

Protein Structure

Polypeptide: Single chain of amino acids
Protein: 1 or more polypeptide chains
Therefore: All polypeptides are proteins
Some proteins contain > 1 polypeptide

Example: Hemoglobin (O₂ binding protein)
4 polypeptides in functional protein
2 alpha chains; 2 beta chains
2 chains encoded by different genes

Sickle cell anemia: Altered beta chain
Single AA change (#6 Glu to Val)
Consequence: Protein polymerizes
Change in RBC shape ---> phenotypes

Amino Acids: 20 different types in proteins
Joined through peptide bonds

Structure:

	R			R =	H
					CH ₃
H ₂ N	C	COOH			CH ₂ OH
					CH ₂ SH
	H				16 more

Peptide bonds form through condensation reaction:

Dipeptide: Two amino acids involved

Polypeptide: Many amino acids involved

NH₂: Amino End (N-terminus)
COOH: Carboxyl End (C-terminus)

Typical polypeptide: 100 - 1,000⁺ amino acids

Large polypeptides encoded by long mRNAs

Amino Acid Nomenclature:

Old: 3 letter symbol (Gly, Val, Leu, Trp)

New: 1 letter symbol (G, V, L, W)

New symbol take less space for genomics work

Levels of Protein Structure:

Primary: AA Sequence (GVLSWTH etc)
Difficult to predict final 3-D shape

Secondary: Regular folding of parts of chain
Examples: Alpha helix, Beta pleated sheet
Determined by H-bonding

Tertiary: 3-D shape of single polypeptide
H-bonding, Disulfide bonds
Hydrophilic/hydrophobic interactions

Quaternary: Arrangement of polypeptides in multimeric protein

Protein Folding: Essential for Normal Protein Function
Partially spontaneous
Facilitated by chaperone proteins

Targeting Proteins to Proper Location in Cell:

Ribosomes on ER: Proteins deposited into lumen
N-terminus of polypeptide: Signal sequence

Targets protein to proper compartment
Later removed (upon arrival at destination)
Alter location by changing signal
Important in biotechnology

Relationship Between Genes and Proteins

Alkaptonuria: *Heritable metabolic disorder*
Studied by Garrod (~1900)
Single heritable factor
Infants: black urine
Accumulate homogentisic acid
Severity influenced by diet:

Increase [Phe] ---> Increase [HA] in affected people
No change in "normal" individuals

Conclude: *Affected individuals cannot metabolize HA*
Genetic material controls chemical reactions

Pheylketonuria (PKU): *Related metabolic pathway*

Common mutation (1 in 11,000 births)
Disrupts Phe metabolism
Control symptoms by restricting Phe in diet
No Nutrasweet (Poly-Phe compound)

Beadle and Ephrussi (1930's)

Drosophila mutants with altered eye pigments

Wild-type: *Red-brown eyes*
Red + brown pigments

Mutants: *Bright red eyes*
Loss of brown pigment
Examples: vermilion (v); cinnabar (cn)

Approach: *Transplant larval imaginal disks*

Conclude: *Mutations disrupt different steps in biosynthesis of brown pigment*

Beadle and Tatum (1940's)

Auxotrophic mutants of Neurospora
Require supplemental nutrient for growth
Amino acid, vitamin, nucleoside
Wild-type (prototroph) grow on basal media

Isolated arginine-requiring mutants
Tested growth on citrulline, ornithine
Precursors in biosynthetic pathway

3 classes of mutants found:

- 1. Grew on Arg, Cit, Orn*
- 2. Grew on Arg, Cit*
- 3. Grew on Arg*

Consistent with proposed pathway:

Precursor --> Ornithine --> Citrulline --> Arginine

Conclusion: 1 gene encodes 1 enzyme

Later: 1 gene : 1 protein; 1 gene : 1 polypeptide

Examples of exceptions:

Genes encoding RNAs that are not translated

Genes encoding RNAs that are differentially spliced

So What Exactly is a Gene?

Region of nucleic acid (usually ds DNA)

Transcription unit: capable of producing RNA

Typically encodes single polypeptide

Nucleotide sequence in gene determines

amino acid sequence in polypeptide

Mutations alter phenotype by changing:

Nucleotide sequence in gene, mRNA

AA sequence in polypeptide

Protein function; Cell function

Mutations – Alleles – Protein Function

Wild-type allele: *Most common form in population*

Usually codes for functional protein; Usually dominant

Single copy --> sufficient protein for cell function

Mutant allele: *Sequence differs from wild type*

Usually codes for non-functional protein

Usually recessive; Many different types in population

Simple Dominance (Aa):

A: Codes for functional protein

a: Codes for defective protein

Aa: Mixture of functional and defective proteins

Sufficient normal protein for cell function

Defective protein does not interfere

aa: Only defective protein made

Semidominance: *Aa:* Intermediate phenotype
Normal protein insufficient for cell function

Recessive Mutant Alleles Differ in Strength:

Weak: Partial loss of protein function
Often missense mutations; minor change in protein

Strong: More complete loss of protein function
Disruption of critical protein domains

Null: Complete loss of protein function
Gene deletions; nonsense mutations

Dominant Mutant Alleles:

Less common than recessive mutant alleles

Usually result in gain of protein function

Not masked by wild-type allele

Examples of Dominant Mutations:

- 1. Over-expression of wild-type allele
Too much normal protein made
Mutations often in promoter, regulatory regions*
- 2. Inappropriate expression of wild-type allele
Wrong place or wrong time*
- 3. Production of altered protein with novel function
Example: Enzyme with new substrate specificity
Effect seen in presence of normal protein product*
- 4. Altered protein antagonistic to normal protein
Defective protein interferes with normal protein*