Heredity and Genetic Counseling

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The relationship between genetics and heredity is well known. Currently, everyone knows that diseases can be inherited. For that very reason, patients seek their doctors' advice because they are concerned about unborn children, family members, or themselves. An aspiring doctor must, therefore, be able to provide genetic counseling and diagnosis. The following article addresses the different modes of heredity, explains important tools, for e.g., family pedigree creation and analysis, and illustrates their application using a case of cystic fibrosis, a frequent genetic disease.

What is Genetic Counseling?

Genetic counseling is the sharing of knowledge related to genetic aspects of illness by trained professionals with individuals at an increased risk of acquiring a heritable disease or its transmission to their offspring. It involves a genetic counselor who talks to the patient about hereditary illnesses and the risk of their recurrence.

Counseling is intended for **diagnostic** screening or etiological classification. It is also used for prognostic evaluation of genetic diseases, e.g., via **pedigree creation** or **molecular genetic testing**. It is critical that the physician provides information without influencing the patients' opinion or decision-making. **This approach ensures the patient's autonomy.**

Creation and Analysis of Family Pedigrees

A pedigree (or family tree) is used for a **clear presentation of family history** and thus facilitates the identification of **abnormal inheritance patterns**. A pedigree chart reveals the phenotypes of a specific gene among family members and their ancestors. The 1st step in creating a pedigree is a consultation with the patients and systematically questioning them about their 1st-degree relatives.

Most often, **3 generations** are sufficient to obtain reliable results. Inquiries related to **names, birthdays** and **clinically relevant information**. Provenance, miscarriages, or unwanted childlessness can also be of interest. The symbols are the same in almost all pedigrees.

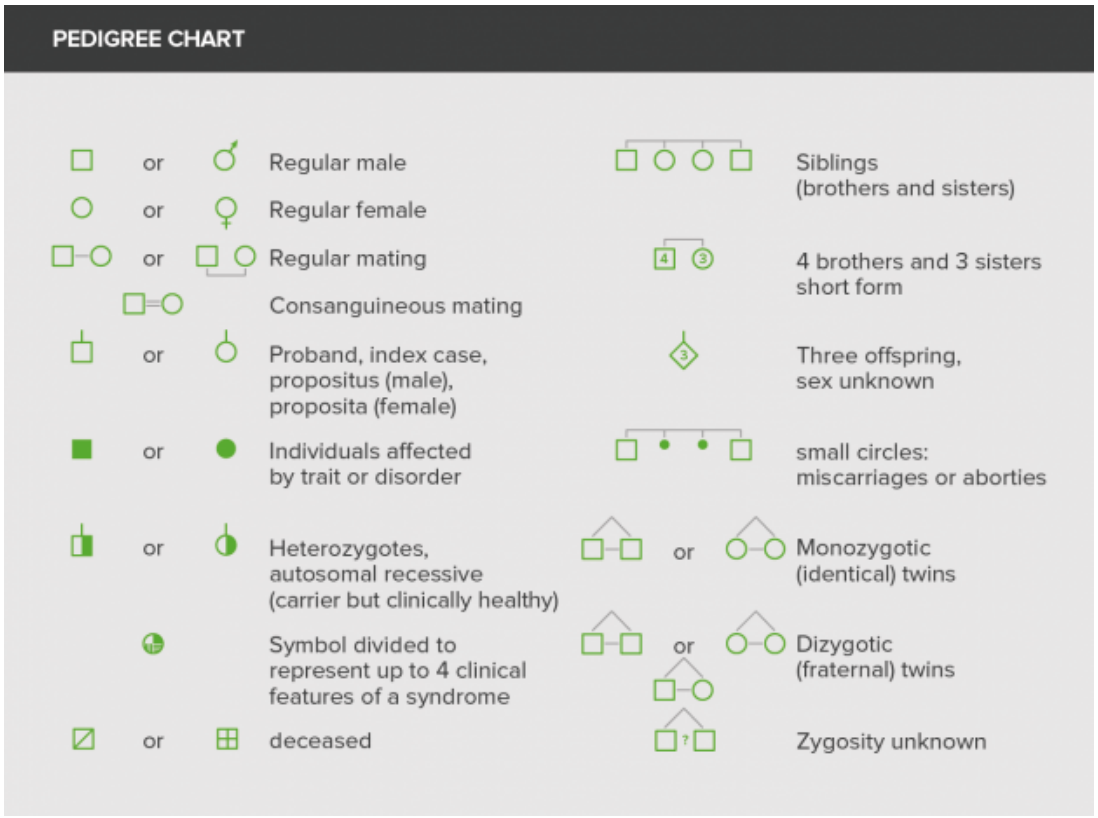

Image by Lecturio

Preliminaries: Mendelian Genetics

A meaningful interpretation requires familiarity with the basic rules of **Mendelian genetics**. The rules are based on the **premise that genetic traits are transmitted from one generation to the next via a distinct system**.

The rules are as follows:

Law of Dominance: The descendants of opposite homozygous parents are all uniformly heterozygous. All the alleles are not phenotypically expressed. When 2 different alleles are inherited, the phenotypic features of the organism are determined by the dominant allele whereas the other allele that is silent is known as the recessive allele.

Law of Segregation: The descendants of heterozygotes are not uniform. However, the phenotypes split in a specific ratio during the production of gametes.

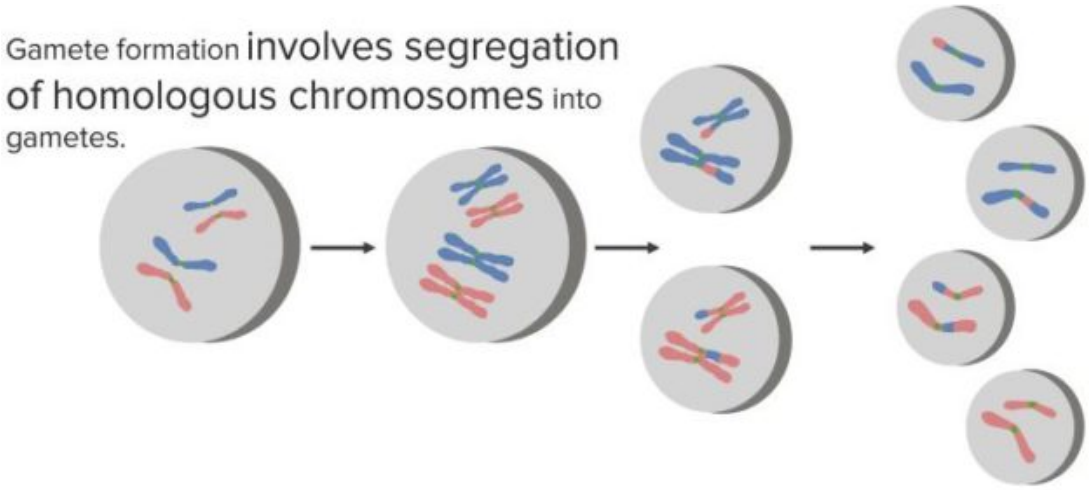

Image: Homologous chromosomes (alleles) separate during Meiosis. By Lecturio

Law of independent assortment: The different characteristics are distributed independently in the next generation.

Two **alleles** or genes control each trait. One allele is inherited from the mother, and the other allele from the father. If the alleles are present on an autosome, it is known as **autosomal inheritance**. If they exist on a sex chromosome, it is considered **gonosomal inheritance.** It depends on a number of specific factors.

If both alleles result in the same effect, the genotype (i.e., the combination of genes) is **homozygous.** If the effect varies, it is a **heterozygous genotype**. The **phenotype** (the physical appearance of the genetic trait) depends on the mode of inheritance.

Different alleles are often represented by upper and lower case letters. A trait can display gene variation ‘A’ and gene variation ‘a’. A homozygous genotype is then represented by ‘AA’ or ‘aa’, and a heterozygous genotype by ‘Aa’. In most cases, the upper case denotes the **dominant allele,** and the lower case represents **the recessive allele**.

Modes of Inheritance

There are 8 different modes of inheritance.

1. Codominant inheritance

In the case of heterozygous genotypes, **both characteristics manifest physically in parallel**. An example of codominant inheritance of that of the ABO system of blood types. In a genetic heterozygote AB, both A and B features are phenotypically expressed on the erythrocyte surface.

2. Intermediate inheritance

In the case of a heterozygous genotype, both traits are manifested but not in parallel. Instead, there is an intermediate phenotype, i.e., a **blending of both characteristics**. The simplest example is the color of a flower: a red allele and a white allele result in a pink phenotype.

3. Autosomal dominant inheritance

One allele is dominant to another allele. If both dominant and non-dominant alleles exist in a heterozygous genotype, only the dominant allele is manifested. In genetic

counseling, autosomal dominant inheritance suggests a 50% chance that the fetus will acquire the disease. It is often referred to as vertical transmission from the parent to the offspring. Taking the ABO system as an example again, A and B are each dominant to O. Therefore, the genotype AO results in the phenotype A.

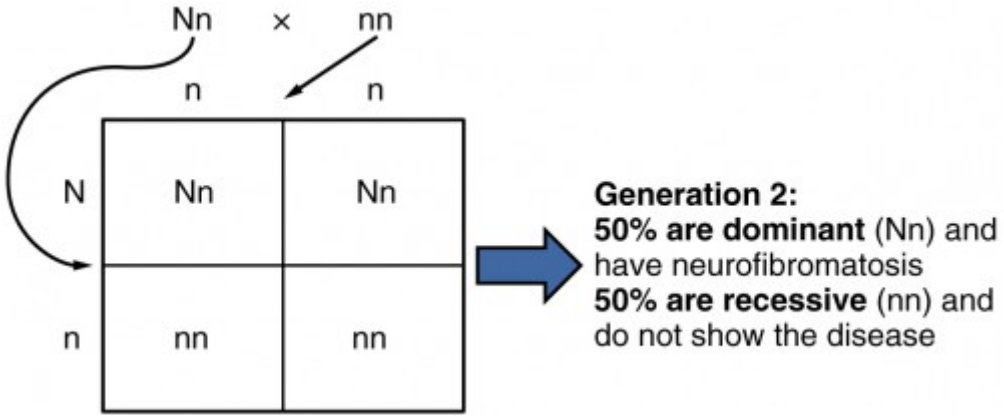

Image: Autosomal dominant inheritance. By Phil Schatz, License: CC BY 4.0

4. Autosomal recessive inheritance

A trait associated with recessive alleles only manifests phenotypically when in homozygous individuals. The blood type O is therefore only possible if the genotype is OO. Several individuals carry heterozygous genotypes that do not manifest physically. Two copies of an allele are required to phenotypically express the disease. Diseases with such a pattern of inheritance include sickle cell disease and cystic fibrosis, which are found in consanguineous relationships that carry an increased risk of identical genetic mutations.

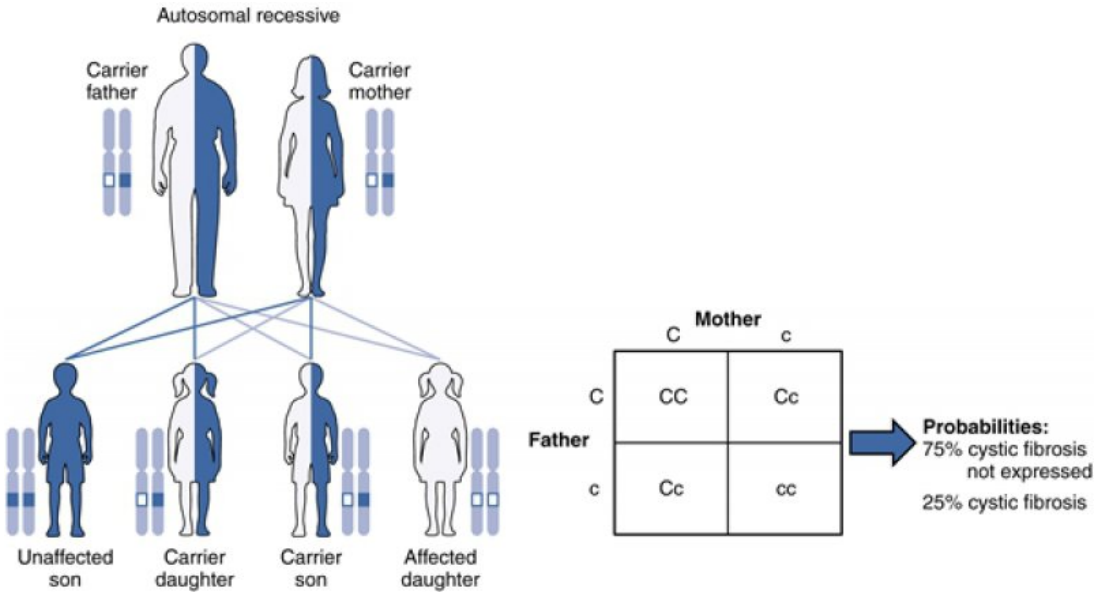

Image: Autosomal Recessive Inheritance. By Phil Schatz, License: CC BY 4.0

5. X-linked recessive inheritance

The allele in question, or the disease-causing mutation, is on the **X chromosome** and is **recessive**. In a **man**, the allele will **always be expressed** due to the presence of only a single X chromosome. In a woman, the likelihood of manifestation is very low due to the

presence of a second X chromosome. The trait will manifest only if there is a **non-random inactivation** of the healthy X chromosome. In case of children born to a **hemizygous healthy man** and a **woman, and heterozygous for X-linked recessive genetic disease**, the following conditions apply:

- The **male offspring** carry a **50%** risk of developing the disease.
- The **female offspring** carry an almost **0%** risk of disease; however, there is a 50% **risk** that they are **carriers.**

If the man is hemizygous for the mutant allele, all-male offspring are healthy (since the X chromosome is derived from the mother!) and all daughters are healthy female carriers (because their second X chromosome is derived from the father, which is present only in its mutant form!).

6. X-linked dominant inheritance

Only a single copy of the disease allele is required for phenotypic expression as in autosomal dominant inheritance. However, in x-linked dominant inheritance, the disease allele is located on the X chromosome. This type of mutation is **often fatal in male offspring**, since they are hemizygous, and the changes are severe. In heterozygous women, the disease also manifests but is attenuated by the second X chromosome. According to the **Lyon hypothesis,** the female body consists of a mosaic of cells where either one or the other X chromosome is activated.

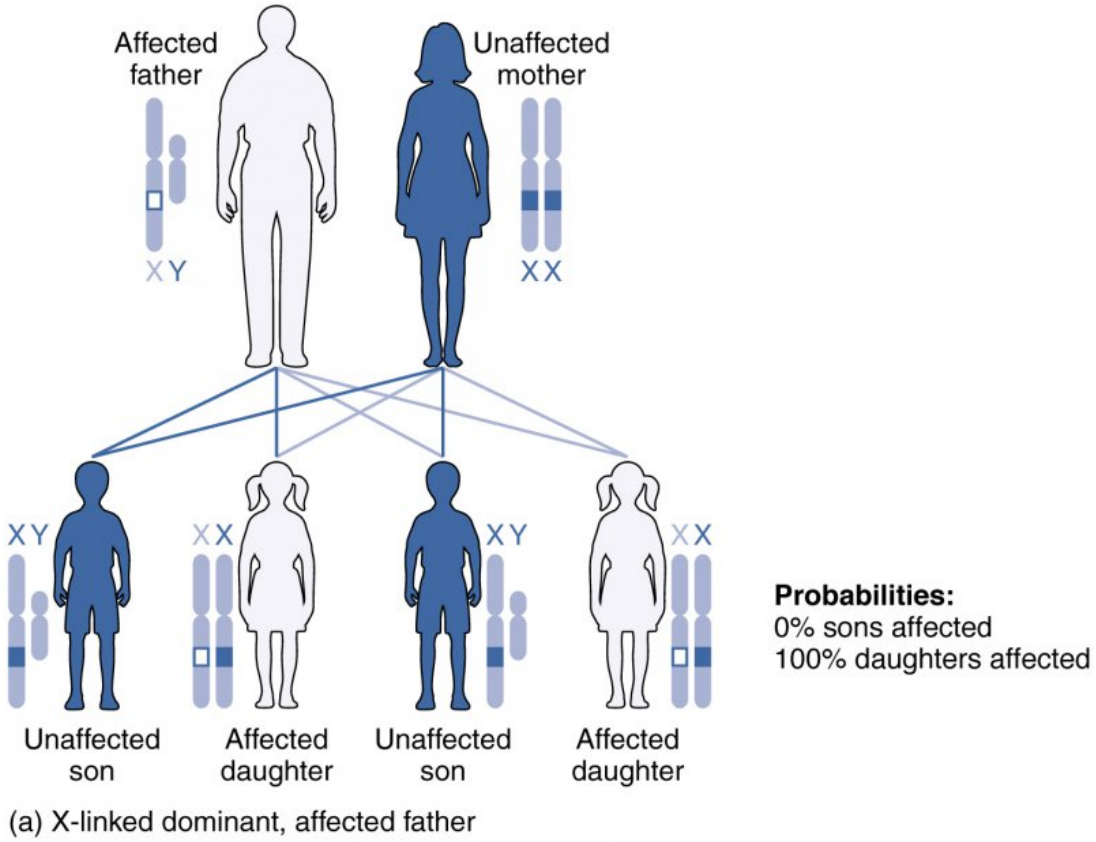

Image: X-Linked Patterns of Inheritance. By Phil Schatz, License: CC BY 4.0

7. Y-linked inheritance

In the case of a **holandric inheritance**, a diseased father passes on the mutation to all

his sons, who will also be ill. However, there are hardly any known diseases showing this pattern of inheritance.

8. Mitochondrial inheritance

Genetic defects associated with mitochondria can cause diseases. Mitochondria are **always inherited from the mother**. All of the mother's children are affected, whereas a father carrying this type of genetic mutation cannot transmit it.

Modes of inheritance	Pattern of inheritance	Affected individuals	Risk of disease
Autosomal dominant	Vertical	Several affected generations; each diseased person has a diseased parent	50% in case of affected parent
Autosomal recessive	Horizontal	One or more siblings are affected	25% for siblings of a diseased individual
X-linked recessive	'Knight's move' (diagonal)	Diseased boys often have diseased maternal uncles, i.e. diseased men are related to each other through female relatives	50% for brothers of a diseased person (50% for sisters as carriers)
X-linked dominant	Vertical	All daughters but no sons of a diseased father; women are more easily affected than men	100% for daughters of a diseased man (0% for sons)
Y-linked	Vertical	All sons of a diseased man; no women	100% for sons of a diseased man
Mitochondrial	Vertical	Children of a diseased woman	Not established; high variability within a family

Definition: Carrier Status

Any individual carrying a heterozygous genotype for a recessive hereditary disease is a carrier, suggesting that the **disease does not manifest** due to the presence of a non-mutated gene. However, he/she can **pass it on to offspring**, so that the disease occurs in the next or next-but-one generation. Thus, he/she is the carrier of a hereditary disease. In some diseases, a slight pathology is observed in carriers; however, this varies among individuals.

Case Study: Cystic Fibrosis

Cystic fibrosis (CF), also called mucoviscidosis, is an **autosomal recessive hereditary disease**. It is caused by a defective **chloride channel** due to the mutant or **missing** gene. Therefore, the **composition of different secretions** in the body is **significantly changed**.

Distribution of the Gene Defect

CF is one of the **most common metabolic diseases** in our population, with an incidence of 1:2500, and 1 in 20 Northern Europeans is a carrier. This means the probability of 2 heterozygous parents is 1:400, and the probability for such parents to have a diseased child is 1:1600.

Pathogenesis: Symptoms of Cystic Fibrosis

- Increased viscosity of mucus in the lungs causes lung damage and increased risk of infections
- Meconium ileus
- Exocrine pancreatic insufficiency
- Increased chloride and sodium concentrations in sweat

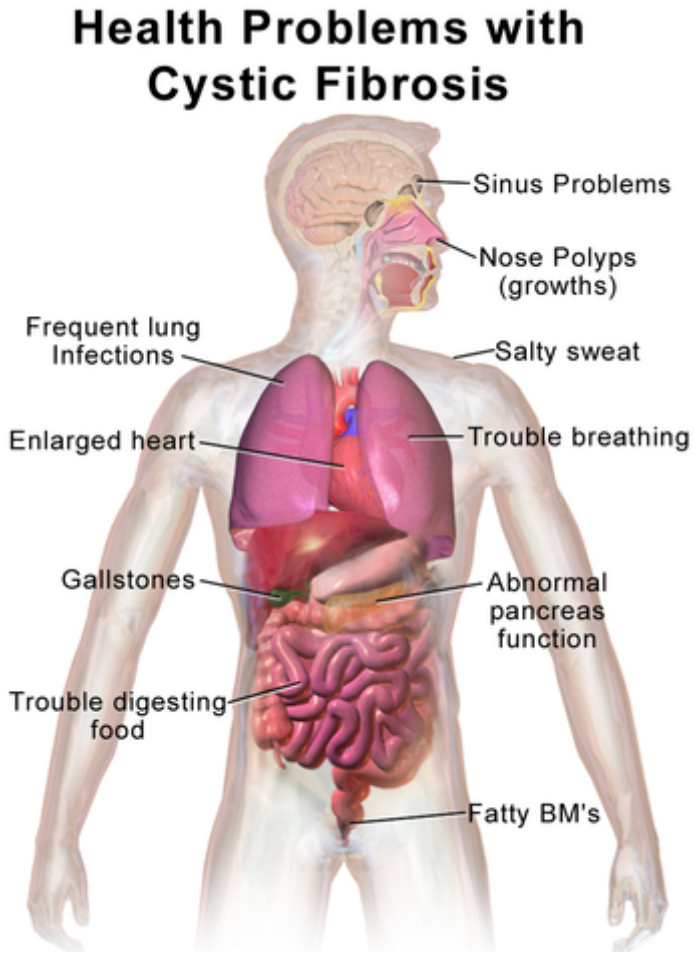

Image: Health problems with cystic fibrosis. By Blausen.com staff, License: CC BY 3.0

Genetic Counseling

The following example is adapted from ‘New Clinical Genetics’, a textbook designed to teach clinical genetics to medical students.

David and Pauline already have a 4-year-old healthy boy, and they have another child, a girl named Joanne. Since her birth, Joanne has hardly gained weight. She often suffered from colds and coughs. At 5 months, she develops severe pneumonia and is hospitalized. The hospital staff notes the voluminous, foul-smelling bowel movement and the lack of development since she is now at a lower percentile than at her birth.

Suspected CF is confirmed via a sweat test. A pedigree analysis, however, identifies Joanne as the only diseased family member. It is a typical manifestation of the autosomal recessive disease since a single mutation in one allele only results in inconspicuous carriers. A molecular genetic test is conducted in order to establish the type of mutation

carried by Joanne and is especially important for relatives who might also be carriers. The relatives can get tested for the corresponding mutation.

Molecular Genetics of Cystic Fibrosis

The autosomal recessive disease is triggered by a mutation involving the ***CFTR* gene on chromosome 7** (exact location: 7q31.2). The defective protein in the CF patient can be traced to a **homozygous gene defect** since both genes are mutated and thus the protein is inactive.

However, the result does not suggest that the patient carries the same mutations on both alleles. There are approximately 1000 identified *CFTR* mutations and the weaker mutation determines the disease progression. This state is known as **compound heterozygosity**. Among these 1000 mutations, only a few occur frequently. The most important mutation is **p.Phe508del**, which is responsible for 70–80% of all CF cases in Northern Europe.

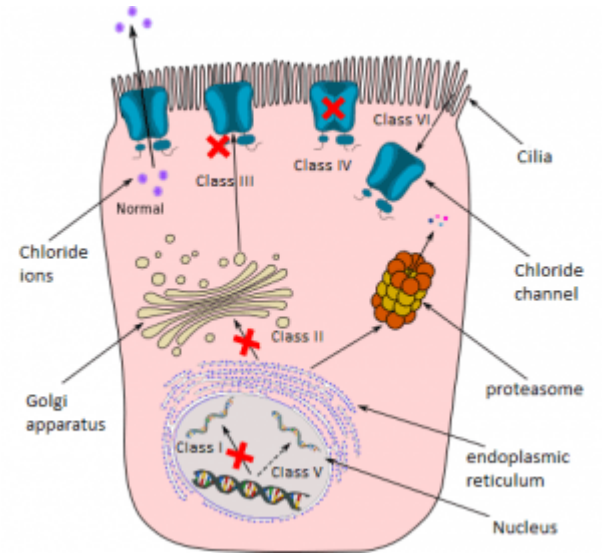

Image: Cystic fibrosis. By Kuebi, License: CC BY 3.0

Joanne has been tested for the most common mutations by PCR. She is heterozygous for the mutation p.Phe508del, which means she carries a second, yet unknown mutation. Further testing reveals a maternal mutation, which has been identified in other CF patients.

Joanne's relatives can now get tested for these 2 mutations.

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Notes