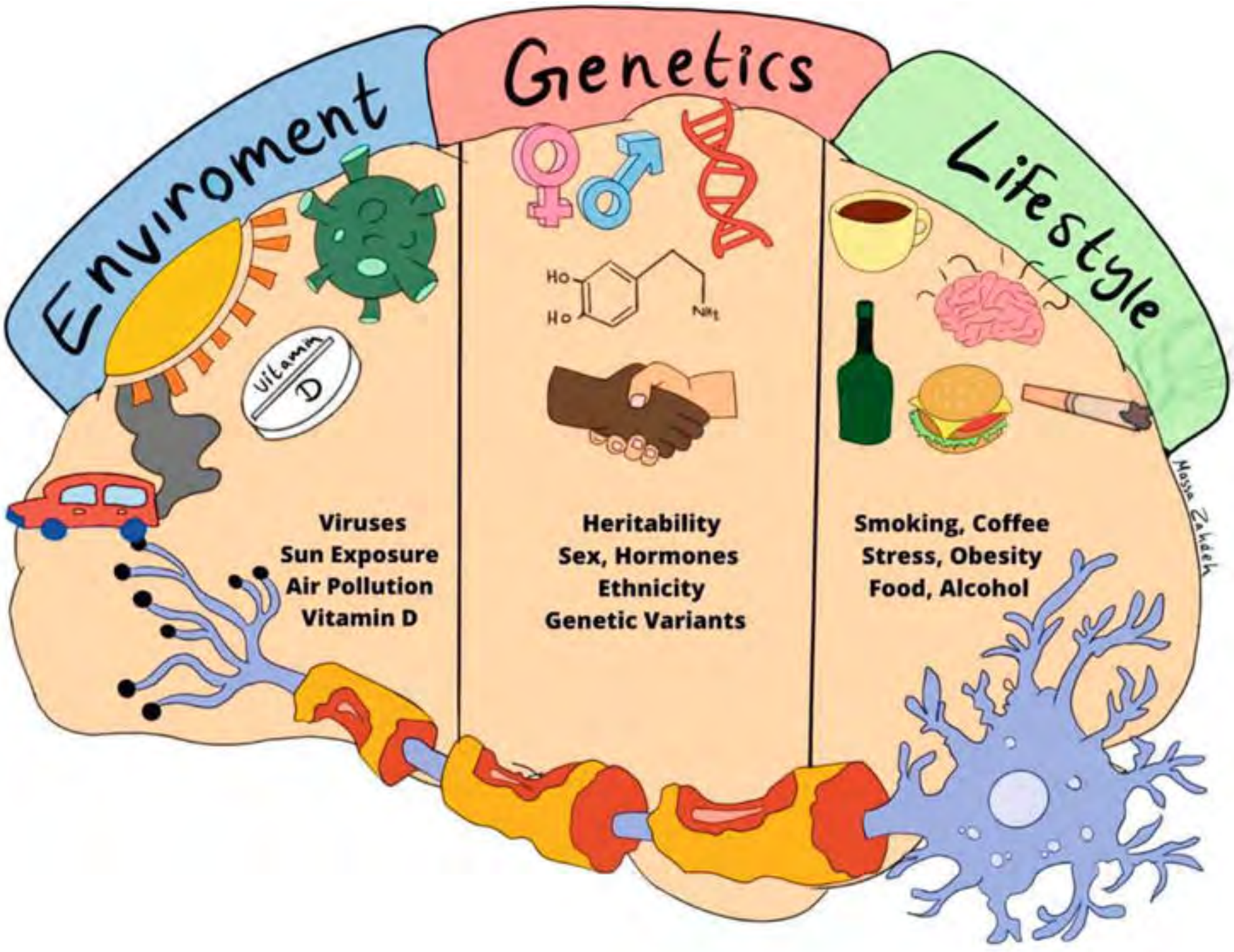
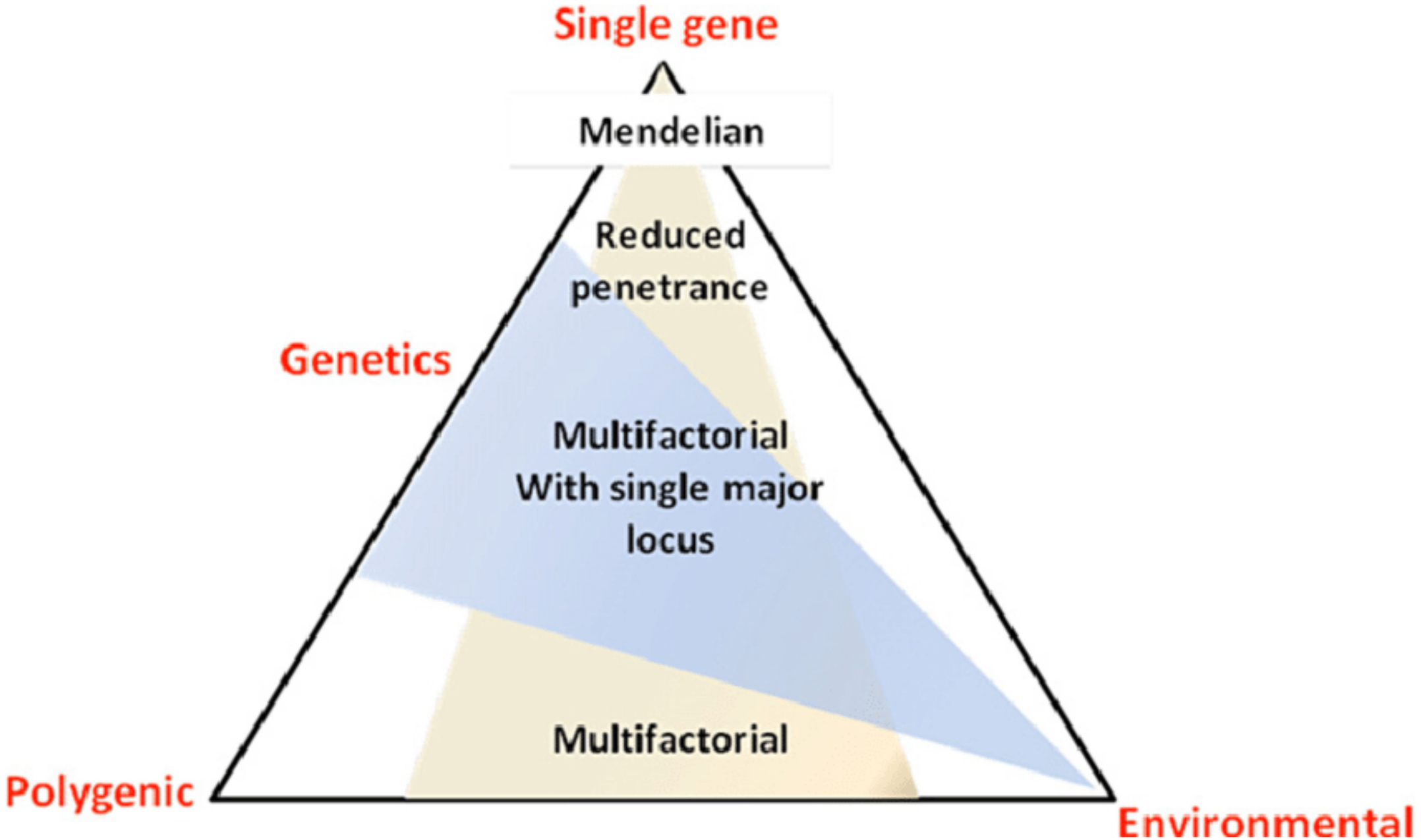
Введение в молекулярную биологию

Лекция 5. Медицинская генетика и генетические заболевания

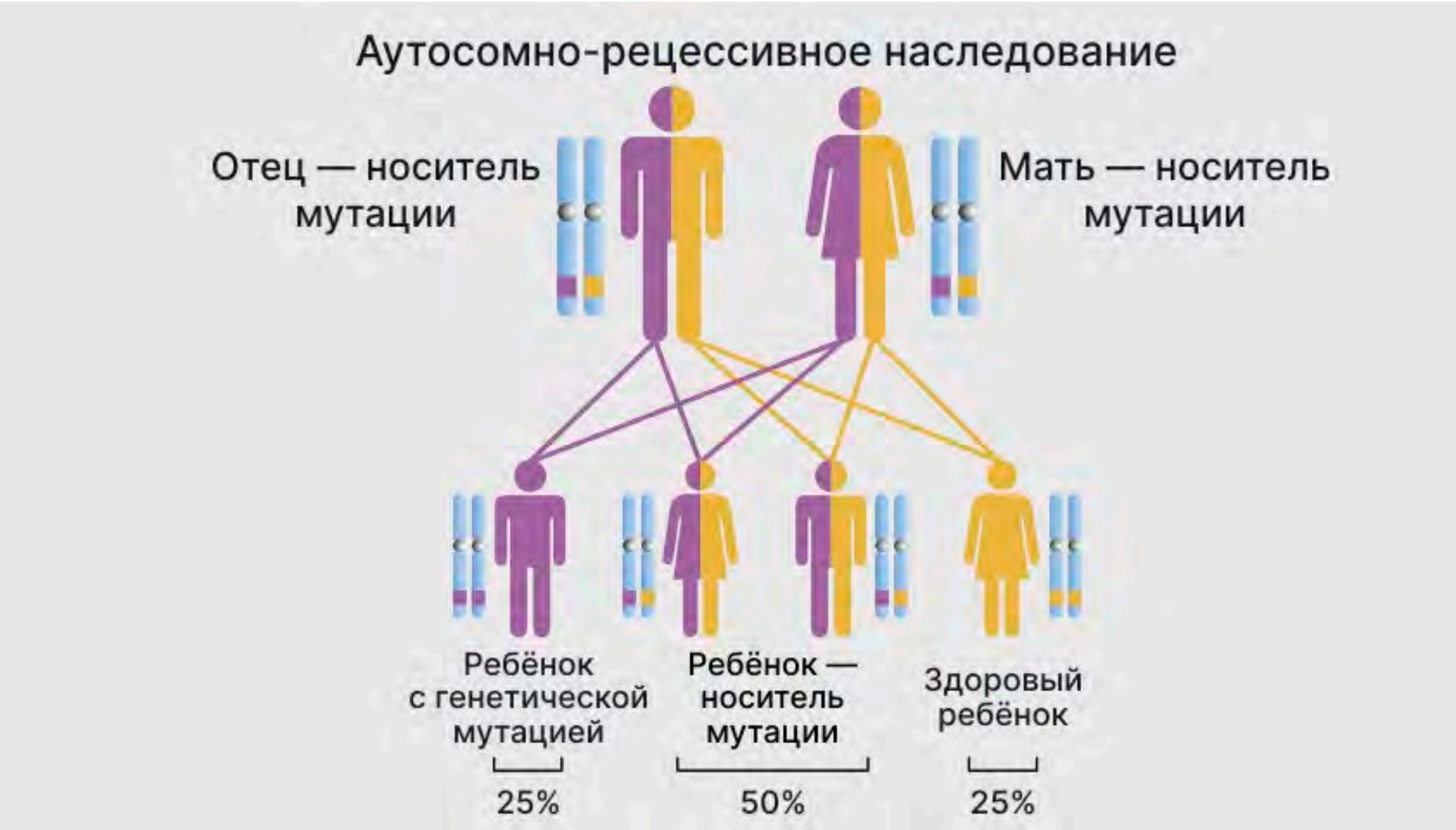
Важность генетических заболеваний



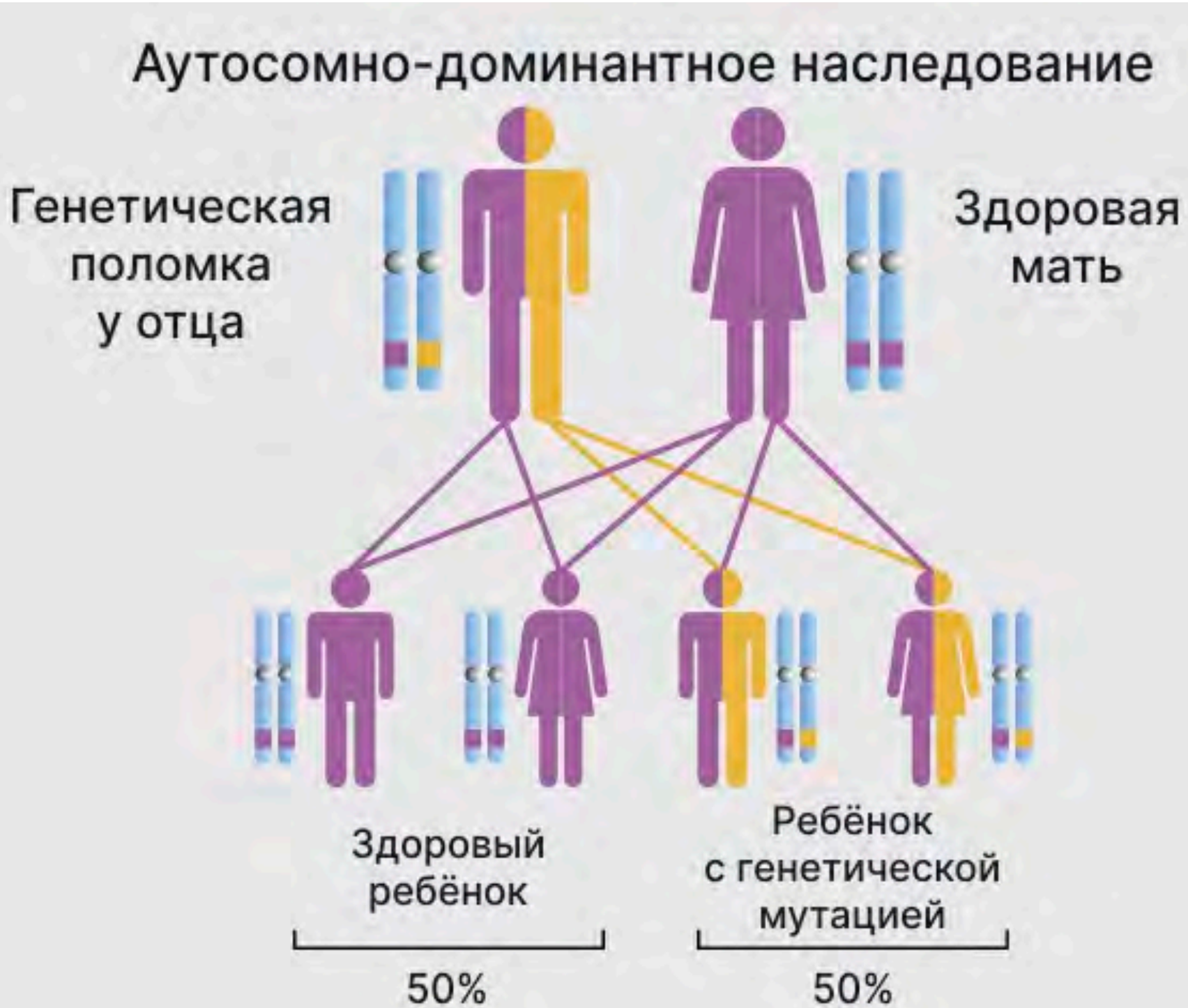
Классификация наследственных заболеваний



Моногенные заболевания



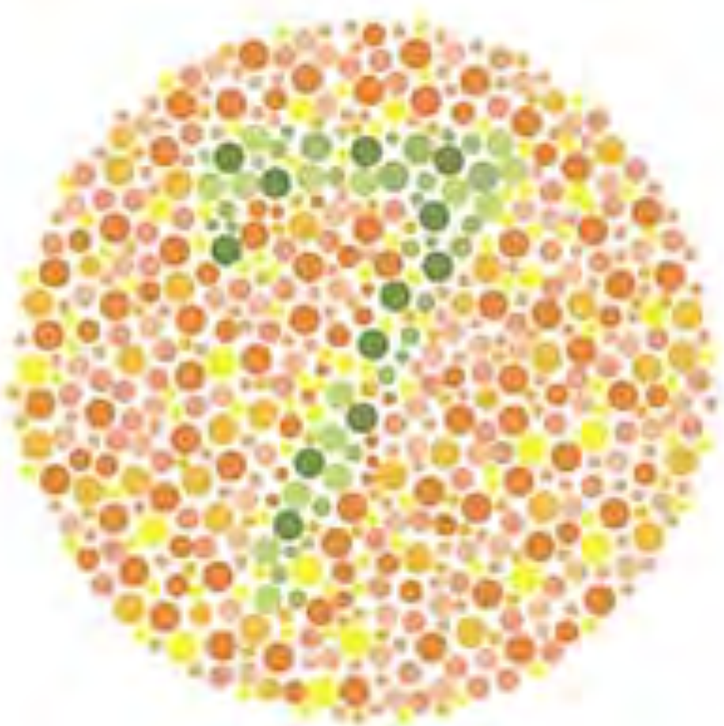
Моногенные заболевания

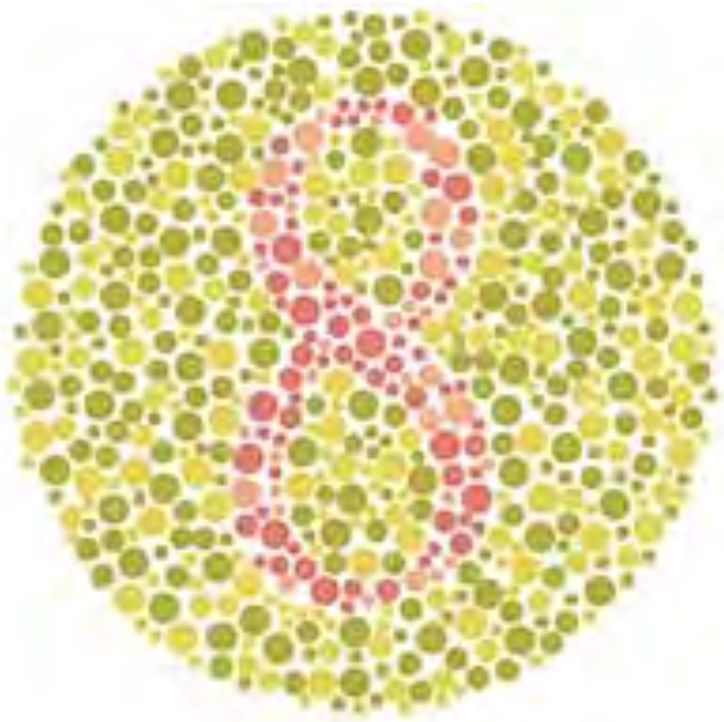
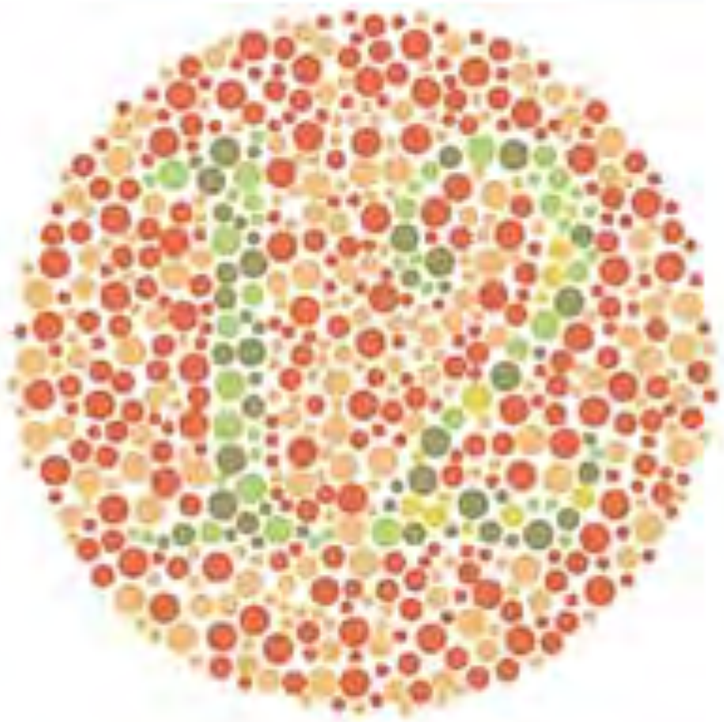
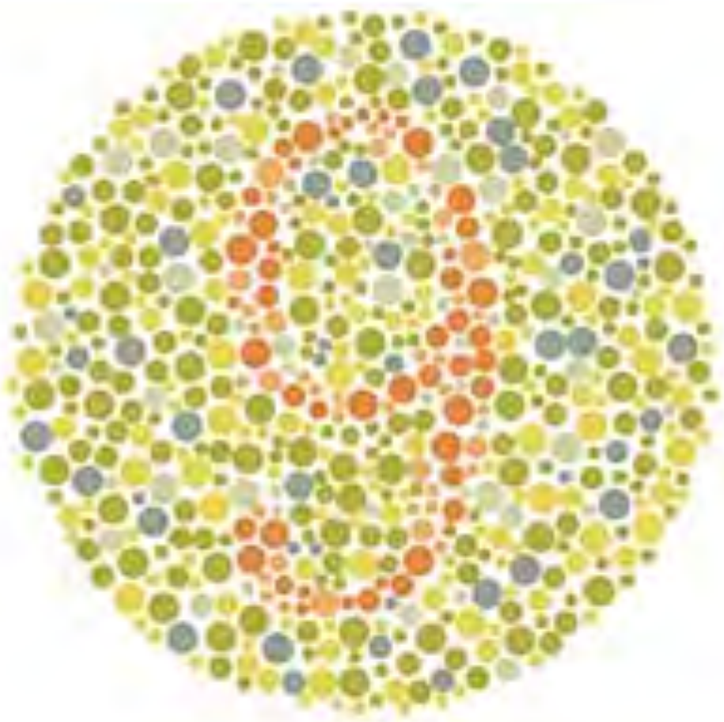


Примеры моногенных заболеваний

Наследственное заболевание	Средняя продолжительность жизни	Максимальная частота встречаемости
Муковисцидоз	18	1 : 10 000
Фенилкетонурия	70	1 : 7000
Несиндромальная форма снижения слуха	70	1 : 2000
Спинальная мышечная атрофия	10–12	1 : 10 000
Галактоземия	70	1 : 16 242
Адреногенитальный синдром	70	1 : 9500
Врождённый гипотиреоз	70	1:4000
Глутаровая ацидурия тип 1	6–70	1 : 50 000
Тирозинемия тип 1	1–60	1 : 120 000
Лейциноз	зависит от формы	1 : 120 000
Метилмалоновая/пропионовая ацидурия	3–70	1 : 75 000
Недостаточность биотинидазы	от нескольких недель до взрослого возраста	1 : 40 000
Недостаточность среднецепочечной ацил-КоА-дегидрогеназы жирных кислот	до 70	1 : 18 500

Сцепленное с полом наследование

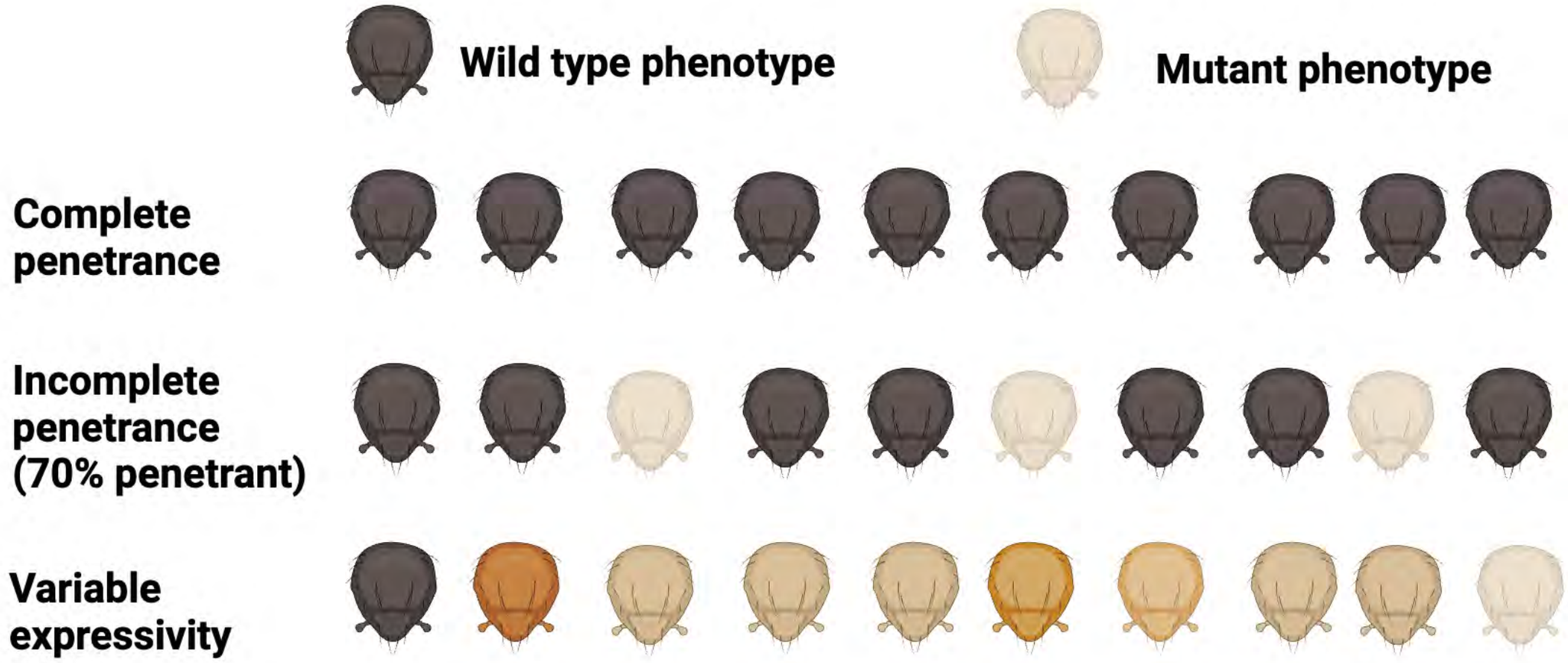


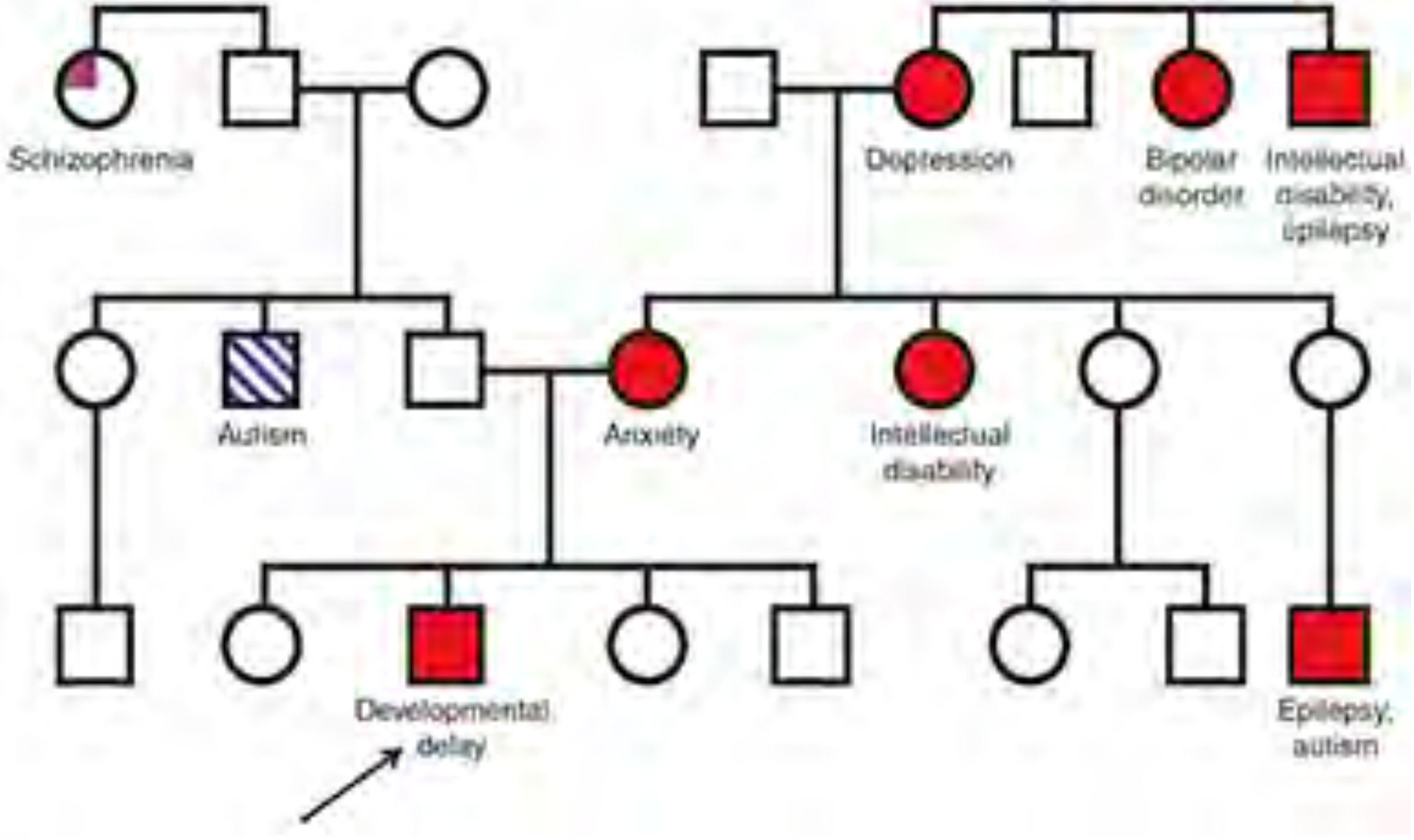
Сцепленное с полом наследование

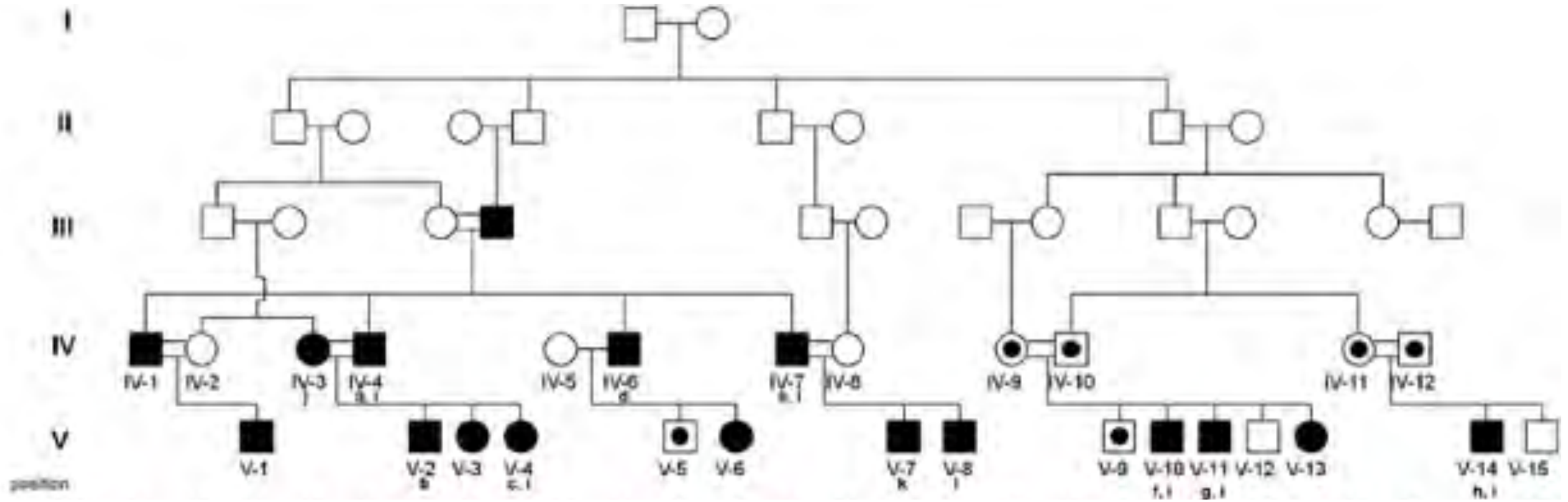
Тип наследования	Локализация генов	Примеры
X-сцепленный рецессивный	Негомологичный участок X-хромосомы	Гемофилия, разные формы цветовой слепоты, отсутствие потовых желез, некоторые формы мышечной дистрофии и пр.
X-сцепленный доминантный	Негомологичный участок X-хромосомы	Коричневый цвет зубной эмали, витамин D устойчивый рахит и пр.
Y-сцепленный	Негомологичный участок Y-хромосомы	Перепончатость пальцев ног, гипертрихоз края ушной раковины

Неполная пенетрантность и вариабельная экспрессивность



FMR1 expansions




I
II
III
IV
V
IV-1
IV-2
IV-3
IV-4
IV-5
IV-6
IV-7
IV-8
IV-9
IV-10
IV-11
IV-12
V-1
V-2
V-3
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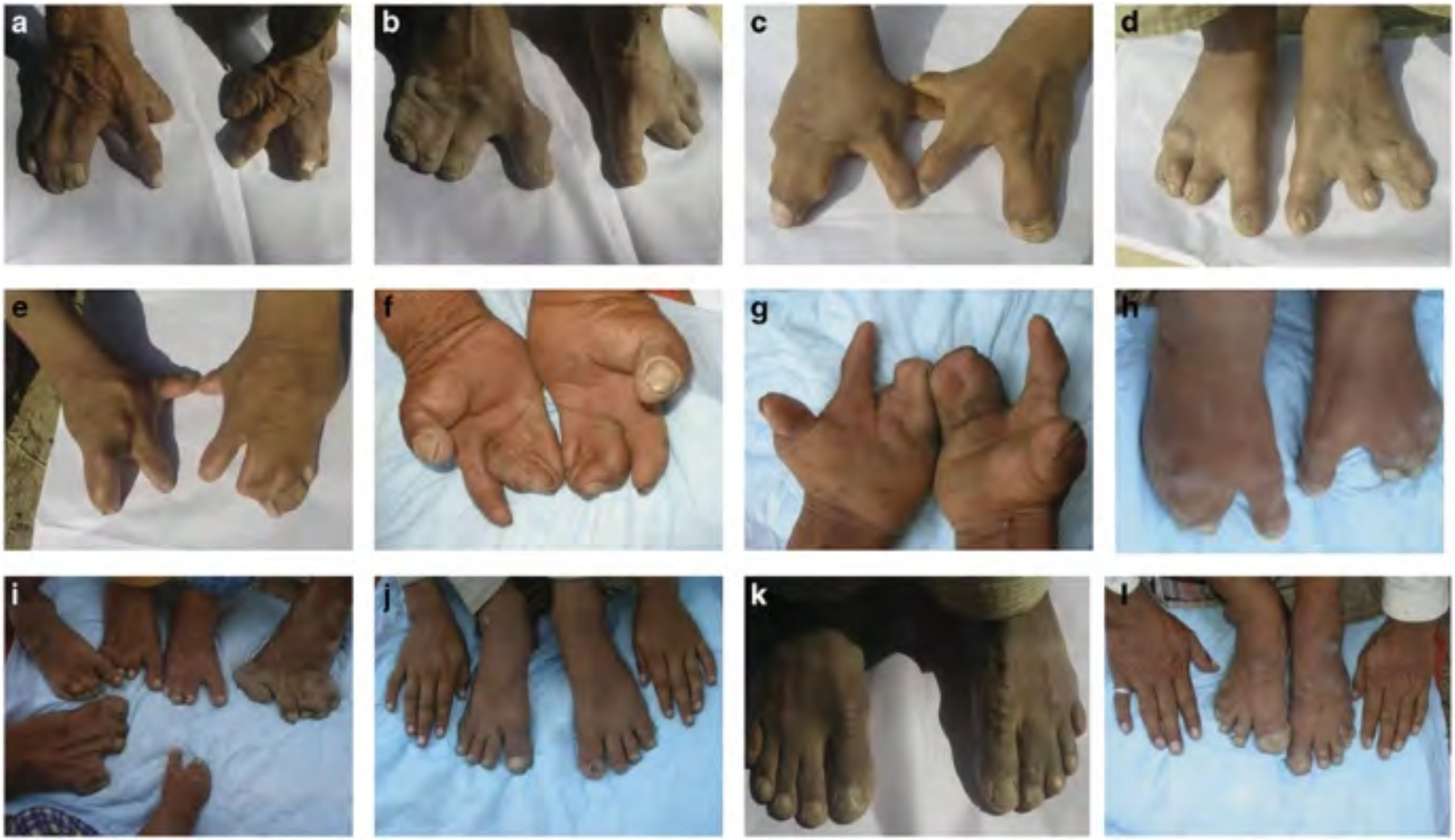
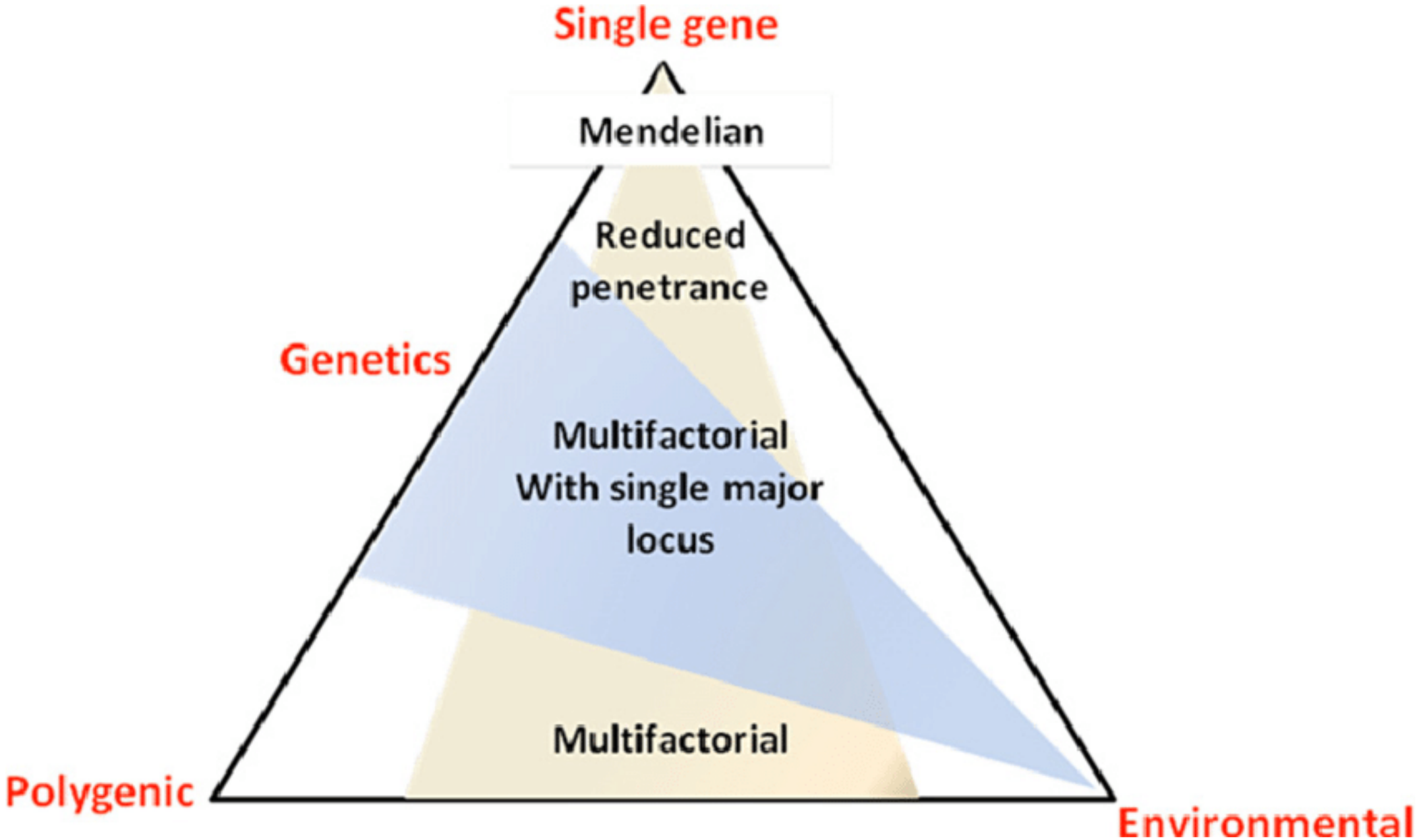
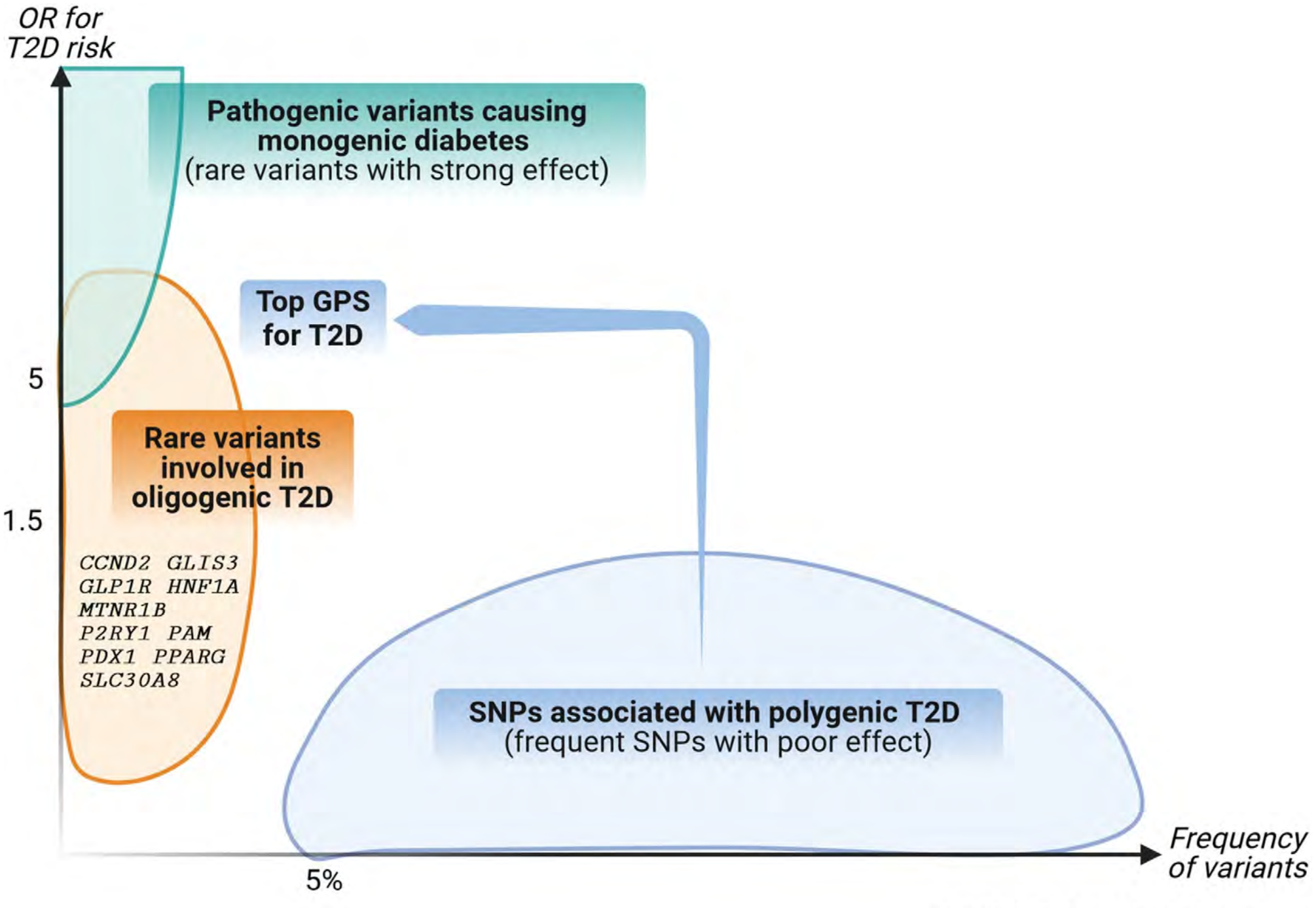
V-10
V-11
V-12
V-13
V-14
V-15


a
b
c
d
e
f
g
h
i
j
k
l

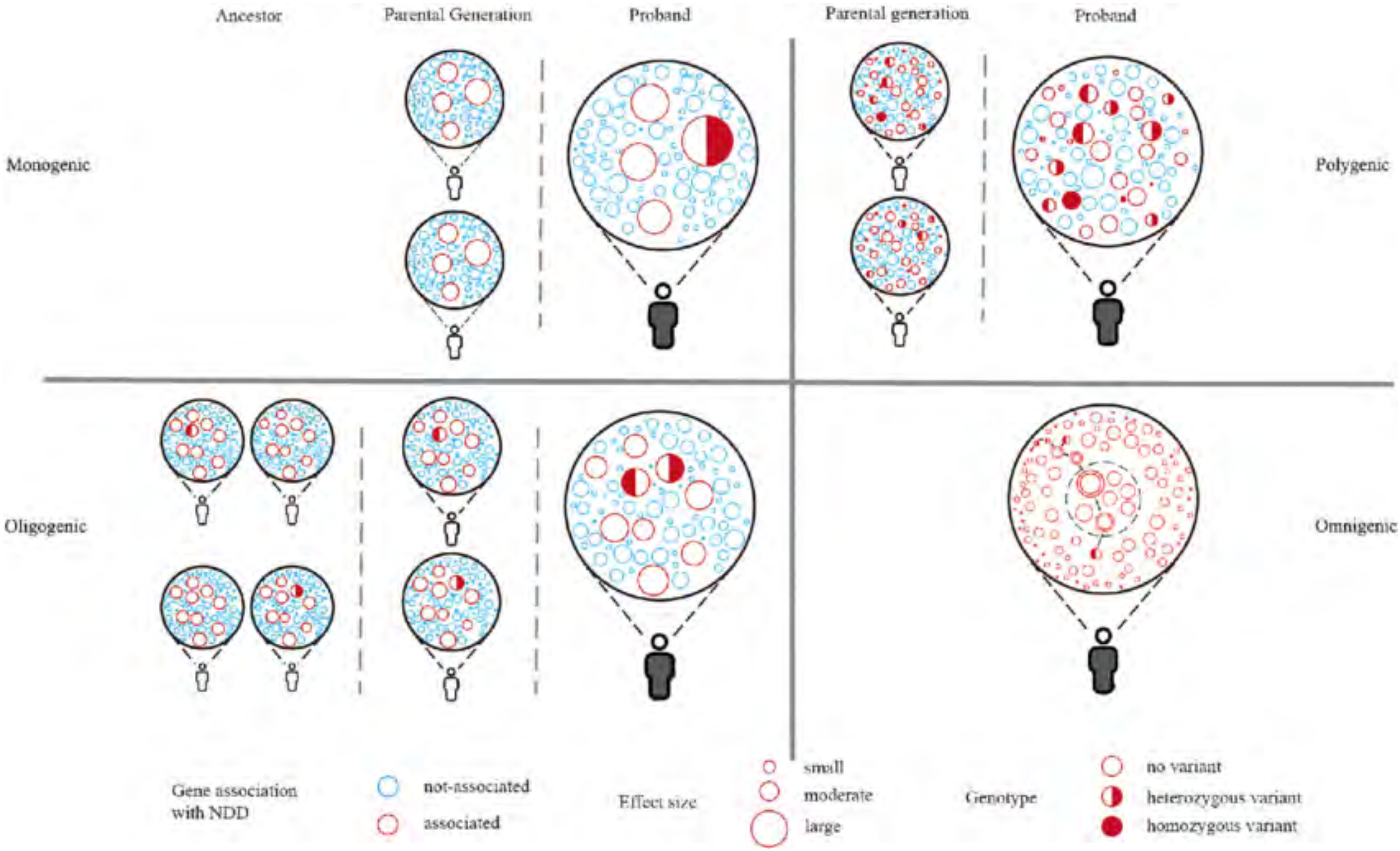
Классификация наследственных заболеваний



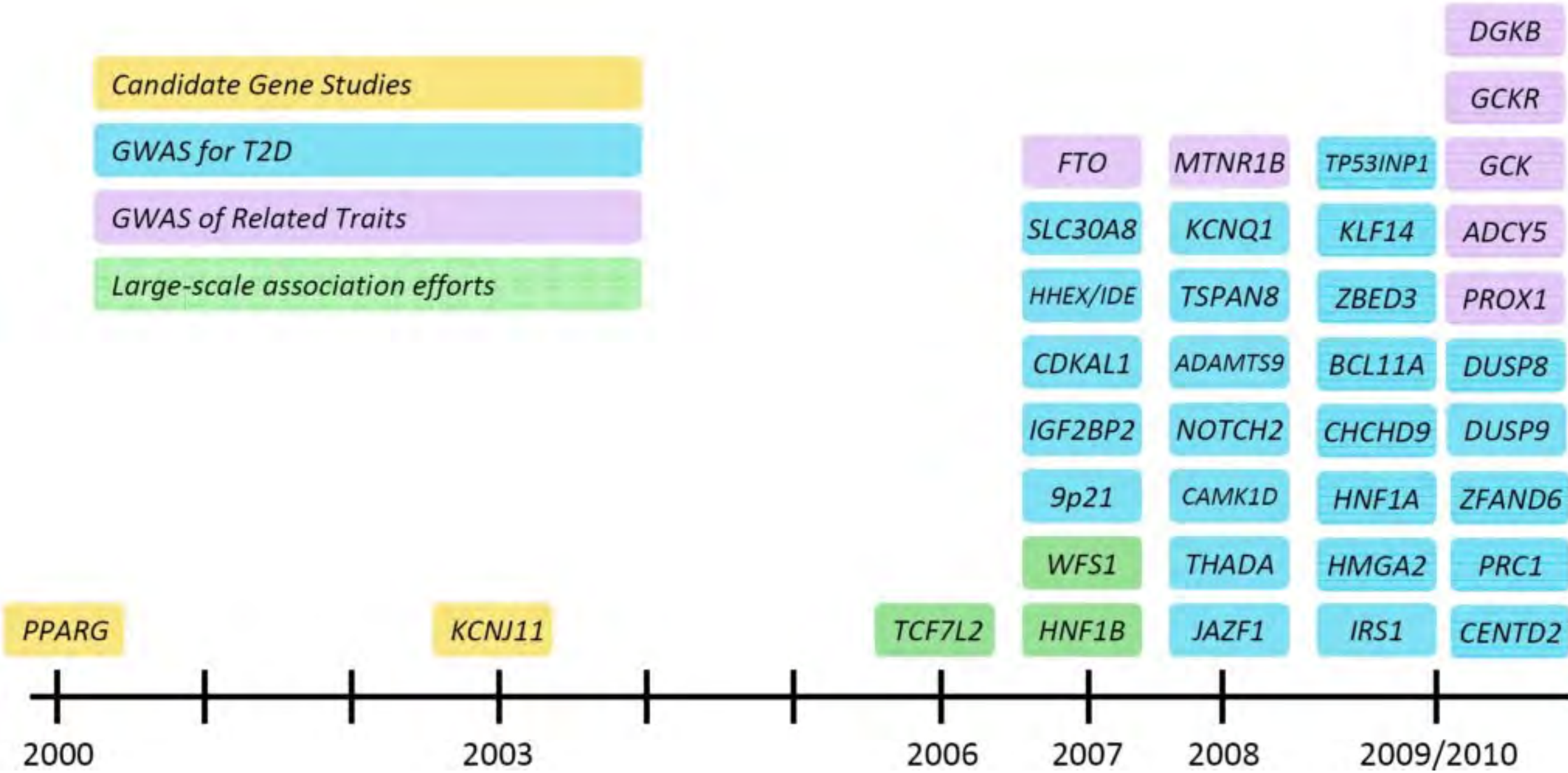
Олигогенные заболевания



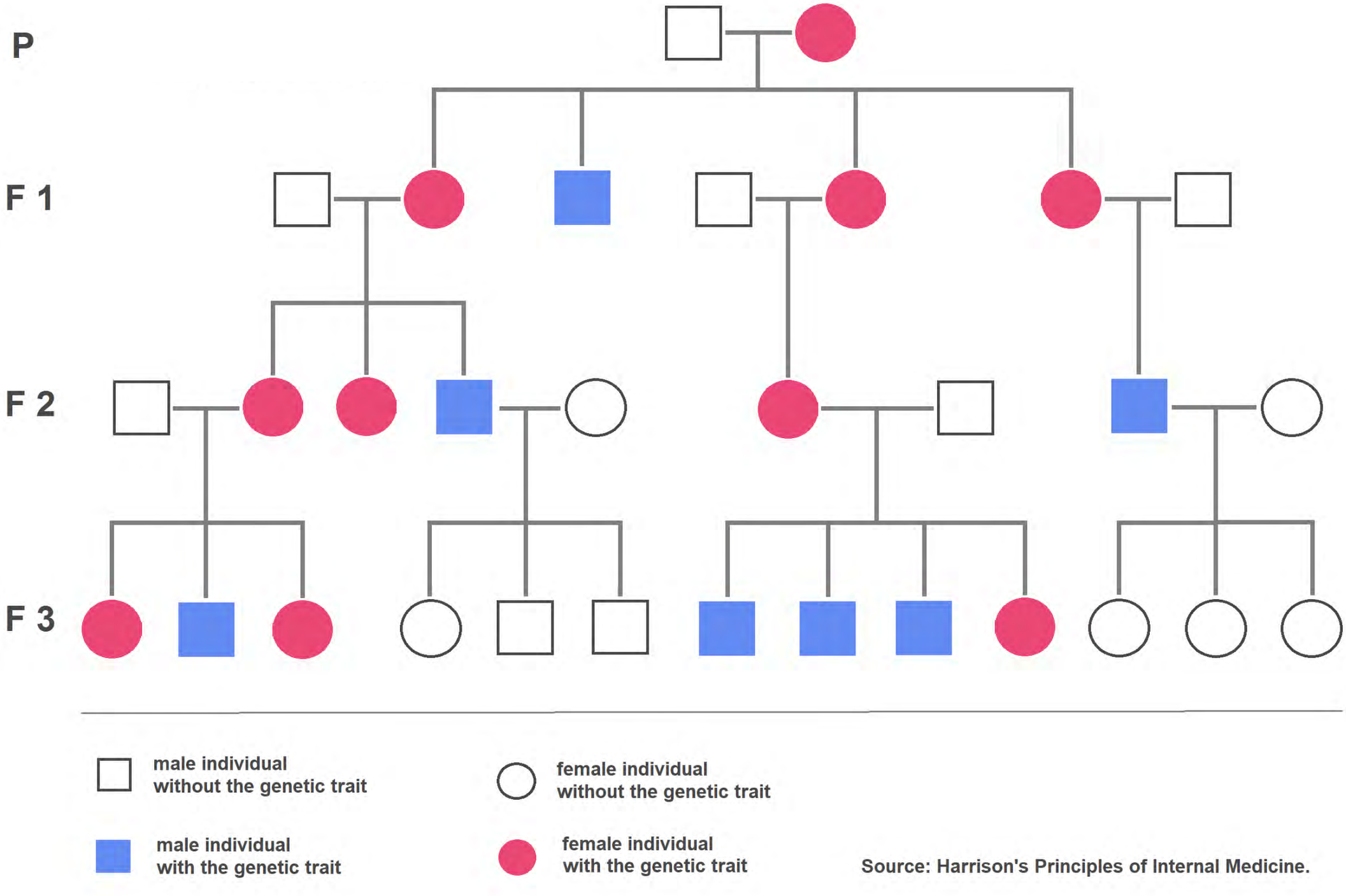
Полигенные заболевания



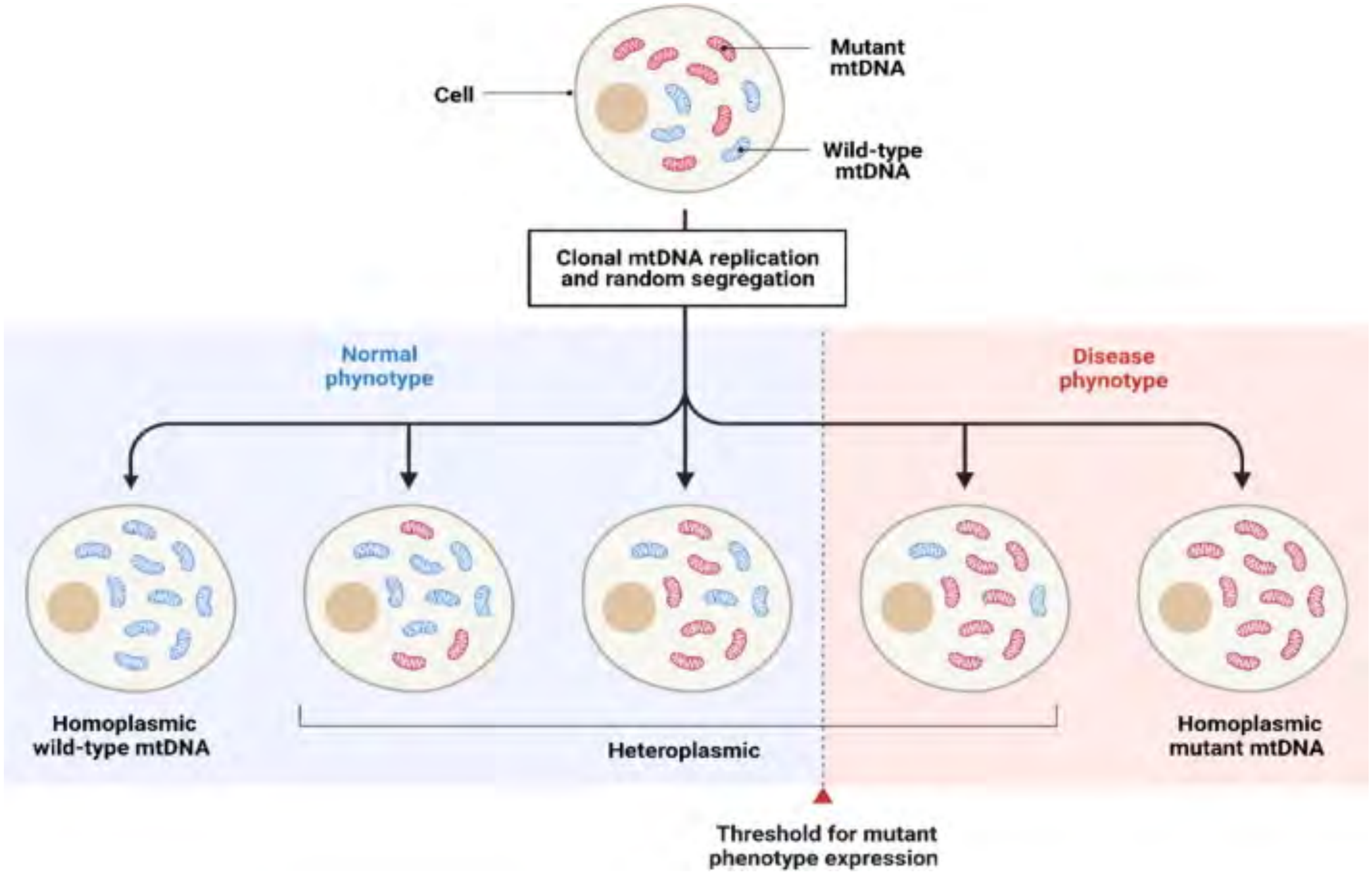
Диабет 2 типа — полигенное заболевание



Митохондриальные заболевания



Митохондриальные заболевания



Mutations

Point

Affect one or more nucleotides

- **According to the effect on the amino acid sequence**
  - Synonymous or silent — Coding for the same original amino acid
  - Without sense — Coding for a smaller protein (usually non-functional)
  - Missense — Coding for another amino acid
- **According to the change in the type of nucleotides**
  - Substitution
    - Transitions
    - Transversions
  - Deficiency or deletion
  - Insertions or additions
- **Depending on the affected site**
  - Regions associated with RNA processing
  - Coding regions

Chromosomal or structural

Affect chromosome structure

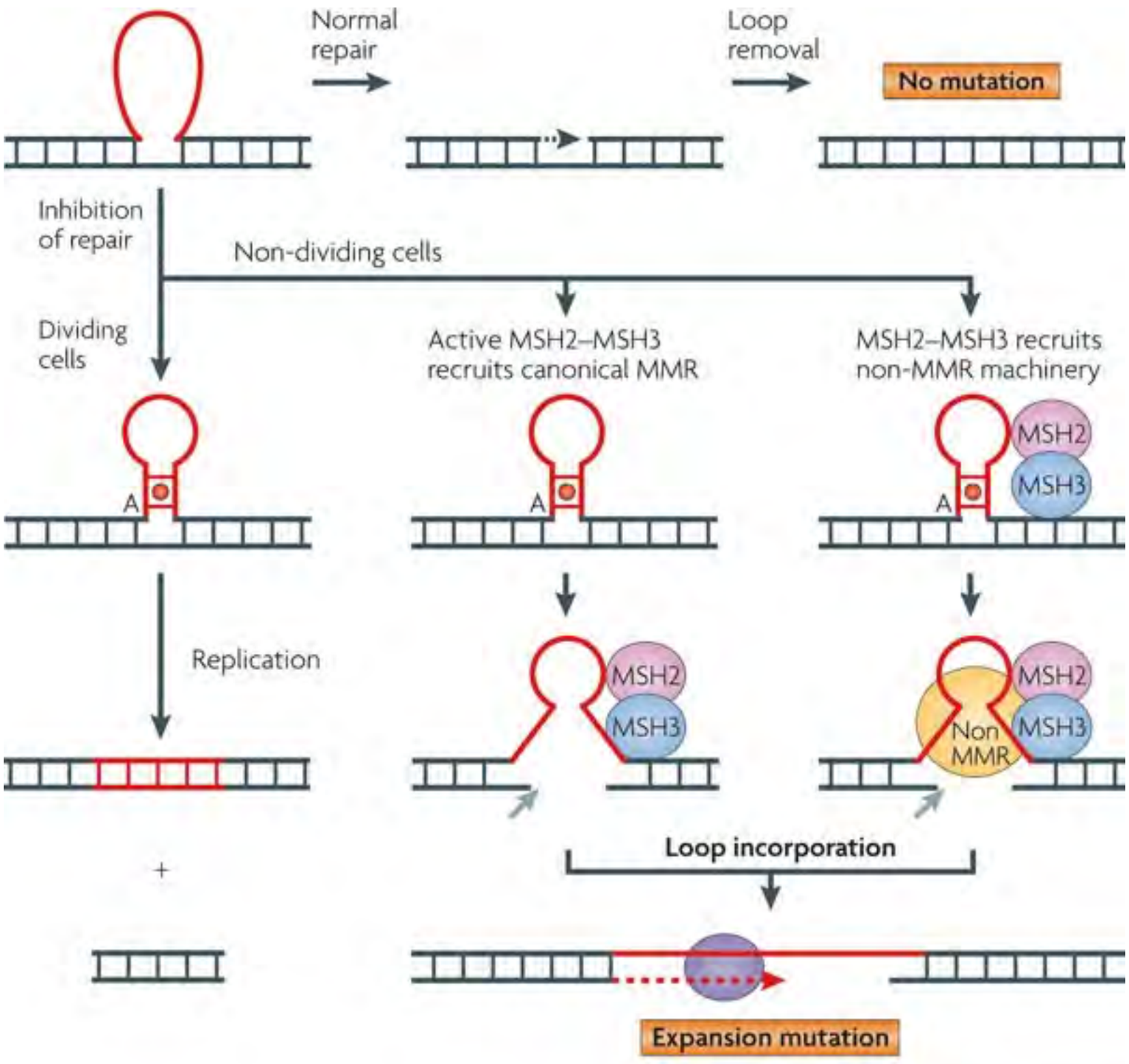
- Deletion
- Ring chromosomes
- Duplication
- Inversion
- Translocation

Genomic or numeric

Affect the number of chromosomes

- Aneuploidy
  - Monosomy
  - Trisomy
- Polyploidies

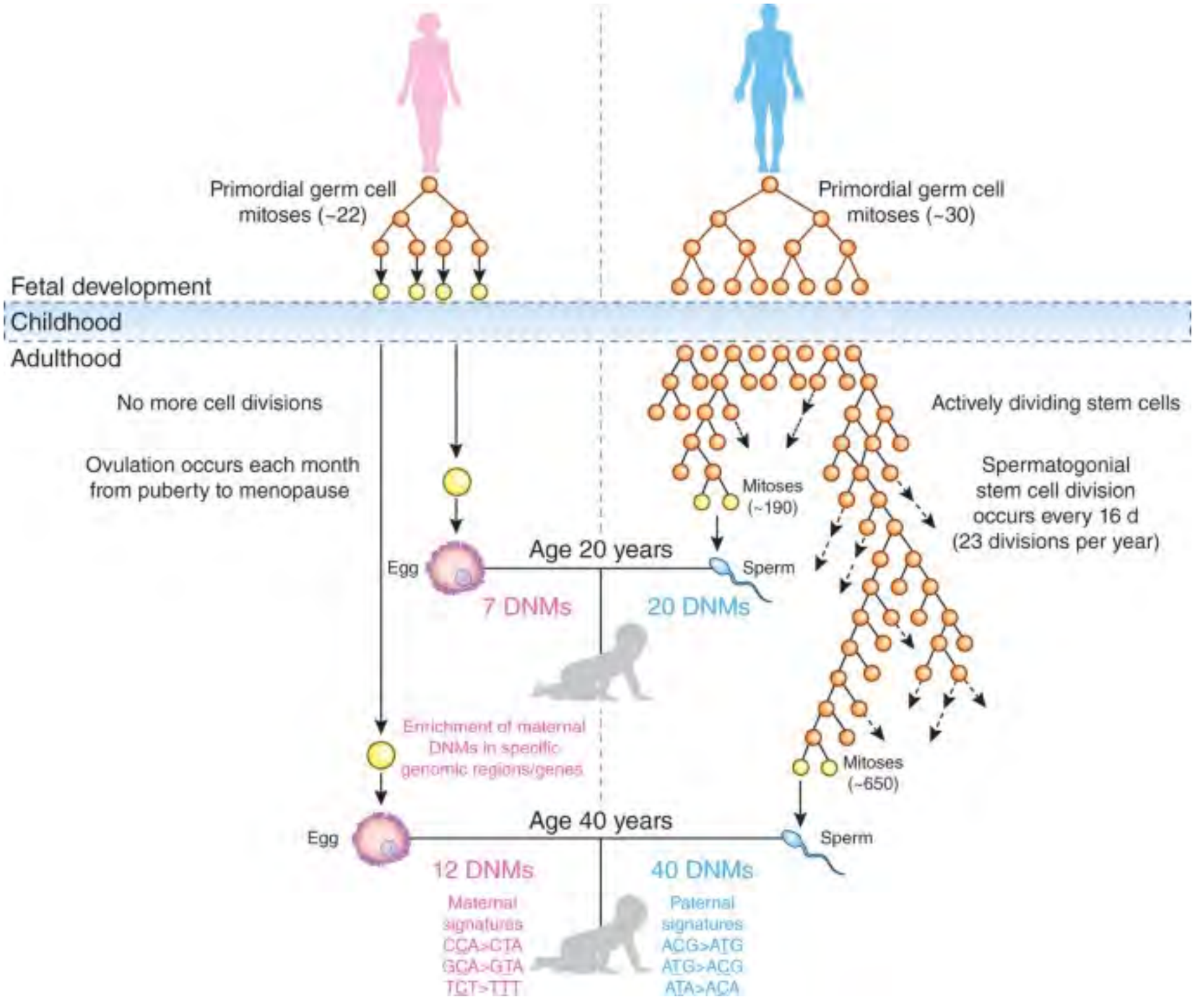
Динамические мутации



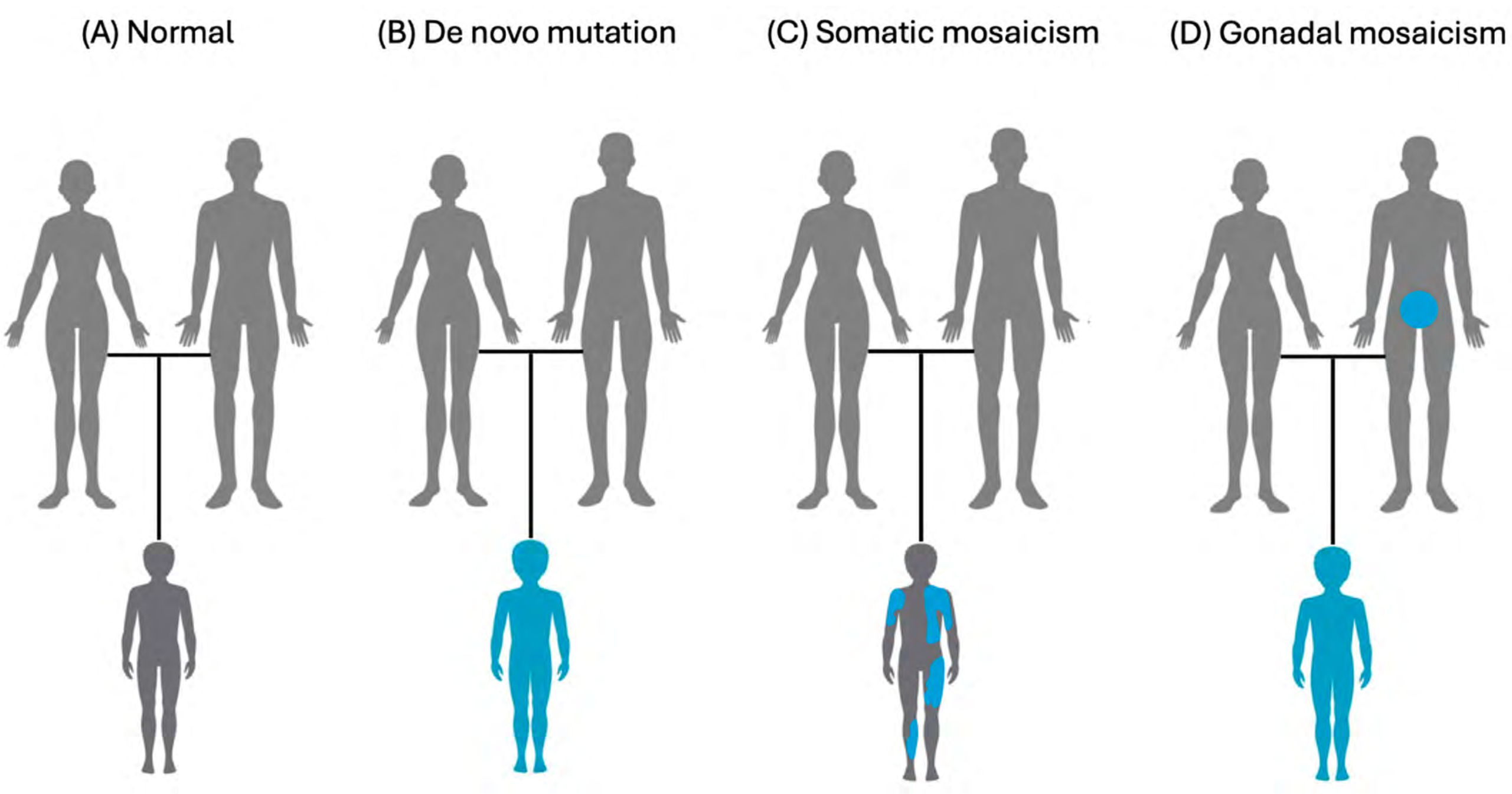
Динамические мутации

Disease	Repeated sequence	Number of copies of repeat	
		Normal range	Disease range
Spinal and bulbar muscular atrophy	CAG	11–33	40–62
Fragile-X syndrome	CGG	6–54	50–1500
Jacobsen syndrome	CGG	11	100–1000
Spinocerebellar ataxia (several types)	CAG	4–44	21–130
Autosomal dominant cerebellar ataxia	CAG	7–19	37–~220
Myotonic dystrophy	CTG	5–37	44–3000
Huntington disease	CAG	9–37	37–121
Friedreich ataxia	GAA	6–29	200–900
Dentatorubral-pallidoluysian atrophy	CAG	7–25	49–75
Myoclonus epilepsy of the Unverricht-Lundborg type*	CCCCGCCCCGCG	2–3	12–13

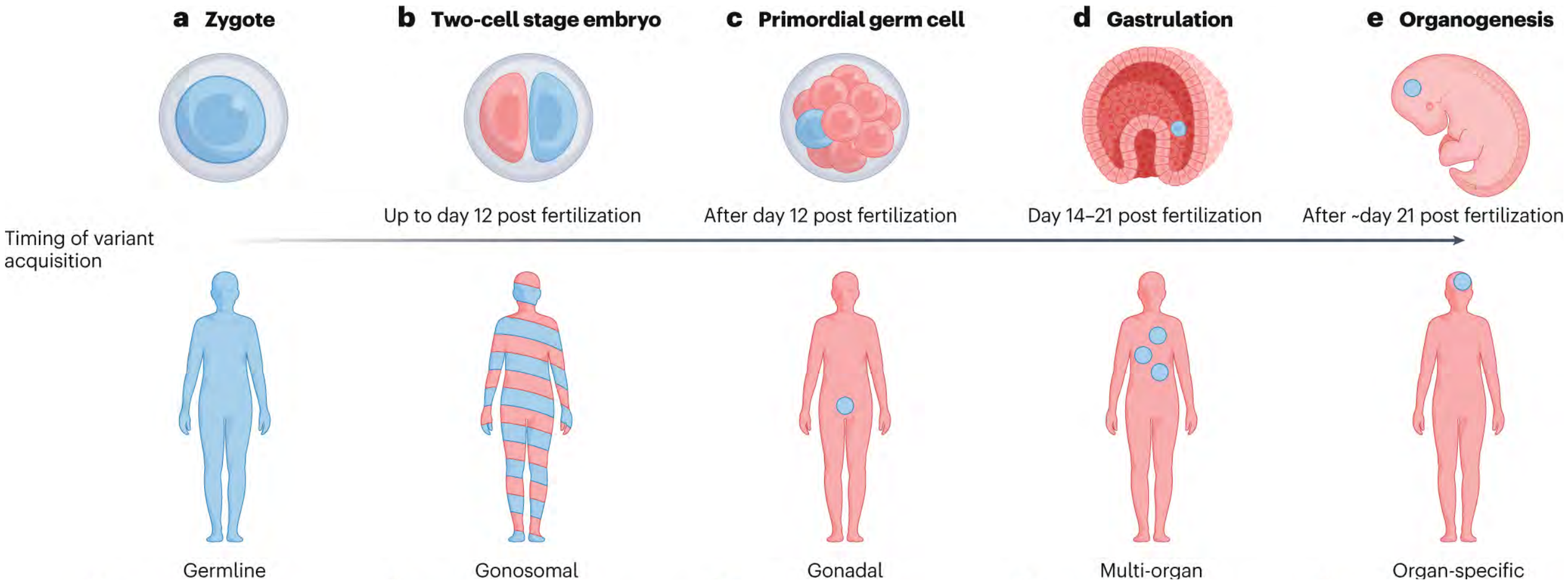
Мутации de novo



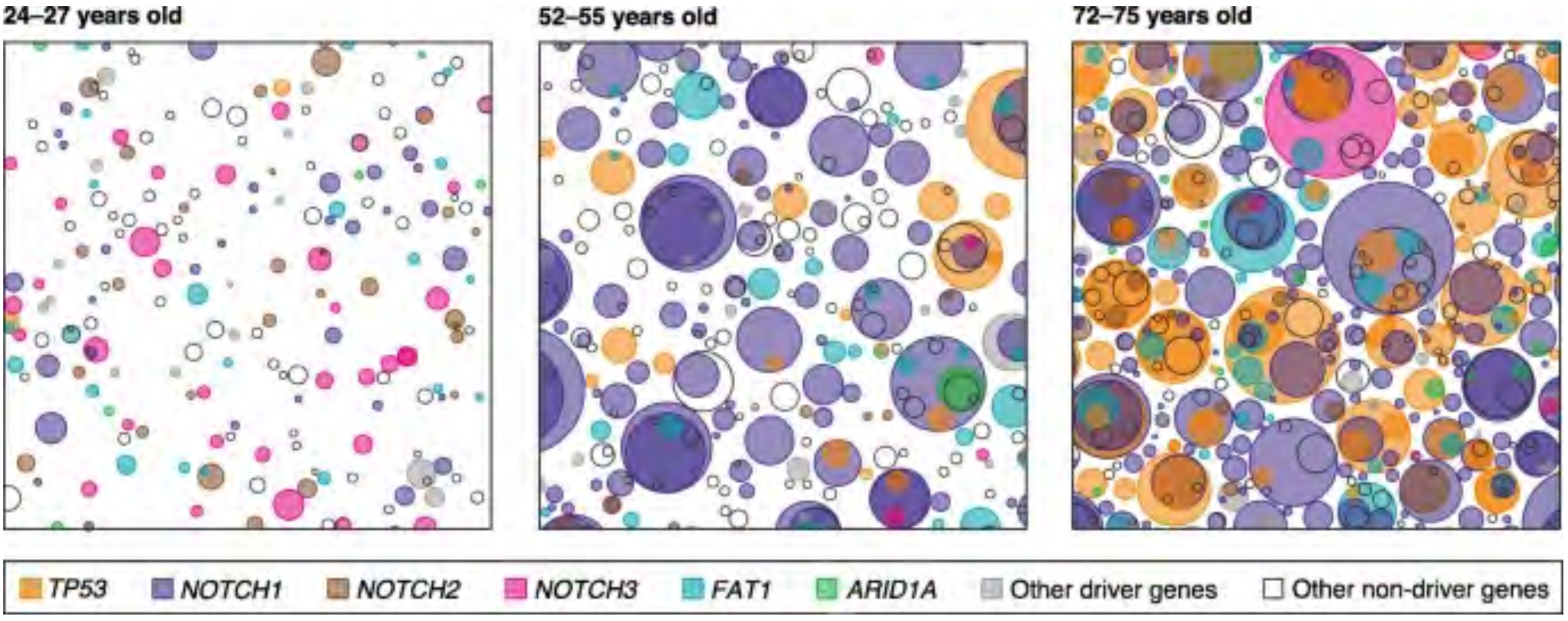
Мозаицизм


(A) Normal
(B) De novo mutation
(C) Somatic mosaicism
(D) Gonadal mosaicism

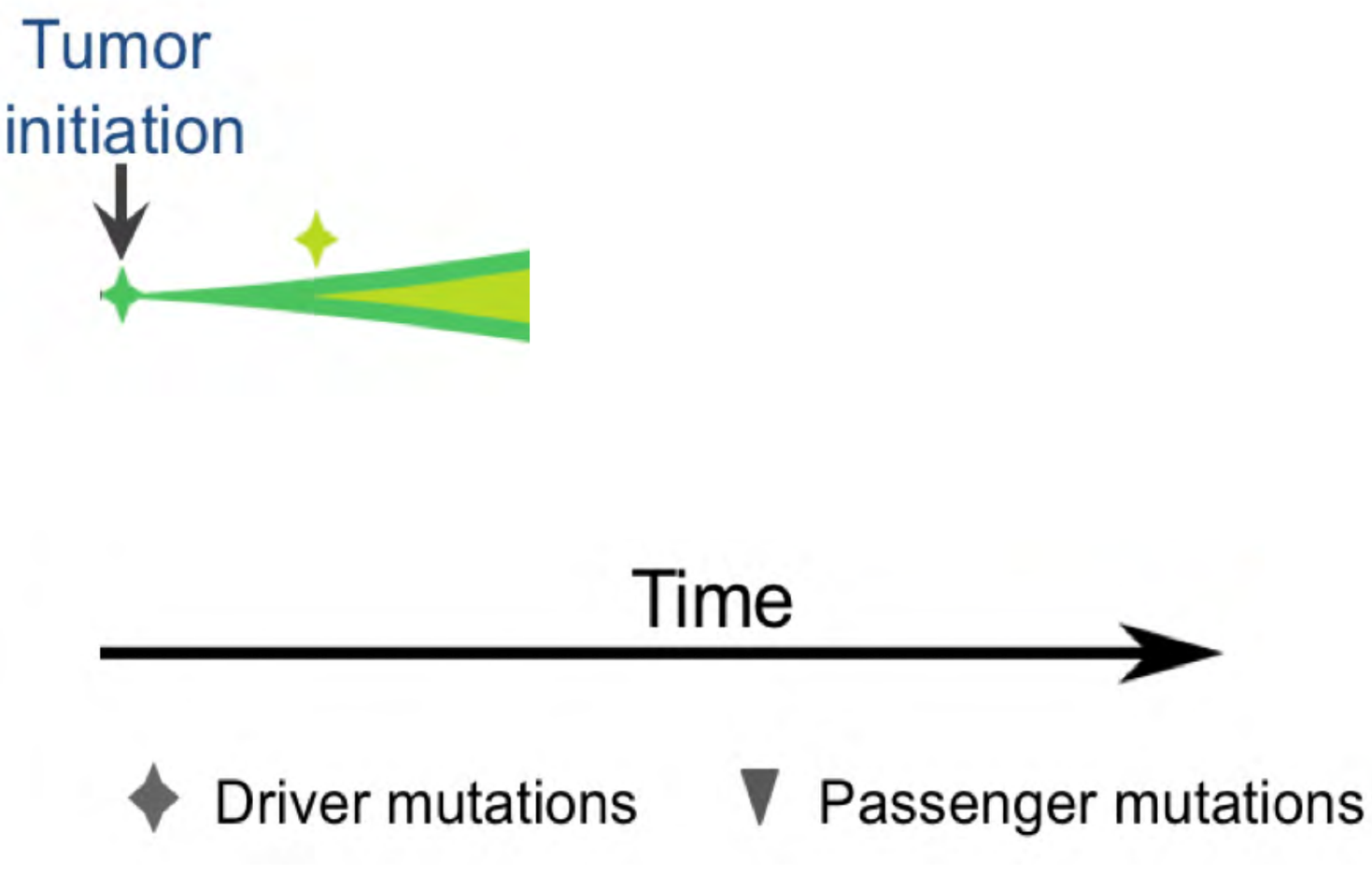
Мозаицизм


a Zygote
b Two-cell stage embryo
c Primordial germ cell
d Gastrulation
e Organogenesis
Timing of variant acquisition
Up to day 12 post fertilization
After day 12 post fertilization
Day 14–21 post fertilization
After ~day 21 post fertilization
Germline
Gonosomal
Gonadal
Multi-organ
Organ-specific

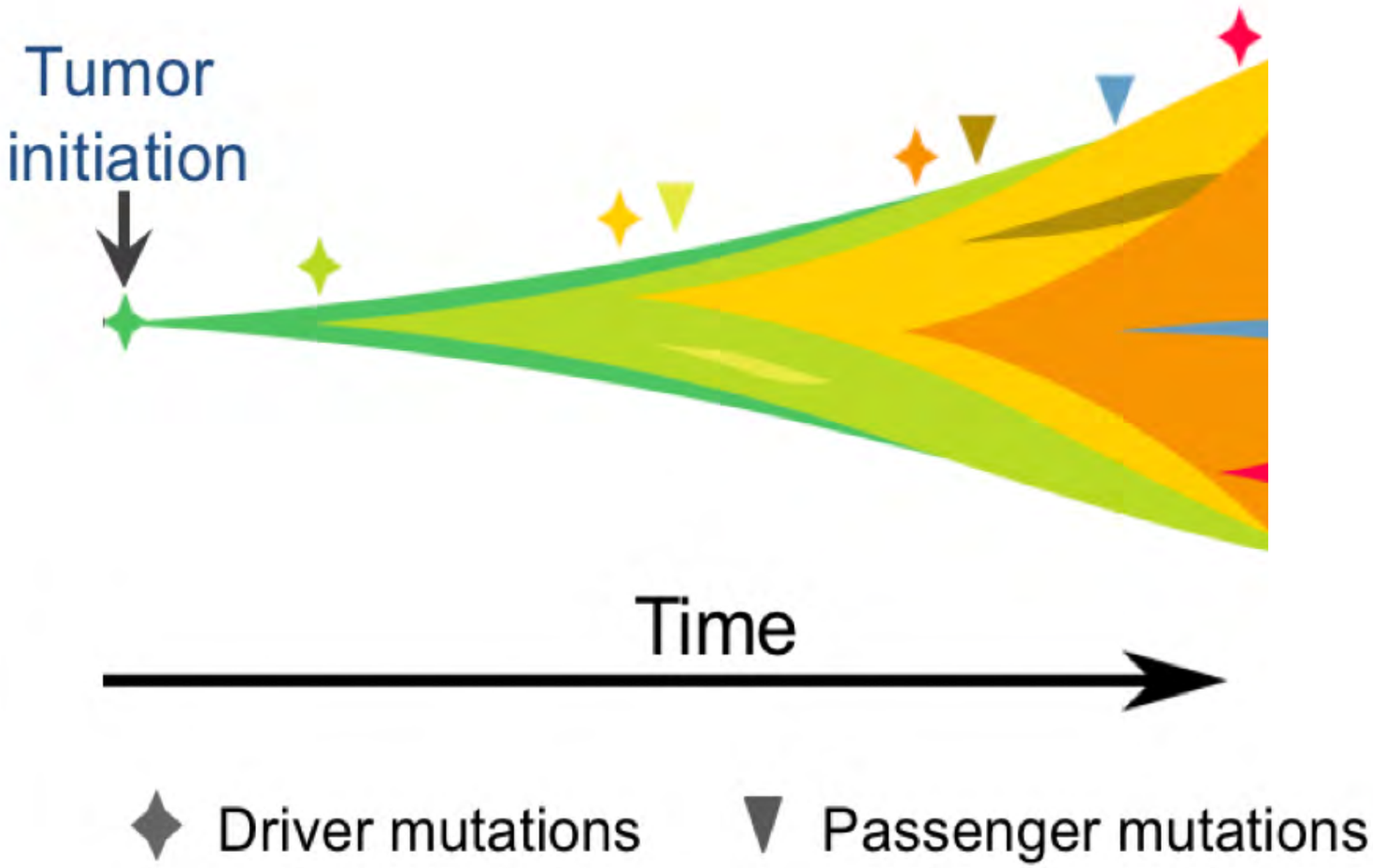
Соматические мутации



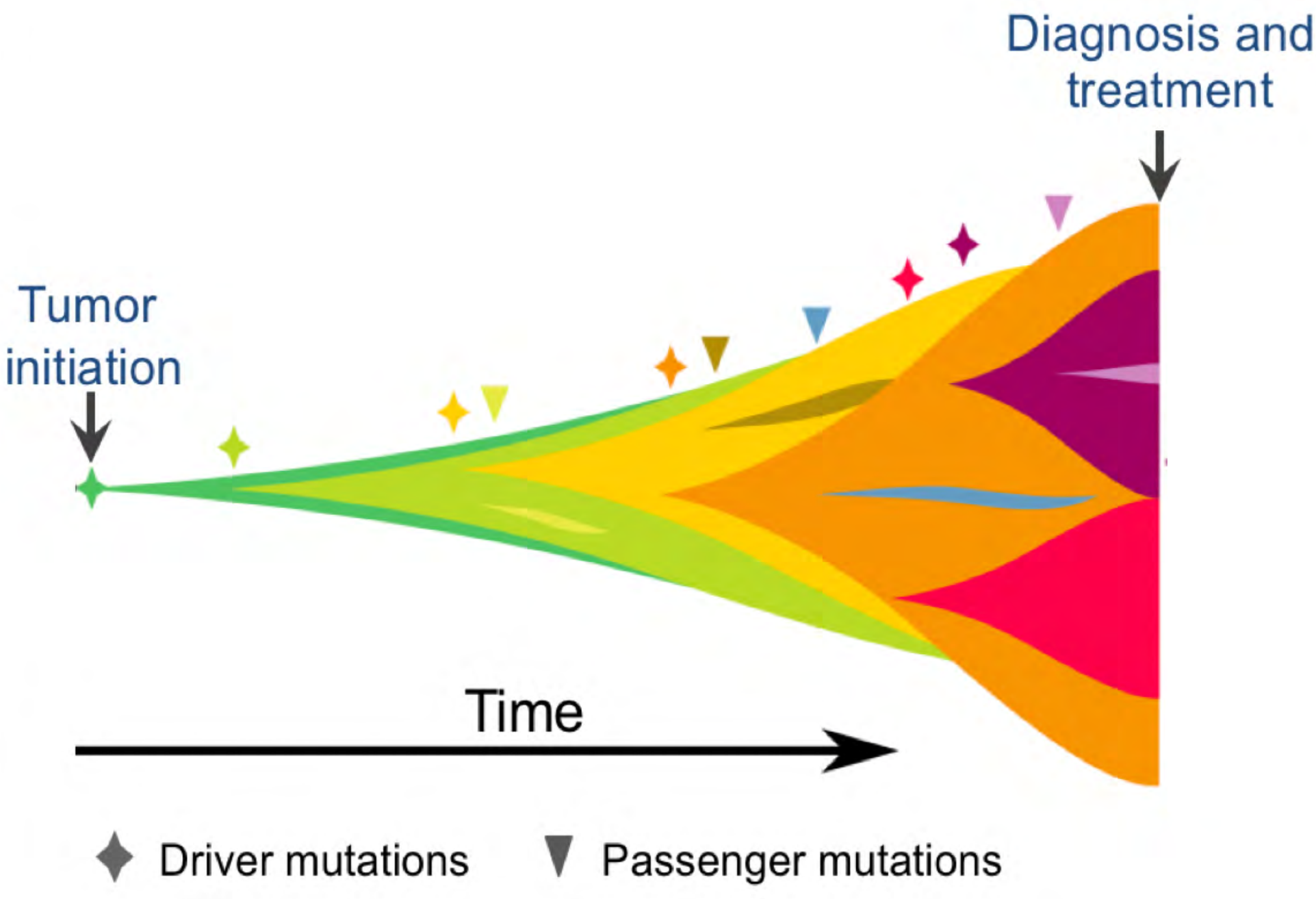
Соматические мутации



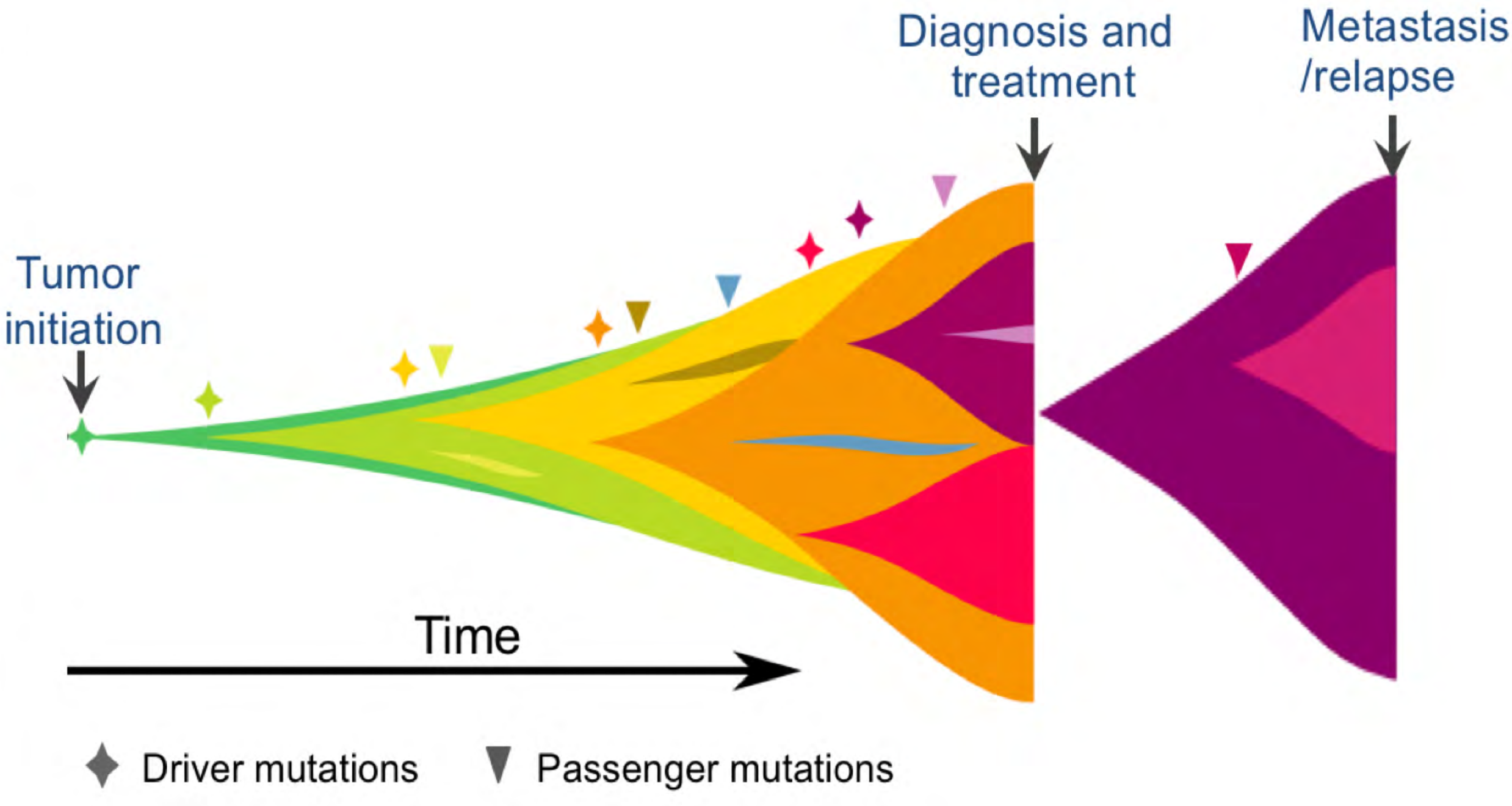
Соматические мутации



Соматические мутации

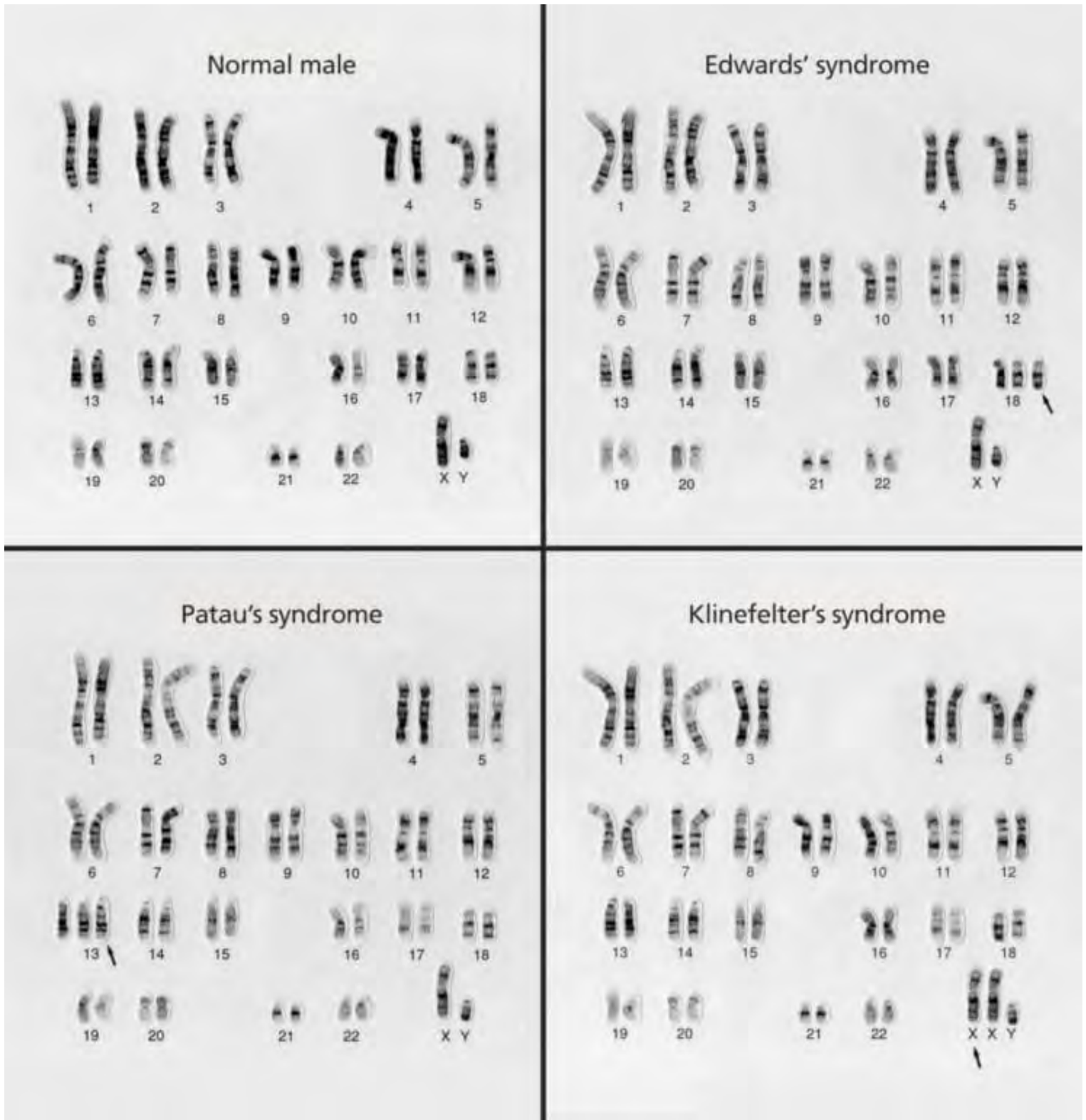


Соматические мутации

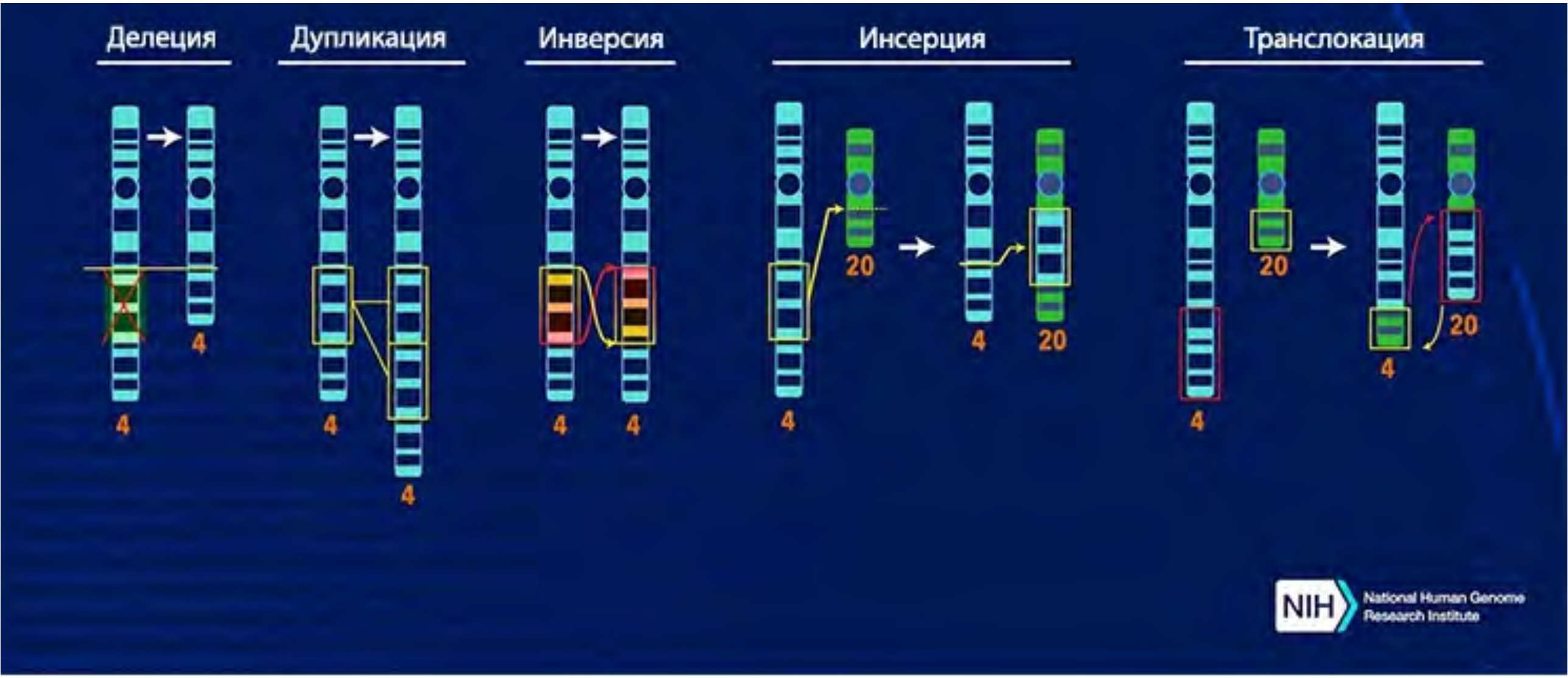


Хромосомные аномалии

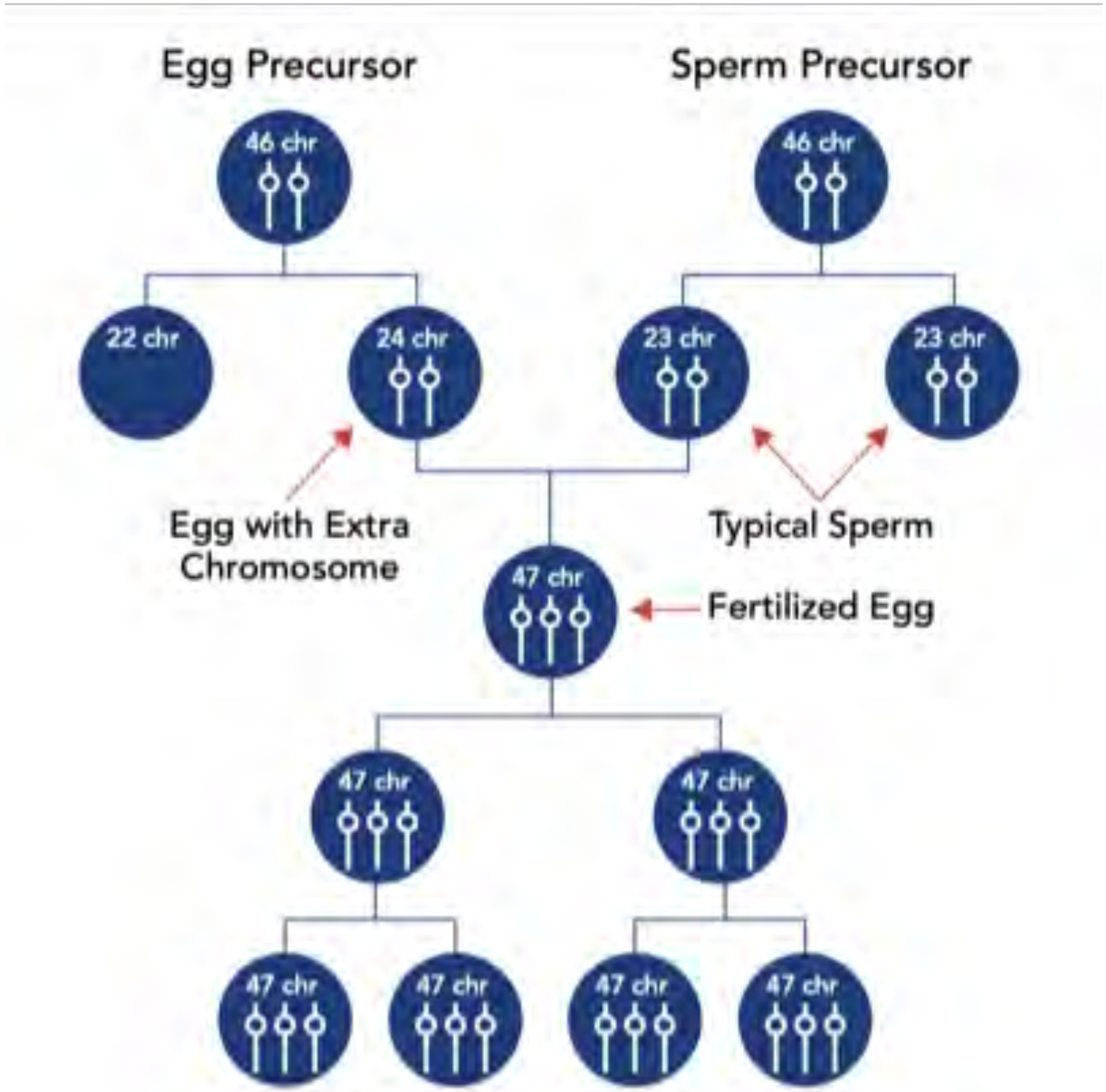
Трисомии


Normal male
Edwards' syndrome
Patau's syndrome
Klinefelter's syndrome

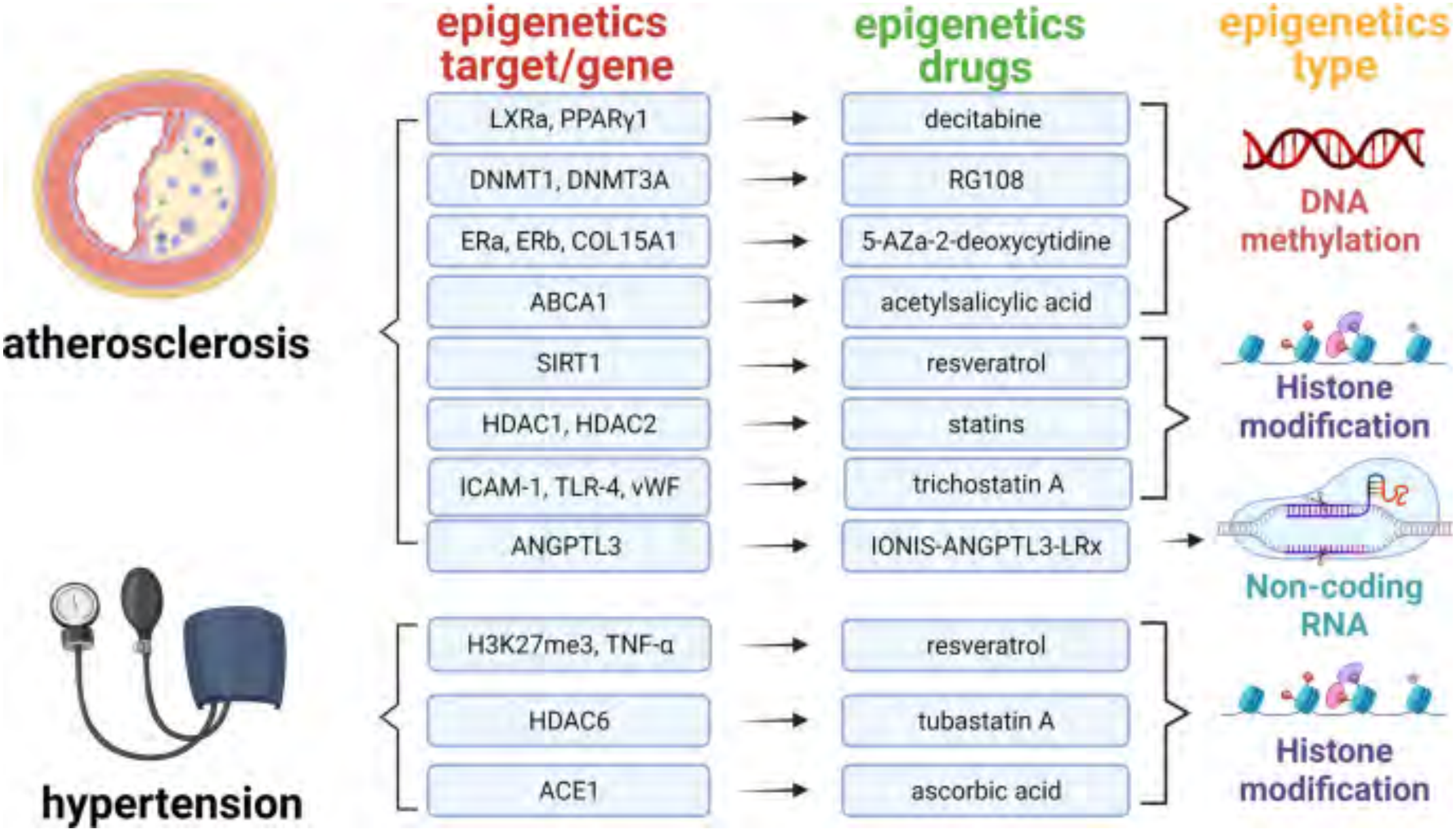
Структурные аномалии хромосом



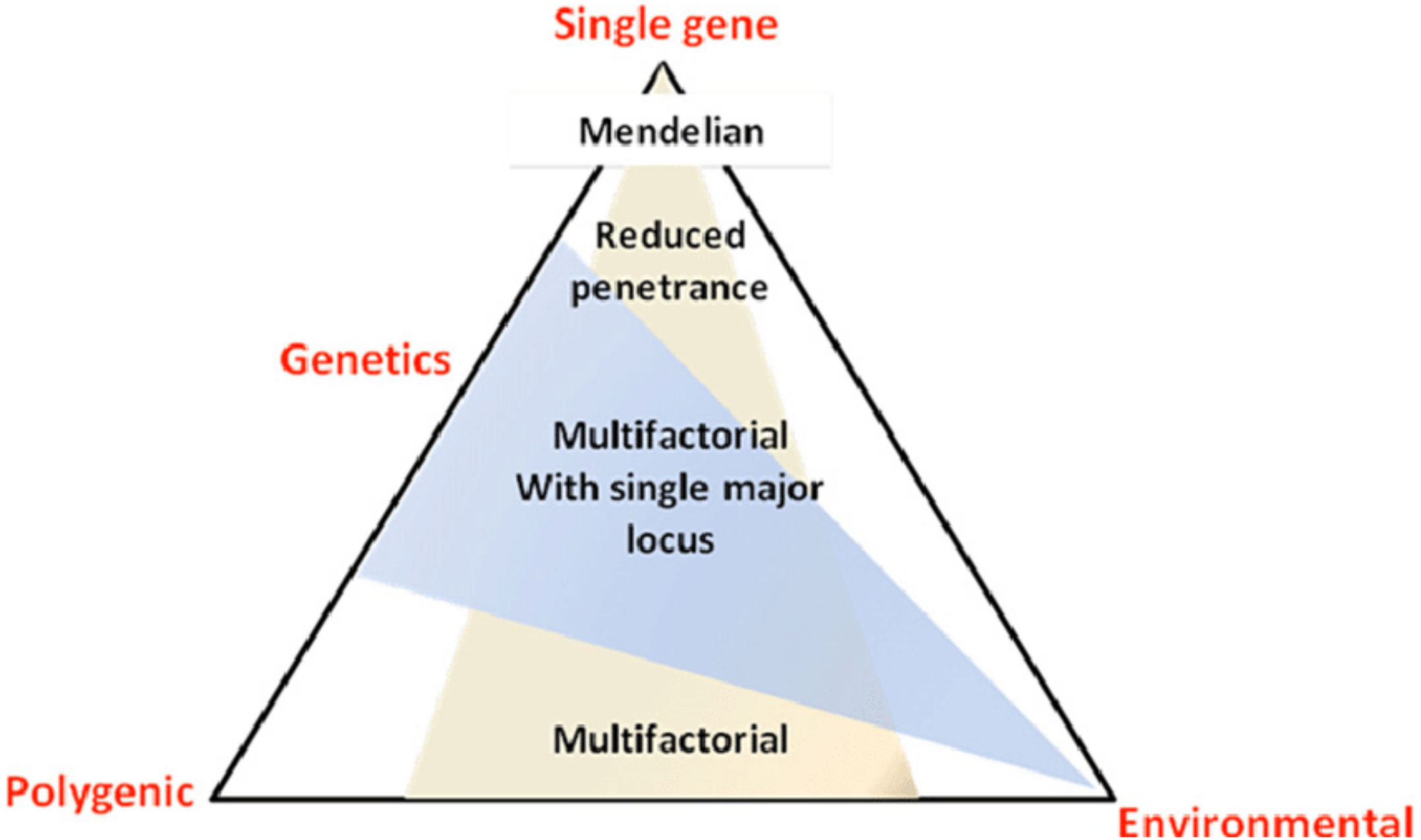
Синдром Дауна



Эпигенетические изменения



Классификация наследственных заболеваний



Ген-генные взаимодействия (эпистаз)

Доминантный эпистаз

A – оранжевая окраска
a – зелёная окраска

I – эпистатичный ген
i – не влияет на окраску

P:  x 

Aali Aali

F_1:   

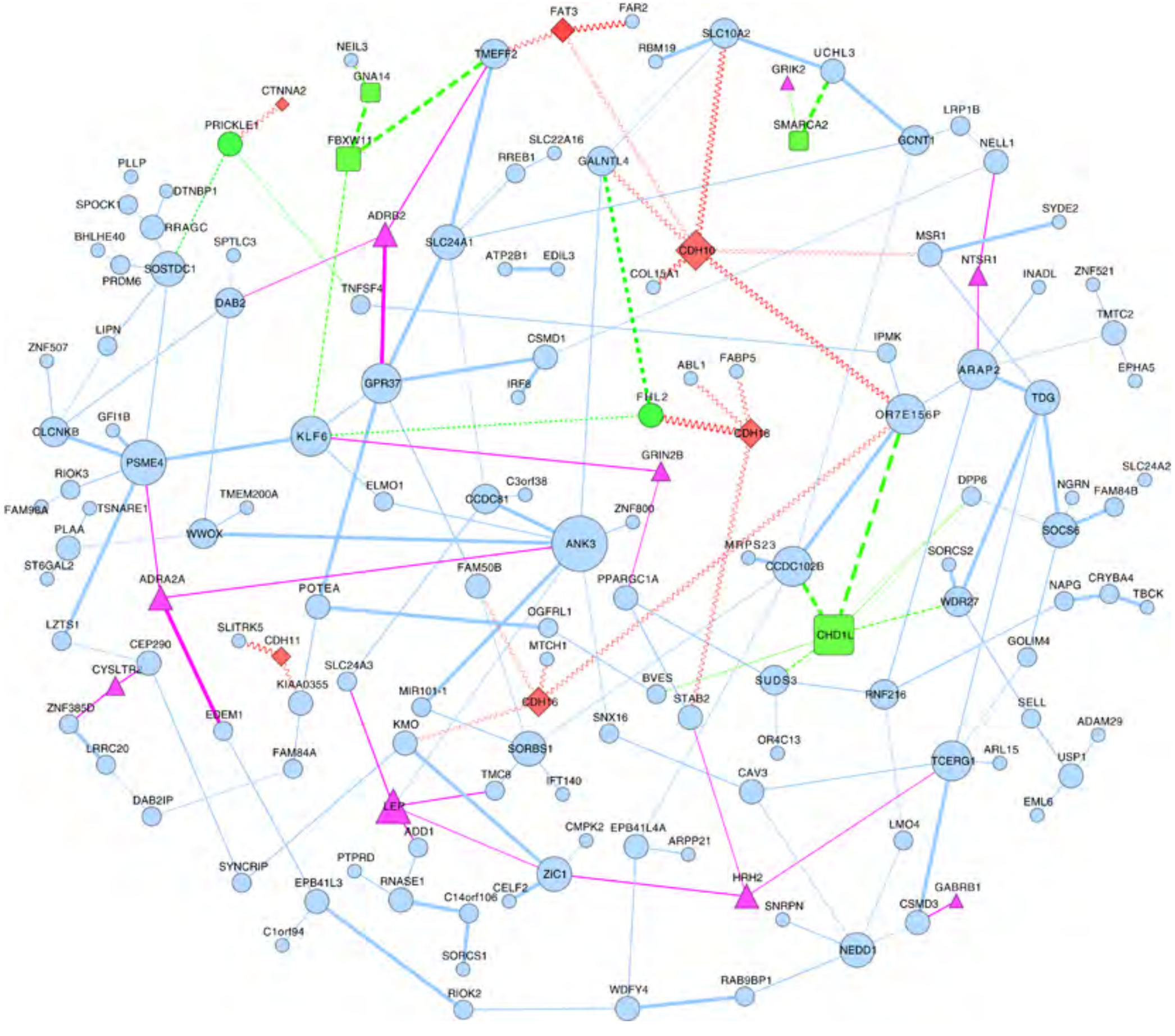
Подавляют синтез пигмента

Ген A даёт оранжевую окраску

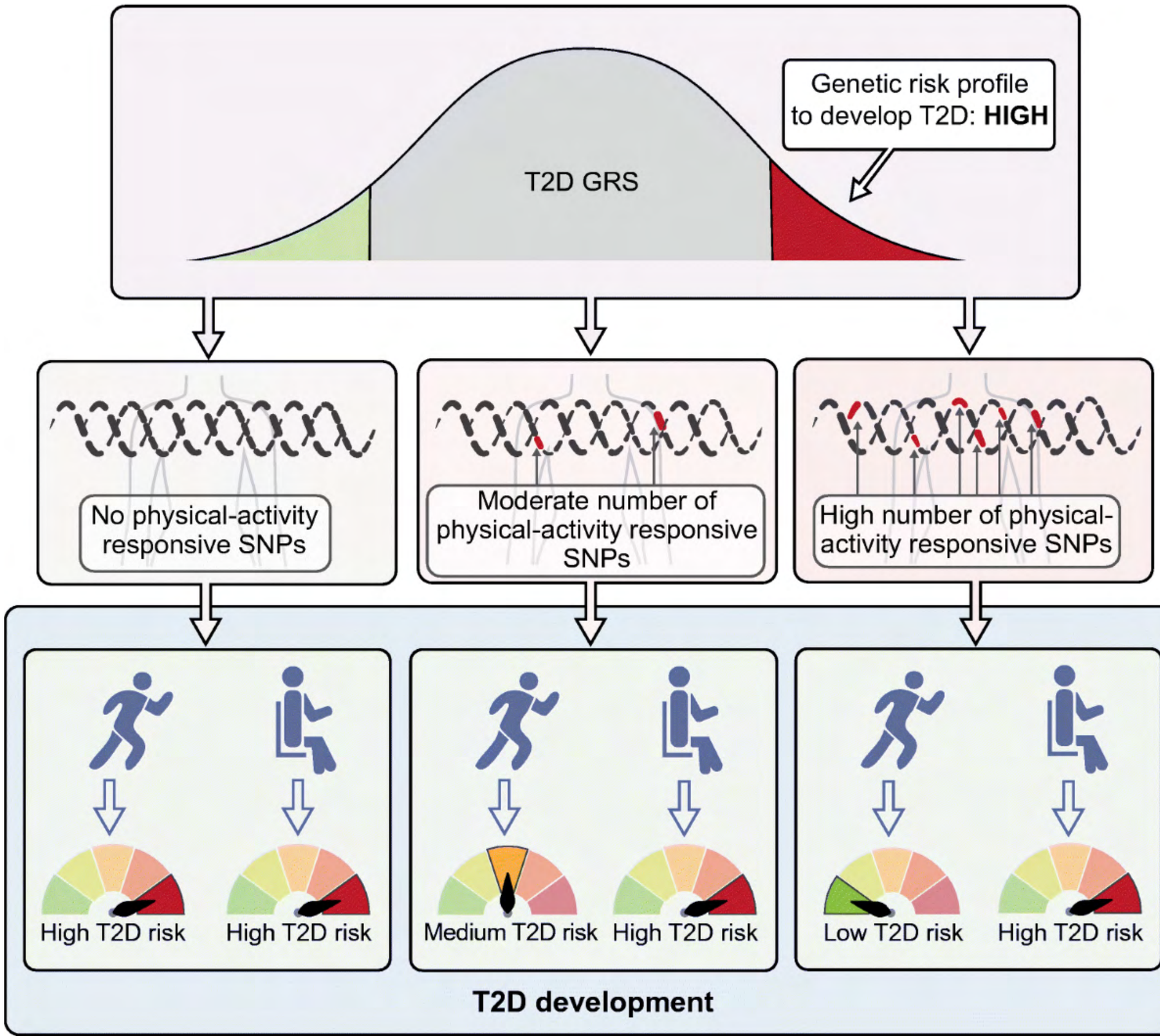
aa даёт зелёную окраску

A_I_ , aaI_ A_ii aaii

12 : 3 : 1


FAT3
FAR2
NEIL3
TMEFF2
RBM19
SLC10A2
UCHL3
GNA14
GRIK2
CTNNA2
PRICKLE1
SMARCA2
LRP1B
FBXW11
SLC22A16
GCNT1
NELL1
RREB1
GALNTL4
PLLP
DTNBP1
SPOCK1
ADRB2
SYDE2
RRAGC
MSR1
BHLHE40
SLC24A1
SPTLC3
ATP2B1
EDIL3
CDH10
NTSR1
PRDM6
SOSTDC1
COL15A1
INADL
ZNF521
TNFSF4
DAB2
TMTC2
LIPN
IPMK
CSMD1
ZNF507
ABL1
FABP5
ARAP2
EPHA5
GPR37
IRF8
FHL2
TDG
GFI1B
OR7E156P
CLCNKB
KLF6
CDH16
GRIN2B
PSME4
SLC24A2
RIOK3
ELMO1
C3orf38
DPP6
NGRN
FAM84B
TMEM200A
CCDC81
FAM96A
TSNARE1
ZNF800
SOCS6
PLAA
WWOX
ANK3
MRPS23
SORCS2
ST6GAL2
FAM50B
CCDC102B
CRYBA4
ADRA2A
PPARGC1A
NAPG
TBCK
POTEA
WDR27
OGFRL1
LZTS1
SLITRK5
CDH11
CHD1L
GOLIM4
CEP290
MTCH1
CYSLTR2
SLC24A3
BVES
SUDS3
KIAA0355
RNF216
MIR101-1
CDH16
STAB2
SELL
ZNF385D
EDEM1
SNX16
ADAM29
KMO
OR4C13
SORBS1
LRRC20
FAM84A
ARL15
TCERG1
USP1
TMC8
IFT140
CAV3
DAB2IP
EML6
LEF
CMPK2
EPB41L4A
LMO4
ADD1
ARPP21
PTPRD
SYNCRIP
ZIC1
HRH2
GABRB1
EPB41L3
RNASE1
CELF2
SNRPN
CSMD3
C14orf106
C1orf94
NEDD1
SORCS1
RIOK2
WDFY4
RAB9BP1

Диабет 2 типа: генетика и факторы риска



Методы изучения многофакторных заболеваний

Геномные исследования (GWAS): выявление генетических вариаций, связанных с заболеваниями.

Эпигенетический анализ: изучение метилирования ДНК и модификаций гистонов.

Транскриптомика и протеомика: анализ экспрессии генов и белковых профилей для выявления паттернов, связанных с болезнью.

Метаболомика: исследование метаболических изменений, отражающих патологические процессы.

Близнецовые исследования

Близнецовый метод изучает соотносительную роль генотипа и среды в развитии признака

$$H = \frac{К_{МБ(в\%\%)} - К_{ДБ(в\ \%\%)}}{100\% - К_{ДБ(в\ \%\%)}}$$

H – показатель наследуемости признака (от 0 до 1)

$К_{МБ}$ – показатель конкордантности в %% у монозиготных близнецов

$К_{ДБ}$ – показатель конкордантности в %% у дизиготных близнецов

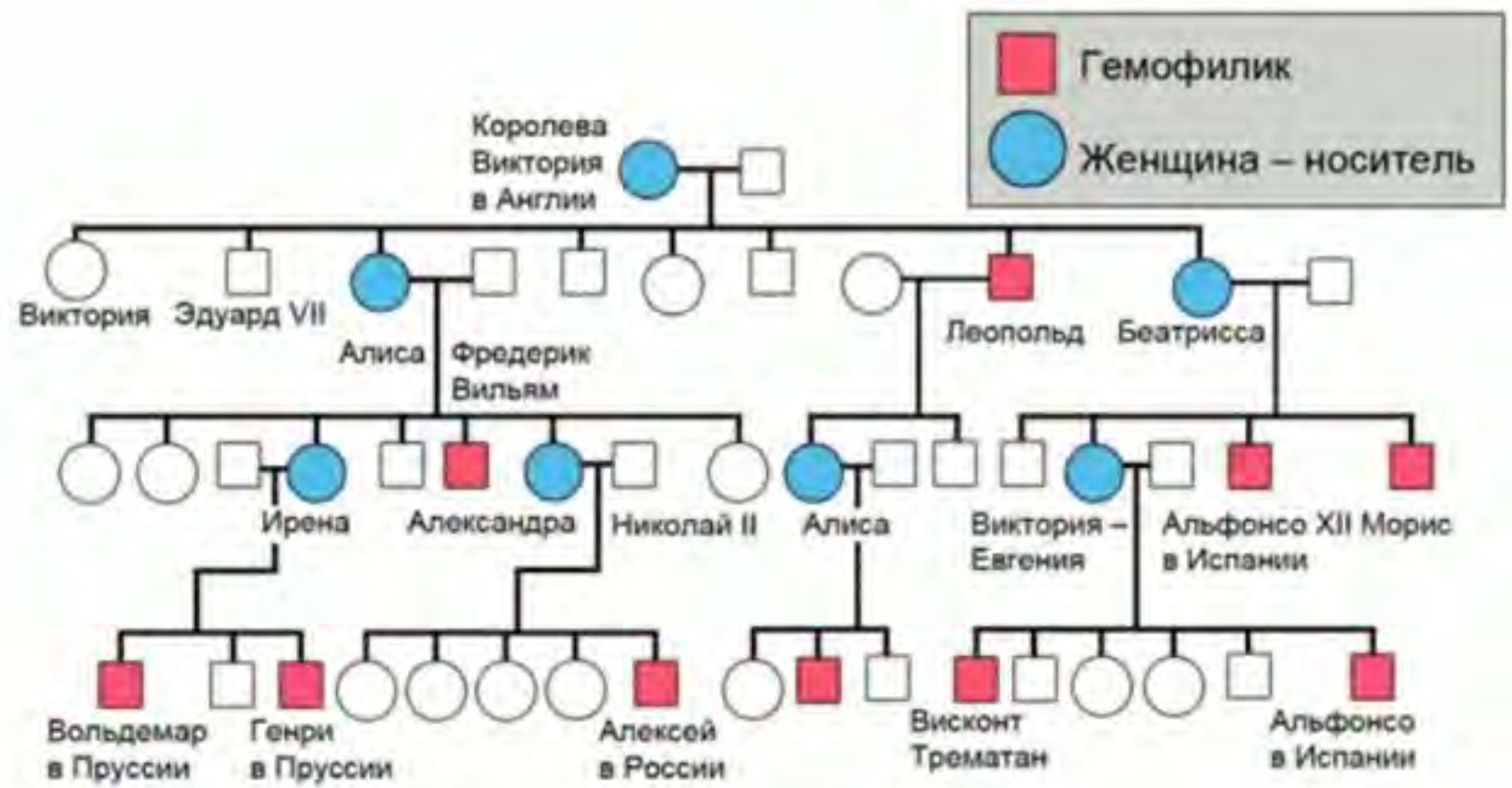
Близнецовые исследования

	MZ concordance rate (%)	DZ concordance rate (%)	Heritability (%)	Reference
Alzheimer's Disease	83	46		(Gatz et al. 2006)
Type 1 diabetes	53	11		(Kyvik et al. 1995)
Type 2 diabetes	50	37		(Poulsen et al. 1999)
Schizophrenia	41–65	0–28		(Cardno and Gottesman 2000)
Obesity	74	32		(Maes et al. 1997)
Autistic disorders	92	10		(Bailey et al. 1995)
Celiac disorder	83	17		(Nistico et al. 2006)

Близнецовые исследования

	MZ concordance rate (%)	DZ concordance rate (%)	Heritability (%)	Reference
Alzheimer's Disease	83	46	69%	(Gatz et al. 2006)
Type 1 diabetes	53	11	47%	(Kyvik et al. 1995)
Type 2 diabetes	50	37	21%	(Poulsen et al. 1999)
Schizophrenia	41–65	0–28		(Cardno and Gottesman 2000)
Obesity	74	32	62%	(Maes et al. 1997)
Autistic disorders	92	10	91%	(Bailey et al. 1995)
Celiac disorder	83	17	80%	(Nistico et al. 2006)

Семейные исследования



Введение в критерии ACMG

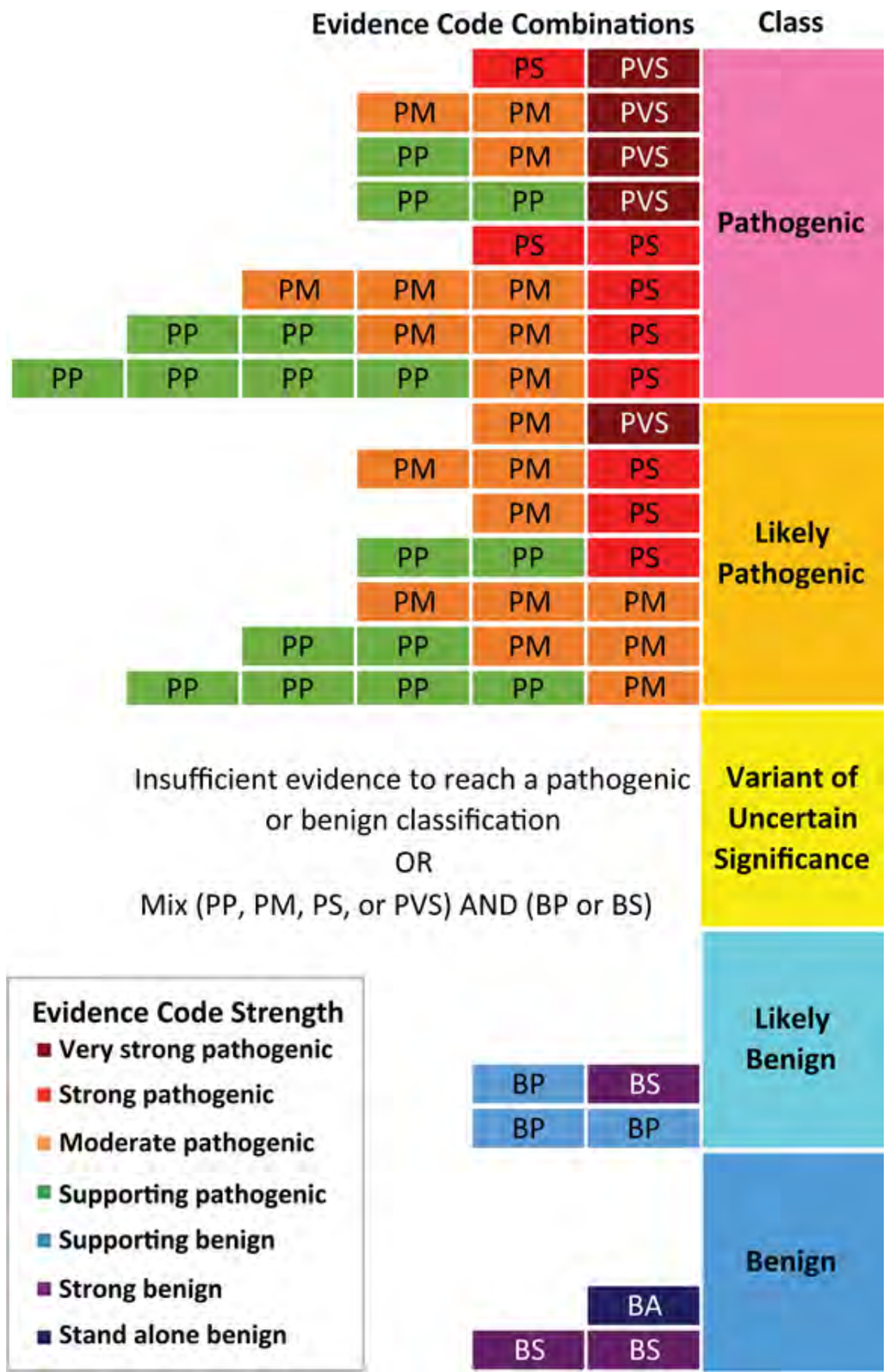
		BENIGN CRITERIA		PATHOGENIC CRITERIA			
Strength of evidence		Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Odds of Pathogenicity*		–18.7	–2.08	2.08	4.33	18.7	350.0
Evidence Category and Corresponding ACMG/AMP Codes	Population Data	*BA1* BS1 BS2			PM2	PS4	
	Allelic Evidence & Cosegregation Data	BS4	BP2 BP5	PP1 →	PM1 PM6	PS2	
	Computation & Predictive Data		BP1 BP3 BP4 BP7	PP2 PP3	PM1 PM4 PM5	PS1	PVS1
	Functional Data	BS3				PS3	
	Other		BP6	PP4 PP5			

	Benign ←		→ Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

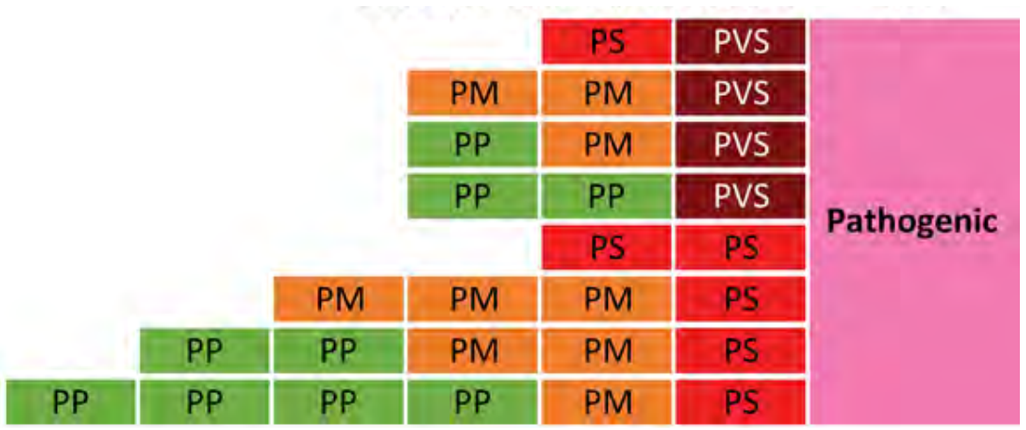
Классификация генетических вариантов

Class 1	Pathogenic
Class 2	Likely pathogenic
Class 3	Variant of uncertain significance (VUS)
Class 4	Likely benign
Class 5	Benign

Алгоритм оценки по ACMG



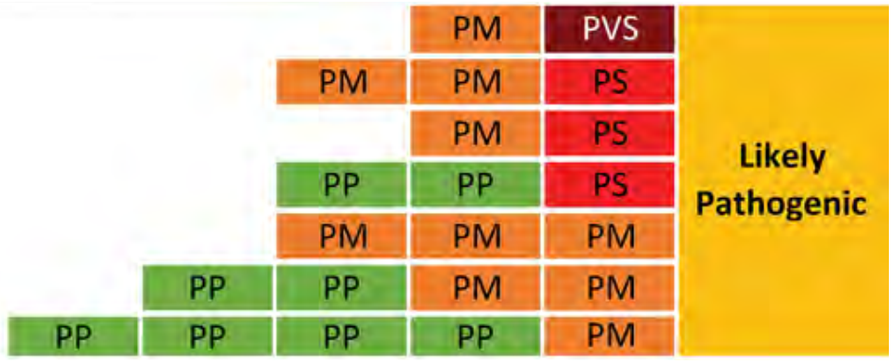
Патогенные варианты



Pathogenic

Supporting	Moderate	Strong	Very strong
	Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Cosegregation with disease in multiple affected family members PP1	Increased segregation data →	→	
	De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
	For recessive disorders, detected in trans with a pathogenic variant PM3		
Reputable source = pathogenic PP5			
Patient's phenotype or FH highly specific for gene PP4			

Вероятно патогенные варианты



Pathogenic

Supporting	Moderate	Strong	Very strong
	Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
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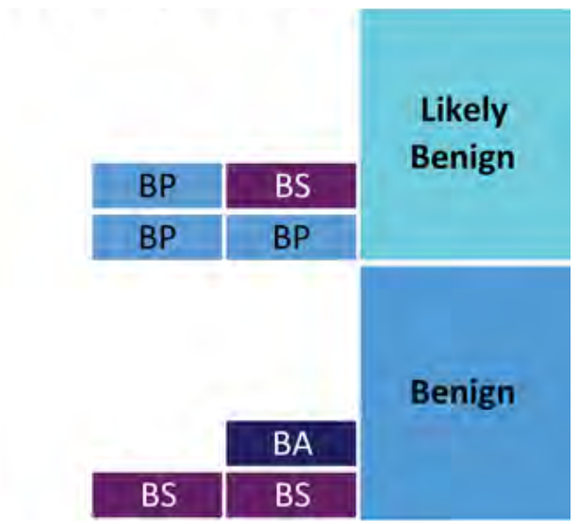
	De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
	For recessive disorders, detected in trans with a pathogenic variant PM3		
Reputable source = pathogenic PP5			
Patient's phenotype or FH highly specific for gene PP4			

Варианты неопределенного значения (VUS)

Вопрос: Что делать с вариантами, чья клиническая значимость не ясна?

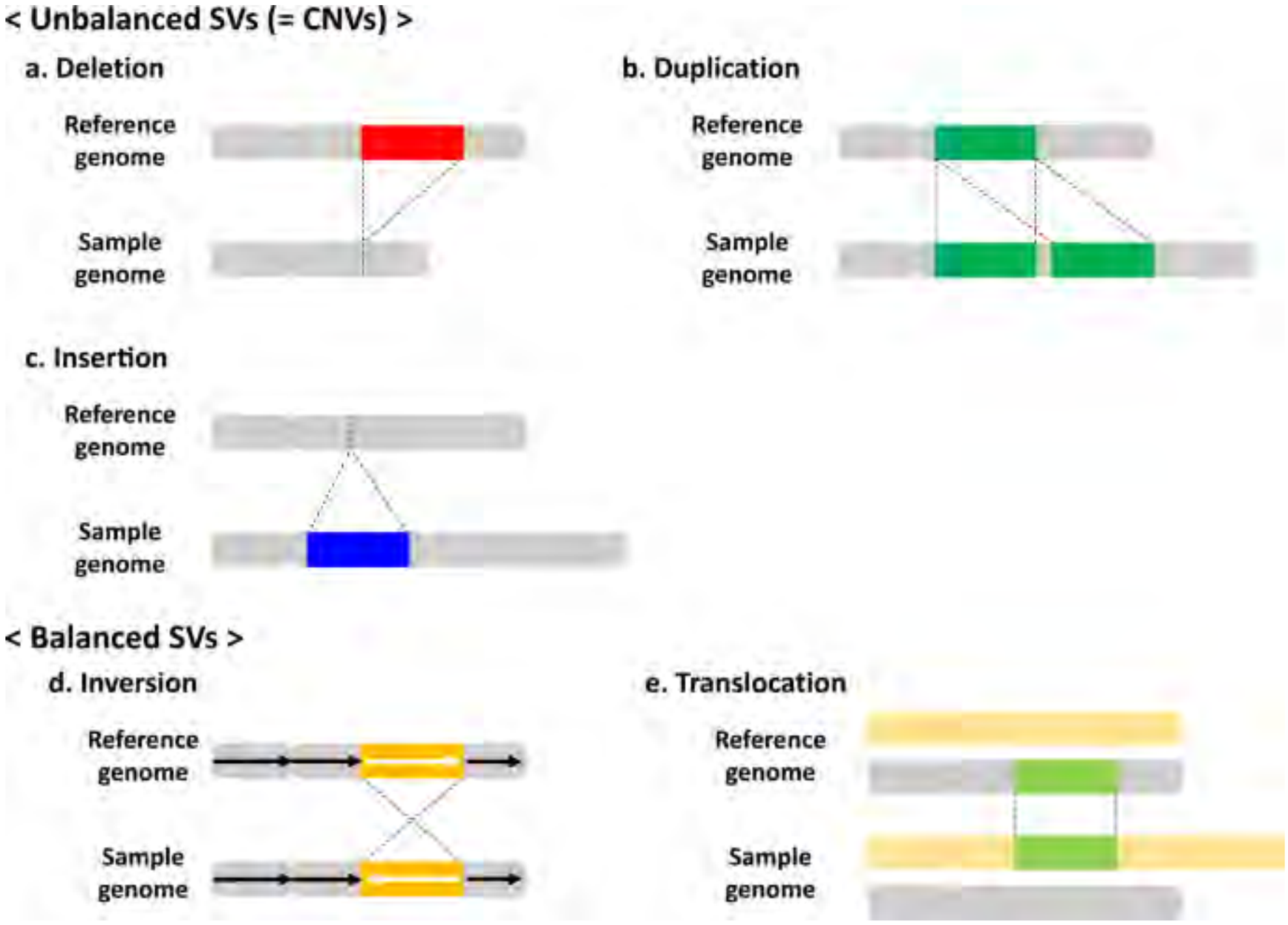
Ответ: Никто не знает.

Доброкачественные и вероятно доброкачественные варианты

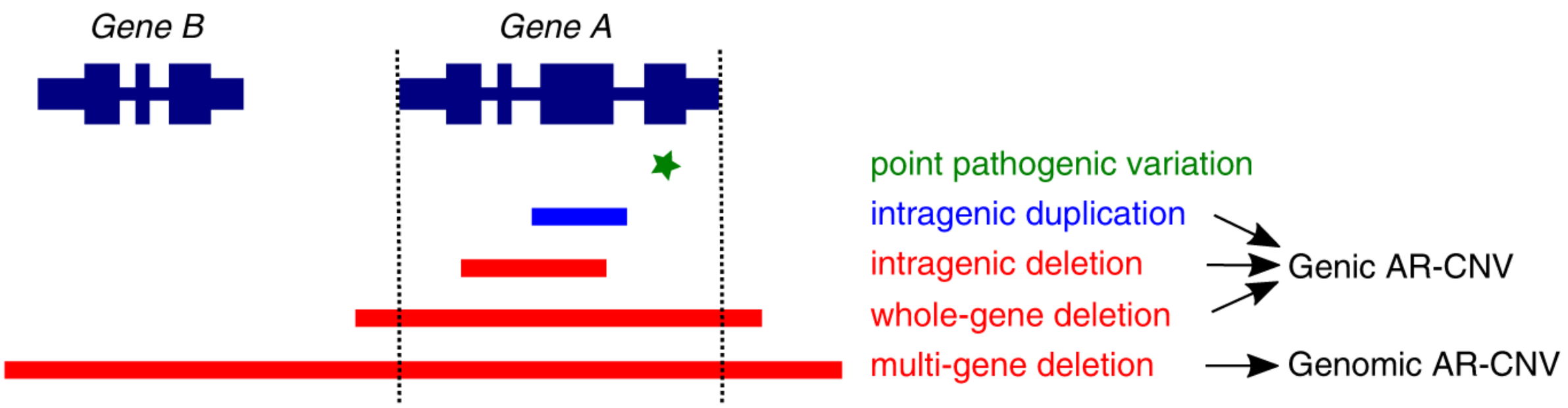


	Benign ← Strong	Supporting →
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3
Functional data	Well-established functional studies show no deleterious effect BS3	
Segregation data	Nonsegregation with disease BS4	
De novo data		
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2
Other database		Reputable source w/out shared data = benign BP6
Other data		Found in case with an alternate cause BP5

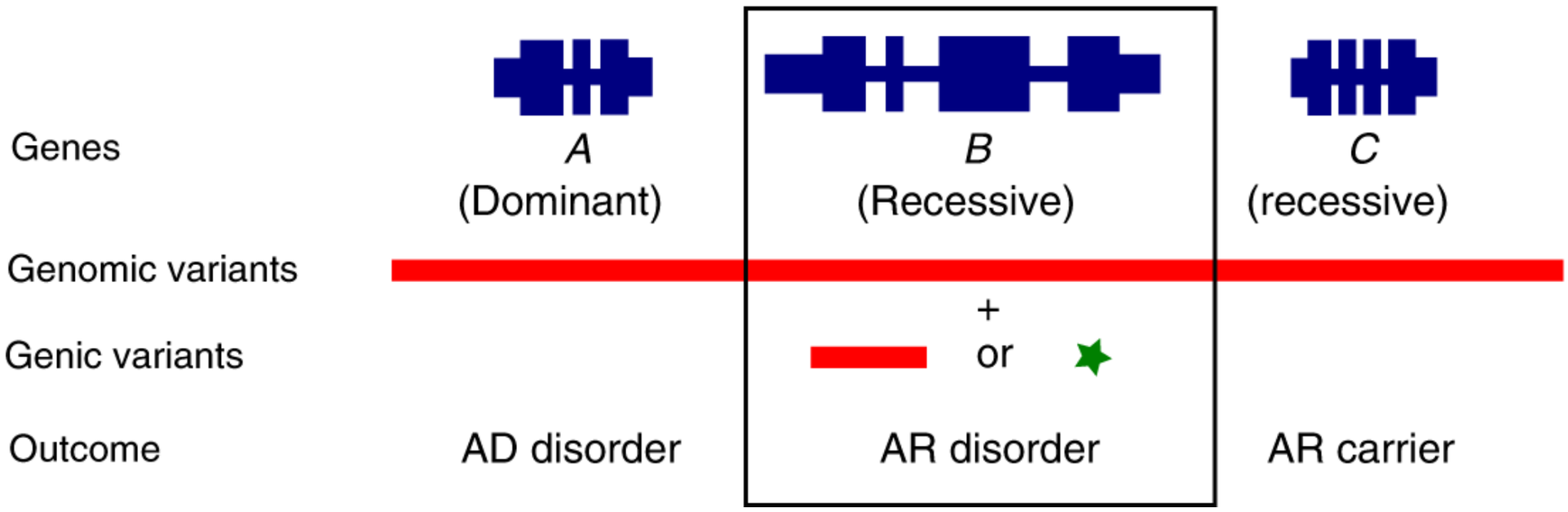
Что такое CNV



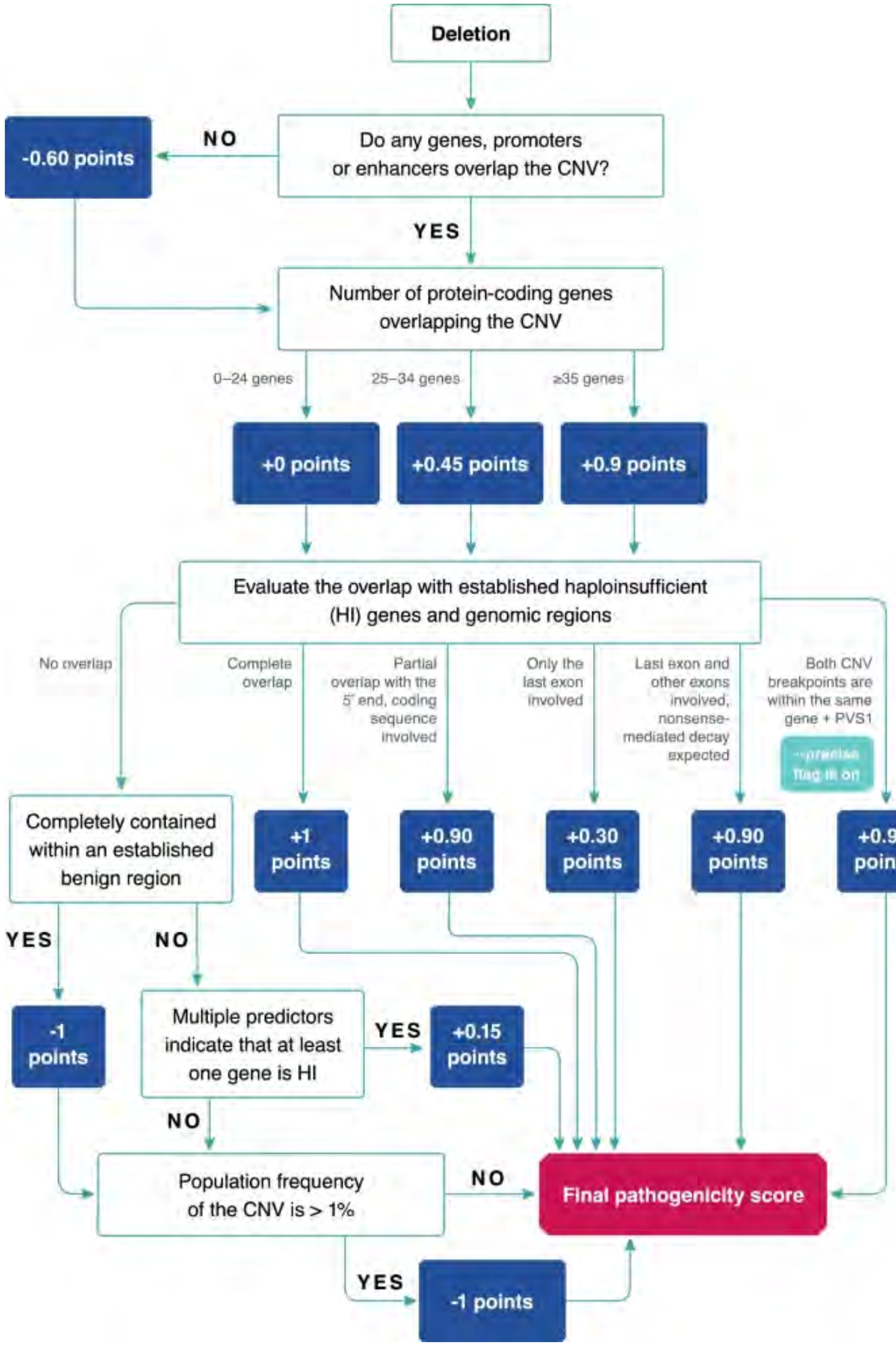
Влияние CNV на заболевания

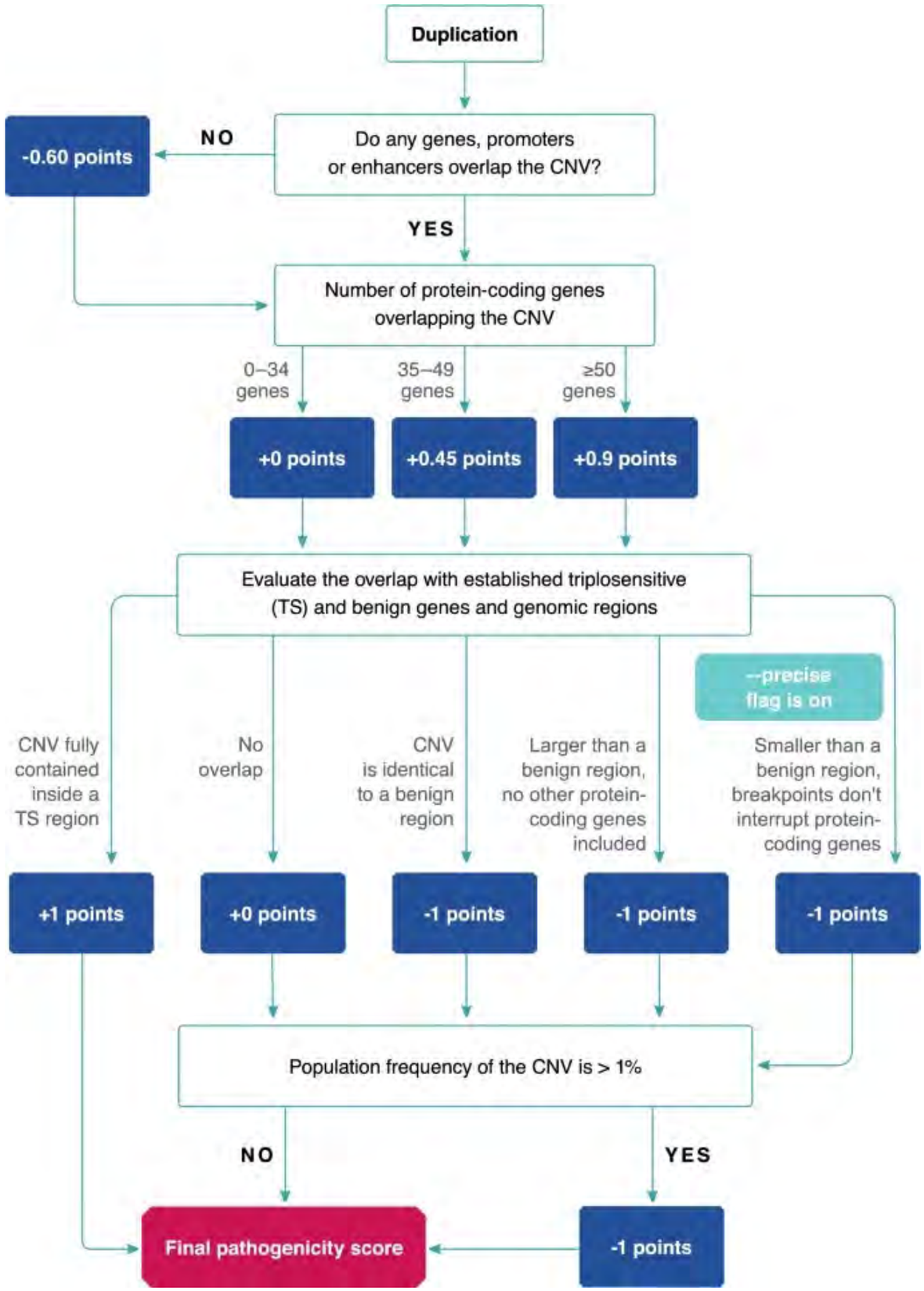


Влияние CNV на заболевания

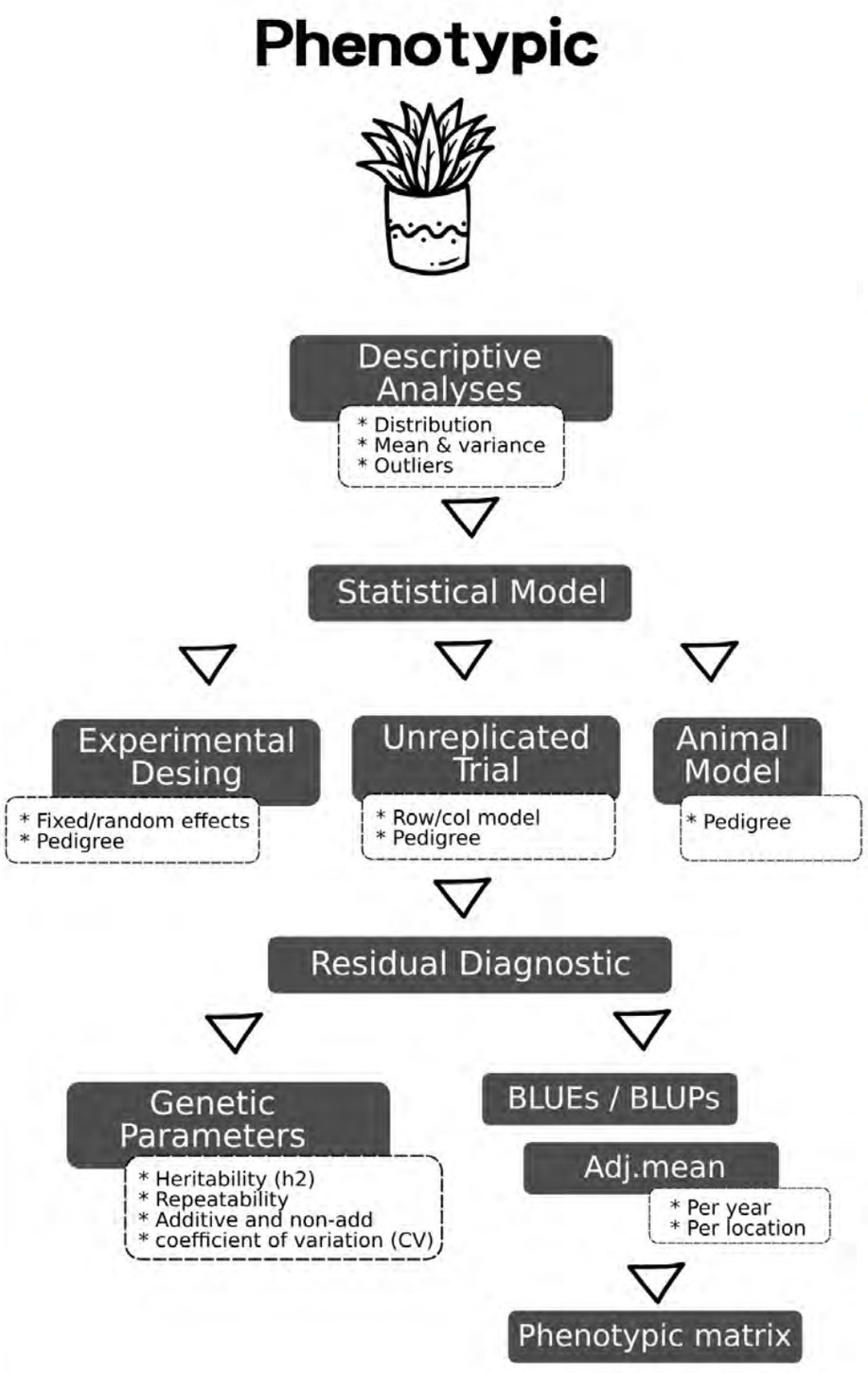


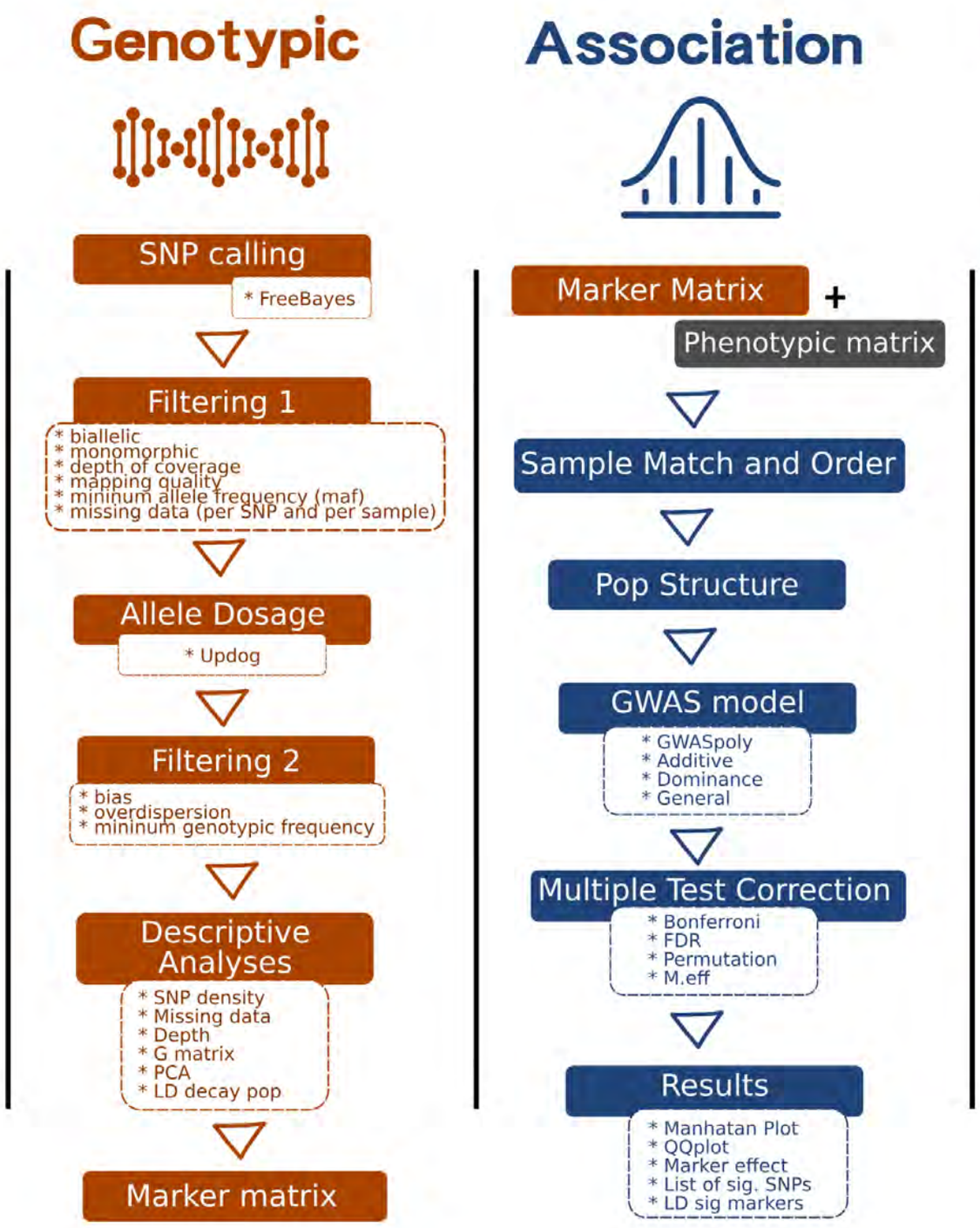
Критерии ACMG оценки клинической значимости CNV

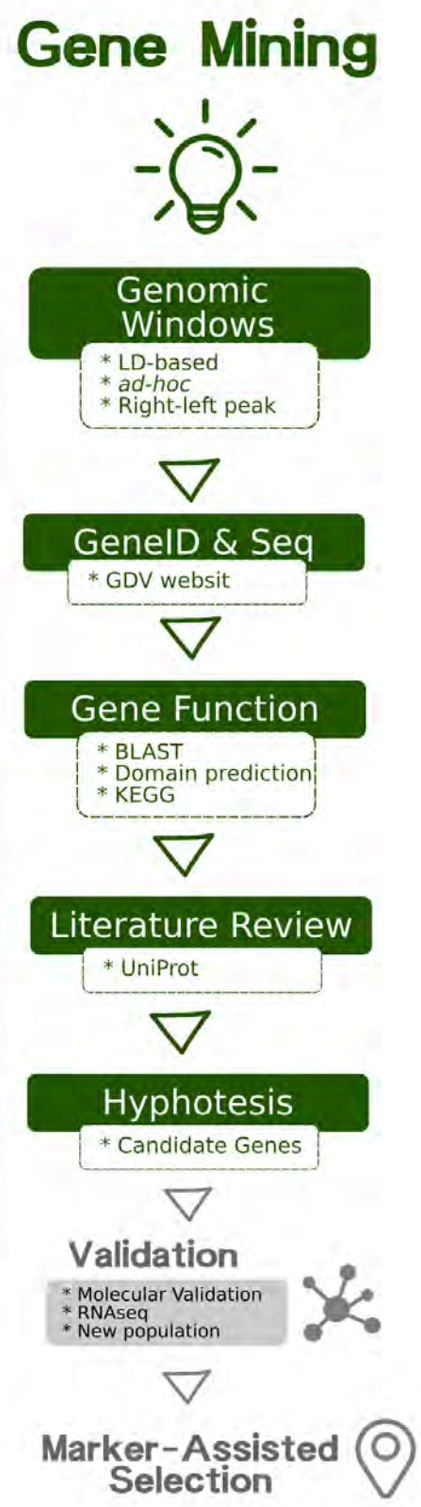

Deletion
Do any genes, promoters or enhancers overlap the CNV?
NO
-0.60 points
YES
Number of protein-coding genes overlapping the CNV
0–24 genes
25–34 genes
≥35 genes
+0 points
+0.45 points
+0.9 points
Evaluate the overlap with established haploinsufficient (HI) genes and genomic regions
No overlap
Complete overlap
Partial overlap with the 5' end, coding sequence involved
Only the last exon involved
Last exon and other exons involved, nonsense-mediated decay expected
Both CNV breakpoints are within the same gene + PVS1
--precise flag is on
Completely contained within an established benign region
+1 points
+0.90 points
+0.30 points
+0.90 points
+0.90 points
YES
NO
-1 points
Multiple predictors indicate that at least one gene is HI
YES
+0.15 points
NO
Population frequency of the CNV is > 1%
NO
Final pathogenicity score
YES
-1 points


Duplication
Do any genes, promoters or enhancers overlap the CNV?
NO
-0.60 points
YES
Number of protein-coding genes overlapping the CNV
0–34 genes
35–49 genes
≥50 genes
+0 points
+0.45 points
+0.9 points
Evaluate the overlap with established triplosensitive (TS) and benign genes and genomic regions
--precise flag is on
CNV fully contained inside a TS region
No overlap
CNV is identical to a benign region
Larger than a benign region, no other protein-coding genes included
Smaller than a benign region, breakpoints don't interrupt protein-coding genes
+1 points
+0 points
-1 points
-1 points
-1 points
Population frequency of the CNV is > 1%
NO
YES
Final pathogenicity score
-1 points

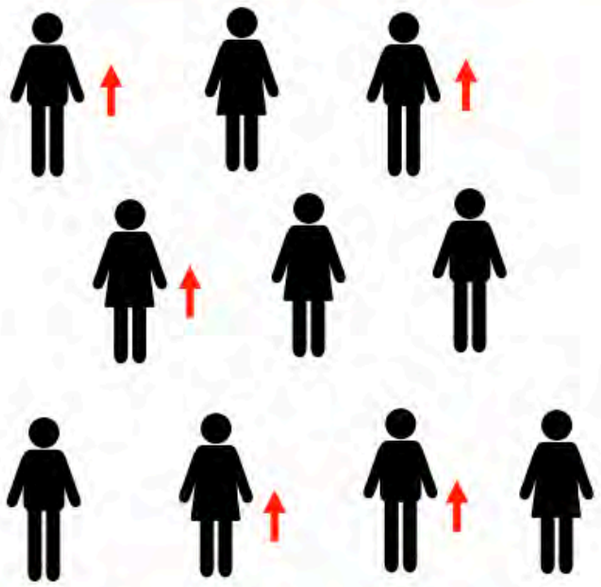
Genome-Wide Association Study (GWAS)





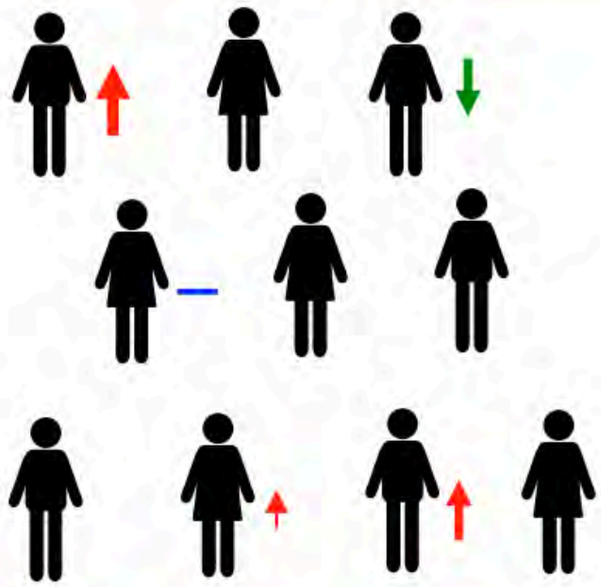


A



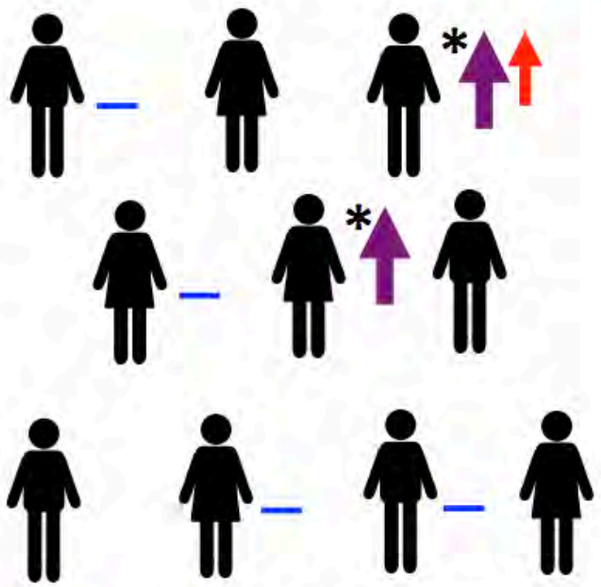
Simple additivity: Common variant increases risk by small amount in all carriers (population OR = individual RR)

B



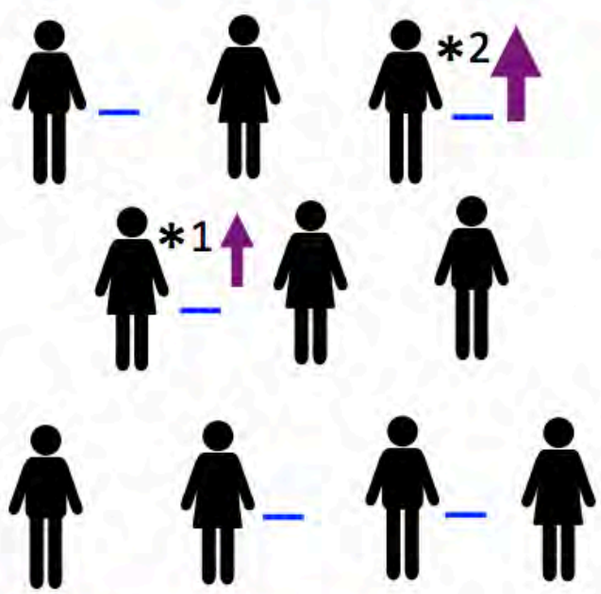
Epistatic interactions: effect of common variant varies with genetic background

C



Modifier: Common variant increases risk dramatically, but only in presence of rare mutation (*)

D



Synthetic association: Common variant has no effect but tags haplotype carrying rare mutations ($*^1$, $*^2$)

New candidate genes
by GWAS+Network

co-functional
gene network

Assigning SNP to gene

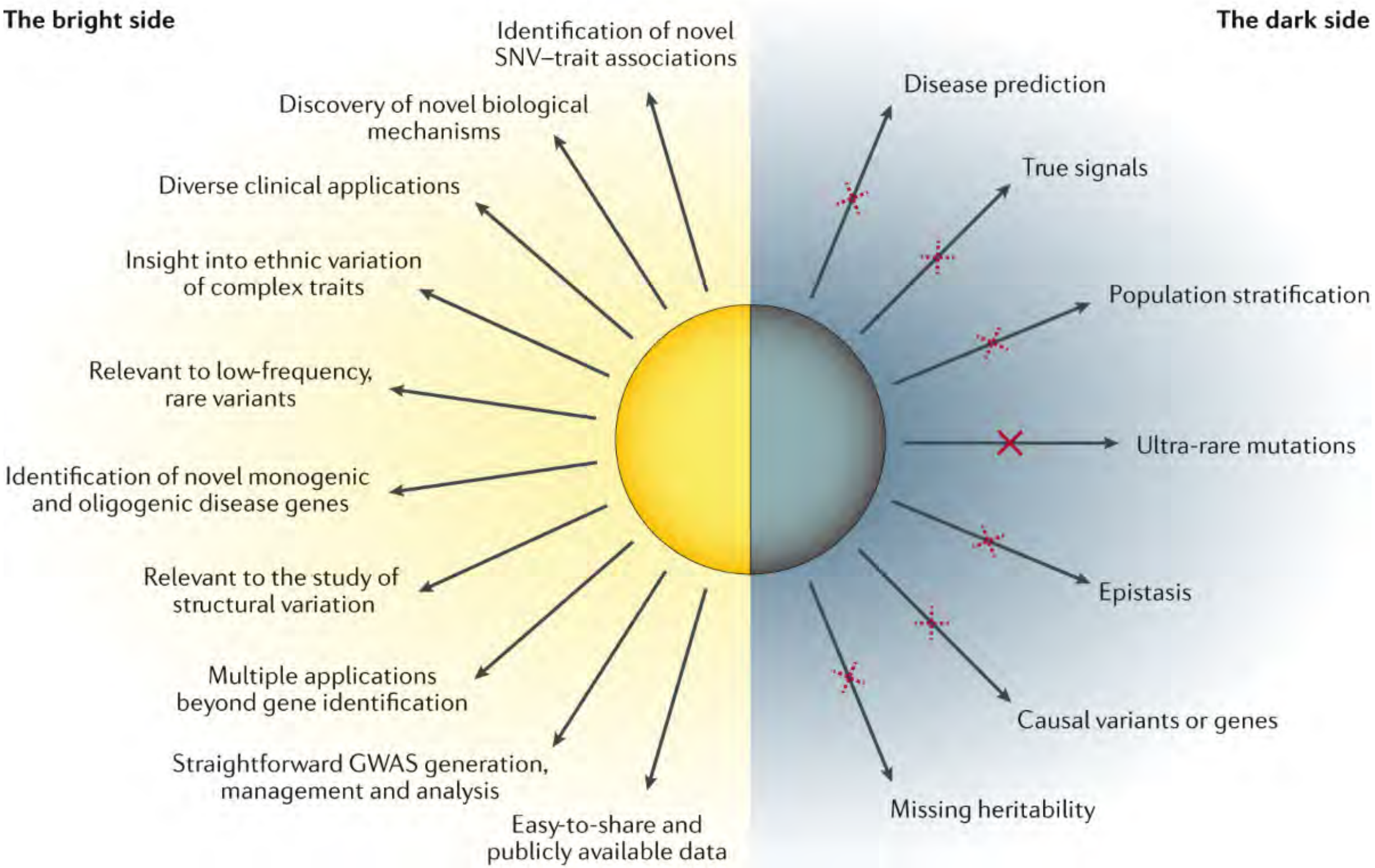
GWAS
significance
($-\log_{10}$P)

15
10
5
0

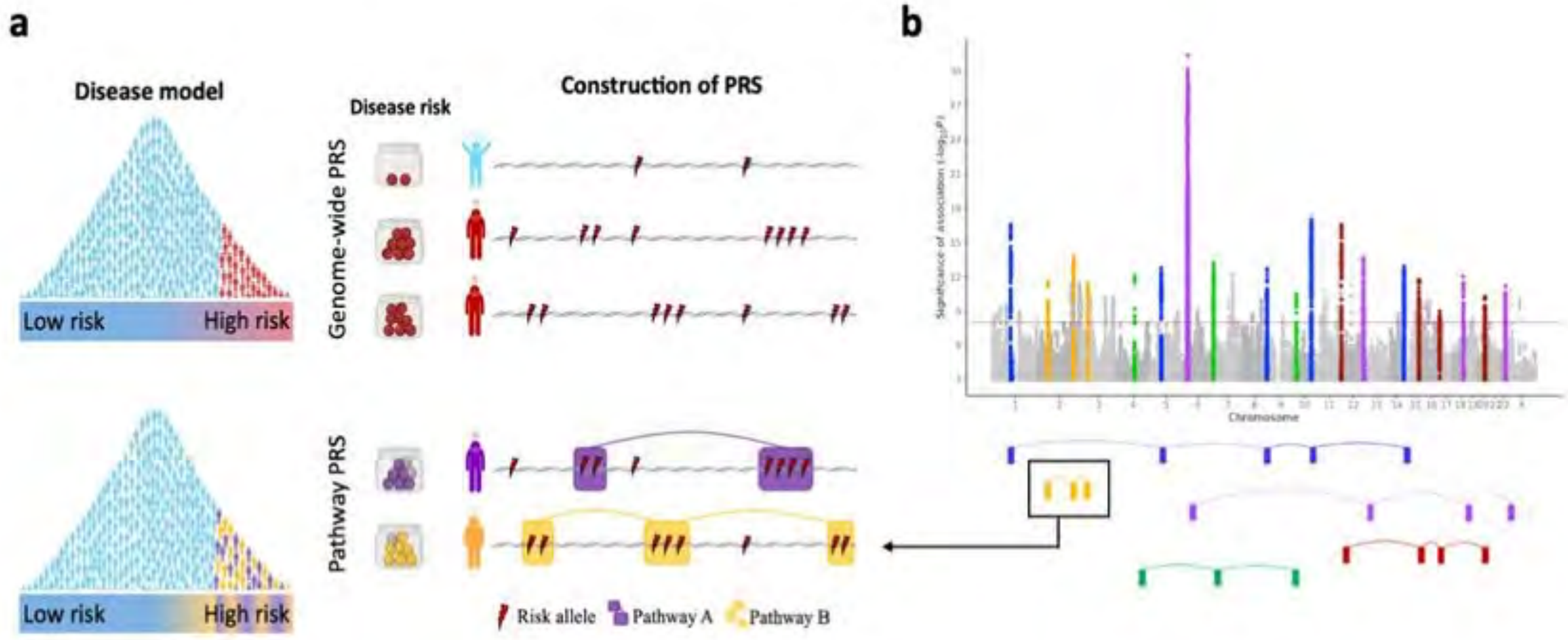
threshold

chromosome

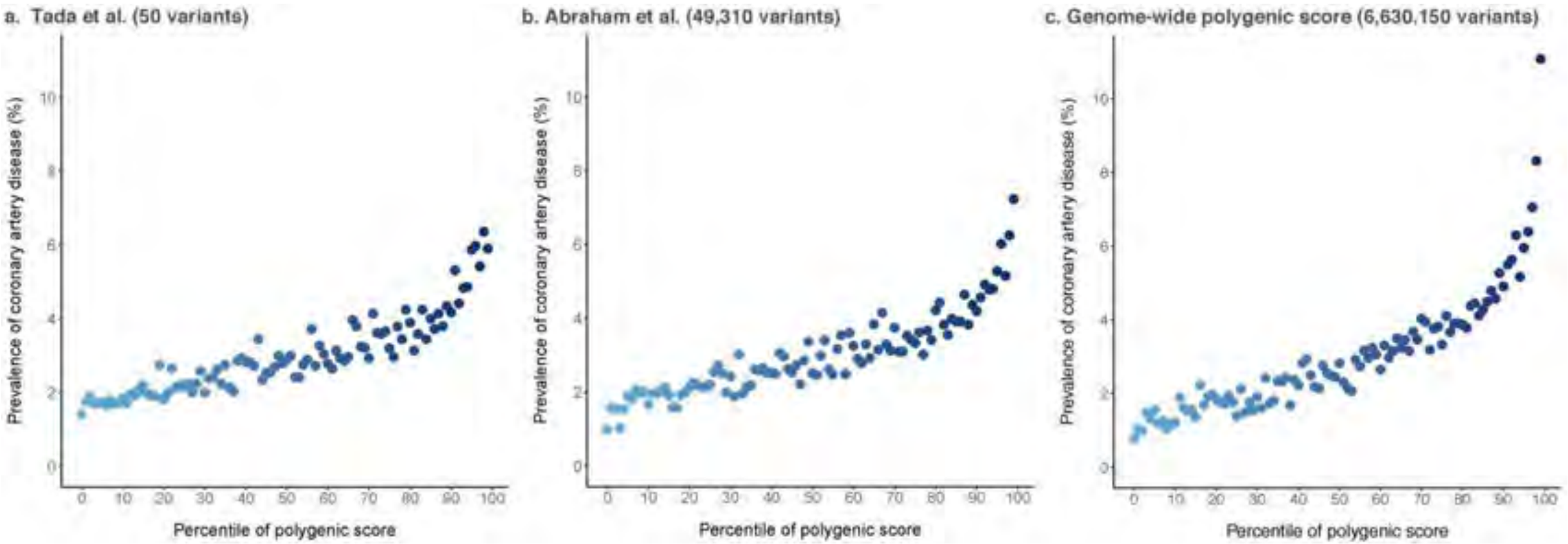
Ограничения и критика GWAS

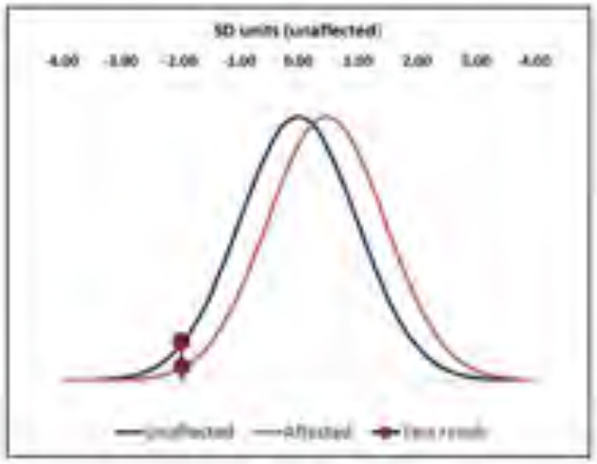


Методики расчета полигенных шкал



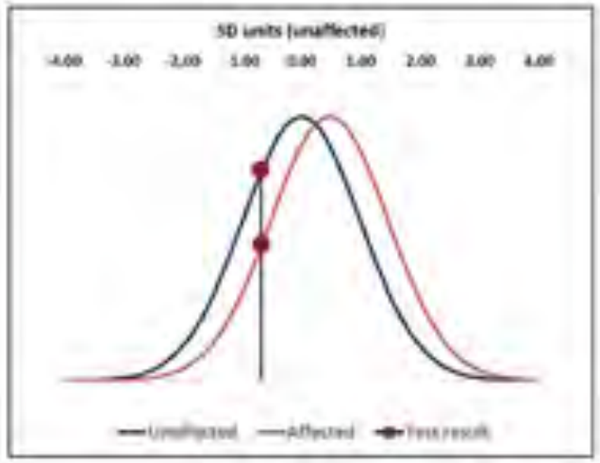
Концепция полигенных шкал риска





LR 0.35
Odds 1:54

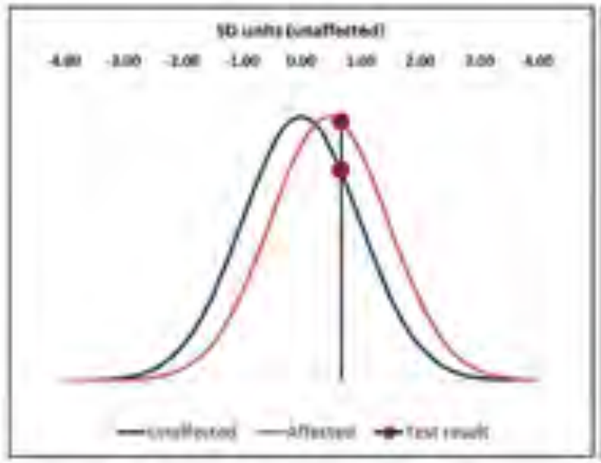
2.5th



LR 0.65
Odds 1: 29

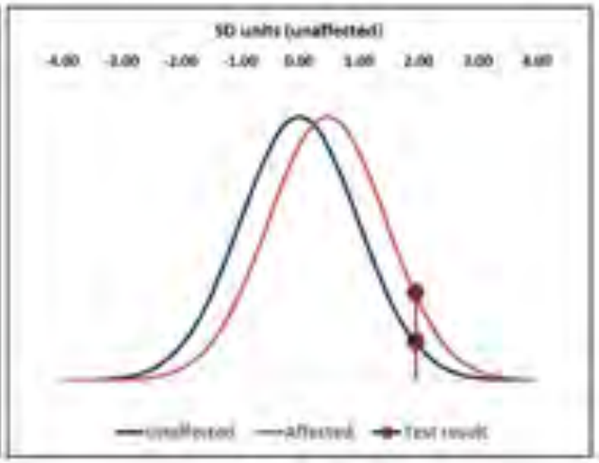
25th

Coronary artery disease
(background odds 1:19)



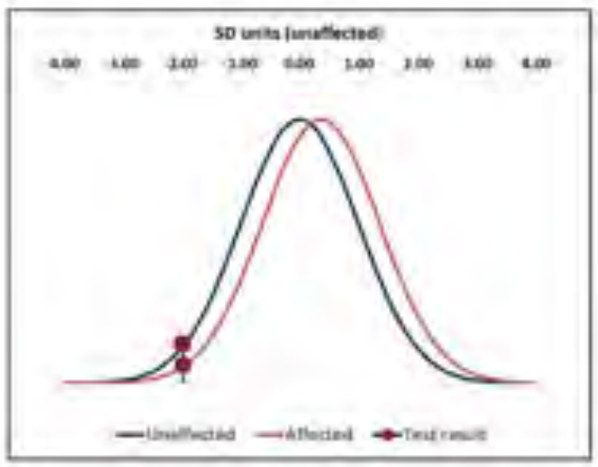
LR 1.23
Odds 1:15

75th

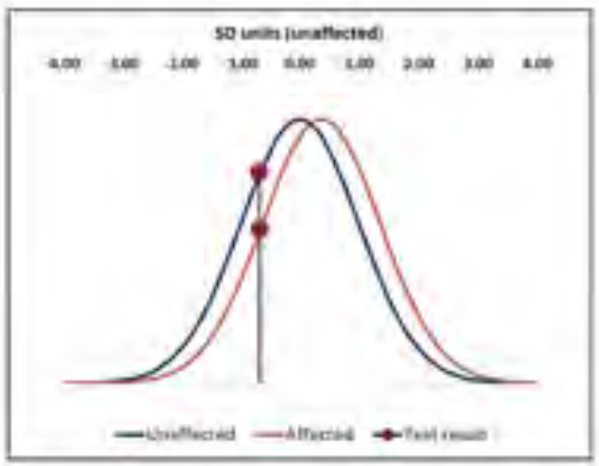


LR 2.27
Odds 1:8

97.5th

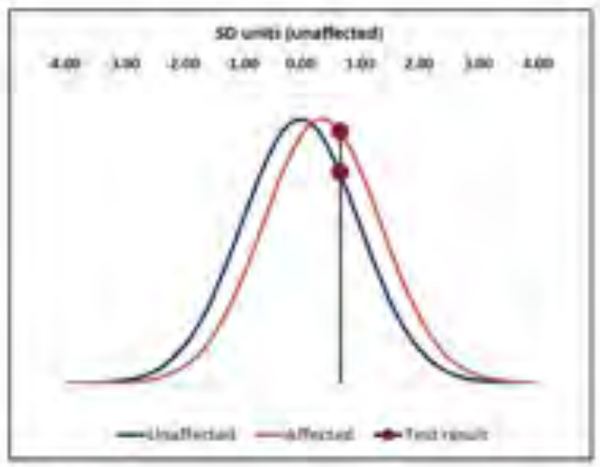


LR 0.45
Odds 1:91

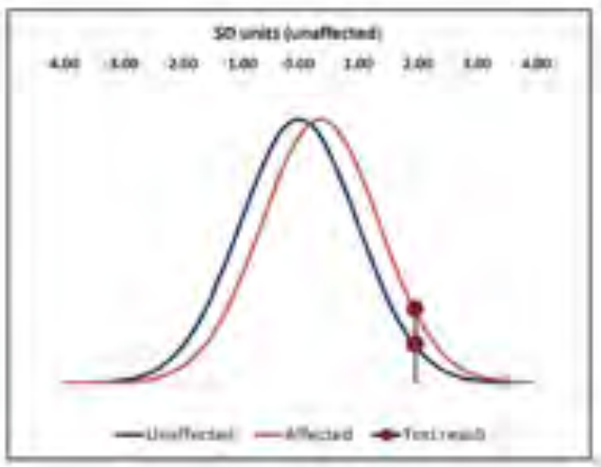


LR 0.73
Odds 1: 56

Breast cancer
(background odds 1:41)

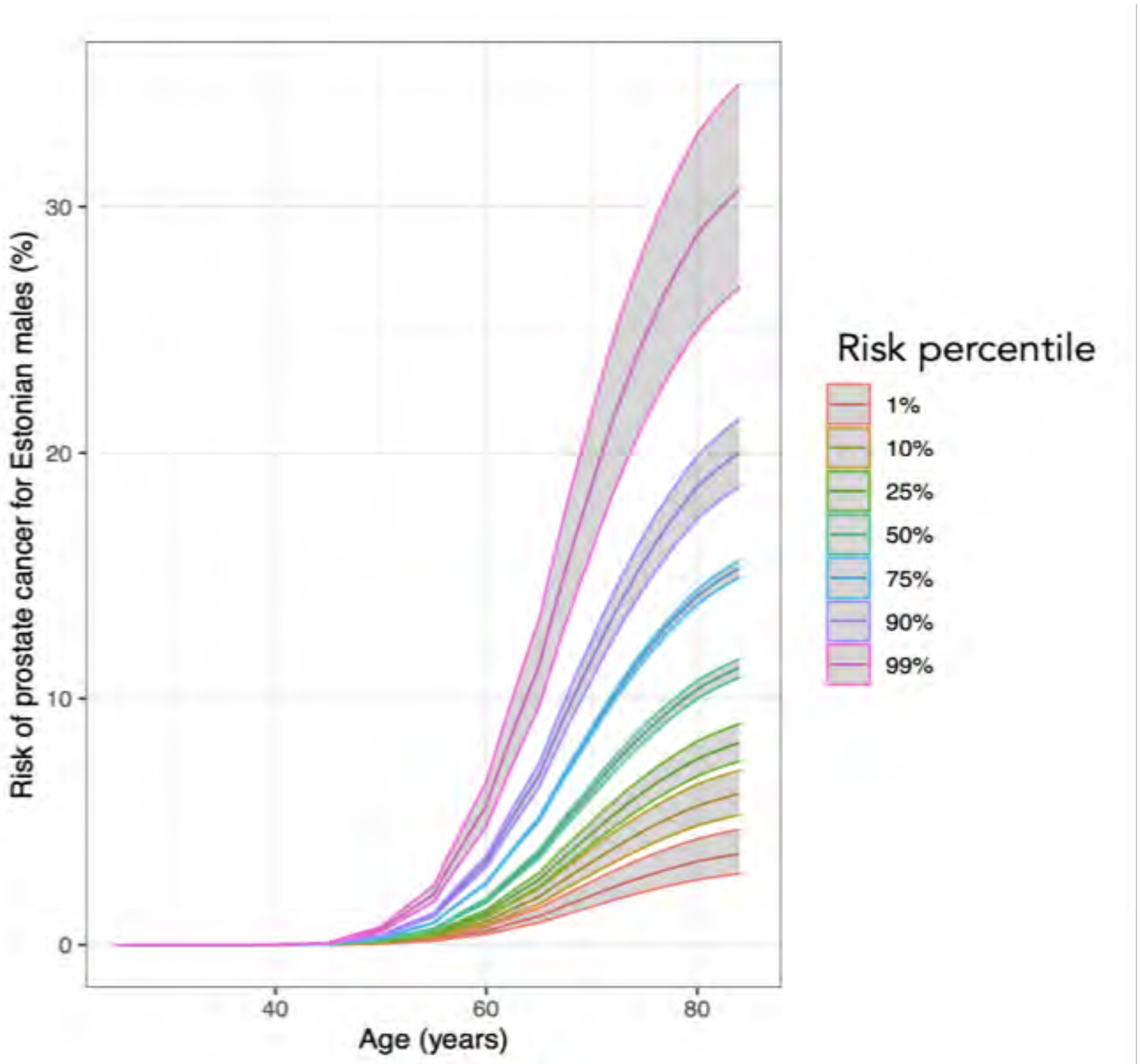


LR 1.2
Odds 1:34

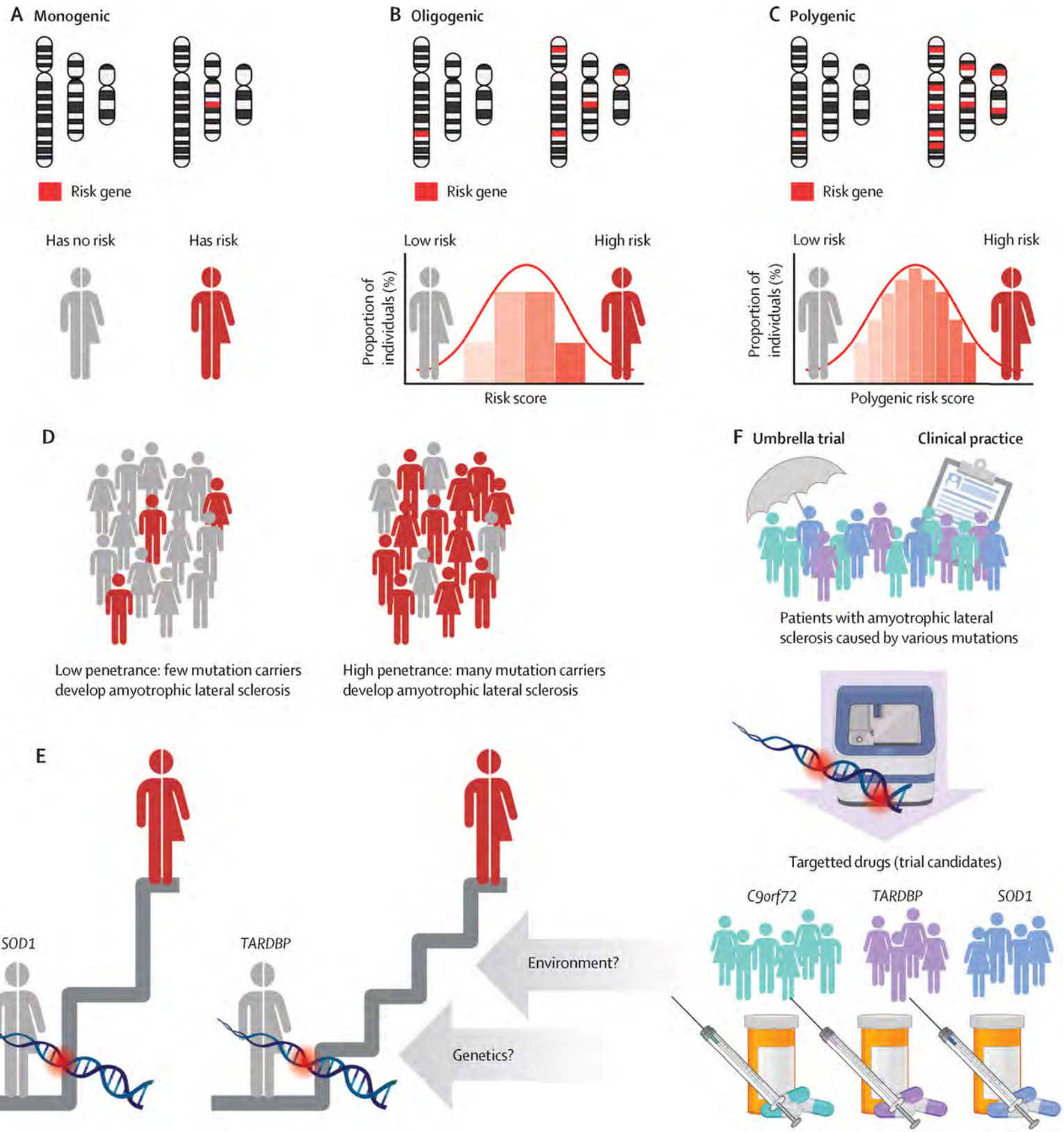


LR 1.93
Odds 1:21

Концепция полигенных шкал риска



Персонализированная медицина



Этические аспекты генетики

- **Конфиденциальность:** необходимость защиты генетических данных от несанкционированного доступа.
- **Генетическая дискриминация:** недопустимость использования генетической информации для ограничения прав и возможностей человека.
- **Информированное согласие:** важность добровольного и осознанного участия в генетических исследованиях.
- **Генное редактирование:** моральные дилеммы, связанные с изменением генома человека.

Вопросы и обсуждение