

Facts on *NKX2-5* and Atrial Septal Defect with Atrioventricular Block

- **Atrial septal defects (ASDs) affect about 1 in 1000 individuals, account for ~10% of all congenital heart defects, and are one of the most prevalent congenital heart defects seen in adults.**
[Warnes CA, et al. \(2001\) J. Am. Coll. Cardiol. 37\(5\):1170-1175](#)
- **ASDs are usually well tolerated in children and are often not noticed until the development of symptoms in adulthood, after irreversible damage to the heart and lungs has already occurred or after movement of small blood clots through the ASD has led to stroke.**
[Webb G, et al. \(2006\) Circ. 114:1645-1653](#); [Epstein JA, et al. \(2005\) Circ. 112:592-597](#)
- **8-19% of familial and up to 4% of sporadic ASDs are associated with mutations in the *NKX2-5* gene.**
 - Familial *NKX2-5*-related ASDs are highly penetrant and characteristically associated with AV block.
 - Sporadic *NKX2-5*-related ASDs have low penetrance and are typically not associated with AV block.
 - *NKX2-5* mutations are also associated with other congenital heart defects, including tetralogy of Fallot.
[Hirayama-Yamada K, et al. \(2005\) Am. J. Med. Genet. 135A:47-52](#); [Sarkozy A, et al. \(2005\) J. Med. Genet. 42\(2\):e16](#); [McElhinney D, et al. \(2003\) J. Am. Coll. Cardiol. 42:1650-1655](#)
- **The initial clinical manifestation of familial ASD with AV block may be related to either the ASD or the AV block.**
 - Individuals with ASDs usually present initially with dyspnea, fatigue, and/or exercise intolerance. Less common initial manifestations include palpitations and syncope.
[Webb G, et al. \(2006\) Circ. 114:1645-1653](#)
 - The most common initial presenting symptoms of AV block are dizziness, lightheadedness, and syncope.
[Smits JP, et al. \(2005\) Europace 7:122-137](#)
- **Without proper treatment, the prognosis of individuals with significant ASDs and/or AV block is often poor.**
 - Most adults with ASDs will develop symptoms, often in the third or fourth decade of life. If not treated, adults with ASDs are at high risk of atrial arrhythmias, congestive heart failure, stroke, and Eisenmenger's syndrome.
[Webb G, et al. \(2006\) Circ. 114:1645-1653](#)
 - Individuals with AV block are at high risk of life-threatening cardiac arrhythmias.
[Smits JP, et al. \(2005\) Europace 7:122-137](#)
- **If diagnosed early, proper treatment can lead to more favorable prognoses in patients with ASD and/or AV block.**
 - Patients with ASDs who undergo surgical or percutaneous device closure while young have a very favorable prognosis.
[Roos-Hesselink JW, et al. \(2003\) Eur Heart J. 24:190-197](#)
 - After a diagnosis of AV block, pacemaker implantation can prevent the development of life-threatening cardiac arrhythmias.
[Michaelsson M, et al. \(1995\) Circ. 92:442-449](#)
- **Genetic testing can alert patients with ASDs to the risk of AV block later in life, allow early diagnosis and treatment of family members of patients with *NKX2-5*-related ASDs, and identify family members who do not harbor the mutation and are not at risk.**