Is Afib Genetic?

Atrial fibrillation is the most common abnormal heart rhythm. It is a complex disease with a number of known risk factors such as high blood pressure, heart failure, valvular heart disease, alcohol overuse, sleep apnea, and increasing age. However, up to 30% of atrial fibrillation occurs in people with no known risk factors (i.e. lone AFib). Also, atrial fibrillation can run in families. Both of these suggest that there are underlying genetic factors contributing to atrial fibrillation.

Indeed, over the past decades, researchers have identified a genetic link for atrial fibrillation. Atrial fibrillation genetic research is ongoing and rapidly evolving. Numerous genes have been identified which are associated with atrial fibrillation. This makes genetic testing for some types of atrial fibrillation possible, however, the clinical implications of this are still being explored. In the future, it is possible that the presence of specific genetic mutations could help guide a person's AFib treatment.

Does atrial fibrillation run in families?

Epidemiologic studies have shown that 30% of people with atrial fibrillation have someone in the family with atrial fibrillation. The risk of developing atrial fibrillation is particularly increased if that family member is a first-degree relative, especially a parent, with early-onset (age less than 65 years) of atrial fibrillation. Studies have shown that this is independent of the presence of other risk factors like high blood pressure, diabetes, and heart disease.

A population study in Iceland also found a strong likelihood of atrial fibrillation heritability. This was especially true amongst patients with early-onset (defined as age less than 60 years) and amongst first and second-degree relatives.

What is the genetic basis of atrial fibrillation?

The association between heredity and atrial fibrillation is complex. As described above, atrial fibrillation seems to cluster in families. Having a family member with atrial fibrillation confers up to a 40% increased risk of an individual developing atrial fibrillation. If there is a genetic basis for atrial fibrillation, researchers think it is most commonly secondary to what is called polygenic inheritance.

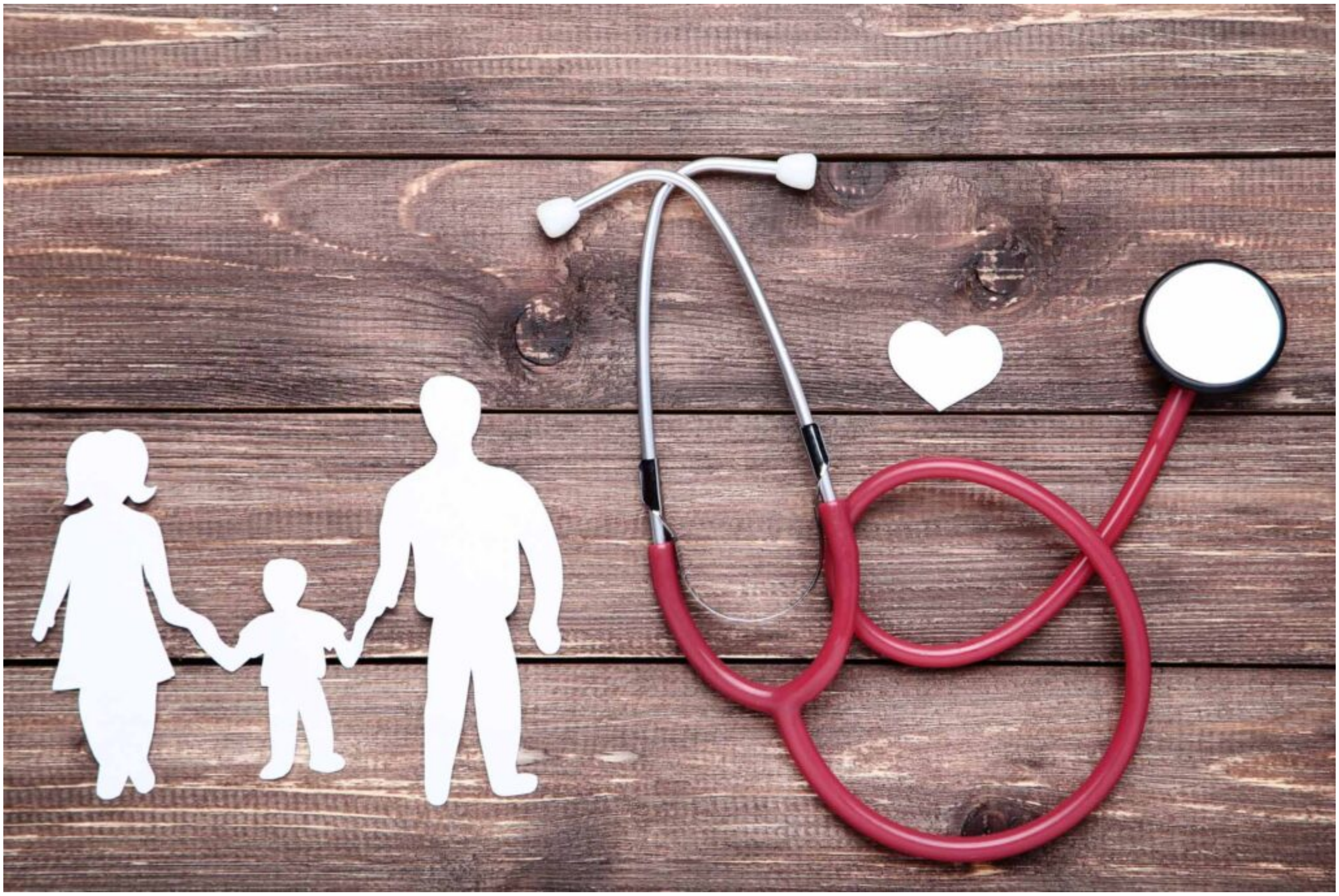
In polygenic inheritance, the development of atrial fibrillation results from the combined effect of multiple genes and the influence of environmental factors. Heritability is complex and variable. With the polygenic phenomenon, the risk of atrial fibrillation cannot be reliably quantified. This makes polygenic inheritance different from the Mendelian-pattern of inheritance that is seen with monogenic familial atrial fibrillation.

What is familial atrial fibrillation?

Rare cases of familial atrial fibrillation have been reported since the early to mid-1900s. For example, in the 1940s a physician reported on the presence of inherited atrial fibrillation amongst three brothers. Families such as this demonstrated what is called monogenic inheritance. Monogenic atrial fibrillation is the result of a single disease-causing gene and it follows a typical, linear genetic pattern of inheritance. It tends to cause more severe and early onset of disease.

Over the years a small number of families with familial atrial fibrillation have been identified. In each of these families, a single genetic mutation has been identified in their atrial fibrillation. Monogenic inheritance can be autosomal dominant or recessive and both have been observed in familial AFib.

Researchers have reported on a large family in Uruguay that has evidence of an autosomal recessive pattern of atrial fibrillation. Autosomal recessive means that a person has 2 abnormal copies of a gene, one from each parent. In this family, atrial fibrillation was seen during fetal life. There was also an increased incidence of sudden infant death, ventricular arrhythmias and heart failure.



Autosomal dominant monogenic AFib has also been described. For example, there is a genetic variant which causes a gain of function mutation in potassium channels. Ion channels utilizing potassium, sodium and calcium are what initiate electrical conduction within muscle cells. This mutation is thought to cause and maintain atrial fibrillation because the change in the function of the potassium channels changes the electrical conduction of the atrial muscle cells. It makes them fire faster and then be ready to fire again more quickly than normal heart muscle cells.

Another autosomal dominant form of atrial fibrillation affects the sodium channel gene in the heart. This genetic mutation is often also seen in association with an enlarged and failing heart (dilated cardiomyopathy). In a report of people with this mutation, many of them had early onset atrial fibrillation (average age at diagnosis 28 years) and ultimately went on to develop dilated cardiomyopathy years later.

What is lone atrial fibrillation?

The term lone atrial fibrillation refers to people with atrial fibrillation who do not have structural heart disease or other diseases, like diabetes or high blood pressure, which increase the risk of developing AFib. They have early onset atrial fibrillation, with the majority having their first episode at less than 60 year of age. Up to 30% of atrial fibrillation is thought to be lone atrial fibrillation. A growing body of evidence points to underlying genetic causes for lone atrial fibrillation.

Genetics research and atrial fibrillation

Researchers are still trying to understand the role of atrial fibrillation genetics on the AFib disease process. Research has shown that specific gene mutations and genetic variants are associated with electrical and structural changes in the atria which are thought to contribute to atrial fibrillation.

For example, variants in ion channel genes, which affect potassium channel and sodium channel function, have been associated with electrical conduction changes which are seen with atrial fibrillation. Variants in structural genes have also been associated with atrial fibrillation. The exact relationship between the effects of these genetic variations on the AFib disease process and the potential treatment implications is an area of continued research.

Can information on atrial fibrillation genetics be used to guide treatment?

Treatment of atrial fibrillation currently focuses on addressing modifiable risk factors and treating AFib triggers, which are predominantly in the pulmonary veins. Treating the trigger is done with antiarrhythmic medications and ablation. However, AFib recurrence can be common with both of these approaches. Researchers postulate that, in the future, there will be greater success in treating atrial fibrillation by also addressing the underlying substrate that contributes to maintenance of atrial fibrillation.

It has been proposed that atrial fibrillation is actually an atrial cardiomyopathy. In atrial cardiomyopathy, the upper chambers of the heart do not function normally. It is thought that this abnormal functioning is influenced by various genetic and epigenetic components which cause electrical and structural changes.

As described above, genetic mutations can change potassium and sodium ion channel function which is associated with abnormal atrial electrical conduction. Genetic variations are also associated with structural changes to the substrate of the atria. These changes include increased fibrosis (stiffening), inflammation, autonomic nervous system activation and atrial enlargement. This atrial remodeling increases the probability of AFib initiation and maintenance.

The concept of atrial remodeling as a major contributor to atrial fibrillation has broadened potential treatment options. Researchers have begun to investigate if medications which are traditionally used to treat cholesterol or high blood pressure may have direct effects on the atrial substrate and could potentially help prevent or reverse atrial remodeling. Antioxidants like Vitamin C have also been studied.

Statins are traditionally used to treat high cholesterol. In addition to lowering cholesterol, they also have antioxidant and antiinflammatory effects and have been shown in dog models to decrease AFib triggers and atrial fibrillation inducibility. Vitamin C administered during open heart surgery has been shown to decrease atrial fibrillation after surgery.

Two common types of blood pressure medications are angiotensin converting enzyme inhibitors (i.e. lisinopril, captopril, enalapril, etc.) and angiotensin receptor blockers (i.e. candesartan, valsartan, losartan, etc.). Heart muscle cells have high concentrations of angiotensin receptors. These receptors are involved in atrial electrical conduction. Animal models have shown that blocking angiotensin receptors helps regulate atrial electrical conduction. In humans, it has been observed that both of these medications reduce the incidence of atrial fibrillation after a heart attack or in the presence of heart failure.

Another contributor to atrial fibrillation is the autonomic nervous system. The autonomic nervous system includes the sympathetic (i.e. flight or fight) and parasympathetic (i.e. rest and digest). Both the sympathetic and parasympathetic nervous system have been shown to contribute to the development of atrial fibrillation. Sympathetic activation leads to the release of stress hormones. This increases inflammation and can lead to atrial fibrillation. Studies have shown that exercise-induced atrial fibrillation may be related to sympathetic activation. The parasympathetic nervous system is thought to contribute to atrial fibrillation in young people with structurally normal hearts. The vagus nerve is an important part of the parasympathetic nervous system. In animal studies, vagal stimulation has been shown to change patterns of electrical conduction in the heart and thereby contribute to atrial fibrillation.

Can atrial fibrillation genetic research influence the future of atrial fibrillation treatment?

CALCULATE YOUR RISK

A number of genetic variants have been implicated in the development of atrial fibrillation. Researchers have investigated how these mutations contribute to the atrial fibrillation triggers and substrate which are responsible for the initiation and maintenance of AFib.

In the era of personalized medicine, knowing the underlying genetic precursors for atrial fibrillation may help with risk stratification and could potentially help tailor treatment strategies. Since we cannot yet treat the genetic mutations themselves, treatments which target the effects of the mutations may lead to significant improvements in atrial fibrillation treatment success.