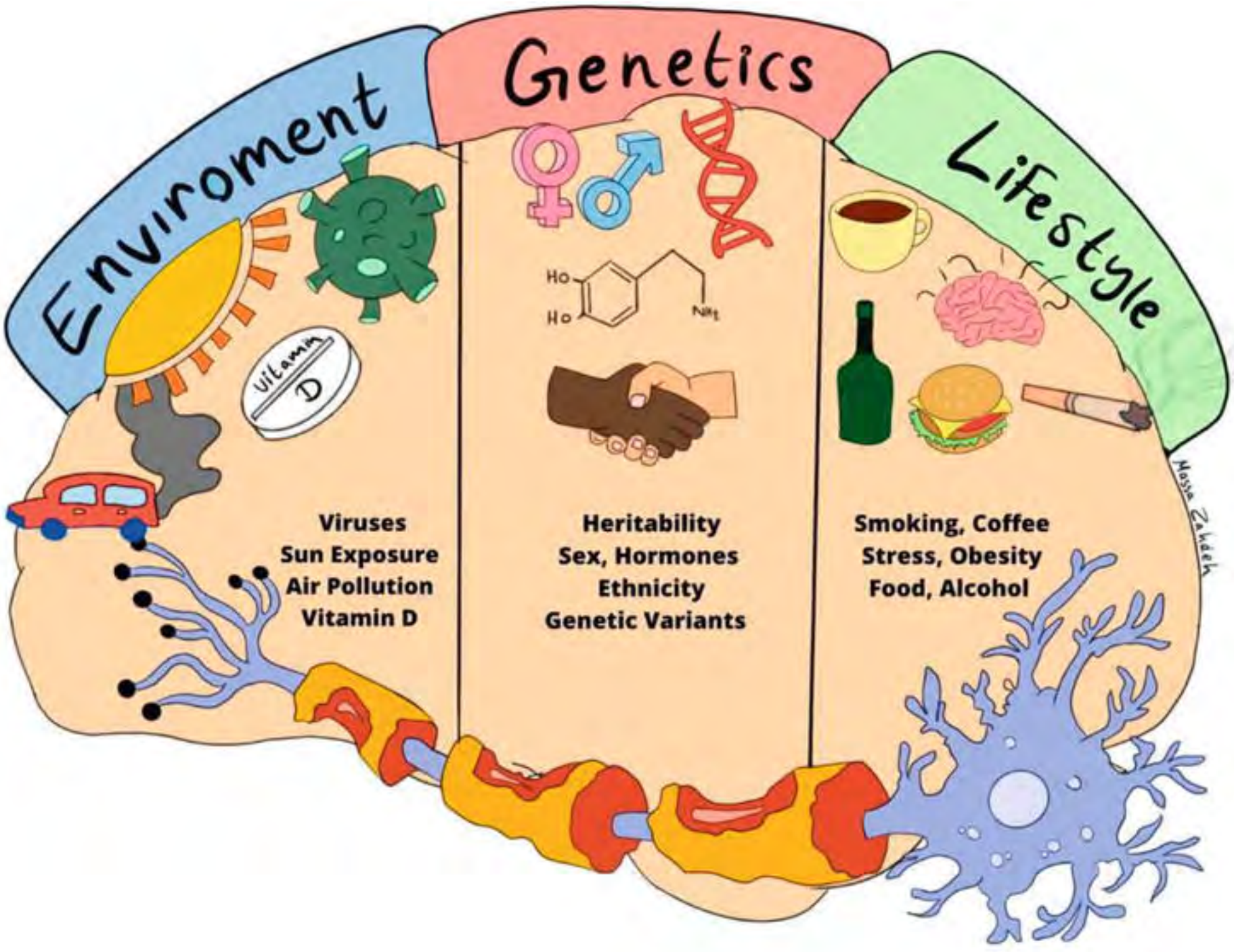
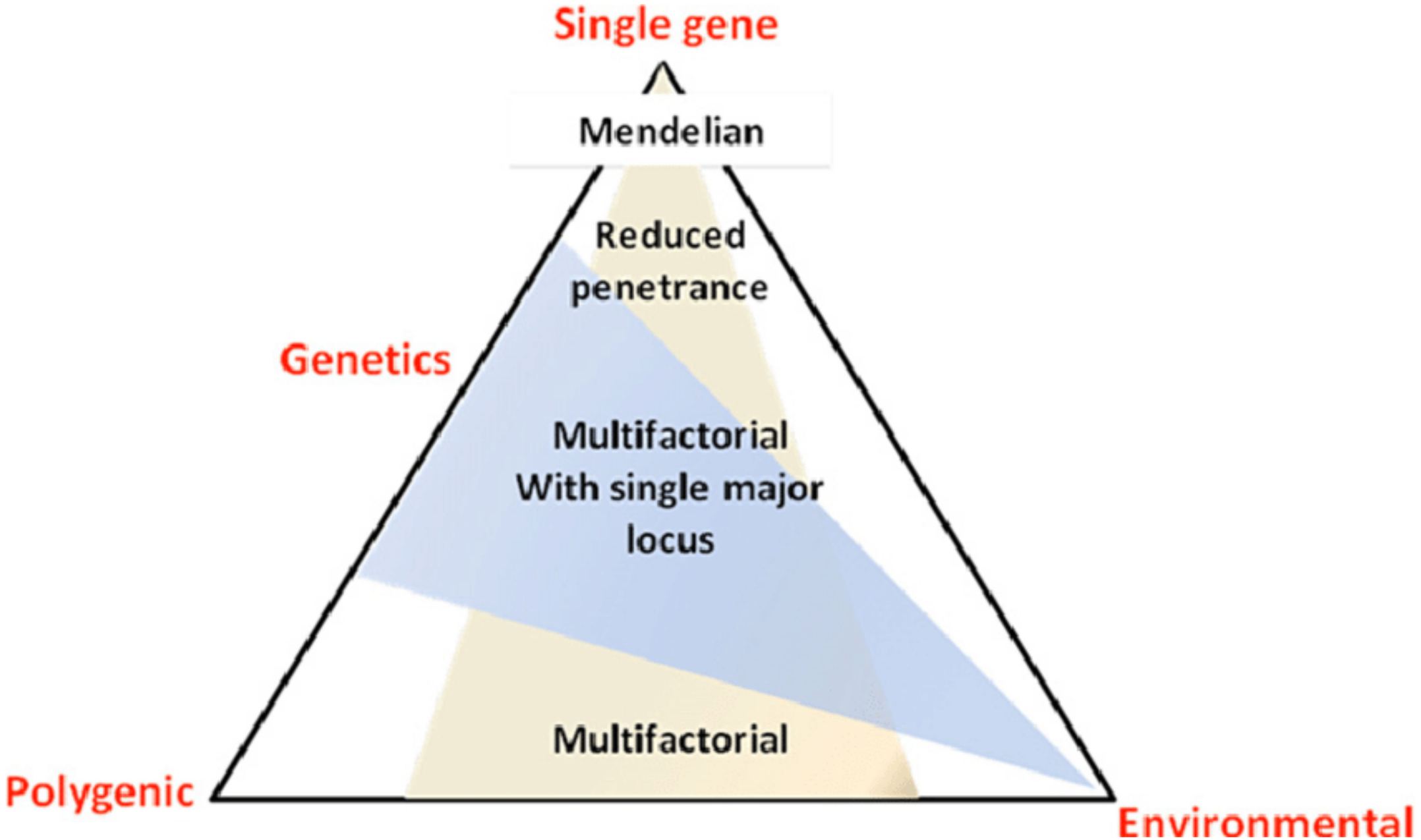
Введение в молекулярную биологию

# Лекция 5. Медицинская генетика и генетические заболевания

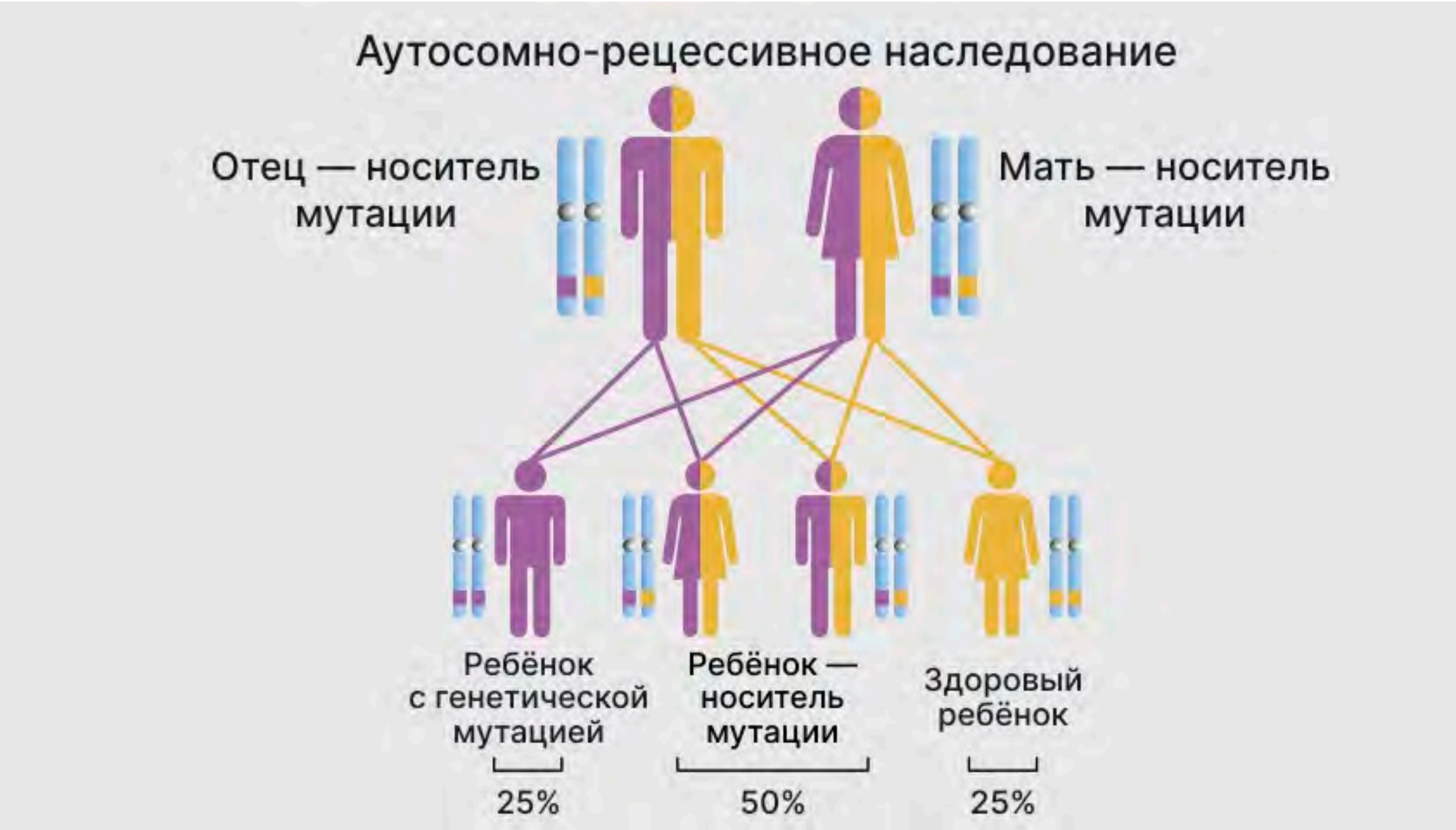
# Важность генетических заболеваний



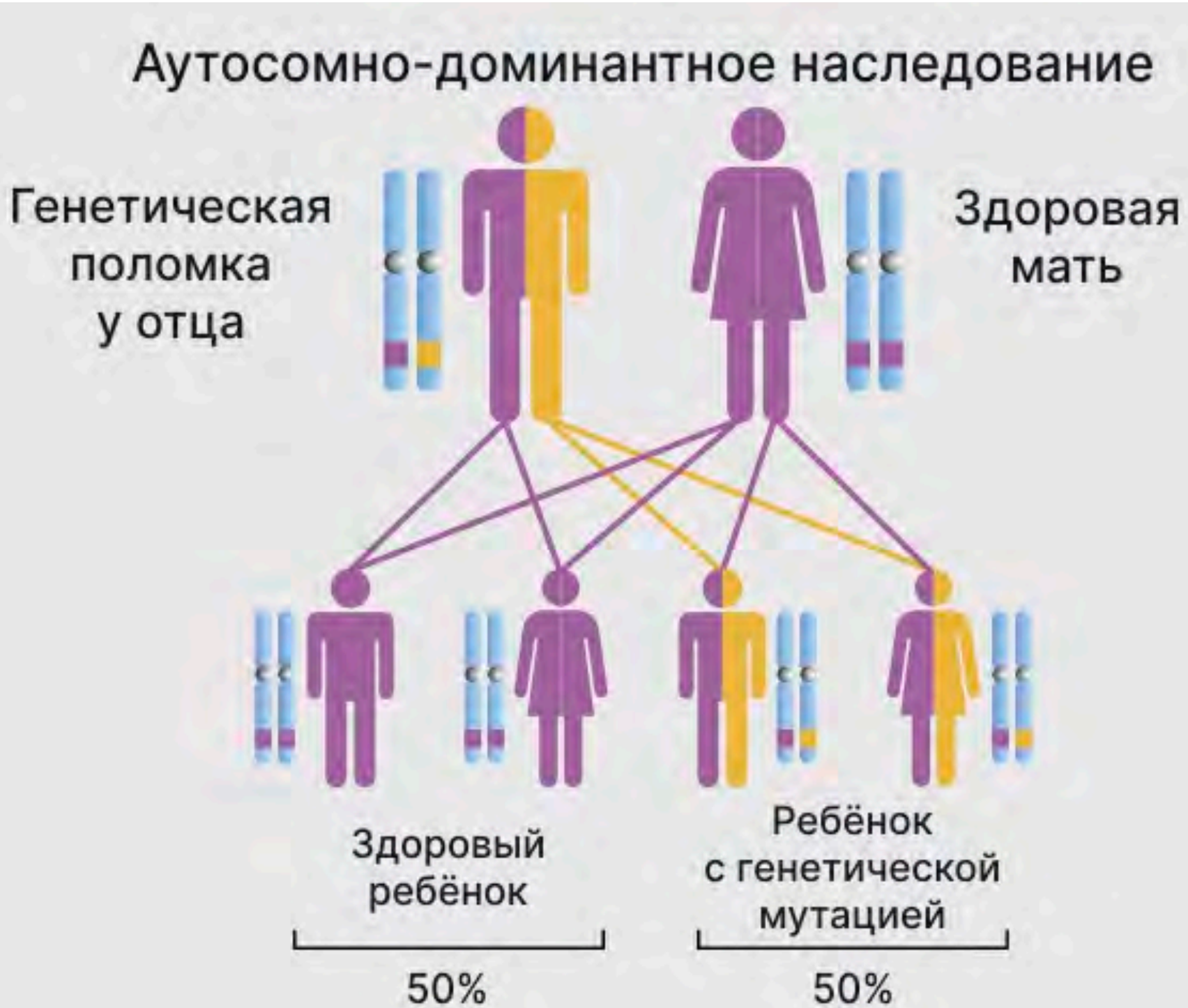
# Классификация наследственных заболеваний



# Моногенные заболевания



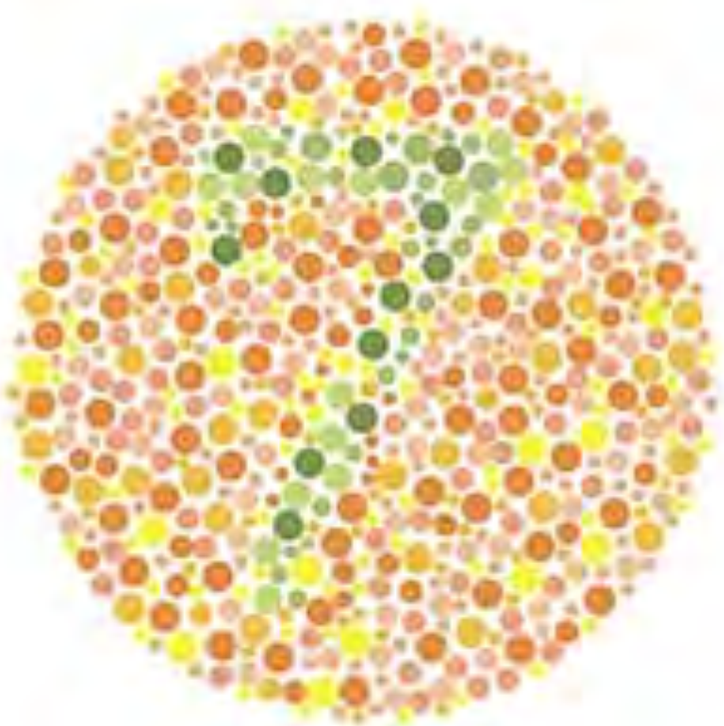
# Моногенные заболевания

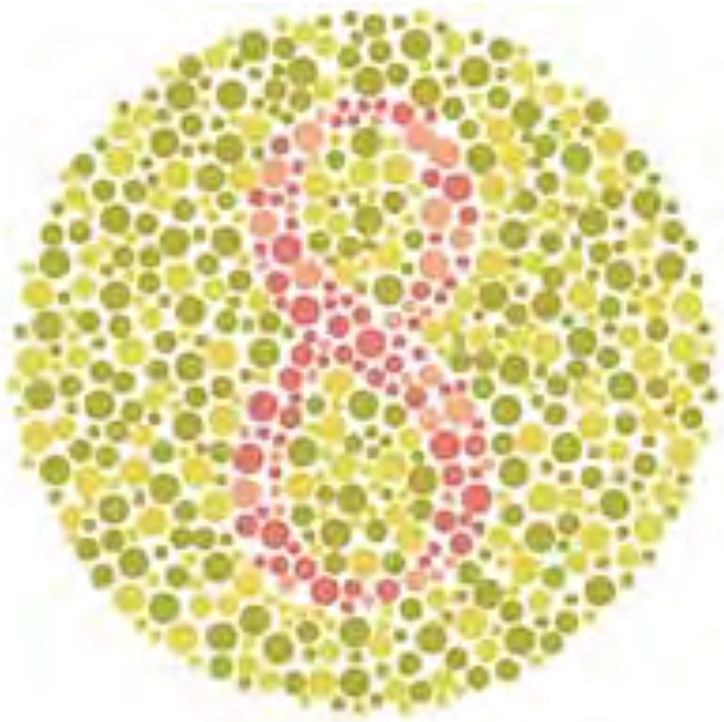
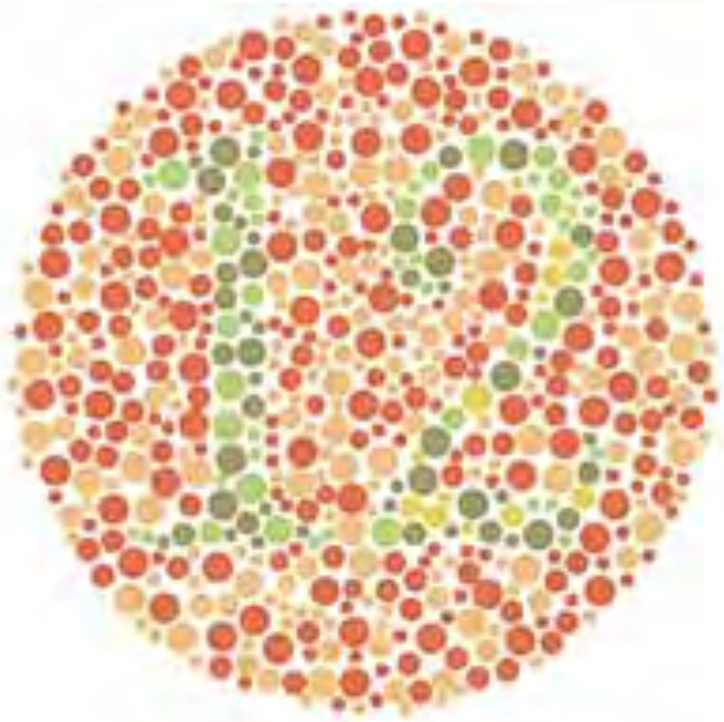
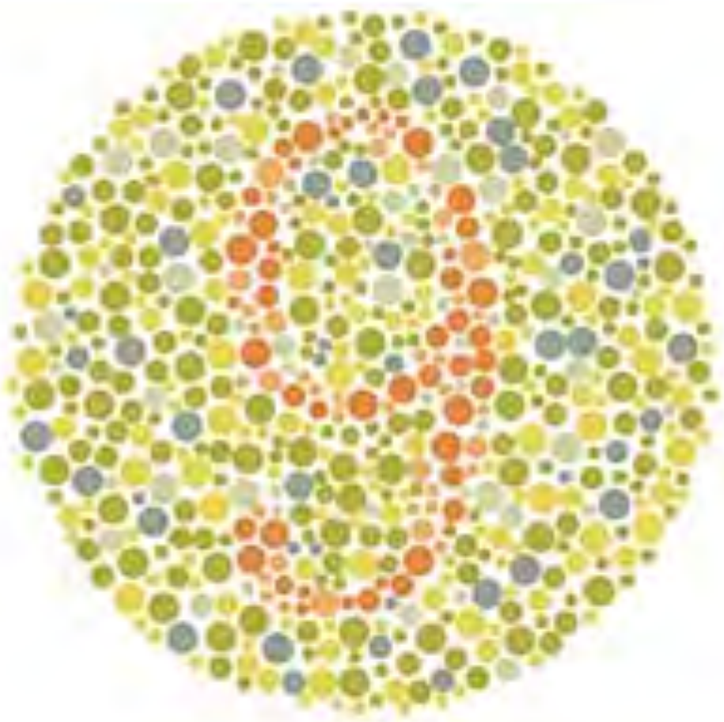


# Примеры моногенных заболеваний

| 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

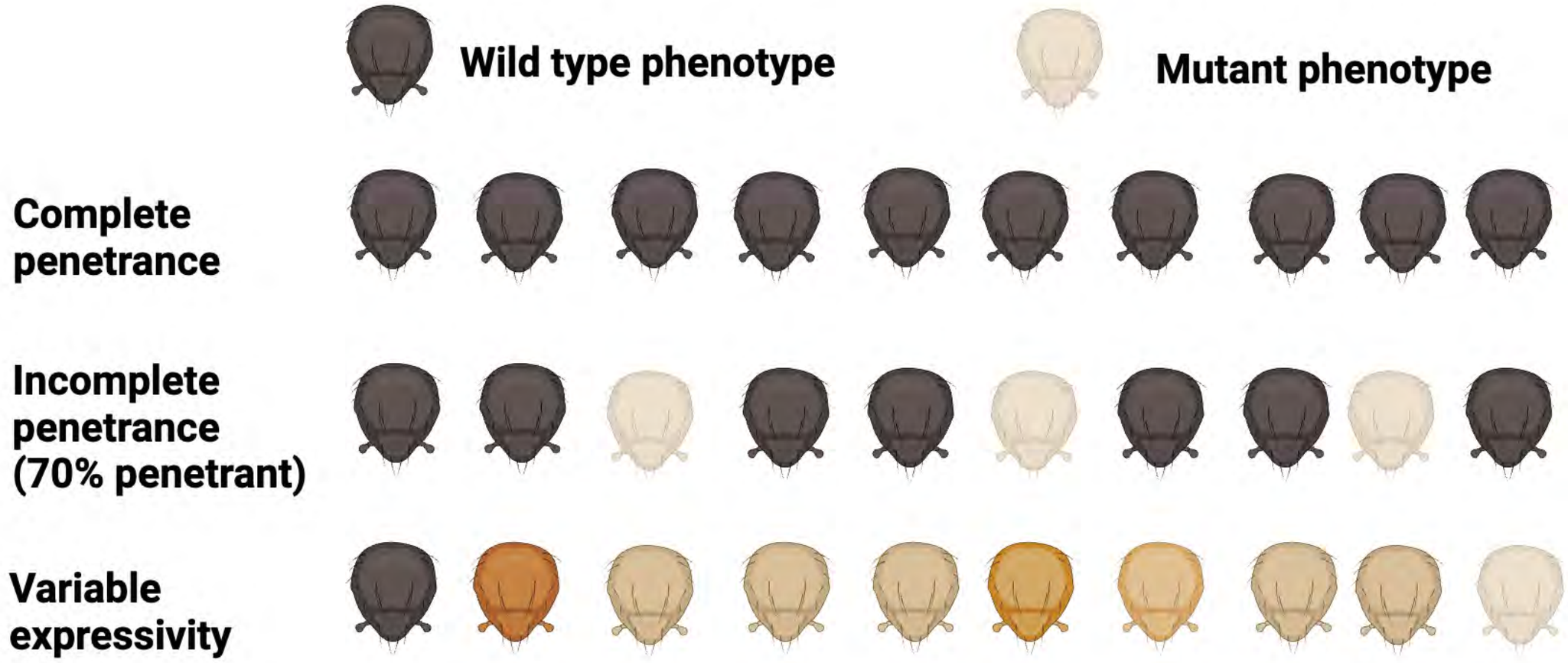


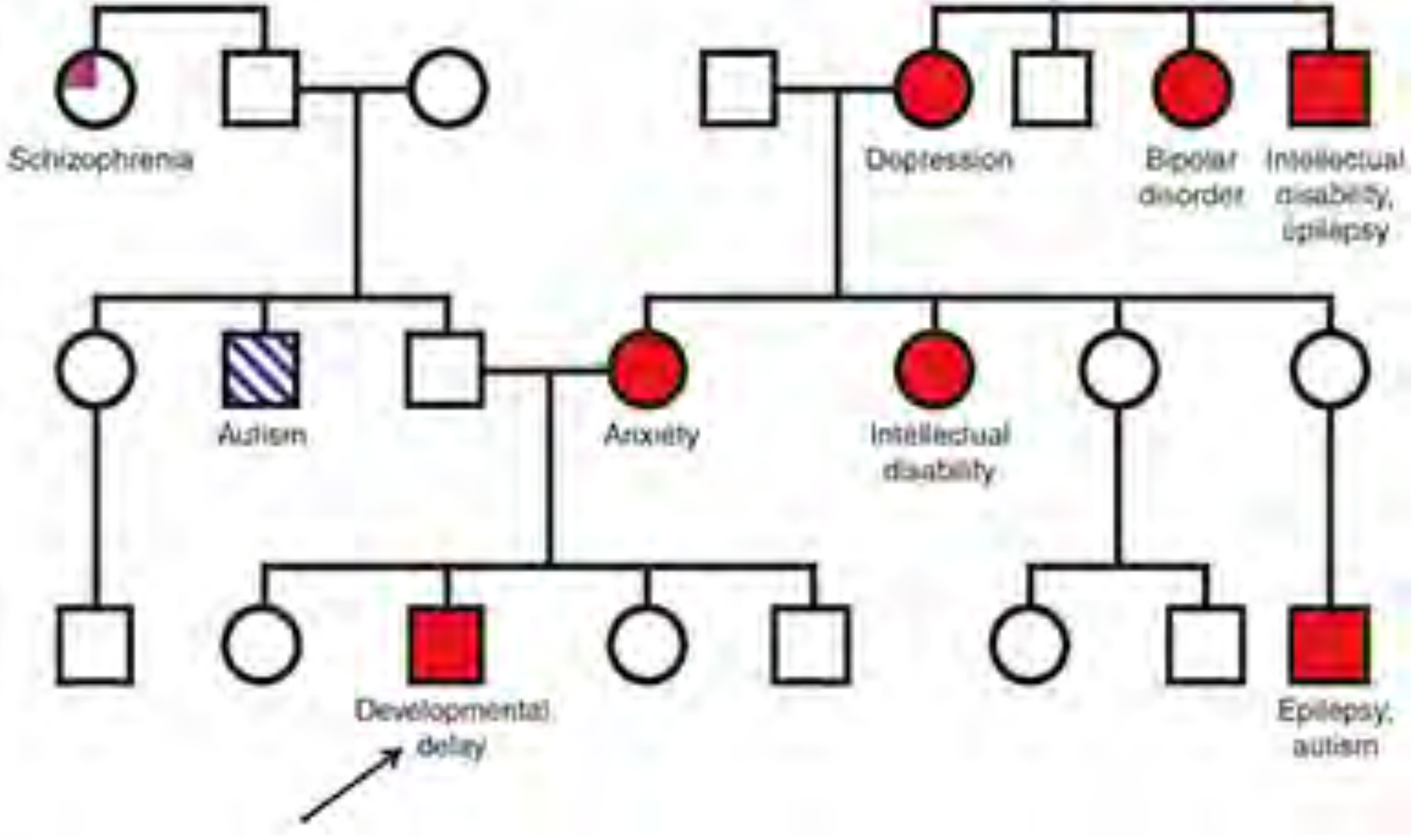
# Сцепленное с полом наследование

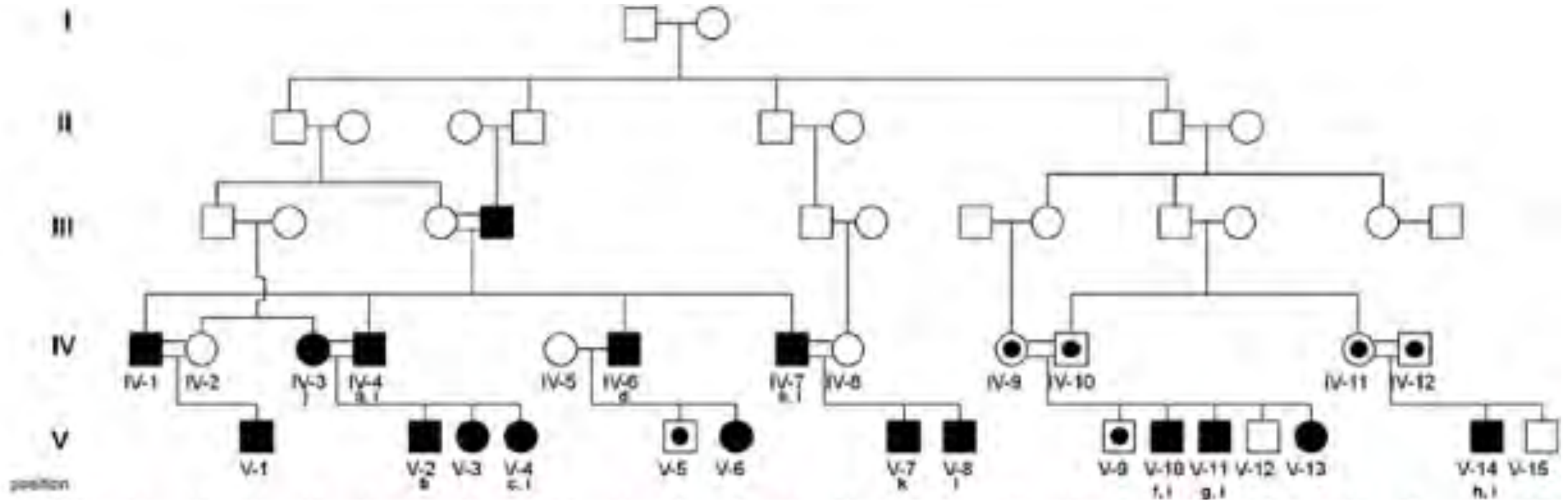
| Тип наследования | Локализация генов | Примеры |
|---|---|---|
| X-сцепленный рецессивный | Негомологичный участок X-хромосомы | Гемофилия, разные формы цветовой слепоты, отсутствие потовых желез, некоторые формы мышечной дистрофии и пр. |
| X-сцепленный доминантный | Негомологичный участок X-хромосомы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

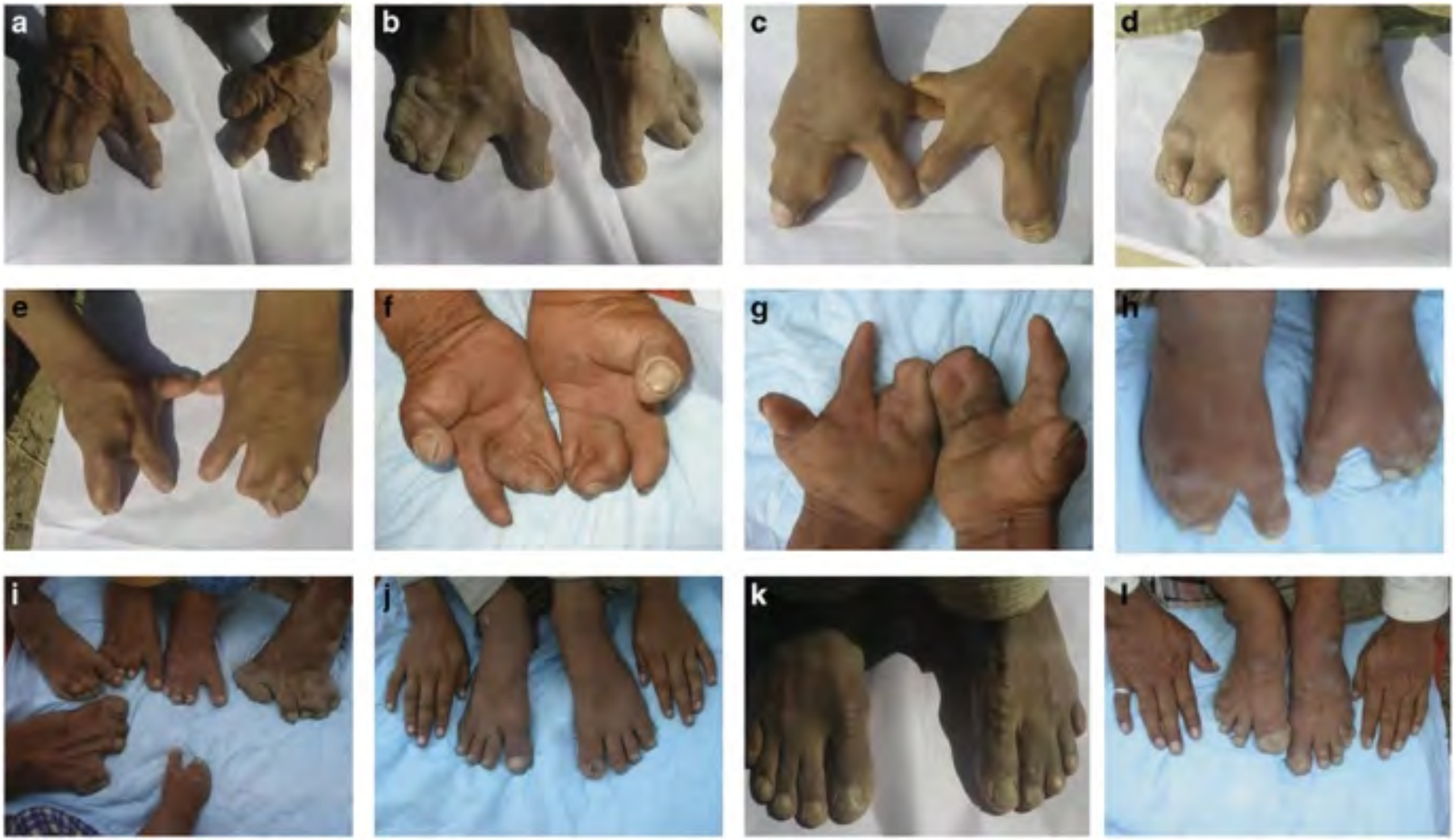
# Неполная пенетрантность и вариабельная экспрессивность



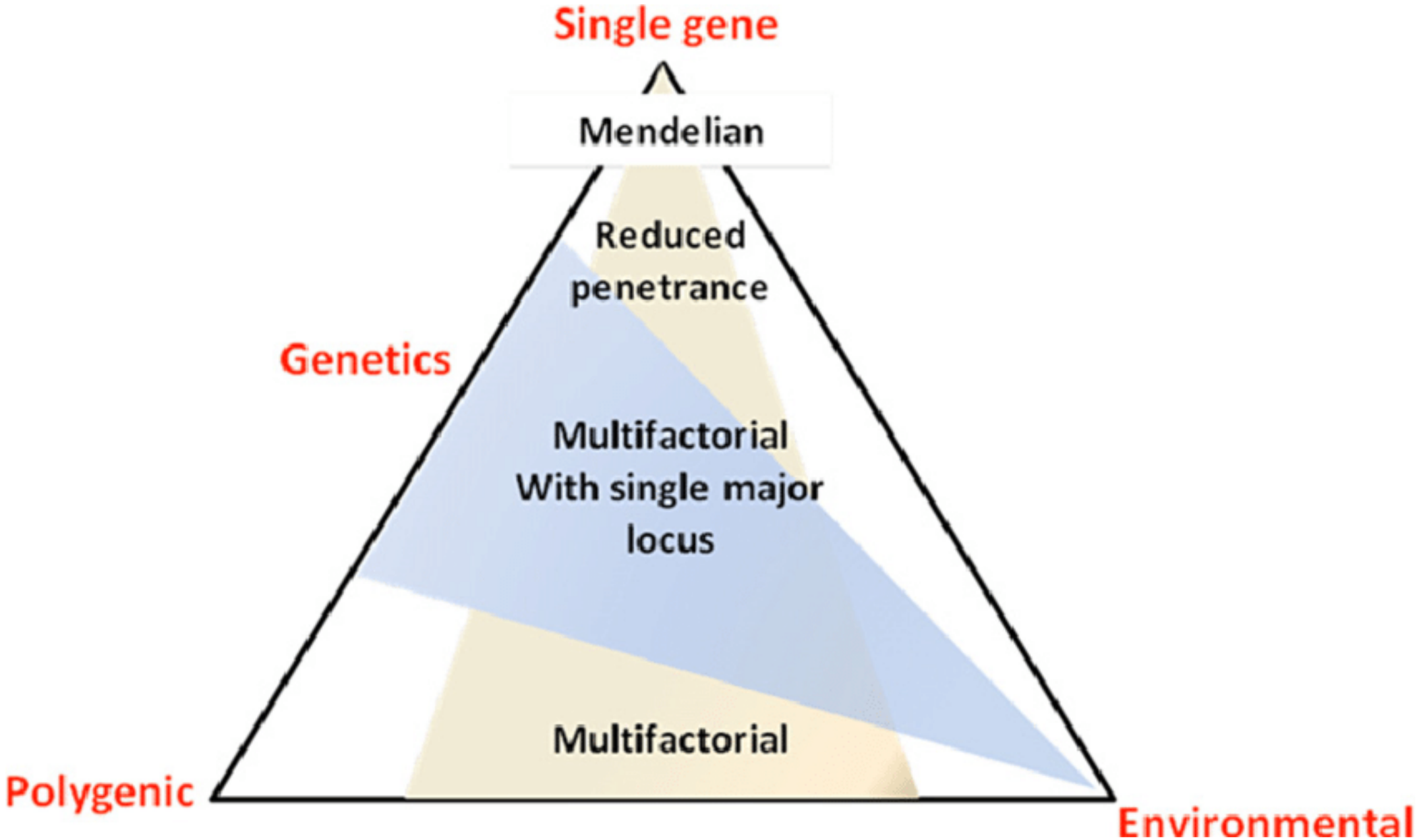
*FMR1* expansions



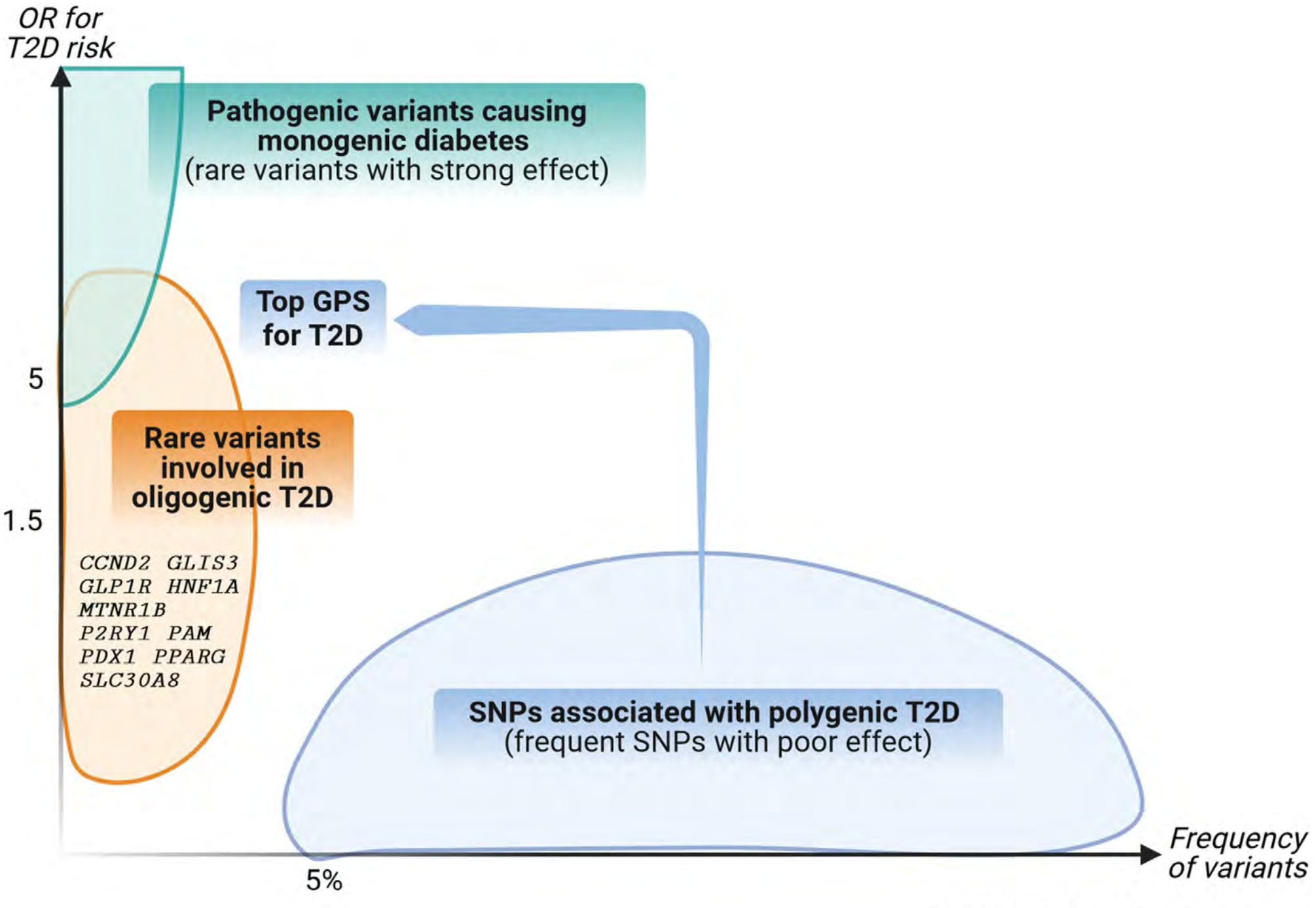

I
II
III
IV
V
IV-1
IV-2
IV-3
IV-4
IV-5
IV-6
IV-7
IV-8
IV-9
IV-10
IV-11
IV-12
V-1
V-2
V-3
V-4
V-5
V-6
V-7
V-8
V-9
V-10
V-11
V-12
V-13
V-14
V-15


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

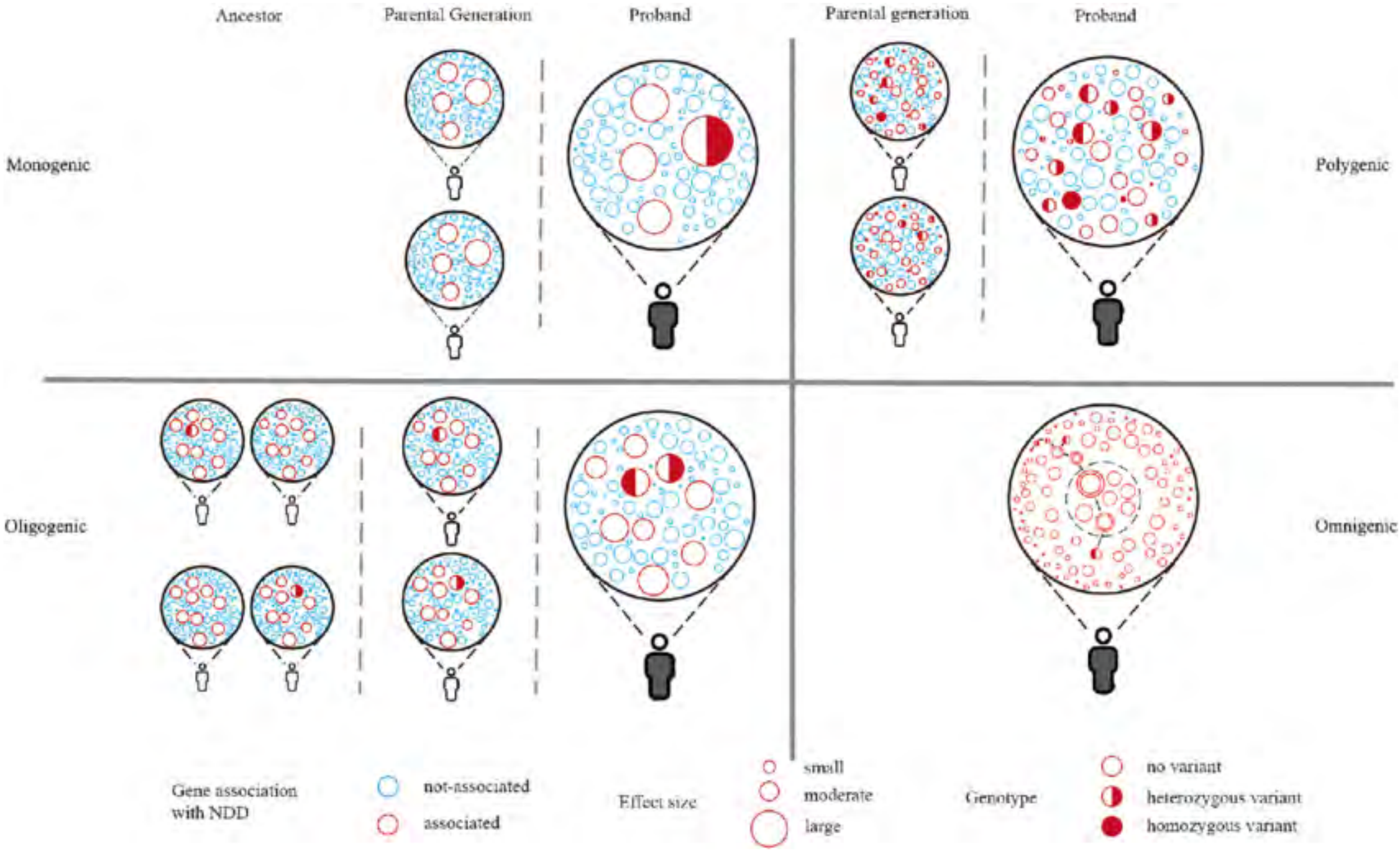
# Классификация наследственных заболеваний



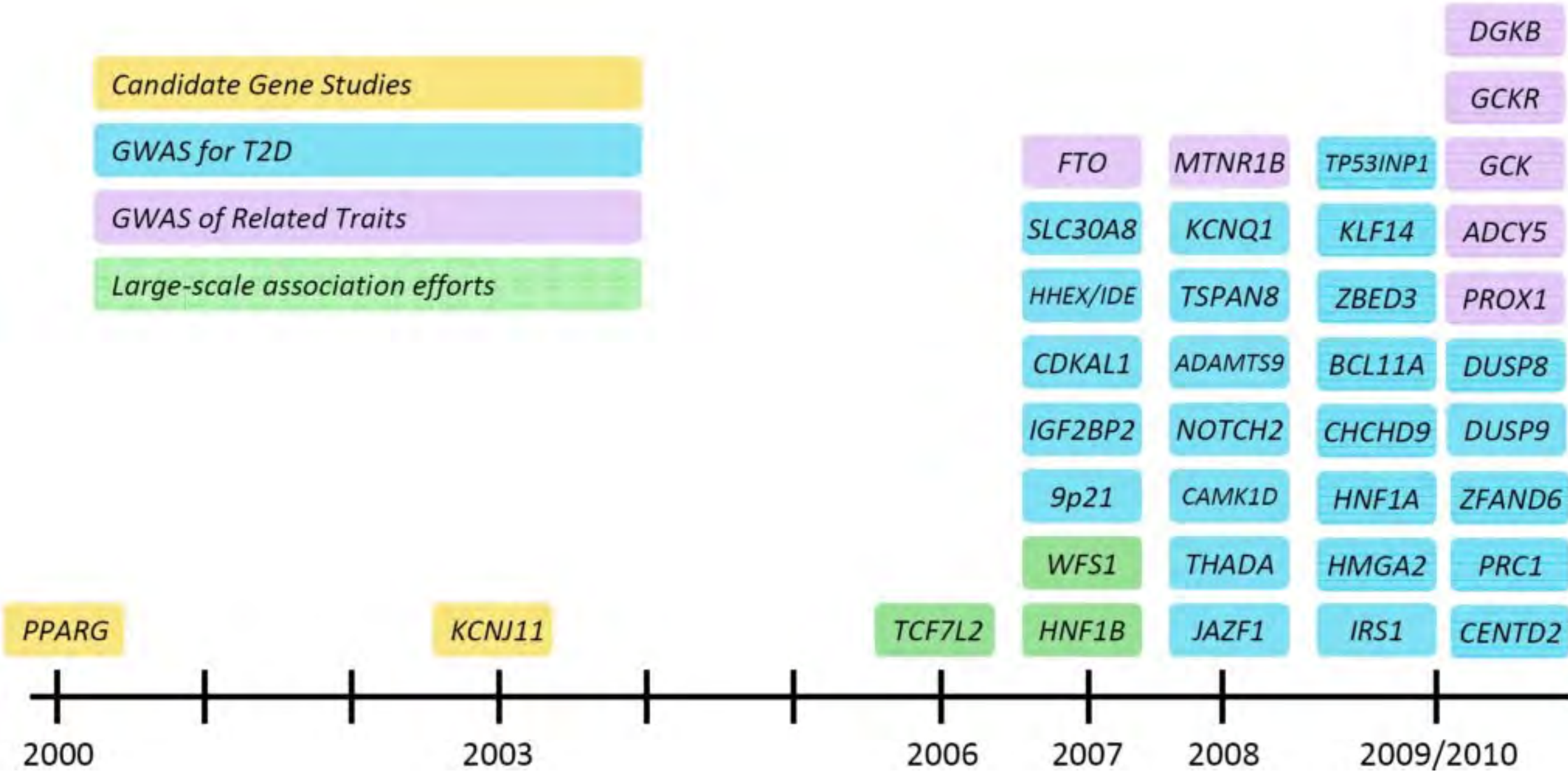
# Олигогенные заболевания



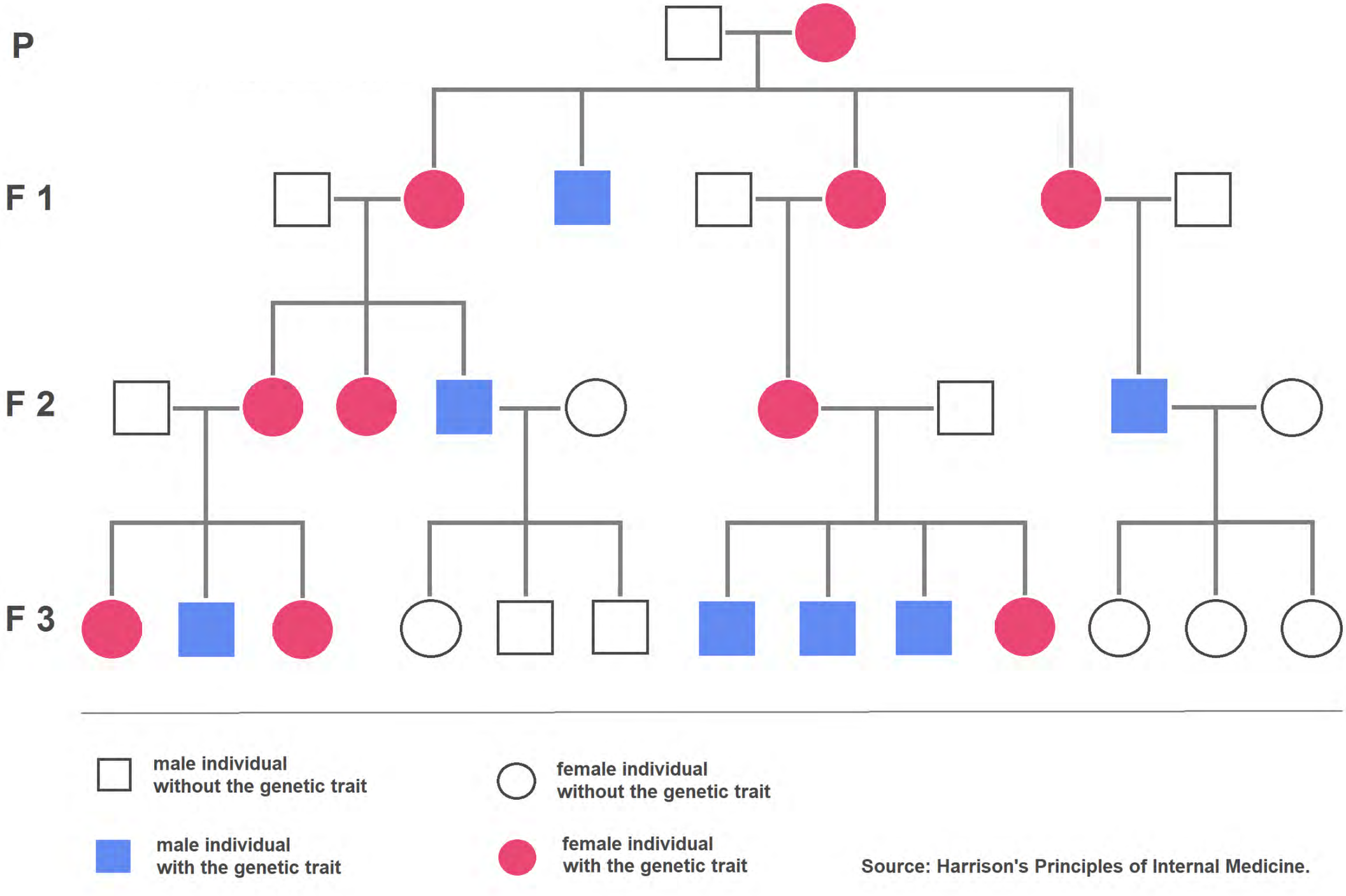
# Полигенные заболевания



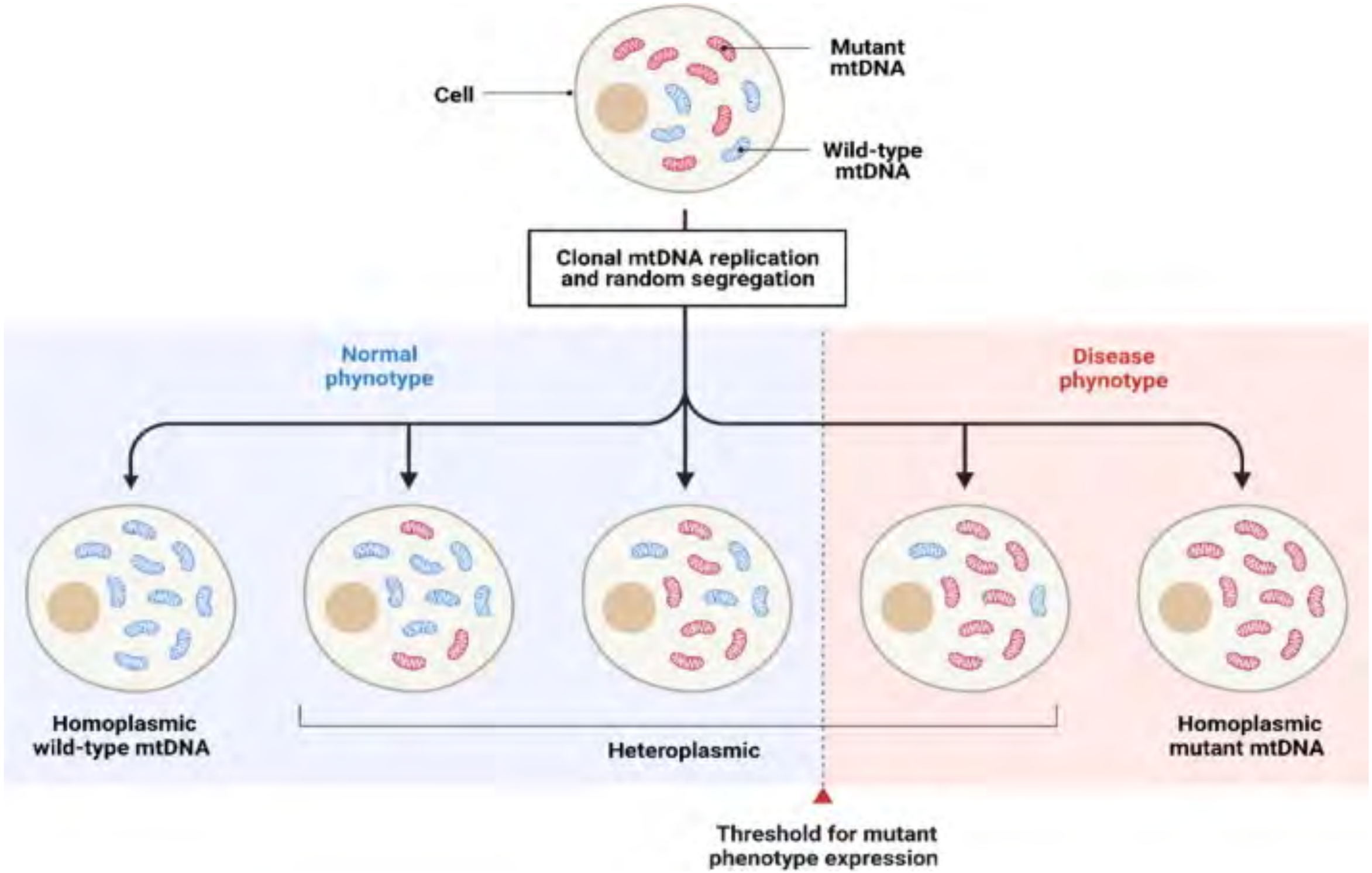
# Диабет 2 типа — полигенное заболевание



# 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**

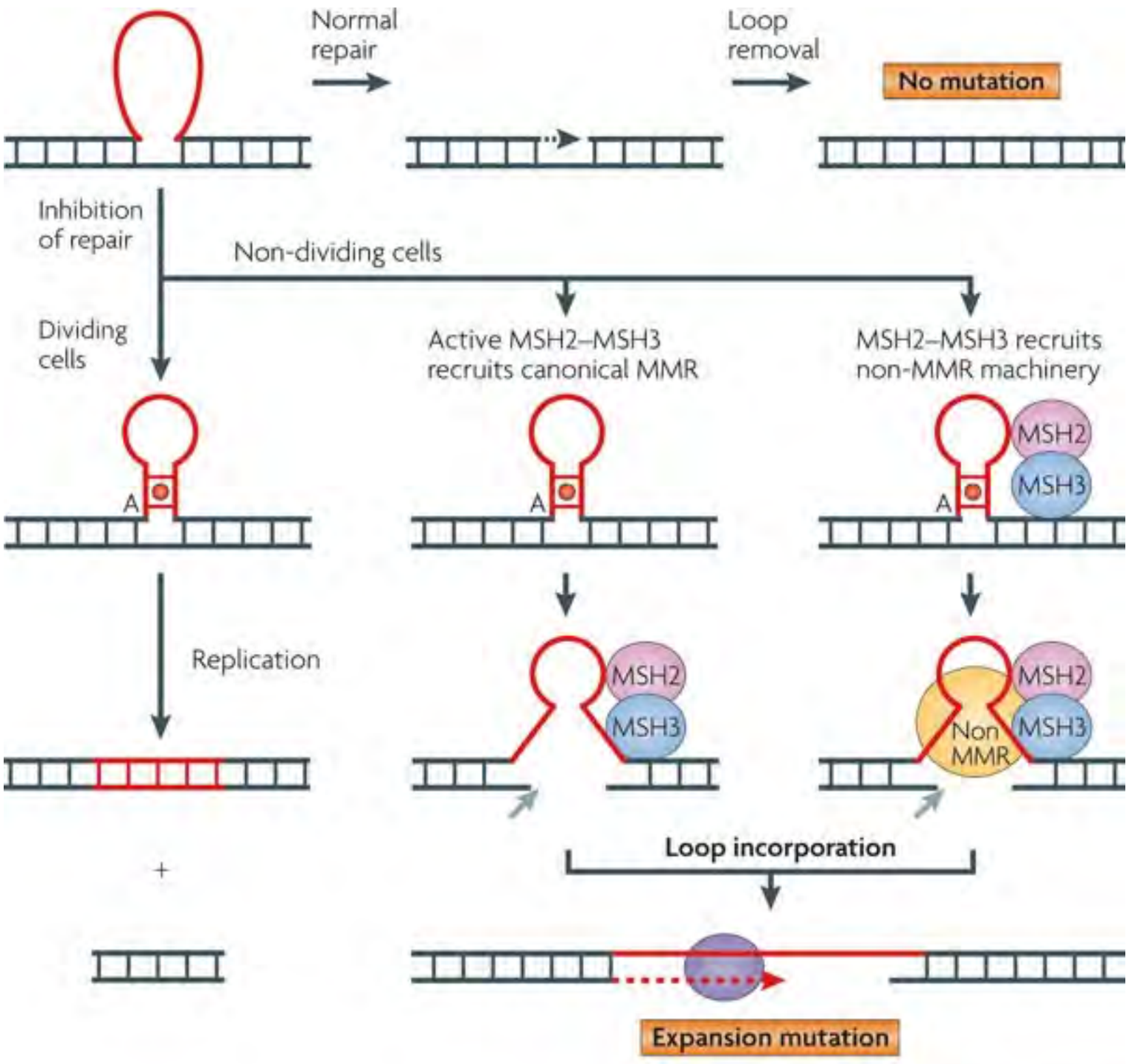
- Deletion
- Ring chromosomes
- Duplication
- Inversion
- Translocation

## Genomic or numeric

**Affect the number of chromosomes**

- Aneuploidy
  - Monosomy
  - Trisomy
- Polyploidies

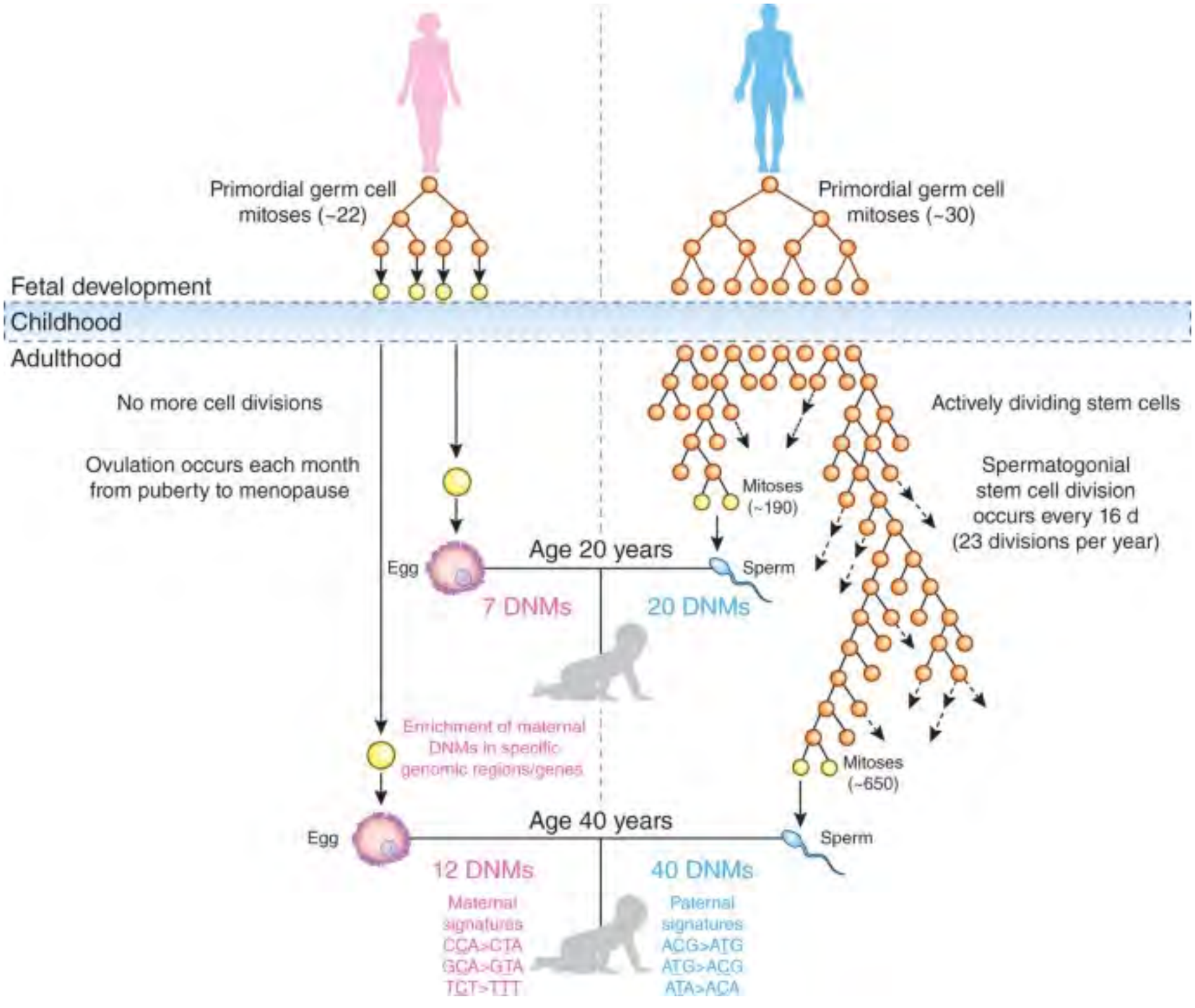
# Динамические мутации



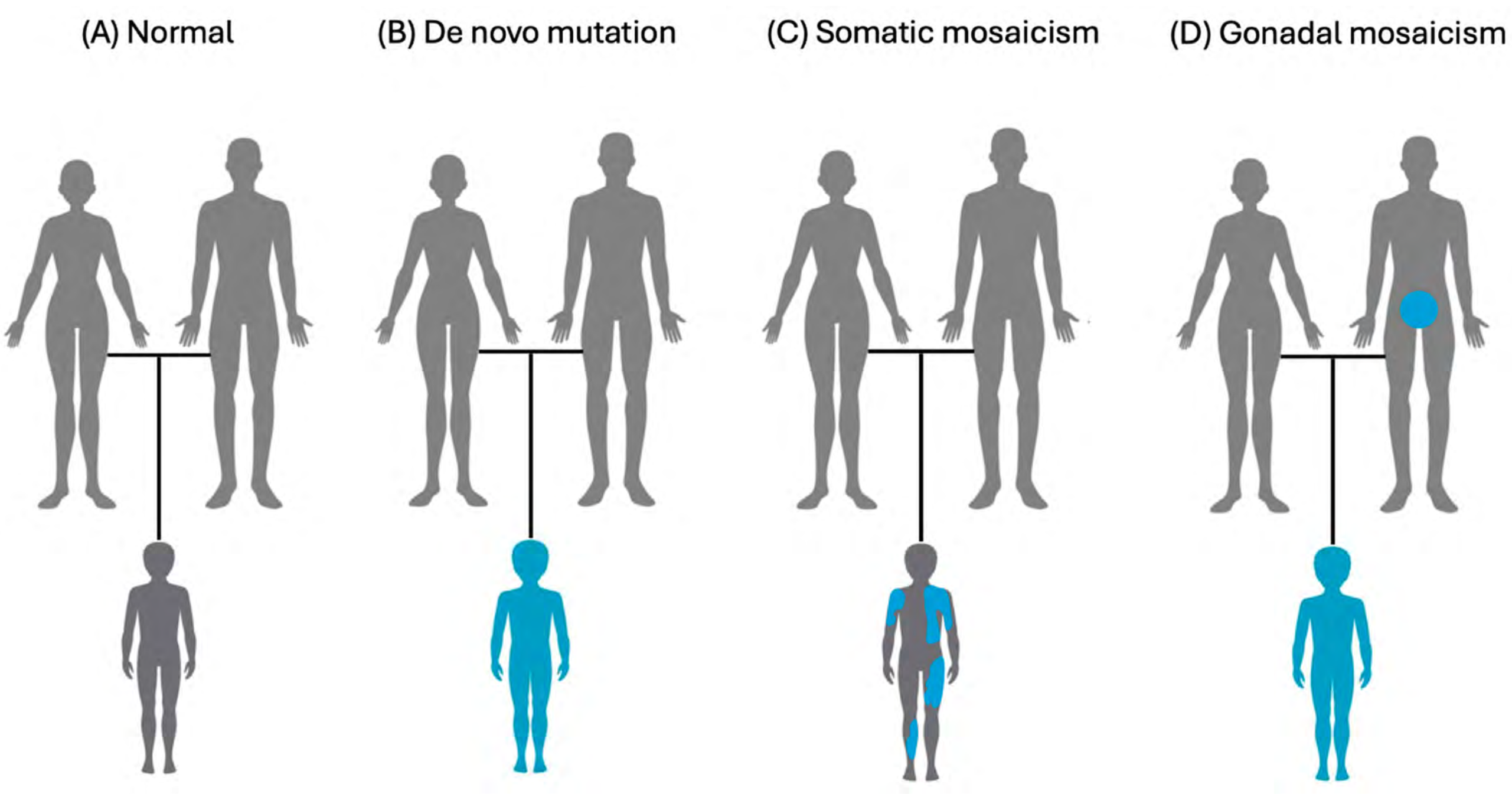
# Динамические мутации

| 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 |

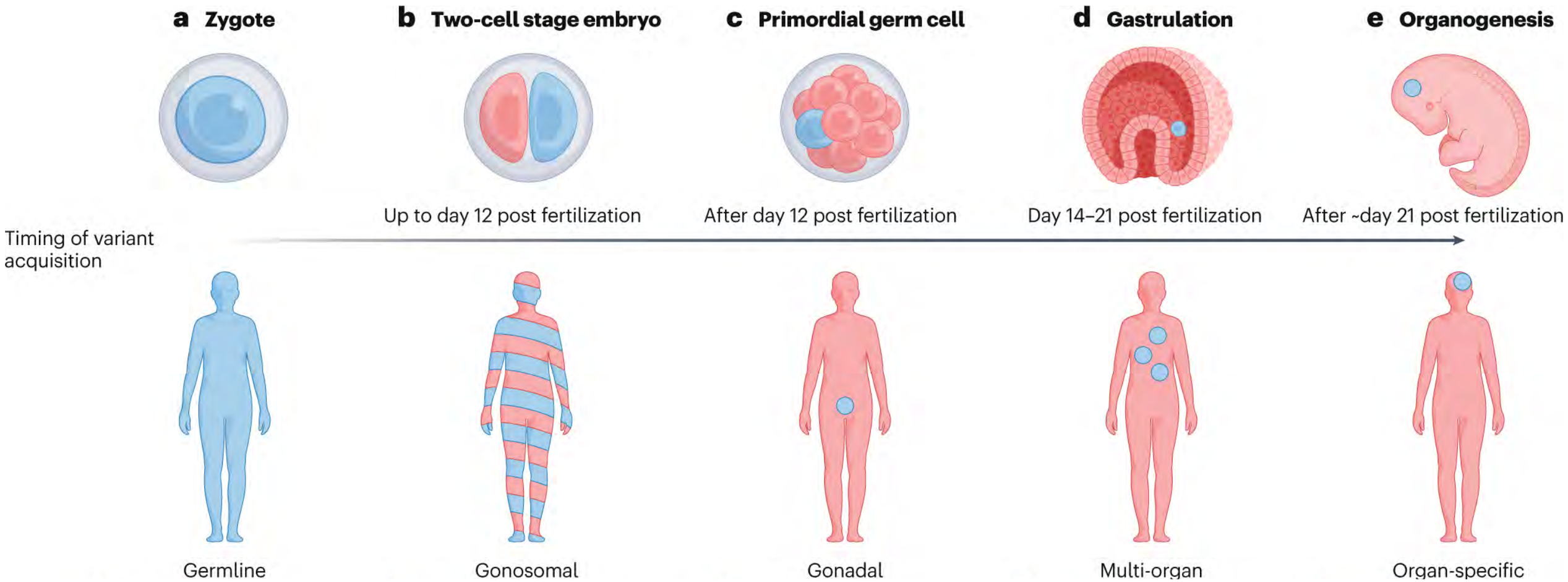
# Мутации de novo



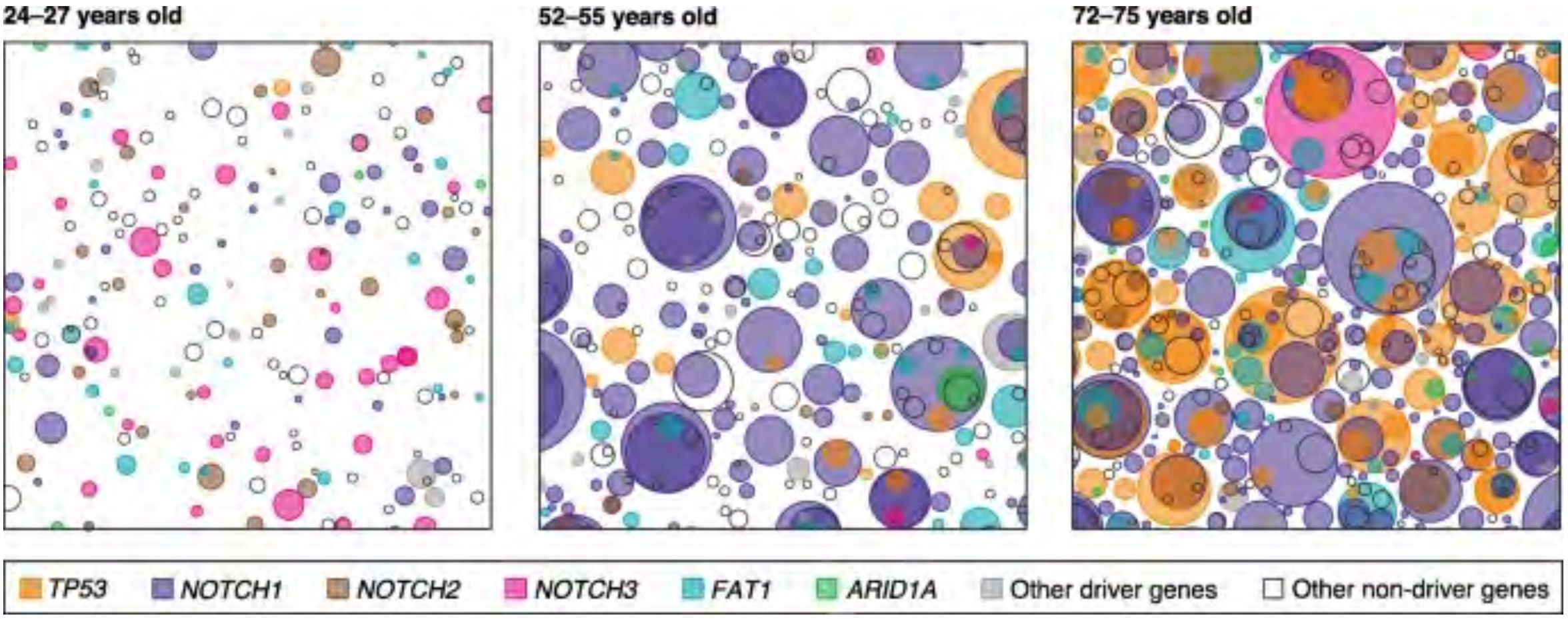
# Мозаицизм


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

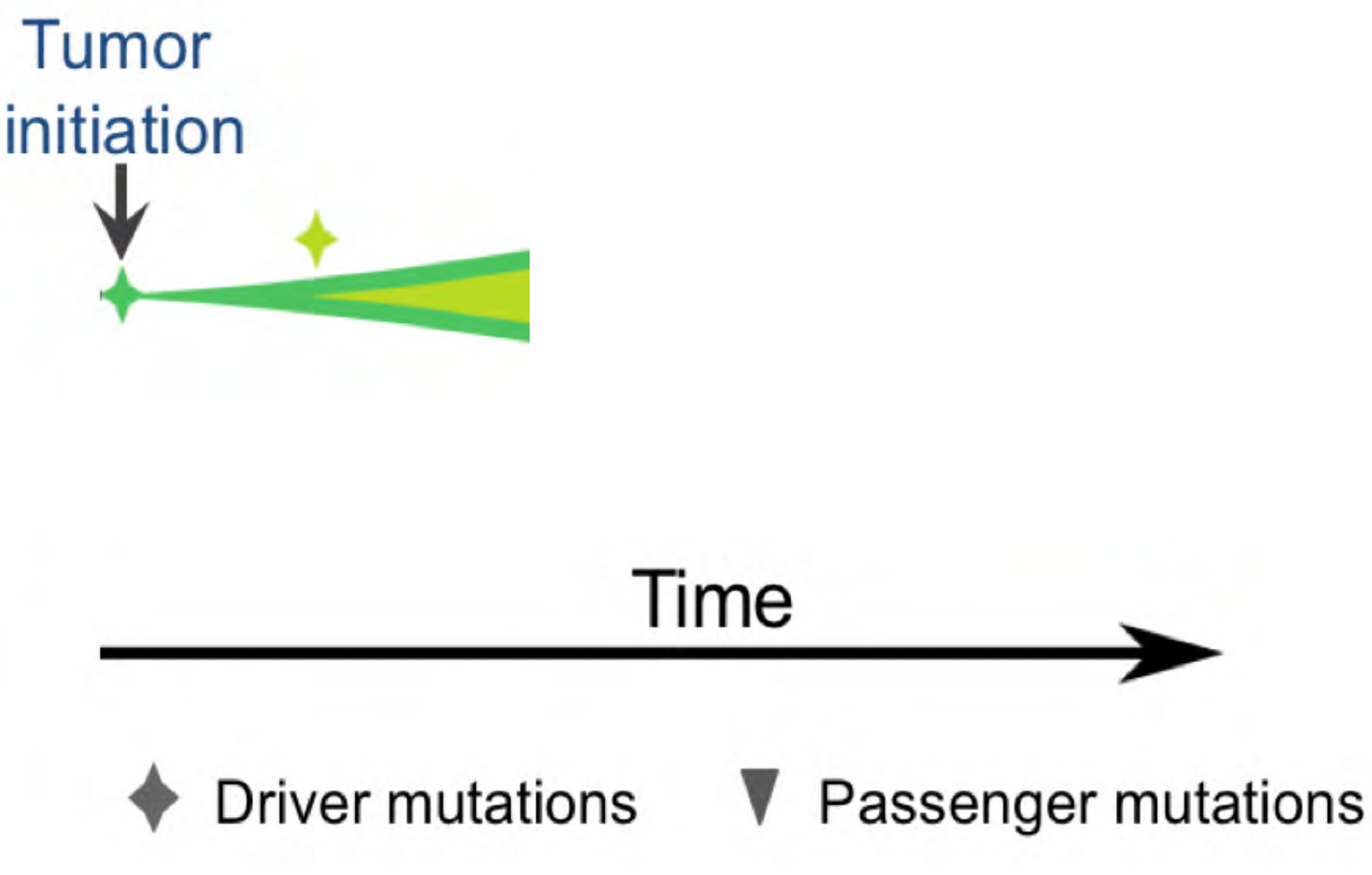
# Мозаицизм


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

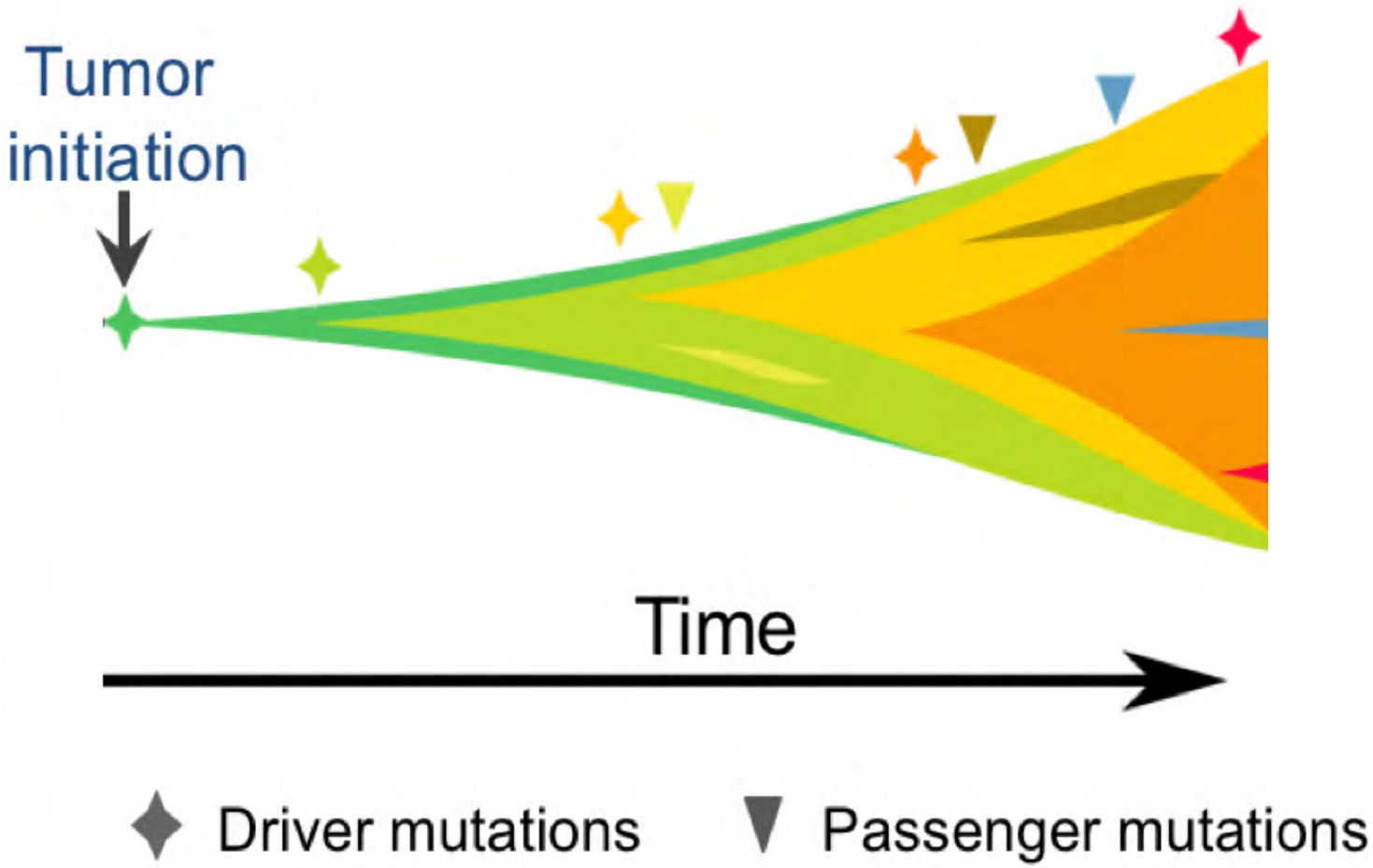
# Соматические мутации



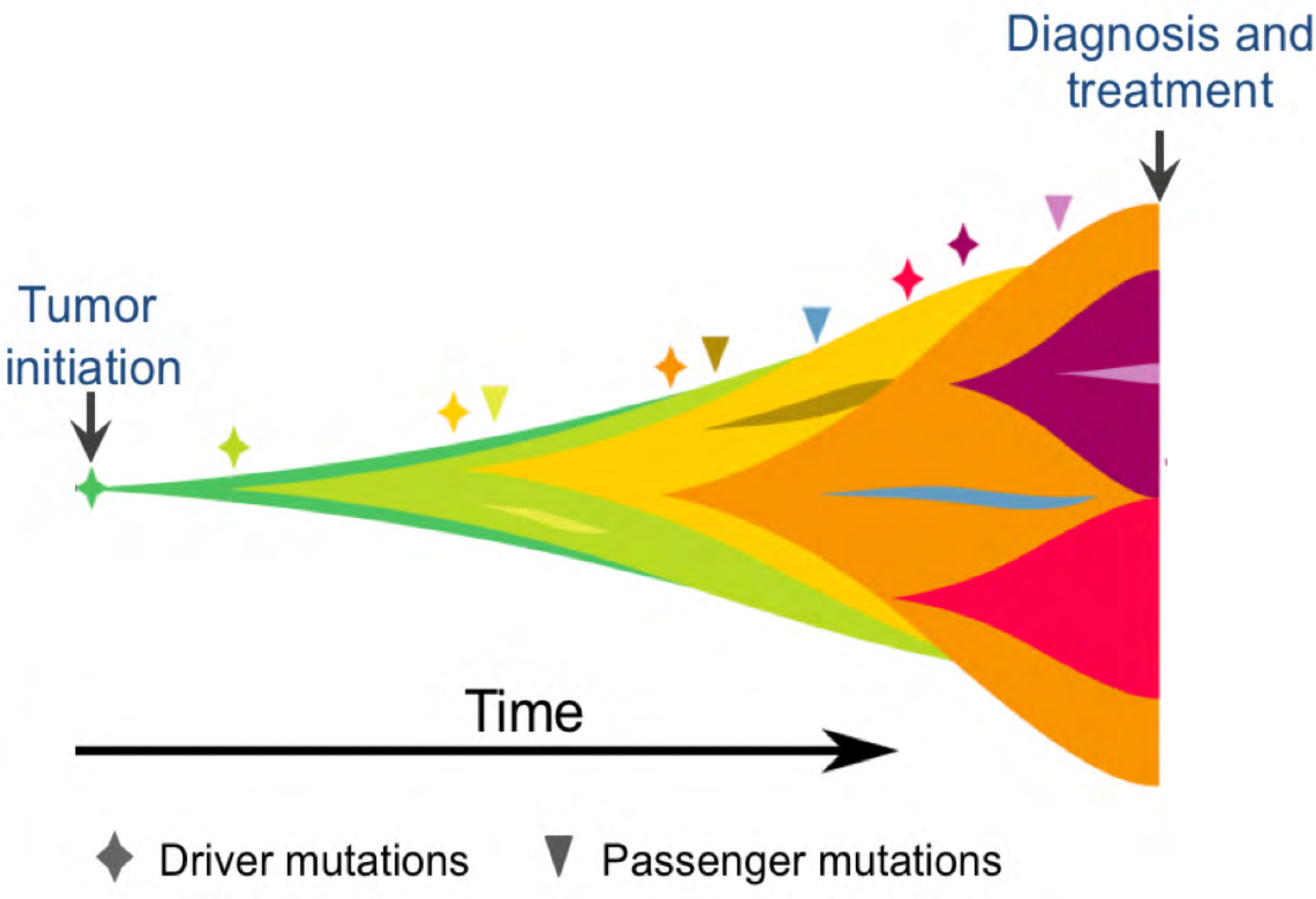
# Соматические мутации



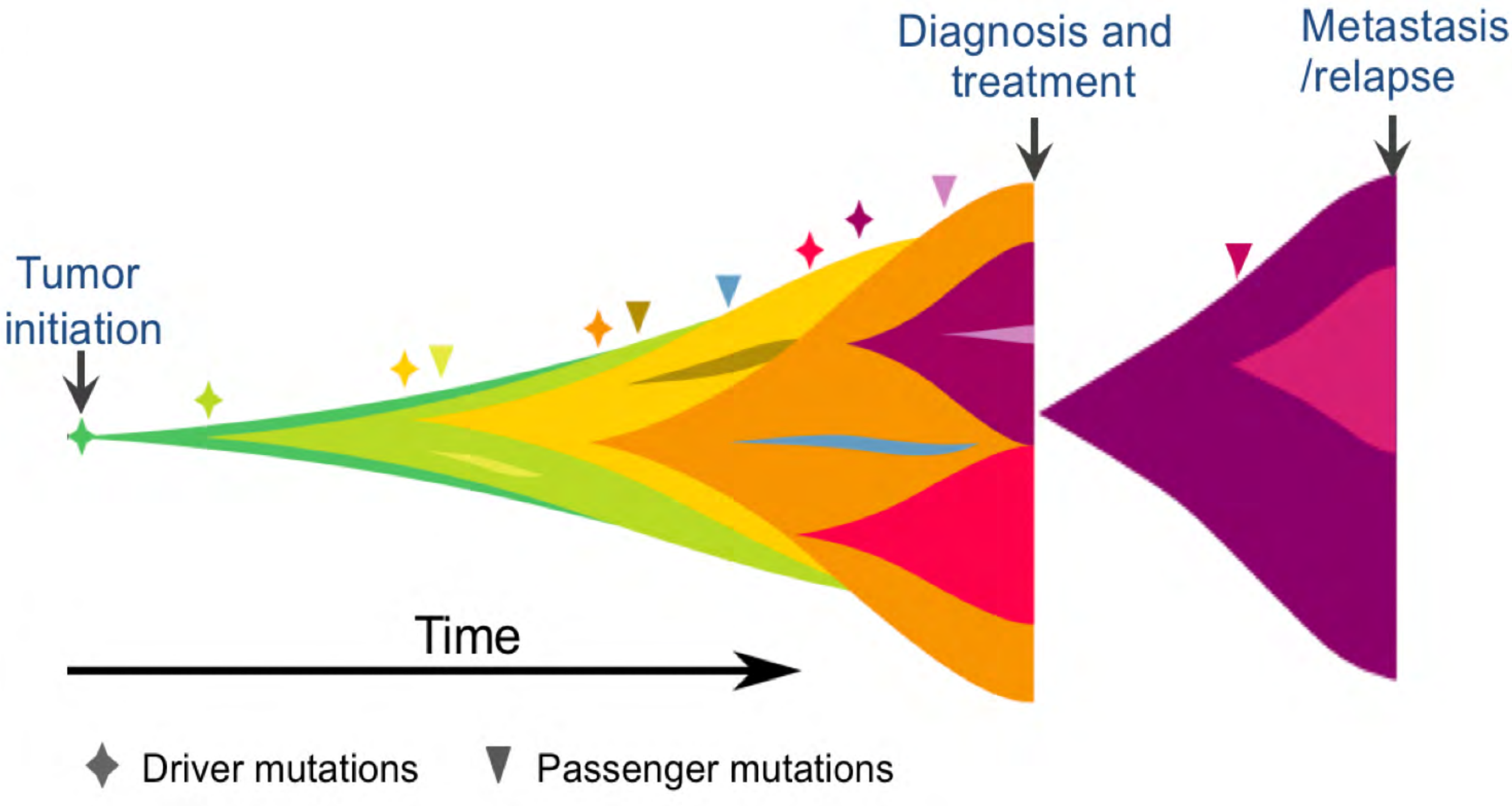
# Соматические мутации



# Соматические мутации

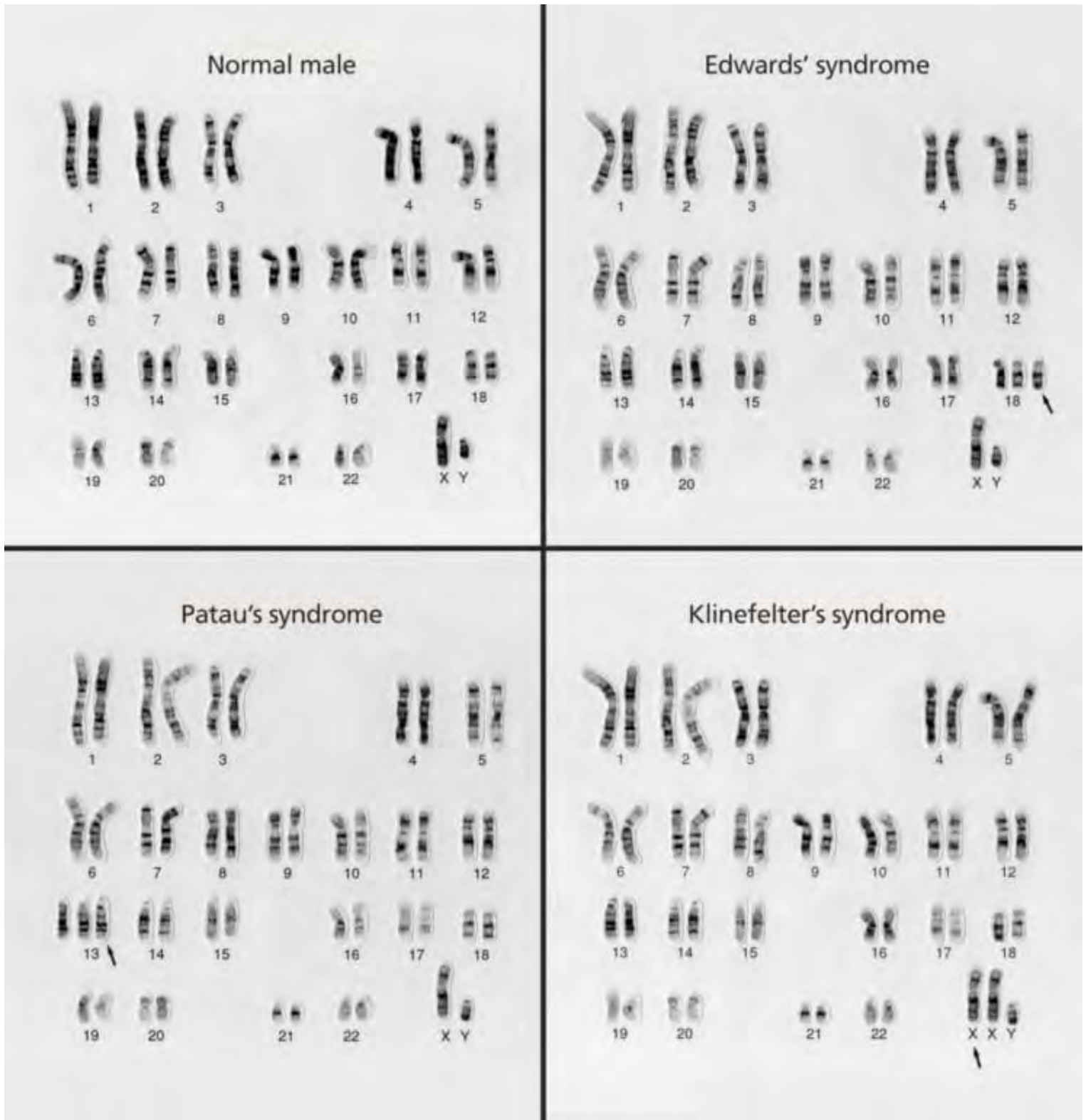


# Соматические мутации

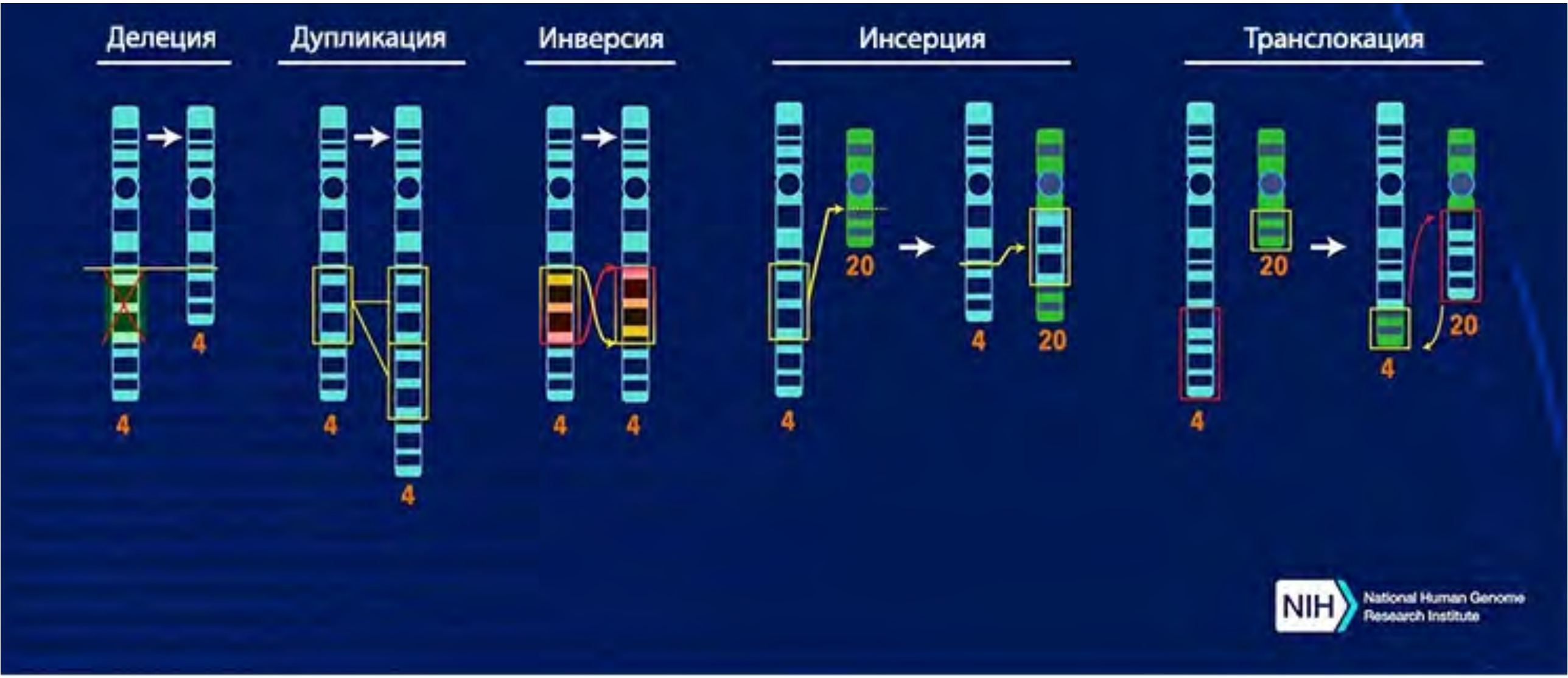


# Хромосомные аномалии

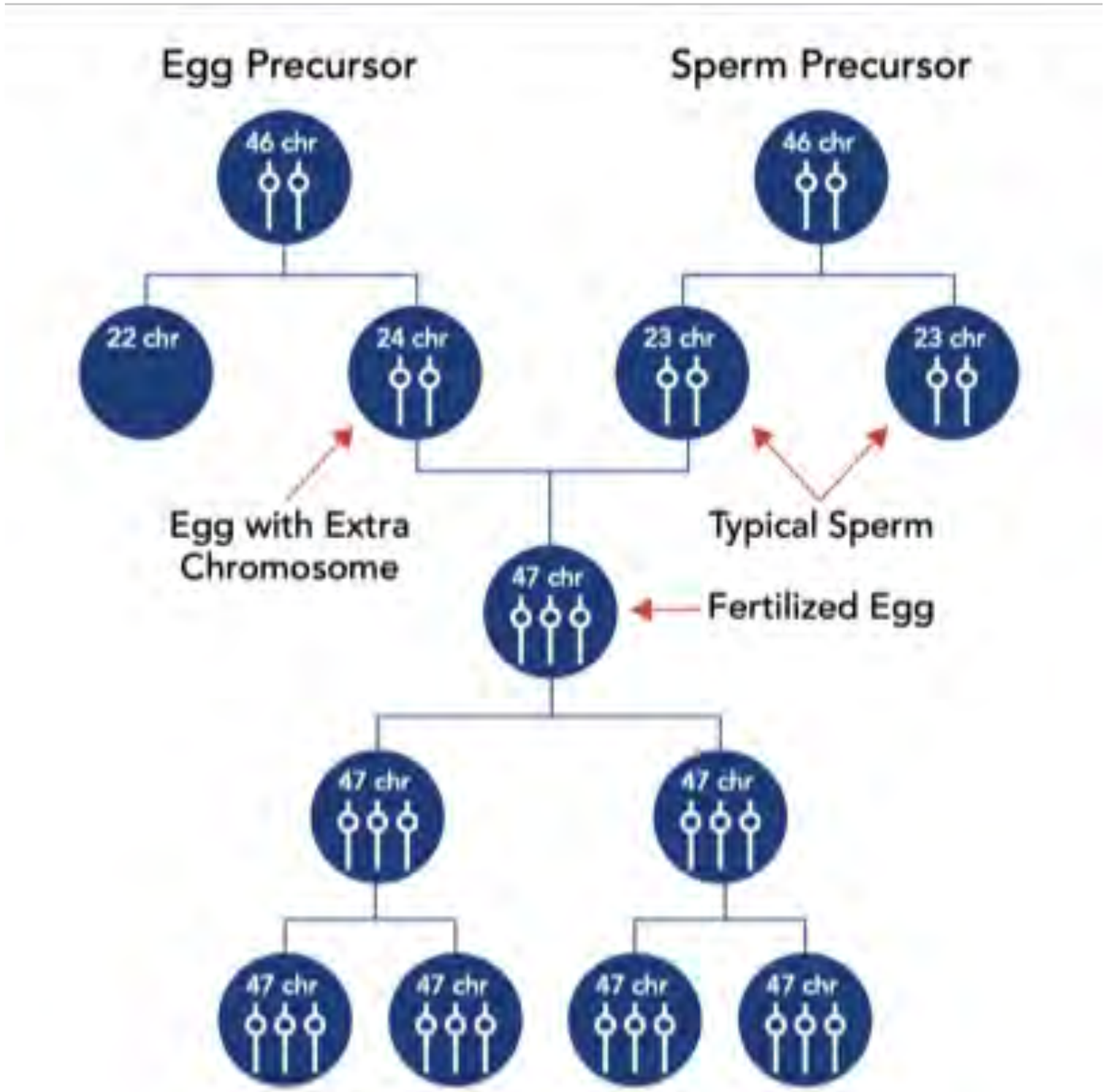
# Трисомии


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

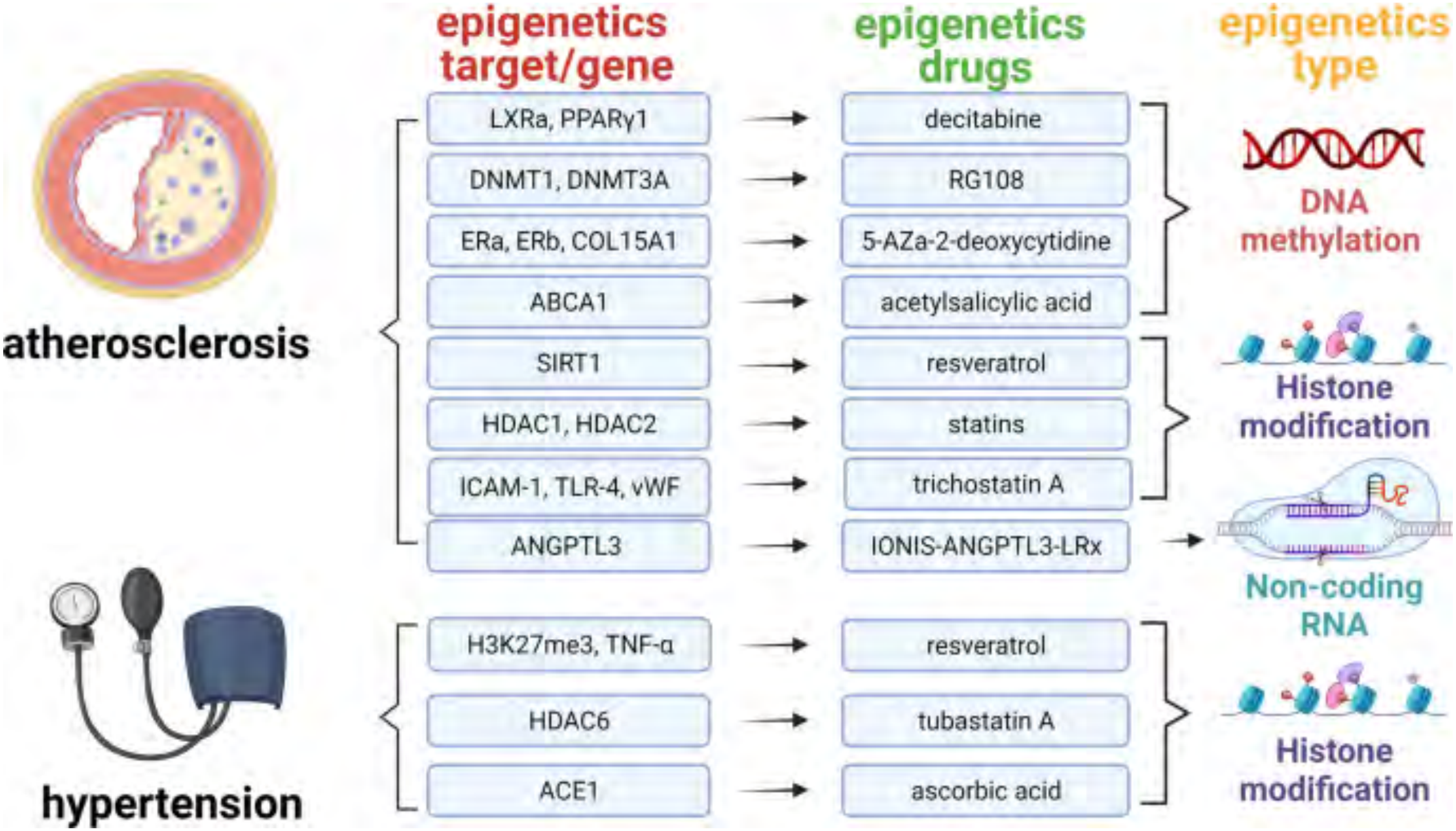
# Структурные аномалии хромосом



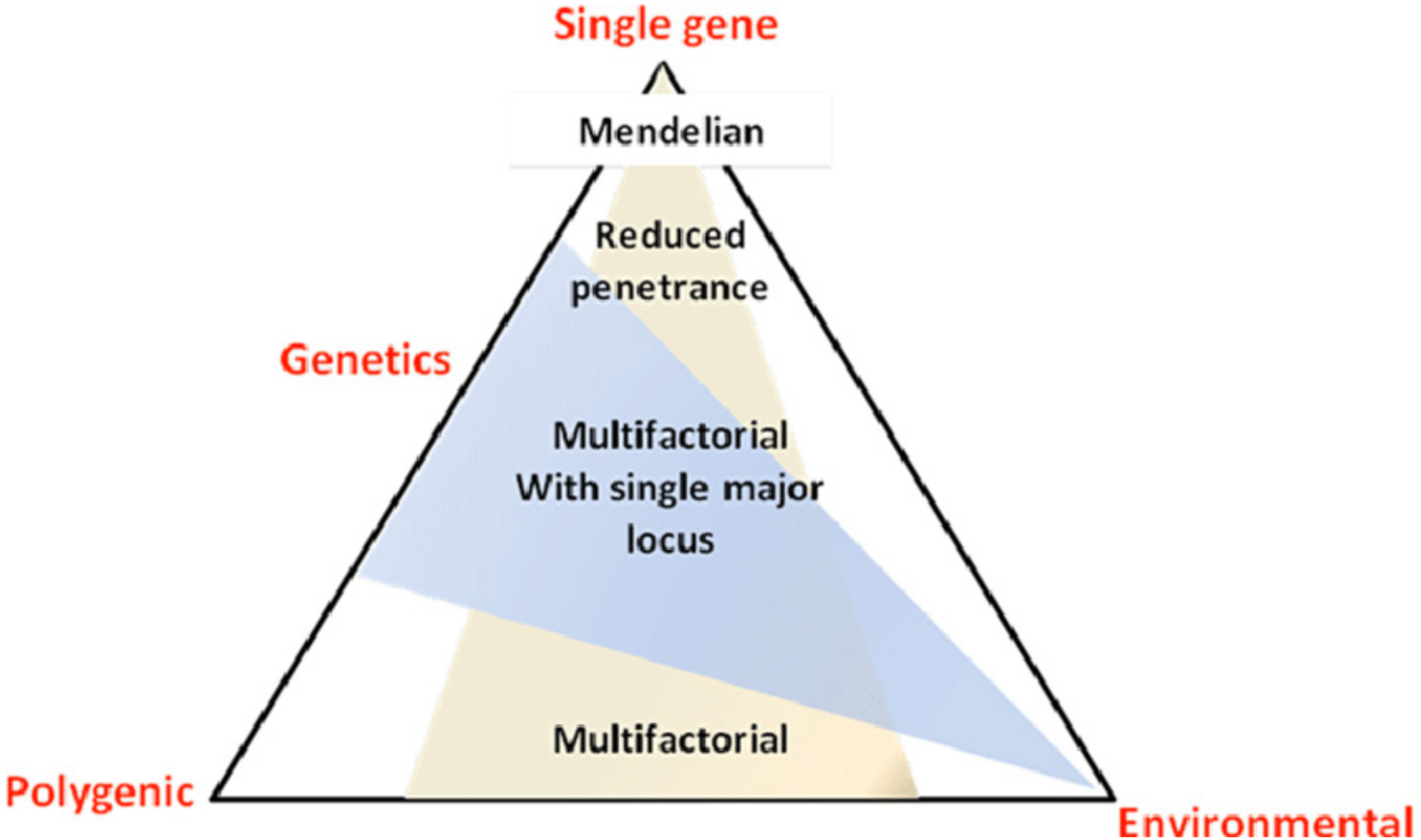
# Синдром Дауна



# 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

$F_1$:   

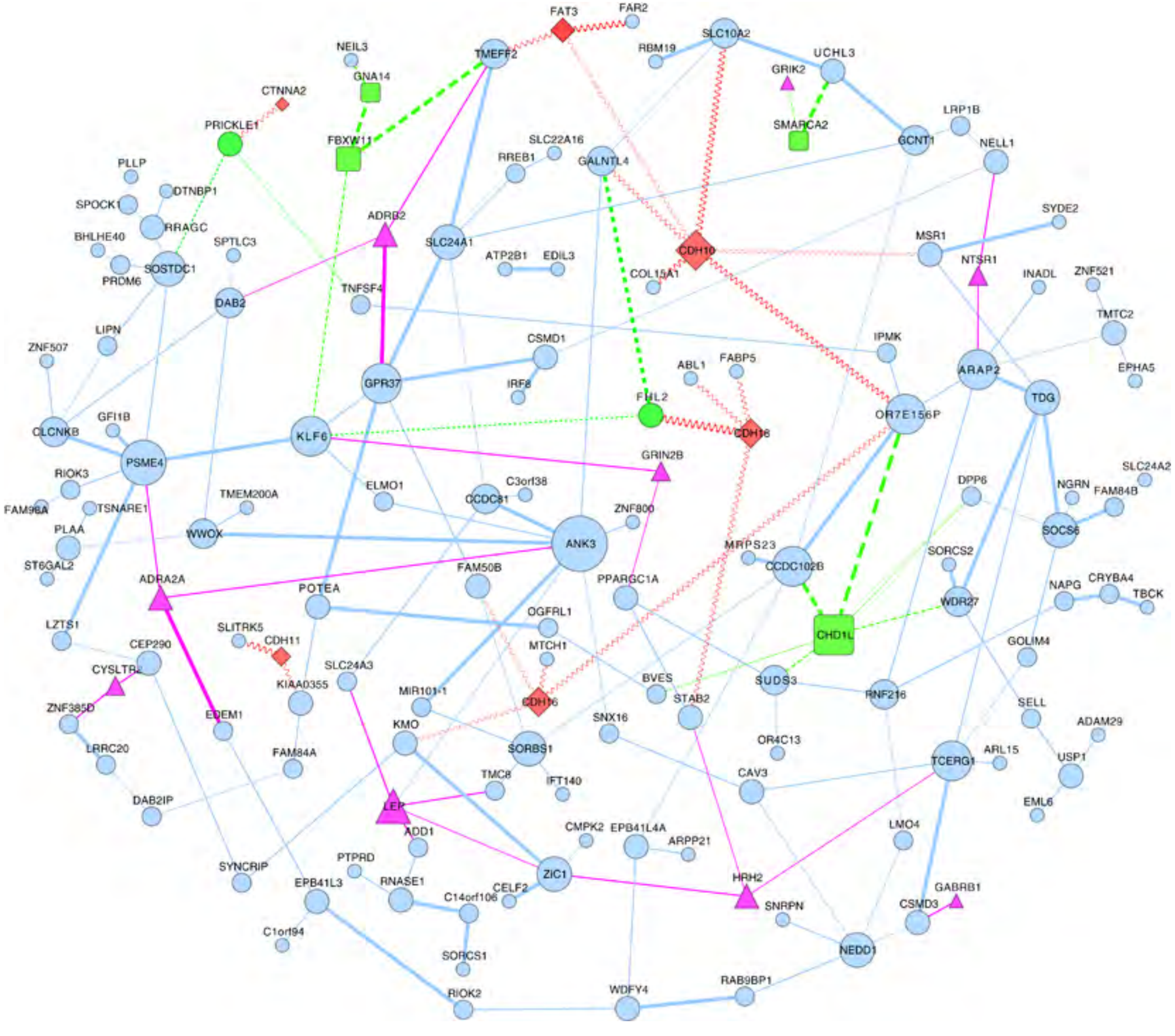
Подавляют синтез пигмента

Ген A даёт оранжевую окраску

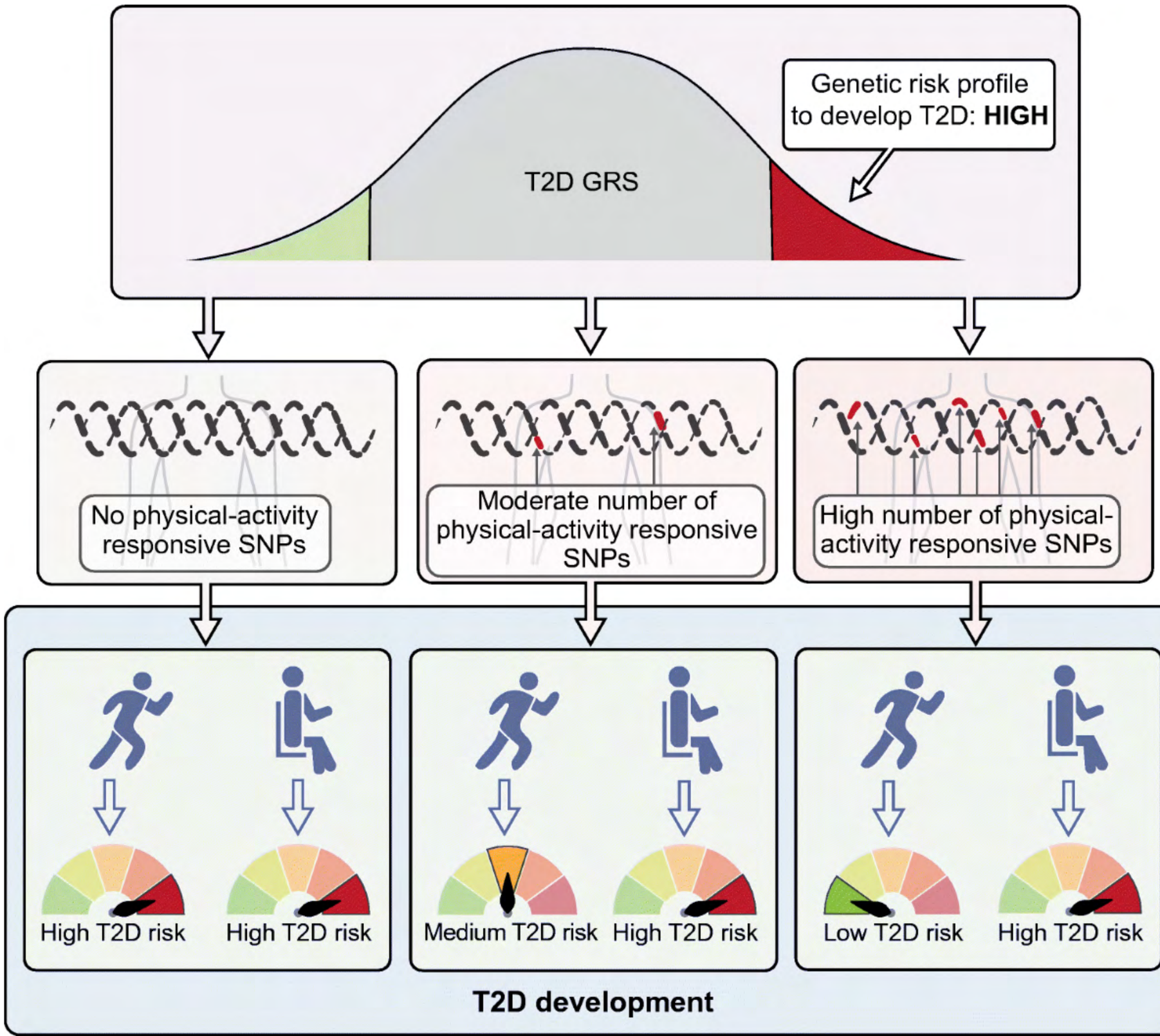
aa даёт зелёную окраску

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

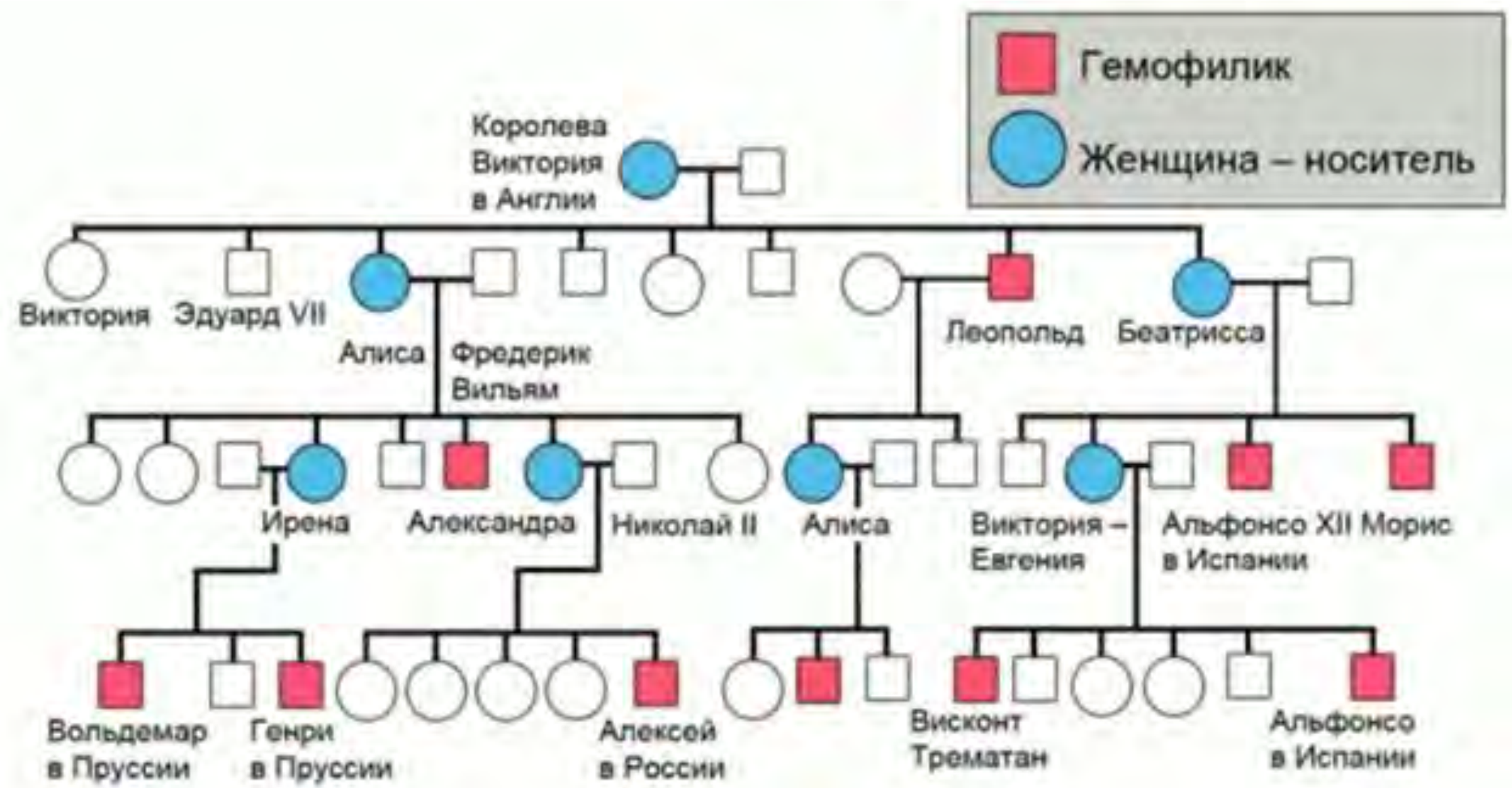
# Близнецовые исследования

| | 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

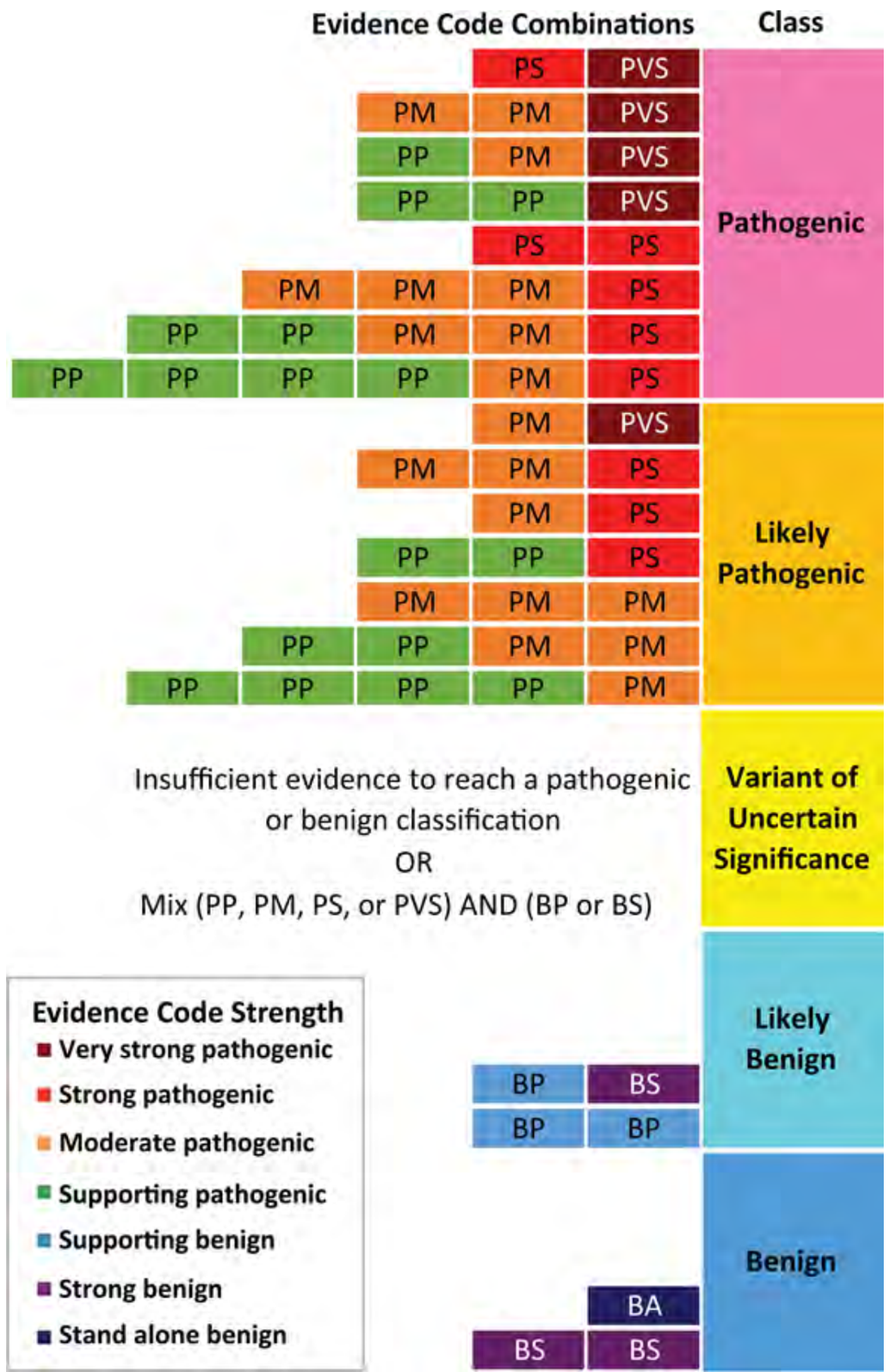
| | | BENIGN CRITERIA | | PATHOGENIC CRITERIA | | | |
|---|---|---|---|---|---|---|---|
| Strength of evidence | | Strong | Supporting | Supporting | Moderate | Strong | Very Strong |
| Odds of Pathogenicity* | | –18.7 | –2.08 | 2.08 | 4.33 | 18.7 | 350.0 |
| Evidence Category and Corresponding ACMG/AMP Codes | Population Data | *BA1*<br>BS1<br>BS2 | | | PM2 | PS4 | |
| | Allelic Evidence & Cosegregation Data | BS4 | BP2<br>BP5 | PP1 → | PM1<br>PM6 | PS2 | |
| | Computation & Predictive Data | | BP1<br>BP3<br>BP4<br>BP7 | PP2<br>PP3 | PM1<br>PM4<br>PM5 | PS1 | PVS1 |
| | Functional Data | BS3 | | | | PS3 | |
| | Other | | BP6 | PP4<br>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<br><br>Missense in gene where only truncating cause disease BP1<br><br>Silent variant with non predicted splice impact BP7<br><br>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<br><br>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<br><br>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 | | | |

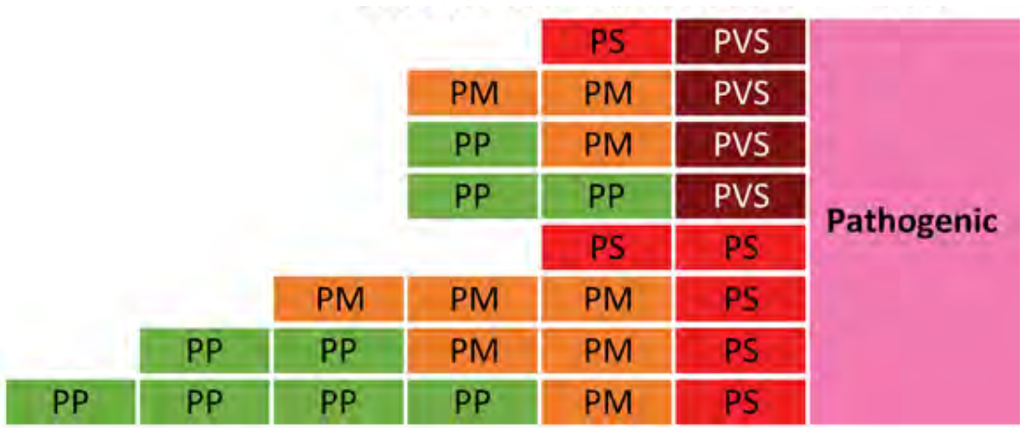
# Классификация генетических вариантов

| | |
|---|---|
| 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



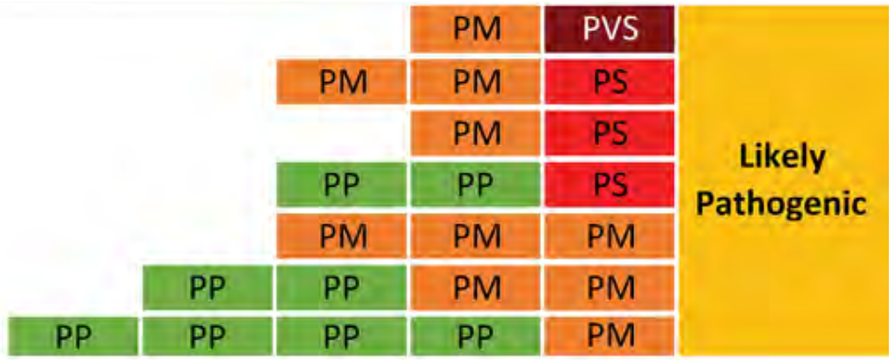
# Патогенные варианты




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<br><br>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 | |
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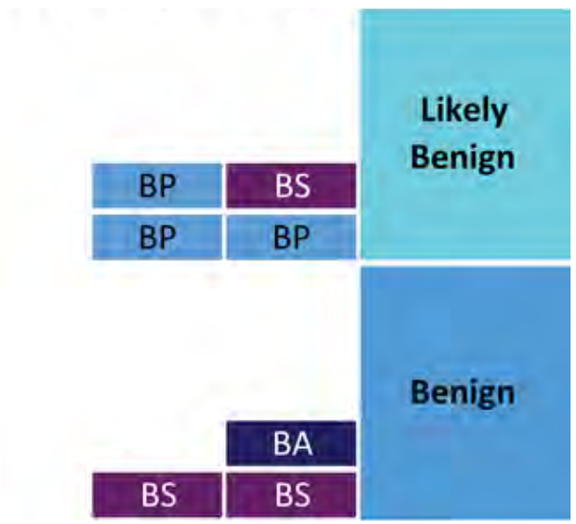
| | De novo (without paternity & maternity confirmed) PM6 | De novo (paternity and maternity confirmed) PS2 | |
| | For recessive disorders, detected in trans with a pathogenic variant PM3 | | |
| Reputable source = pathogenic PP5 | | | |
| Patient's phenotype or FH highly specific for gene PP4 | | | |

# Варианты неопределенного значения (VUS)

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

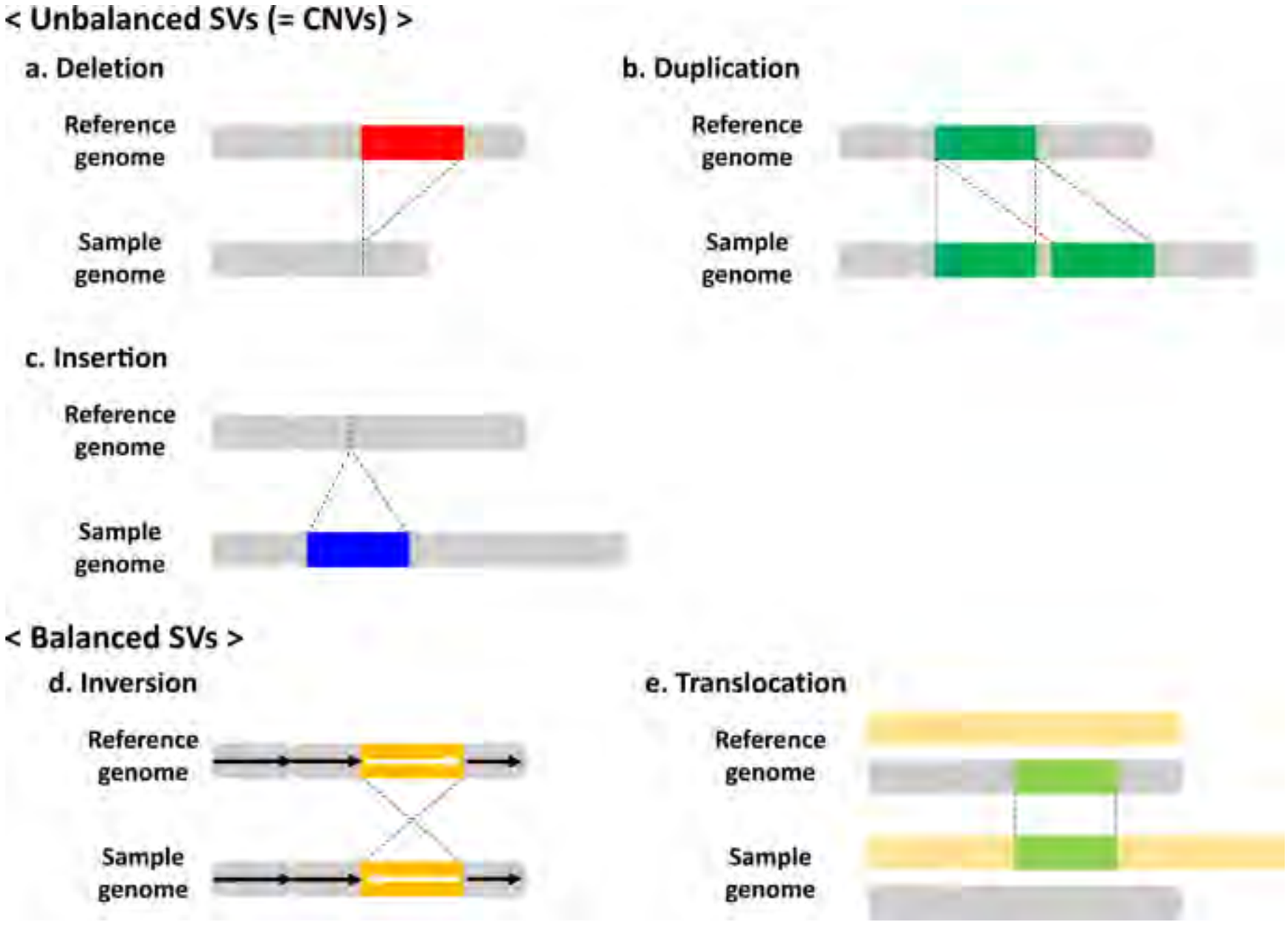
Ответ: Никто не знает.

# Доброкачественные и вероятно доброкачественные варианты

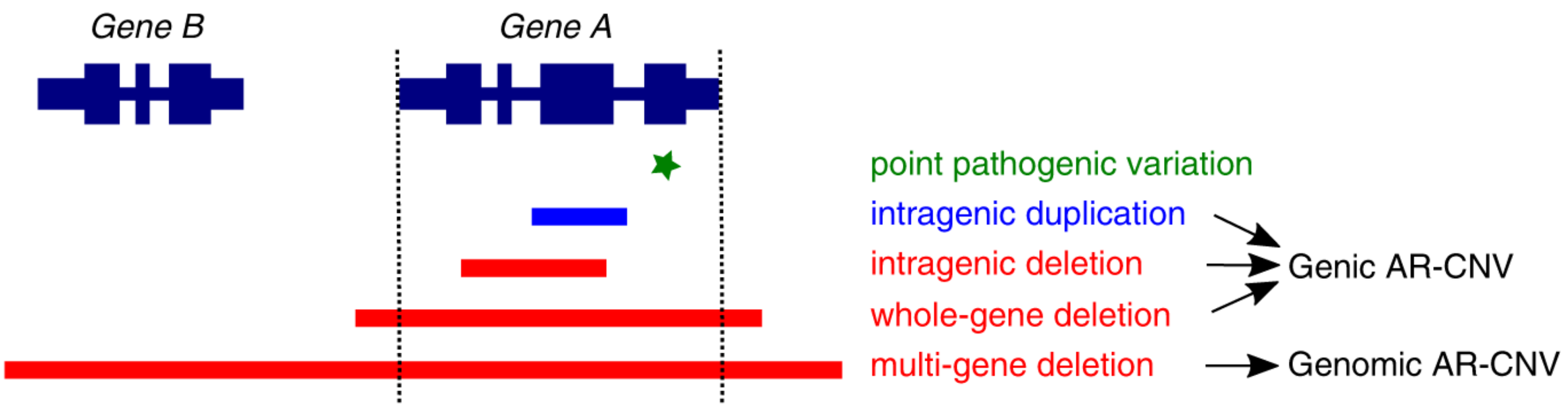



| | Benign ← Strong | Supporting → |
|---|---|---|
| **Population data** | MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2 | |
| **Computational and predictive data** | | Multiple lines of computational evidence suggest no impact on gene /gene product BP4<br><br>Missense in gene where only truncating cause disease BP1<br><br>Silent variant with non predicted splice impact BP7<br><br>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<br><br>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 |

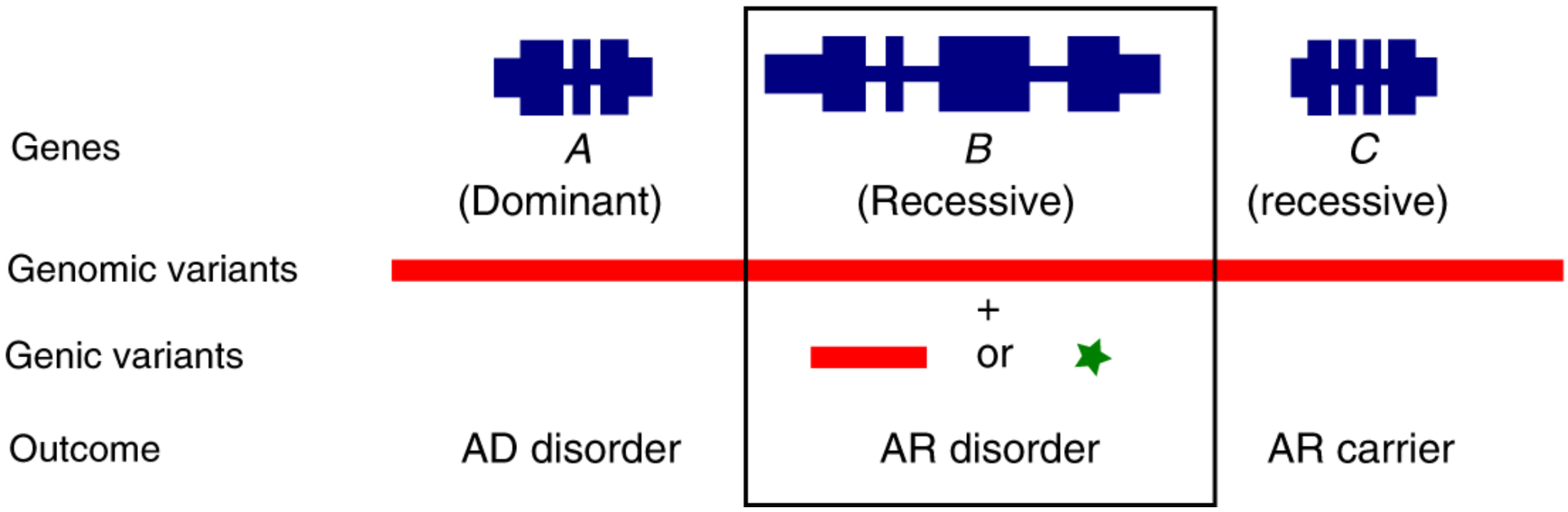
# Что такое CNV



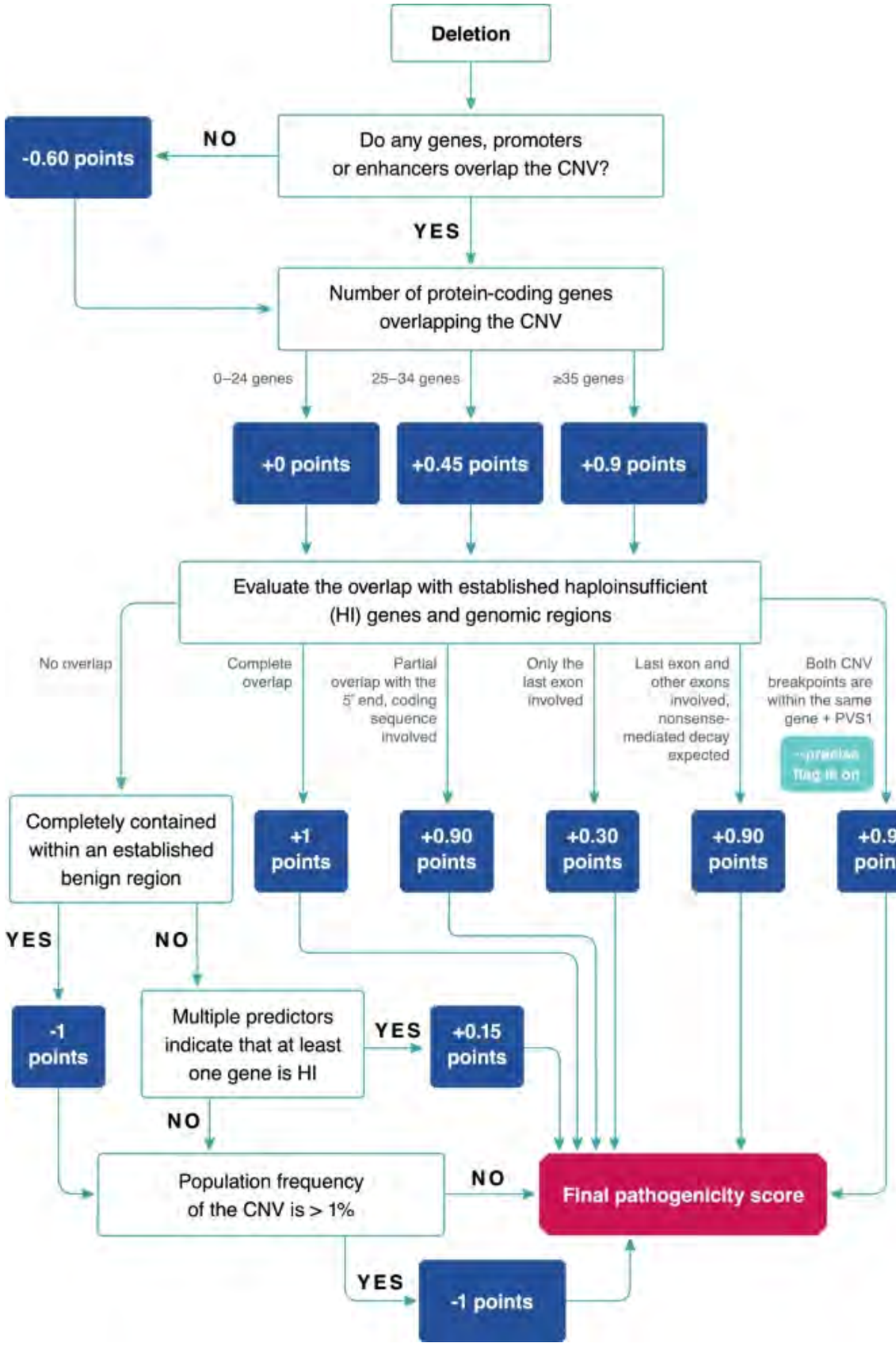
# Влияние CNV на заболевания

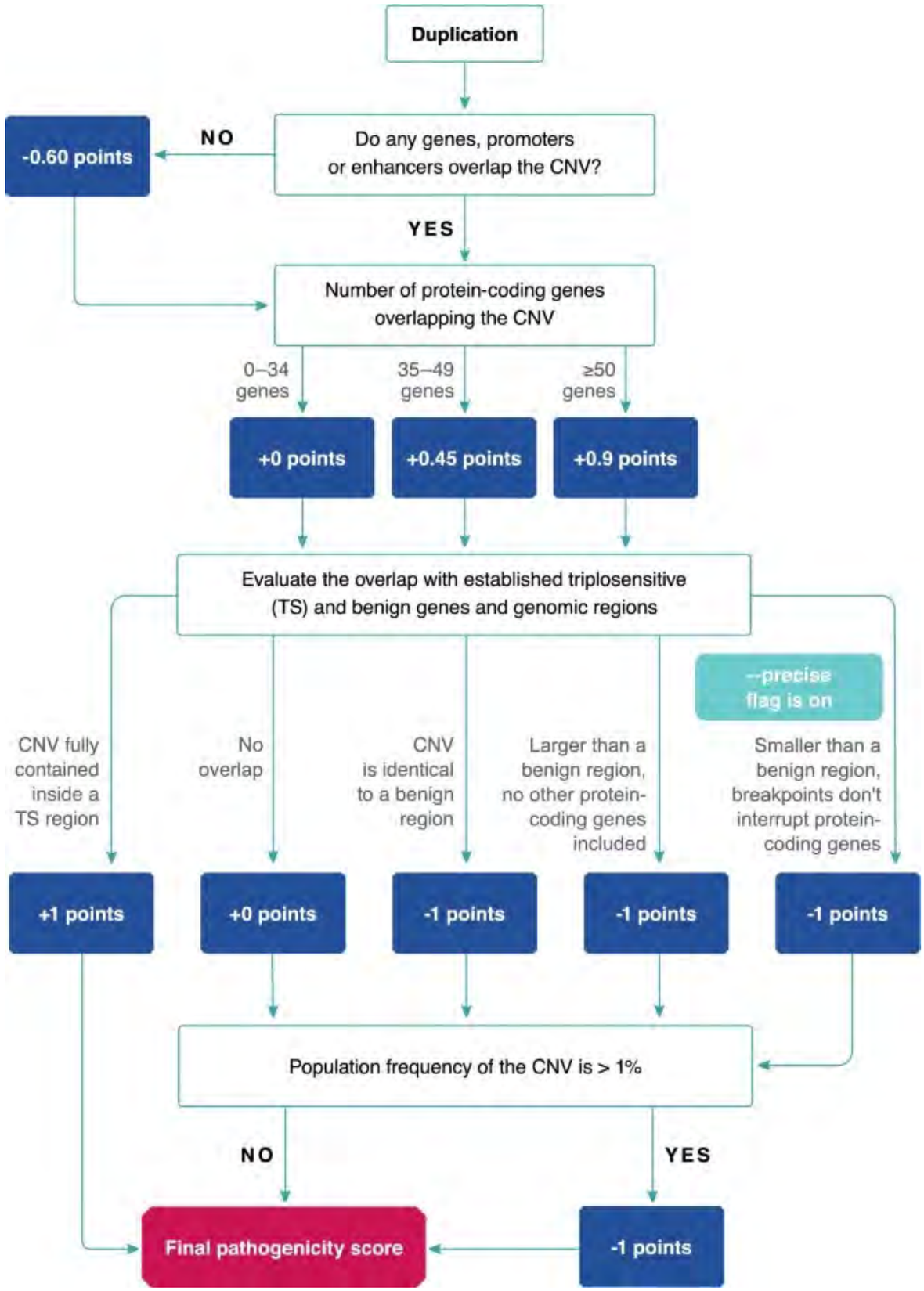


# Влияние CNV на заболевания

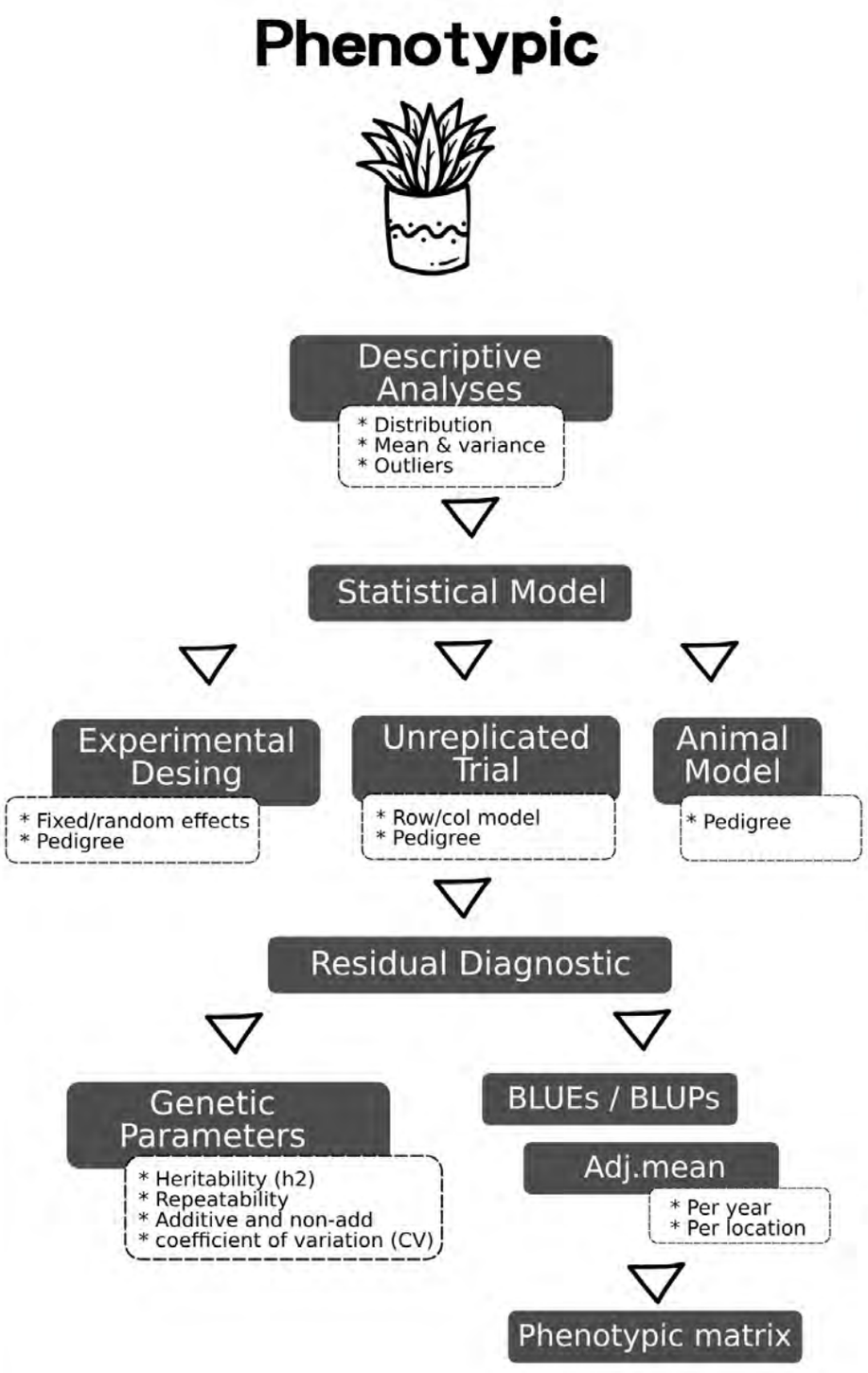


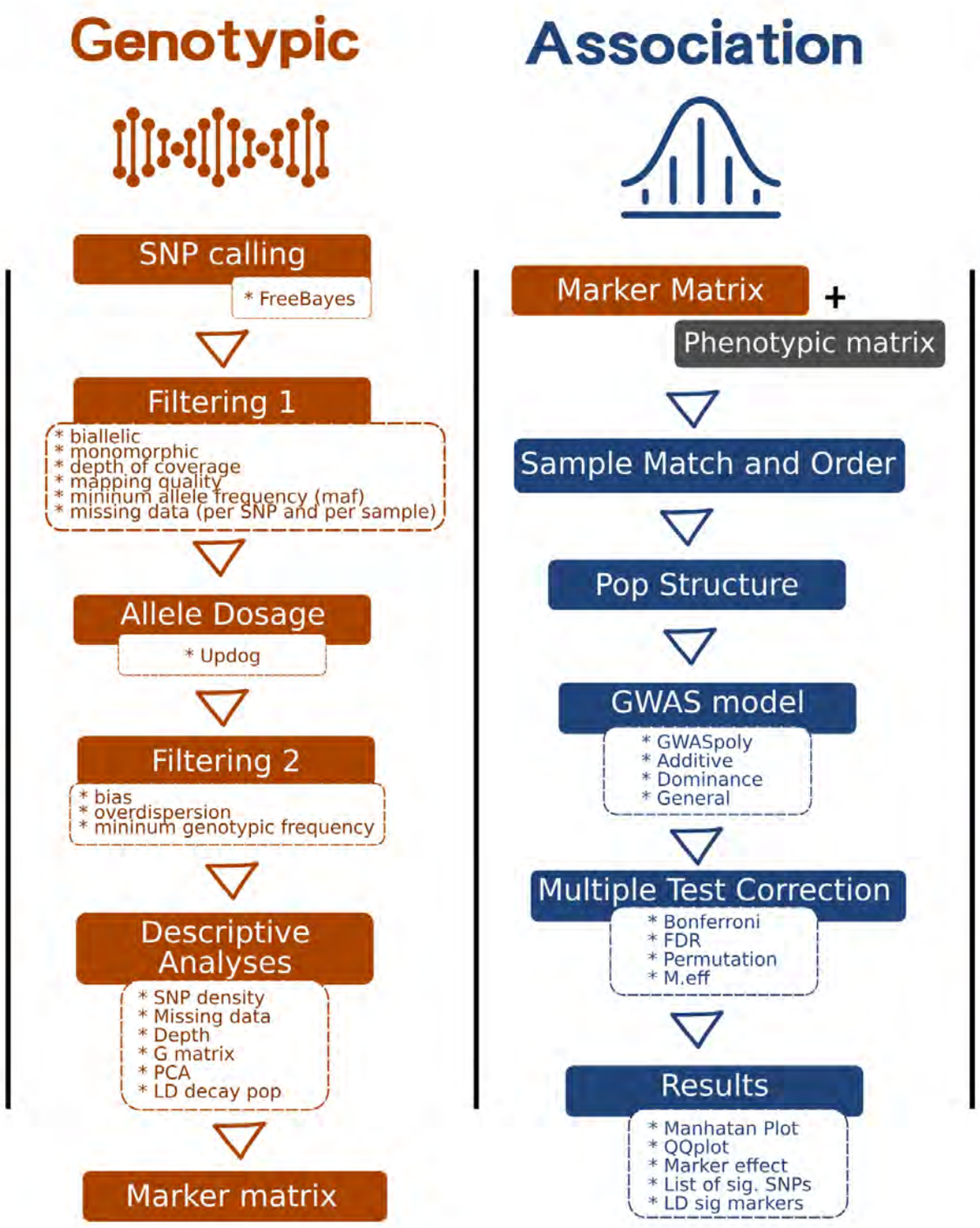
# Критерии ACMG оценки клинической значимости CNV


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

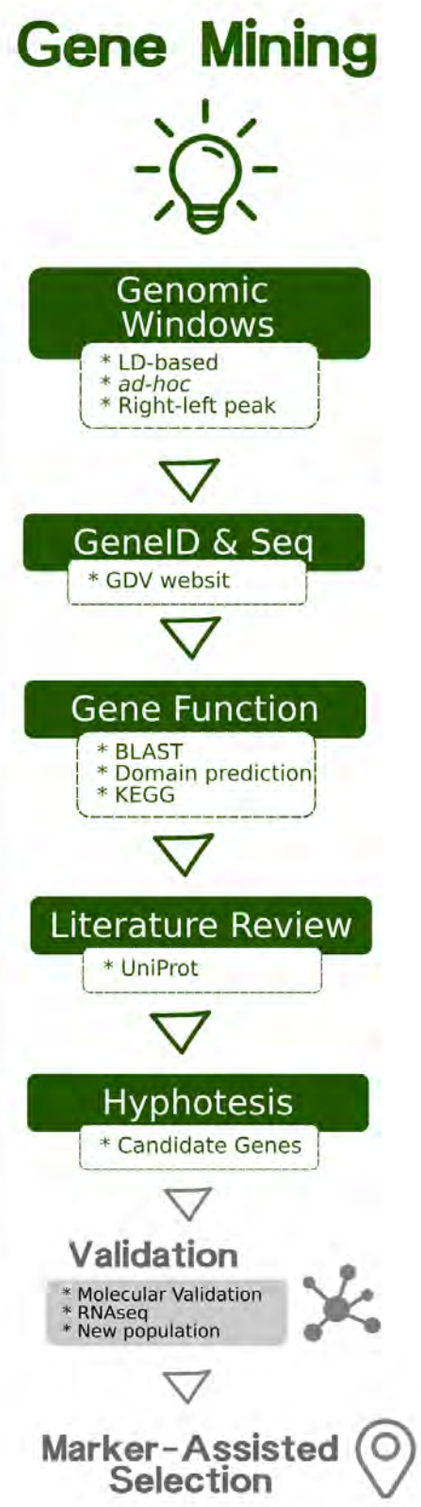
# Genome-Wide Association Study (GWAS)



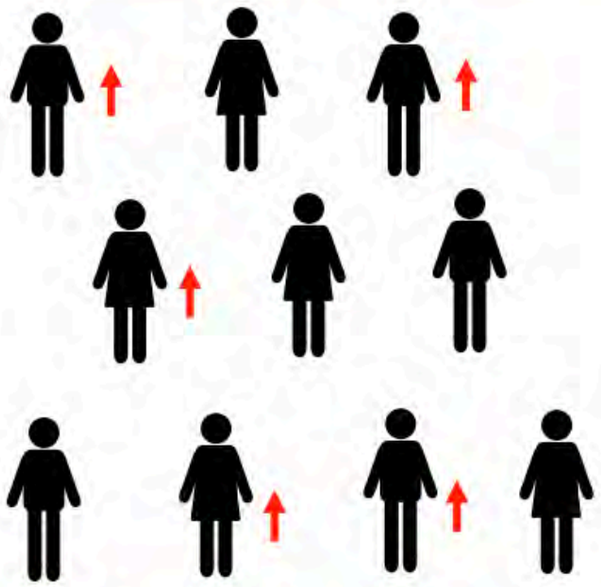







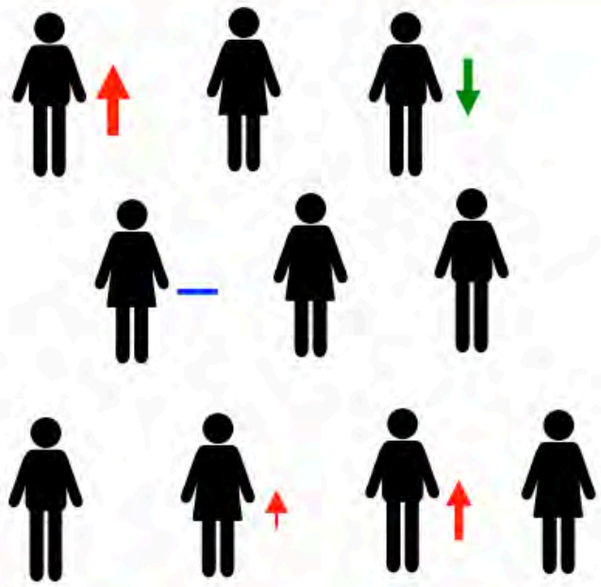


A



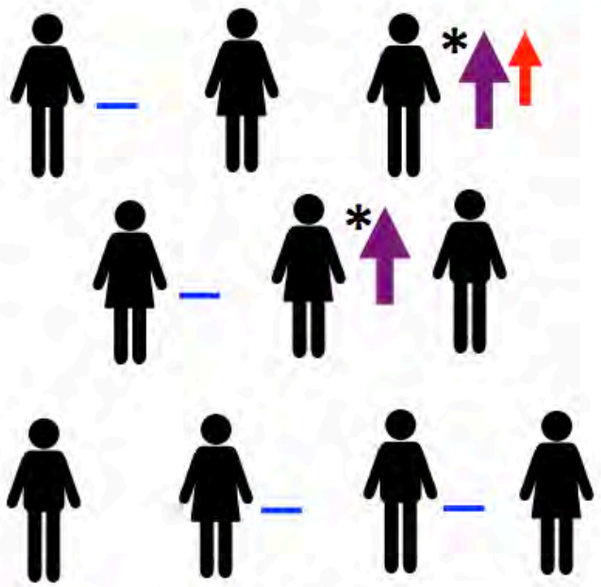
Simple additivity: Common variant increases risk by small amount in all carriers (population OR = individual RR)

B



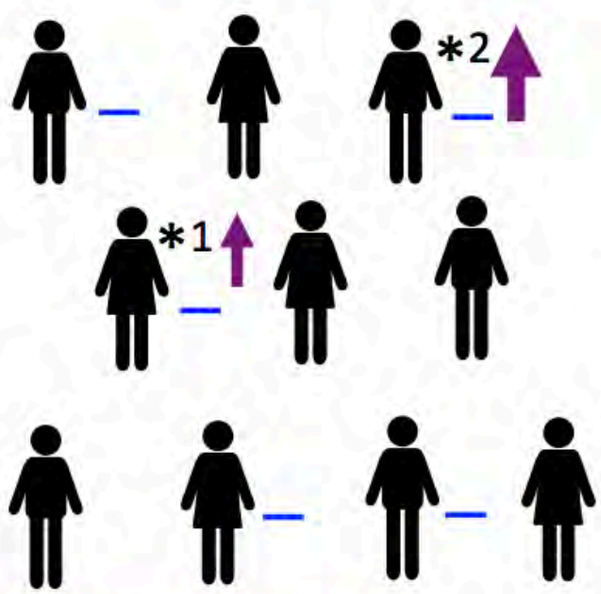
Epistatic interactions: effect of common variant varies with genetic background

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*

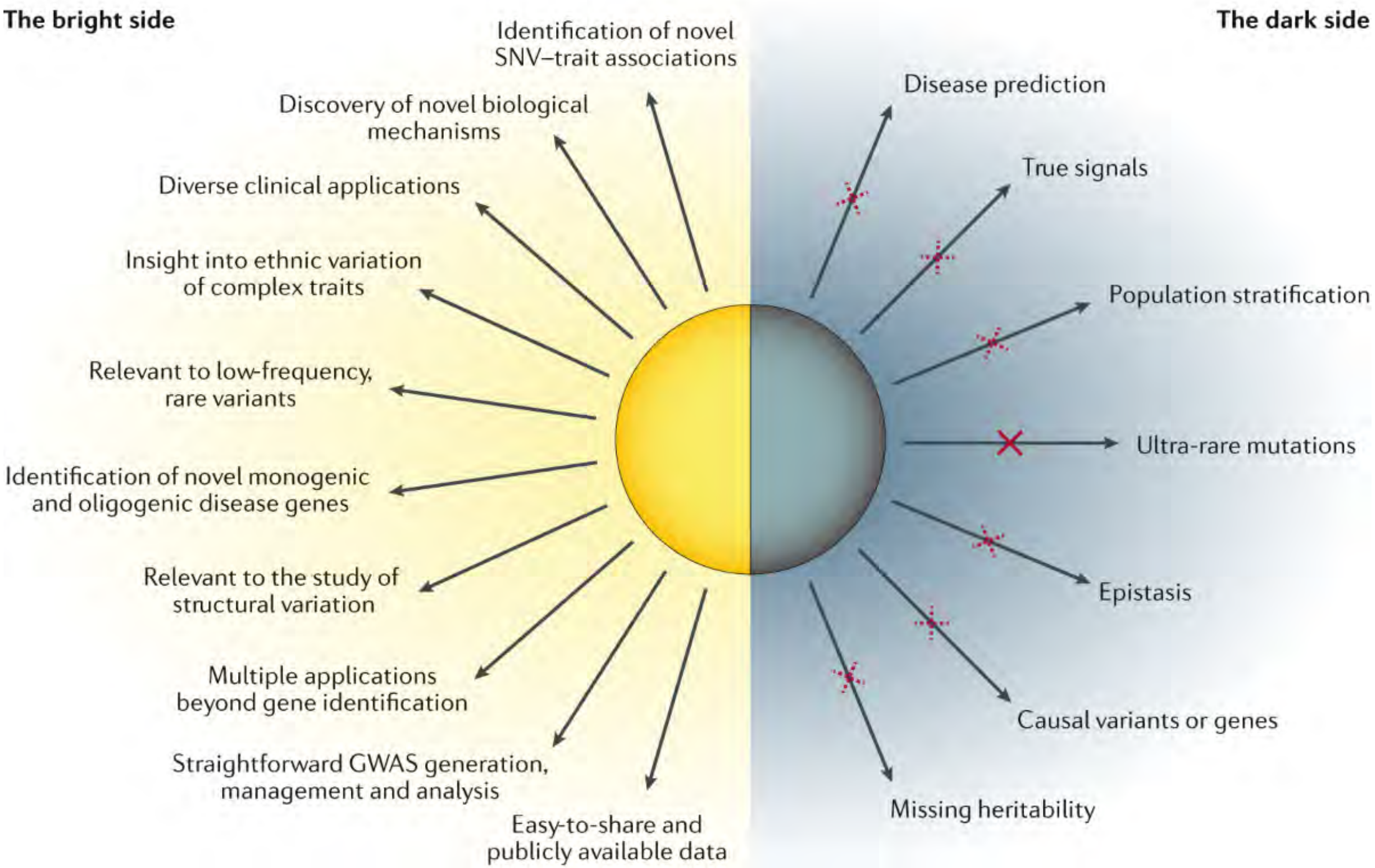
GWAS
significance
($-\log_{10}$P)

15
10
5
0

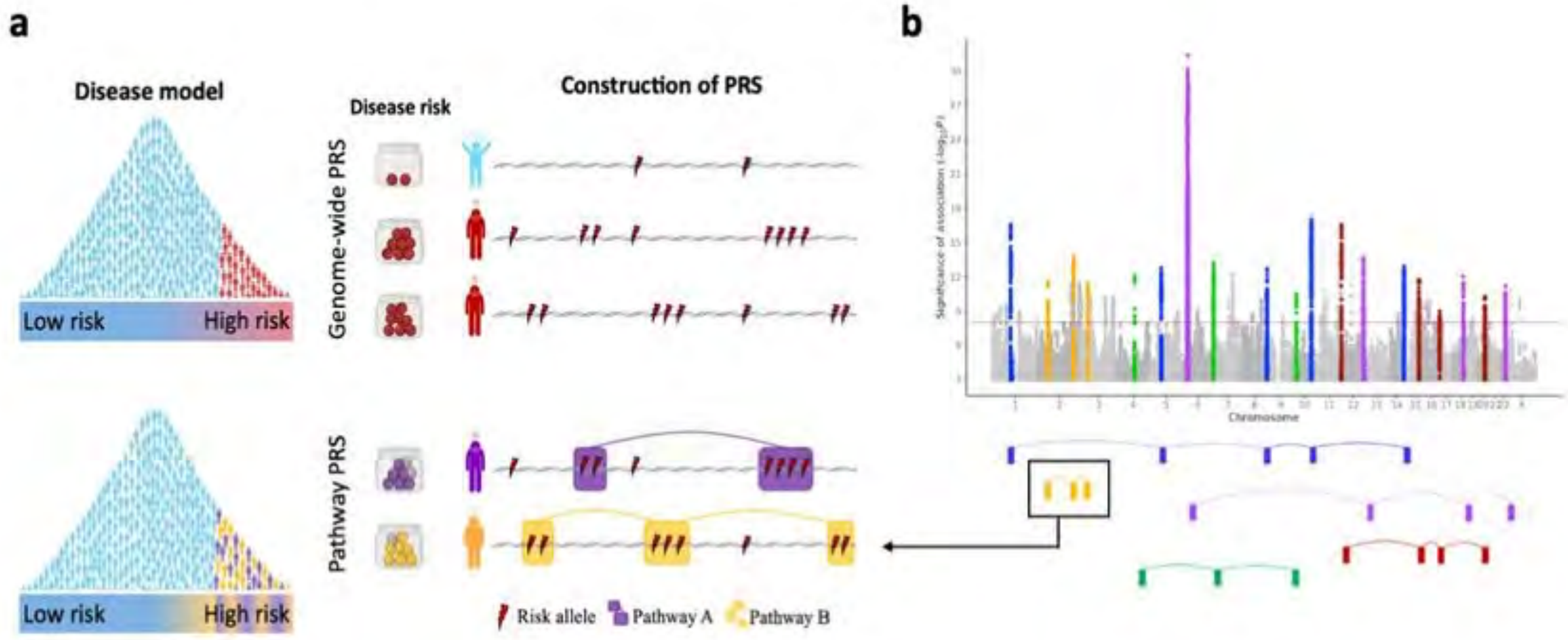
***threshold***

chromosome

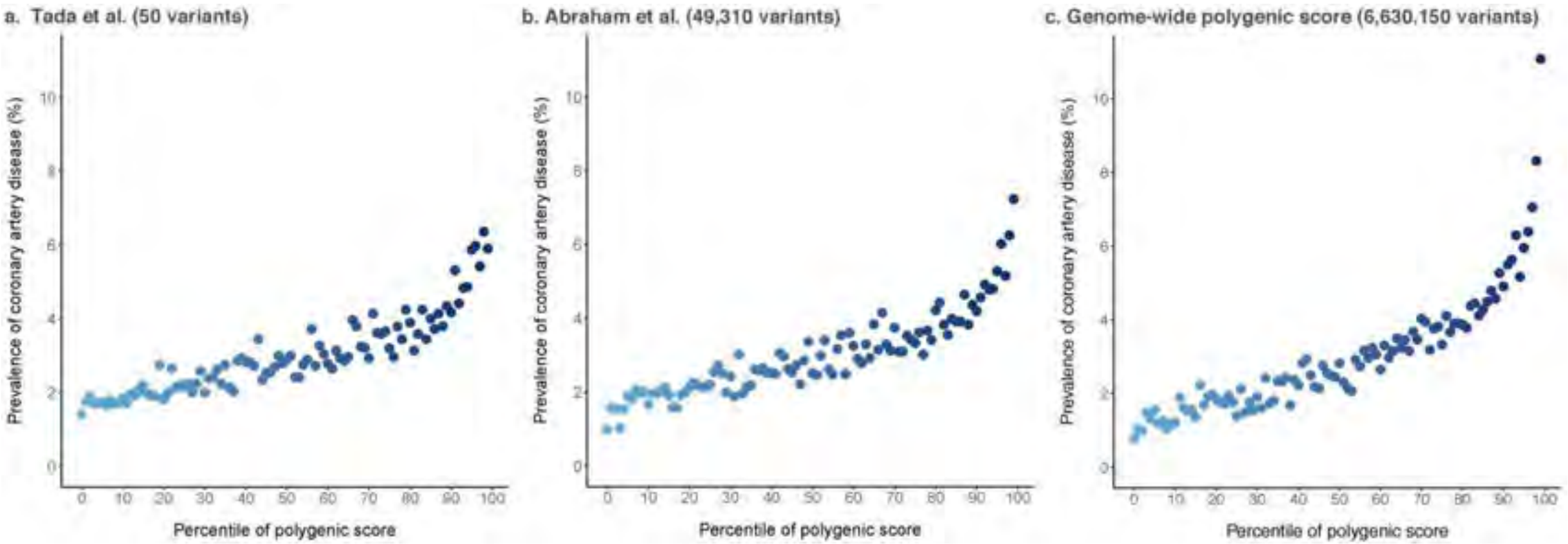
# Ограничения и критика GWAS

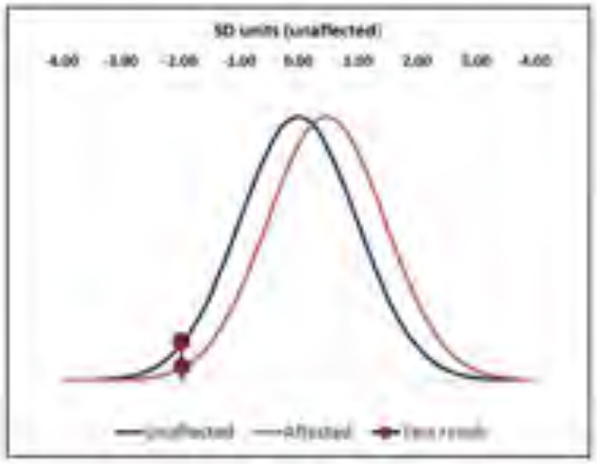


# Методики расчета полигенных шкал



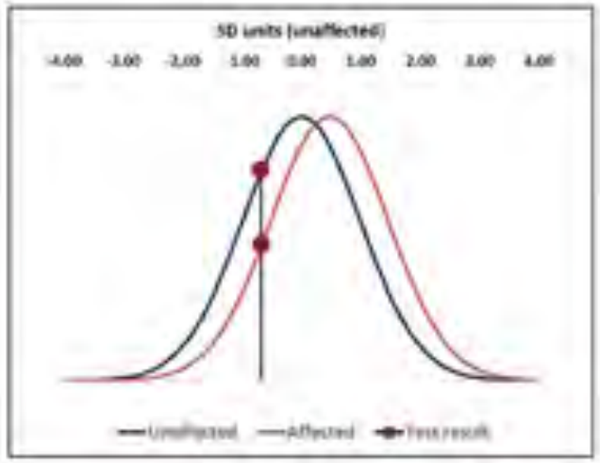
# Концепция полигенных шкал риска






LR 0.35
Odds 1:54

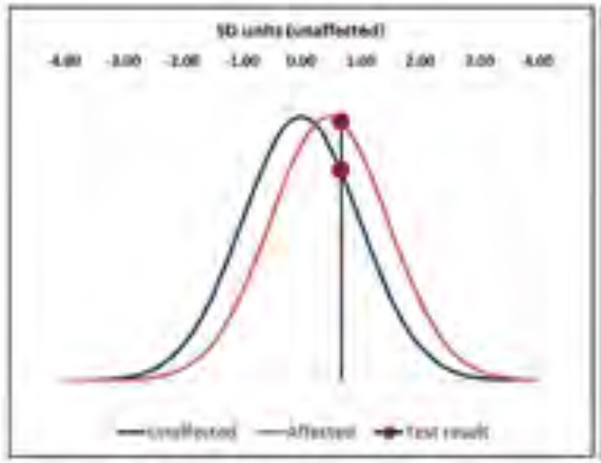
2.5th




LR 0.65
Odds 1: 29

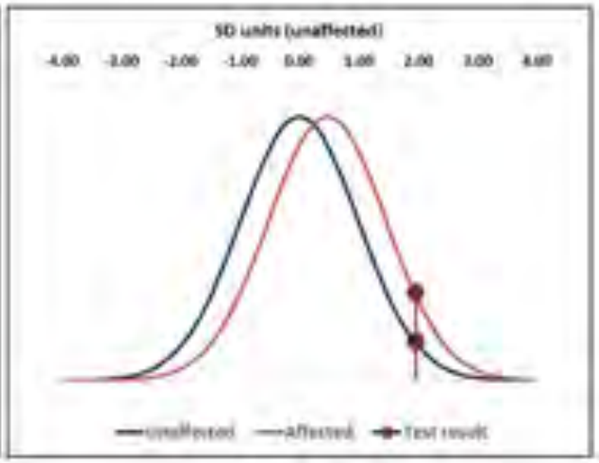
25th

**Coronary artery disease**
**(background odds 1:19)**



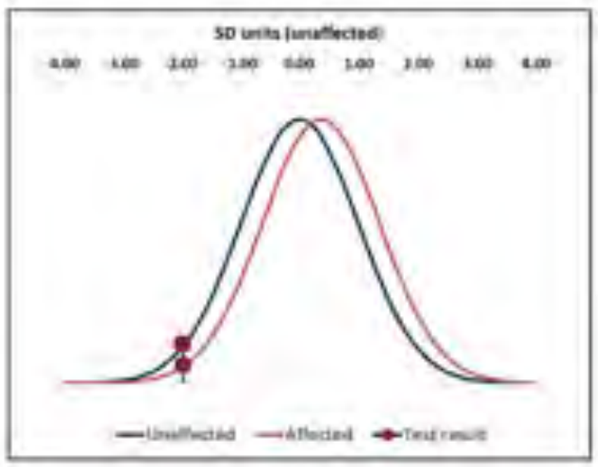

LR 1.23
Odds 1:15

75th

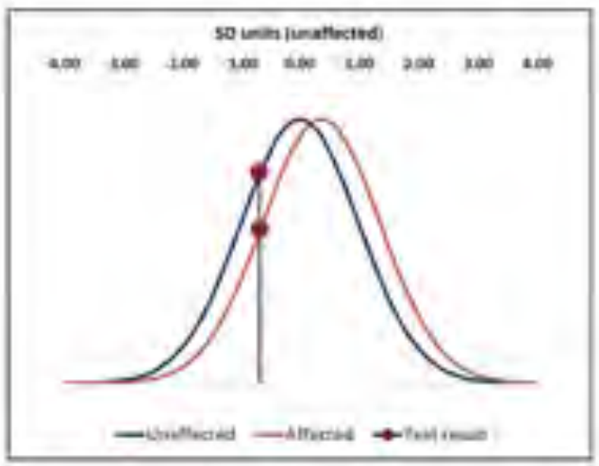



LR 2.27
Odds 1:8

97.5th

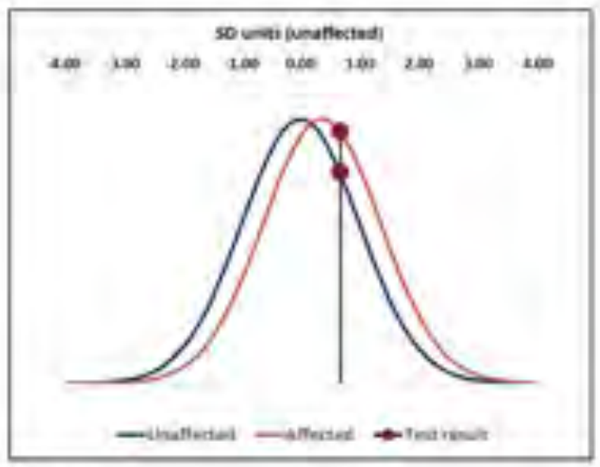



LR 0.45
Odds 1:91

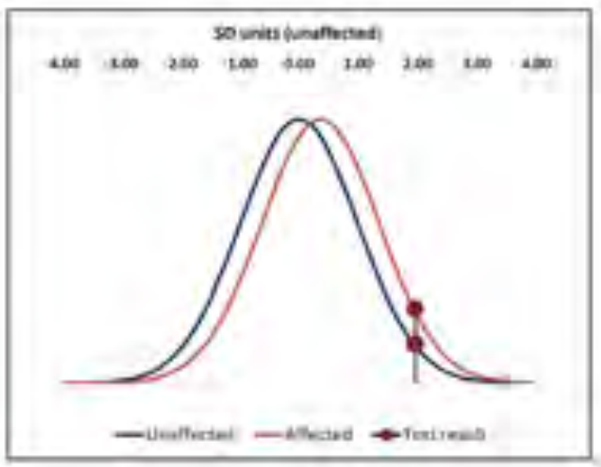



LR 0.73
Odds 1: 56

**Breast cancer**
**(background odds 1:41)**

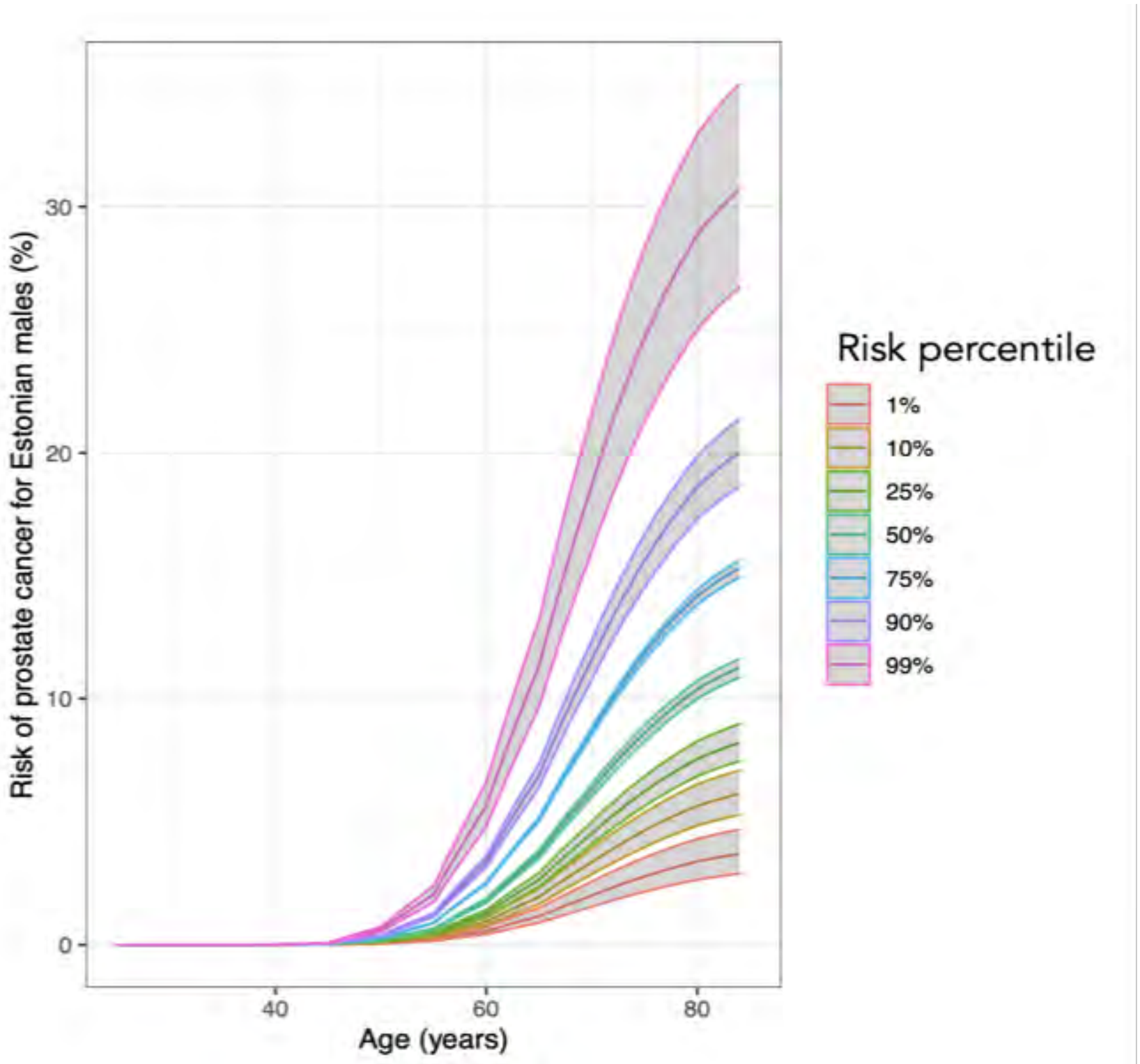



LR 1.2
Odds 1:34

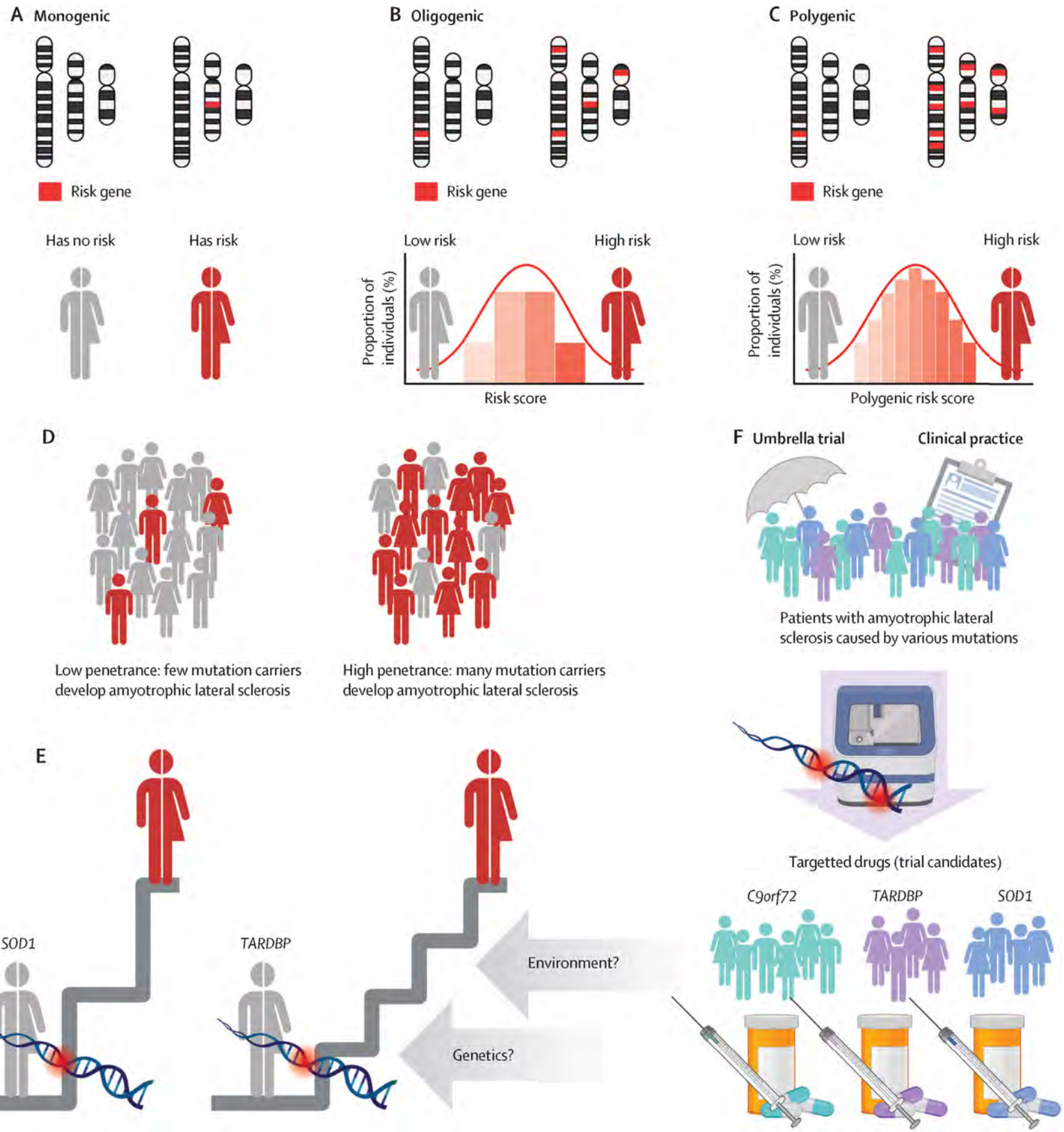



LR 1.93
Odds 1:21

# 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