1. **Define Epistasis**
   Epistasis and modifier genes Epistasis is a phenomenon that consists of the effect of one gene being dependent on the presence of one or more modifier genes Type of polygenic inheritance where alleles at one gene locus can hide or prevent expression of alleles at second gene locus.
2. **VNTR and Applications of VNTR**

   VNTR are short nucleotide sequences organized as a tandem repeats on genomes.

   Found on many chromosomes

   Show variations in length between individuals.

Applications of VNTR

- Microbiology
- DNA fingerprinting
- Genetic diversity
- Forensics
- Mapping of genomes
- Breeding patterns of wild or domesticated animals

3. **Genomic Imprinting**
   Genomic Imprinting Epigenetic marking of a locus on the basis of parental origin. Results in monoallelic gene expression. Some genes are expressed only from the maternal genome and some only from the paternal genome. It is estimated that about 40 genes are imprinted and they can be found on several different chromosomes .

4. Point mutations
   - Point mutations affect single sites on DNA.
   - Substitution of one base for another.
   - Deletion/addition of a single base or small number of bases.

   Transitions

   - If purines (A/G) is replaced by purines and pyrimidines (T/C) is replaced by pyrimidines.

   Transversion

   - If purine substitutes for pyrimidines or pyrimidine is replaced by purines. It is called as transversions.

   Result of point mutations

   - Silent mutations
   - Missense mutations
   - Nonsense mutations
   -

5. Frameshift mutations
   result in all amino acids downstream from the mutation site being completely different from wild type. These proteins are generally nonfunctional.

Mutation - Forward, Reverse and Neutral

Forward mutation

- Mutation that changes the wild type phenotype into mutant type phenotype.
- Any mutation which changes a functional wild genotype or wild phenotype to nonfunctional form.

Wild type phenotype/ genotype

- Most common phenotype in natural populations of the organism is called a wild type phenotype.

reverse mutation

- Mutation that changes a mutant phenotype back into the wild type.

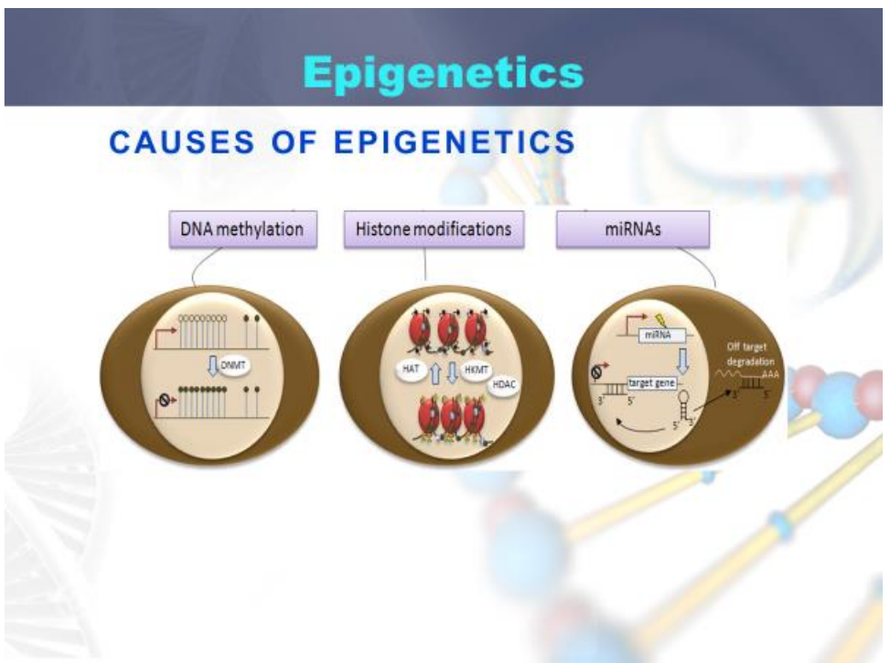
neutral mutation

- Mutation that alters the amino acid sequence of the protein but does not change its function as replaced amino acid is chemically similar or the affected amino acid has little influence on protein function.

6. # Epigenetics

the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself. One **example** of an **epigenetic** change is DNA methylation — the addition of a methyl group, or a "chemical cap," to part of the DNA molecule, which prevents certain genes from being expressed. Another **example** is histone modification. Histones are proteins that DNA wraps around

Epigenetics An epigenetic trait is a stable heritable phenotype resulting from changes in chromosome without alterations in the DNA sequence.



Autosomal Dominant diseases

7. Marfan syndrome

8. Huntington's disease
9. Retinoblastoma
10. Waardenburg syndrome
11. Myotonic dystrophy
12. Polycystic kidney disease
13. Achondroplasia
14. Polydactyly
15. Heredity hearing loss

Examples of **autosomal** recessive **disorders** include cystic fibrosis, sickle cell anemia, and Tay-Sachs **disease**

7. Mutation nomenclature

Nomenclature

- While describing sequence variants, it should be written according to HGNC rules.
- All variants should be described at the most basic level, i.e. DNA level.
- Descriptions should always be in relation to a reference sequence, either a genomic or a coding DNA sequence.
- Although theoretically a genomic reference sequence seems best, in practice a coding DNA reference sequence is preferred.
- Good for promoters, alternative splicing etc.
- When the entire genomic sequence is not known, a cDNA reference sequence should be used.
- To avoid confusion in the description of a variant it should be preceded by a letter indicating the type of reference sequence used.
- Several different reference sequences can be used.
- "c." for a coding DNA sequence (like c.76A>T)
- "g." for a genomic sequence (like g.476A>T)
- "m." for a mitochondrial sequence (like m.8993T>C,)
- "r." for an RNA sequence (like r.76a>u)
- "p." for a protein sequence (like p.Lys76Asn)
- Describing genes / proteins, only official HGNC (HUGO gene nomenclature committee) gene symbols should be used (www.genenames.org)

9. How mutations alter gene function_to add some data

splice site mutations have severe Effects

- Splice sites site mutations usually have severe effects on protein functions.
- Often this kind of mutation produce one or more exon skipping or larger fragments of DNA. **Effects of null allele and hypomorph**
- Null allele results in loss of function. Usually no gene product.

- Hypomorph alleles results in decreased activity of the proteins.

Effects of mutation on gene function

- Gain of function - increased activity.
- Dominant negative-antagonizes normal product.
- Neomorph - novel activity

Predicting that a gene product won't do the job

- Deletion, nonsense, frameshift of sequence is deleterious.
- Mutation in splice site usually has severe effects.

Predicting that a gene product won't do the job

- Missense mutations have sometimes severe effects on protein function while some times less severe effects. It depends on the type of amino acid which was replaced.

Predicting that a gene product won't do the job

- Missense mutations depends on location in protein.
- Is it in non-conservative
- Is amino acid is conserved in evolution

10. **Genetic Disorders**: A genetic disease or disorder appears as a result of mutations in an individual's DNA. Change in DNA sequence may be small or large like deletions/addition of entire chromosome.

Multifactorial diseases: Genetic disorders controlled by many genes plus the effects of the environment.

11. **Common X-linked dominant diseases**

- Rett syndrome
- Alport syndrome
- Goltz syndrome
- Fragile-X Syndrome

12. Short Tandem Repeat Polymorphism

Short tandem repeat sequences

- STR are repeats of nucleotide sequences.
- AAAAAA… mononucleotide
- ATATAT… dinucleotide
- TAGTAGTAG…trinucleotide
- TAGTTAGTTAGT… tetranucleotide
- TAGGCTAGGCTAGGC… pentanucleotide
- Different alleles contain different numbers of repeats.

13. complications in basic inheritance pattern

Complications in basic inheritance pattern

Single genes -Non-mendelian inheritance

Differences in gene actions can generate more complex inheritance patterns.

Single gene can give codominance, incomplete dominance, overdominance.

Complications to inheritance patterns

Multiple genes - epistasis, polygenic traits Genes & the environment - sex-influenced traits, incomplete penetrance

Complications

- A common recessive inheritnace can give dominant pattern
- Autosomal dominant inheritance with non-penetrance
- Autosomal dominant inheritance with variable expression.

Pedigrees with complicated inheritance pattern

Complications

- A common recessive can give dominant pattern
- Autosomal dominant inheritance with non-penetrance
- Autosomal dominant inheritance with variable expression

14. **Frequency of autosomal dominant disorders**

Frequency of autosomal dominant disorders varies between 3 – 9.5 per 1000 individuals

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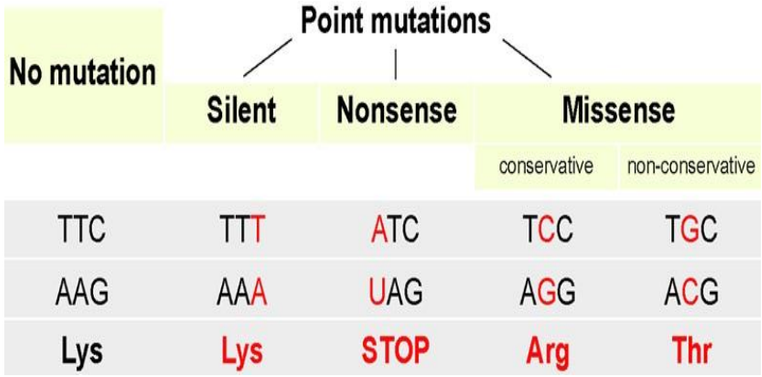
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Point mutations

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Common mitochondrial diseases

16. Myoclonic epilepsy
17. Mitochondrial recessive ataxia
18. Leber hereditary optic neuropathy
19. Sensory ataxia neuropathy

    17.