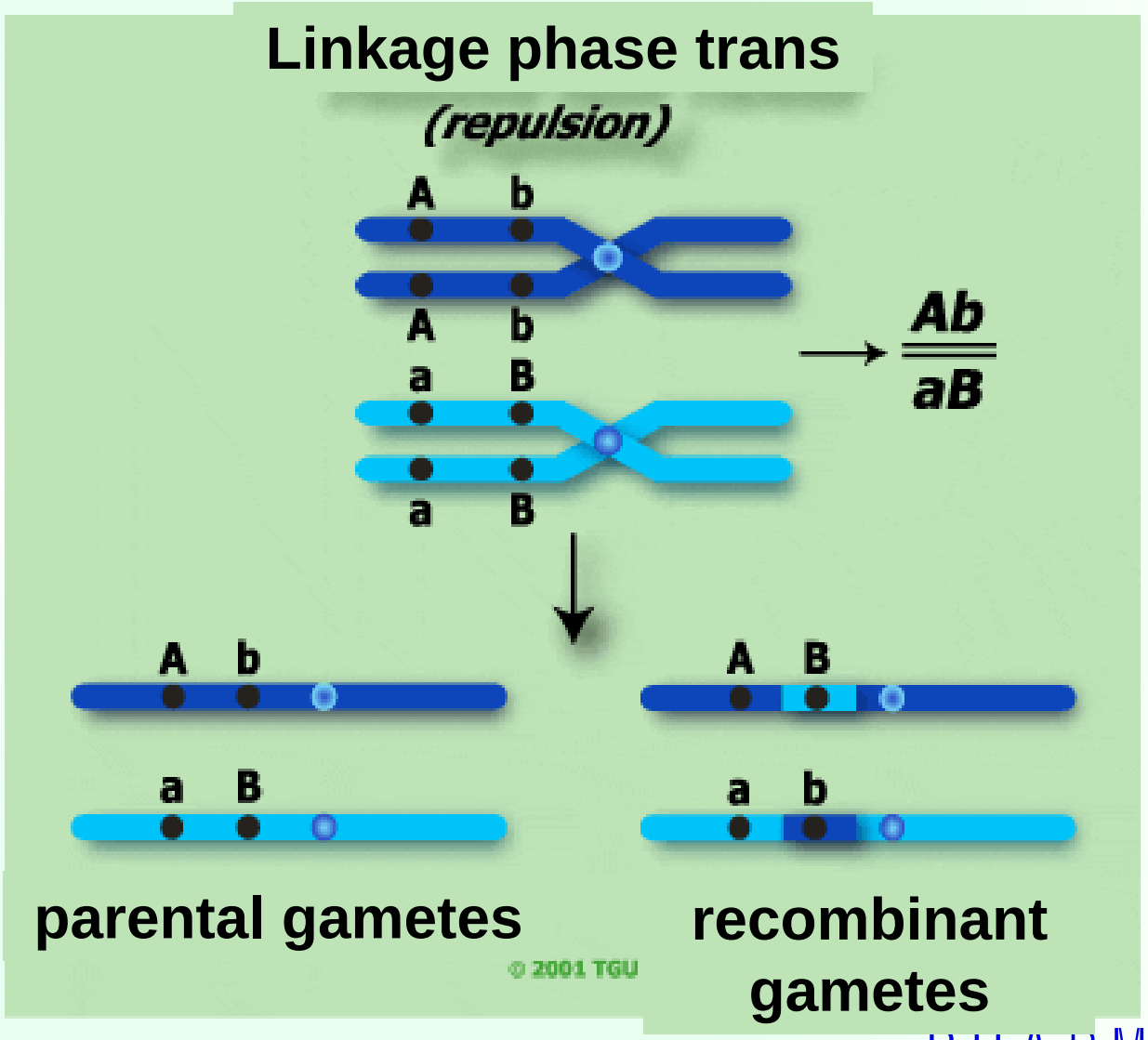
Gene linkage

- **when two genes are linked, free combinability does not apply** = deviations from the phenotypic split ratio of 9:3:3:1 in F2 and 1:1:1:1 in B1 generation
- genes on one chromosome are linked to each other
- **trans phase** - dihybrid AaBb, which has genes A and B located **on different pairs of chromosomes**, forms gametes of genotypes AB - Ab - aB - ab in a ratio of 1 : 1 : 1 : 1
- **cis phase** - dihybrid AaBb, which has genes A and B located **in one pair of chromosomes**, forms gametes of type AB – Ab – aB – ab in different proportions
- the reason is **crossing-over between non-sister chromatids**
  - gametes with non-recombined (AB, ab) and recombined (Ab, aB) genotypes are produced
  - the probability of crossing-over decreases with the distance between the two monitored genes
- **the linkage strength** (= distance between genes) is determined by **Morgan's number**, which expresses the proportion of recombinants and is given in centimorgans (1 cM = 1% recombinant), the recombination process occurs with a relatively low probability

Linkage phase cis/trans





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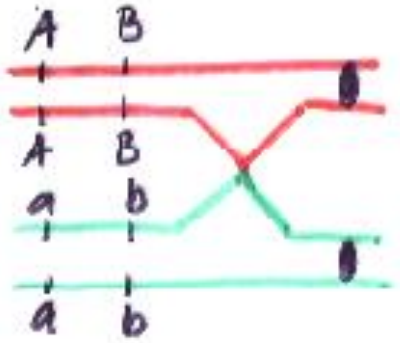
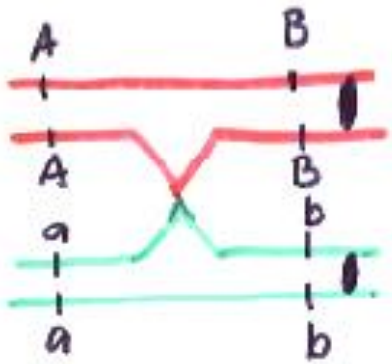
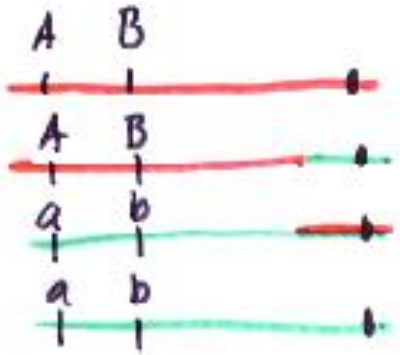
Two possibilities of exchanges between non-sister chromatids

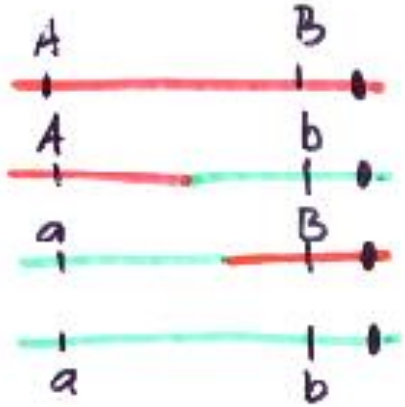
Chromosome pair

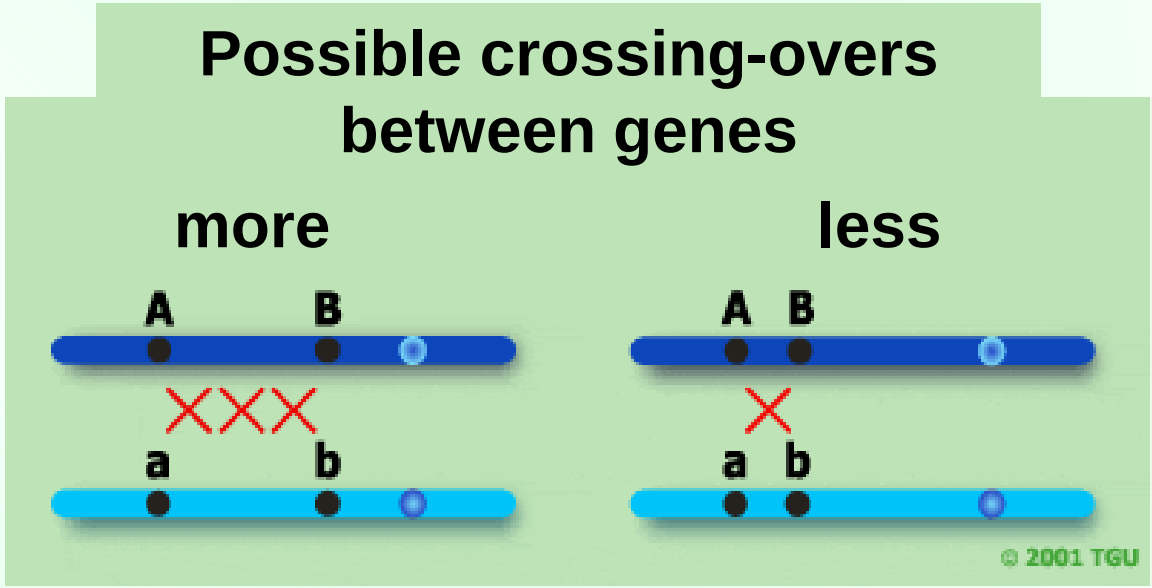




gametes







https://user.mendelu.cz/urban/vsg1/mendel/klas_vazba1.html

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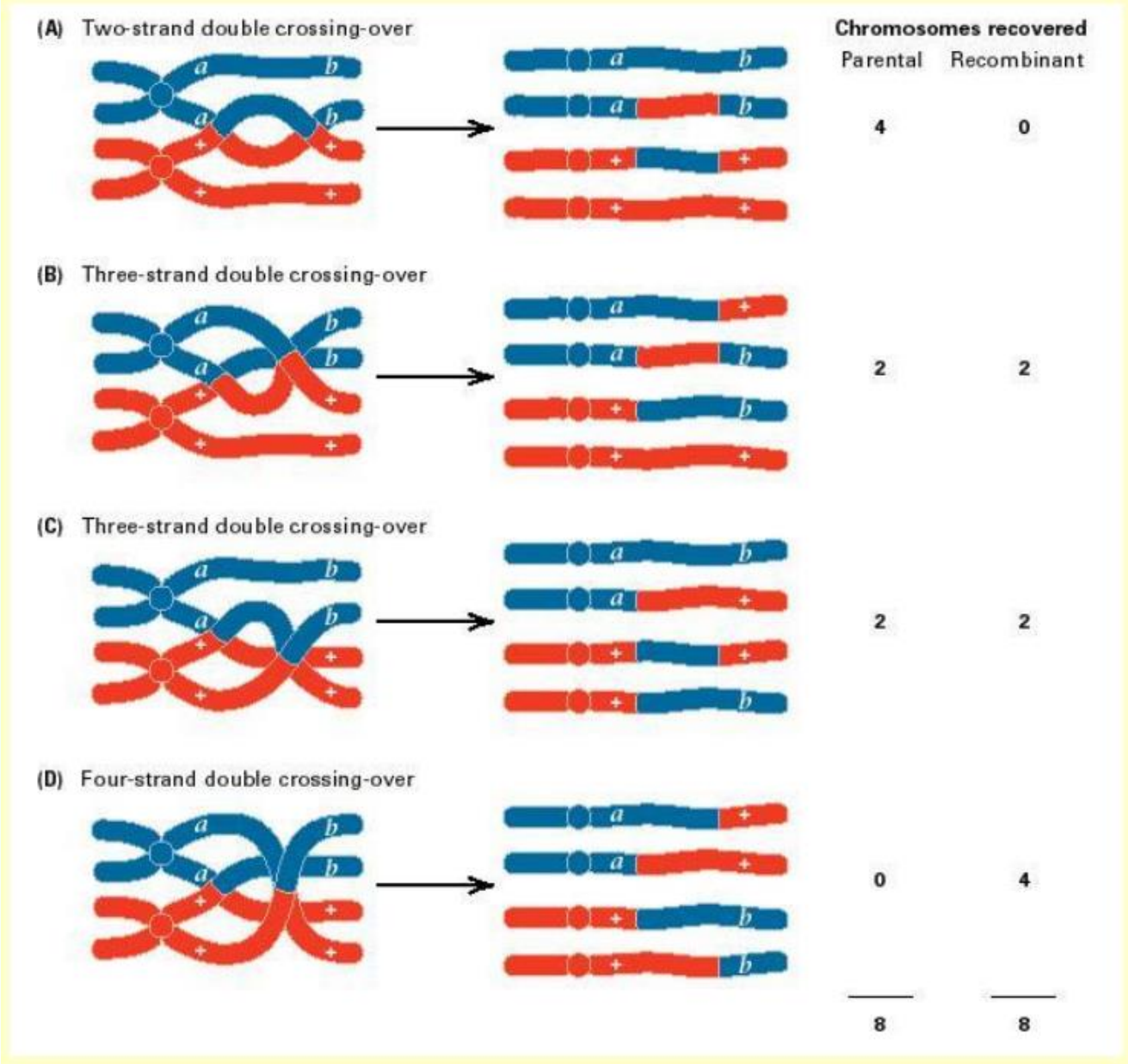
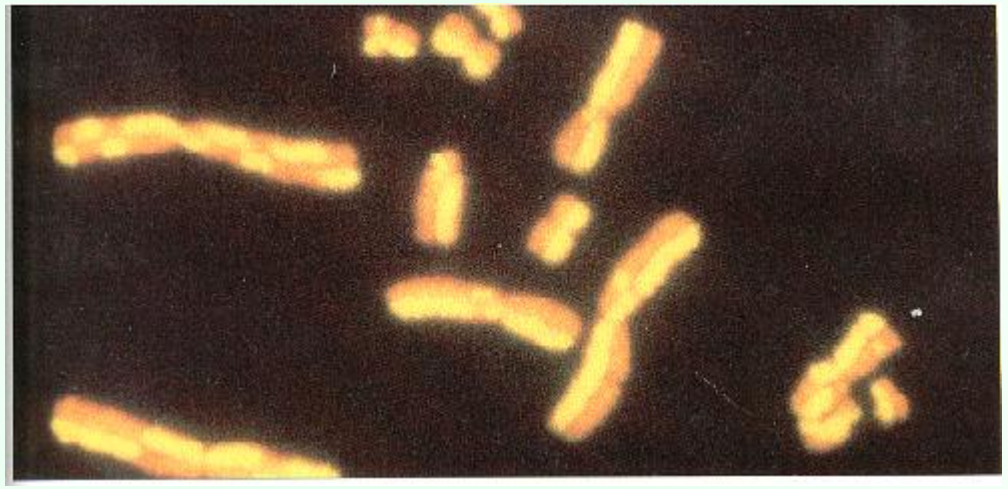
Possibilities of chromatid recombination



Incorporation of BrDU during S-phase



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Gene interaction

- Reciprocal interaction
  - interaction without a change in the cleavage ratio, the observed trait occurs in multiple forms, each of which is determined by one of the combinations of parental gene alleles
- Epistasis
- Inhibition
- Complementarity

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9 : 3 : 3 : 1

F-O- : F-oo : ffO- : ffoo

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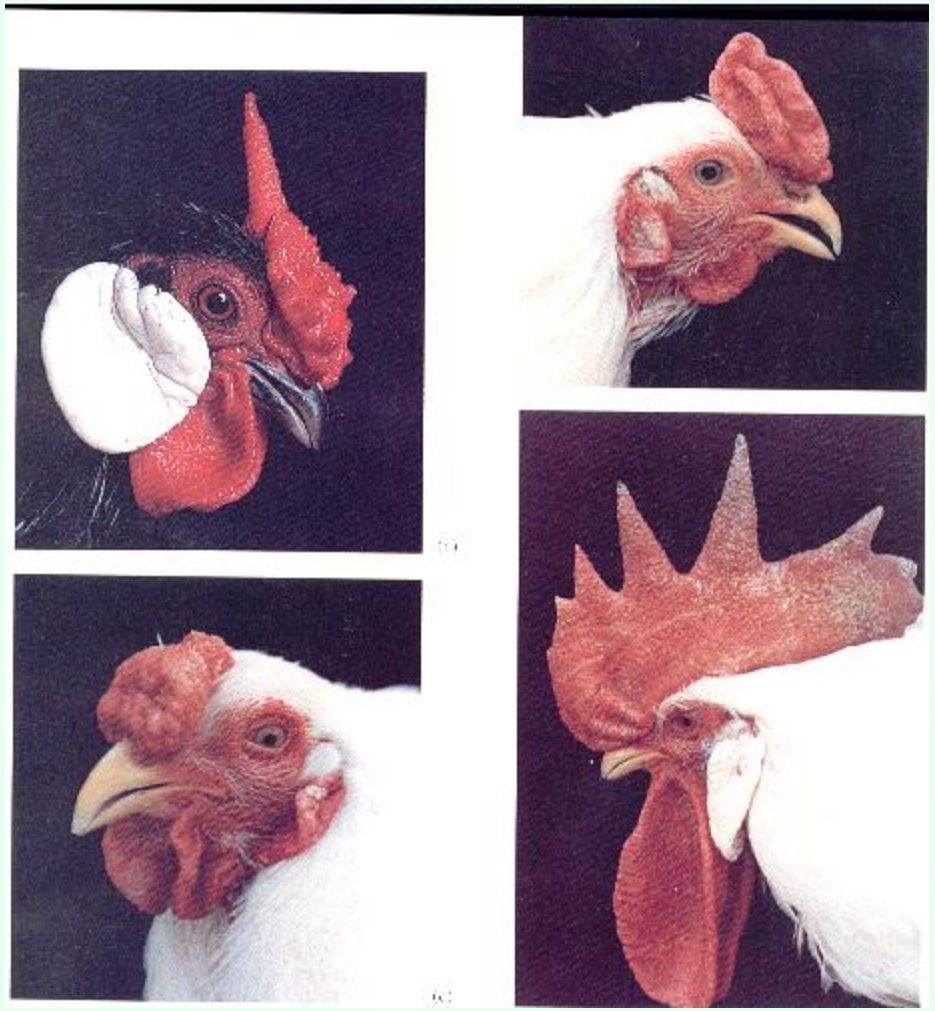
Reciprocal interaction

(a)
Wyandotts
R- pp



(b)
Brahmans
rr P-

Hybrid
(a) x (b)
R- P-

Leghorns
rr pp

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Gene interaction

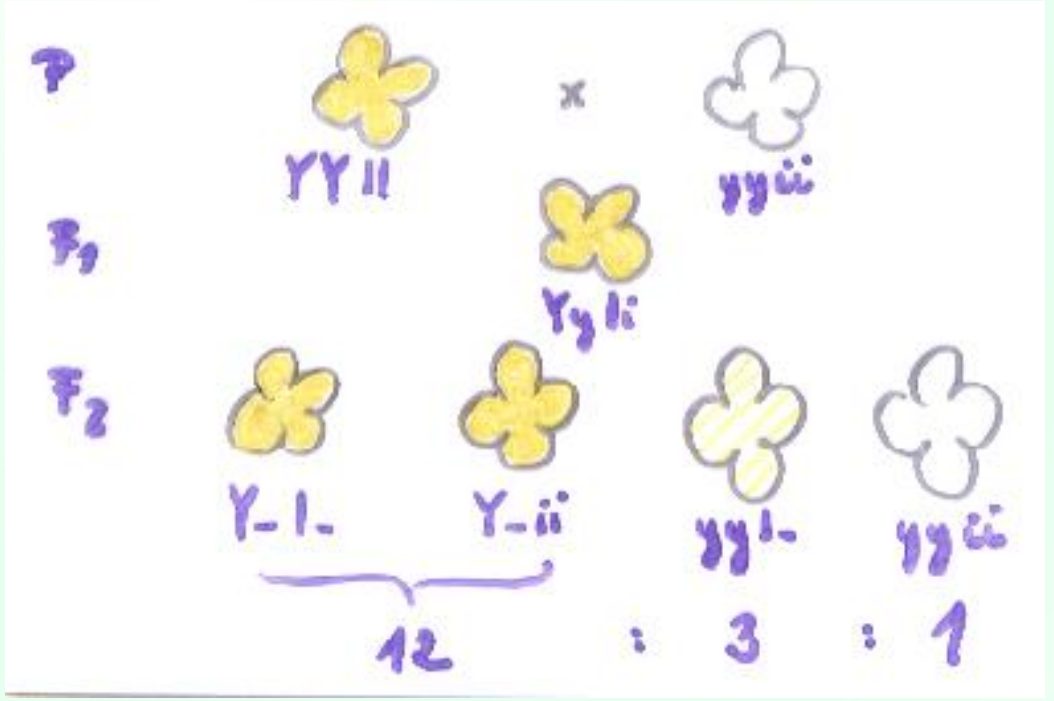
- Reciprocal interaction
- Epistasis
  - gene encoding the corresponding trait has no chance to express itself, because its superior gene does not allow it
  - The cleavage ratio is changed
- Inhibition
- Complementarity

Dominant epistasis

- In dominant epistasis, it is sufficient for at least one dominant allele to be present in the epistatic trait pair to suppress the effect of the subordinate allelic pair. Dominant homozygotes and heterozygotes in an epistatic pair therefore have the same phenotype regardless of what traits they carry in the hypostatic pair.

epistatic gene (allele) *Y*
hypostatic gene *I, i*

***Y*...intense yellow flavone**
***I*... creamy yellow flavone**



Dahlia variabilis

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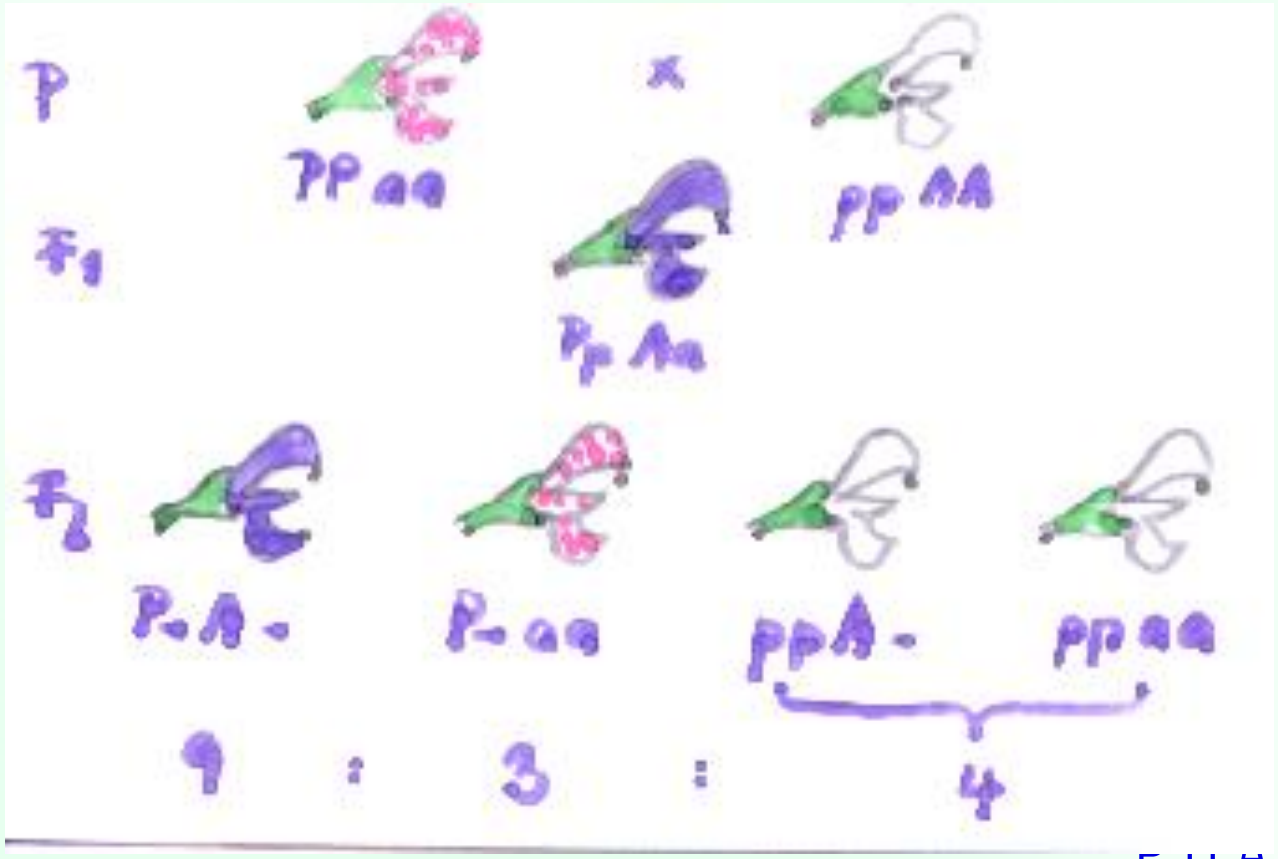
Recessive epistasis

- In recessive epistasis, the dampening effect of an epistatic trait pair is only manifested if an individual is recessive homozygous for that trait.

Salvia viridis
var. horminum

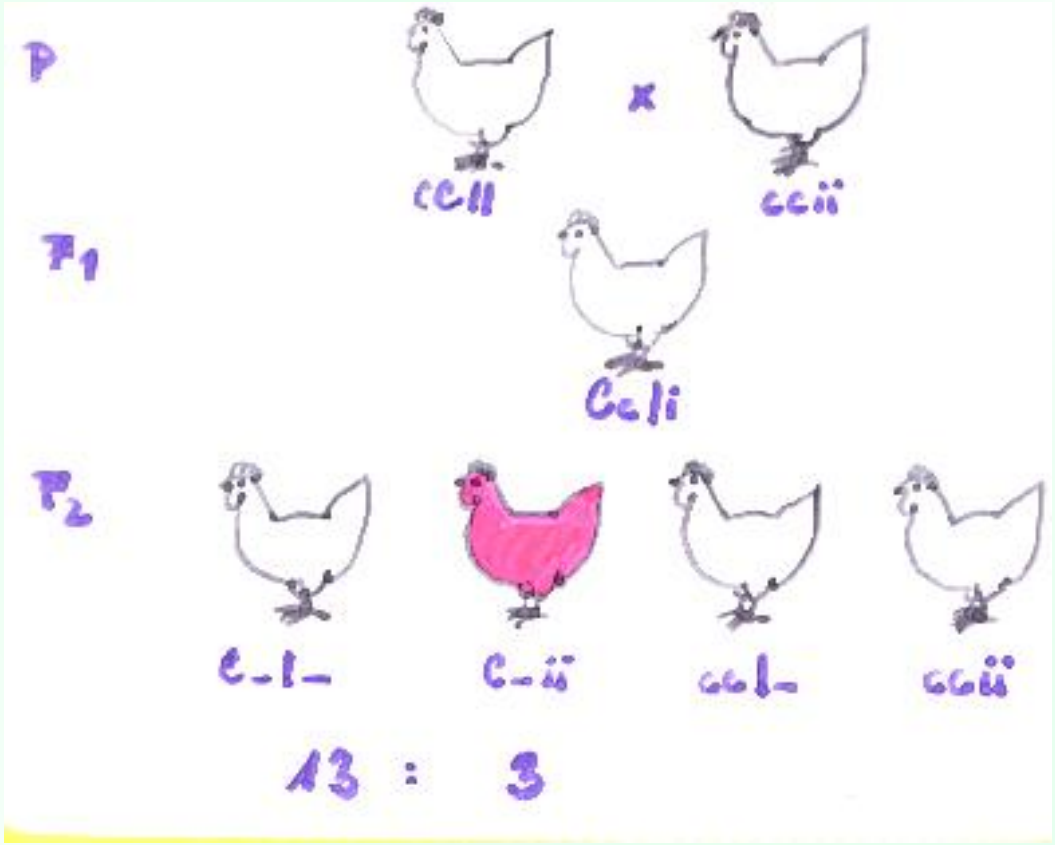


***P*... pink antocyan**
***A*... pink → purple**

pp > A-

Inhibition

- Inhibition is similar to dominant epistasis in many ways. However, the superior trait pair has no own phenotypic expression, its dominant allele only blocks the effect of other traits. They can therefore only manifest if the inhibitory allelic pair is in a recessive homozygous state.



C **… red coloring**
I **… color inhibitor**

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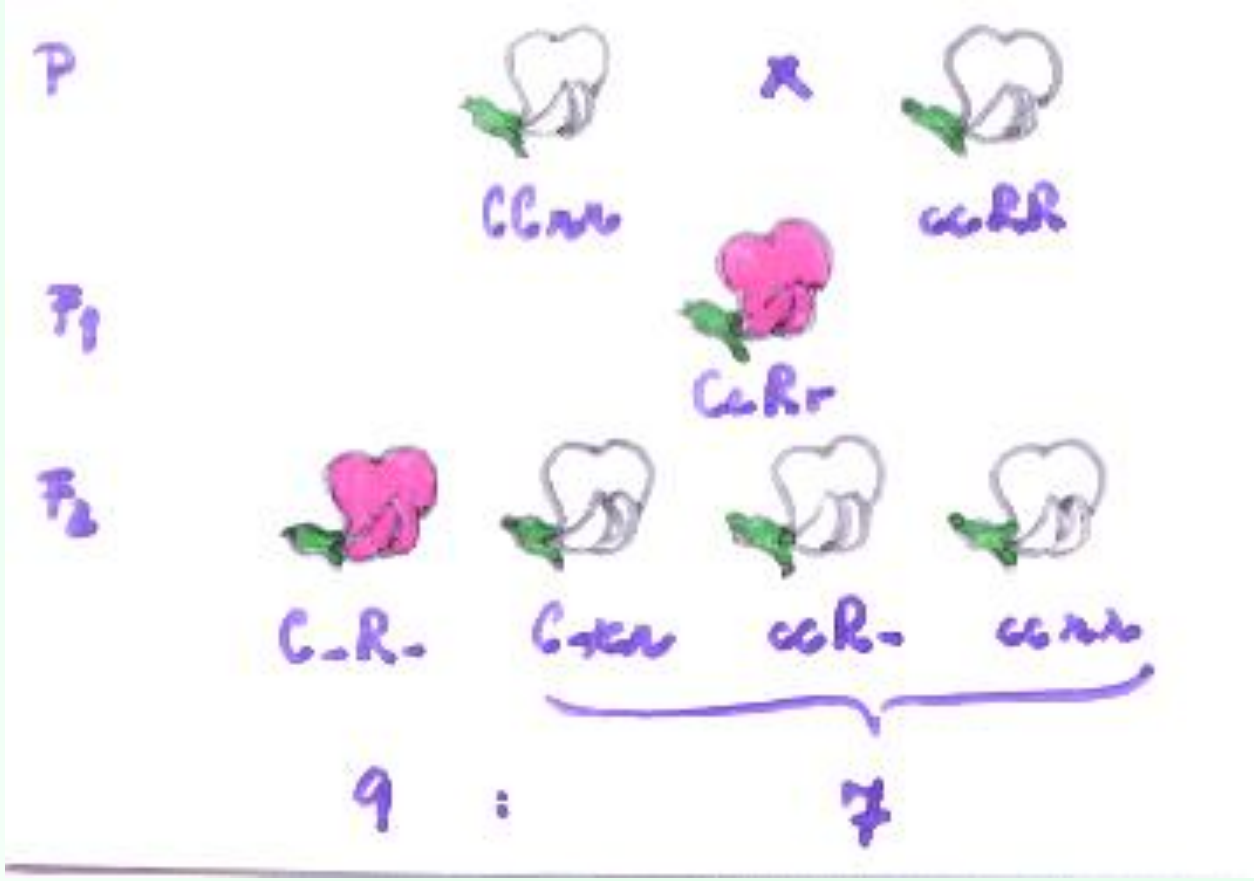
Complementarity

- If the interaction of dominant alleles from two or more trait pairs is needed for a certain phenotypic manifestation, this is called complementarity, or double or duplicate recessive epistasis.



Lathyrus odoratus

***C*... dye precursor**
***R*... enzyme**

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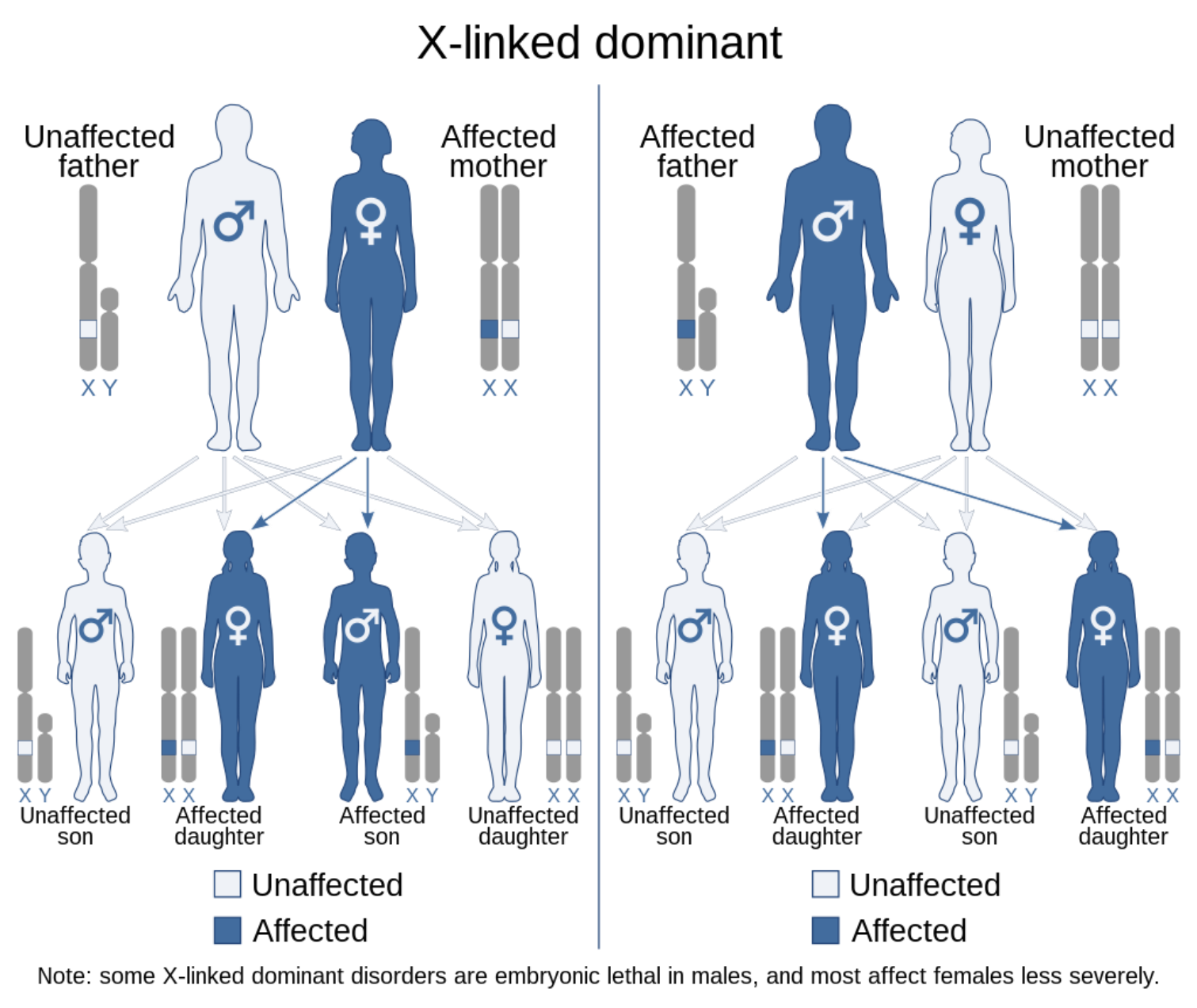
Linkage to gender

- The gene is found on the gonosomes → phenotypic manifestation depending on sex



https://en.wikipedia.org/wiki/X-linked_dominant_inheritance

Further deviations from Mendelian cleavage ratios

- **Extranuclear inheritance -** mitochondrial DNA from mother only
  - in plants, chloroplast DNA from the female plant only
- **Polygenic inheritance –** the trait is coded by several genes → the rules for n-hybrids and crossing-over apply here at the same time
- the trait has **incomplete penetrance** - it may not manifest itself in 100% of individuals, but in some people it does not manifest, or the trait is obscured and difficult to observe
- the trait has a **variable expression** - in people with the same genotype, we observe different intensity of manifestations of the same trait

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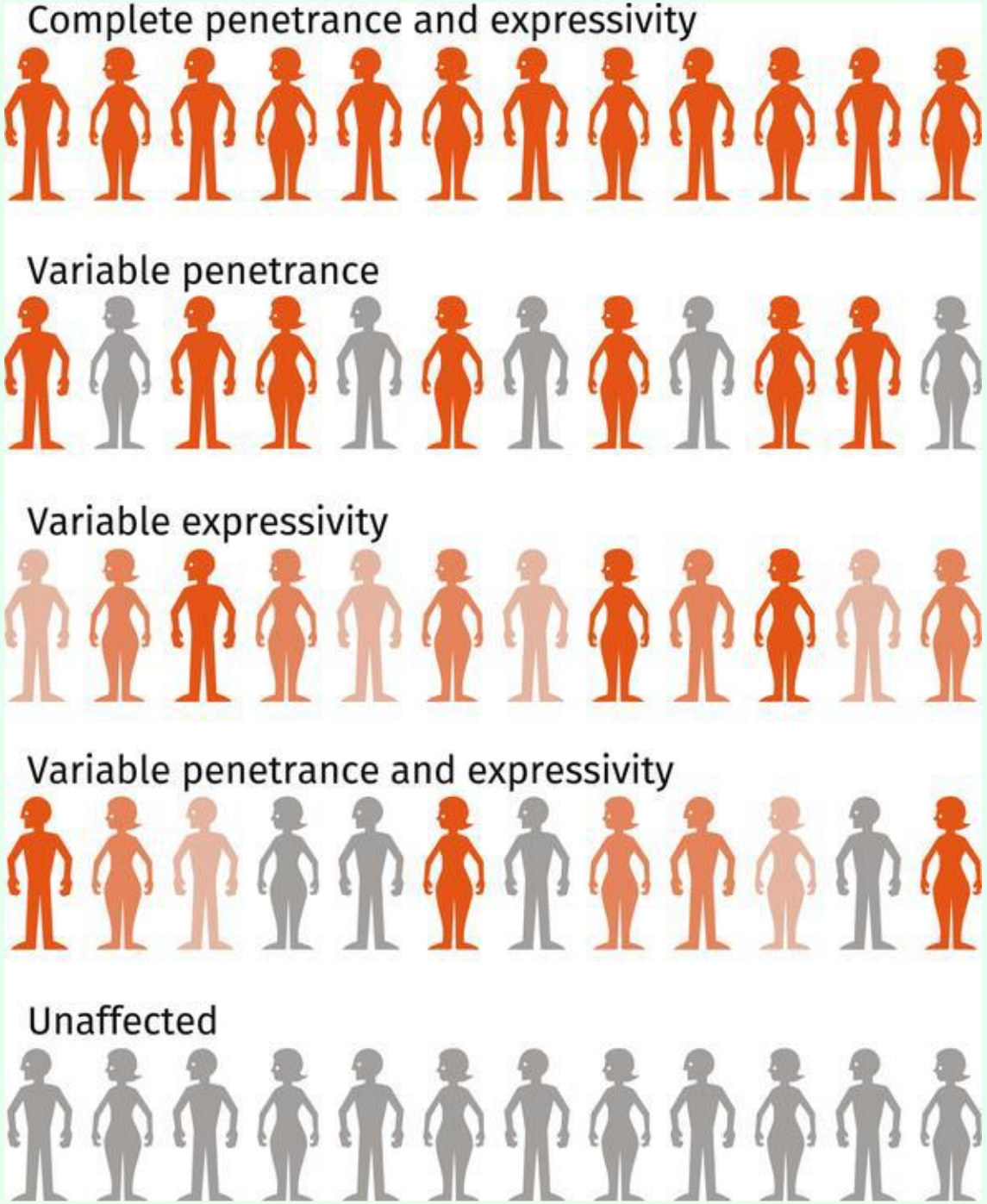
Complete penetrance and expressivity
Variable penetrance
Variable expressivity
Variable penetrance and expressivity
Unaffected

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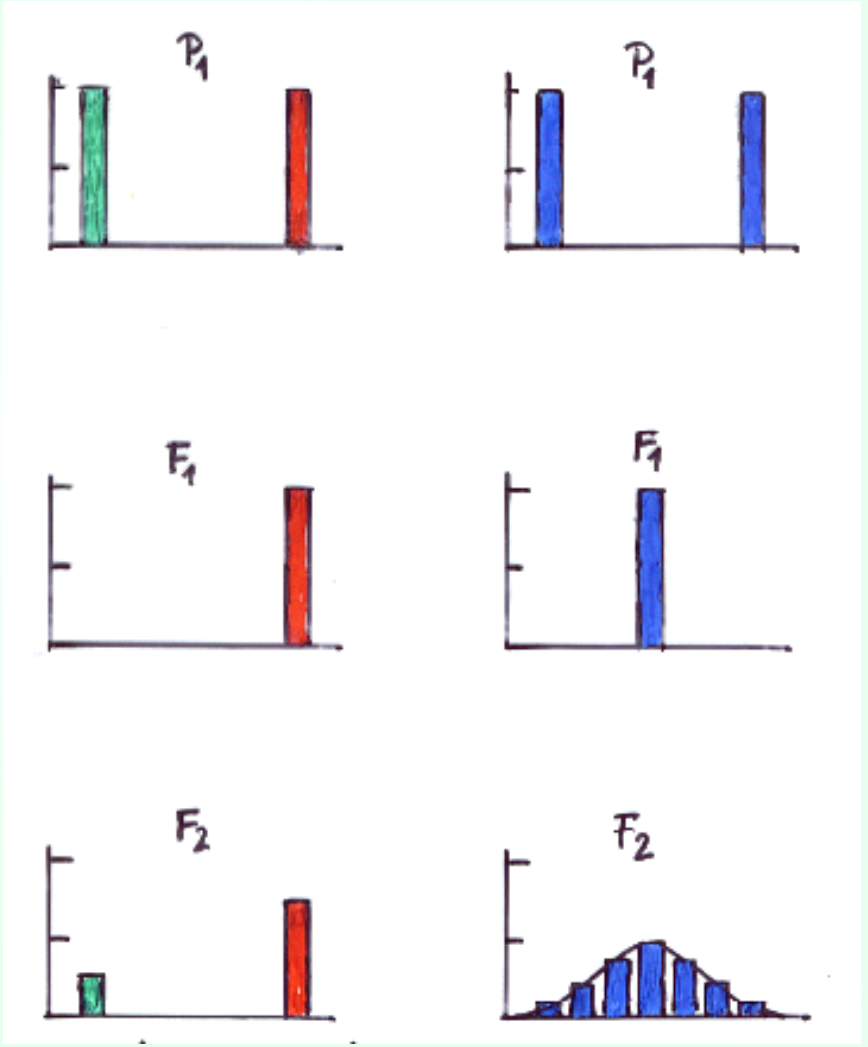
Inheritance of quantitative traits

- The manifestation of the trait takes on different values → continuous variability

Qualitative trait vs. quantitative trait

Mendel's experiment with plant height



Galton's experiment with seed diameter

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Inheritance of quantitative traits

- for research on the polygenic and multifactorial inheritance of human hereditary traits, the follow-up of **twins** is particularly useful
  - **dizygotic twins,** growing up in the same environment, give us a picture of how the same external factors act on two individuals with different (albeit slightly) genotypes
  - **monozygotic twins** provide us with a unique opportunity to evaluate two individuals with the same genotype
  - if these monozygotic twins also grow up each in a different environment, we can evaluate the effect of different environments on individuals with the same genotype
- we evaluate:
  - **concordance** for a certain trait (match - both individuals have the observed trait)
  - **discordance** for a certain character (disagreement - one of the twins does not have the given character)
  - **heritability** is a value indicating to what extent the value of traits depends on the genotype of an individual and how much the final value of a trait is the result of external factors

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Heritability estimates for various traits (%)

	Trait	heritability H_B (%)
mouse	tail lenght	60
	litter size	15
friut fly	number of abdominal hairs	52
	wing length	45
human	asthma	80
	diabetes	70

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Concordance of some characters in monozygotic (MZ) and dizygotic (DZ) twins

trait	Conkordance (%)	
	MZ	DZ
Blood groups	100	66
Eye color	99	28
Mental retardation	97	37
Measles	95	87
Idiopathic epilepsy	72	15
Schizophrenia	69	10
Blood pressure	63	36
Diabetes	65	18
Identical allergy	59	5
Tuberculosis	57	23
Cleft lip	42	5
Crooked legs	32	3
Breast cancer	6	3

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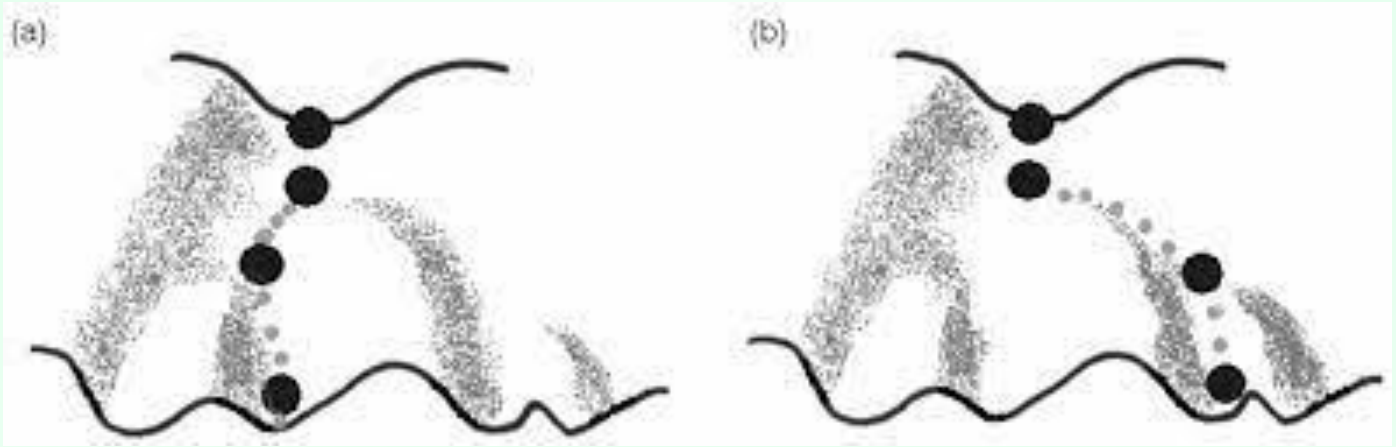
Epigenetics

- **Epigenesis** - explains the principle of individual development: the resulting organism is not preformed, but arises creatively on the basis of inherited information and internal and external influences.
- **Epigenetics** - studies heritable changes in gene expression that occur without changing DNA sequences.
- **Genomic imprinting** - a reversible process where sex-specific modification of genes in the parental generation leads to functional differences between the paternal and maternal genomes (alleles) in the offspring



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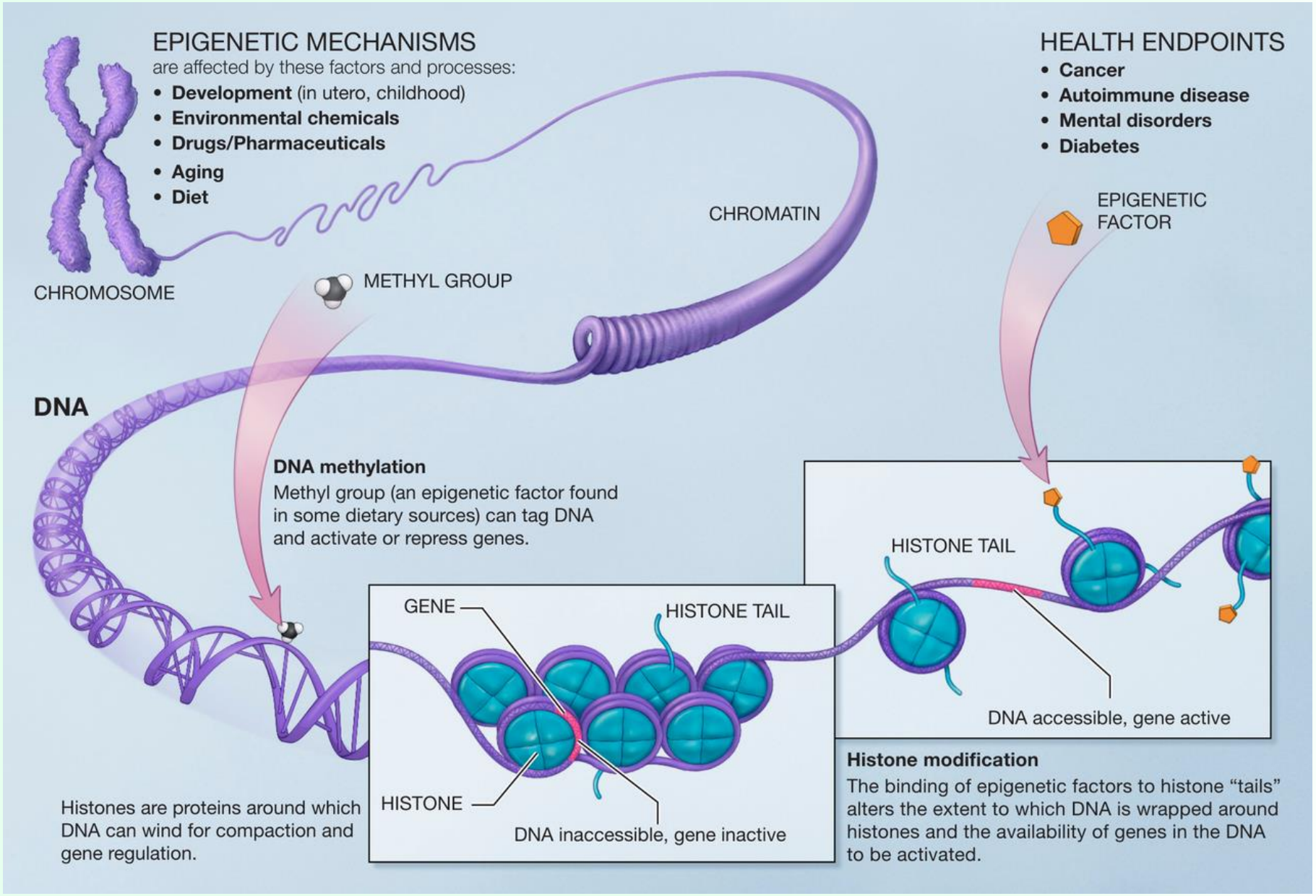
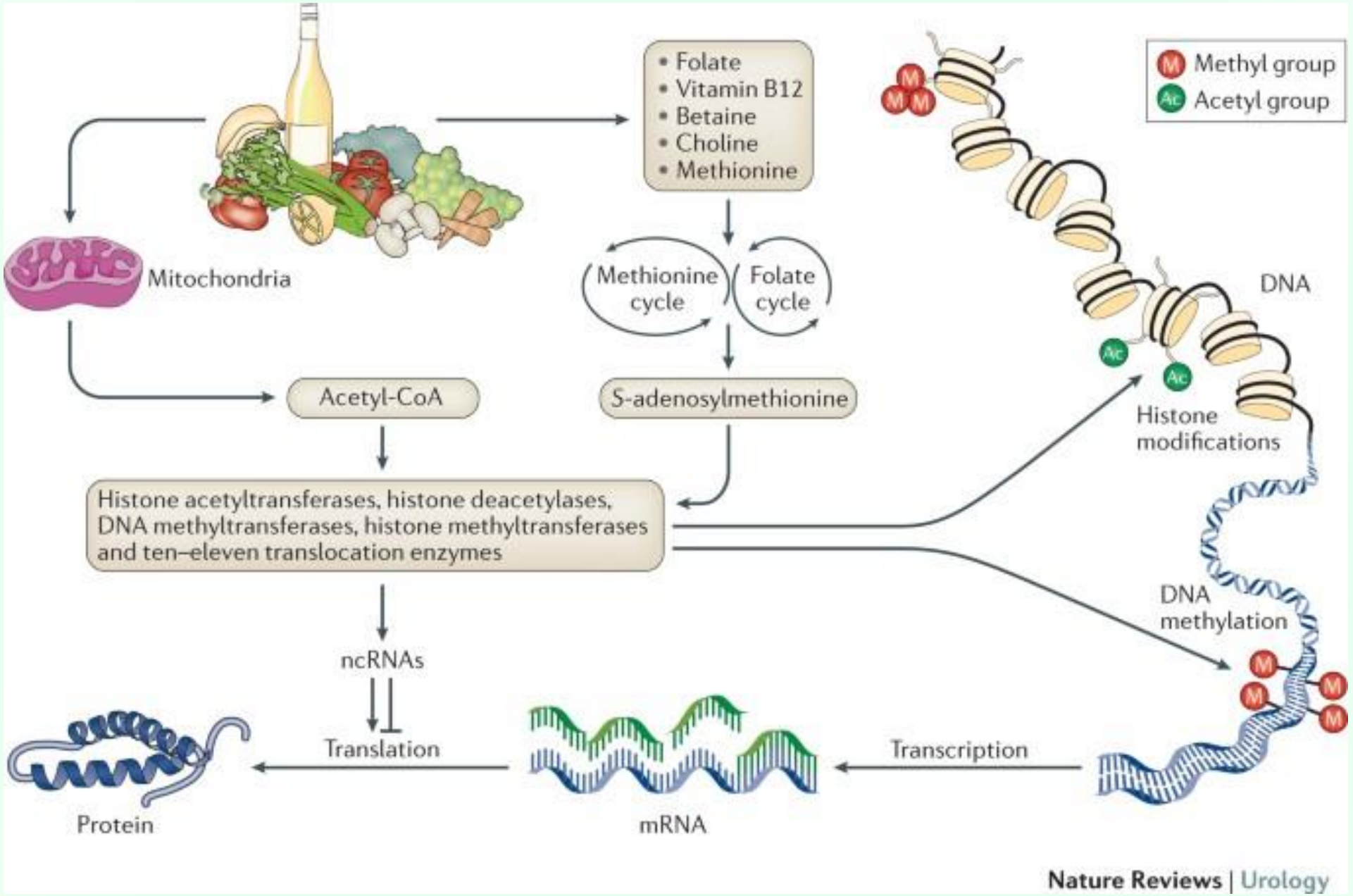
Mechanisms of imprinting

- DNA metylation
- Acetylation of histones





Schagdarsurengin, U., Steger, K. Epigenetics in male reproduction: effect of paternal diet on sperm quality and offspring health. *Nat Rev Urol* **13**, 584–595 (2016). https://doi.org/10.1038/nrurol.2016.157

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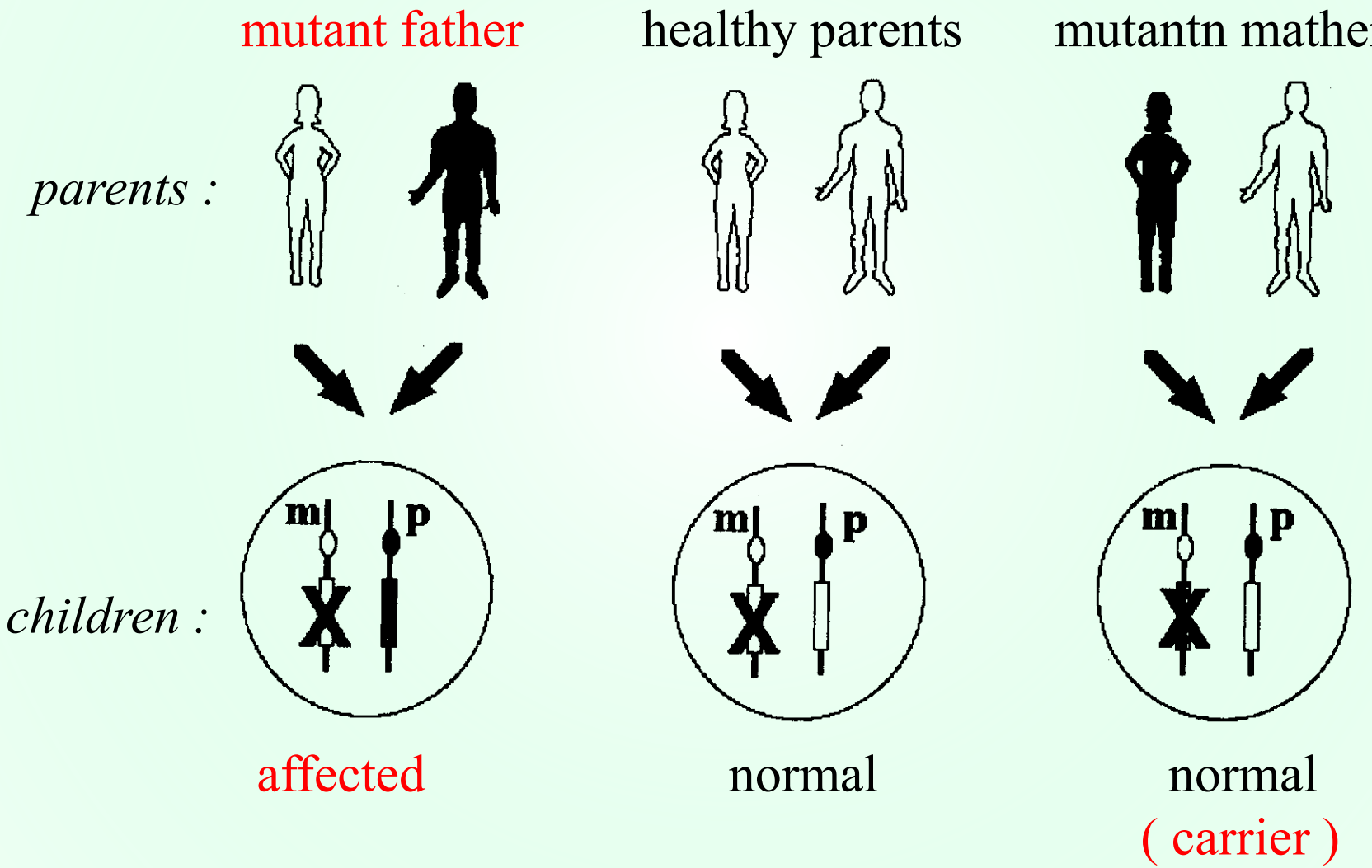
Maternal imprinting of the mutated locus results in a different phenotype of the offspring



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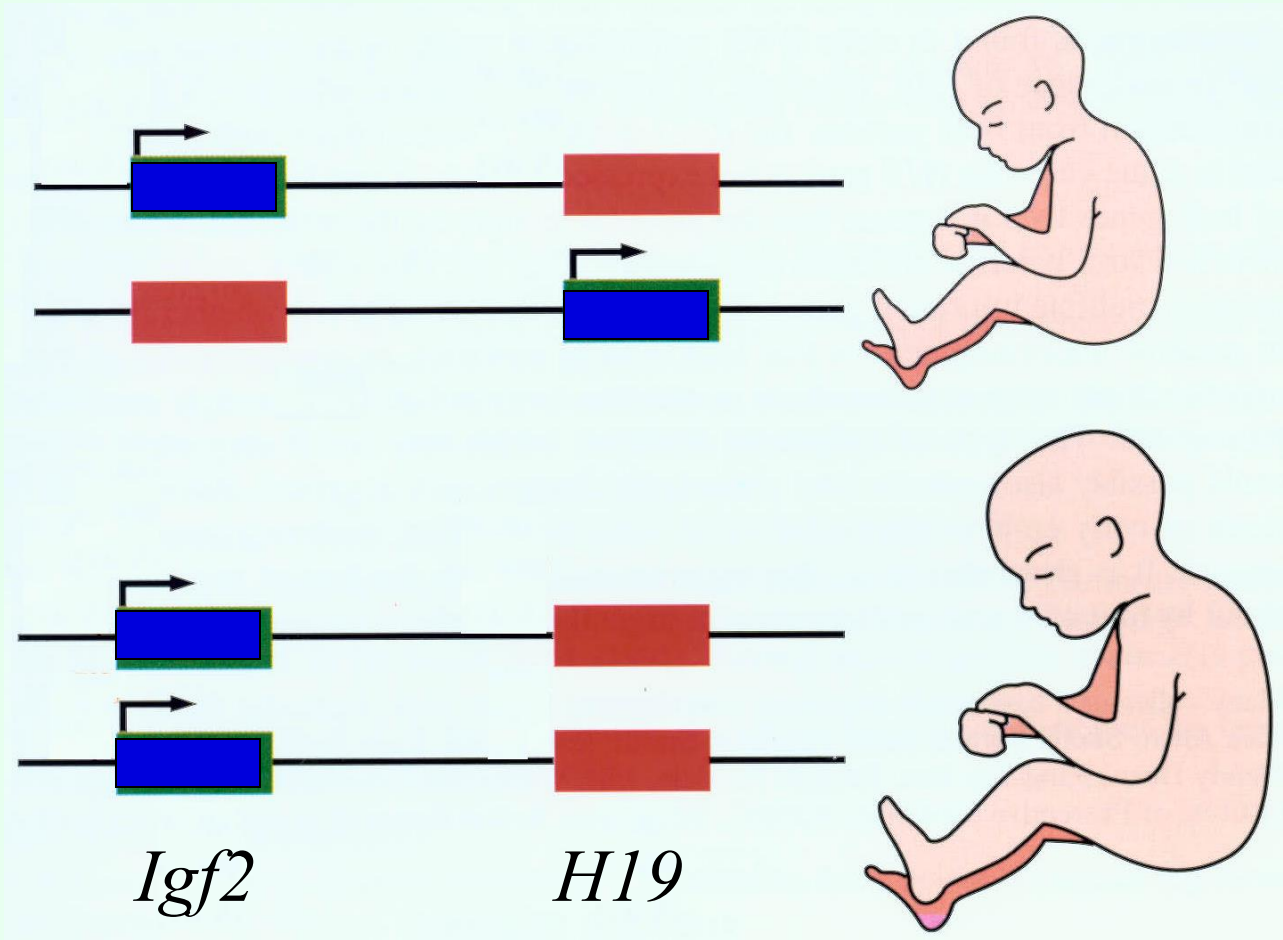
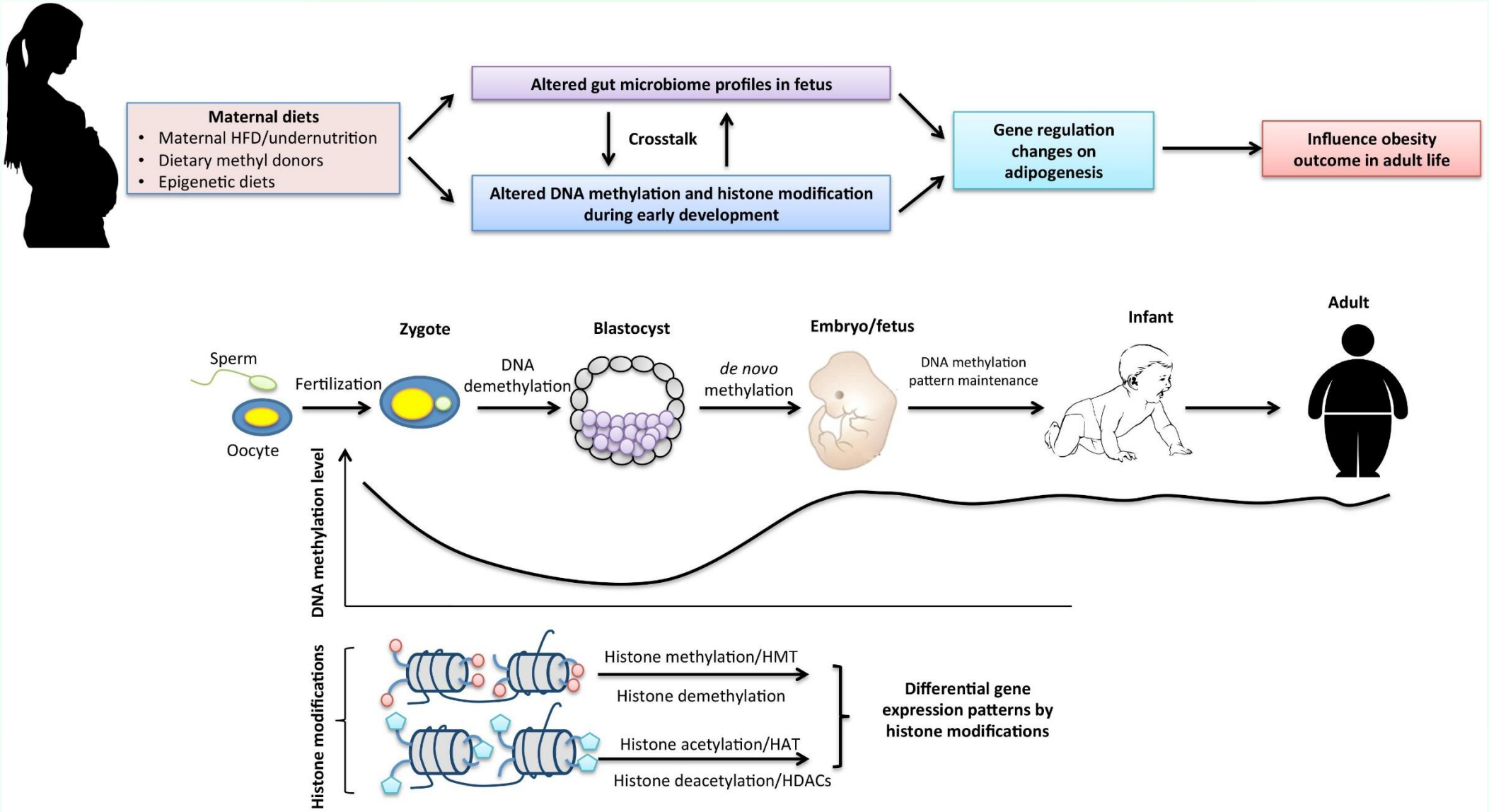
Incorrect imprint of P-allele (insuline growth factor) or M-allele (growth-suppressing H19-RNA) leads to Beckwith-Wiedemann‘s syndrome



normál

BWS

(J. B. Beckwith & H. R. Wiedemann 1964)



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Maternal diets or supplementation	Epigenetic mechanisms	Microbiota	Specific gene changes	Clinical effects in offspring
Over nutrition (e.g., high fat diet [HFD])	Induce altered DNA methylation, histone acetylation and histone methylation patterns in offspring epigenome (Aagaard-Tillery et al., 2008; Dudley et al., 2011; Suter et al., 2012; Lee, 2015; Masuyama et al., 2015; Indrio et al., 2017)	Altered gut microbiome profiles in the offspring (Chu et al., 2016b; Zhou and Xiao, 2018)	Adipogenesis-related genes such as *adiponectin*, *leptin*, and *PPAR-γ* (Aagaard-Tillery et al., 2008; Dudley et al., 2011; Suter et al., 2012; Masuyama et al., 2015)	Increased birth body weight and high risk of development of metabolic disorders and obesity in later life (Parlee and MacDougald, 2014)
Under nutrition	Induce DNA methylation and histone modification changes as well as microRNA profile changes (Fu et al., 2004; Tosh et al., 2010; Slater-Jefferies et al., 2011; Zheng et al., 2017)	Maternal protein-deficient diets modulate gut microbiome profiles in the offspring (Chu et al., 2016b)	Adipogenesis- and metabolism-related *IGF-1*, *PPAR-α*, *CPTI C/EBPβ* genes (Fu et al., 2004; Tosh et al., 2010; Slater-Jefferies et al., 2011; Zheng et al., 2017)	Maternal food restriction resulted in fetal intrauterine growth restriction (IUGR) and increased susceptibility to insulin resistance and diabetes in the offspring (Li et al., 2010; Parlee and MacDougald, 2014)
Methyl donor (e.g., folate acid)	Restriction of maternal folate resulted in widespread epigenetic alterations in DNA methylation (Sinclair et al., 2007)	Folate is produced by gut *Bifidobacteria* (Pompei et al., 2007)	Maternal folate deficiency induced hyperacetylation of *PPAR-γ* coactivator, *PGC-1α* (Gueant et al., 2014)	Maternal folate deficiency resulted in increased risk of insulin resistance, elevated blood pressure and obesity-related metabolic disorders in adult offspring (Gueant et al., 2013; Wang et al., 2016)
Soybean (e.g., genistein)	Maternal soybean genistein led to global modification in the fetal epigenome (Dolinoy et al., 2006)	Soybean genistein is bio-converted by gut microbiome and it can also modulate the microbiome profiles (Paul et al., 2015, 2017)	Maternal soybean genistein resulted in hypermethylation of the ectopic *agouti* gene expression (Dolinoy et al., 2006)	Maternal soybean genistein led to reduction of prevalence of obesity in the mouse offspring (Dolinoy et al., 2006)
Cruciferous vegetables (e.g., sulforaphane)	Sulforaphane is a potent histone deacetylase inhibitor and maternal broccoli sprouts lead to global epigenetic changes in mouse offspring (Myzak et al., 2004; Li et al., 2014; Li et al., 2018)	Sulforaphane is bio-converted by gut microbiome and it also modulates the microbiome profiles (Paul et al., 2015)	Tumor-related genes such as *p53, p16, c-Myc*, and *hTERT* (Li and Tollefsbol, 2010; Hardy and Tollefsbol, 2011; Li et al., 2014)	Sulforaphane counteracts HFD-induced body weight and metabolic disorders (Nagata et al., 2017)
Green tea polyphenols (e.g., EGCG)	EGCG is a DNA methyltransferase inhibitor and can induce reactivation of DNA methylation-silenced gene expression (Fang et al., 2003). Green tea polyphenol EGCG inhibits maternal HFD-induced neural tube defects by inhibiting DNA hypermethylation (Zhong et al., 2016).	Green tea polyphenols reversed HFD-induced gut microbial diversity changes by decreasing *Firmicutes* to *Bacteroidetes* ratio (F/B ratio) in C57BL/6J mice (Wang et al., 2018).	Tumor suppressor genes such as *p16*, *RNRβ*, *MGMT*, and *hMLH1* (Fang et al., 2003); Neural tube closure essential genes, including *Grhl3*, *Pax3*, and *Tulp3* (Zhong et al., 2016)	Small amount green tea during pregnancy may provide transplacental protection against carcinogenesis and obesity in the offspring (Castro et al., 2008)
Probiotics	Various metabolites of gut microbiota such as short-chain fatty acid (SCFAs) and butyrate can influence epigenetic pathways (Pompei et al., 2007; Hamer et al., 2008; Berni Canani et al., 2012; Paul et al., 2015; Cortese et al., 2016).	*Lactobacillus* and *Bifidobacterium* (Chu et al., 2016b; Indrio et al., 2017; Zhou and Xiao, 2018)	Probiotic supplementation during pregnancy affects DNA methylation status of certain promoters of obesity and weight gain-related genes both in mothers and their children (Luoto et al., 2010; Wickens et al., 2017; Vähämiko et al., 2018)	Probiotic intake during pregnancy and lactation attenuates maternal HFD-induced detrimental nutritional programming of offspring obesity (Paul et al., 2016)

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