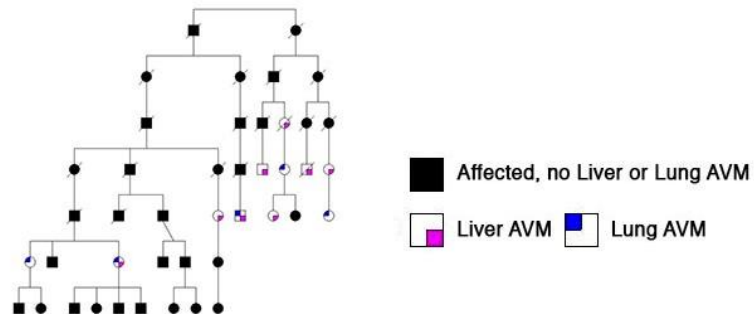


Dr. Whitney Wooderchak-Donahue investigates why not all HHT patients are created equal

Many genetic diseases that run in families tend to give each affected person similar symptoms. However, HHT is a genetic disease with varying penetrance. This means not every affected individual displays the same symptoms, or phenotype. Dr. Whitney Wooderchak-Donahue from ARUP Laboratories is studying the genetic information of HHT patients to learn more about how this occurs.

In this figure from Dr. Wooderchak-Donahue's work, a family pedigree (pattern of HHT throughout the family) is shown. Some members of this family have arteriovenous malformations (AVMs) in the liver, lungs, in both organs, or in neither. This is an example of



how members of the same family with the same genetic mutation causing HHT can have different symptoms. Dr. Wooderchak-Donahue's work examines the genetic information of HHT patients in order to identify genetic modifiers that would cause these varying phenotypes.

Our DNA is the set of genetic instructions that make up our bodies. In each cell, DNA gets transcribed, or rewritten, into RNA. Very simply put, the body takes the important genetic information from our DNA and creates a message that instructs the cells to make specific proteins. In many HHT cases, there is a known mutation (often a deletion of information) in the affected individual's DNA that causes the downstream message to be incomplete or make a malfunctioning protein.

For example, HHT type 1 patients have a mutation in the *ENG* gene, which instructs the cell to make the protein endoglin. When endoglin does not function properly because of the genetic mutation, HHT can occur. However, a mother and son can have the same mutation in their *ENG* gene, but the mother could have severe nosebleeds and no AVMs, while the son may not have any nosebleeds and several AVMs.

Dr. Wooderchak-Donahue and her team are analyzing the transcriptome (all those genetic messengers written from the DNA) of this family and others in order to identify differences among family members with the same DNA mutation. They have chosen to analyze samples from individuals with widely varying symptoms, which will help tease out the differences in their genetic information. This information will also be compared to healthy individuals who are not affected with HHT as a way to further highlight the differences caused specifically by HHT.

As mentioned previously, most HHT families have a known genetic mutation, but around 10-15% of HHT patients have an unknown mutation causing their disease. Dr. Wooderchak-Donahue is using similar technology and procedures to identify these unknown mutations. Her work will help give more HHT patients a diagnosis, and very importantly can guide medical providers in management and treatment of HHT patients.