REVIEW ARTICLE

Atrial Septal Defects and Genetic Linkage

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Definition and Overview

Atrial Septal Defects or ASD's are congenital non-physiological communications between the two atrias of the heart, allowing for shunting between the left systemic circulation and the right pulmonary one [1]. They constitute 10–15% of congenital cardiac defects, and up to 40% of congenital defects presenting in adulthood. Most children with ASD's are asymptomatic but as they grow older the progressive left to right shunting results in right-sided volume overload of the heart. This can lead to long term complications such as pulmonary hypertension, heart failure and atrial arrhythmias. Therefore, older ASD patients may experience dyspnea on exertion, fatigue and palpitations [2]. Diagnosis is usually carried out by echocardiography and treatment is performed through transcatheter device closure or surgical repair. ASD's are anatomically categorized by the affected atrial septum structure, with ostium secondum being the most common form. Other less prevalent subtypes, include ostium primum and sinus venosus [3].

Moreover, ASD's are amongst the most common types of congenital heart diseases, being the second most frequent form after ventricular septal defects [4]. They account for 10-15% of all CHD's globally and have a high current prevalence rate of 1.6 cases per 1000 live births in 2019 [5]. Nonetheless, given its asymptomatic nature, ASD's remain the most common type of CHD's that stay undetected during childhood, where approximately up to 40% of newly diagnosed cases are discovered after 30 years of age [6]. Therefore, discovering ways to identify and diagnose the condition early on is of paramount important to prevent any long-term complications and treat the condition before it progresses.

Although most ASD's occur sporadically and in isolation, many of them can have genetic linkages or can be part of other syndromes that have a genetic correlation. The atrial septum is one of the cardiac structures that is extremely susceptible to environmental or genetic factors [7]. Several clinical studies have highlighted the impact of different proteins and transcription factors on the atrial septogenesis process. The main genes implicated in non-syndromic ASD formations are NKX2.5 and GATA4 [8]. However, ASD's can also be part of various syndromes, such as Holt-Oram and Lutembacher Syndromes [9].

Types of ASD's

- Ostium secundum defects (70–80%): These are the most frequent kind of ASD and involve the fossa ovalis. It is important to note that this class of defect should not be mistaken with a patent foramen ovale; which affects approximately 25% of individuals and arises when the septum primum to the left of the foramen ovale incompletely merges with its sides in the postnatal period. This leads to the phenomenon called 'probe patency.' Secundum ASDs can affect the Inferior Vena Cava and typically occurs

due to the formen ovale expanding, insufficient development of the septum secundum or disproportionate absorption of the septum primum. Mitral Valve Prolapses are also present in individuals with ostium secundum ASDs in approximately 10 to 20% of people [10].

- Ostium primum defects (20%): Defects in the ostium primum are frequently classified as atrioventricular septal defects, however, they can occasionally be categorized as atrial septal defects. Ostium primum defects are not as frequent as ostium secundum defects. This classification of defect is typically linked with Down syndrome. By definition, this defect is associated with cleft mitral valve and is a type of AV defect [11].
- Sinus venosus defects (10%): The sinus venous ASD is a kind of atrial septum defect. This defect can either affect the venous inflow of either the superior or inferior vena cava. Ones that involve the superior vena cava contribute to 2-3% of all interatrial communication. These types are situated at the junction of the superior vena cava and the right atrium. Instead of the normal drainage of the pulmonary veins into the left atrium; this defect is typically associated with drainage of the right-sided pulmonary veins into the right atrium. Around 90% of the sinus venosus ASD's are associated with partial anomalous pulmonary venous drainage [7].
- Coronary sinus defects (<1%): Defects in the tissues surrounding the coronary sinus can lead to various communications between the coronary sinus and the left atrium. This is also known as an unroofed coronary sinus. In this condition there is always a concurrent persistent left superior vena cava [12]. All the types of defects can clearly be seen in figure 1.

Pathophysiology and Mechanism

In normal individuals, the left sections of the heart are under higher pressures compared to the right sections because the left ventricle has to produce a sizeable amount of pressure to pump blood throughout the whole human body, while the right ventricle only requires to produce enough pressures to pump blood to the adjacent lungs [13].

When dealing with a large ASD of more than 9mm, a clinically significant shunt may occur from the left system to the right system. The shunting of blood occurs from the left atrium to the right atrium, specifically. The extra blood that is shunted from the left atrium to the right atrium will result in a volume overload of the whole right system, including both the right atrium and right ventricle. If left untreated, this state can cause a significant enlargement of the whole right side of the heart which will ultimately result in heart failure [14].

Any mechanism that leads to an increase in the pressure of the left system can further exacerbate the left to right shunt. This includes hypertension, where the pressure in the left ventricle increases during ventricular systole to enable the opening of the aortic valve. Another example is coronary artery disease which can also stiffen the left ventricle, increasing its filling pressure during diastole. The left to right shunt caused by ASD's increases the overall filling pressures or preload of the right side of the heart, therefore forcing the right ventricle to pump out more blood compared to the ventricle on the left side. This continuous overloading of the right section of the heart leads to

a direct overload of the complete pulmonary vasculature. This can directly result in pulmonary hypertension later down the line [11].

Pulmonary hypertension will increase the afterload that faces the right ventricle. This means that the right ventricle will now have to generate increased pressures to overcome this increased afterload. Subsequently, right ventricular failure will occur as the right ventricle will become dilated and its systolic function will decrease [12].

If the ASD is not treated, then the pulmonary hypertension will progress further and the pressures of the right system will become higher than that of the left system of the heart. This significant switch of the pressure gradients will cause the shunting through the ASD to reverse, becoming a right to left shunt instead. This process is known as Eisenmenger's Syndrome. Once this reversal occurs, part of the deoxygenated blood gets pumped to the left side of the heart and out to the body, causing severe cyanosis which significantly jeopardizing the patient's health condition [13].

Moreover, in rare cases, the open connection between the atrias may also allow venous emboli to travel into the arterial circulation causing cerebral or systemic thromboembolic events in a process called, paradoxical embolization [2].

Genetic Linkages of ASD's

ASD's mostly occur in sporadic forms. However, the atrial septum is one of the cardiac structures most sensitive to environmental or genetic factors. Therefore, many affected individuals have some sort of family history of septal defects or other congenital heart problems. Current research and evidence highlight the implication of various genes and syndromes in the formation of ASD's. Therefore, it is of vital importance to be aware of these genetic linkages in order to encourage early detection, enable quick treatment and halt disease progression. Some cases of ASD appear to run in families. In such rare cases, the two forms, ostium primum and ostium secundum defects seem to be inherited as autosomal dominant genetic traits [1].

The genes and syndromes that seem to be associated with the formation of ASD's are:

1. **NKX2.5**

   Mutations in the *NKX2.5* gene, which is a member of the NK-2 category of homeobox genes, have been associated with autosomal dominant ASD's occurring alongside atrioventricular blocks. It is also associated with around 1-4% of sporadic ASD's. Multiple studies have proved the relationship between this genetic mutation and ASD's. A study examining more than 6 family members across 4 generations is an example of this correlation. 2 sisters had ASD's and mitral insufficiency, while the 4 others had ASD's with conduction abnormalities [16].

   Another study also proves the presence of an autosomal dominant mutation that results in the formation of ASD's alongside AV blockage. Around 10 family members across 4 generations have been found to have ASD's with PR prolongation. There conditions were discovered following either catheterizations, surgery, history or examinations. After thorough genetic

testing, they all had mutations in the NKX2.5 genes [17].

Moreover, another systematic study proves the link between NKX2.5 Mutations and ASD's. A review of the provided literature showed around 59 different NKX2-5 mutations in around 202 patients. Mutations were found in all familial cases. The wide majority of patients, around 74% were found to have ASD's alongside conduction defects [18].

2. **GATA4**

Mutations to the GATA4 gene has been shown to cause ASD's associated with other congenital heart diseases but without conduction defects or noncardiac abnormalities. Up to 3 families with autosomal dominant ASD's and without conduction abnormalities have been identified to have heterozygous mutations in the GATA4 zinc finger transcription factor gene. These individuals with these specific mutations have also been shown to have other concurrent congenital heart diseases, such as pulmonary vein stenosis [19].

3. **TLL1**

Mutations in the TLL1 Gene have also been shown to cause ASD's alongside intraarterial septum aneurysms and cardiac arrythmias. Studies have shown a relationship, but more evidence needs to be collected to fully support this correlation [20].

4. **Holt-Oram Syndrome & TBX5 Gene**

One of the most documented syndromes that is associated with ASD's is the Holt-Oram Syndrome. This is an autosomal dominant condition that affects patients' bone structure of their upper limbs and causes cardiac abnormalities. The syndrome can include the absence of a forearm radial bone, an ASD or heart block. It has a prevalence rate of 1 in 100,000 people in 2018 [21].

All patients with Holt-Oram syndrome have, as a minimum, one abnormal wrist bone that is usually detected via X-RAY. There are many bone abnormalities that are associated with this syndrome and can widely vary in severity. This includes a missing thumb, a triphalangeal thumb, unequal or underdeveloped upper limbs, clavicular abnormalities or scapular defects. These abnormalities can affect one or both sides of the body, however research shows that the left side is much more greatly affected [14].

Around 75% of patients with Holt-Oram syndrome also have some sort of congenital heart defect. The most common heart defect found in the majority of patients is an ASD. Patients of this syndrome have also been found to have cardiac conduction abnormalities leading to a wide variety of bradycardias, fibrillations and nodal blockages. Nonetheless, the most common cardiac abnormality in these patients is an ASD [9].

After many years of analyses and investigations, it has been found that mutations in the TBX5 gene causes the

Holt-Oram Syndrome. This gene produces a specific protein that is crucial for the fetal physiological development of both the cardiac tissues and the upper musculoskeletal system. Studies have shown that this mutation has an autosomal dominant inheritance pattern, which explains the prominent prevalence of this condition across many generations in the affected families [8].

5. **Lutembacher Syndrome**

Another syndrome that involves ASD's is the Lutembacher Syndrome. Patients with this syndrome have a long-standing ASD alongside an acquired mitral stenosis. The ASD is classically of an ostium secundum type and the mitral stenosis is commonly rheumatic instead of congenital. Studies have shown that the ASD is actually protective for these patients because it provides a conduit to decompress the left atrium and the pulmonary vasculature. Nonetheless, the mitral stenosis can still worsen the prognosis because it adds strain onto the right side, increasing right ventricular work and overall pulmonary blood flow. This subsequently can result in pulmonary hypertension later down the line. Central venous pressure is also increased in patients with this syndrome. Many studies have concluded that Lutembacher Syndrome is inherited in an autosomal dominant fashion and therefore can affect multiple family members across several generations [22].

6. **Down Syndrome**

Finally, patients with Down syndrome have higher rates of ASDs. As many as one half of Down syndrome patients have some type of septal defect. Atrial septal defect was the most common isolated cardiac defect (33% of the total) and ostium secundum ASD was the most frequent type [23].

Conclusion

ASD's constitute a great portion of congenital heart diseases around the world, thus it is of vital importance to shed light on the genetic linkages associated with the condition. Doing so could possibly lead the way to increase its early detection and treatment in other family members, preventing the late complications of the condition.

Figures:

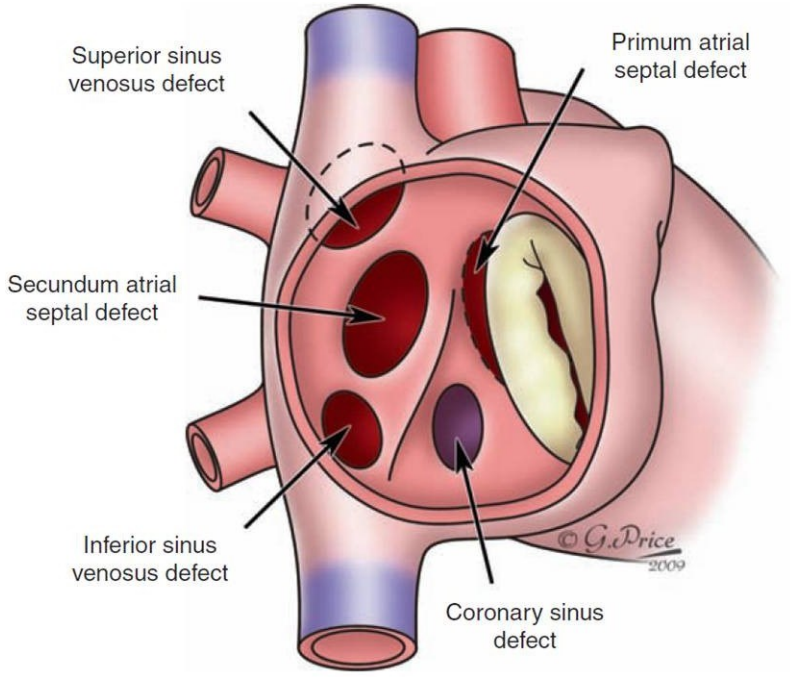

Figure (1): Detailed Annotation of the Types of Atrial Septal Defects [24].

References:

1. Celermajer, D., 2017. Atrial septal defects: even simple congenital heart diseases can be complicated. *European Heart Journal*, [online] 39(12), pp.999-1001. Available at: <https://academic.oup.com/eurheartj/article/39/12/999/4675085> [Accessed 17 November 2021].
2. Thompson, E., 2016. Atrial septal defehttps://journals.lww.com/jaapa/fulltext/2013/06000/atrial_septal_defect.16.aspxct. *Journal of the American Academy of Physician Assistants*, [online] 26(6), pp.53-54. Available at: <https://journals.lww.com/jaapa/fulltext/2013/06000/atrial_septal_defect.16.aspx> [Accessed 17 November 2021].
3. Syamasundar, P., 2012. Atrial Septal Defect - A Review. *INTECH*, [online] Available at: <https://www.intechopen.com/books/atrial-septal-defect/atrial-septal-defects-a-review> [Accessed 17 November 2021].
4. Xuan Tuan, H., The Phuoc Long, P., Duy Kien, V., Coung, L. and Van Son, N., 2019. Trends in the Prevalence of Atrial Septal Defect and Its Associated Factors among Congenital Heart Disease Patients in Vietnam. *Journal of Cardiovascular Development and Disease*, [online] 7(1), p.2. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151091/> [Accessed 17 November 2021].
5. McDaniel, N., 2011. Ventricular and Atrial Septal Defects. *Pediatrics in Review*, [online] 22(8), pp.265-270. Available at: <https://pedsinreview.aappublications.org/content/22/8/265> [Accessed 17 November 2021].
6. Adiele, D., Arodiwe, I., Chinawa, J., Eze, J., Gouthami, V., Murthy, K., Obidike, E. and Ujunwa, F., 2014. Atrial septal defects: Pattern, clinical profile, surgical techniques and outcome at Innova heart hospital: A 4-year review. *Nigerian Medical Journal*, [online] 55(2), p.126. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4003714/> [Accessed 17 November 2021].
7. Lage, K., Greenway, S., Rosenfeld, J., Wakimoto, H., Gorham, J., Segre, A., Roberts, A., Smoot, L., Pu, W., C. Pereira, A., Mesquita, S., Tommerup, N., Brunak, S., Ballif, B., Shaffer, L., Donahoe, P., Daly, M., Seidman, J., Seidman, C. and Larsen, L., 2012. Genetic and environmental risk factors in congenital heart disease functionally converge in protein networks driving heart development. *Proceedings of the National Academy of Sciences*, [online] 109(35), pp.14035-14040. Available at: <https://www.pnas.org/content/109/35/14035> [Accessed 17 November 2021].
8. Posch, M., Perrot, A., Berger, F., Özcelik, C. and Stewart, J., 2009. Molecular genetics of congenital atrial septal defects. *Clinical Research in Cardiology*, [online] 99(3), pp.137-147. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830584/> [Accessed 17 November 2021].
9. Sarkozy, A., Conti, E., Neri, C., Agostino, R. and Digiliono, N., 2017. Spectrum of atrial septal defects associated with mutations of NKX2.5 and GATA4 transcription factors. *Journal of Medical Genetics*, [online] 42(2), pp.e16-e16. Available at: <https://jmg.bmj.com/content/42/2/e16> [Accessed 17 November 2021].
10. Kuijpers, J., Mulder, B. and Bouma, B., 2015. Secundum atrial septal defect in adults: a practical review and recent developments. *Netherlands Heart Journal*, [online] 23(4), pp.205-211. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4368528/> [Accessed 18 November 2021].

11. Briggs, L., Kakarla, J. and Wessels, A., 2012. The pathogenesis of atrial and atrioventricular septal defects with special emphasis on the role of the dorsal mesenchymal protrusion. *Differentiation*, [online] 84(1), pp.117-130. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3389176/> [Accessed 18 November 2021].
12. Sivakumar, K., Quadros, S., Pavithran, S. and Agrawal, R., 2018. Coronary sinus atrial septal defect without persistent left superior vena cava: Three-dimensional imaging of a rare defect. *Annals of Pediatric Cardiology*, [online] 11(1), p.103. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5803963/> [Accessed 18 November 2021].
13. Le Glaun, L., 2021. *pathophysiology of atrial septal defects ncbi*. [online] NCBI. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6174151/> [Accessed 18 November 2021].
14. Martin, S., 2021. *Atrial Septal Defects – Clinical Manifestations, Echo Assessment, and Intervention - Seth S. Martin, Edward P. Shapiro, Monica Mukherjee, 2014*. [online] SAGE Journals. Available at: <https://journals.sagepub.com/doi/10.4137/CMC.S15715> [Accessed 18 November 2021].
15. Savis, A., 2018. Echocardiographic approach to catheter closure of atrial septal defects: patient selection, procedural guidance and post-procedural checks. *Echo Research and Practice*, [online] 5(2), pp.R49-R64. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5937057/> [Accessed 18 November 2021].
16. Weikel, A., 2021. Autosomal dominant hereditary atrial septal defect with heart conduction defects and mitral valve insufficiency. *CTS*, [online] 12(3), p.201. Available at: <https://pubmed.ncbi.nlm.nih.gov/960976/> [Accessed 18 November 2021].
17. Lynch, H., 1978. Hereditary Atrial Septal Defect. *American Journal of Diseases of Children*, [online] 132(6), p.600. Available at: <https://pubmed.ncbi.nlm.nih.gov/148839/> [Accessed 18 November 2021].
18. Ellesøe, S., Johansen, M., Bjerre, J., Hjortdal, V., Brunak, S. and Larsen, L., 2015. Familial Atrial Septal Defect and Sudden Cardiac Death: Identification of a NovelNKX2-5Mutation and a Review of the Literature. *Congenital Heart Disease*, [online] 11(3), pp.283-290. Available at: <https://pubmed.ncbi.nlm.nih.gov/26679770/> [Accessed 18 November 2021].
19. Yang, Y., Wang, J., Liu, X., Chen, X., Zhang, W. and Wang, X., 2013. Mutation spectrum of GATA4 associated with congenital atrial septal defects. *Archives of Medical Science*, [online] 6, pp.976-983. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902718/> [Accessed 18 November 2021].
20. Stańczak, P., Witecka, J., Szydło, A., Gutmajster, E., Lisik, M., Augusciak-Duma, A., Tarnowski, M., Czekaj, T., Czekaj, H. and Sieroń, A., 2008. Mutations in mammalian tolloid-like 1 gene detected in adult patients with ASD. *European Journal of Human Genetics*, [online] 17(3), pp.344-351. Available at: <https://pubmed.ncbi.nlm.nih.gov/18830233/> [Accessed 18 November 2021].
21. Vanlerberghe, C., Jourdain, A., Ghoumid, J., Frenois, F., Mezel, A., Vaksmann, G., Lenne, B., Delobel, B., Porchet, N., Cormier-Daire, V., Smol, T., Escande, F., Manouvrier-Hanu, S. and Petit, F., 2018. Holt-Oram syndrome: clinical and molecular description of 78 patients with TBX5 variants. *European Journal of Human Genetics*, [online] 27(3), pp.360-368. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articl

es/PMC6460573/> [Accessed 18 November 2021].
22. Kulkarni, S., Sakaria, A., Mahajan, S. and Shah, K., 2012. Lutembacher's syndrome. *Journal of Cardiovascular Disease Research*, [online] 3(2), pp.179-181. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3354470/> [Accessed 18 November 2021].
23. Yoon, K., 2019. Atrial Septal Defect with Down Syndrome and Postsurgical Pulmonary Hypertension. *Journal of Cardiovascular Imaging*, [online] 27(4), p.254. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6795566/> [Accessed 18 November 2021].
24. Sridharan, S., Price, G., Tann, O. and Clover, J., 2021. *Detailed Annotation of the Types of Atrial Septal Defects*. [online] EPOS. Available at: <https://epos.myesr.org/posterimage/esr/ecr2012/112981/mediagallery/389379> [Accessed 7 December 2021].