How Important are Genetics in the Management of Thoracic Aortic Aneurysms and Acute Aortic Syndromes? What do we Know Today?

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Citation: Syrengela A, Shahjahan S, Bulut HI, Ttofi I, Djordjevic J, et al. (2023) How Important are Genetics in the Management of Thoracic Aortic Aneurysms and Acute Aortic Syndromes? What do we Know Today?. J Surg 8: 1818 DOI: 10.29011/2575-9760.001818

Received Date: 20 May, 2023; Accepted Date: 24 May, 2023; Published Date: 26 May, 2023

Abstract
Thoracic Aortic Aneurysm pertains to the segment of the aortic organ with a weakened wall resulting in dilation or even rupture. Through many years of research, this condition is now associated widely with mutations of specific genes—most significantly, FBN1 and TGFBR1/TGFBR2 genes resulting in Marfan Syndrome and Loeys-Dietz Syndrome, respectively. These mutations were found to affect the degree of clinical manifestations and the decision on aortic surgery. In this review, we discussed the effect of genetic markers on aortic aneurysms and their importance in the modern world when considering primary prevention, prophylactic treatment, and counseling of both patients and their families.

Keywords: Aortic surgery; Genetics; Loeys-Dietz Syndrome; Marfan Syndrome; Mutation; Thoracic Aortic Aneurysms

Introduction
Thoracic Aortic Aneurysm (TAA) is a dangerous and even life-threatening condition, difficult to diagnose before dissection and rupture occur. It is believed that 95% of TAA are asymptomatic before complications arise. Less than 50% of symptomatic patients admitted to the emergency department are diagnosed before death [1]. There is an increasing incidence of thoracic aortic aneurysms, usually found incidentally when performing imaging studies for other reasons [2]. There is increased mortality with age, female gender, and present comorbidities—e.g., hypertension and smoking [3]. The complications of an aneurysm, including rupture and dissection, resulting in admission to hospitals with a mortality of 39.4%. In recent years, admissions have increased due to elective aortic repair performance that eventually decreases the major in-hospital complications with mortality of 6.2%, as well as the length of patients staying in the hospital compared to acute aortic syndromes' admissions [2].

It was believed that TAAs are the result of extensive, persistent high blood pressure and biomechanical stress. After conducting further investigations in recent years, a strong genetic correlation was revealed. Thoracic aneurysms are divided into syndromic— which includes clinical manifestations not only from the aorta but also from other systems— and non-syndromic. For further categorization, they are subdivided into familial, where other family members are also diagnosed with the same mutations, and non-familial or sporadic. (Table 1) [4] Given the lethal consequences that an aneurysm may have, it is of utmost.
importance to identify patients who are at risk and to provide preventative repair before it develops dissection and rupture.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Frequency (%)</th>
<th>Age of Dissection</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan Syndrome Gene FBN1</td>
<td>16%</td>
<td>38 y.o</td>
<td>15/100,000</td>
<td>[4,5]</td>
</tr>
<tr>
<td>Loeys-Dietz Syndrome- Genes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGFBR1</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGFBR2</td>
<td>4%</td>
<td>Early ages- as early as 3 months old</td>
<td>52 Families</td>
<td>[4,5]</td>
</tr>
<tr>
<td>SMAD3</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGFB2 (8)</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos Syndrome - Gene COL3A1</td>
<td>6%</td>
<td>29y.o</td>
<td>1/100,000</td>
<td>[4,5]</td>
</tr>
<tr>
<td>BAV - Gene NOTCH</td>
<td>12%</td>
<td>56y.o</td>
<td>1-2%</td>
<td>[4,5]</td>
</tr>
<tr>
<td>Gene ACTA2</td>
<td>12-21%</td>
<td>Type A dissection-36y.o</td>
<td></td>
<td>[4,6,7]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type B dissection-27y.o</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Syndromic Thoracic Aortic Aneurysms.**

**Aortic Organ**

The aorta is the largest blood vessel in the human body. Its paramount function is delivering oxygenated blood from the left ventricle to the rest of the body. It has four segments, the aortic root, the ascending aorta, the aortic arch, and the descending aorta. Descending aorta is further subdivided into the thoracic and the abdominal aorta. The ascending aorta originates from the left ventricle with a diameter of 2.5cm. It continues as aortic arch at the level of the second sternocostal articulation, which follows an upward, backward, and left pathway as it passes in front of the trachea. Then it moves backward and to the left of the trachea. From the level of T4 vertebra, it is now called the descending aorta until the bifurcation of the common iliac arteries [8,9]. Microscopically three layers surround the aorta- innermost tunica intima, middle tunica media, and externally tunica adventitia. Tunica intima is composed of endothelial cells and an elastic lamina at the outer border, necessary for the blood to flow smoothly without forming thrombi. Tunica media consists of smooth muscle cells and elastic fibers, components significant for the proper expansion and contraction while the blood is pumped out of the heart. The tunica adventitia is the outermost layer of the aortic wall with collagen, fibroblasts, and mast cells that provide support and structure to the aorta [8].

The development of the thoracic aorta and the great vessels supplying the head and neck is a complex process of events that begins on the 20th to 22nd day of gestation. Angioblasts fuse together and form a network of endothelial channels, which gives rise to paired ventral and dorsal aortae and aortic arches, respectively. The ventral aortae combine to form an aortic sac, which communicates with the heart via the truncus arteriosus. Consequently, the aortopulmonary septum divides the truncus arteriosus into the ascending aorta and the pulmonary trunk. The dorsal aortae fuse together partially to form a single dorsal aorta, the precursor of the descending aorta. In addition, there are six aortic arches also called pharyngeal arches which communicate with both the aortic sac and the dorsal aorta. They do not develop simultaneously and regress at different paces. The fourth arch is remarkable in this case as it contributes to the formation of the true aortic arch [16].

Certain factors change the anatomy of the aorta and result in its pathology (Table 2).
The aorta undergoes vascular aging, a process that starts from birth and is accelerated during middle age. The changes affect the thickness of the aortic wall and the size of the vascular lumen [9]. The elastic properties of the aortic wall begin to regress, and the vessel will become stiffer. This results from the loss of the elastic fibers and the remodeling of the collagen in the tunica media due to mechanical stress. In addition, as age progresses, the tunica media remains constant, while the tunica intima increases its width as smooth muscle cells migrate from the tunica media, also known as smooth muscle cell migration [8]. According to European Guidelines on the diagnosis and treatment of aortic diseases (2010), the aortic diameters in healthy individuals do not normally exceed 40 mm and gradually decrease. The rate of aortic expansion is about 0.9 mm in men and 0.7 mm in women for each decade of life [11].

### Atherosclerosis

Atherosclerosis is a condition that is associated with advanced age and lifestyle habits, for example smoking, consumption of lipid-rich food and obesity. However, it can also be attributed to genetic hypercholesterolemia, with a frequency of 1:500. The atherosclerotic plaque located in the tunica intima may rupture creating a peripheral embolism or it may penetrate the tunica media forming a dissection or false aneurysm. The aneurysm attributed to atherosclerosis is a result of the progressive decreasing width of the tunica media due to the release of proteases. [12].

### Hypertension

Hypertension is a condition associated with increased wall stress. It is the leading cause of aortic dissection (85%), especially in older patients, affecting both the ascending and the descending aorta [13].

### Inflammatory Disease

Chronic inflammation of the aortic wall and, in some cases extending to the periaortic space are conditions called aortitis and periaortitis, respectively. Aortitis is associated with inflammatory damage to the elastic properties and tissue oedema [14] - of all three layers of aortic wall. It can affect any part of the aorta and expand through the larger vessels. Aortitis can result from non-infectious factors, including large vessel vasculitis and rheumatological disorders (for example, lupus erythematosus, rheumatoid arthritis, Bechet disease, ankylosing spondylitis). In giant cell arteritis and Takayasu arteritis, there is a thickening of intimal layer, and disruption of the media along with aneurysms in larger arteries like the thoracic aorta. There is also IgG-4 aortitis that affects mostly the aortic arch and accounts for most cases of non-infections aortitis [15]. Aortitis can also result from infectious factors as a complication to infective endocarditis (also from Salmonella, Staphylococci, and Pneumococci infection). Furthermore, syphilitic aortitis, caused by Treponema pallidum is a characteristic of the third stage of the disease. It affects the tunica media causing necrosis with giant cells and disruption of the layer, forming a sacciform aneurysm in 40% of patients [13], which is very susceptible to rupture [12].

### Neoplasms

Aortic neoplasms can be categorized as primary or secondary. In the first category, primary sarcoma is included, which arises from the tunica intima. In the latter category, carcinoma of the esophagus may infiltrate the aorta due to the close anatomical relation between two organs and cause massive gastrointestinal hemorrhage.

### Thoracic Trauma

Penetrating and blunt trauma is responsible for the direct rupture of the aorta. The most common location is the aortic arch due to its connection with the pulmonary artery with the arterial ligament. When stretching occurs, most likely, a pseudoaneurysm will form, which will eventually rupture [12].

### Pregnancy

Pregnancy is a state that tends to affect both the stress towards
the aorta and its structure. During that time, there is an increase in maternal blood volume, stroke volume, heart rate, cardiac output, and eventually blood pressure. These changes take place from the first trimester, but they are eminent in the third trimester and peripartum. As a result, there is increased wall tension of the aorta and greater shear forces. It is still controversial whether the wall is weakened during pregnancy [16].

## Associated Genes

The aortic tissue of patients with TAA exhibits abnormalities in the Extracellular Matrix (ECM) in the aortic media and the smooth muscle cells along with the TGF-β signaling pathway. The genetic mutations and the proteins they encode have been found to play an essential role in the disruption of the homeostasis of the ECM, the smooth muscle cells, and the decrease, or increase in certain cases, of the TGF-β pathway [17] (Figure 1).

**Gene FBN1**

FBN1 encodes for one member of the family of fibrillins, Fibrillin-1. Fibrillins are glycoproteins, which are part of the microfibrils of the ECM. Their roles include interaction with elastin in elastic tissues and binding to latent transforming growth factor β binding proteins (LTBPs). [18] Mutations in FBN1 are linked to both syndromic, Marfan Syndrome (MFs), and non-syndromic TAAD. MFs an autosomal dominant condition. The loss of function of FBN1 results in abnormal sequestration of TGF-β and an increase of its activity which has a strong correlation with aortic aneurysms.[5] As far as sporadic TAAs are concerned, the prevalence of this mutation is calculated to be 3.9% [19].

**Genes TGFBR1, TGFBR2, SMAD3, TGFB2**

Mutations in Transporting Growth Factor β receptor I (TGFBR1) and Transporting Growth Factor β Receptor II (TGFBR2) were the first to be linked to Loeys-Dietz syndrome (LDS), an autosomal dominant disorder and are classified as LDS Type I and Type II respectively. They are the most common subtypes. The activation of TGFBR1 and, subsequently, TGFBR2 will lead to a cascade of TGF-beta signaling. Moreover, LDS Type III and Type IV are attributed to mutations in decapentaplegic homolog 3 (SMAD3) and Transforming Growth Factor β II (TGFB2), respectively. These two subtypes have also been found to affect the TGF-β signaling pathway. The clinical manifestations pertaining to the cardiovascular system, aneurysm, and dissection are more aggressive than those in Marfan Syndrome. Patients with Type I and II LDS tend to have ruptured aneurysms earlier and in smaller diameters [20].

**Gene ACTA2**

The mutated gene encoding for smooth muscle cell-specific isoform of alpha-actin (ACTA2) is responsible for an autosomal...
dominant disease, with the main vascular manifestation being the aortic aneurysm and its risk of dissection, which is detected in about 1.5-21% of the cases. [6] The actin is involved in the contractility of the vessel and is responsible for providing vascular structure. [21] The occurrence of dissection is also age-related, with 35 years as the median age at which the dissection is more likely to occur. Another important finding is that a dissection may occur without a preexisting aneurysm in patients with this mutation [4].

Bicuspid Aortic Valve (BAV)

BAV is a common congenital heart abnormality that often leads to aortic dilation, especially in the segment of the aortic root and ascending aorta from early ages. Abnormal aortic valves generate a faster blood flow resulting in greater wall stress for the aorta. [22] It is inherited with an autosomal dominant pattern. However, there is not a single gene model that could explain the phenotype of this malformation. It has been linked to genes responsible for thoracic aneurysm syndromes, specifically in Marfan Syndrome, Ehlers-Danlos syndrome, vascular Loeys-Dietz syndrome, and Thoracic Aortic Aneurysm and Dissection syndrome (ACTA2 gene). Moreover, NOTCH1 mutations, which account for about 4% of the cases, have been associated with aortic valve abnormalities since calcification is increased along with oxidative stress and inflammation [23].

Gene COL3A1

Gene COL3A1 encodes collagen type III alpha 1, which is found in extensible vascular connective tissue. [24] Mutations of this gene characterize the vascular Ehlers-Danlos Syndrome (vEDS), previously known as Ehlers-Danlos Type IV. It is an autosomal dominant inherited syndrome and accounts for 5-10% of the cases with EDS. [17] Compared to other types of the syndrome, it is the most serious due to sudden death attributed to the rupture of larger arteries. It is associated with syndromic features, including facial dysmorphism, very thin skin with visible veins, and susceptible to bruising, pneumothorax, and bowel rupture. In general, the clinical manifestations of the syndrome may be heterogeneous even among members of the same family. [25] TAA is less common in the vEDS; however, dissection of large or medium-size arteries without preexisting dilation is possible [17].

Gene MYLK

Myosin Light Chain Kinase (MLCK) is encoded by the MYLK gene and is highly expressed in smooth muscle cells. It aims to phosphorylate the Regulatory Light Chain (RLC) in myosin type II in SMCs and, therefore, plays a vital role in their contraction. The mutated gene due to two missense alterations- p.S1759P and p.R1480X- is responsible for decreased contraction of SMC, especially in the ascending aorta, which makes it hard to withstand its heavy load. Interestingly, patients with this mutation often experience dissection without a pre-existing dilation of the aorta. Increased proteoglycan deposition is the key abnormality in progressive aortic disease [26].

Genes ELN and EFEMP2

Elastin and EGF Containing Fibulin Extracellular Matrix Protein 2 are both essential components of elastic fibers and the formation of connective tissues. [27,28] Mutations in ELN result in a benign [29] autosomal dominant cutis laxa and mutations in EFEMP2 in the severe [29] autosomal recessive form of the condition. Cutis laxa – a connective tissue disorder characterized by damage to the elastic fibers of connective tissue throughout the body. This condition is associated with syndromic features. There are skin abnormalities; the patients have loose skin along with cardiovascular manifestations, more specifically, severe aortic dilations due to elastic fibers degeneration in the medial zone[29]. It is connected to aneurysm of the ascending aorta [17,30].

Gene MYH11

MYH11 is a gene that encodes for smooth muscle myosin that belongs to the family of myosin heavy chains. Its primary function is to contribute during the contraction by converting chemical to mechanical energy. [31] A mutation of this gene is responsible for non-syndromic TAAD. The aneurysms associated with mutated MYH11-driven by IGF-1 and Angiotensin II- are found mainly in the ascending aorta. Pathology results from the aortic tissue of the affected area showed an increase in proteoglycans and a decrease in elastic fibers and periodic areas with increased and decreased smooth muscle cells [32].

Gene PRKG1

The gene PRKG1 is responsible for Type I cGMP-dependent protein kinase (PKG-1), which plays a key role in nitric oxide (NO)/cGMP signaling pathway. After the activation of PRKG1 due to the binding of GMP, it phosphorylates threonine and serine, proteins responsible for functions like smooth muscle contraction. [33] The p.Arg177Gln gene alteration causes the kinase to be cGMP-independent and increases its activity, and therefore, the phosphorylation of RLC and the contraction of SMCs are decreased. It is linked to dissection of the thoracic aorta or mild to severe dilation of the aortic root. Dissections observed at relatively younger ages; do not correlate with gender [34].

Management

Management of aortic aneurysms should aim to prevent further dilation, dissection, and rupture of the dilated area. Along with Abdominal Aortic Aneurysms, TAA is considered the 17th leading cause of death among individuals above the age of 65 years worldwide. [35] According to statistics, acute Type A aortic dissection (ATAAD) occurs between 2.1 and 16.3/100,000...
persons. [36] 20% of patients with TAAD die before reaching the hospital. If the patients with TAAD receive no treatment, then the mortality rate is between 1% and 3% per hour during the first 24 hours, 30% at 1 week, 80% at 2 weeks, and 90% at 1 year [7].

There are several recommendations for these patients besides surgical intervention. Firstly, the patient’s blood pressure should be well controlled, preferably under 140/90, by anti-hypertensive drugs, such as beta-adrenergic blockers. [16] They help decrease the inotropic stress of the heart and the impact of the ejected blood in the aorta. Patients with BAV who are not candidates for surgical intervention and do not experience aortic regurgitation are recommended treatment with B-blockers if the aneurysm is in the ascending aorta with a diameter >4.0cm. It has also been found that ACEs tend to decrease SMC apoptosis, which contributes to the support of the aortic wall. ARBs help reduce the aneurysm’s expansion due to “antagonistic” interaction with TGF-β. [35] In addition, patients with dyslipidemia are advised to follow a treatment with statins to maintain their LDL levels below 70mg/dl. [16] Smoking Cessation and avoidance of any contact with tobacco is also recommended. According to several studies, tobacco exposure leads to a faster aneurysm expansion, approximately 0.4mm/year. [11] In the case of female patients planning a pregnancy, they should be counseled about the possibility of dissection, closely monitored for their arterial blood pressure by beta blockers- since pregnancy is a contraindication for ACEs and ARBs. They should have a monthly or twice a month imaging of the aorta. Aortic dissection and rupture are more common during the third trimester at 50% and the peripartum period at 33%. These female patients are advised to deliver the fetus via cesarean section in a hospital with a cardiothoracic department. It is recommended that the patients have a follow-up in specific time frames with imaging studies to evaluate whether the dilation increases and calculate the risk for dissection [16] (Table 3).

<table>
<thead>
<tr>
<th>Patients diagnosed with Marfan syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat echocardiogram 6 months after the diagnosis.</td>
</tr>
<tr>
<td>Repeat echocardiogram annually if the aneurysm remains constant</td>
</tr>
<tr>
<td>More frequent echocardiograms if the aortic diameter is ≥4.5cm or it grows rapidly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with LDS or confirmed mutation in TGFBR1, TGFBR2, FBN1, ACTA2, or MYH11 should</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete aortic imaging 6 months after the diagnosis</td>
</tr>
<tr>
<td>Complete annually MRI</td>
</tr>
</tbody>
</table>

Table 3: Follow-up guidelines for patients with gene mutations.

Surgically Ascending Thoracic Aorta Aneurysms are typically managed with an open-heart surgery via median-sternotomy with cardiopulmonary bypass. It usually requires replacement of the aortic root, ascending aorta, and reimplantation of the coronary artery. Descending Thoracic Aortic Aneurysms can be repaired by either open surgery or endovascular grafts. The latter is associated with fewer perioperative complications but less durability. [35].

According to the 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases and 2022 ACC/AHA Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease, there are several criteria for patients to consider surgical repair (Table 4).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients with Marfan Syndrome with a maximum aortic diameter &gt;50mm</td>
<td>Patients with Marfan syndrome and a nondissected aneurysm of the aortic arch, descending thoracic aorta, or abdominal aorta of ≥5.0 cm, surgical intervention to replace the aneurysmal segment is recommended.</td>
</tr>
<tr>
<td>When there are other risk factors present</td>
<td></td>
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<tr>
<td>- Family member with aortic dissection</td>
<td></td>
</tr>
<tr>
<td>- Increase in diameter &gt;0.3mm/year</td>
<td></td>
</tr>
<tr>
<td>- Severe aortic regurgitation</td>
<td></td>
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<tr>
<td>- Desire for Pregnancy</td>
<td></td>
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<tr>
<td>limit decreases to &gt;45mm.</td>
<td></td>
</tr>
<tr>
<td>Patients with marfanoid manifestation without fulfilling Marfan syndrome’s criteria should be treated the same as patients with MFS.</td>
<td></td>
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</table>
**Clinical Validity of Genes**

As mentioned before, aneurysms of the aorta are “silent killers. Therefore, early detection and surgical intervention of aneurysms at risk for dissection is a critical factor in reducing mortality and morbidity rates if the more conservative treatments are inadequate [4]. In our generation, large multi-panel testing is introduced, in which genes that are involved in a certain phenotype, either if it is rare or if it is more frequent, can be tested. The improvement of technology led to lower costs of this process and, therefore, made it easily accessible. [38] Given that the scientific data has proved the association of mutated genes with aortic disease, genetic testing for HTAAD has been established in clinical practice. However, this rapid growth of sequencing comes also with risks. Genes that do not have the appropriate evidence to justify their connection to TAAD may be included. The variants of these genes have to be classified as Variants of Uncertain Significance (VUS). It was found that the proportion of variants versus pathogenic genes associated with diseases is 3:1. For a gene to be included in a diagnostic panel and an exome/genome sequencing, it needs to be clinically valid. Clinical validity refers to the strength of the evidence that this gene leads to a specific disease. For example, some genes have been linked to borderline dilation of the aorta- ascending aorta and aortic root- without evidence supporting that this dilation leads to dissection. An example that supports it is the mutated FBN2 gene. Some genes lead to dissection without pre-existing dilation of the aorta, i.e., COL3A1 [39]. Thus, a large panel of genes may lead to false-positives results. Each variant should be a topic of research in published literature and online databases to find out if it is included in a sufficient number of cohort studies. [38] Otherwise, the results of each genetic test may create unreasonable stress for the family and the individuals, confusion for the clinical doctors when considering the management of the patient, a false usage of our resources, and, of course, genetic discrimination.

**ClinGen**

With the guidance of a semiquantitative framework provided by the Clinical Genome Resource (ClinGen), a resource that identifies the clinical relevance of genes to be used in clinical medicine and research, the Aortopathy Working Group aimed to create a panel of genes associated with TAAD. This classification is based on genetic, clinical, and experimental evidence. They wanted the genes associated with HTAAD to be clinically significant in terms of dilation and dissection, in order to prompt aortic imaging, plan for conservative versus surgical treatment to prevent the lethal consequences and be used in a predictive manner for testing for family members at risk.

Category A1 and A2 contain genes with a “definitive” or “strong” correlation with HTAAD and may cause either syndromic or non-syndromic manifestations. In this study, a gene could only be marked as definitive when it is classified as strong, and it is on publication for years. Early in the process, the genes that were identified included ACTA2, COL3A1-due to their severity of causing acute dissections-FBN1, MYH11, MYLK, SMAD3, TGFB2, TGFB1, and TGFB2. Later in the process, PRKG1 and
LOX were added. Variants of these genes have a high diagnostic value. The family members of these patients are advised to go through genetic screening, imaging, and medical intervention.

Category B includes the “Potentially Diagnostic Genes,” more specifically, those that help us diagnose the aortic dilation but are not risky for dissection. These genes are primarily associated with other clinical manifestations and less with aortic aneurysms and dissection-EFEMP2, ELLN, FBN2, FLNA, NOTCH1, SLC2A10, SMAD4, SKI. The family members of these patients are at lower risk comparing to those in the first category. But the time frame for follow-up or surgical intervention is still unclear.

Category C encloses genes with limited evidence for HTAAD, and their diagnosis depends on clinical features outside the cardiovascular system. For example, renal disease may indicate mutations in COL4A5, PKD1, and PKD2, while homocystinuria in CBS. These genes are not considered useful to be reported and closely monitored.

Category D, the final category, is the one with no evidence that these genes result in HTAAD or that they result in HTAAD in humans but are based on experiments. 23 genes belong to this category: “ACVRL1, ADAMTS10, B3GAT3, COL1A1, COL1A2, COL4A1, COL5A1, COL5A2, COL9A1, COL9A2, COL11A1, COL18A1, EMILIN1, ENG, GATA5, GJA1, JAG1, MED12, PLOD1, PLOD3, SMAD6, UPF3B, and VCAN.”

FIGURE 2: [39] Panel of gene category of syndromic and non-syndromic TAAD. Category A1 and A2 contain genes that have a “definitive” or “strong” correlation with HTAAD and may cause either syndromic or non-syndromic manifestations. Category B includes the “Potentially Diagnostic Genes,” more specifically those that help diagnose aortic dilation but are not risky for dissection. Category C encloses genes that have limited evidence for HTAAD and their diagnosis depends on clinical features outside the cardiovascular system. Category D, is the one with no evidence that these genes result in HTAAD or that they result in HTAAD in humans but are based on experiments.
These groups are open to revision until a new discovery is made. After further investigations, genes may fall into a different category with less or stronger correlation with TAAD, or even new genes may be added. For example, “BGN, FOXE3, HCN4, MAT2A, MFAP5, SMAD2, and TGFB3” have been recently identified based on clinical data, but there are no publications yet supporting their association with the disease [39].

MicroRNAs

Except for DNA sequencing, MicroRNAs (miRNAs) is also a useful resource for forming a comprehensive decision about the monitoring and the appropriate treatment of a patient and are currently under investigation. They can be used as biomarkers for TAAD. Recent studies have shown that miR-574-5p, miR-122-3p, miR-438-3p can be used for distinguishing patients with TAA. [4] In addition, concerning the BAV-related TAA, it has been found that miRNA can be used as a circulating biomarker and help clinicians identify the BAV malformation- miR-1, miR-21, miR-122, miR-130a, miR-486-, confirm the aortic dilation- miR-718, miR-17, miR-106a, miR-15b, miR-20a-, and the loss of elastic properties of the aortic wall – miR-34a [22].

Screening Recommendations

The genetic factors’ involvement with the development of a certain phenotype increases with an increased size of the aortic organ (> 4.5cm), earlier age of diagnosis, either before the age of 50 or between 50 and 60 years of age without hypertension, positive family history and the presence of syndromic features, including ocular, cardiovascular, myoskeletal, cutaneous or other features. Positive family history usually refers to first-degree family members diagnosed with the disease [40]. According to the National Genomic Test directory, gene testing is available for patients with Thoracic Aortic Aneurysms and Dissection (R125) that meet certain criteria. Patients diagnosed with thoracic aortic aneurysms or dissection before the age of 50 or before the age of 60 with positive family history, features compatible with aortopathy or absence of other cardiovascular risk factors are eligible for gene testing. In addition, patients presenting with characteristics associated with Loeys-Dietz syndrome or Marfan syndrome, or any other syndrome predisposing to aortic disease should be investigated. Any deceased individual whose autopsy results reveal TAA and their relatives will be benefited from gene testing is also a candidate. [41]

As far as the patient’s family members are concerned, the existing guidelines are very vague and recommend referring to family testing. The European guidelines recommend testing to first-degree relatives only, while the American guidelines extend the testing to second-degree relatives if at least one first-degree relative is identified with the mutated gene.

Recommendations on this topic suggest that if there is a mutation linked to the development of the disease in the proband or if there is no mutation revealed but the patients fulfill one of the above criteria, then gene testing for family members is encouraged. The follow-up should include a Transthoracic Echocardiogram (TTE), which gives clear imaging of the aorta, especially the aortic root, and in case of poor evaluation with TTE, CT or MRI should be included. For Familial TAA, family members should start screening at the age of 25 years or 10 years before the patient’s age on disease onset and end at the age of 65. If they had their first screening above the age of 60, then they should have one more follow-up. The intervals should be 5 or 10 years, depending on the expansion rate and the size of the aneurysm [40,42,43].

Conclusion

The mutations of the genes FBN1, TGFBR1, TGFBR2, SMAD3, TGFBR2, SMAD3, TGFBR2, ACTA2, NOTCH1, COL3A1, MYLK, ELN, EFEMP2, MYH11, PRKG1 have been reported to cause dilation of the aortic organ and affect both the patient and their family members. Patients with aneurysms should be treated either by conventional treatment or by surgically. The aortic surgery, however, is offered to those who meet size criteria mainly based on the mutated gene they carry as it makes them susceptible to rupture at different stages of the aneurysmal development. It is important to develop a better understanding of the association of genes and biomarkers and the correlation and progression of thoracic aortic aneurysms to establish improved genetic profiles. In addition, constant revision of inclusion criteria and guidelines should be done to develop specific protocols for early investigations and interventions. This will ensure early management and reduced mortality due to this unfortunate condition.

References

Citation: Syrengela A, Shahjahan S, Bulut HI, Ttofi I, Djordjevic J, et al. (2023) How Important are Genetics in the Management of Thoracic Aortic Aneurysms and Acute Aortic Syndromes? What do we Know Today?. J Surg 8: 1818 DOI: 10.29011/2575-9760.001818


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