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The European
Rare Kidney Disease
Reference Network

european
society for
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nephrology

WELCOME TO

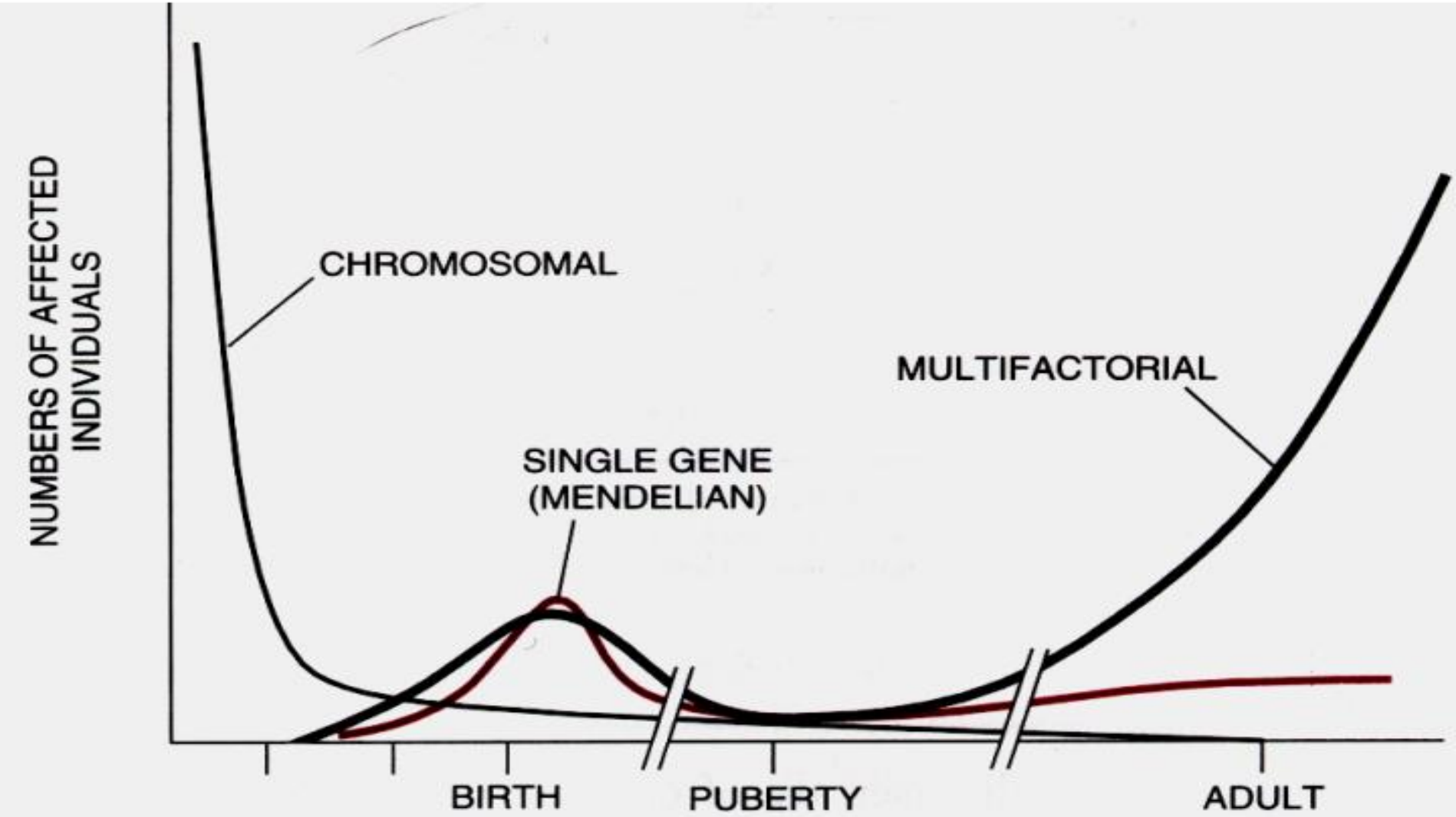
ESPN/ERKNet
Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

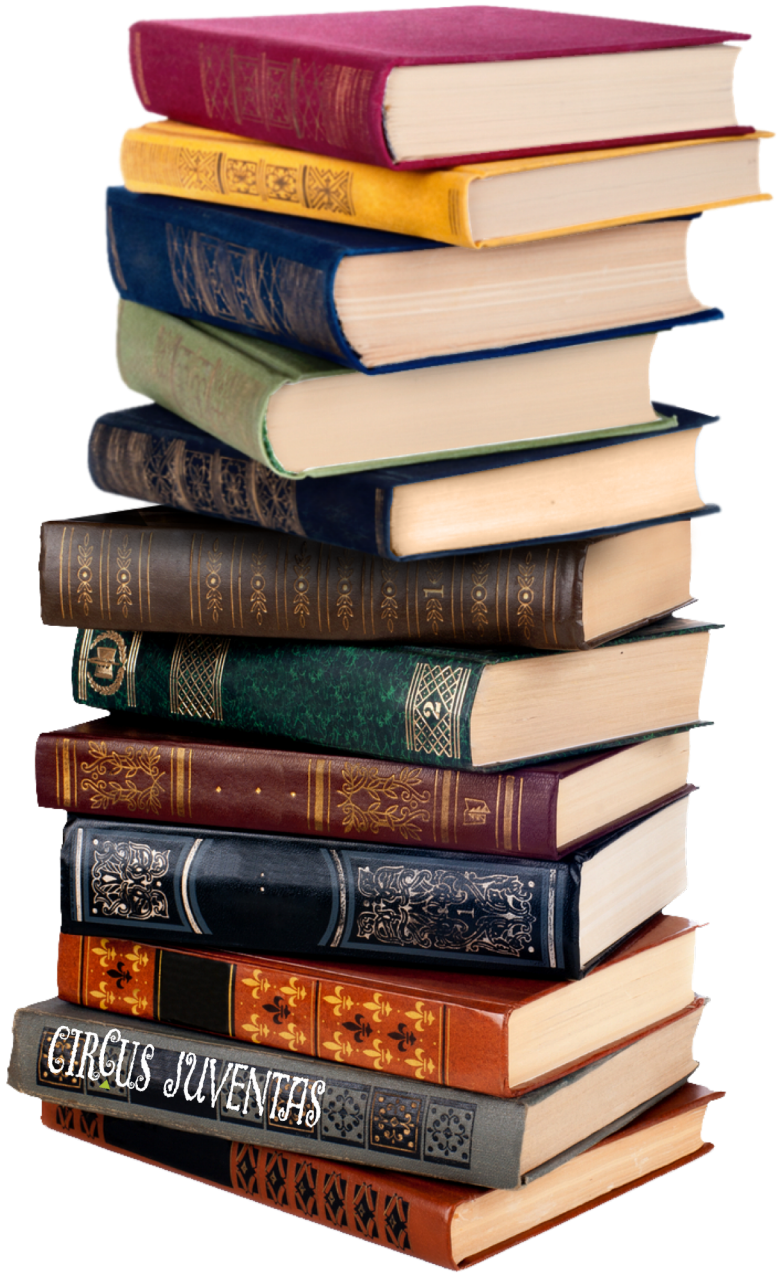
Date: 11 February 2020

Topic: Genetics – basic concepts and testing

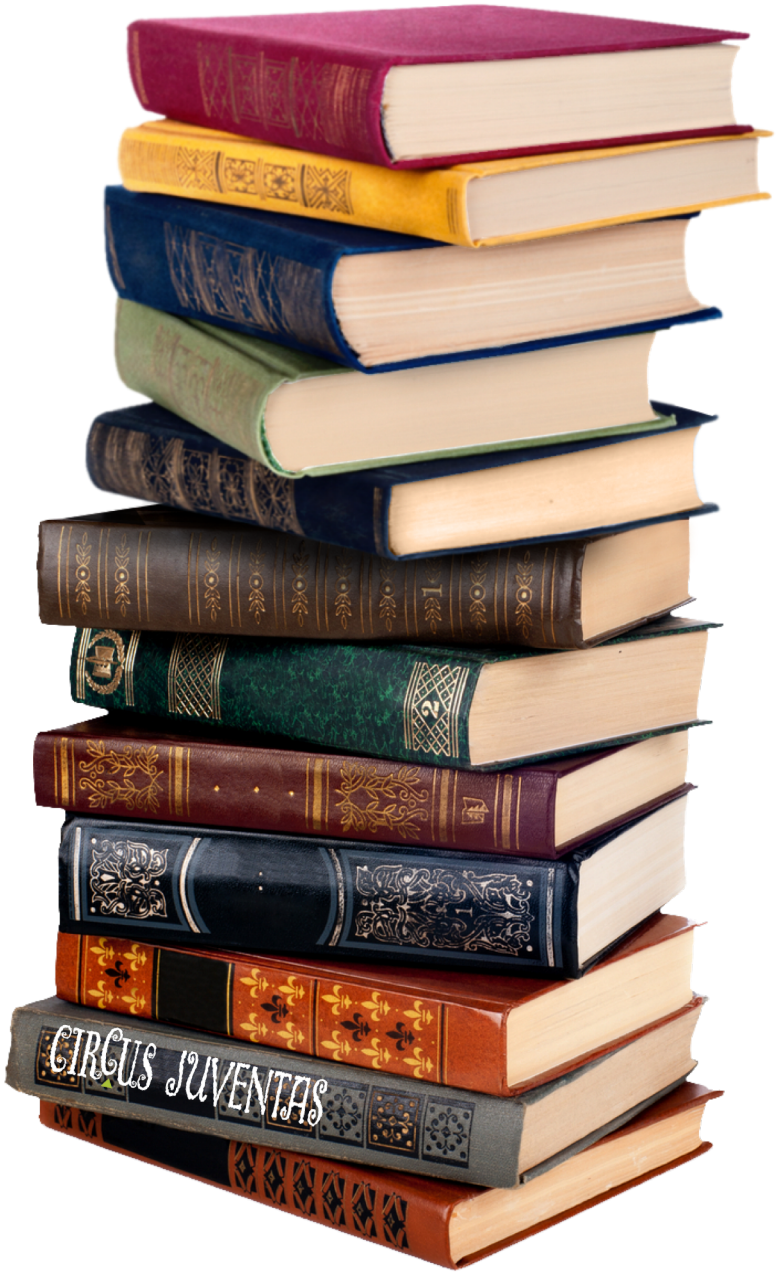
Speaker: Beata Lipska-Zietkiewicz

Not all congenital diseases are hereditary but all hereditary diseases are congenital, even if the symptoms occur later in life.





a pocket dictionary to the GENETIC LANGUAGE



Mutation

- Variant classification and assessment
- Homozygosity, heterozygosity, compound heterozygosity

Penetrance

Expresivity

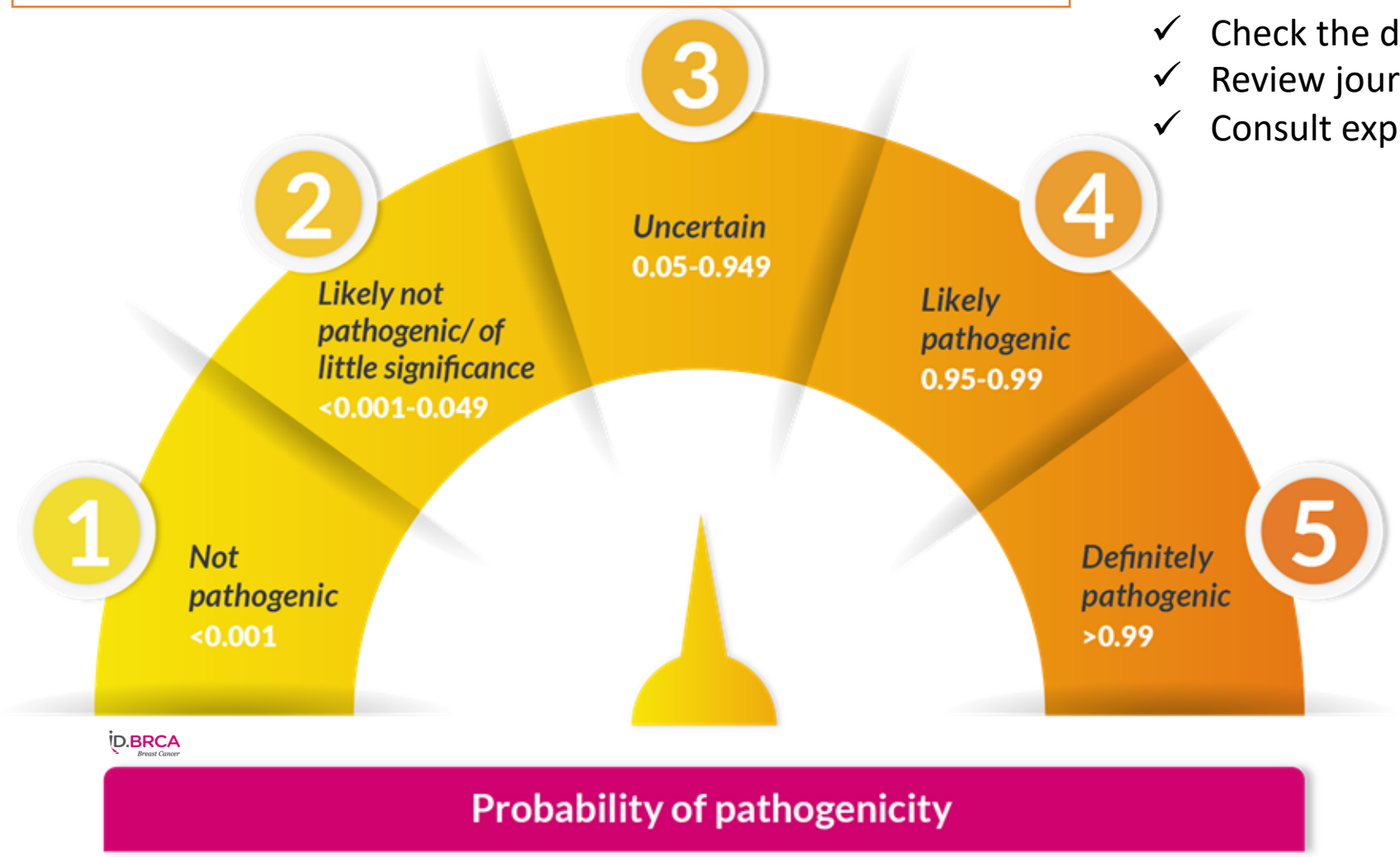
Genetic heterogenity

- Locus heterogenity
- Allele heterogenity

Mosaicism

Mutation

- **Variant** classification and assessment

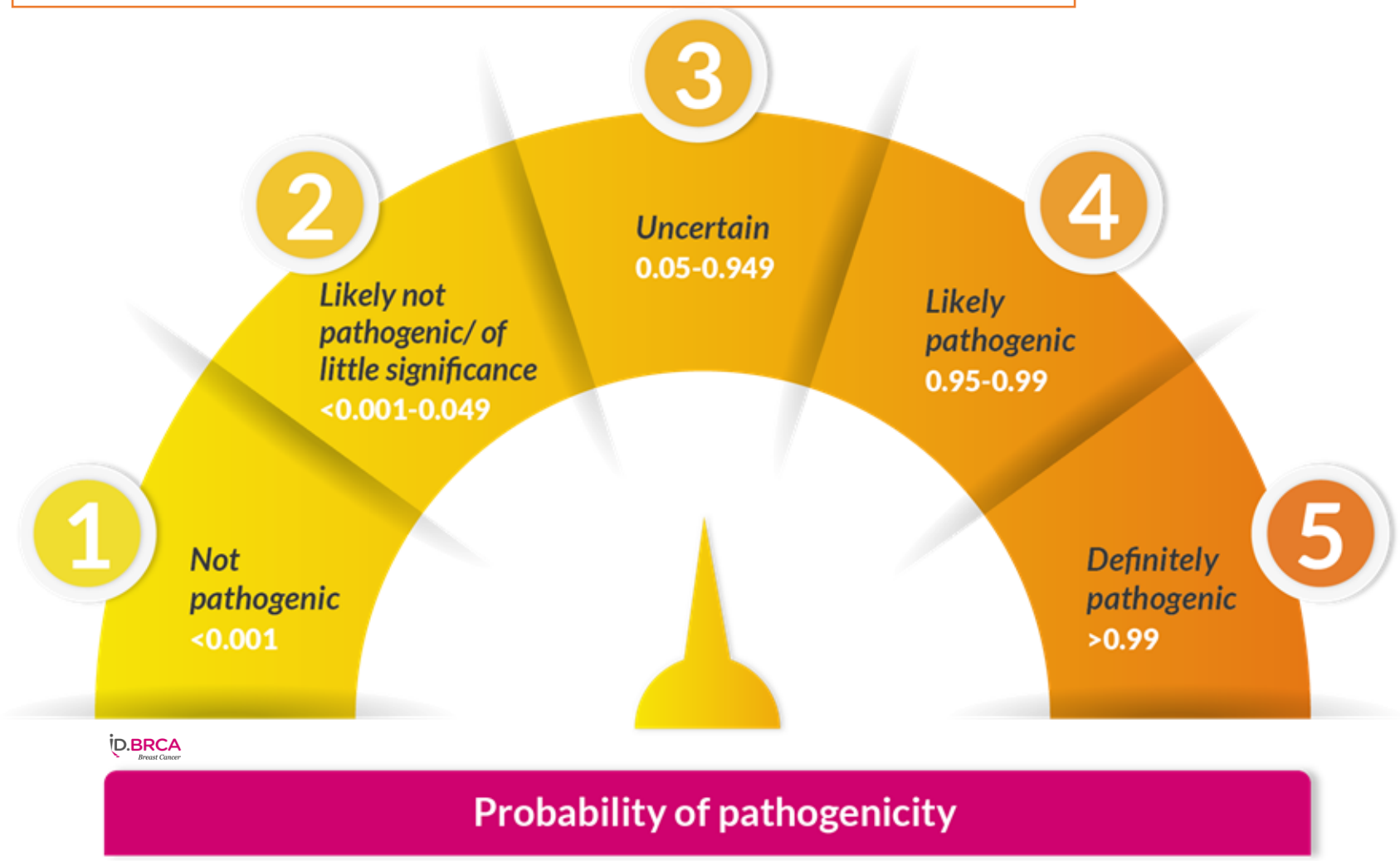


ACMG criteria 2015

- ✓ Discussion in the multidisciplinary environment
- ✓ Check the databases: ClinVar, GnomAD, LOVD, HGMD,…,
- ✓ Review journal papers, GeneReviews
- ✓ Consult experts e.g. CPMS vis ERKnet

Mutation

- Variant classification and assessment



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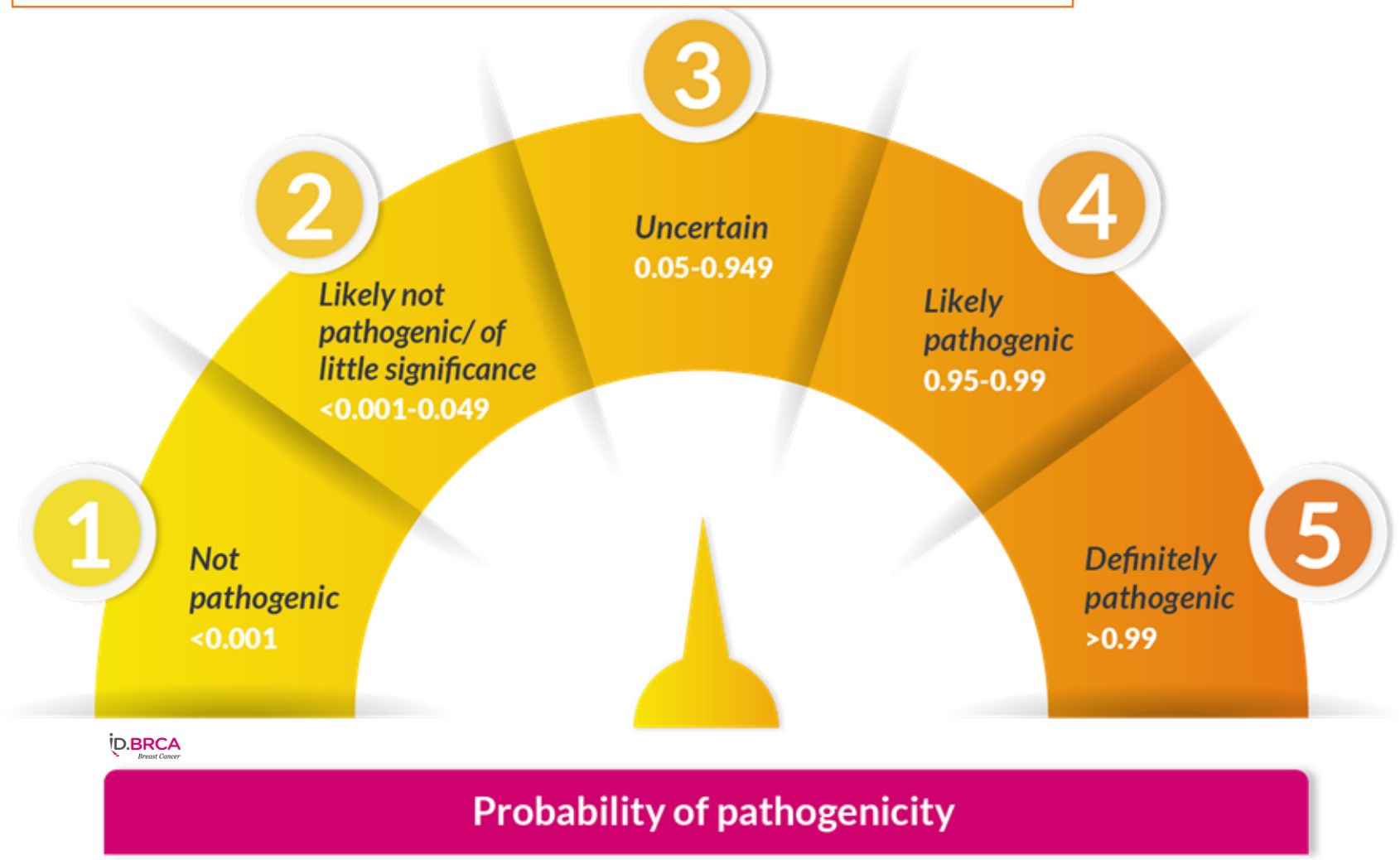
Example Mutation	Previously reported variant with a recognised deleterious impact. E.g. early termination of the protein.
Impact on patient management	Disease-associated mutation detected. Result can be used for clinical management of the patient.

Mutation

- Variant classification and assessment



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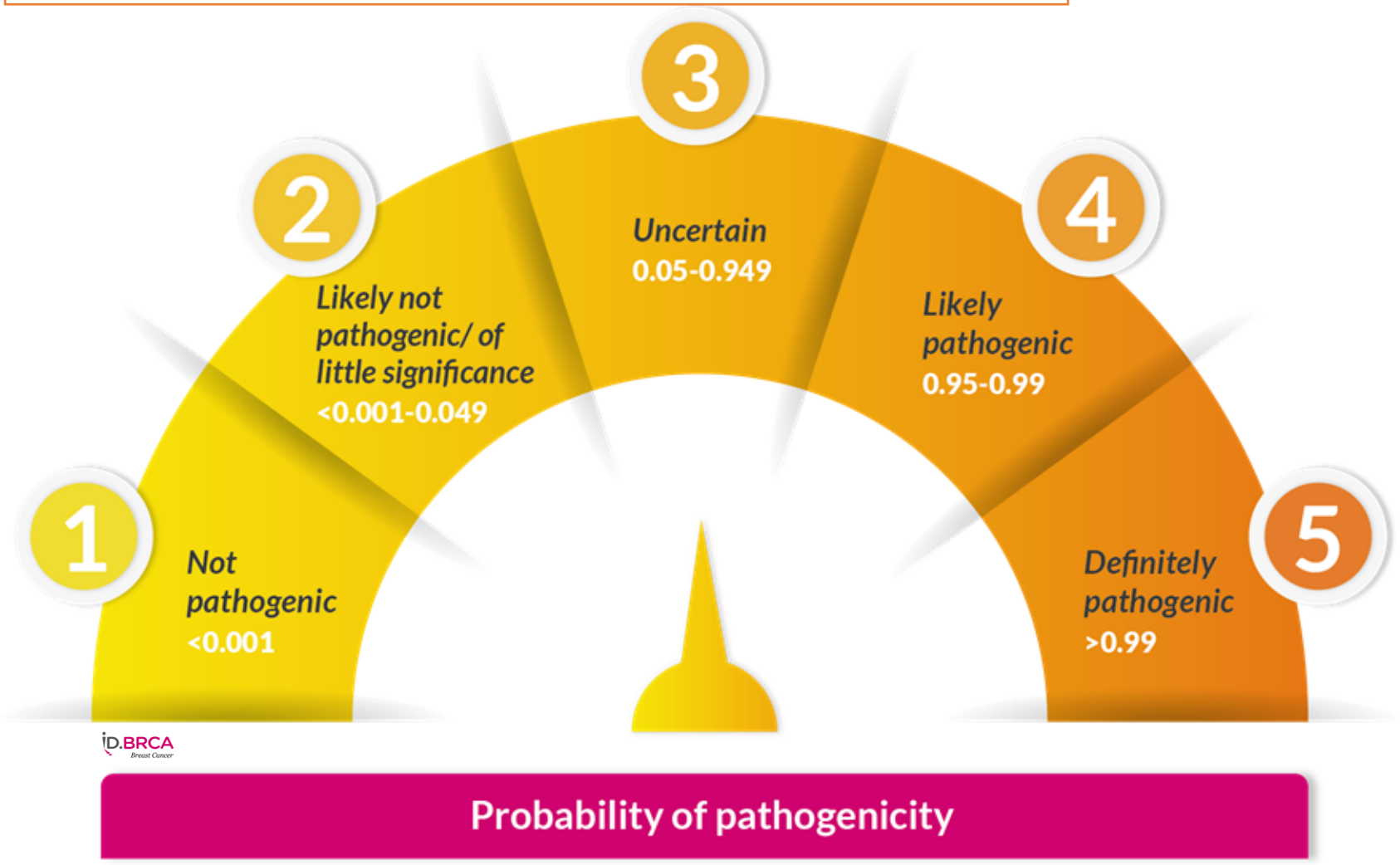
Example Mutation	Variants that are previously unreported but are expected to be deleterious
Impact on patient management	Treat as Class 5 patients, despite small risk of over-treatment. May warrant additional follow up studies to assess significance and potentially reclassify, e.g. segregation studies.

Mutation

- Variant classification and assessment



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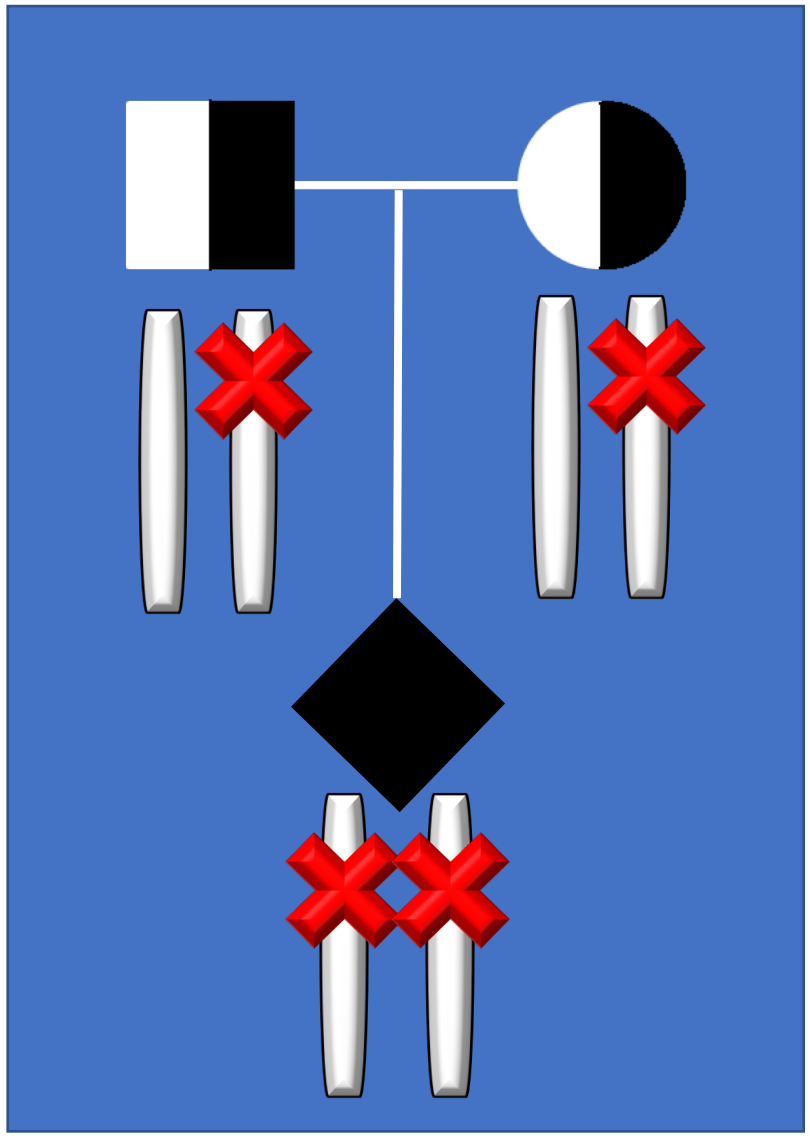
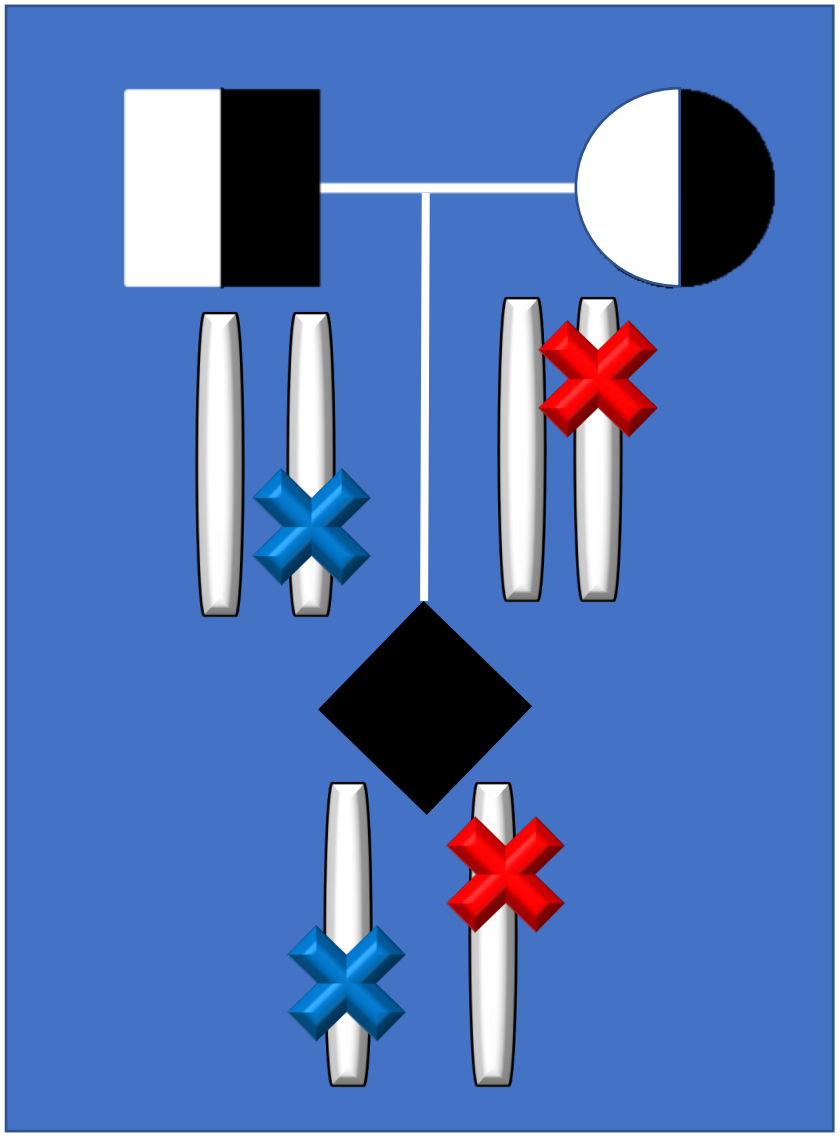
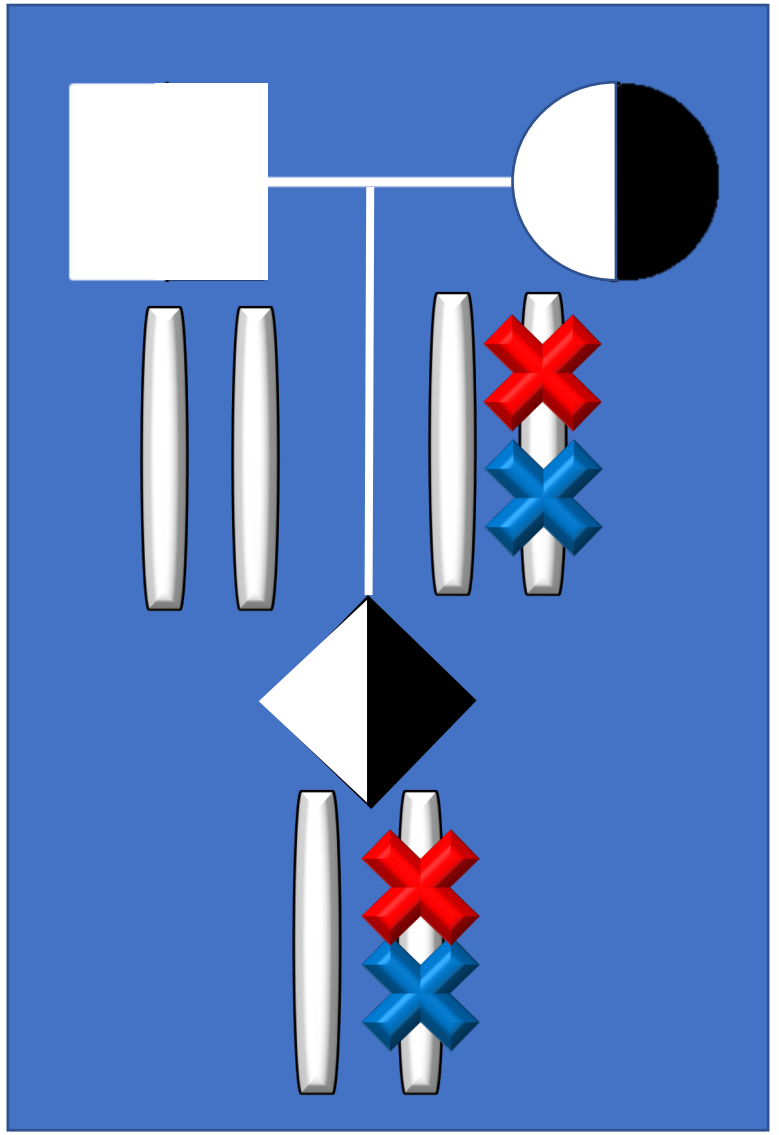
Example Mutation	Clinical significance unknown
Impact on patient management	Additional follow up studies necessary to assess significance and potentially reclassify, e.g. segregation studies, in-vitro/in-vivo assays...



HOMOZYGOTE



COMPOUND HETEROZYGOTE

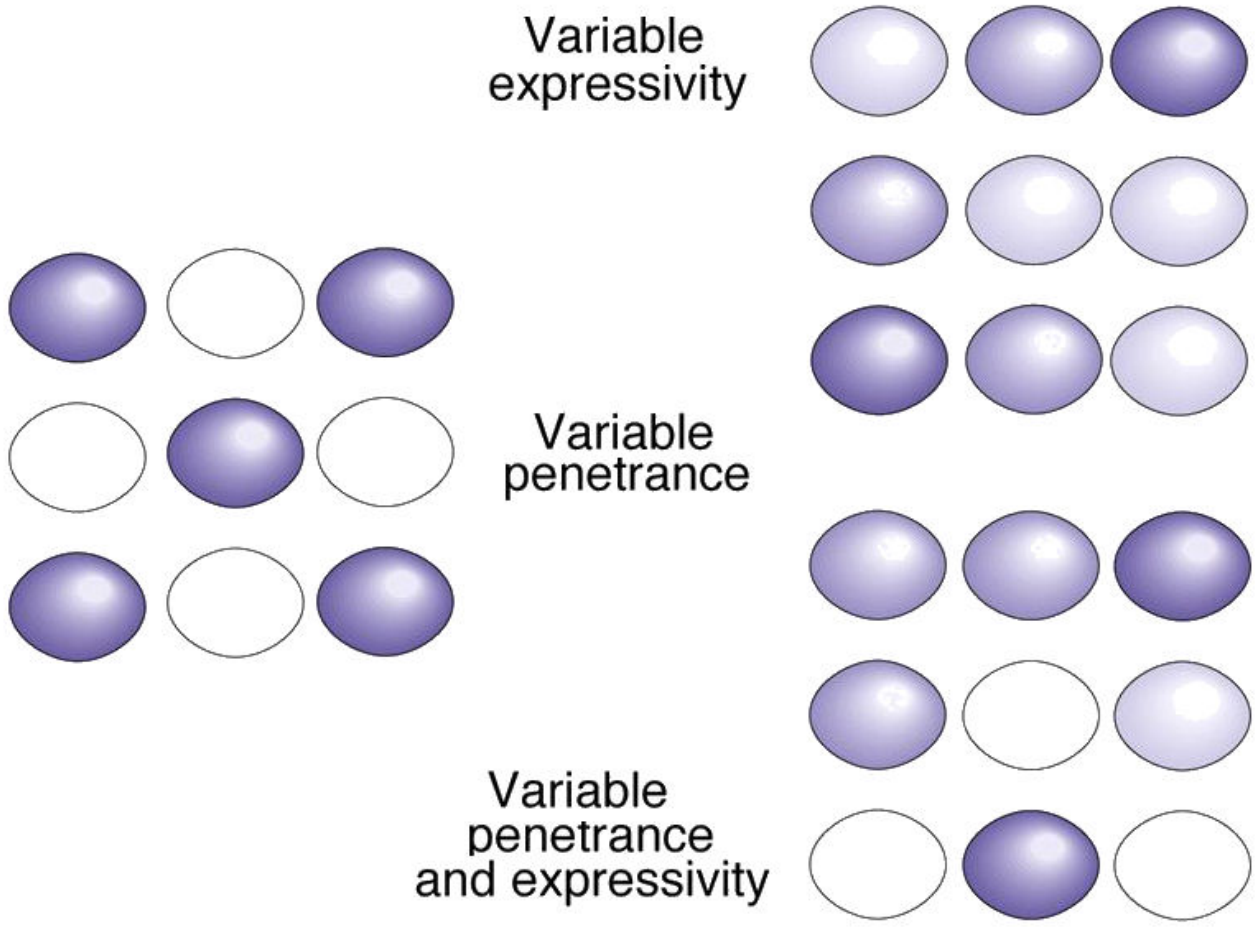


HETEROZYGOTE

Penetrance

Expresivity

PENETRANCE
frequency of expression of a particular gene expressed in percentages or numerical values, indicating the proportion of people with the mutant allele, in which a particular trait (e.g. symptoms of the disease) exhibit a phenotype.

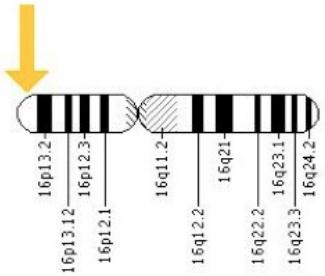


EXPRESIVITY
Determines to what extent (and in which clinical form) the particular allele reveals in phenotype of the individual.

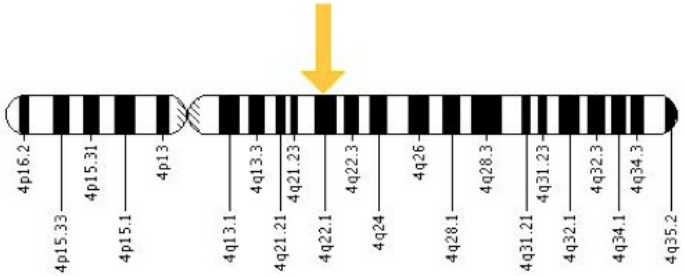
Genetic heterogenity

- Locus heterogenity
- Allele heterogenity

LOCUS HETEROGENITY
producing similar phetotypes by mutations located in different *loci*.

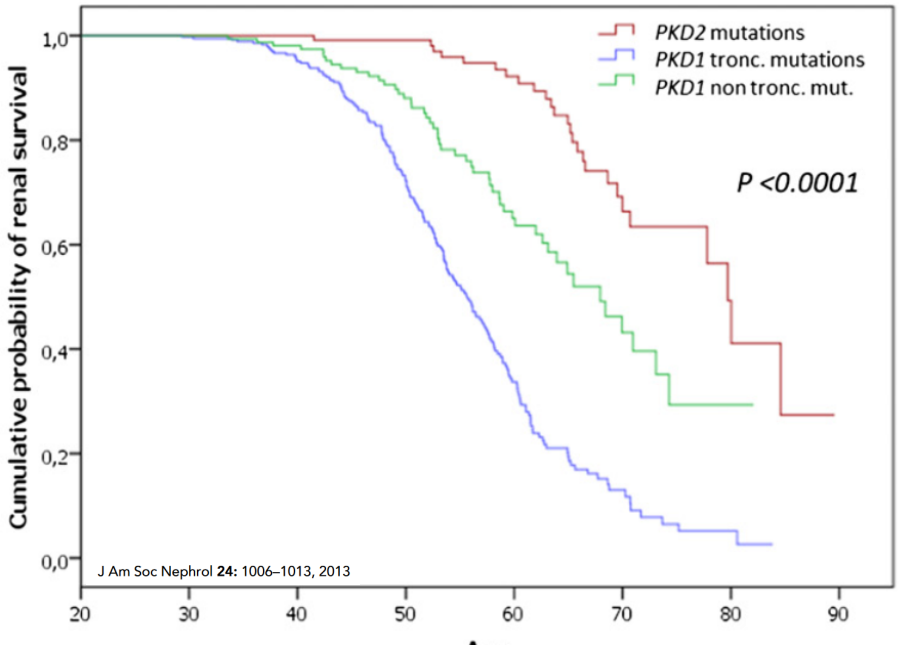


The *PKD1* gene is located on the short (p) arm of chromosome 16 at position 13.3.

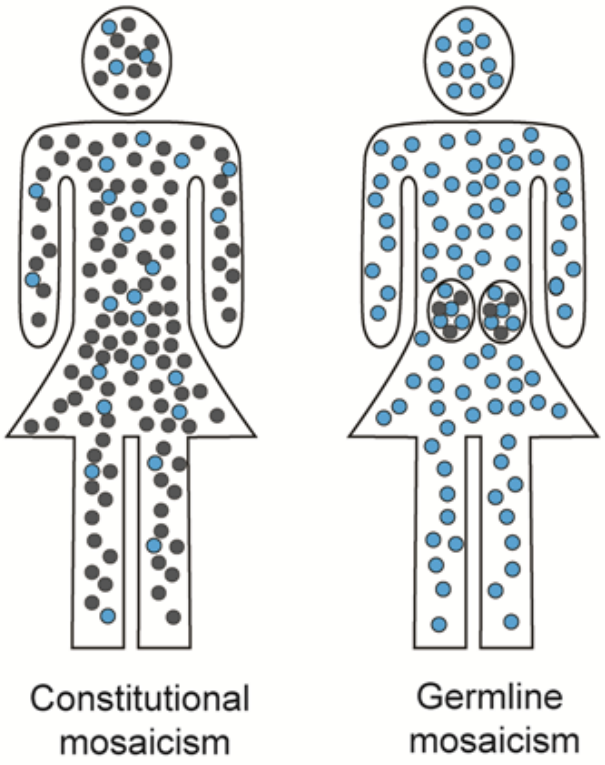


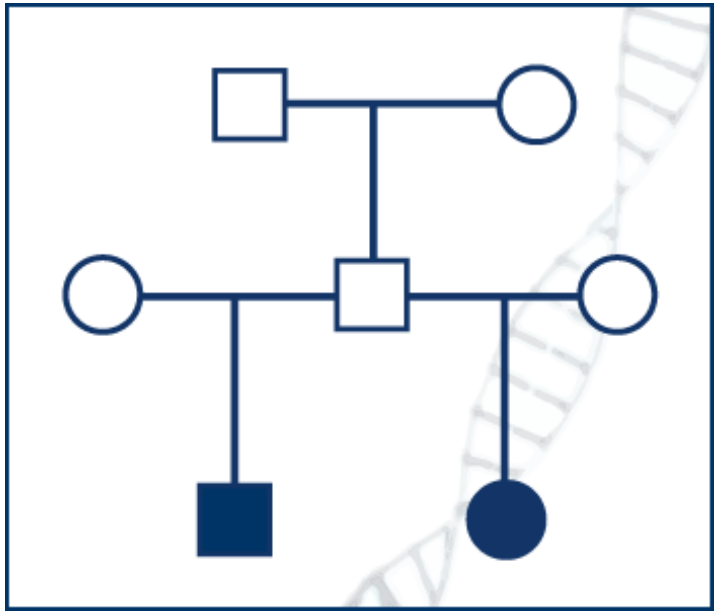
The *PKD2* gene is located on the long (q) arm of chromosome 4 at position 22.1.

ALLELE HETEROGENITY
producing different phetotypes by various mutation affecting the same gene (*locus)*.



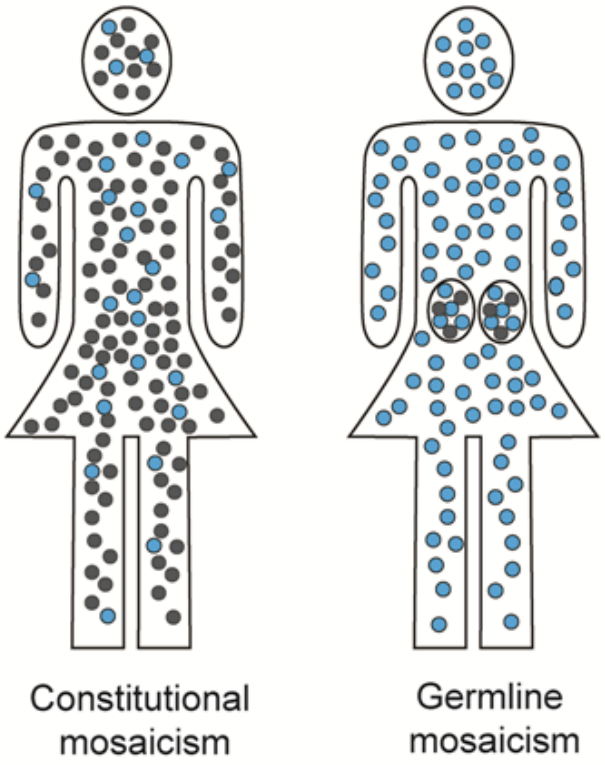
Mosaicism

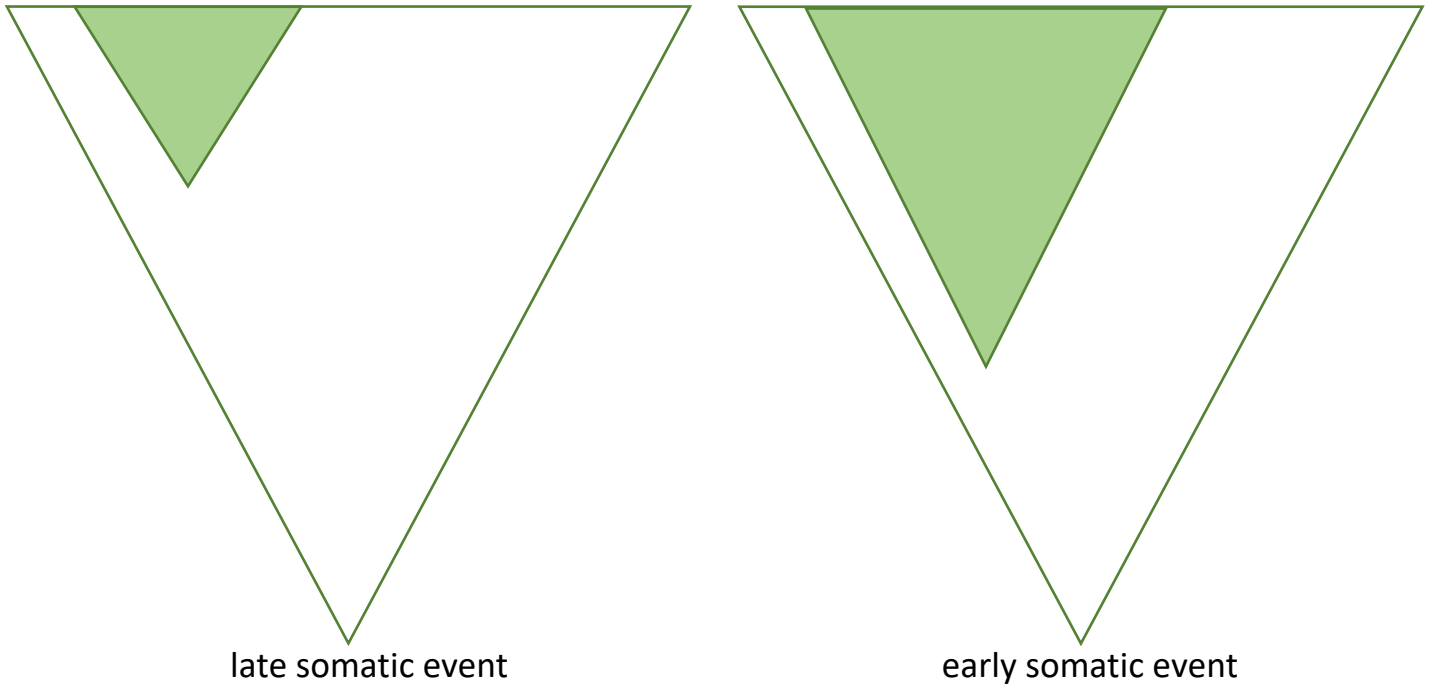




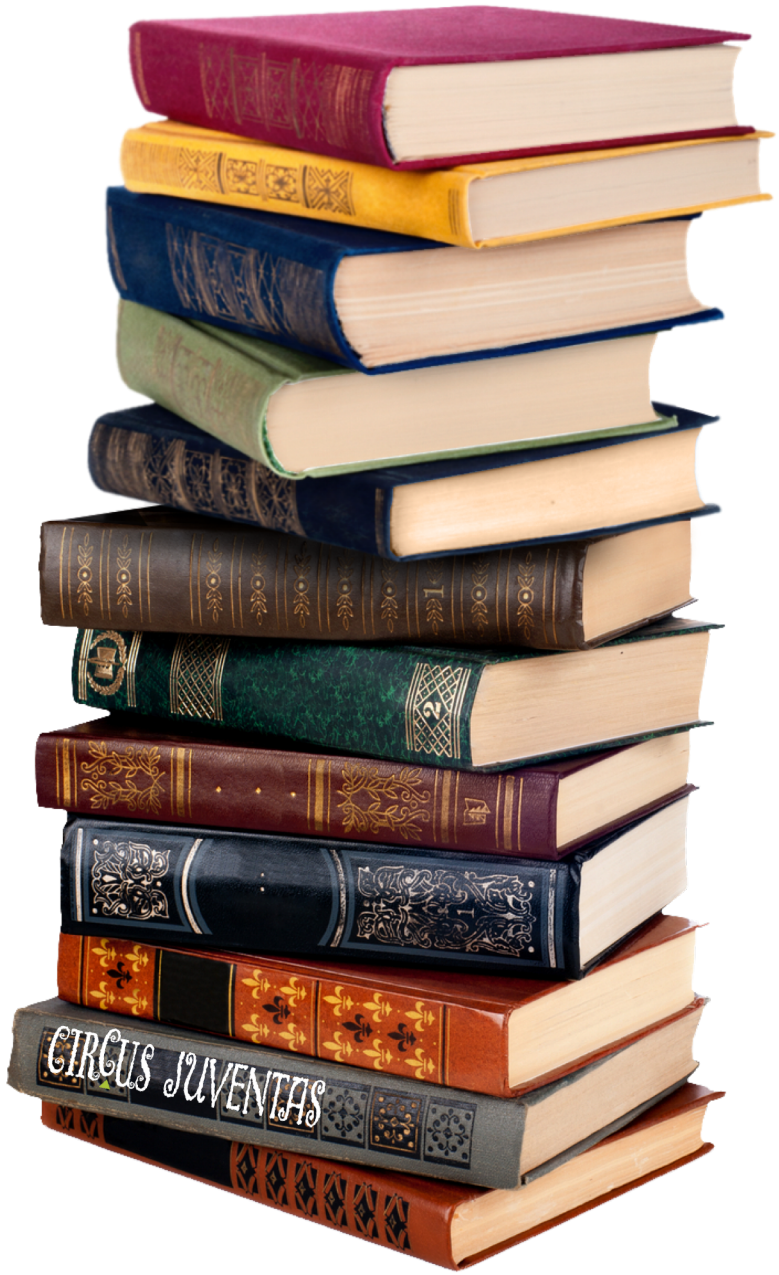
Mosaicism - the presence in a single person two or more cell lines, which were created from one zygote

Mosaicism

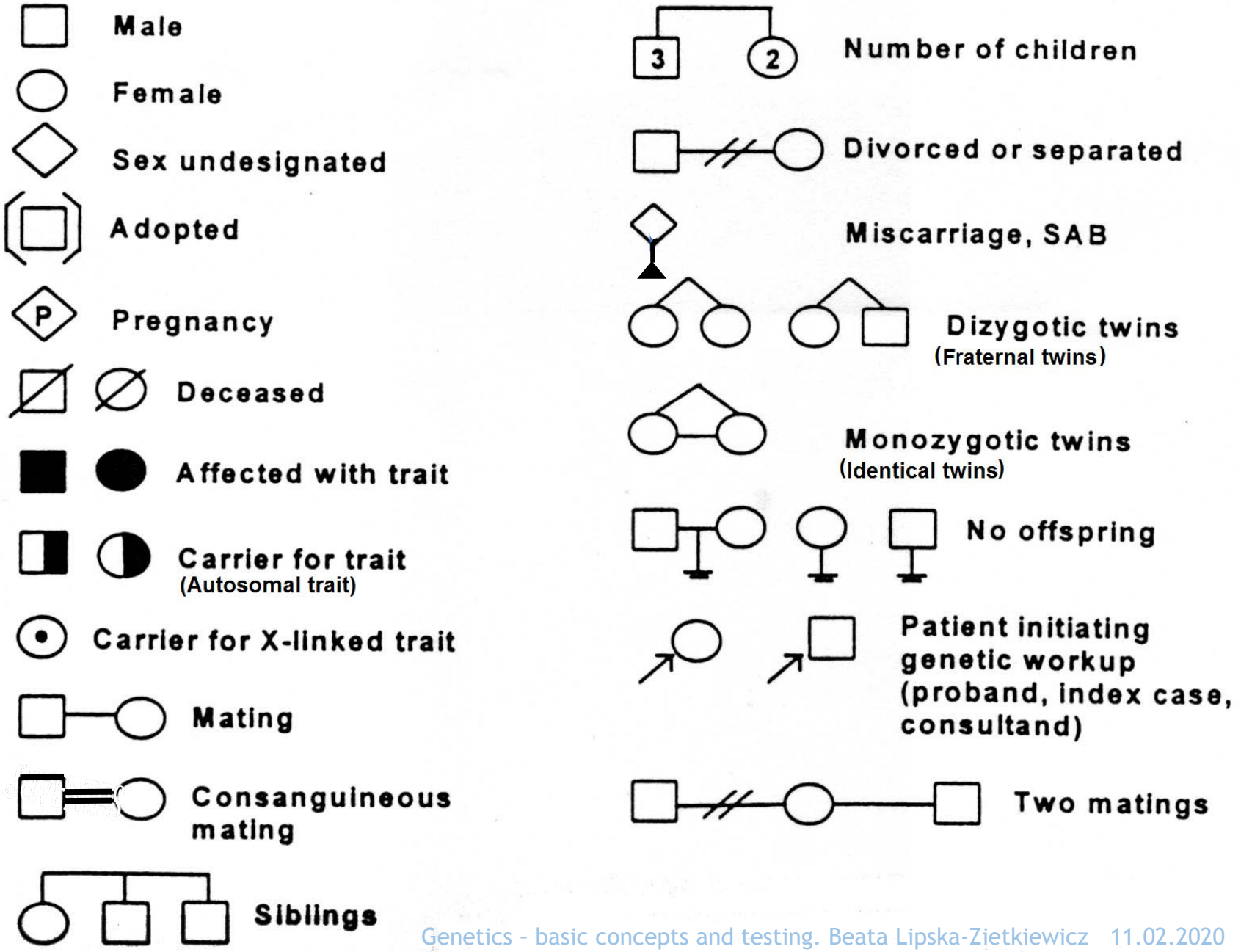




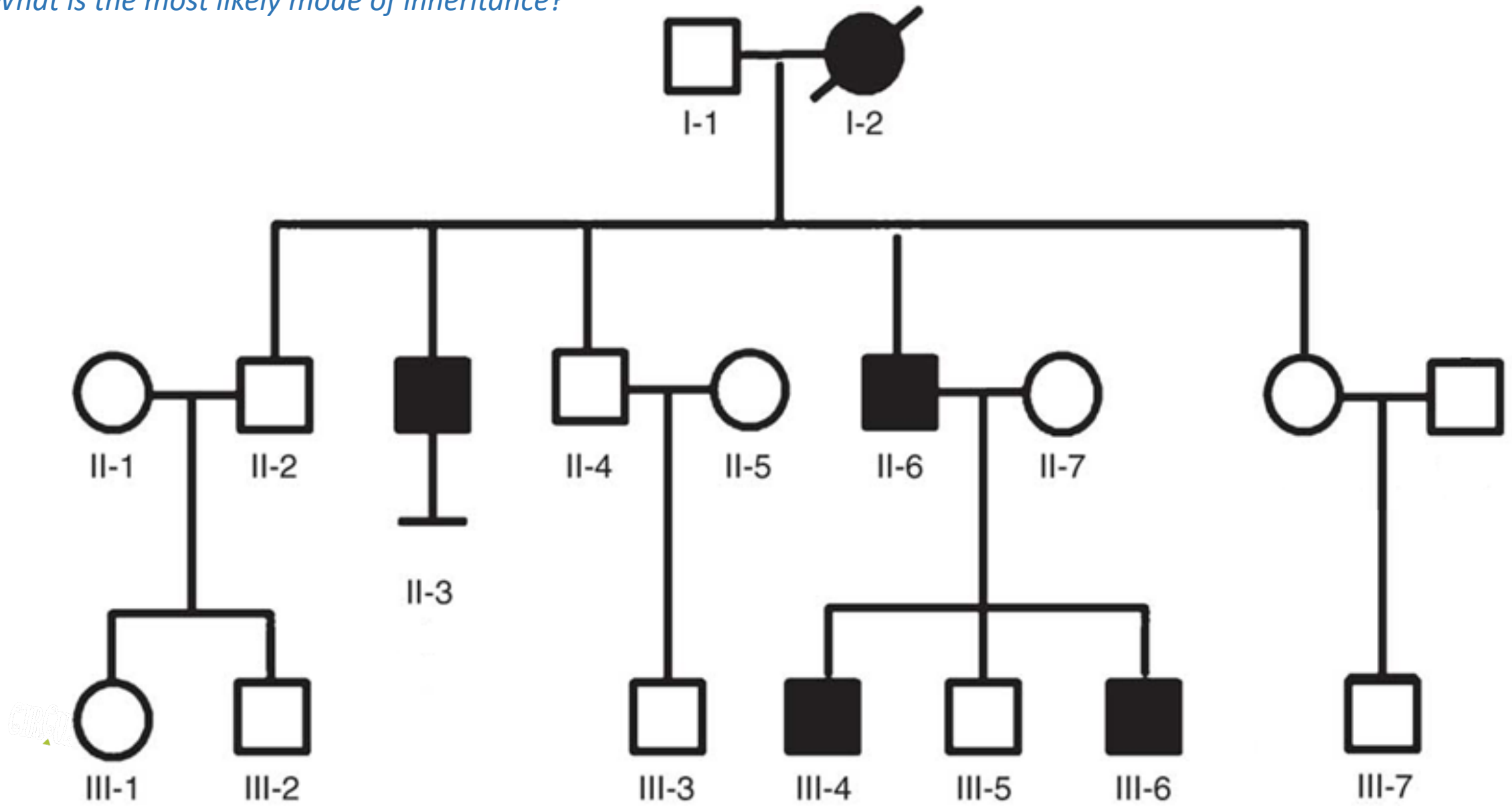
Mosaicism - the presence in a single person two or more cell lines, which were created from one zygote

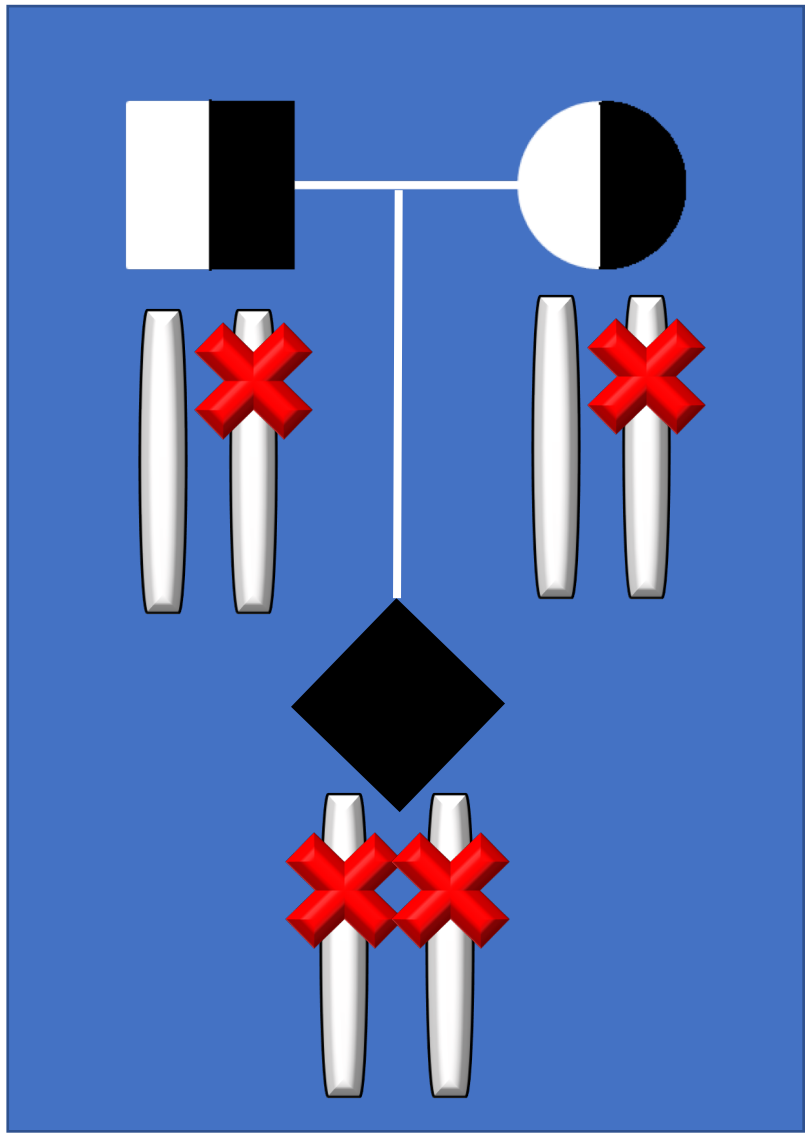


Pedigree – the GENETIC alphabet


Male
Female
Sex undesignated
Adopted
P
Pregnancy
Deceased
Affected with trait
Carrier for trait
(Autosomal trait)
Carrier for X-linked trait
Mating
Consanguineous mating
Siblings
3
2
Number of children
Divorced or separated
Miscarriage, SAB
Dizygotic twins
(Fraternal twins)
Monozygotic twins
(Identical twins)
No offspring
Patient initiating genetic workup (proband, index case, consultand)
Two matings

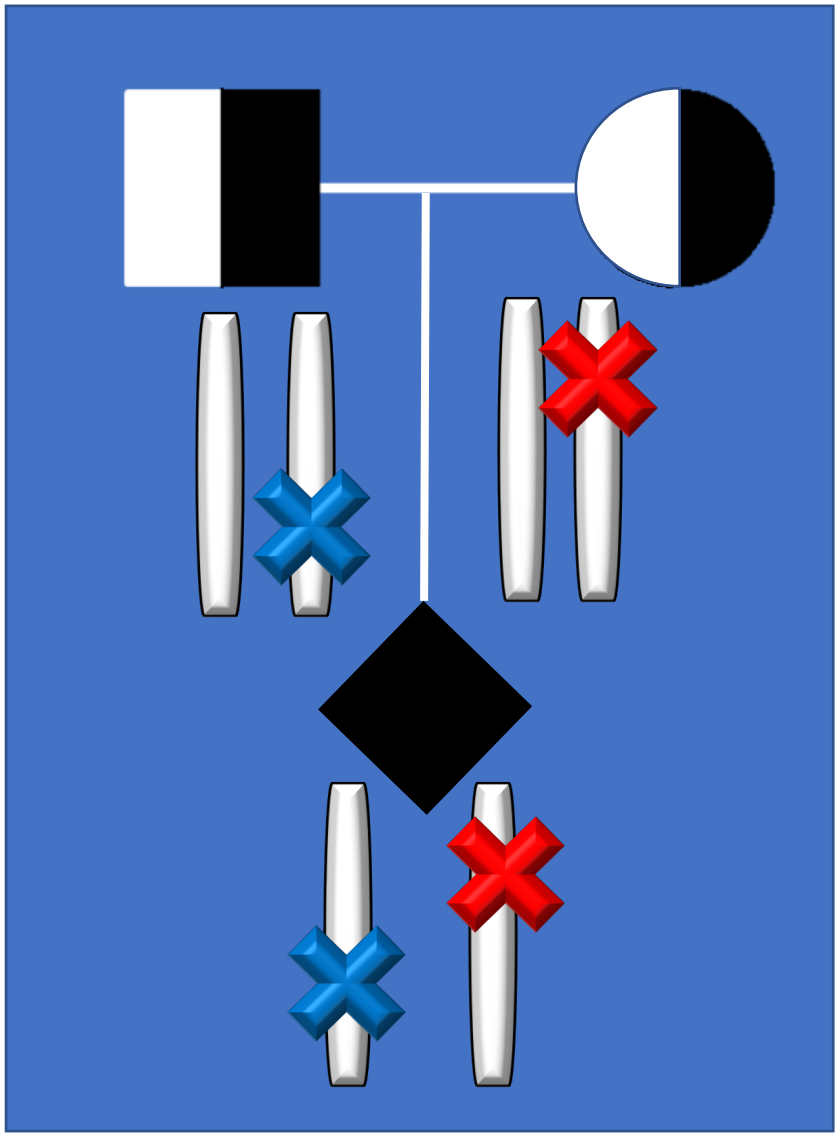
What is the most likely mode of inheritance?





HOMOZYGOTE

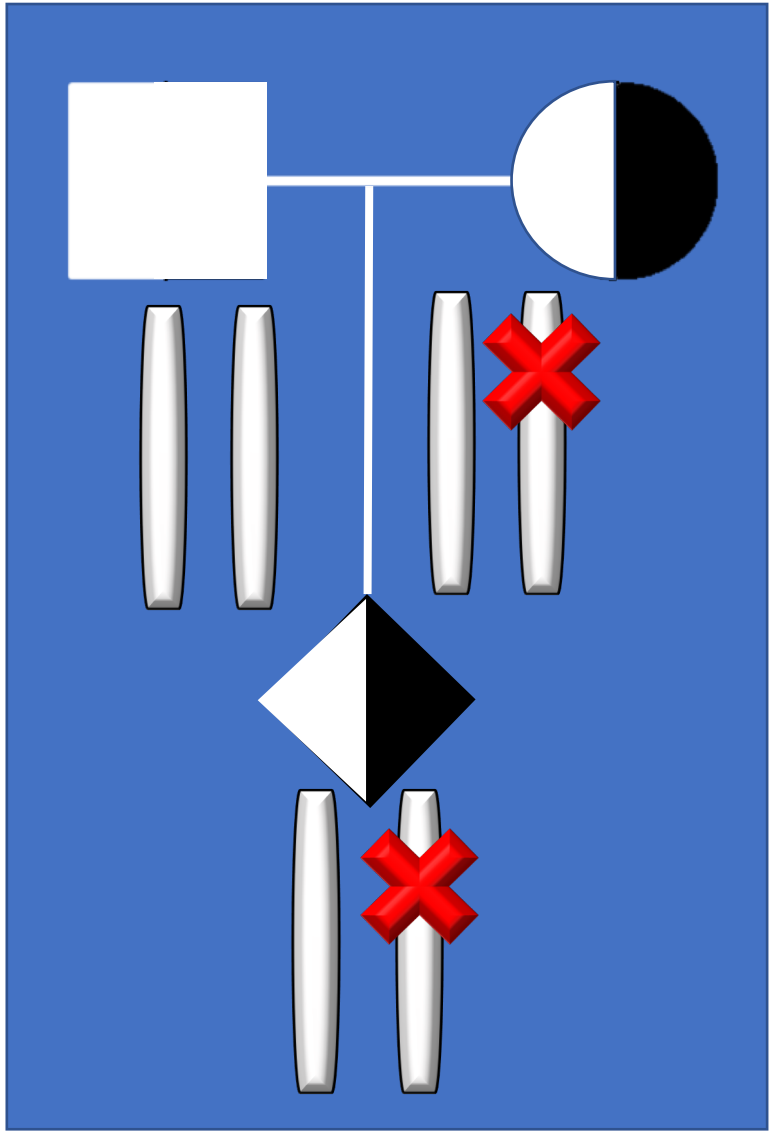
NM_014669.4:c.[1772G>T];[1772G>T]



COMPOUND HETEROZYGOTE

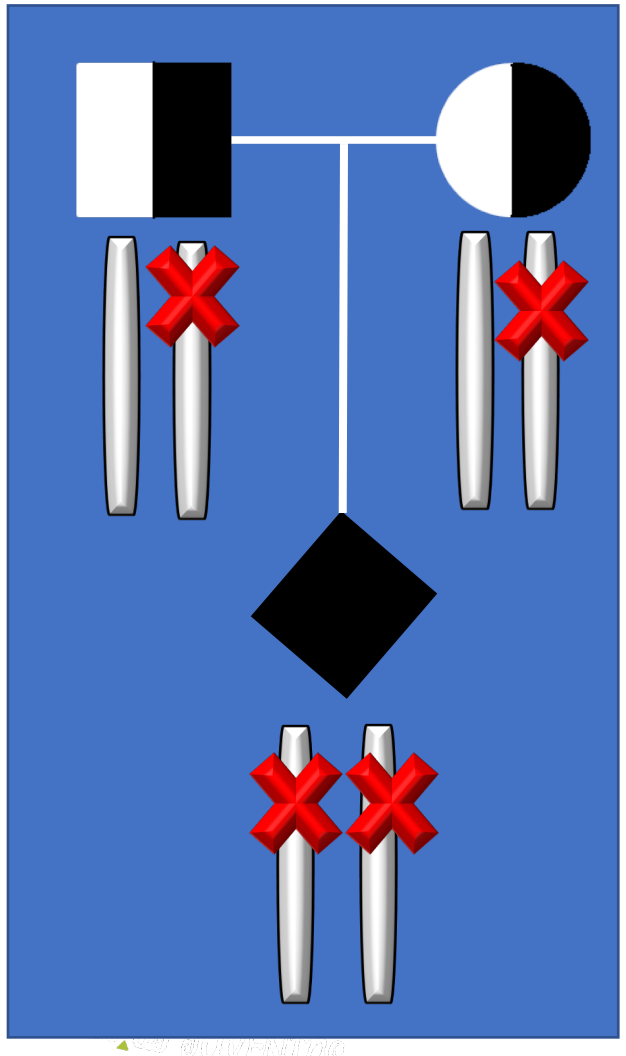
NM_000092.4:c.509G>A(;)4063G>A

NM_000092.4:c.[509G>A];[4063G>A]

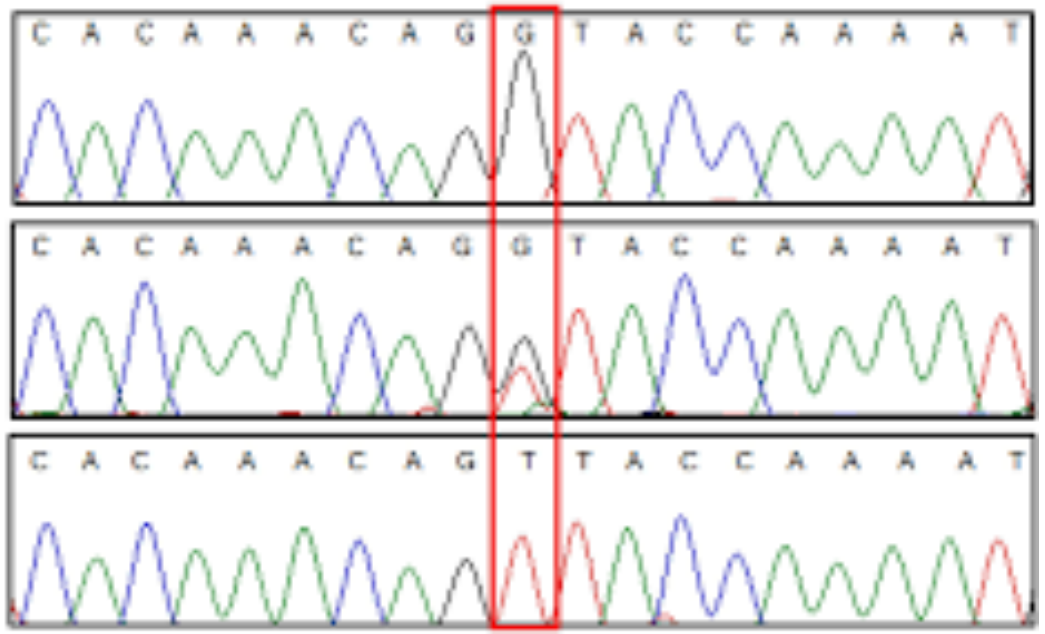


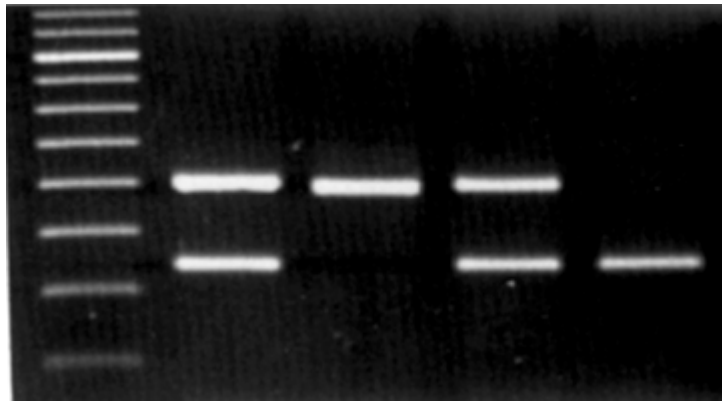
HETEROZYGOTE

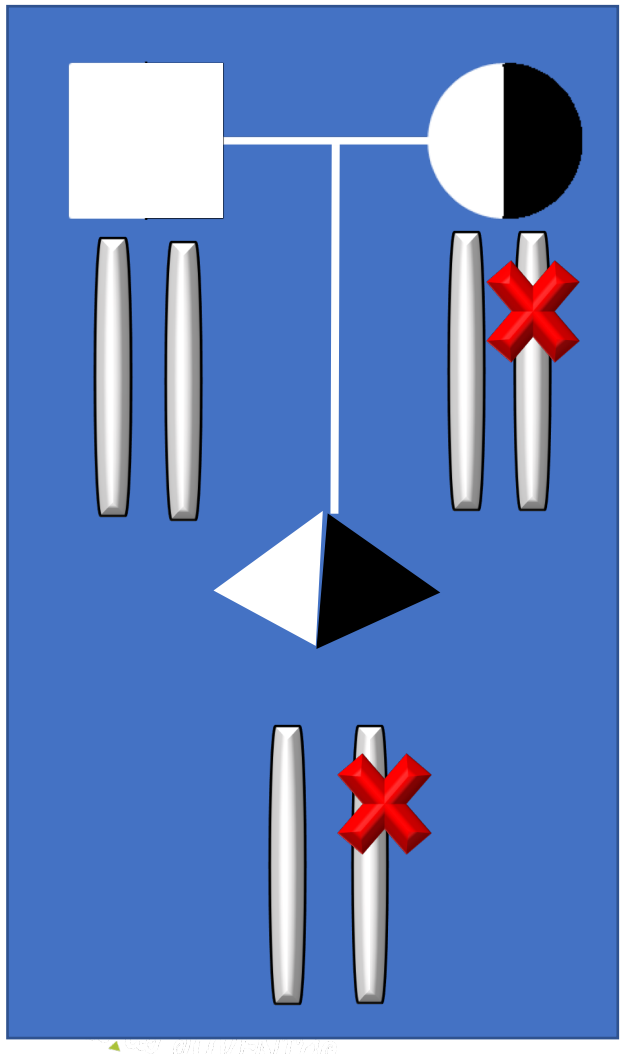
NM_000495.5:c.[512G>A];[=]



HOMOZYGOTE

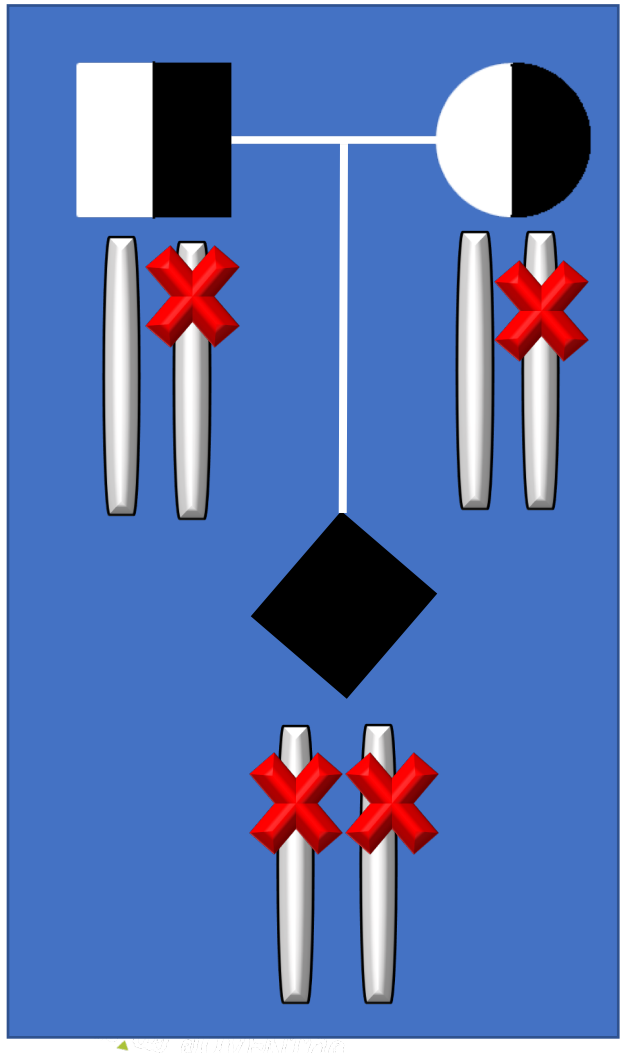


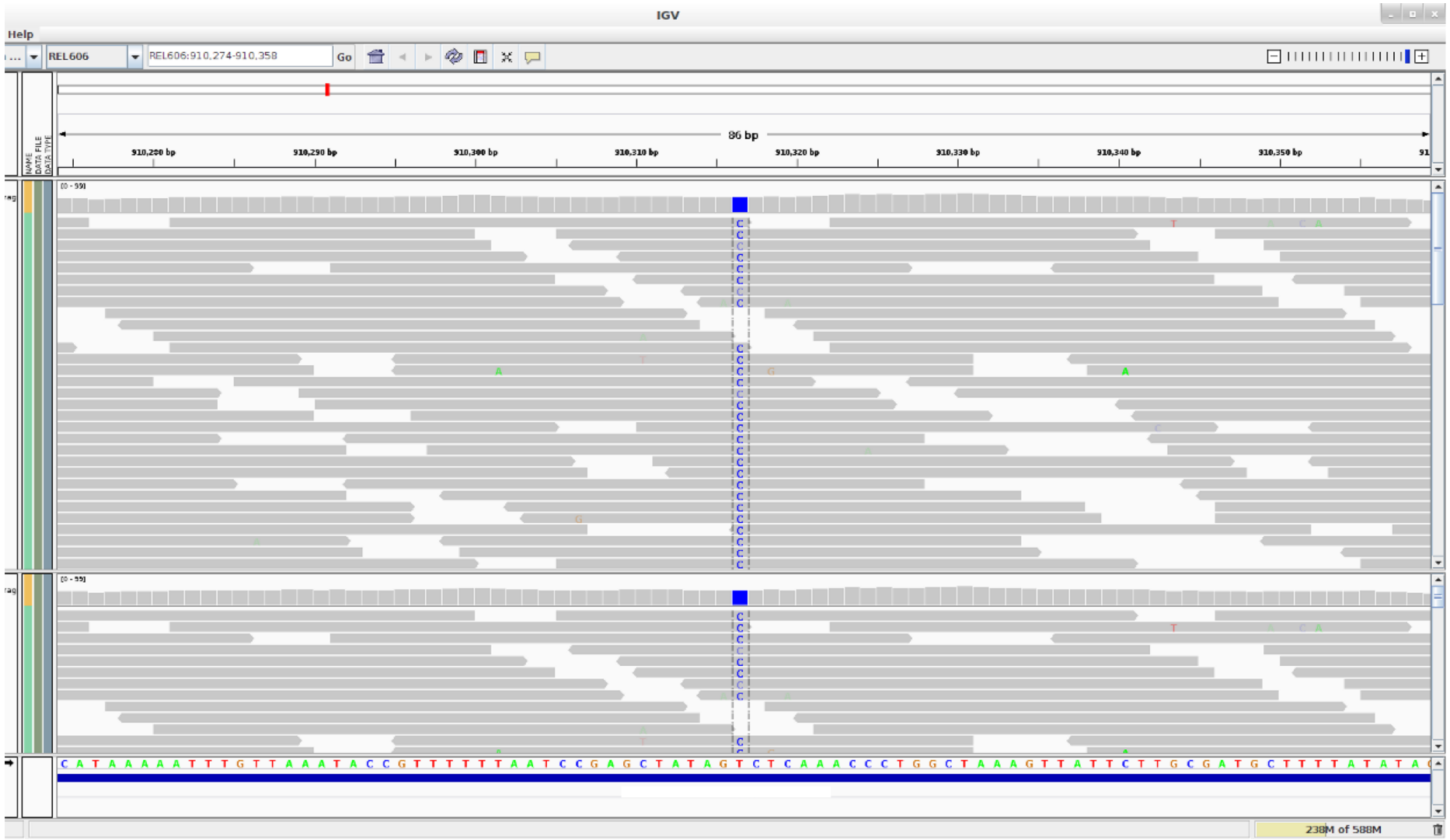




HETEROZYGOTE

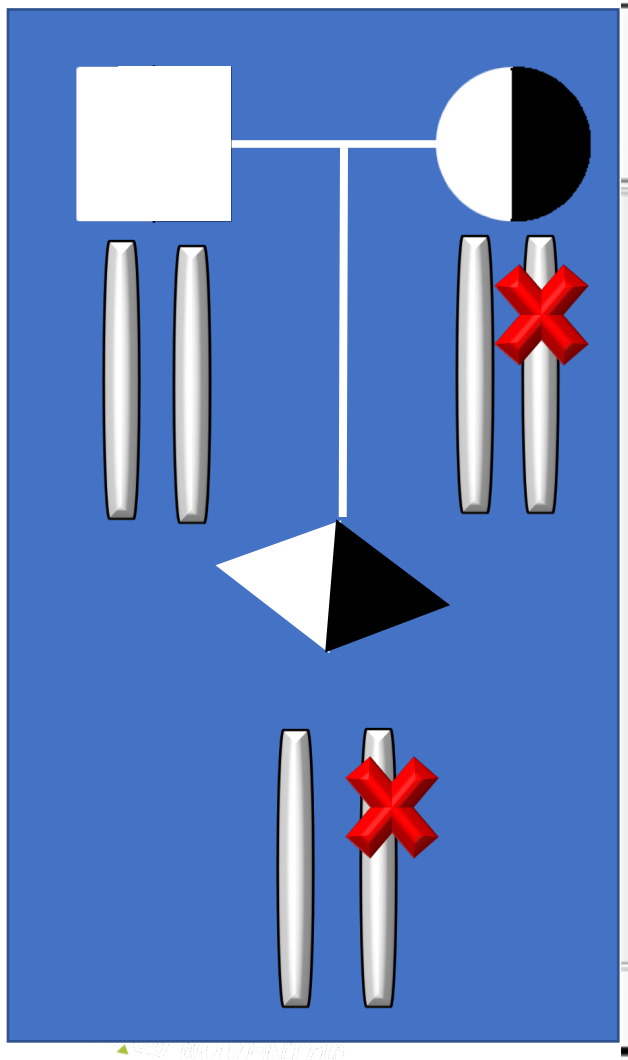
HOMOZYGOTE

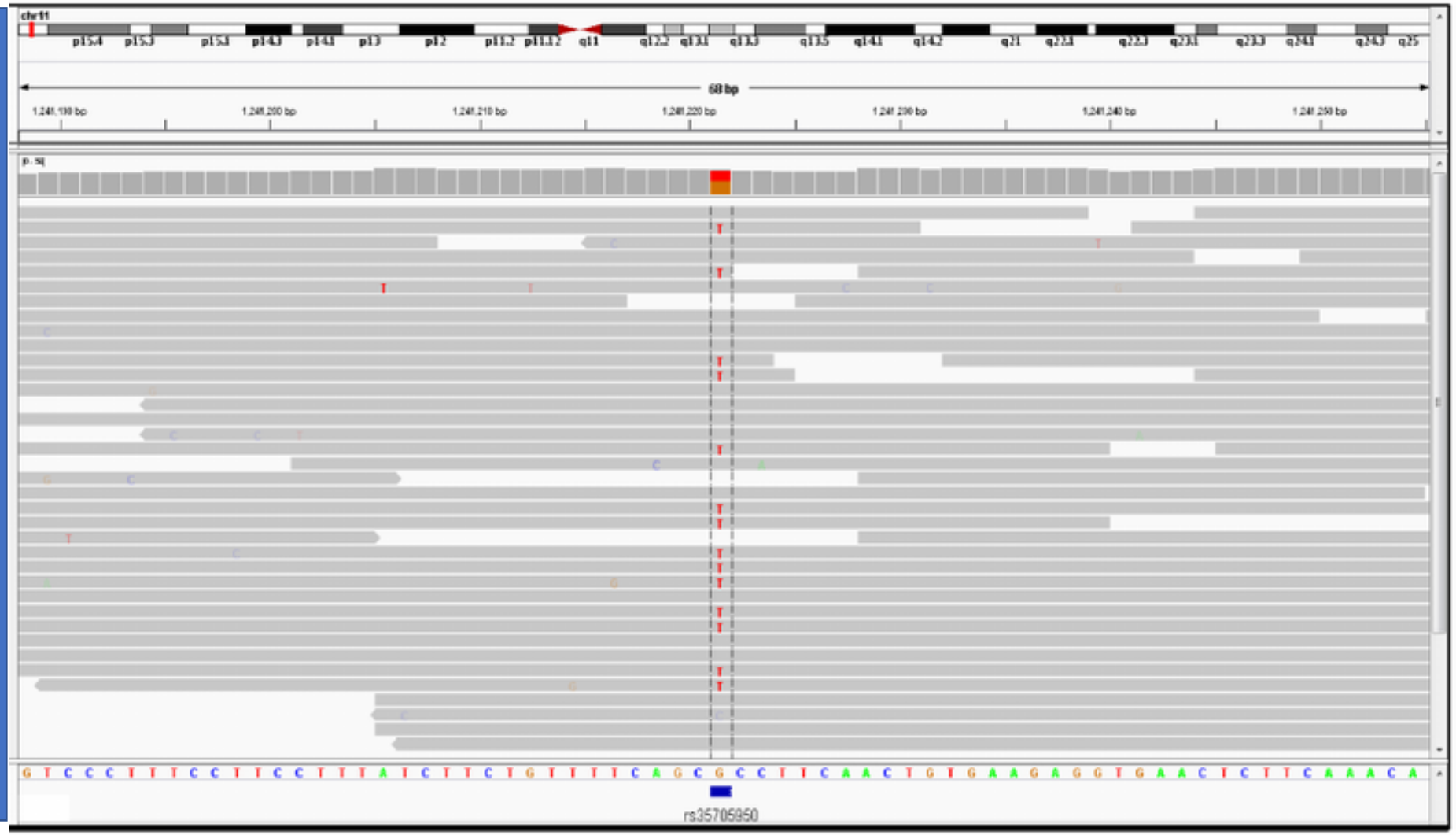




c.[1772T>C];[1772T>C]

HETEROZYGOTE





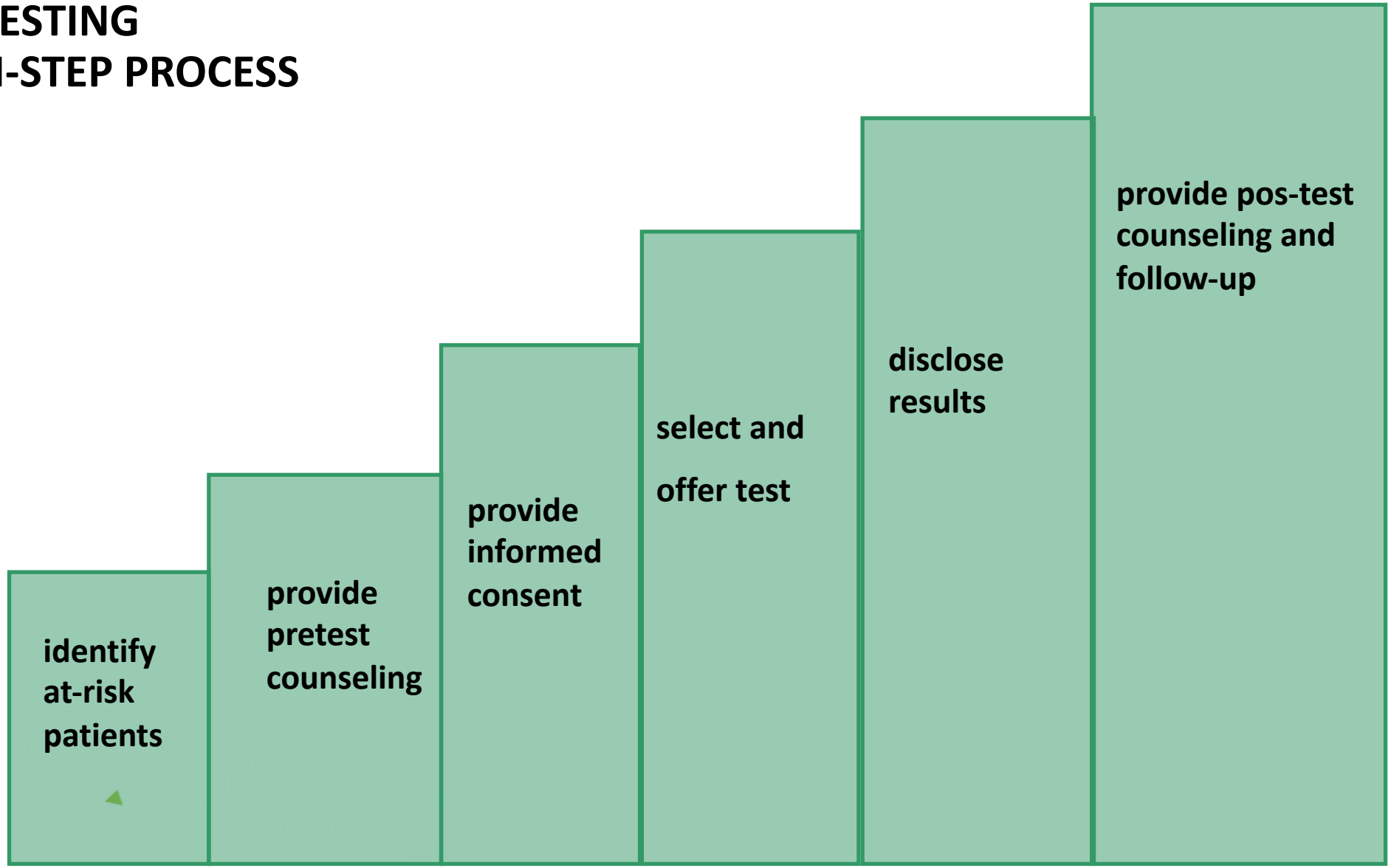
c.[1772T>C];[=]

Approach to the patient:

	Clinics	vs. Genetics
DISEASE STATE:	symptomatic cancer patient	at-risk for mutation
CAUSATIVE AGENT	somatic mutation	germline mutation
LOCUS:	organ	pleotropic
DIAGNOSIS:	tissue pathology	DNA test
INTERVENTION:	medication(s) renal replacement therapy	predictive risk counselling
FAMILY:	patient support	shared risk status

Adopted after: McKellin W „Knowledge translation in cancer : the implications of genetics for cross-cultural cancer care"
Hereditary Cancer Program BCCA www.bc**cancer**.bc.ca/NR/rdonlyres/ E46D73B9-B315-490D-81CF-48F51DD19ABE/6203/BillMcKellinKeynote.ppt

GENETIC TESTING
IS A MULTI-STEP PROCESS



A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology.

Test results should always be interpreted in the context of clinical findings, family history, and other relevant data.

Next Webinars

ERKNet
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IPNA International Pediatric Nephrology Association
GREAT CARE FOR LITTLE KIDNEYS. EVERYWHERE

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ERKNet Advanced Webinars on Rare Kidney Disorders

Date: **25 February 2020**

Speaker: **John Sayer**

Topic: **Joubert Syndrome: molecular genetics and therapy**

IPNA Clinical Practice Webinars

Date: **03 March 2020**

Speaker: **Dieter Haffner**

Topic**: Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease.**

ESPN/ERKNet Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Date: **10 March 2020**

Speaker: **Carl Bates**

Topic: **Anomalies of Kidney and Urinary Tract**

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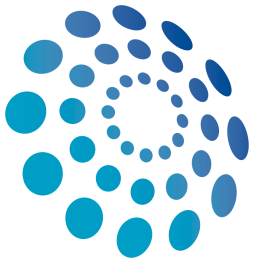

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