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TOPIC 2C: GENE EXPRESSION AND GENETICS

Advanced Level Complete Study and Revision Notes

1. Molecular Basis of Gene Mutations

A **mutation** is defined as a permanent, irreversible change in the nucleotide sequence of an organism's DNA [cite: 1538, 1655]. Mutations can manifest in somatic (body) cells during normal cell divisions, potentially resulting in localized anomalies such as cancers [cite: 1539, 1584, 1644]. However, the most critical mutations occur during the formation of **gametes** (haploid sex cells) [cite: 1539, 1645, 1656]. When mutant gametes fuse during fertilization, the altered code is replicated across the entire offspring, presenting as a structural genetic disorder passed through successive generations [cite: 1494, 1581, 1645].

Types of Point Mutations (Gene Mutations)

Point mutations affect a small number of nucleotides within a single gene sequence [cite: 1546, 1656]. There are three fundamental architectural classifications of point mutations [cite: 1549]:

- **Substitution:** One specific base is swapped out and replaced by an alternate nucleotide [cite: 1550, 1657]. This alters only a single codon [cite: 1590].
- **Insertion:** An additional nucleotide base is integrated into the gene sequence [cite: 1552, 1659]. This shifts the entire downstream reading frame (frameshift mutation).
- **Deletion:** A nucleotide base is completely lost from the molecular sequence [cite: 1551, 1658], also disrupting the reading frame.

> **Why Some Mutations are Phenomenally "Silent"**
>
> Most point mutations exhibit no observable physical effect on the phenotype of the organism [cite: 1534, 1585]. This phenotypic neutrality arises due to two major molecular characteristics:
>
> 1. **Non-Coding Intergenic Regions:** The mutation may occur within non-coding introns or spacer DNA, which does not impact protein synthesis instructions [cite: 1586].
> 2. **Degeneracy of the Genetic Code:** The triplet code possesses redundant combinations [cite: 1587]. If an altered base creates a codon that specifies the exact same amino acid as the original triplet, the downstream primary protein structure remains entirely unmodified [cite: 1575, 1587].

Case Study: Point Mutation in Sickle Cell Disease

Sickle cell disease is a classic manifestation of a catastrophic point mutation involving a single base substitution within the gene coding for the β-polypeptide chains of hemoglobin [cite: 1589, 1590].

Condition	DNA Sequence (Sense Strand - Codons 6 to 8)	Translated Amino Acid Sequence
Healthy Hemoglobin	... CCT — **GAG** — GAG ... [cite: 1599]	... Proline — **Glutamic Acid** — Glutamic Acid ... [cite: 1599]
Sickle Cell	... CCT — **GTG** — GAG ... [cite: 1599]	... Proline — **Valine** — Glutamic Acid ... [cite: 1599]

This molecular swap replaces a hydrophilic amino acid (Glutamic Acid) with a hydrophobic one (Valine) [cite: 1599]. This single shift alters the overall tertiary folding structure of the finished protein [cite: 1590, 1612]. Deoxygenated mutant hemoglobin molecules aggregate into solid, rigid fibrous rods that mechanically deform red blood cells into a sickle profile [cite: 1591]. These misshapen erythrocytes block microvascular capillary beds, triggering severe ischaemic pain, organic failure, and heightened mortality [cite: 1592, 1593].

2. Fundamental Patterns of Monohybrid Inheritance

Diploids possess two sets of chromosomes arranged in matching **homologous pairs** [cite: 1681], carrying the same genes at an identical spatial position or **locus** [cite: 1683, 1684]. Variations of a specific gene are known as **alleles** [cite: 1688, 1977].

ESSENTIAL GENETIC NOMENCLATURE

Genotype	The precise allelic composition of an organism regarding a particular locus [cite: 1675, 1975].
Phenotype	The physical expression of a trait, driven by interaction between genotype and environment [cite: 1673, 1675].
Homozygote	An organism carrying two completely identical alleles at a specified locus (e.g., TT or tt) [cite: 1690, 1707, 1710].
Heterozygote	An organism carrying two completely different alleles at a specified locus (e.g., Tt) [cite: 1691, 1709].
Dominant	An allele that is expressed in the phenotype regardless of whether the organism is homo- or heterozygous [cite: 1692].
Recessive	An allele expressed only when matching as a homozygote (tt) [cite: 1715, 1980].

Monohybrid Genetic Cross & Punnett Square

When tracking a single factor via a monohybrid cross between two pure-breeding (homozygous) parents, the first filial generation (F_1) expresses the dominant phenotype uniformly [cite: 1720, 1724]. Crossing the heterozygous F_1 generation yields a characteristic phenotypic ratio of **3:1** in the second filial (F_2) generation [cite: 1726, 1728].

F_1 Heterozygous Cross ($Rr \times Rr$) — Seed Shape Example (R = Round, r = Wrinkled) [cite: 1732, 1754, 1755]

Gametes	R [cite: 1758]	r [cite: 1763]
R [cite: 1760]	**RR** (Round) [cite: 1761]	**Rr** (Round) [cite: 1762]
r [cite: 1759]	**Rr** (Round) [cite: 1764]	**rr** (Wrinkled) [cite: 1765]

Predicted F_2 Metrics: Genotypic Ratio = 1 RR : 2 Rr : 1 rr | Phenotypic Ratio = 3 Round : 1 Wrinkled [cite: 1727, 1728, 1766, 1767]

The Purpose of a Test Cross

Organisms expressing a dominant phenotype can be either homozygous dominant or heterozygous [cite: 1772]. To deduce this unknown genotype, breeders execute a **test cross** by mating the individual with a known **homozygous recessive** individual [cite: 1777, 1778]:

- If the parent is *homozygous dominant* (YY), 100% of the offspring will express the dominant phenotype (all genotypes are Yy) [cite: 1796, 1830, 1832].
- If the parent is *heterozygous* (Yy), the offspring will split into a distinct **1:1 ratio** of dominant to recessive phenotypes (50% Yy, 50% yy) [cite: 1849].

Codominance in Multiple Allele Systems

Codominance occurs when both different alleles present at a single locus are fully and simultaneously expressed in a heterozygote's phenotype without blending [cite: 1857, 1983]. A prime model is the human ABO blood group system, which involves three alleles: I^A, I^B, and I^O [cite: 1853].

- The I^O allele is fully recessive and codes for no surface antigens [cite: 1854, 1855].
- The I^A and I^B alleles code for distinct A and B antigens respectively [cite: 1854]. They are dominant to I^O, but strictly **codominant** to each other [cite: 1855, 1857].

- An individual inheriting a heterozygous $I^A I^B$ genotype expresses both distinct antigens simultaneously, presenting with blood group AB [cite: 1858].

3. Sex Determination and Sex Linkage

In mammals, gender is dictated by the distribution of the final matching pair of chromosomes, known as the sex chromosomes [cite: 1683, 1712]. Females possess two structurally matched X chromosomes (XX) and are termed **homogametic** [cite: 1712]. Males carry one X chromosome and a significantly reduced, smaller Y chromosome (XY), making them **heterogametic** [cite: 1712].

The Y chromosome contains only a limited number of genes, primarily the master testicle-determining SRY locus. In contrast, the substantial X chromosome codes for over 1000 unrelated somatic proteins, such as clotting factors and retinal photo-pigments.

> **Mechanics of Sex-Linked Disorders**
>
> Traits controlled by genes situated explicitly on the X chromosome are described as **sex-linked traits** [cite: 1897, 1984]. Because males are hemizygous (possessing only one copy of the X chromosome), any recessive or mutated allele on their single X chromosome will be expressed in the phenotype, even if the trait is recessive in females [cite: 1496]. Females are protected by their second, normal X chromosome. Consequently, sex-linked disorders are significantly more prevalent in males [cite: 1496].

Model 1: Red-Green Colour Blindness

Red-green colour blindness is caused by an X-linked recessive mutation impacting photopigment synthesis. Let X^C denote normal vision and X^c denote colour blindness:

- A carrier female ($X^C X^c$) possesses normal vision but can pass the mutation to her children.
- If a carrier female reproduces with a normal-sighted male ($X^C Y$), there is a 50% chance that any son born will inherit the maternal mutant X^c chromosome and present with colour blindness ($X^c Y$). Any daughter has a 50% chance of becoming a carrier ($X^C X^c$).

Model 2: Haemophilia A

Haemophilia A is a severe, life-threatening X-linked recessive condition where the body cannot manufacture vital blood-clotting Factor VIII. This leaves individuals prone to excessive bleeding from minor injuries or spontaneous internal joint haemorrhages. Recombinant gene technology is utilized to mass-produce pure therapeutic Factor VIII via engineered bacteria to manage this condition.

4. Pathology of Cystic Fibrosis (CF)

Cystic fibrosis is a classic genetic disorder caused by inheriting two copies of a mutated, recessive allele located on autosomal chromosome 7 [cite: 1516, 1583, 1668, 1684]. This gene codes for the **Cystic Fibrosis**

Transmembrane Conductance Regulator (CFTR) channel protein [cite: 1668]. The most prevalent mutation is a specific deletion known as **ΔF508**.

Cellular Pathophysiology

In healthy epithelial tissue, functional CFTR protein channels actively pump chloride ions (Cl^-) out of the cytoplasm and into the exterior mucous layer. This accumulation of ions sets up a solute gradient that pulls water outward via osmosis, maintaining a hydrated, slippery mucous layer that cilia can easily sweep away.

In an individual with cystic fibrosis, the CFTR channel protein is either entirely absent or non-functional. Consequently, chloride ions remain trapped inside the epithelial cells, and water moves into the cell via osmosis rather than out into the mucus. This causes the fluid surrounding the cells to become severely dehydrated, drying the mucous secretions into a sticky layer.

> **Systemic Clinical Presentation of Cystic Fibrosis**
>
> - **Respiratory System:** Cilia become immobilized under the weight of the thick mucus layer. This restricts airflow and traps inhaled dust and bacterial pathogens, leading to chronic lung infections and progressive tissue scarring.
> - **Digestive System:** Thick mucus plugs block the pancreatic duct, preventing digestive enzymes from reaching the duodenum. This results in severe malabsorption of nutrients and can damage insulin-producing cells, causing CF-related diabetes.
> - **Reproductive System:** Mucus secretions block key reproductive structures, such as the cervix in females or the vas deferens in males, leading to infertility.

5. Methodologies of Genetic Screening

Genetic screening involves testing populations or at-risk individuals to diagnose mutations associated with severe genetic disorders [cite: 1499]. This allows clinical groups to initiate early therapeutic interventions [cite: 1516].

Prenatal Screening Methodologies

1. **Amniocentesis:**
   Executed around weeks 14 to 16 of a pregnancy. A fine needle is guided through the abdomen to extract roughly 20 cm^3 of amniotic fluid, which contains shed fetal cells. These cells are cultured in a lab for 2 to 3 weeks before karyotyping or genetic analysis can be completed.

   Disadvantages: Carries a 0.5% — 1.0% risk of inducing a miscarriage, and results take several weeks to return, delaying decision-making.

2. **Chorionic Villus Sampling (CVS):**

Performed significantly earlier in pregnancy, typically between weeks 8 and 10. A small sample of embryonic tissue is harvested directly from the developing placenta using a syringe or catheter. Because a large sample of fetal cells is obtained, results are available quickly without requiring cell cultures.

Disadvantages: Carries a slightly higher risk of miscarriage than amniocentesis (approximately 1.0%), and all paternal X chromosomes are inactivated in placental tissue, which can confound certain sex-linked tests.

3. **Preimplantation Genetic Diagnosis (PGD):**
   Utilized in conjunction with *in vitro* fertilization (IVF). After fertilizing eggs outside the body, the zygotes divide in culture. At the 8-cell stage, a single cell is safely removed from each embryo and checked for known mutant alleles. Only healthy embryos free of the genetic disorder are selected for implantation into the mother's uterus.

Ethical and Social Considerations

Genetic screening technologies introduce significant ethical and personal dilemmas:

- **Sanctity of Life vs. Termination:** Positive prenatal tests can leave parents facing difficult decisions regarding whether to continue a pregnancy, which may conflict with personal or religious values.
- **Risk of False Results:** A false-positive result can cause severe psychological distress, while a false-negative can leave families unprepared for the realities of a genetic condition.
- **Social Pressure:** Universal testing can inadvertently introduce social pressure to select for specific traits, raising concerns about standard definitions of health.