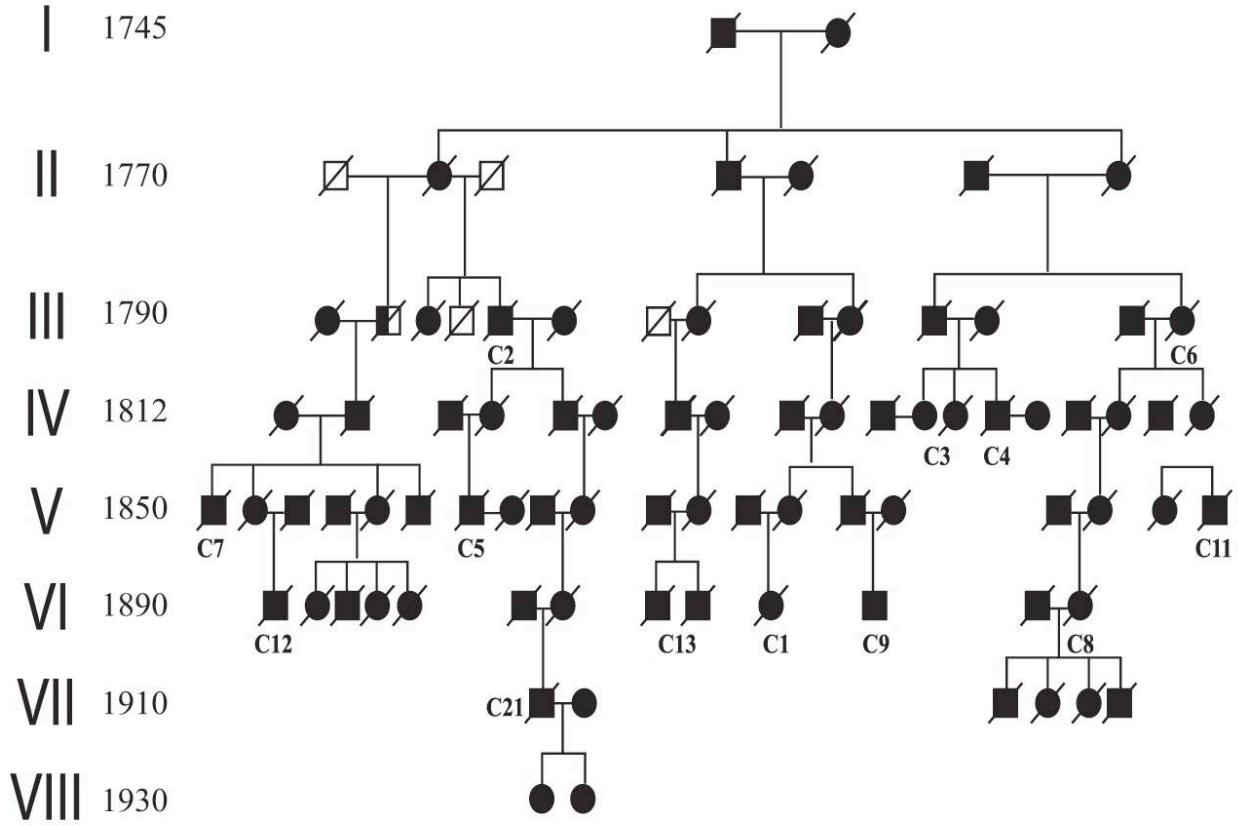
HOW TO USE THIS RESOURCE

Show the figure below to your students along with the caption and background information. The "Interpreting the Figure" and "Discussion Questions" sections provide additional information and suggested questions that you can use to guide a class discussion about the characteristics of the figure 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 a brain disease that 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 FIGURE

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 following:

- Graph Type: A pedigree of family members that shows which members have a mutation of 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:
Lalli, M.A., *et al*. Origin of the PSEN1 E280A mutation causing early–onset Alzheimer's disease. 2014. *Alzheimers Dement*. 10(0): S277–S283.e10.

View Article: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019728/

Further reading:

Kosik, K., et al. Homozygosity of the autosomal dominant Alzheimer disease presenilin 1 *E280A* mutation. 2015. *Neurology*. 84(2): 206–208.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336083/

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