

## UNDERSTANDING THE GENETICS OF HHT

### **What does it mean to say HHT is inherited?**

An inherited trait is any feature such as blue eyes, dark hair or a disease that can be passed from parent to child. For any trait to be passed to the next generation, the code for that trait must be in the DNA.

### **What is DNA?**

DNA (deoxyribonucleic acid) is a molecule found in almost every cell of our body. It carries the instructions (sometimes referred to as “blueprints”) for the formation of all parts of our body during development, as well as for the substances our body needs in order to work and maintain itself over the course of our lifetime.

### **What is a Chromosome?**

All a human being’s DNA is packaged into 46 chromosomes. These 46 chromosomes are found inside almost every cell of our body. Chromosomes, which look like worms under a microscope, are each made up of compactly coiled and folded long strands of DNA. There are 24 unique human chromosomes, that, under the microscope look different from each other (based on size as well as a pattern of light and dark stripes that is characteristic for each chromosome). This difference in appearance of chromosomes under a microscope makes it easier to talk about them individually. Each chromosome has been given either a number or letter name; such as “chromosome 9” or the “X chromosome”. A woman has 2 copies of each chromosome number 1-22 and two “X” chromosomes to make up her total of 46 chromosomes inside the cells of her body. A man has 2 copies of each chromosome number 1-22 as well, but he will have one copy of an “X” chromosome and one copy of a “Y” chromosome to make up his 46 chromosomes. Chromosomes number 1-22 are sometimes called the “autosomes”. The X and Y are called the “sex” chromosomes since it is genes on these 2 chromosomes that determine whether an embryo develops into a male or female.

### **What is a Gene?**

A gene is a tiny portion of DNA that contains the instructions for one particular building block of the body or one substance the body needs in order to work (i.e. a protein or an enzyme). An analogy that is often used to explain genes, chromosomes and DNA is that genes on a chromosome are like beads on a necklace- strung one after another. The DNA of a particular chromosome would be like all the beads on the necklace. Each chromosome carries 100s or even thousands of genes. Human cells normally have 46 chromosomes inside them- combined they carry about 100,000 genes.

### **How do genes get passed from generation to generation?**

A mother gives 23 chromosomes to her baby in her egg and a father gives 23 chromosomes to his baby in his sperm. After the egg and sperm unite, the resulting single cell will multiply millions of times over to form the baby. These cells that are “copies” of that initial single cell should all contain the same 23+23 (46) chromosomes. Furthermore, these 23 chromosomes carry exactly one copy of every type of gene that parent had. So the resulting baby then has 2 copies (one from each parent) of every type of gene needed to form and maintain the human body.

### **What does it mean to say HHT is a “dominant” genetic disorder?**

It means that it takes only one copy of a specific pair of genes to be abnormal to cause the disorder (in “recessive” diseases, both copies of a specific pair of genes must be abnormal to cause the disease). In other words, HHT results from inheriting a gene for HHT from either your father or mother, but not both. The “matching” or “partner” gene inherited from the other parent would be normal. HHT can thus almost always be traced to just one side of an individual’s family.

### **What is the chance a dominant genetic disorder, like HHT, will get passed on to children?**

Since individuals with HHT actually have two copies of the “HHT gene”—one normal and one abnormal— each of their children has a 50% (1/2) chance of having HHT. This is because each egg and sperm has only one copy of each gene pair, not both. But whether it is the normal or abnormal copy of the HHT gene in a specific egg or sperm is completely random. The example of a coin toss is often used to explain the chance that a parent with a dominant genetic disorder will pass it on to any particular child. The normal/abnormal HHT genes would be on the two sides of the coin rather than heads/tails. Each time the parent tosses the coin it is equally likely to come up normal gene (heads) as abnormal gene (tails). This analogy also helps understand that if a person with HHT has 4 children, it does not necessarily mean that 2 will have it and 2 will not.

### **What does it mean to say that HHT has “variable expression”?**

Different people that inherit the same “abnormal” gene can have very different effects from the gene. Therefore, even if one of your children inherits your gene for HHT, this child may have very different symptoms from others in the family- including you.

### **What does it mean to say that HHT exhibits “incomplete penetrance”?**

Indeed, some people with an abnormal HHT gene never show any signs of having HHT. This is rare (usually at least mild signs and symptoms exist), but is known to occur in HHT. This possibility that the HHT gene wouldn't express itself is called “incomplete penetrance”.

### **What is “genetic heterogeneity”?**

“Genetic heterogeneity” describes the fact that different gene abnormalities can cause the same disorder. For instance, changes in a gene on either chromosome 9 or chromosome 12 can cause HHT. Because HHT can result from an abnormality in more than one gene, and each gene occupies a specific site (locus) on a chromosome, this type of genetic heterogeneity is called “locus heterogeneity”. Even within the same gene, different changes (also called “mutations”) can cause HHT. This type of genetic heterogeneity is called “allelic heterogeneity” because each gene has many variations—each called an “allele”. HHT is thus said by geneticists to have both locus and allelic heterogeneity. Many other genetic disorders do not.

Data so far suggests that almost every family with HHT has a different genetic variation causing HHT. Both locus and allelic heterogeneity make “genetic testing” for HHT more difficult than for many other genetic disorders.

### **I've heard HHT referred to as an “autosomal” dominant genetic disorder. What does this mean?**

This simply means that the genes responsible for HHT are located somewhere on chromosomes 1-22. (In the case of HHT on chromosomes 9 and 12, as you now know) Some other genetic disorders are caused by genes located on either the X or Y chromosome and are thus called “X-linked” or “sex linked” disorders. The fact that the genes for HHT are located on “autosomes” explains why both men and women, in equal numbers, have HHT. This makes sense since men and women are indistinguishable in terms of their chromosomes numbered 1-22.

### **What is the role of chromosome 9 in HHT?**

The first identification of a specific gene that causes HHT was in 1994. This gene, called “endoglin”, is on chromosome 9. Because this was the first HHT gene discovered, HHT due to a defect in endoglin is sometimes called HHT type 1, or simply HHT1.

### **What is the role of chromosome 12 in HHT?**

In 1996, a second gene that can cause HHT was discovered. This gene is called the “activin receptor-like kinase 1” (or ALK1) gene and is located on chromosome 12. Since this was the second gene discovered to cause HHT, HHT caused by a defect in ALK1 is called HHT type 2, or simply HHT2.

### **Could my family have more than one of these genes involved?**

No. Although different genes can cause HHT, in any single family with HHT only one of these is abnormal.