Transmission Genetics
An Integrative Approach

ALZHEIMER’S DEMENTIA

Dhairya Bhatt1,a, David Devcic1,b, Catherine Burzynski1,a, Zahra Syed1,b, Jade Atallah1,c

PREREQUISITES

Karyotype
Autosomes vs Sex-chromosomes
Central Dogma of Biology: Replication, transcription, translation
Gene structure: Promoter, start codon, stop codon, intron, exon, 5’ untranslated region, 3’ untranslated region, template strand, non-template strand, etc.
Genes & allelic variants
Types of mutations: deletion, insertion, substitution, frameshift, nonsense, missense, etc.
Functional effects of mutations: null, hypomorphic, hypermorphic, neomorphic, etc.
Dominance relationships
Law of Independent Assortment
Syntenic genes
Polygenic traits
Epistasis
Environmental effects on phenotype
Basic cell cycle stages, nondisjunction consequences
Pedigree Analysis

DESIGN OF LEARNING EXPERIENCE

One indicator of advanced intellectual development is the ability to integrate new information in the context of prior knowledge (Felder and Brent, 2004). Such integrative learning promotes the establishment of relationships between concepts, priming the mind for creativity and innovation when the opportunity arises (Deller et al., 2015). Current research highlights case studies and problem-based learning as key activities that promote integrative thinking (Felder and Brent, 2004).

Consequently, we have designed this learning experience to promote extensive integration between transmission genetics topics, as well as integration with cell and molecular biology topics.

The context of choice here is Alzheimer’s Dementia (AD). Learners will have the opportunity to explore given background information followed by a series of questions that promote integrative thinking while problem solving. The detailed learning outcomes of this experience are highlighted below.

LEARNING OUTCOMES

Upon completing this learning experience, students will be able to:

- Solve transmission genetics problems while maintaining perspective of underlying cell and molecular mechanisms where applicable.
- Perform basic pedigree analysis of a polygenic phenotype with epistatic and environmental effects.
- Communicate a genotype graphically in the context of a karyotype, chromosome composition, cell cycle stage, and DNA template/non-template strand.
- Communicate a genotype graphically in the context of a chromosome, its homolog, DNA template/non-template strands, gene components relevant to transcription and translation, alterations in allelic variants, structure-function consequences of protein products, and consequent phenotypic effects.
- Formulate hypotheses on dominance relationships between alleles based on molecular structure of allelic variants and given phenotypic determinants.

REFERENCES


Alzheimer’s disease (AD) is a neurodegenerative disorder that affects 33.9 million people globally. It is the most common form of dementia (Barnes and Yaffe, 2011).

One model that explains AD involves the growth of β-Amyloid plaques (Barnes and Yaffe, 2011) that disrupt neuronal pathways (Figure 1A).

In reality AD is polygenic (Combarros et al., 2009), but for the purposes of this exercise, we will reduce the group of genes underlying AD to 2 theoretical autosomal and non-syntenic genes.

β-Amyloid precursor protein (APP) is a transmembrane protein (Figure 1B). The product of Gene A on chromosome 11 cleaves APP into β-Amyloid peptides (Figure 1B), which can form plaques when produced in excess. Allele A functions normally, whereas the recessive a allele is a hypermorph associated with excessive cleaving activity. The product of Gene B on chromosome 7 clears plaques. Allele B functions normally, whereas the recessive b allele is a hypomorph with reduced clearance activity.

Additionally, cognitive conditions play a role. This environmental factor has also been oversimplified for the purposes of this exercise. The relationship between these loci, the environment, and AD is summarized in (Table 1).

### PROBLEM SETS

**A** healthy dihybrid mother without exposure to an enriched environment marries. Design a pedigree in which all her children are unaffected regardless of any factors. Indicate all possible genotypes for all individuals.

**B** draw chromosome 7 at G1, horizontally. Depict a single strand of DNA as 1 line. Draw the homologous chromosome below the 1st chromosome, also horizontally. Show the plaque clearance gene where the genotype is Bb. Label the template strand, non-template strand, promoter region, 5’UTR, 3’UTR, 2 exons, 1 intron, and transcription direction. Describe a genetic aberration of your choice that makes allele b different from allele B, in a manner that affects the final product. Using a shape of your choice, draw the final product of both alleles showing any relevant differences.

**A** genotype for a specific locus can be deemed to produce only one phenotype. True or False? Explain.

### Table 1

<table>
<thead>
<tr>
<th>Gene A: APP cleavage</th>
<th>Gene B: β-Amyloid clearance</th>
<th>Enriched Cognitive Environment</th>
<th>Poor Cognitive Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>No Onset</td>
<td>No Onset</td>
</tr>
<tr>
<td>Abnormal (High)</td>
<td>Normal</td>
<td>No Onset</td>
<td>Late Onset</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal (Low)</td>
<td>Late Onset</td>
<td>Early Onset</td>
</tr>
<tr>
<td>Abnormal (High)</td>
<td>Abnormal (Low)</td>
<td>Early Onset</td>
<td>Early Onset</td>
</tr>
</tbody>
</table>

**A** draw chromosome 7 at G1, horizontally. Depict a single strand of DNA as 1 line. Draw the homologous chromosome below the 1st chromosome, also horizontally. Show the plaque clearance gene where the genotype is Bb. Label the template strand, non-template strand, promoter region, 5’UTR, 3’UTR, 2 exons, 1 intron, and transcription direction. Describe a genetic aberration of your choice that makes allele b different from allele B, in a manner that affects the final product. Using a shape of your choice, draw the final product of both alleles showing any relevant differences.

Consider a nonsense mutation in the APP cleavage gene with an extremely early stop codon. This mutation is recessive to wildtype and called a’. Hypothesize what the AD consequences would be for individuals homozygous for a’.

**A** draw the a’ allele with its relevant parts. Depict how you envision the product of this allele would be different from A. Hypothesize on dominance relationships between a and a’ with respect to AD.

Hypthesize the consequences relevant to AD in a hypothetical case of trisomy for chromosome 11.