What are the causes of genetic ataxia? (1/2)

INFORMATION FROM PATIENTS AND FAMILIES
A NATIONAL ATAXIA NETWORK INITIATIVE
MOVEMENT DISORDERS SOCIETY OF INDIA

- Genetic ataxias are forms of ataxia caused by a fault in one or more genes.
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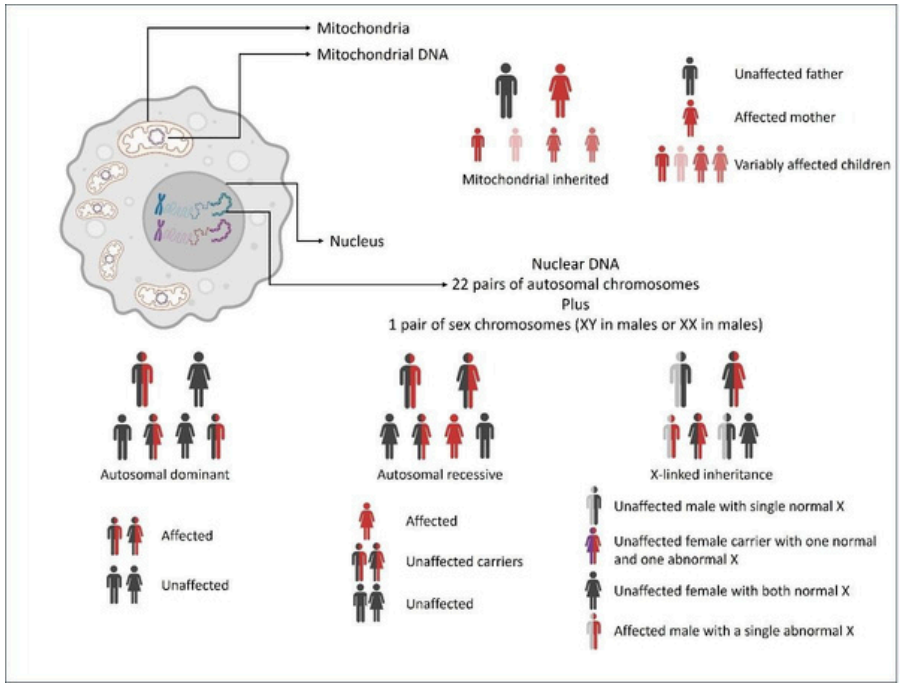
- Genes act as blueprints for making proteins and other molecules that keep our body's cells healthy and functioning properly. Humans have around 30,000 different genes, and more than 150 genes are known to cause ataxia when altered.
- Each person carries **two copies of most genes** — one inherited from the father and the other from the mother, as shown below.



- Depending on which gene is affected and how it is inherited, genetic ataxias can be grouped into the following categories:

- **1. Autosomal Dominant Ataxias**
- In this type, a defect in just **one copy** of the gene is enough to cause disease.
- These ataxias often run in families, affecting **multiple generations**, including parents and grandparents. However, they can also occur *without a family history*, when the mutation arises for the first time in the affected individual. This is known as a **de novo mutation** (meaning "newly formed").
- **Examples:**
  - *Spinocerebellar ataxias (SCA)* such as types 1, 2, 3, and 12
  - *Dentatorubral-Pallidoluysian Atrophy (DRPLA)*
  - *Episodic ataxias*
  - *POLG gene–related ataxia*

- **2. Autosomal Recessive Ataxias**
- These occur only when **both copies** of a gene are faulty.
- Parents of an affected child typically carry one faulty copy each but do not show symptoms themselves. The disease appears when a child inherits **two abnormal copies** — one from each parent.
- A family history may sometimes be seen among siblings, cousins, or uncles and aunts, especially in families where **consanguineous marriages** (marriages between close relatives) occur. However, these conditions can also appear in non-consanguineous families, and not all consanguineous marriages result in disease in the children.

What are the causes of genetic ataxia? (2/2)

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- **Examples:**
- Friedreich's ataxia
- Ataxia telangiectasia
- Ataxia with oculomotor apraxia
- Abetalipoproteinemia
- Ataxia with vitamin E deficiency
- ARSACS (Autosomal Recessive Spastic Ataxia of Charlevoix–Saguenay)

3. X-Linked Ataxias

Humans have 23 pairs of chromosomes, including one pair of sex chromosomes — X and Y.

- Males have one X and one Y chromosome.
- Females have two X chromosomes and no Y.

If a gene on the X chromosome is faulty, it results in X-linked ataxias. These usually affect males more severely, since they have only one copy of the X chromosome. Females, with two X chromosomes, may not develop the disease or may have only mild symptoms because their second, healthy X copy can compensate.

Examples:

- Adrenoleukodystrophy
- Pelizaeus–Merzbacher disease
- Fragile X–associated tremor/ataxia syndrome (FXTAS)

- **4. Mitochondrial-Inherited Ataxias**
- Each cell in our body contains tiny structures called **mitochondria** — the "powerhouses" that produce energy.
- Mitochondria have their own set of genes, separate from the nuclear DNA. Mutations in these mitochondrial genes can lead to **mitochondrial-inherited ataxia**.
- Unlike nuclear genes, mitochondrial genes are passed **only from the mother**, because all mitochondria in the embryo come from the egg. The severity of the disease can vary within a family depending on how many of the mitochondria in each cell carry the faulty gene.
- In addition, some *nuclear genes* also control mitochondrial function. Faults in these genes can cause what are called **mitochondrial ataxias**, which include both mitochondrial-inherited and non-mitochondrial-inherited types.
- **Mitochondrial-inherited ataxias** are passed only from the mother.
- **Mitochondrial ataxias** (in general) can be inherited from either parent.
- **Examples:**
- *Mitochondrial-inherited ataxias*: MELAS, MERRF, NARP, Leigh disease
- *Mitochondrial ataxias*: POLG-related ataxia, tRNA synthetase–related ataxia

- **Important Points to Remember**
- **The faulty gene is present since birth, but symptoms may begin at any age — from infancy to late adulthood.**
- **Not all genetic ataxias "run in families."**
  - **Some arise due to new (de novo) mutations, especially in autosomal dominant ataxias.**
- **In autosomal recessive ataxias, parents may be carriers without symptoms but can have affected children if both pass on the faulty copy.**