

Genetic Testing to Detect Atrial Septal Defect with Atrioventricular Conduction Block (ASD-AV Block)



What is an Atrial Septal Defect?

An Atrial Septal Defect (ASD), sometimes called a “hole in the heart”, is an abnormal opening between the two upper chambers of the heart (called the right and left atrium). ASDs are a birth defect that occurs in about 1 of 1,000 people.¹

Unlike many birth defects (also called congenital defects), ASDs cause few symptoms in the young. Therefore, ASDs can easily go undetected in children, unless found during routine exams. However, ASDs can cause gradual, irreversible damage to the heart and lungs and eventual heart failure if not treated early enough. ASDs can also lead to strokes.^{2,3}

What causes Atrial Septal Defects?

ASDs result from defective development of the heart prior to birth. Some ASDs are familial and caused by a genetic defect. Mutations in a gene called NKX2-5 are responsible for up to 20% of such familial ASDs.⁴ If a patient has a familial ASD due to a mutation in NKX2-5, about half of his or her children will also have ASDs. In contrast to other types of ASDs, NKX2-5-related ASDs are often associated with an additional defect, namely a block in the heart's conduction system – the system that controls the beating of the heart. This second NKX2-5-related defect, which is called atrioventricular (AV) block, can lead to sudden, life-threatening disturbances in the heart's rhythm. Identification of a mutation in NKX2-5 as the underlying cause of an ASD can therefore alert patient and physician to the risk of AV block later in life.⁵

How are Atrial Septal Defects and Atrioventricular Block diagnosed?

ASDs have characteristic signs that can be observed by a doctor during a routine physical exams. These signs include altered heart sounds, a heart murmur, and subtle changes in the position and size of the heart and the major blood vessels. A diagnosis can be confirmed by tests such as a chest X-ray or a heart MRI. However, the absence of these signs does not guarantee that no ASD is present. In addition, these signs may simply be missed during routine physical exams. About half of all individuals with ASDs are not diagnosed until adulthood, after the ASDs have started to cause symptoms.²

Usually, symptoms from untreated ASDs first occur in early adulthood. The most common initial symptoms are shortness of breath, fatigue, and reduced ability to exercise. Less commonly, fainting spells or heart palpitations – sensations of forceful or irregular heartbeats - may be the initial symptoms. Older untreated patients may experience cyanosis (a bluish coloring of the skin caused by a lack of oxygen in the blood), stroke, or heart failure.²

The characteristic signs of AV block - a slow or irregular heartbeat and electrical disturbances detectable by an electrocardiogram (EKG) - typically don't appear until early adulthood. AV block may lead to such symptoms as dizziness, lightheadedness, fainting spells, or even sudden death. In a patient with both ASD and AV Block, the symptoms of AV Block may appear before or after the symptoms of the ASD.⁵



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How are Atrial Septal Defects and Atrioventricular Block treated?

The key to effective treatment of both ASD and AV Block is early diagnosis. ASDs are treated by closing the opening – this can be done either by open-heart surgery or by insertion of a closing device into the hole through a blood vessel. If an ASD is closed while the patient is still young and presymptomatic, the prognosis is excellent. However, closure is often less effective in older patients who have already experienced symptoms, because the gradual damage to the heart caused over the course of decades cannot be undone, even if the ASD is closed. It is also important to realize that patients with familial NKX2-5-related ASDs remain at risk of developing AV Block even after successful closure of their ASDs.^{2,5,6}

Patients with AV Block may be at high risk of life-threatening disturbances in the heart's rhythm. It is important that such patients receive regular exams to determine the severity of their AV Block. Severe AV Block is treated by implantation of a pacemaker; a device that controls the heart's rhythm and prevents disturbances. After pacemaker implantation, the prognosis of patients with severe AV Block is generally good.^{4,7}

Genetic testing can aid in the early identification of Atrial Septal Defects with Atrioventricular Block.

Since mutations in NKX2-5 have been linked to ASD-AV Block, detection of a disease-causing mutation in this gene allows diagnosis of ASD-AV Block. Such a diagnostic test that looks for a mutation in a gene is referred to as a "genetic test". In contrast to other diagnostic methods, genetic testing can allow diagnosis of a disease before any symptoms develop. Finding a mutation in NKX2-5 in a patient with ASD can also alert patient and physician to the risk of AV Block later in life. Once a disease-causing mutation has been found in one patient in a family, genetic testing can easily identify other affected family members by screening for presence of the same (familial) mutation. Affected family members can then be rigorously examined for ASDs, and regularly monitored for the presence of AV Block, so that ASDs can be closed before symptoms develop and a pacemaker can be implanted at the first sign of severe AV Block.^{6,7}

Importantly, genetic testing can also identify unaffected family members, who then no longer have to worry about having ASD or AV Block or about passing these conditions on to their children.

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