Origin of a Gene Mutation Causing Early-Onset Alzheimer’s Disease

HOW TO USE THIS RESOURCE
Show the figure below to your students along with the caption and background information. The “Interpreting the Graph” and “Discussion Questions” sections provide additional information and suggested questions that you can use to guide a class discussion about the characteristics of the graph and what it shows.

Caption: Pedigree of an extended family in Antioquia, Colombia, showing a mutation in the PSEN1 gene, which causes early-onset familial Alzheimer’s disease. Black circles (female) and squares (male) indicate individuals afflicted with the disease. Half-shaded shapes indicate individuals with an uncertain disease status. White shapes indicate unaffected individuals. Shapes with a line through them indicate that the family member is deceased. Roman numerals mark each generation and the approximate year that the generation began. This pedigree combines 13 subpedigrees (each labeled with a C plus a number) that all share a common ancestor.

BACKGROUND INFORMATION
Alzheimer’s disease is characterized by the accumulation of amyloid plaques and tangles as well as the loss of connections between nerve cells and the death of nerve cells in the brain. There are two types of Alzheimer’s disease, early-onset and late-onset. The early-onset type affects people age 30 to 60 and represents less than 5% of all people with Alzheimer’s. Most early-onset cases are genetic and are caused by a mutation in one of three genes: presenilin-1 (PSEN1), presenilin-2 (PSEN2), or amyloid precursor protein (APP). Researchers studied a large extended family in Antioquia, Columbia, that has a high prevalence of early-onset familial Alzheimer’s disease due to a mutation in the PSEN1 gene. They performed whole-genome sequencing on living individuals in this family, which allowed them to confirm that all affected members of this family carried the same mutation. By using...
historical records and interviewing living family members, they determined which deceased family members had
developed early-onset Alzheimer’s disease and constructed a pedigree of 13 families with shared ancestry.

INTERPRETING THE GRAPH
Inheritance of the PSEN1 mutation is a highly penetrant autosomal dominant mutation, meaning that inheritance
is not linked to the sex of the offspring and all carriers of the gene mutation will have the disease. However, it is
not possible to determine this from the pedigree alone because of the prevalence of the disease throughout the
family. The earliest ancestors in this pedigree, a married couple in 1745, both had the disease. The mutation was
present at least eight generations ago, but it does not indicate whether the mutation first appeared in a prior
generation or if it arose independently.

One family member had two different marriages to spouses who did not have the disease. One of those
marriages resulted in one child without the disease (white square), and the other marriage resulted in a child with
an uncertain disease status (half-shaded square). The mother of the child without the disease must be
heterozygous for the mutation, giving her a 50% chance of having unaffected offspring, since inheritance is
dominant.

Teacher Tip: Prompt your students to explain the parts of the graph as applicable:
- **Graph Type:** A pedigree that shows which family members have a mutation in the PSEN1 gene.
- **Data Represented:** Number of children each couple produced, whether offspring were male or female,
whether individuals are currently alive or deceased, and whether they were affected by the disease-
causing mutation.

DISCUSSION QUESTIONS
- Is it possible to tell from the pedigree whether inheritance of the PSEN1 gene mutation is dominant or
recessive? Explain your answer.
- Is it possible to tell from the pedigree whether inheritance of the PSEN1 gene mutation is autosomal or
sex-linked? Explain your answer.
- The PSEN1 gene mutation in this study was previously determined to be autosomal dominant. Knowing
this, would the mother of the unaffected child in generation III (white square) be heterozygous or
homozygous for the mutation? Explain your answer.
- Give the probability of having offspring without the mutation in the following scenarios:
  - One parent is homozygous for the mutation and the other parent does not have the mutation.
  - One parent is heterozygous for the mutation and the other parent does not have the mutation.
  - Both parents are heterozygous for the mutation.
- Is it possible to determine from the pedigree when the PSEN1 gene mutation first occurred? If so, how? If
not, why not?
- How was it possible for the scientists to construct this pedigree when the majority of family members are
deceased and their DNA is not available for analysis?

SOURCE
Figure 1B from:
Dement. 10(0): S277–S283.e10.
View Article: [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019728/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019728/)
Further reading:

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