

Family Health History



This material is provided by UCSF Weill Institute for Neurosciences as an educational resource for health care providers.

Why is family health history important?

With origins in genealogy, family health history has for centuries revealed that maladies can occur in families for reasons other than environment. Today, medical textbooks discuss family history as a useful tool for recognizing inherited factors involved in a patient's condition. Family health history is usually collected in the form of a pedigree.

Obtaining the pedigree facilitates the following:

- Making a medical diagnosis
- Determining genetic test strategies
- Identifying at-risk relatives
- Calculating disease risks for at-risk relatives
- Determining reproductive options for a patient or their offspring
- Distinguishing genetic risk factors from other factors
- Developing patient rapport
- Exploring a patient's understanding of dementia and familial experience with it
- Educating patients about the genetic contribution to dementia

What information should be obtained when taking a family health history?

A pedigree including a minimum of three generations should be obtained. The health history of first-degree relatives (i.e., parents, siblings, children), second-degree relatives (i.e., grandparents, uncles/aunts, nephews/nieces, half-siblings), and third-degree relatives (i.e., cousins) should be carefully explored. Both living and deceased relatives should be documented, as the total number of relatives is a useful reference compared with the number of relatives affected (or unaffected) with dementia. For unaffected relatives, age at death and cause of death should be noted. For relatives with a diagnosis of frank dementia, information about the clinical syndrome together with age at diagnosis and how the diagnosis was rendered should be documented. In addition, age of onset of symptoms (usually distinguishable from age at diagnosis), characterizations of first symptom and disease progression, followed by date of death should be obtained. Paternal and maternal ethnicity should be noted. Whenever possible, corroborating documentation about affected relatives, including medical records, autopsy reports, and/or results from genetic testing (if performed), should be obtained. When documenting the family health history, asking specific questions generates more information than general ones. For example:

- Has anyone had cognitive impairment, including memory loss or dementia?
- Has anyone had behavioral problems or personality changes?
- Has anyone had trouble with language (i.e., knowledge about words, objects, concepts) or speaking (i.e., expressing words)?
- Has anyone had mental illness (i.e., depression, anxiety,
- Has anyone had psychiatric hospitalization?
- Has anyone attempted or committed suicide?
- Has anyone had movement problems (i.e. tremor, jerky movements, stiffness, unusual posturing)?

- Has anyone had trouble walking (i.e., shuffled gait, imbalance with falls)?
- Has anyone had any muscle weakness?
- Has anyone had amyotrophic lateral sclerosis (ALS) or Parkinson's disease?
- Has anyone had multiple sclerosis?
- Has anyone had migraines?
- Has anyone had recurring stroke or stroke-like events?
- Has anyone had a neurological diagnosis?

Most individuals with a single gene cause of dementia have at least one first-degree relative with the same or related syndrome. Exceptions arise from misdiagnosis or missed diagnoses in family members. Exceptions also arise from unknown, incomplete, or unreliable family history information or from sociocultural factors that complicate family relationships: unknown or false paternity, adoption, and cultural biases in family health history reporting (i.e., how dementia is defined or perceived across different cultural perspectives). In some situations, early death or small family size may mask a single gene cause of dementia. Consanguinity may complicate interpretation of family history, and its presence should be noted. Careful attention to a family history that appears negative or unremarkable is critical. True sporadic cases should be distinguished from apparently sporadic ones.

The three-generation pedigree should be updated at subsequent patient visits, as family health history may change.

What are some “red flags” in the family health history?

When obtaining your patient's family history, consider the following features, which may warrant further investigation. With few exceptions, no one feature by itself is an automatic proxy for monogenic dementia in a family.

- **Young age of onset of a common dementia** (i.e., Alzheimer's disease; however, the diagnosis of early onset Alzheimer's disease in a relative is not synonymous with monogenic Alzheimer's disease)
- **Two relatives in the family with the same or related dementia**
 - **Uncommon dementia** (i.e., two relatives with progressive supranuclear palsy (PSP) syndrome due to PSP pathology)
 - **Dementia known to be caused by mutations in a single gene** (i.e., Huntington's disease)
 - **Dementia related by neuropathology or autopsy findings** (i.e., one relative with frontotemporal dementia and another with ALS, or one relative with both)
- **Dementia with symptoms affecting multiple organs** (i.e., hepatosplenomegaly and cognitive/motor symptoms in late-onset Tay Sachs disease)
- **Dementia in the less frequently affected sex** (i.e., a woman with behavioral variant-frontotemporal dementia)
- **Dementia that is particularly common in a specific ethnic group** (i.e., spinocerebellar ataxia 3 among individuals of Portuguese/Azorean descent)

Which family health history patterns warrant further investigation or referral to a genetics professional?

There are numerous patterns of dementia inheritance, any of which may warrant referral to a genetics professional. Genetic testing, when available, could be appropriate for all patterns except dementia with complex or multifactorial inheritance.

- Complex or multifactorial
- Autosomal dominant
- Autosomal recessive
- X-linked
- Mitochondrial

Complex or multifactorial inheritance

Most types of dementia follow a complex or multifactorial inheritance pattern and are consequently considered sporadic [See Family History Assessment Figure]. Complex inheritance means the dementia resulted from complex interactions between multiple predisposing factors, including DNA changes, called variants, at multiple genetic locations and environmental variables. For the majority of dementia types, genetic risk variants contributing to underlying pathology are not well characterized. Many genetic risk variants are being investigated in the research setting, and molecular testing to identify them is not clinically available. *APOE* $\epsilon 4$ is the only clinically testable common genetic risk variant for dementia. *APOE* $\epsilon 4$ does not cause Alzheimer's disease directly. *APOE* genotyping is clinically available, but is not recommended. [See When Should I Order Genetic Testing?] A patient whose family history is consistent with complex inheritance may benefit from genetic counseling, even when genetic testing is not warranted.

Autosomal dominant inheritance

Of the single gene forms of dementia, most follow an autosomal dominant inheritance pattern, including genetic Alzheimer's disease, genetic frontotemporal dementia, and genetic prion disease. Some forms of genetic amyotrophic lateral sclerosis and genetic Parkinson's disease follow an autosomal dominant inheritance pattern. Dementia with autosomal dominant inheritance means a pathogenic variant (disease-causing mutation) in **one** copy (allele) of a gene causes the signs and symptoms of dementia. The gene harboring the pathogenic variant is not sex-linked. The presence of different alleles of a gene pair (i.e., due to one gene copy harboring a pathogenic variant) is called *heterozygosity*. Specific principles of family history assessment, arise from the identification of an autosomal dominant inheritance pattern. [See Family History Assessment Figure.] An autosomal dominant family history pattern may be complicated by reduced penetrance and variable expressivity. Reduced or incomplete penetrance refers to the proportion of individuals with a particular pathogenic variant who do not develop signs and symptoms of dementia by a certain age, despite the variant's clear causal role in disease. It addresses the question, "Among those with the mutation, who develops dementia?" Variable expressivity refers to the range of signs and symptoms of dementia among individuals who share the

same pathogenic variant, both within the same family and across unrelated families. It addresses the question, "Among those with the mutation, which dementia signs and symptoms manifest?" Both reduced penetrance and variable expressivity result from genetic, epigenetic, and stochastic factors that are not completely understood.

Autosomal recessive inheritance

Some single gene forms of dementia follow an autosomal recessive inheritance pattern. Dementia with autosomal recessive inheritance means a pathogenic variant (disease-causing mutation) in **two** copies (alleles) of a gene causes the signs and symptoms of dementia. The gene harboring the pathogenic variant is not sex-linked. The presence of the same alleles of a gene pair (i.e., due to both gene copies harboring the same pathogenic variant) is called *homozygosity*. Parents of the individual with a recessive form of genetic dementia are considered healthy carriers. Specific principles of family history assessment arise from the identification of an autosomal recessive inheritance pattern [See Family History Assessment Figure].

X-linked inheritance

Some single gene forms of dementia follow an X-linked inheritance pattern. Dementia with X-linked inheritance means that a pathogenic variant (disease-causing mutation) on one X chromosome causes fulminant disease in male carriers and variably mild to no disease in female carriers. Males with a pathogenic variant on the X chromosome are hemizygous carriers, because males have only one X chromosome. Females with one pathogenic variant on the X chromosome may have varying signs or symptoms of disease because of random X chromosome inactivation. Though rare, fulminant disease can occur in females with a pathogenic variant on each of their X chromosomes. Females with two pathogenic variants are homozygous carriers. Specific principles of family history assessment arise from the identification of an X-linked inheritance pattern [See Family History Assessment Figure].

Mitochondrial inheritance

Many mitochondrial diseases feature signs and symptoms of dementia. Mitochondria, which are energy-producing organelles of the cell, contain their own genome (mitochondrial genome). This is separate from the genome located within the nucleus of the cell (nuclear genome). Whereas a person inherits nuclear DNA from both father and mother, mitochondrial DNA is inherited from the mother only. This is because mitochondria are supplied by the egg at fertilization. Sperm contain no mitochondria. Dementia with mitochondrial inheritance means that a proportion of a person's mitochondrial genome carries a pathogenic variant (disease-causing mutation) or deletion, which leads to signs and symptoms of dementia. Despite carrying the same familial mitochondrial variant, siblings with dementia due to mitochondrial inheritance could have signs and symptoms different from each other and from their mother, owing to what proportion of each person's mitochondrial genome carries the pathogenic variant or deletion. Specific principles of family history assessment arise from

the identification of a mitochondrial inheritance pattern [See Family History Assessment Figure].

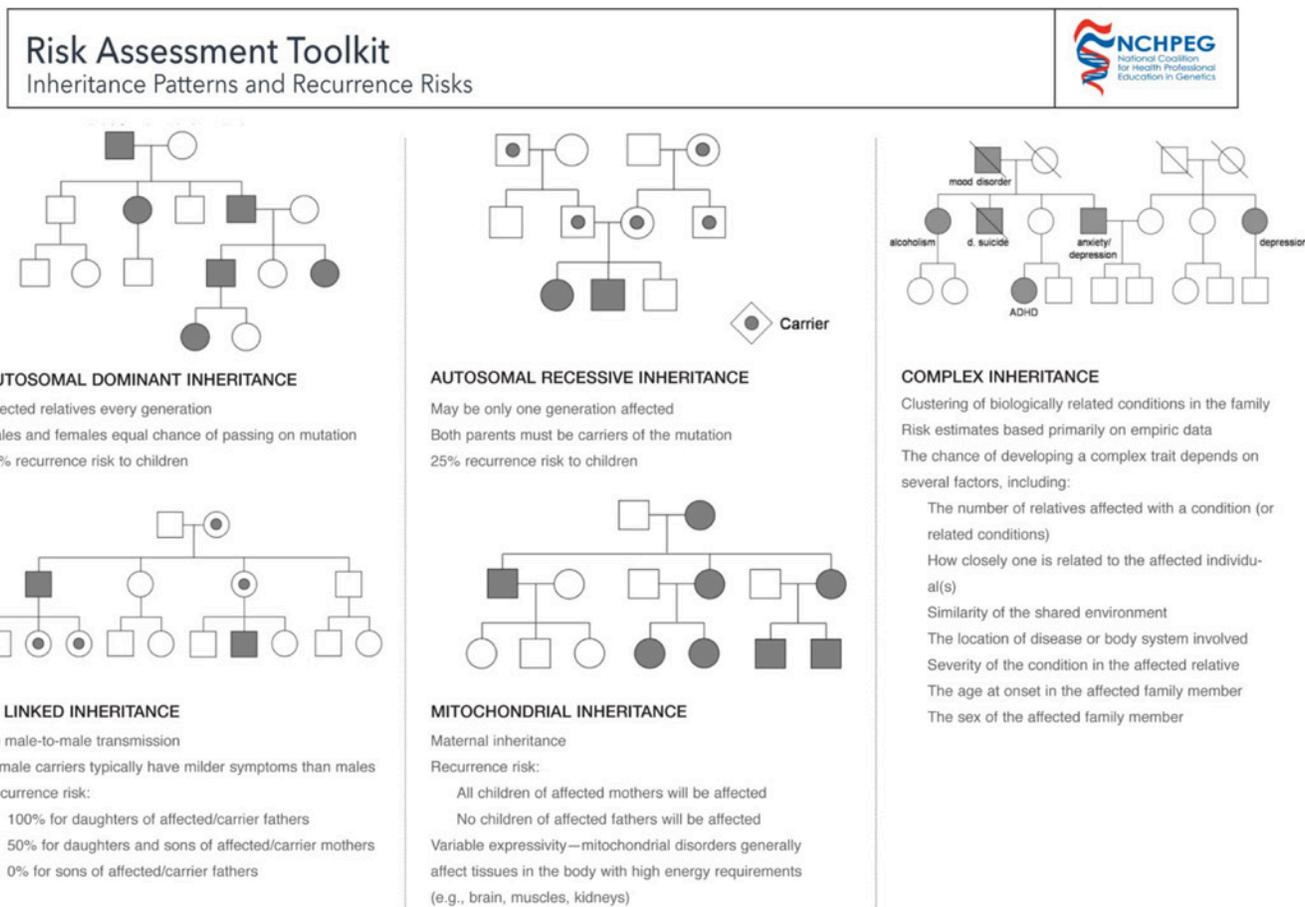
Mitochondrial **disease** is distinct from mitochondrial **inheritance**. Mitochondrial disease may follow any pattern of inheritance, including dominant, recessive, and X-linked, and will display corresponding family history patterns. This is because nuclear DNA is involved in mitochondrial pathways of the cell. Disease with mitochondrial inheritance is due solely to pathogenic mutations or deletions occurring in the mitochondrial genome.

When is a referral to a genetics professional warranted in the absence of a clear inheritance pattern derived from the family health history?

In the absence of a clear family history inheritance pattern, consider assessing genetic risk broadly. The number of affected relatives, their ages of onset, their clinical diagnoses (either suspected

or confirmed), and their degree of relatedness to your patient are key considerations for broad risk assessment. For example, individuals who have no relatives with Alzheimer’s disease or who have one first-degree relative with Alzheimer’s disease at an older age generally have low risk for an inherited form of dementia. Genetic testing is usually not recommended. Referral to a genetics professional is not critical but may be helpful. Individuals who have two or more relatives with Alzheimer’s disease, each of whom is at least a third-degree relative of the index case, generally have a moderate risk for an inherited form of dementia. Genetic testing may or may not be warranted. Referral to a genetics professional is appropriate. When in doubt, please consult with or refer to a genetics professional.

Figure 1. Family History Assessment Figure



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