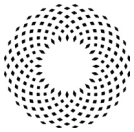
CODEX
BEAUTY LABS

Chapter: Genetics and The Science of Decoding Skin

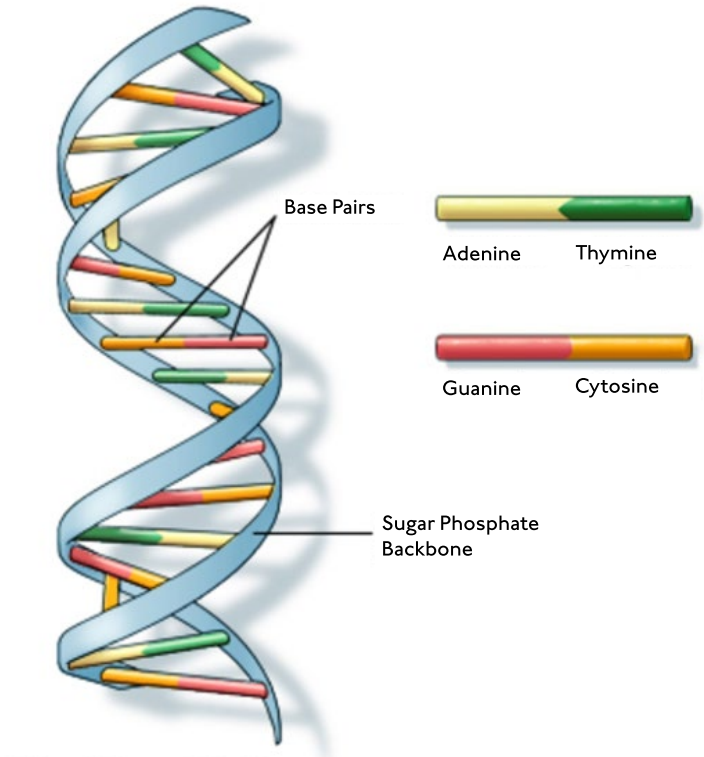
SECTIONS



01 DNA 101

Human beings are made up of cells that contain DNA, a.k.a., deoxyribonucleic acid, a hereditary material present in humans and almost all other organisms. Nearly every cell in a person's body has the same DNA. The majority of a person's DNA is present within the cell nucleus and, as such, is referred to as "nuclear DNA". There is, however, also a small amount of DNA called "mitochondrial DNA" present in a cell. Mitochondria are structures within cells that enable energy found in food to be converted into a form that cells can use.

Information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion of these bases, with more than 99% of those bases being the same in all people. The order/sequence in which these bases appear represent the biological information used for building and maintaining an organism in the same way that letters of the alphabet appear in a certain order/sequence to form words and sentences. These DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base, however, is also attached to both a sugar and phosphate molecule to form a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder as is seen in the Figure below. An important property of DNA is its ability to replicate, i.e., make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.



National Library of Medicine

Credit: U.S. National Library of Medicine

DNA, in turn, is packaged into structures known as chromosomes which contain numerous "genes" possessing the above-referenced A-T-C-G DNA bases, together with genetic material called exons which communicate information to proteins. All genetic material present in chromosomes is referred to as "the genome".

02 What are genetic variants?

The term "genetic variant" refers to a permanent change in a gene's DNA sequence that can affect one or more DNA building blocks (nucleotides) within a gene. Genetic variants are either inherited from a parent or occur on their own during a person's lifetime. Inherited/hereditary variants are passed from parent to child and are present throughout a person's life in virtually every cell in the body. When an egg and a sperm cell unite, the resulting fertilized egg cell contains DNA from both parents. Any variants that are present in that DNA will be inherited by their offspring.

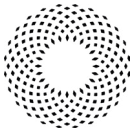
Non-inherited variants, a.k.a. "somatic variants" occur at some point during a person's lifetime and are only present in certain cells. These types of variants cannot be passed on to subsequent generations. There are numerous factors that can cause non-inherited variants to occur such as, for example, exposure to UV radiation. This type of variant can also occur if an error is made while DNA replicates itself during cell division.

The most common genetic variants are called single nucleotide polymorphisms (SNPs) because they describe a change in a single nucleotide within the genome. Each SNP represents a difference in a single DNA base (A, C, G or T) in a person's DNA. A nucleotide change is considered an SNP if it is observed in more than 1% of the human population. An SNP variant occurs, on average, in one out of every 300 nucleotides which amounts to approximately 10 million SNP occurrences in a person's genome. The majority of these are harmless and are oftentimes used by scientists as biological markers when investigating genes associated with a medical condition. Some SNPs, however, are directly responsible for causing specific medical issues.

Copy number variants (CNVs) are regions of the genome that vary in copy and number, either due to duplication or deletion. These are classed as structural changes and recent scientific research suggests that up to 9.5% of the human genome may consist of copy number variants. Like SNPs, some CNVs exist that have no phenotypic consequence and simply contribute to the genetic variation between two individuals, whereas others exist that are condition causing.

Huntington's condition is caused by repetition of the three base pairs (known as a tri-nucleotide repeat) CAG in the HTT gene. In a healthy individual, these 3 bases are repeated between 10 and 35 times, but in an individual with Huntington's the repeats can number from 36 up to 120. CNVs are also used to describe repeats of a whole gene. The human alpha-amylase 1 gene AMY1A, which codes for an enzyme that breaks down starch into sugars, can be present multiple times in a person's genome, with one study reporting 14 copies of the gene in one individual. Interestingly, the number of repeats of this gene was found to be higher in populations with high-starch diets.

Most variants do not lead to development of condition, and those that do are uncommon in the general population. Some variants occur often enough in the population to be considered common genetic variation. Several such variants are responsible for differences between people such as eye color, hair color, and blood type. Although many of these common variations in the DNA have no negative effects on a person's health, some may influence the probability of developing certain disorders.



03 What is DNA sequencing and what role does it play in genetic testing?

It is clear the influence that genetic variation can have on the health of an individual. Assessing the degree of influence, however, can be complicated. Large changes to a person's genome can have no effect at all, whereas the change of a single nucleotide can have a huge impact.

DNA sequencing involves determining the order of the four chemical building blocks (A-T-C-G DNA bases) that make up the DNA molecule. The sequence informs scientists of the kind of genetic information that is carried in a particular DNA segment. For example, scientists can use sequence information to determine which portions of DNA contain genes and which portions carry regulatory instructions that turn genes on or off. In addition, and importantly, sequence data can highlight changes in a gene that can impact biological functions within the body and, in a worst-case scenario, shed light on a person's propensity to possibly develop a condition. This is where genetic testing comes into play.

Genetic testing is a type of medical test that identifies changes in genes, chromosomes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. There are currently tens of thousands genetic tests in use with many others being developed. Genetic testing involves looking for changes in genes, chromosomes, and proteins. Gene tests study DNA sequences to identify variations (mutations) in genes that can cause or increase the probability of a genetic disorder. Gene tests can be narrow or large in scope, analyzing an individual DNA building block (nucleotide), one or more genes, or the entirety of a person's DNA, i.e., their genome. Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that may cause a genetic condition. Biochemical genetic tests assess the amount or activity level of proteins or enzymes with abnormalities in either being potentially indicative of changes to the DNA that can be a sign of a genetic disorder.

04 What types of genetic tests are available and what purpose do they serve?

Genetic tests can be divided into three general categories depending on their purpose. Diagnostic tests are mainly used to find the cause of an existing condition. Predictive tests are used to determine whether a person has certain characteristics that may influence the effectiveness of a certain type of treatment, or lead to the development of a condition or condition with the goal being to use the information ascertained from the test to develop a treatment plan. Prognostic tests help to predict one's probability of experiencing a condition or condition in the future.

05 How is genetic testing performed?

Although genetic tests are most often performed on a blood or cheek swab sample, they may also be done on samples of hair, saliva, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. The collected sample is then sent to a laboratory certified to perform such tests.

Once the DNA sample is received by the lab, it must then be prepared for genetic testing. First, the DNA is sheared into fragments, each comprised of about 1,000 nucleotides. Next is the adapter ligation step, which involves adding a synthetic DNA sequence to both ends of each DNA fragment. These synthetic ends allow the DNA fragment to interact with the sequencing system, while also tagging the DNA to a specific patient sample. Finally, the adapted DNA fragments are copied multiple times in a process called enrichment which produces enough of the necessary DNA for successful sequencing.

Once the DNA sample has been properly prepared for genetic testing, the next step involves choosing the appropriate genetic test. There are a number of different kinds of genetic tests with no single genetic test being available for detecting all genetic conditions. The approach to genetic testing is individualized based on the condition being tested for. For example, single gene tests look for changes in only one gene, whereas panel genetic test looks for changes in numerous genes at one time. Genetic testing panels are usually grouped into categories based on different kinds of medical concerns. Panel genetic tests can also be comprised of genes that are all associated with a higher probability of developing certain kinds of cancer such as breast or colon cancer.

Exome testing looks at either all the genes in the DNA (whole exome) or just the genes that are related to specific medical conditions (clinical exome), whereas genome testing is the largest genetic test that looks at a person's entire DNA, not just their genes. Exome and genome sequencing, referred to as "large-scale genomic testing" is ordered by a medical doctor for people with complex medical histories. Large-scale genomic testing is also used in research to learn more about the genetic causes of conditions.

06 How can I be sure that a genetic test is valid and useful?

A genetic test is valid if it provides an accurate result based on analytical and clinical validity, together with clinical utility. Analytical validity refers to how well the test predicts the presence, or absence, of a particular gene or genetic mutation, i.e., whether the test can accurately detect whether a specific genetic variant is present or absent. Clinical validity relates to how well the genetic variant being analyzed influences the presence, absence, or probability of a specific condition. Clinical utility refers to whether the test can provide helpful information about diagnosis, treatment, management, or prevention of a condition.

All laboratories that perform health-related testing, including genetic testing, are subject to federal regulatory standards called the Clinical Laboratory Improvement Amendments (CLIA) or even stricter state requirements. CLIA standards cover how tests are performed, the qualifications of laboratory personnel, and the quality control and testing procedures for each laboratory. By controlling the quality of laboratory practices, CLIA standards are designed to ensure the analytical validity of genetic tests. CLIA standards do not, however, address the clinical validity or clinical utility of genetic tests. The Food and Drug Administration (FDA) requires information about clinical validity for some genetic tests, particularly those tests that have been produced by a lab (known as laboratory-developed tests). Additionally, states may require additional information on clinical validity for laboratory tests performed for people living in that state. Test takers and medical providers in conjunction with the research community are typically the ones who evaluate the clinical utility of a genetic test.

07 What do the results of genetic tests mean?

The results of genetic tests are not always straightforward, which often makes them challenging to interpret and explain. Therefore, it is recommended for individuals to discuss the results of their genetic test with a licensed medical professional and/or a genetic counselor to help decipher them.

That being said, a positive test result generally means that the testing laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose for the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic variant, identify an increased probability of developing a condition (such as eczema or psoriasis), or suggest a need for further testing. It is important to note that a positive result of a predictive genetic test usually cannot establish the exact probability of developing a disorder. Also, health care providers typically cannot use a positive test result to predict the severity of a condition. Though rare, test results can be false positive which typically occurs when results indicate an increased probability for a genetic condition even though the person does not appear to be suffering from the condition.

Conversely, a negative test result means that the laboratory did not find a variant that is known to affect health or development in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic variant, or does not have an increased probability of developing a certain condition. It is possible, however, that the test failed to identify a condition-causing genetic variation since many tests cannot detect all genetic changes that can cause a particular disorder. Further testing, or re-testing at a later date, may be required to confirm a negative result. The likelihood of obtaining false negative test results is quite rare and typically occur only when the results indicate a decreased probability of a genetic condition even though the person appears to be suffering from the condition.

Lastly, in some cases a test result might not yield any useful information. This type of result is referred to as uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because the general population has common, natural variations in their DNA, called polymorphisms, that do not affect health. For these variants, there may not be enough scientific research to confirm or refute an association with a particular condition or the research may be conflicting. An uninformative result cannot confirm or rule out a specific condition, and it cannot indicate whether a person has an increased risk of developing a disorder.

08 What to think about prior to getting a genetic test?

One should consider both the pros and cons of genetic testing before taking the plunge. The pros include gaining valuable insight into whether you have a genetic propensity for developing or suffering from a particular condition. This type of information can also provide valuable insight into the optimal treatments for managing the condition. The test results from genetic testing can also help alleviate any uncertainty or concern a person may have that either they, or a family member may possibly suffer from the same condition, i.e., the test can provide a certain degree of peace of mind. Lastly, having this type of information can enable a person to be more proactive in terms of their lifestyle (diet, exercise, hydration) to help mitigate the affects of a particular condition identified by the test and/or seek additional testing if the severity of the condition warrants it.

The cons primarily include the cost of the test, failure of the condition to be mitigated in view of the treatment regimen selected based on the results, and of course, an inaccurate test result. While the cost of the test is something that should be taken into consideration for obvious reasons, the importance of consulting a licensed medical professional and/or genetic counselor once the results are in should help to address the cons of lack of mitigation and/or inaccurate diagnosis. Accepting the fact that no test is infallible should also be taken into consideration when deciding whether to take a genetic test.

Lastly, when it comes to genetic tests sold directly to the public, it can be challenging for the average person to determine their quality in advance. Some providers of direct-to-consumer genetic tests are not CLIA-certified, so it can be difficult to tell whether their tests are valid. If providers of direct-to-consumer genetic tests offer easy-to-understand information regarding the scientific basis of their tests, it can help people make more informed decisions.

ADDITIONAL REFERENCES

https://medlineplus.gov/genetics/understanding/testing/validtest/