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Volume 1

IAP Pediatric OSCE Masterclass

for Postgraduates

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CHAPTER 2

Medical Genetics

Chapter Co-ordinators: *Ashwin Dalal, Naresh Tayade*
Ashwin Dalal, Prajnya Ranganath, Naresh Tayade, Vinu N

Q1. **The human body is made up of trillions of cells that work together in the form of tissues, organs, and systems for the individual's normal functioning. The information regarding an individual's genetic makeup is coded inside the cell's nucleus.**

a. Which molecule inside the nucleus codes for an individual's genetic makeup?
b. What is the central dogma?
c. Which organelle besides the nucleus harbors the genetic material inside the cell?
d. What is a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that does not involve a change in the underlying genetic sequence?
e. Name the process that brings about the attachment of sugars, lipids, etc., to proteins after they are synthesized.

Ans.

a. Deoxyribonucleic acid (DNA)
b. Flow of genetic information from DNA → RNA → Protein
c. Mitochondria
d. Epigenetic changes
e. Posttranslational modification

Q2. **The DNA sequence in chimpanzees and humans is 99% similar. The DNA sequence of all humans is 99.9% identical. The minute difference of 0.1% of our DNA makes us all different from each other. These changes in DNA can either lead to phenotypic differences among individuals or result in various genetic diseases.**

a. What is the term for DNA change that results in the substitution of one amino acid for another?
b. Some DNA changes do not lead to changes in amino acids. What are they called?
c. What is the change in amino acid sequence that results from an insertion or deletion of two nucleotides?
d. What is the name of the DNA variant which results in premature termination of protein synthesis?
e. Name the effect wherein the abnormal protein product actively interferes with the function of the normal protein product.

Ans.

a. Missense variant *OR* nonsynonymous variant
b. Synonymous variant *OR* Wobble variant *OR* silent variant
c. Frameshift
d. Nonsense variant *OR* stop gain variant
e. Dominant negative effect

Note: "Mutation has been replaced with term variant but can be considered as answer, so candidate answering mutation in place of variant can be considered acceptable answer."

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Q3.

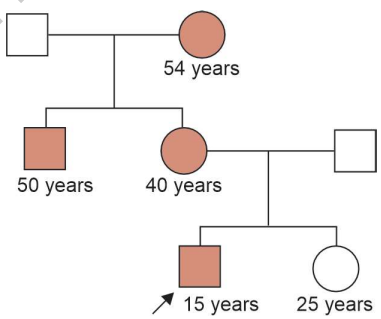


a. What is the name of the investigation?
b. Which anticoagulant is preferred for blood collection for this test?
c. What is the phase of mitosis that this test is done?
d. What is the most common cause of intellectual disability detected by this test?
e. What is the total number of chromosomes in humans?

Ans.

a. Chromosomal analysis *OR* karyotyping
b. Heparin
c. Metaphase
d. Down syndrome
e. 46

Q4. The pedigree below depicts the family members affected with Huntington disease with the age of onset of symptoms.



a. What is the most probable inheritance pattern?
b. What is the name of a phenomenon seen with respect to the age of onset of symptoms in a patient?

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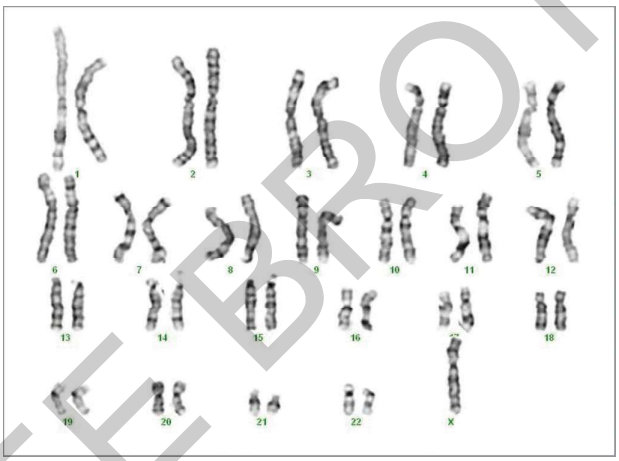
c. What is the type of testing if a genetic test is done on a 25-year-old female to check if she is likely to be affected with disease in future?
d. What is the type of mutation seen in this disorder?
e. Is it ethically correct to do genetic testing on a 6-year-old female child in a similar family to check if she is likely to be affected with the disease in the future? Why?

Ans.

a. Autosomal dominant
b. Anticipation *OR* age-dependent penetrance
c. Presymptomatic testing/triplet repeat primed polymerase chain reaction (TP-PCR)
d. Triplet repeat expansion
e. No. Presymptomatic detection of disease will not lead to any intervention leading to cure or control of disease but will rather lead to social stigma and psychological effects. Presymptomatic testing in such conditions should be offered only after 18 years of age and after proper genetic counseling.

Q5.



a. What is the karyotype of the patient?
b. What are the likely clinical features in the patient?
c. What is the significance of looking for the presence of Y chromosome mosaicism in these patients?
d. What is the suggested treatment if Y chromosome mosaicism is identified?
e. What is the single gene disorder which shows phenotypic similarity to the phenotype of this patient?

Ans.

a. 45, X OR Turner syndrome
b. Primary amenorrhea, lymphedema, increased carrying angle, web neck, short stature, cognitive impairment, cardiac defect, etc.
c. 15–30% risk of developing gonadoblastoma
d. Laparoscopic gonadectomy
e. Noonan syndrome

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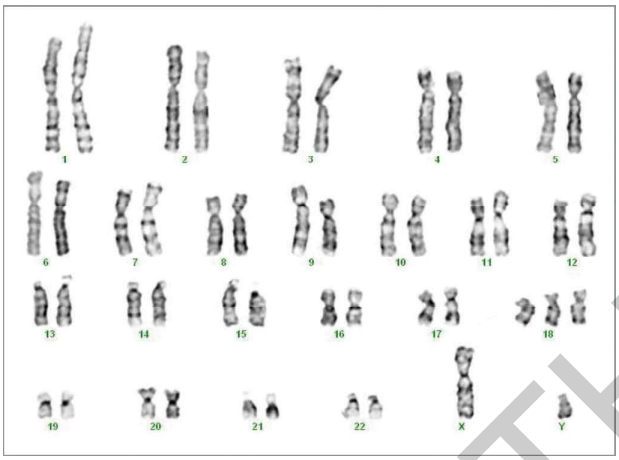
Q6.

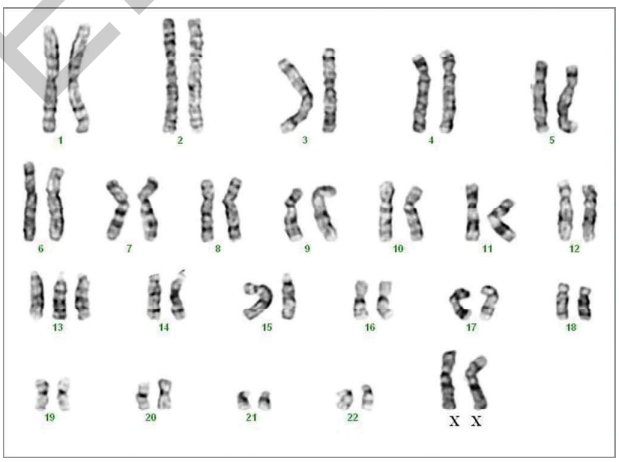


a. What is the karyotype of the patient?
b. What is the clinical diagnosis in this patient?
c. What are the likely clinical features in the patient?
d. What is the recurrence risk if both parents have normal karyotype?
e. What are other chromosomes whose nonmosaic aneuploidy is compatible with postnatal survival?

Ans.

a. 47,XY,+18 *OR* trisomy 18
b. Edward syndrome
c. Low birthweight, closed fists with overlapping fingers, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, intellectual disability
d. Up to 1%
e. 21, 13, X, Y

Q7.



a. What is the karyotype of the patient?
b. What is the clinical diagnosis in this patient?

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c. What are the likely clinical features in the patient?
d. What is the recurrence risk if both parents have normal karyotype?
e. What are other chromosomes whose nonmosaic aneuploidy is compatible with postnatal survival?

Ans.

a. 47,XX,+13 *OR* trisomy 13
b. Patau syndrome
c. Cleft lip often midline; flexed fingers with postaxial polydactyly; ocular hypotelorism, low-set, malformed ears; microcephaly; cerebral malformation, especially holoprosencephaly; microphthalmia, cardiac malformations; scalp defects, etc.
d. Up to 1%
e. 21, 18, X, Y

Q8.



a. What is the karyotype of the patient?
b. What is the clinical diagnosis in this patient?
c. What are the likely clinical features in the patient?
d. What is the recurrence risk if both parents have normal karyotype?
e. What are other chromosomes whose nonmosaic aneuploidy is compatible with postnatal survival?

Ans.

a. 47,XX,+21 *OR* trisomy 21
b. Down syndrome
c. Characteristic facies, developmental delay, congenital heart disease, simian crease, increased sandal gap, hypotonia, gastrointestinal malformations, etc.
d. Up to 1%
e. 18, 13, X, Y

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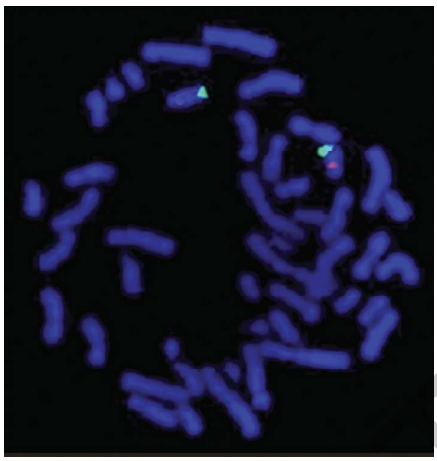
Q9.

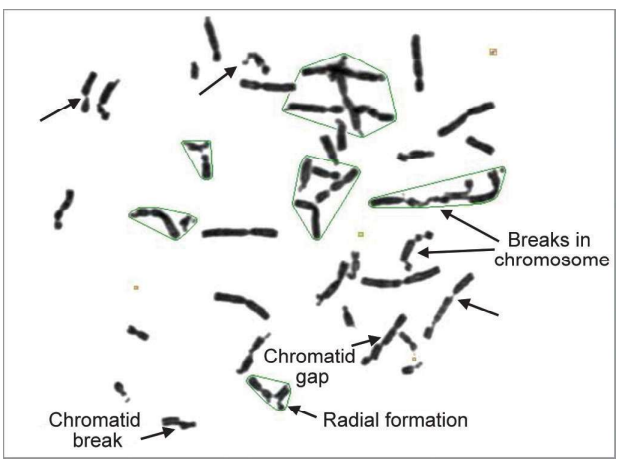


a. What is the name of the investigation?
b. The result shows binding of DNA oligo probes on chromosome 15q11.2 region. What are the likely diagnosis in this patient?
c. What are the likely clinical features of Prader–Willi syndrome?
d. What is the recurrence risk if both parents do not show any abnormality in this test?
e. What are the examples of other diseases detected using the same test?

Ans.

a. Fluorescence in-situ hybridization (FISH)
b. Prader–Willi syndrome/Angelman syndrome
c. Neonatal hypotonia, slow infant growth, small hands and feet, intellectual disability, hypogonadism, hyperphagia leading to severe obesity, etc.
d. Up to 1%
e. Williams syndrome, Angelman syndrome, DiGeorge syndrome, Smith–Magenis syndrome, Miller–Dieker syndrome, etc.

Q10. The below figure shows chromosomal breakages, radial, and triad formation on chromosomal analysis after adding mitomycin C to the culture.



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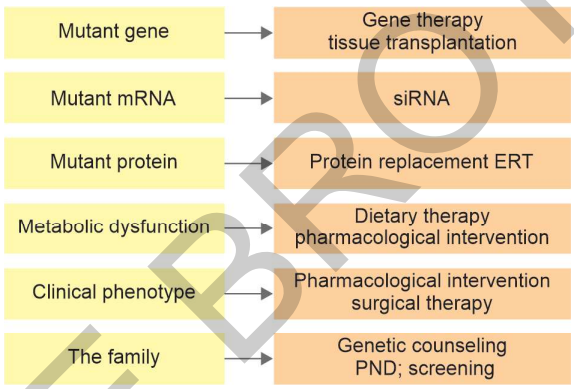
a. What is the likely clinical diagnosis in this patient?
b. What are the likely clinical features in the patient?
c. What is the other chemical which can be used to induce similar chromosomal breaks in these patients?
d. What is the most common mode of inheritance for this disease?
e. What are examples of other chromosomal instability syndromes?

Ans.

a. Fanconi anemia
b. Short stature, microcephaly in 1/3 of cases, radial ray defects including thumb anomalies, pancytopenia, skeletal anomalies, renal anomalies, café-au-lait macules, ear abnormalities, and hearing loss, etc.
c. Diepoxybutane
d. Autosomal recessive
e. Bloom syndrome, ataxia telangiectasia, Roberts-SC phocomelia syndrome, Nijmegen syndrome, Werner syndrome, etc.

Q11. The figure below shows the various levels at which management can be done for a genetic disease.



a. Give one example of a therapy based on replacement of protein.
b. What are the conditions/diseases that can be treated with dietary therapy?
c. Give one example of surgical therapy for a congenital malformation.
d. Give one example of approved gene therapy for a genetic disease.
e. What is the pharmacological intervention drug used in treatment of Wilson disease?

Ans.

a. Enzyme replacement therapy for Gaucher disease, Pompe disease, etc.
b. Phenylketonuria, isovaleric acidemia, propionic acidemia etc. (*All inborn errors of metabolism (IEMs) in which diet therapy available can be considered answer*).
c. Plastic surgery for polydactyly, surgery for cleft lip/palate, surgery for congenital heart disease (*All surgically amenable complications to consider as answer*).
d. Gene therapy for Leber congenital amaurosis, hemophilia A, hemophilia B, spinal muscular atrophy, etc.
e. Penicillamine, trientine

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Q12. The table below shows the various genetic tests available for diagnosis of a genetic disease.

Sr No.	*Genetic testing modality*
1.	Karyotyping
2.	Fluorescent in-situ hybridization
3.	Multiplex ligation dependent probe amplification
4.	Sanger sequencing
5.	Triplet primed PCR
6.	Exome sequencing

Mention the first investigation of choice to use in each of the below situations:

a. Identification of a point mutation in a gene of four exons.
b. Identification of deletion/duplication of exons in case of Duchenne muscular dystrophy.
c. Genetic diagnosis for a case suspected to be affected with Fragile X syndrome.
d. Genetic investigation in a patient with Noonan syndrome-like features.
e. Genetic analysis in a patient with features of Down syndrome.
f. Genetic testing in a patient with hypocalcemia, conotruncal heart defect, facial dysmorphism, intellectual disability for identification of microdeletion of DiGeorge syndrome.

Ans.

a. Sanger sequencing
b. Multiplex ligation dependent probe amplification (MLPA)
c. Triplet primed PCR
d. Exome sequencing
e. Karyotyping
f. Fluorescent in-situ hybridization FISH or MLPA

Q13. The table below shows the various types of genetic testing scenarios.

Sr No.	*Genetic testing scenario*
1.	Diagnostic testing
2.	Carrier screening
3.	Presymptomatic testing
4.	Direct to consumer testing
5.	Histocompatibility testing

Mention the scenario that fits each of the genetic testing examples:

a. Testing of both parents by hemoglobin electrophoresis to look for increased levels of HbA2 in a family with history of thalassemia.
b. Testing in a healthy 28-year-old male for Huntington disease since his father is found to have a triplet repeat expansion.
c. Testing done since there is need of a donor for bone marrow transplantation in a child with thalassemia.
d. Genetic testing done in a patient with weakness of lower limbs and increased serum creatinine phosphokinase.
e. Testing done by a company by obtaining samples of saliva from individuals through a supermarket advertisement.

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Ans.

a. Carrier screening
b. Presymptomatic testing
c. Histocompatibility testing
d. Diagnostic testing
e. Direct to consumer testing

Q14. The table below shows the various mechanisms of genetic disease causation.

Sr No.	*Mechanism of genetic disease*
1.	Haploinsufficiency
2.	Gain of function
3.	Dominant negative
4.	Copy number variation
5.	Somatic mutation

Identify the most common/likely mechanism for the below diseases:

a. Charcot–Marie–Tooth disease
b. Osteogenesis imperfecta due to *COL1A1* mutation
c. Achondroplasia
d. Retinoblastoma
e. Familial hypercholesterolemia

Ans.

a. Copy number variation
b. Dominant negative
c. Gain of function
d. Somatic mutation
e. Haploinsufficiency

Q15. The table below shows the various mechanisms of congenital abnormalities.

Sr No.	*Mechanism*
1.	Malformation
2.	Disruption
3.	Dysplasia
4.	Deformation
5.	Sequence

Identify the mechanism involved in each of the below situations.

a. Amniotic bands leading to amputation of a limb
b. Preaxial polydactyly
c. Congenital talipes equinovarus in baby of a mother with a large intrauterine fibroid
d. Patient with conical teeth, absent sweating, absent scalp hair, eyebrows, and eyelashes
e. Baby with a small jaw which resulted in glossoptosis and cleft palate.

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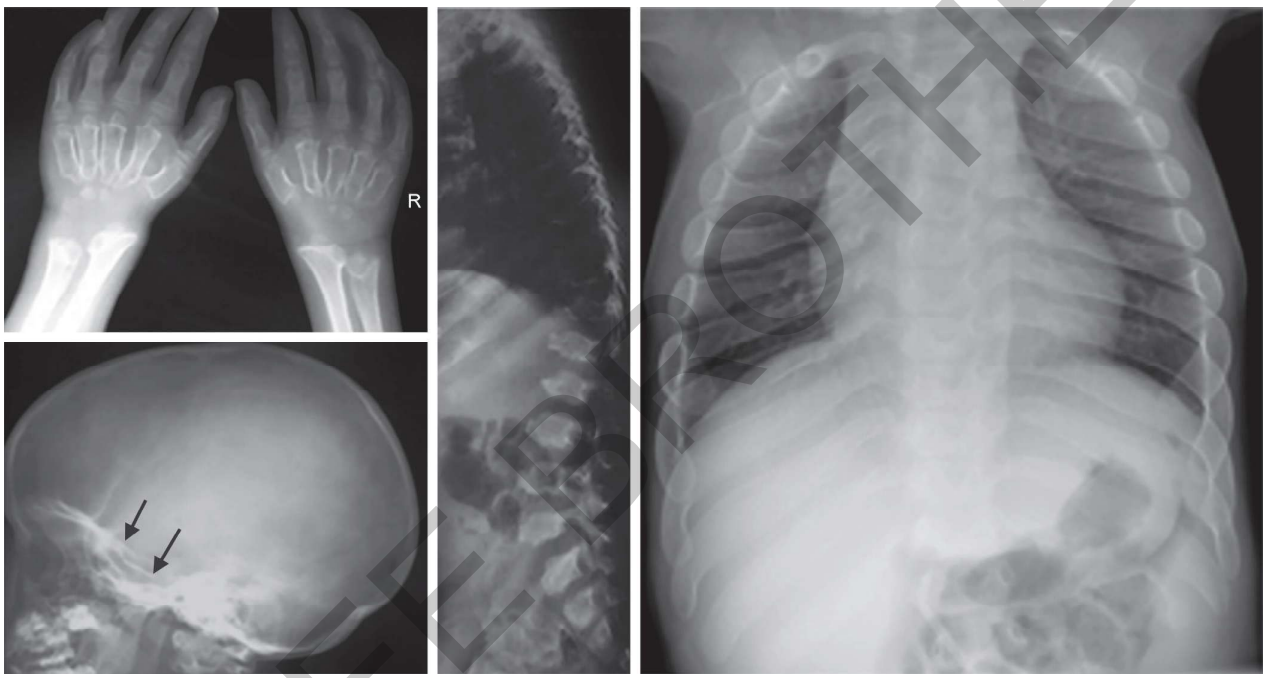
Ans.

a. Disruption
b. Malformation
c. Deformation
d. Dysplasia
e. Sequence

Q16. The figure below shows the X-ray findings in a patient with coarse facies, corneal clouding, and intellectual disability.



a. What is this constellation of findings called?
b. What abnormality is seen in X-ray skull?
c. What abnormality is seen in X-ray spine lateral view?
d. What abnormality is seen in X-ray hands with wrist?
e. What abnormality is seen in X-ray chest?

Ans.

a. Dysostosis multiplex
b. J-shaped sella turcica
c. Anterior and inferior beaking of the vertebrae
d. Proximal pointing, wide (expanded) short metacarpals and phalanges, thin cortices/*hypoplastic and irregularly shaped metacarpals/bullet-shaped phalanges*
e. Oar-shaped ribs (widened anteriorly and tapered posteriorly)/paddle shaped

Q17. Mucopolysaccharidoses are characterized by a characteristic constellation of clinical features, radiologic findings, and pattern of glycosaminoglycans excreted in urine.

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Identify the most likely type of mucopolysaccharidosis in each of the below situations.

a. A 3-year-old female presenting with severe intellectual disability, coarse facies, hypertrichosis, no corneal clouding, no organomegaly, and predominant excretion of heparan sulfate in urine.

b. A 6-year-old male presenting with pigeon chest, disproportionate short stature (short trunk dwarfism), normal intellectual functioning, coarse facies, no corneal clouding, no organomegaly and predominant excretion of keratan sulfate in urine.

c. A 3-year-old male presenting with severe intellectual disability, coarse facies, no corneal clouding, short stature, grouped skin papules, joint stiffness, and predominant excretion of heparan sulfate in urine.

d. A 2-year-old male presenting with severe intellectual disability, coarse facies, corneal clouding, short stature, joint stiffness, hepatosplenomegaly, and predominant excretion of heparan sulfate and dermatan sulfate in urine.

e. A 5-year-old male presenting with short stature, normal intellectual functioning, coarse facies, corneal clouding, joint stiffness, hepatosplenomegaly, and predominant excretion of dermatan sulfate in urine.

Ans.

a. Mucopolysaccharidosis type III or Sanfillipo disease
b. Mucopolysaccharidosis type IV or Morquio syndrome
c. Mucopolysaccharidosis type II or Hunter syndrome
d. Mucopolysaccharidosis type I or Hurler syndrome
e. Mucopolysaccharidosis type VI or Maroteaux–Lamy syndrome

Q18. The human genome can be studied and investigated in many different ways. The table below lists some of the sub-fields of medical genetics/human genetics.

Sr No.	*Genetic testing modality*
1.	Cytogenetics
2.	Pharmacogenetics
3.	Metabolomics
4.	Epigenetics
5.	Transcriptomics
6.	Genomics

Identify the field of study related to below explanations:

a. Study of how variants contribute to interindividual variability in drug response.

b. Study of the entire set of intermediary molecules within in a cell/tissue/organelle following a specific cellular process including biomarker assays.

c. Study of global gene expression patterns and their changes with respect to time and environment.

d. Study of all of a person's genes, including interactions of those genes with each other.

e. Study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence.

f. Study of chromosomes and their abnormalities

Ans.

a. Pharmacogenetics
b. Metabolomics
c. Transcriptomics
d. Genomics
e. Epigenetics
f. Cytogenetics

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Q19. Gene therapies are being developed for a large number of genetic diseases using different gene editing/therapy approaches. The table below shows some of the approaches.

Sr No.	*Genetic editing/therapy approaches*
1.	Adeno-associated virus (AAV)-mediated expression of the normal gene
2.	Homology-directed repair (HDR)
3.	Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR- associated protein 9 (Cas9)
4.	Antisense oligonucleotides (ASOs)
5.	Chimeric antigen receptor (CAR)-T cell therapy cell therapy

Identify the gene editing approach based on the descriptions below:

a. The process of DNA site-specific double-strand breaks (DSBs) induced by the endonuclease and a template encompassing the wild-type sequence to be used as a substrate for repair.
b. Process of cutting DNA strands at specific sites so that the normal copy of gene can be inserted for gene therapy.
c. Therapy involving collecting T cells from the patient and re-engineering them in the laboratory to produce proteins on their surface.
d. Process of transfer of normal copy of gene packaged in viral genome to human cells.
e. Short synthetic nucleic acids that hybridize with cellular RNA using classic base pairing to modulate gene expression.

Ans.

a. Homology-directed repair (HDR)
b. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9)
c. Chimeric antigen receptor (CAR)- T Cell therapy cell therapy
d. Adeno-associated virus (AAV)-mediated expression of the normal gene
e. Antisense oligonucleotides (ASOs)

Q20. A 13-year-old boy (see figure) presented with history of developmental delay, features of autism, and on examination also had large ears and macro-orchidism.

a. What is the most probable diagnosis?
b. What is the mechanism of mutation in this condition?
c. What is the test of choice for diagnosis of this condition?
d. What is the late onset phenotype in a male and female carrier of a permutation in this condition?
e. What is the special mode of inheritance of this condition?



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Ans.

a. Fragile X syndrome
b. Triplet repeat expansion beyond 200 repeats in *FMR1* gene
c. Triplet primed PCR or Southern blot
d. *Female:* Premature ovarian failure; *Male:* Fragile X tremor ataxia syndrome
e. X-linked semidominant

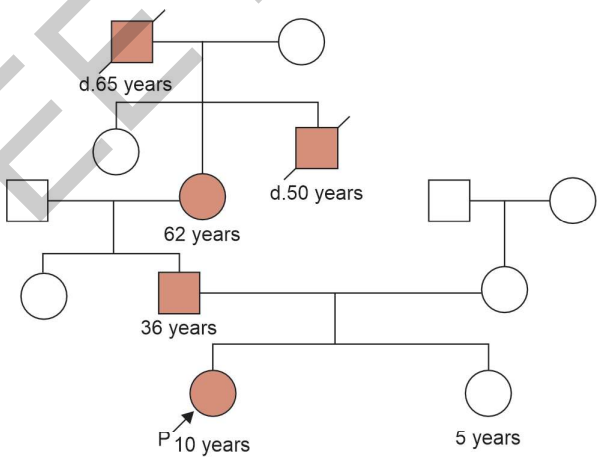
Q21. Mrs X is referred for prenatal genetic counseling and testing at 8 weeks of gestation. Her brother had severe hemophilia A and died at 15 years of age; her maternal uncle also had severe hemophilia A and died at 18 years of age.

a. What is the pattern of inheritance of hemophilia A?
b. What is the chance of Mrs X being a carrier of hemophilia A?
c. If Mrs X is found to be a carrier for hemophilia A, what would be the risk of recurrence of the disorder in her offspring?
d. If Mrs X is found to be a carrier for hemophilia A, what would be the chance of her offspring being carriers?
e. Name three other disorders which have the same pattern of inheritance.

Ans.

a. Hemophilia A has an X-linked recessive pattern of inheritance.
b. The chance of Mrs X being a carrier for hemophilia A is 50%. As her brother and her maternal uncle are affected with the disorder, her mother would be an obligate carrier. Therefore, as her mother is a carrier, there is a 50% chance that she will inherit the mutation from her mother.
c. If Mrs X is found to be a carrier, there would be 50% risk of the disorder in each of her male offspring.
d. If Mrs X is found to be a carrier, there would be 50% chance of carrier status in each of her female offspring.
e. Examples of other disorders which follow an X-linked recessive pattern of inheritance are: Hemophilia B, Duchenne muscular dystrophy, and mucopolysaccharidosis type II (Hunter syndrome).

Q22.



This is the pedigree of a family with multiple members affected with a disorder associated with skin lesions.

a. What is the most likely pattern of inheritance based on the given pedigree and why?
b. Different affected individuals with this disorder can have different ages of onset and severity and varying manifestations of the disease. What is this phenomenon called?
c. For disorders which follow this inheritance pattern, if an affected individual has an affected parent, what would be the risk of recurrence in each of his/her siblings?

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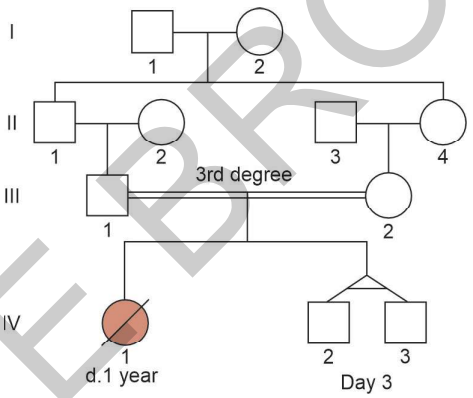
d. Why does this pedigree not fit into mitochondrial inheritance?
e. Name three disorders which follow this pattern of inheritance.

Ans.

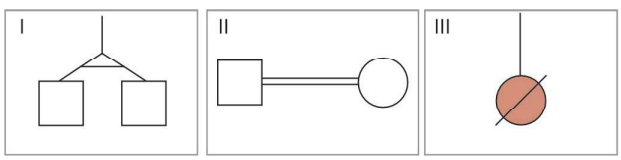
a. The most likely pattern of inheritance based on the given pedigree is autosomal dominant inheritance. Both males and females are affected, and there is a vertical pattern of transmission, with at least one affected member in each generation.
b. This phenomenon, where different individuals affected with the same genetic disorder from within the same family (intrafamilial) or from different families (interfamilial) show variability in their clinical manifestations (including the age of onset and severity), is called variable expressivity.
c. The risk of recurrence of a disorder which has an autosomal dominant pattern of inheritance will be 50% in each sibling of an affected person, if one parent is also affected.
d. This pedigree shows transmission of the disorder from an affected male to his offspring, which does not occur with mitochondrial inheritance, because the male gamete (sperm) does not pass on its mitochondria to the zygote. *Mitochondrial disorders are maternally transmitted.*
e. Examples of disorders which follow an autosomal dominant pattern of inheritance are neurofibromatosis type I, tuberous sclerosis, and Huntington disease. *All AD disorders should be considered as answer.*

Q23.



The family presented for evaluation of the children IV-2 and IV-3. Their elder sibling had died due to methylmalonic aciduria at 1 year of age.

a. What is the risk of recurrence of the disease in IV-2 and IV-3 if their elder sibling IV-1 was affected and why?
b. If IV-2 is found to be affected, what is the likelihood for IV-3 being affected and why?
c. What do the following pedigree symbols represent?



Ans.

a. Methylmalonic aciduria is an autosomal recessive disorder. Therefore, as their elder sibling (IV-1) was affected with the disease, the risk of recurrence in IV-2 and IV-3 is 25%.
b. As per the pedigree, IV-2 and IV-3 are monozygotic twins. Therefore, if IV-2 is found to be affected, the risk of the disease in IV-3 will be 100%.

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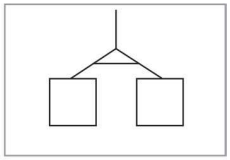
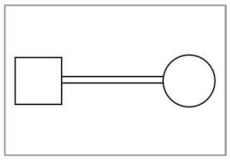
c. The pedigree symbols represent the following:

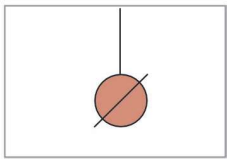
i. Monozygotic male twins



ii. Consanguineous mating



iii. Deceased affected individual (female)



Q24. Mr X presents with the history of ataxia and tremors since 25 years of age. His father and paternal grandfather were similarly affected. His father started manifesting the symptoms at around 38 years of age and his paternal grandfather first noticed the symptoms at around 45 years of age.

a. What is the likely molecular mechanism of this disease?

b. Why are the mutations causing such disorders called dynamic mutations?

c. What is this phenomenon called where the disease manifests at an earlier age and with more severity in subsequent generations?

d. Name four disorders which occur due to this molecular mechanism.

Ans.

a. The likely molecular mechanism of this disease is trinucleotide repeat expansion.

b. There can be an expansion in the number of trinucleotide repeats during gametogenesis, which results in the affected offspring having a larger repeat number compared to the transmitting parent. This is why these mutations are called dynamic mutations.

c. The increasing number of trinucleotide repeats leads to increasing severity and earlier onset of the disease in successive generations. This phenomenon is called anticipation.

d. Four examples of trinucleotide repeat expansion disorders are:

i. Huntington disease—CAG repeats expansion in *HTT* gene

ii. Fragile X syndrome—CGG repeats expansion in *FMR1* gene

iii. Friedreich ataxia—GAA repeats expansion in *FXN* gene

iv. Myotonic dystrophy—CTG repeats expansion in *DMPK* gene

Q25. The disease Leber hereditary optic neuropathy (LHON) shows mitochondrial inheritance. Mr X is diagnosed to have LHON. His sister and mother are also known to be affected with LHON. The family is referred for genetic counseling.

a. What is the risk of recurrence of LHON in Mr X's offspring?

b. Define the terms "homoplasmy" and "heteroplasmy".

c. How many protein-coding genes are present in the mitochondrial genome?

d. Name two other disorders which are caused by mutations in the mitochondrial genome.

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Ans.

a. As mitochondrial mutations follow a matrilineal pattern of inheritance, there is no significant risk of recurrence of LHON in Mr X's offspring.
b. If the mutation is present in only some of the mitochondrial genomes within a mitochondrion and/or in only a proportion of the mitochondria within a cell/within a tissue, it is referred to as heteroplasmy. If the mutation is present in all or at least a majority of the mitochondrial genomes of an individual, the condition is called homoplasmy.
c. There are 13 protein-coding genes in the mitochondrial genome.
d. Examples of disorders caused by mutations in the mitochondrial genome are MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged-red fibers), Kearns–Sayre syndrome, and NARP (neuropathy, ataxia and retinitis pigmentosa).

Q26.



a. What is the dysmorphic feature seen in this clinical photograph called?
b. Which syndrome is typically associated with this finding? What are the other findings seen in this syndrome?
c. Name two other dysmorphic features involving the eyes/periorbital region and at least one syndrome associated with each of them.

Ans.

a. This dysmorphic feature is called synophrys. In this condition, the eyebrows are fused together in the middle above the bridge of the nose. It is also known as a unibrow.
b. Synophrys is typically associated with Cornelia de Lange syndrome. In this syndrome, the affected individuals have typical craniofacial dysmorphism (including microcephaly, synophrys, thick bushy eyebrows, long eyelashes, and short nose), growth retardation, intellectual disability, and upper limb reduction defects.
c. Some other dysmorphic features involving the eyes/periorbital region are:
    i. Hypertelorism—seen in syndromes such as Noonan syndrome, Aarskog–Scott syndrome, Robinow syndrome, and Frontonasal dysplasia
    ii. Hypotelorism—seen in conditions such as holoprosencephaly, trisomy 13, Smith–Lemli–Opitz syndrome, etc.
    iii. Epicanthal folds—seen in syndromes such as Down syndrome

Q27. Mr A has a heterozygous pathogenic variant in gene A, a gene related to retinitis pigmentosa, but he is asymptomatic. Mrs A has a heterozygous pathogenic variant in gene B, another gene related to retinitis pigmentosa, but she is also asymptomatic. However, their daughter who is heterozygous for both the pathogenic variants (one in gene A and one in gene B) develops retinitis pigmentosa.
a. Define the term "heterozygous".
b. What is this phenomenon called where the disease occurs only when there is one heterozygous variant each in two different genes?
c. What is an individual who is heterozygous for one variant in two different genes called?
d. What is the risk of recurrence of the disease (retinitis pigmentosa) in each offspring of the couple in this given example?
e. Give one more example of disorder which occurs due to digenic inheritance.

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Ans.

a. When the variant/mutation is present in only one of the two copies (alleles) of a gene, it is said to be "heterozygous".
b. The phenomenon where presence of one heterozygous variant each in two different genes is required to cause the disease is called "digenic inheritance". Digenic inheritance is an example of oligogenic inheritance.
c. An individual who is heterozygous for one variant each in two different genes is called a "double heterozygote".
d. The risk of recurrence retinitis pigmentosa due to digenic inheritance in each offspring of the couple in this given example is 25%.
e. Bardet–Biedl syndrome is another example of a disease with digenic inheritance. It shows digenic triallelic inheritance (biallelic mutations in *BBS2* gene along with one heterozygous mutation in *BBS6* gene), etc. (other disorders with digenic inheritance can also be considered as the right answer).

Q28. Master A is a 10-year-old boy who is brought for evaluation of obesity, global developmental delay, and intellectual disability. On evaluation through FISH, he is found to have a microdeletion in chromosome 15q11-q13 cytoregion.

a. Identify the condition in this boy.
b. Define the term "genomic imprinting".
c. The microdeletion of 15q11-q13 cytoregion has to be present in the copy derived from which parent for this syndrome to occur?
d. Name other mechanisms by which this disorder can occur.
e. What syndrome is caused by the microdeletion present in this same cytoregion, if it is present in the copy derived from the opposite parent?

Ans.

a. The condition described here is Prader–Willi syndrome (PWS), which is characterized by obesity, global developmental delay with predominant motor delay, hypotonia and feeding problems in infancy, intellectual disability, and hypogonadism.
b. The term "genomic imprinting" refers to the phenomenon wherein only one of two copies of a gene is expressed and the other is silenced. The gene expression depends on the parent of origin of the chromosome.
c. Prader–Willi syndrome occurs when the microdeletion is present in the paternally derived chromosome 15. Normally, the paternally derived genes in this cytoregion are expressed and the maternal copy is silenced. Hence, deletion of the paternal copy causes the disease.
d. Other than microdeletion of cytoregion 15q11-q13, PWS can occur due to maternal uniparental disomy (UPD) of this region, wherein both copies are derived from the mother, and the paternal copy is missing. Imprinting center defects can also cause PWS.
e. Microdeletion of the 15q11-q13 cytoregion in the maternally derived copy of chromosome 15 causes Angelman syndrome due to silencing of the *UBE3A* gene.

Q29. A 3-month-old male infant is brought with the diagnosis of recurrent vomiting. On evaluation he is found to have congenital hypertrophic pyloric stenosis.

a. What is the common inheritance mechanism associated with congenital hypertrophic pyloric stenosis (CHPS)?
b. What would be the risk of recurrence of this condition in this individual's son?
c. If a female infant has CHPS, what would be the risk of recurrence of the condition in her male offspring?
d. What is the reason for this difference in the risk of recurrence?
e. Name two other congenital malformations which show this inheritance mechanism.

Ans.

a. The usual inheritance mechanism associated with congenital hypertrophic pyloric stenosis is multifactorial inheritance. In this, the disorder is caused by a combination of inherited, environmental, and stochastic factors.

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b. The empiric risk of recurrence of CHPS in each son of a male individual who himself had CHPS is around 5%.
c. If a female individual had CHPS, the risk of recurrence of the condition in her male offspring would be around 18%.
d. This difference in the risk of recurrence is because an affected female individual has a greater genetic susceptibility (with more genetic factors contributing to the multifactorial causation of CHPS) when compared to an affected male individual, and this greater genetic susceptibility gets passed on to her offspring increasing the risk of recurrence in them.
e. Other examples of congenital malformations with multifactorial inheritance include neural tube defects, Hirschsprung disease, and cleft lip/cleft palate.

Q30. An 8-month-old female infant is brought for evaluation of global developmental delay and failure to thrive. She is noted to have significant craniofacial dysmorphism in the form of microcephaly, frontal bossing, ocular hypertelorism with ptosis, a prominent glabella, and a beaked nose, which is suggestive of the "Greek helmet" facies.

a. What is the most likely diagnosis in this child?
b. What is the chromosomal anomaly causing this syndrome?
c. What are the genetic tests that can be performed for confirming the diagnosis?
d. What are the other congenital malformations known to be associated with this syndrome?

Ans.

a. The most likely diagnosis in this child based on the given clinical features is Wolf–Hirschhorn syndrome.
b. The chromosomal anomaly that is associated with this syndrome is deletion of chromosome 4p (short arm of chromosome 4).
c. The genetic tests that are used for confirming the diagnosis include FISH, multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray (CMA).
d. The other congenital malformations known to be associated with Wolf–Hirschhorn syndrome include cardiac anomalies, cleft lip and palate, preauricular tags and pits, and genital anomalies such as absent uterus, hypospadias, and cryptorchidism.

Q31. A 3-year-old boy, the first offspring of third-degree consanguineous parents, is brought for evaluation of pancytopenia. On examination, he is found to have short stature (height at – 3 SD below mean), microcephaly (head circumference at – 3.5 SD below mean), bilateral hypoplastic thumbs, and absent left kidney. His bone marrow studies show evidence of aplastic anemia.

a. What is the most likely diagnosis in this child?
b. What are the typical upper limb defects associated with this syndrome called?
c. What category of single gene disorders does this disease belong to?
d. Name four other disorders which belong to this group.

Ans.

a. The most likely diagnosis in this child is Fanconi anemia.
b. The typical upper limb defects associated with this syndrome are called radial ray defects. Radial ray defects include partial or complete absence of the radius and/or anomalies of radial ray structures such as hypoplasia or absence of the first metacarpal, malformed or absent thumbs, triphalangeal thumb, extra thumb (preaxial polydactyly) etc.
c. Fanconi anemia belongs to the group of chromosomal instability syndromes.
d. Examples of other disorders which belong to the group of chromosomal instability syndromes include Bloom syndrome, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, facial anomalies) syndrome, types I and II, and Werner syndrome, etc.

Q32. A neonate is noted to have a small lumbar meningomyelocele at birth. The mother has a history of epilepsy and was taking sodium valproate in the periconceptional period as well as throughout pregnancy.

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a. How do you classify birth defects?
b. In the given clinical scenario, the mother had a history of intake of valproate during the pregnancy, which led to the occurrence of the neural tube defect in the baby. What are such substances/agents called which lead to birth defects due to fetal exposure to them during pregnancy? Mention the different types of such agents with examples of each.

Ans.

a. Birth defects are classified as isolated defects or multiple defects also known as multiple congenital anomalies (MCAs). Based on the underlying cause of the defect, they are also classified as—malformation, deformation, dysplasia, or disruption.
b. Substances or agents which lead to birth defects, if the fetus is exposed to them during pregnancy, are called teratogens. Majority of teratogens act during the period of embryogenesis, i.e., the first 8 weeks after fertilization. Teratogens can include:
   i. Drugs taken by the mother such as thalidomide, phenytoin, warfarin, valproic acid, isotretinoin etc.
   ii. Maternal infections during pregnancy especially the TORCH infections (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus), syphilis and others such as the Zika virus and varicella zoster virus.
   iii. Maternal illnesses such as diabetes mellitus, autoimmune disorders such as systemic lupus erythematosus (SLE), phenylketonuria, and hyperthermia.
   iv. Maternal intake of toxins and substances such as alcohol, smoking, and cocaine.

Q33. A 2-year-old male child is brought for evaluation of sensorineural deafness. On examination, the child is found to have a white forelock, lateral displacement of the inner canthi of the eyes (telecanthus) and finding as in figure,



a. Identify abnormality in above figure.
b. Identify the syndrome in the child.
c. How do you define a malformation?
d. How do you define multiple malformation syndrome?
e. What is the congenital gastrointestinal anomaly that is known to be associated with this syndrome?
f. Name another monogenic condition which is known to be associated with a white forelock.

Ans.

a. Heterochromia iridis
b. The most likely syndrome in this child is Waardenburg syndrome (WS).
c. A malformation is defined as a structural defect arising from a localized error in morphogenesis that results in the abnormal formation of a tissue or an organ.
d. A multiple malformation syndrome is a disorder where multiple malformations occur in unrelated tissues due to a known unifying cause. For example, Down syndrome due to trisomy 21 and fetal alcohol syndrome due to the teratogenic effect of maternal alcohol intake.
e. The congenital gastrointestinal anomaly that is known to be associated with Waardenburg syndrome is Hirschsprung disease.
f. Piebaldism is an autosomal dominant monogenic condition associated with a white forelock.

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