Thoracic Aortic Aneurysm and Dissection

Subjects: Cardiac & Cardiovascular Systems

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The main challenge in diagnosing and managing thoracic aortic aneurysm and dissection (TAA/D) is represented by the early detection of a disease that is both deadly and “elusive”, as it generally grows asymptomatically prior to rupture, leading to death in the majority of cases. Gender differences exist in aortic dissection in terms of incidence and treatment options. Efforts have been made to identify biomarkers that may help in early diagnosis and in detecting those patients at a higher risk of developing life-threatening complications. As soon as the hereditability of the TAA/D was demonstrated, several genetic factors were found to be associated with both the syndromic and non-syndromic forms of the disease, and they currently play a role in patient diagnosis/prognosis and management-guidance purposes.

Keywords: thoracic aortic aneurysm and dissection ; syndromic aortopathies ; differential diagnosis ; genetics ; biomarkers ; genetic diagnosis

1. Introduction

Despite the considerable advancements pursued over the past decades in pathophysiology knowledge and diagnostic imaging techniques for thoracic aortic aneurysm (TAA), plus the more consistent surveillance programs after diagnosis, it remains a life-threatening and still “subtle” disease for which the true epidemiology is hard to be determined. Ninety-five percent of TAA patients do not show any symptoms unless an acute aortic event occurs [1]. Thus, the estimated prevalence remains at 6–10 cases/100,000 patients/year, with ascending TAAs being more common compared to descending TAAs (60% vs. 35%) [2]. The most feared consequences of TAA are represented by aortic dissections/ruptures, the most common of the catastrophic events affecting the aorta [3]. In this respect too, the true incidence of aortic dissection is not easy to assess, as hospital-based reports clearly do not account for pre-admission deaths, which are known to involve a substantial proportion of TAA individuals [4]. Gender differences in aortic dissection were observed in a recent Swedish population-based study, estimating a decreasing incidence in men during 15 years. Differently, in women, the incidence did not show a significant variation. Moreover, fewer women were treated with thoracic endovascular aortic repair (TEVAR), and they showed a higher postoperative mortality when compared to men [5].

TAA has traditionally been divided based on the presence of extra-aortic clinical manifestations—syndromic TAA—or their absence—non-syndromic TAA. Syndromic TAA patients present with systemic features reflecting the presence of diseases involving connective tissue disorders such as Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS), vascular Ehlers-Danlos syndrome (vEDS), and arterial tortuosity syndrome [6]. Bicuspid aortic valve (BAV) represents another condition often found in association with TAA, which is currently considered an independent risk factor for its development, with the aorta being dilated in some cases, even in the presence of a normally functioning BAV and/or regardless of physical activity, as has been recently assessed in pediatric patients [7][8]. Non-syndromic TAAs account for 95% of all TAA cases [6] and are further classified as sporadic or familial, in the case of at least one of the first-degree family members being affected [9]. The different presentations of TAA share similarities with regards to the molecular pathophysiology underlying dilatation development (impaired extracellular matrix (ECM)), collagen homeostasis, alteration of the TGF-β signaling pathways, disruption of smooth muscle and cytoskeletal apparatus, and, even if with different penetrance, a significant heritability [10].

According to the ESC (European Society of Cardiology) guidelines, TAA presentation has an impact on management, measures of intervention, and therapeutic strategies, as aortic growth speed and progression vary between syndromic and non-syndromic cases and also between sporadic and familial ones [11]. Thus, early identification of asymptomatic patients is crucial to allow timely monitoring and management strategies that could potentially prevent the progression of TAA and TAD [6]. This is especially important in non-syndromic cases in which the lack of distinct clinical manifestations (involving musculoskeletal or ocular signs) may delay detection. From the laboratory point of view, given that syndromic/non-syndromic TAA are most often inherited in an autosomal dominant pattern, molecular-genetic analysis

represents a most valuable tool allowing early identification of affected individual as well as those subjects at higher risk of developing adverse outcomes in terms of aneurysm-growth speed and dissection [12]. This is particularly relevant for TAAs involving the ascending aorta, whose etiology is predominantly linked to a crucial genetic component. In addition, easily detectable and specific circulating biomarkers might further improve diagnosis and overall management of the disease. This entry will address the state of the art of TAA's pathophysiological drivers and related current laboratory tests, as well as genetic approaches and their major implications (most particularly regarding novel technologies/strategies) in supporting the detection and management of a condition with features (slow, gradual, and painless aneurysm formation, usually "accidentally" diagnosed via imaging study carried out for another purpose), that have made it earn, over the years, the sinister reputation of a "silent killer" [13].

2. Drivers of TAA Formation: A Constant Journey through Gene Discovery

The complexity and heterogeneity of TAA characteristics, syndromic presentation, and/or progression is the consequence of multiple but unique cellular and molecular-genetic mechanisms underlying its development, which often result in similar clinical presentation [14]. As familial-aggregation studies have suggested, more than 20% of patients have at least one first-degree family member with an arterial aneurysm, basically defining an increased risk for relatives of the affected individuals [15]. The first clue about the heritability of the trait is derived from case-control studies comparing the prevalence of thoracic aortic aneurysms, thoracic aortic dissections, and sudden death in first-degree relatives of patients referred for thoracic aortic surgery [16], identifying a higher risk for developing those diseases in the proband first-degree relatives with respect to the control groups (with relative risks of 1.8, 10.9, and 1.8 in proband fathers, brothers, and sisters, respectively). More evidence on genetic factors contributing to TAA development was provided by an analysis of a database comprising 598 patients evaluated for TAA in the United States [17], which showed a faster growth rate of aortic aneurysm in patients with familial cases with respect to the sporadic ones, with a younger age of presentation. In addition, pedigrees also showed different patterns of inheritance (autosomal dominant, X-linked, autosomal recessive). The role of genetic factors in causing TAA was further confirmed by more recent studies as well, analyzing different type of aneurysms [18]. It was mainly through genetic and animal models' studies that the combination of disrupted/altered cellular processes driving the TAA formation were elucidated as well as the specific associated genes (**Table 1**). In this regard, it has to be noticed, which some causative genes exert an overlapping effect on both syndromic and non-syndromic TAAs, even if these two conditions have traditionally been considered as distinct entities (e.g., ACTA2, SMAD3) (**Table 1**) [6].

Table 1. Genes associated with TAA/D (syndromic and non-syndromic).

Biological Process/Cellular Compartment	Gene	Protein	OMIM	Syndromic TAA/D	Non-Syndromic FTAA/D	Associated Syndrome/Diseases
Extracellular matrix/remodeling	*BGN*	Biglycan	300,989	+	−	Meester-Loeys syndrome. ARD, TAAD, pulmonary artery aneurysm, IA, arterial tortuosity [19].
	COL3A1	Collagen Type III α1 Chain	130,050	+	−	EDS, vascular type IV. TAAD, early aortic dissection, visceral arterial dissection, vessel fragility [20].
	EFEMP2	EGF Containing Fibulin Extracellular Matrix Protein 2	614,437	+	−	Cutis laxa, AR type Ib. Ascending aortic aneurysms, other arterial aneurysms, arterial tortuosity, stenosis [21].
	ELN	Elastin	123,700 185,500	+	−	Cutis laxa. AD ARD, ascending aortic aneurysm and dissection [22], TAA [23][24], BAV, IA possibly associated with SVAS.
	FBN1	Fibrillin-1	154,700	+	+	Marfan syndrome. ARD, TAA [25], TAAD [26], AAA, other arterial aneurysms, pulmonary artery dilatation, arterial tortuosity [27].
	LOX	Protein-lysine 6-oxidase	617,168	−	+	AAT10. AAA, hepatic artery aneurysm, BAV, CAD, TAAD [28][29].
	MFAP5	Microfibril Associated Protein 5	616,166	−	+	AAT9. ARD, TAA [30][31].
Smooth muscle cells	*ACTA2*	Smooth muscle α-actin	611,788 613,834 614,042	+	+	AAT6, multisystemic smooth muscle dysfunction, MYMY5. Early aortic dissection, CAD, stroke (moyamoya disease), PDA, pulmonary artery dilation, BAV, TAAD, TAA [24] [32].
	FLNA	Filamin A	300,049	+	−	Periventricular nodular heterotopia and otopalatodigital syndrome. Aortic dilatation/aneurysms, peripheral arterial dilatation, PDA, IA, BAV, TAA [32][33].
	MYH11	Smooth muscle myosin heavy chain	132,900	−	+	AAT4. PDA, CAD, peripheral vascular occlusive disease, carotid IA, TAAD, early aortic dissection [32][34][35].
	MYLK	Myosin light chain kinase	613,780	−	+	AAT7. TAAD, early aortic dissections [36][37].

Biological Process/Cellular Compartment	Gene	Protein	OMIM	Syndromic TAA/D	Non-Syndromic FTAA/D	Associated Syndrome/Diseases
TGF-β signaling	*LTBP1*	Latent TGF-β binding protein 1	150,390	+	–	Aortic dilation with associated musculoskeletal findings. Dental anomalies, short stature. TAAD, AAA, visceral and peripheral arterial aneurysm [38].
	LTBP3	Latent TGF-β binding protein 3	602,090			
	SMAD2	SMAD2	619,657 619,656	+	-	Unidentified CTD with arterial aneurysm/dissections. ARD, ascending aortic aneurysms, vertebral/carotid aneurysms and dissections [39], AAA.
	SMAD3	SMAD3	613,795	+	+	LDS type III. ARD, TAAD [40], early aortic dissection [39], AAA, arterial tortuosity, other arterial aneurysms/dissections [9], IA, BAV.
	SMAD4	SMAD4	175,050	+	-	JP/HHT syndrome. ARD, TAAD [39], AVMs, IA.
	SMAD6	SMAD6	602,931	-	+	AOVD2. BAV/TAA [24].
	TGFB2	TGF-β2	614,816	+	+	LDS type IV. ARD, TAA [40], TAAD, arterial tortuosity [39], other arterial aneurysms, BAV.
	TGFB3	TGF-β3	615,582	+	-	LDS type V. ARD, TAAD, AAA/dissection, other arterial aneurysms, IA/dissection [39].
	TGFBR1	TGF-β receptor type 1	609,192	+	+	LDS type I+AAT5. TAAD [40], early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection [9], IA, PDA, BAV.
	TGFBR2	TGF-β receptor type 2	610,168	+	+	LDS type II+AAT3. TAAD [40], early aortic dissection, AAA, arterial tortuosity, other arterial aneurysms/dissection [9], IA, PDA, BAV.

Biological Process/Cellular Compartment	Gene	Protein	OMIM	Syndromic TAA/D	Non-Syndromic FTAA/D	Associated Syndrome/Diseases
Others	***AXIN1/PDIA2 locus***	–	–	+	–	**BAV. BAV/TAA [41].**
	FBN2	**Fibrillin-2**	**121,050**	+	–	**Contractual arachnodactyly. Rare ARD and aortic dissection [42], BAV, PDA.**
	FOXE3	**Forkhead box 3**	**617,349**	–	+	**AAT11. TAAD [30] (primarily type A dissection).**
	MAT2A	**Methionine adenosyl-transferase II α**	**n.a.**	–	+	**FTAA Thoracic aortic aneurysms [30][43]. BAV.**
	NOTCH1	**NOTCH1**	**109,730**	–	+	**AOVD1. BAV/TAAD [24].**
	PRKG1	**Type 1 cGMP-dependent protein kinase**	**615,436**	–	+	**AAT8. TAAD [28][43], early aortic dissection, AAA, coronary artery aneurysm/dissection, aortic tortuosity, small vessel, CVD.**
	ROBO4	**Roundabout guidance receptor 4**	**607,528**	–	+	**BAV. BAV/TAA [24].**
	SKI	**Sloan Kettering proto-oncoprotein**	**182,212**	+	–	**Shprintzen–Goldberg syndrome. ARD, arterial tortuosity, pulmonary artery dilation, other (splenic) arterial aneurysms [36].**
	SLC2A10	**Glucose transporter 10**	**208,050**	+	–	**Arterial tortuosity syndrome. ARD, ascending aortic aneurysms [36], other arterial aneurysms, arterial tortuosity [44], elongated arteries, aortic/pulmonary artery stenosis.**

In bold: genes associated with dissection. AAA: abdominal aortic aneurysm; AAT/TAA: aortic aneurysm, thoracic; AD: autosomal dominant; AOVD: aortic valve disease; ARD: aortic root dilatation; AVM: arteriovenous malformation; BAV: bicuspid aortic valve; CAD: coronary artery disease; CTD: connective tissue disease; CVD: cerebrovascular disease; EDS: Ehlers-Danlos syndrome; FTAA: familial thoracic aortic aneurysm; FTAAD: familial thoracic aortic aneurysm and/or dissection; HHT: hereditary hemorrhagic telangiectasia; IA: intracranial aneurysm; JP: juvenile polyposis; LDS:, Loeys-Dietz syndrome; n.a.: not applicable; PDA: patent ductus arteriosus; SVAS: supravalvular aortic stenosis; TGF: transforming growth factor; TAAD: thoracic aortic aneurysm and/or dissection.

2.1. Extracellular Matrix Components

Among the genes causing and/or influencing TAA development, those codifying the ECM components are always mentioned first due to the amount of data that was collected over the years through animal studies, providing evidence of their impact on maintaining the structural integrity of the aortic wall. Those components are in close relationship and represent key factors, upstream/downstream, and intermediate elements of cellular pathways with impairment that has been demonstrated to have consequences in aneurysm development/predisposition in different ways, namely depletion of the elastic lamina in the aortic wall, lengthening of the ascending aorta, impaired assembly of collagen and elastic fibers, and altered TGF-β signaling (**Figure 1**).

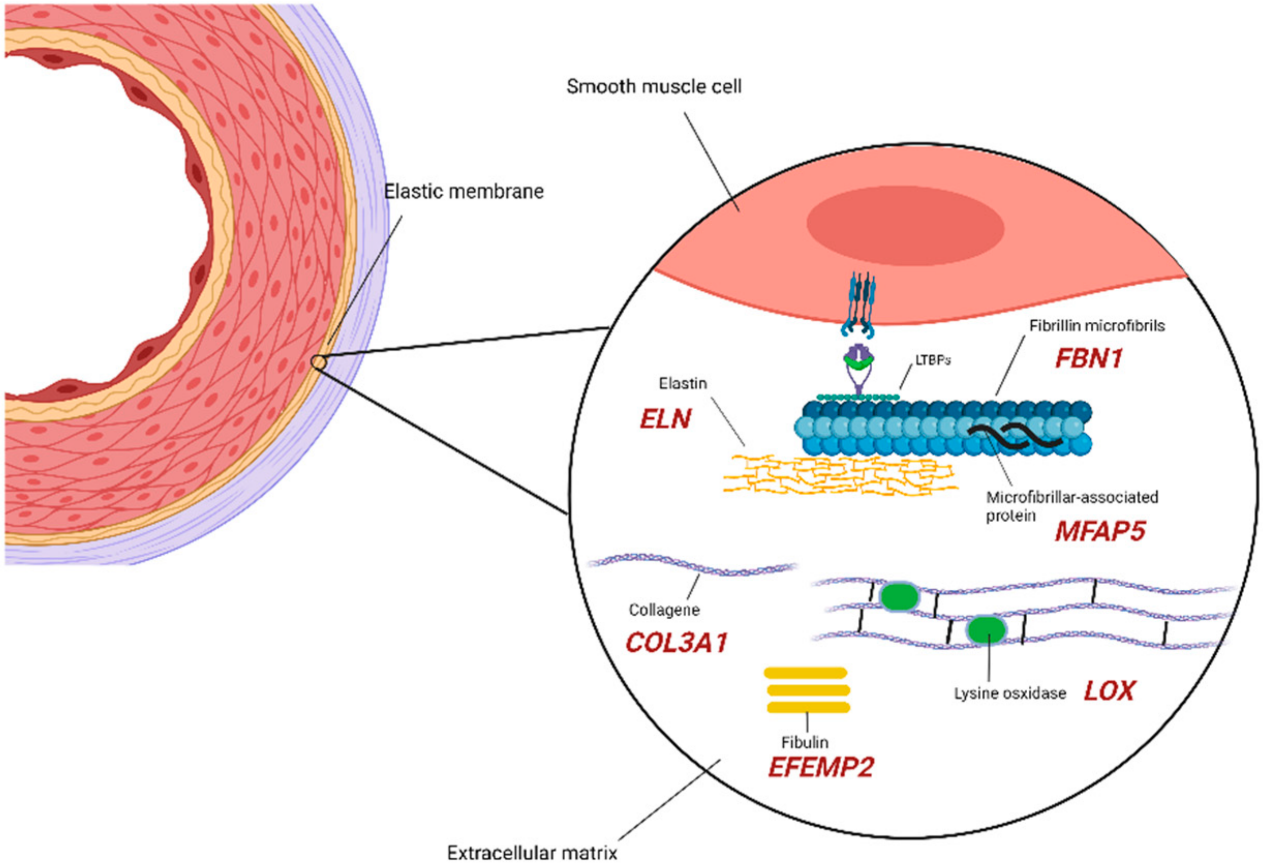

Figure 1. Schematization of the ECM main components. Genes codifying each component are reported in red (created with BioRender.com (accessed on 13 May 2022)).

The *FBN1* gene (15q21.1) encodes the key component of extracellular microfibrils fibrillin-1, with a major role in elastin (encoded by *ELN* gene, 7q11.23) assembly and support by promoting adhesion to vascular smooth muscle cells (VSMCs) through interaction with lysyl oxidase (encoded by *LOX* gene, 5q23.1) and fibronectin [45]. Robust data are available on TAA-causing variants, which were found to be responsible of protein synthesis/secretion's impairment or incorporation of mutant fibrillin in the microfibrillar architecture [46]. *FBN1* represents the causative gene of Marfan syndrome [47] in syndromic TAA (**Table 1**), but mutations involving this gene were found in sporadic, non-syndromic TAA as well [25]; besides, a large Whole Exome Sequencing (WES) performed on syndromic and non-syndromic TAAD reported *FBN1* as the most mutated gene of the cohort [26].

As mentioned, fibrillin 1 regulates the assembly of elastin, a protein that, when dysfunctional and/or depleted, has been found in association with TAA, even if additional mechanisms are required to initiate the dilatation development (altered integrins signaling, focal adhesion) [46]. Mutations involving *ELN* gene are causative of cutis laxa, which has an association with aortic dilatation that was found in 30–50% of patients [22]. Regarding the non-syndromic presentation of TAA, a triplication around the elastin gene was found to segregate in a family with supravalvular non-syndromic aortic aneurysm and in which the diagnosis of cutis laxa was excluded [23].

Stabilization and assembly of elastin is also regulated by the enzymatic activity of the lysyl oxidase protein, encoded by the *LOX* gene (5q23.1), catalyzing the lysin residues' oxidation and those crosslinking reactions required for the stability of the elastin molecules [48]. Inactivating mutations involving the *LOX* gene were found to be causative of TAA development in patients with MFS, familial TAA and dissection (FTAAD), and BAV, through mechanisms that remain to be entirely clarified [28][49].

Fibulin-4 (*EFEMP2 11q13.1*) and type III collagen (encoded by *COL3A1* gene 2q32.2) represent substrates of the enzyme encoded by the *LOX* gene that were shown to promote TAA development as well, when impaired in response to mutations involving the two codifying genes. The matrix glycoprotein fibulin-4 functions as an enhancer of lysyl oxidase activity and as a recruiter of immature elastin molecules: when mutated, the disruption of the elastic fibers and collagens on the aortic wall drives the aneurysm formation, as shown in both human and mouse models [50]. A similar mechanism described for fibulin-4 results from mutations in *COL3A1*, the causative gene of vEDS, with a main function to protect against the catastrophic disruption of the aortic wall that may result from an impaired deposition and maturation of collagen [51], mostly in syndromic forms of TAA [20].

Other ECM key components with dysregulation that has been found to drive TAA formation are the microfibril-associated glycoprotein 2 (*MFAP5* gene, 12p13.3) and biglycan (*BGN*, Xq28). Loss-of-function mutations in the first gene were shown to impair TGF-β and notch-1 signaling, as a consequence of the interaction's loss with fibrillin-1 [52]. A likely pathogenic variant was identified in a patient with mild TAA restricted to the ascending aorta, BAV, and subtle craniofacial features consistent with a connective-tissue disorder [31]. BGN mutations cause syndromic forms of TAA [19]. Its function is once again related to an alteration of the TGF-β signaling pathways, in which it acts as negative regulator, increasing TGF-β bioavailability [53].

2.2. SMCs (Smooth Muscle Cells) Compartment

The aorta is, for the most part, constituted by populations of SMCs, and the maintenance of the contractile properties of their cellular components is highly controlled and regulated. Molecular studies have, in fact, demonstrated that the impairment at different levels of this strictly regulated system predispose individuals to TAA development. Among proteins participating in this cellular machinery, α-smooth muscle aorta encoded by *ACTA2* gene (10q23.31) exerts an important function in maintaining contractility, and its depletion is, in turn, associated with a decrease ability of the monomer to assemble into polymeric filaments, eventually impairing the actin-myosin contractile unit [54]. Decades of study has proven mutations in this gene represent an important cause of familial and nonfamilial non-syndromic TAAD [55][56][57], accounting for 12–21% of TAAD.

Filamin A (*FLNA* gene, Xq28) is an anchoring cytoskeletal protein that, among its diverse functions, acts as a linker between actin filaments [58]. An 18.4% TAA frequency was found in a large systematic analysis of both pediatric and adult patients with periventricular nodular heterotopia carrying loss-of-function *FLNA* mutations [33] and, very recently, in a patient developing TAA with an history of systemic lupus erythematosus [59].

Myosin heavy chain 11 (*MYH11* gene, 16p13.11) interacts with α-actin, controlling its state change and enabling the actin filaments binding. *MYH11* is also traditionally classified as a mostly non-syndromic gene for TAA and was demonstrated to be associated with other manifestations such as aortic stiffness, an early hallmark of the disease [34][60]. However, it has to be noticed that *MYH11* defects account for <1% of all non-syndromic TAAD, with an aorta diameter prior to dissection usually >5 cm [35]. Robust data support the idea of shared defects in *FLNA*, *MYH11*, and *ACTA2* machinery, determining mechanical-strength disruption of the vascular walls and contractility-maintenance failure as significant causes of TAA progression, especially in non-syndromic cases [32].

The *MYLK* gene (3q21.1) encodes the myosin light chain kinase, regulating the actin-myosin interaction and phosphorylating myosin light-chains, and its most destructive mutations were once again mostly found in non-syndromic TAAD [9] (**Figure 2**).

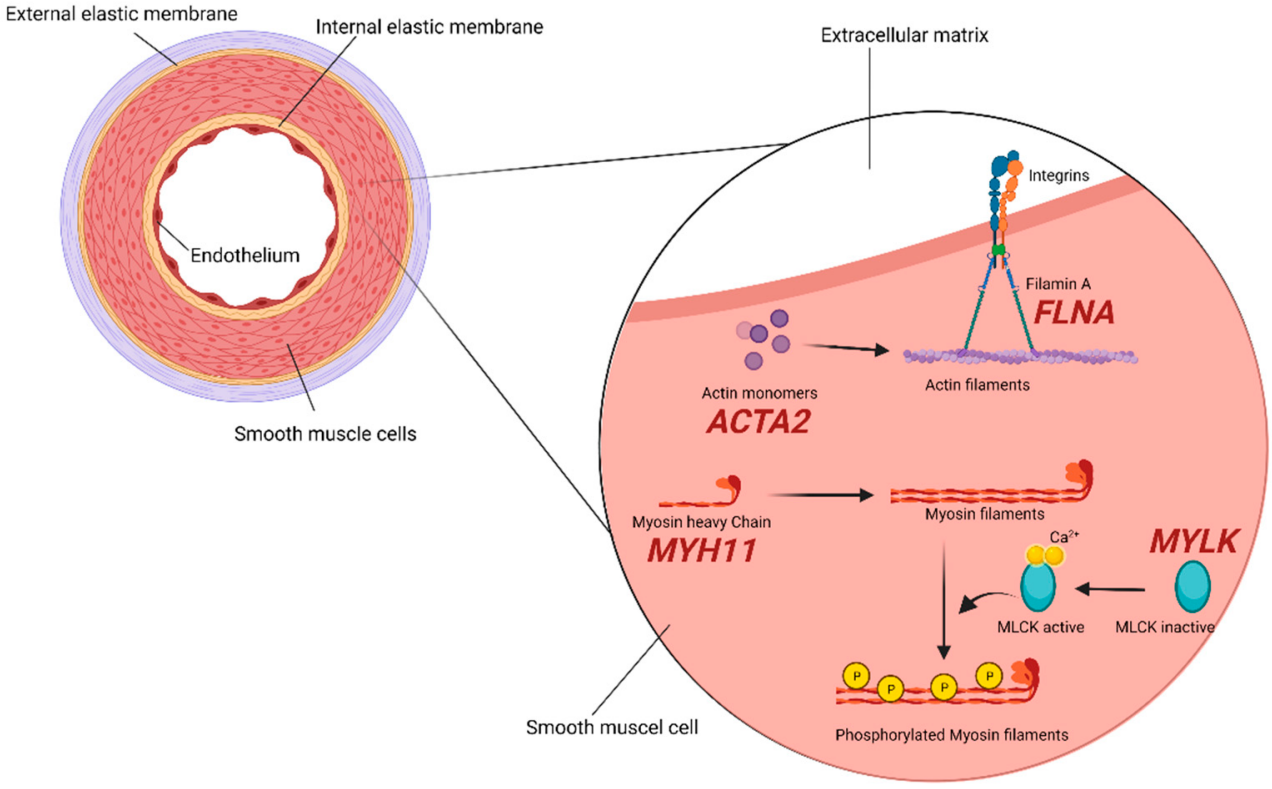

Figure 2. Schematization of the main components of the SMCs compartment. Genes codifying each component are reported in red (created in BioRender.com (accessed on 13 May 2022)).

2.3. TGF-β Signaling

A mutational repertoire in the genes coding for positive and negative regulators of TGF-β signaling has been reported in patients developing TAA in association with MFS and LDS, with those large volumes of animal studies research representing the first, and one of the major, contributions to researchers' understanding of aneurysmal onset and growth [61]. TGF-β signaling, in fact, plays a critical role in a series of vascular cellular processes such as blood-vessel development and maintenance, positive regulation of contractile proteins' expression, cell differentiation, proliferation, and homeostasis, and those mechanisms have been demonstrated to be dysregulated in all types of LDSs [61]. Different models have been proposed as the basis of aortic-wall dilatation, one of those suggesting a reduction in TGF-β signaling that would cause an impaired expression of contractile proteins, resembling the effect of mutations in *ACTA2* and *MYH11* genes [62]. Alternatively, LDS-causing mutations increase the VSMCs' signaling capacity, resulting in a defective responsiveness to the TGF-β of cardiac neural crest-derived VSMCs, which are highly abundant in the proximal thoracic aorta and in excessive activation of TGF-β signaling [63][64]. TGF-β is secreted by many types of cells, including macrophages, as part of a large latent complex that consists of the mature TGF-β cytokine, a dimer of its processed latency associated peptide (LAP), and one of three latent TGF-β binding protein-isoforms (LTBP1, 3, or 4). The latter binds to ECM components such as fibronectin or microfibrils composed of fibrillin-1. Among the LTBP protein family, a deletion involving the *LTBP1* gene (2p22.3) has been found to segregate in a three-generation family presenting with TAA [38], while a variant involving *LTBP3* gene (11q13.1) was suggested to be predisposing to TAA/D development [65]. Upon release, TGF-β binds to its heterodimeric receptor, activating the phosphorylation of the SMAD2 and SMAD3 proteins, which transmit the signal to the nucleus via the association with SMAD4 and, in turn, activate gene transcription [66]. Upon LDS-causing mutations, those affecting elements of the TGF-β signaling pathways involve the receptor heterodimer, made of the two components codified by the *TGFBR1* (9q22.33) and *TGFBR2* (3p24.1) genes; …these mutations result in decreased kinase activity with a reduction in the transduction molecules levels codified by the *SMAD2* (18q21.1) and *SMAD3* (15q22.33) genes [46]. The SMAD2 and SMAD3 proteins belong, in fact, to the receptor-activated (R)-SMAD family, intracellular effectors of the canonical TGF-β signaling pathway, with activated ligands that include the TGF-β2 and TGF-β3 encoded by *TGFB2* (1q41) and *TGFB3* (14q24.3). Mutations involving those genes have been associated with different subtypes of LDS, sharing aneurysm formation as a common clinical manifestation and being characterized by the presence/absence of other systemic features such as aortic or arterial tortuosity, cleft palate, bifid uvula, mitral valve disease, skeletal overgrowth, and so on [39] as well as a different tendency to early aortic dissection. *TGFBR1*, *TGFBR2* and *SMAD3* mutations also account for up to 3%, 5% and 2%, respectively, of non-syndromic FTAAD [32] (**Figure 3**).

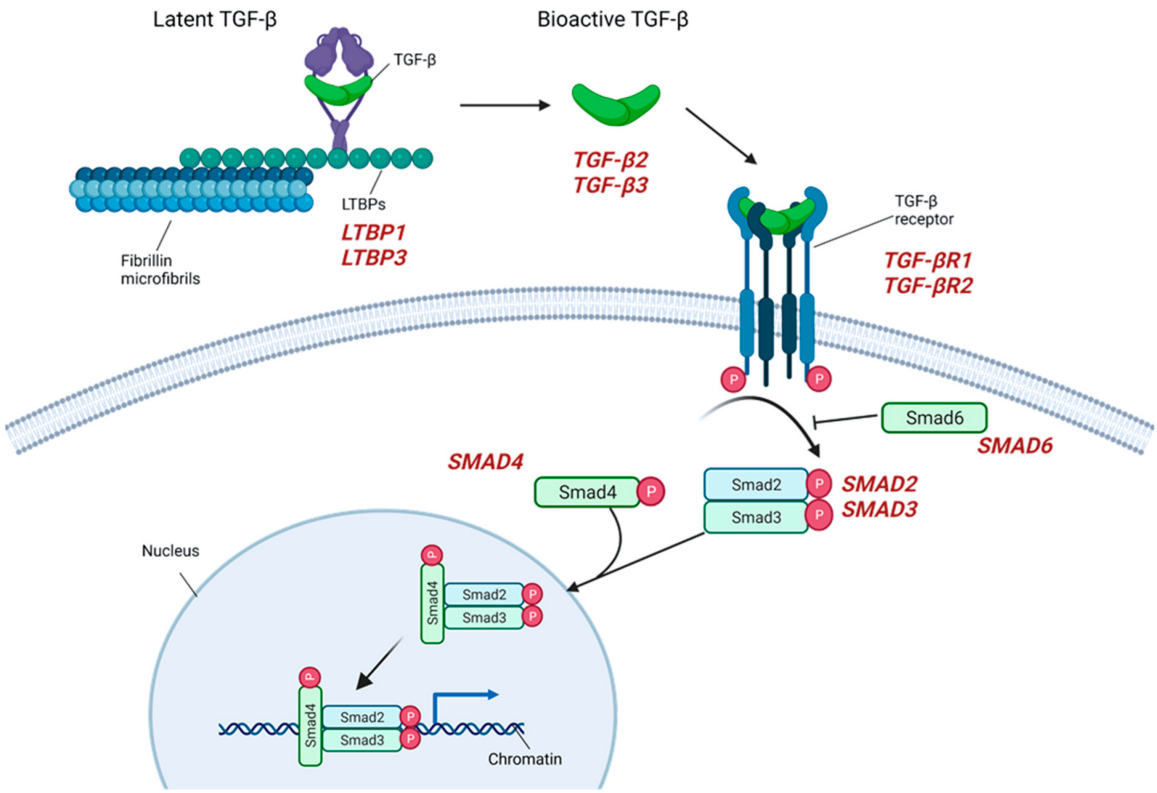

Figure 3. Schematization of the main components of TGF-β signaling. Genes codifying each component are reported in red (created in BioRender.com (accessed on 13 May 2022)).

2.4. TAA in the Context of Bicuspid Aortic Valve and the Role of Proteases

Since approximately 40% of BAV patients are prone to develop ascending aortic dilatation, this congenital heart defect is currently considered as an independent risk factor for TAA [7][67]. As the two phenotypes frequently occur together, and given the autosomal pattern of inheritance with incomplete penetrance that has been proposed for BAV, hypotheses have been made about the pathophysiological mechanisms driving the valve anomaly, along with its more frequent complication that, among others, involves the potential role of genetic syndromic TAA-associated variants such as *NOTCH1*, *ROBO4*, *SMAD6*, *ELN*, *FBN1*, *ACTA2*, and *LOX* [24][68]. Metalloproteases (MMPs) have been hypothesized to participate in TAA development in the context of BAV, following the observation of a significant increase in MMP-2 levels associated with a reduction in TIMP-1 in BAV/TAA compared with TAA subjects, in the context of a normal tricuspid valve; a greater activity of MMP-2 and MMP-9 in aneurysms was associated with BAV, which could explain the higher prevalence of TAA in these patients [69][70]. Apart from BAV, the combination of altered levels of MMPs, ADAMTS, and TIMPs (the main proteases and inhibitors within the media controlling the ECM environment's integrity and maintenance) are proven to actively contribute to the medial degeneration triggering TAA [71]. Studies on human and animal models led to the observation of increased expression of MMP-2 and MMP-9 in TAA intima and media [72] and higher levels of ADAMTS-1 and ADAMTS-4 in sporadic, ascending TAA tissues from human patients [73]. Despite the indisputable value of these observation in understanding TAA pathogenesis and their potential implications in diagnosis, it has to be noticed that those markers are not specific for the phenotype, and their levels are altered in several other processes such as AAA (MMP-2, MMP-9), cancer (MMP-9, TIMP-1, TIMP-2), renal disease (TIMP-2), and so on [74] and are currently not included in the recommended work-up for TAA diagnosis and management nor in the genetic screening.

3. Mechanisms of TAA Progression: The Dissection Menace

As the pathophysiological mechanisms underlying TAA onset in both its syndromic and non-syndromic presentation have been illustrated, and their specific molecular features continue to be unraveled thanks to the advancements in wide genetic-screening technologies, detection of the disease remains a clinical challenge. This is especially relevant with respect to its most catastrophic complications, rupture and dissection, leading to death in the great majority of patients without timely treatment [4][75]. In fact, once aortic dissection has occurred, mortality is 1–2% for each hour afterwards, resulting in a 48-h mortality of approximately 50% [76]. However, in the case of survival, serious complications may follow such as lethal malperfusion syndrome, aortic regurgitation, cardiac failure, and stroke [77]. Dissection represents a considerable diagnostic challenge for physicians due to the rarity of the condition and the characteristic symptomatology often mimicking other, more common diseases, determining a delay in diagnosis in >30% of cases [4]. Thus, the understanding of the pathophysiology, the key features, and the potential biochemical/molecular markers of TAA progression into aortic dissection has been crucial during the last decades to improve outcomes, for long-term prognosis, and eventually for patients' risk-stratification purposes.

3.1. Pathophysiology and Risk Factors

The instability and the deteriorating integrity of the aortic wall may be due to being predisposed to inherited conditions (such as inherited connective tissue disorders) or can be acquired, as happens with atherosclerotic degeneration due to ageing. Two mechanisms have been proposed to initiate the dissection cascade: (1) in most cases, a tear in the intima exposes the medial layer to the pulsatile blood flow; and (2) in fewer cases, the rupture of the vasa vasorum leads to the weakening of the inner aortic wall [78]. In the first scenario, a false lumen derives from the progressive separation of the aortic wall layers, and its propagation leads to aortic rupture where the adventitia is disrupted: rupture quickly leads to exsanguination and death [79]. In the latter case, the bleeding results in intramural hematoma that may progress in aortic dissection. It has actually been hypothesized that a co-existence of these two conditions may, in turn, constitute a spectrum [80]. From a molecular point of view, dissection occurs as a consequence of the aortic-wall structure's remodeling, due to inflammation and ECM-degradation processes. Once again, proteases exert an important role, since the infiltration of the activated macrophages and pro-inflammatory cytokines in the tunica media leads to an excessive production of MMP-1, MMP-9, and MMP-12 and to an imbalance between them and their inhibitors (TIMPs), which, in turn, results in the degradation of collagen and elastin fibers [81][82]. Wall remodeling is also maintained by VEGF-mediated neo-angiogenesis, as the production of VEGF (also functioning as a pro-inflammatory molecule) is increased in degraded medial layers [83].

Among classical risk factors associated with aortic dissection, namely older age, dyslipidemia, and increased levels of apolipoprotein A1, 80% of patients developing dissection have hypertension [84], which has a direct effect on the pathogenic mechanisms described above. Specifically, hypertension is demonstrated to promote a pro-inflammatory environment mainly by inducing macrophage recruitment and activation [85]; hypertensive patients, in fact, show high concentrations of VEGF, IL-6, MMP-2, and MMP-9 [86][87]. Other risk factors are recognized such as the male sex, a smoking habit, and the concurrence of connective tissue disorders such as MFS, LDS, vEDS, and BAV. Aortic dilatation is known to increase the risk of dissection, with the incidence complications reaching 30% at diameters > 60 mm [88]. Still, dilatation is proven not to be essential for developing a dissection, as ~60% of non-syndromic type A aortic dissection have diameters < 55 mm, while, in the absence of hypertension, MFS or BAV patients show a tendency to dissect at larger diameters [89][90]. Rare risk factors for aortic dissection are further represented by vascular inflammation due to autoimmune disorders such as Giant-cell arteritis, Takayasu Arteritis, Behçet disease, and systemic lupus erythematosus, while 1% to 5% of aortic dissections are secondary to aortitis [91].

3.2. Genetic Profiles of Dissection

To date, more than 30 TAAD-causative genes have been discovered (**Table 1**) and in the context of risk-prediction of TAA progression into potentially fatal dissection, it appears of primary interest to identify those genes or the specific type of variants/genetic profiles that, among others, are more prone to trigger and drive those processes eventually leading to sudden aortic-wall rupture. Marked in bold in **Table 1**, those genes were demonstrated to increase the risk of dissection at certain aortic sizes. Some of them represent causative genes of peculiar connective-tissue disorders described in association with TAA in its syndromic presentation. Pathogenic variants in FBN1, the MFS-causative gene, were found to increase the risk for Stanford type A and B dissection, even in the context of a normal or minimally dilated ascending aorta [92][93][94]. Indeed, a diagnosis of MFS is established in ~5% of patients with aortic dissection [95]. Haploinsufficiency, mainly resulting from truncating or splicing FBN1 mutations, is described as the leading mechanism behind the increased rate of aortic events [27]. Some overlapping cardiovascular clinical manifestations characterize MFS and LDS as basically reflecting a predisposition of patients affected by one or the other connective disorder to develop aneurysm and dissections of aorta and other arteries [92]. Implicated genes are *TGFBR1*, *TGFBR2*, and SMAD3, causing LDS type I and III, which have been associated with increased aortic risk of dissection at diameters < 50 mm [9]. *TGFBR1* and *TGFBR2* mutations' carriers are often reported as a comparable clinical picture regarding presentation and natural history, even though clinical differences have actually been observed between the two populations of mutated subjects [96]. Regarding *TGFBR1* families, a gender-based difference in survival has been observed, resulting in significantly better outcomes in women than in men. Differences were also observed in terms of aortic diameter, with *TGBFR2* carriers dissecting at minimal aortic dilatation with respect to *TGFBR1* carriers in which the ascending aorta diameter at the time of type A dissections was 50 mm. A more recent and large multicenter retrospective registry of patients with genetically triggered thoracic aortic disease reported the data of 441 subjects harboring mutations on the TGF-β receptor genes, somewhat confirming the previous observations in *TGFBR2* mutations' female carriers, that type A dissections of moderately dilated ascending aorta appeared more frequently than in males, which was not the case with *TGFBR1*, suggesting a more aggressive aortic disease in *TGFBR2* patients, especially in women [97]. Together with a *TGFBR2* mutation and the female sex, other features such as aortic tortuosity, hypertelorism, and translucent skin were found to be associated with an increased aortic dissection risk and may be taken into consideration in determining the optimal surgical timing (45 mm in the general population, lowered toward 40 in females with low body surface area, harboring a *TGFBR2* mutation, and presenting extra-aortic features). The literature data support the role of *SMAD3* as a dissection-predisposing gene [66][98][99][100], with mutations' carriers having a cumulative risk of dissection or prophylactic surgical repair of 50% by age 50 and 85% by age 80. Interestingly, these subjects are characterized by a later onset of aortic events, possibly leading to a delayed diagnosis if compared, for instance, to MFS patients presenting with wider systemic features [101]. The early recognition of the disease, in this subset of patients, consequently lies in the family history of thoracic aortic disease (as a key element), so this observation remarks on the need to identify those subjects before dissection occurs. The majority (63%) of *SMAD3* mutations are missense and reside in the MH2 domain, which regulates the oligomerization with SMAD2 or SMAD4 and the subsequent activation of transcription, with those variants being associated with earlier aortic events compared to truncating, non-sense, gene-disrupting ones [102]. Even if generally associated with a specific connective-tissue disorder, it must be reasserted that *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* mutations also account for an additional 14% of non-syndromic familial TAA [40], in which the diagnosis of aortic disease may be complicated by the absence of peculiar systemic clinical features.

A vEDS-causing gene, COL3A1, is also among those referenced as dissection associated ones, due to the supporting literature data on population studies and case reports. The dissection was found to develop in different locations of the arterial tree, such as the abdominal aorta, as well as the iliac, coronary, and cervical arteries [103][104][105][106]. Concerning

syndromic TAA in patients diagnosed as vEDS, few post-mortem cases were reported in 2010 [107], and 33 unrelated individuals or families were found to carry COL3A1 splicing mutations or small deletions partially removing splice-junctions sequences [108], and patients developing post-surgical or sudden aortic events are reported [109][110][111]. COL3A1 variants were additionally found to be associated with sporadic forms of TAAD in recent WES and case-control studies [112][113]. The type of variant involving the COL3A1 gene was also been suggested to correlate with the phenotype severity of vEDS; specifically, a subgroup of patients in a large European cohort bearing non-glycine missense and/or genetic variations at the C- and N-termini of type III procollagens was found to develop a later-onset and a milder phenotype with higher rates of aortic complications [114], while mutations at splice-donor sites were associated with higher mortality rates with respect to those involving the splice-acceptor sequences [115]. The literature data on animal models/human cohorts have identified a number of other genes, with mutations that were suggested to increase the risk of aortic dissection, such as EFEMP2 at the level of the ascending aorta [21], MYH11, ACTA2, and MAT2A in the thoracic aorta [43][116], and SLC2A10 at the aorta, as well as the arteries [44] LOX and PRKG1, with more limited data [28][117], and FOXE3 and MFAP5 as identified through WES studies [30][31].

4. Genetic Testing in Supporting TAA/D Diagnostics and In Risk Prediction: Where Do We Stand?

Although primarily considered as surgical disease, TAA's optimal management greatly relies on an appropriate workup with the major purpose of identifying those features suggestive of a rapid progression of the aortic anomaly, thus predicting potentially life-threatening consequences of the disease. In this context, an accurate genetic evaluation/diagnosis serves different purposes: (a) guidance for overall medical management and surgical options; (b) timely evaluation of other organs that could be affected essentially in syndromic forms of TAA; (c) better definition of the prognosis; (d) identification of high-risk first-degree family members; (e) estimation of recurrence risk for future pregnancies in the prenatal diagnosis' framework; and (f) support for imaging techniques in capturing nonsyndromic TAA patients who may be missed while developing dissection or rupture before reaching the guidelines-defined aortic diameter thresholds for aortic intervention [[118]]. As previously mentioned, syndromic and non-syndromic heritable thoracic aortic disease are, in most cases, inherited in an autosomal dominant manner except for rare X-linked and recessive conditions [119]. The accurate clinical evaluation of at-risk relatives is critical in this context, and ordinary and reproductive pre- and post-test genetic counseling allow for the early identification of an undiagnosed aortic disease in the first case and provide awareness about the risk of transmission to the offspring in the latter. Mutations are described to have variable penetrance depending on the TAA presentation, from almost 100% in MFS and 90% in LDS, to 50% in FTAAD and BAV in the presence of ascending aortic aneurysm. In fact, in the case of FTAAD, the causal mutation is found in much fewer cases (<10%) than in MFS or LDS, this discrepancy also being evident at the phenotypic level, presenting with a different severity of clinical manifestations along with age of presentation or diagnosis. When features of a connective-tissue disorder are present, patients should undergo genetic counselling and testing where appropriate [10]. The current ESC guidelines recommend genetic screening in first-degree relatives of TAA or aortic dissection and a diagnosis of familial aortic disease. In absence of a genetic diagnosis, at-risk relatives should undergo examination every 5 years. Screening should cover the entire arterial tree (including cerebral arteries) in families with nonsyndromic familial aortic disease [120]. According to the North American guidelines and related Class I recommendations, in case of identification of a mutation in one of the following genes, FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, and MYH11, which are associated with aortic aneurysm and/or dissection, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging. The guidelines provide some more recommendations (Class IIa and IIb): (a) ACTA2 sequencing should be considered in case of family history of thoracic aortic aneurysm and/or dissection; (b) TGFBR1, TGFBR2, and MYH11 sequencing may be considered in patients with a family history and clinical features associated with mutations in these genes; and c) if one or more first-degree relatives of a patient with known thoracic aortic aneurysm and/or dissection are found to have thoracic aortic dilatation, aneurysm, or dissection, then referral to a geneticist may be considered [121]. Following the exclusion of a syndromic condition, nonsyndromic TAA, in which mutations in genes known to be involved in syndromic forms of TAAD are rarely found, may present suggestive features of a genetic etiology, which might include young age at presentation (<50 years old), multiple aneurysms or dissections, and aortic root aneurysm [122][123]. In this scenario, genetic counseling should begin with the collection of the most detailed information of a three-generation family history, for the presence of aneurysm, dissection, sudden deaths, and syndromic features that would help in determining the inheritance pattern, identifying at-risk relatives, and recognizing syndromic signs [119]. In 2009, Ripperger and co-workers reported three cases of sudden, unexpected death due to thoracic aortic dissection, pointing out the great benefit that could be derived from alerting the at-risk relatives of the deceased about a potential heritable etiology of the disease [124]. The authors propose the development of a standard procedure which includes genetic counseling for at-risk relatives and storage of DNA or unfixed tissue for molecular investigations that would eventually allow differential diagnostic reappraisal from a genetic point of view. In any case, during genetic

consultation, patients should become aware of the limitations, benefits, and personal and familial implications of genetic testing. Besides, awareness should be raised on the possibility of a negative genetic test that would not necessarily exclude a genetic etiology, thus indicating the imaging to be performed anyways in the first-degree family members in the search for aortic disease [121]. In fact, some types of genetic variants may be undetectable by standard assays and, similarly, the causative mutation may involve a gene that has not yet been associated to TAAD, due to absence of data supporting the actual pathological effect of that variant [121]. As a matter of fact, regarding the most appropriate genetic test selection, no specific indications are provided by the European guidelines. Genetic-testing panels vary significantly among laboratories and despite the enthusiasm for the so-called “exome-first” approach in diagnosing such a complex disease as TAA, its actual benefit and routine application in the diagnostic workup currently represent a matter of debate within the international scientific community.

5. Take home message

TAA’s bad reputation of “silent killer” is to be ascribed to its characteristic features, including its slow and gradual formation and the absence of visible signs, with patients remaining asymptomatic. This condition is elusive and yet potentially life-threatening, as it manifests itself only once the aneurysm is large enough to lead to an acute and devastating aortic event, with a significant percentage of patients dying before reaching the hospital. As a result, it is of the utmost relevance to identify biomarkers for the early identification of asymptomatic patients, a task which is both essential and challenging. In this regard, there’s an important distinction to be made between the TAD management within the emergency department, in which the room to maneuver is objectively limited, and those other situations in which the fatal event has not happened yet. In the first case, as Mehta and co-workers pointed out in a very recent review, the margin of intervention is essentially directed to improving the patient’s outcome by different means, including the multidisciplinary collaboration between specialists (emergency physicians, surgeons, radiologists) and identification of the optimal interventional treatment and post-operative care [125]. Traditional circulating biomarkers do not represent a satisfactory and reliable support in the initial patient screening as well, in which, on the contrary, the molecular/genetic evaluation can be diriment. Genetic testing, especially that which interrogates several genes at once in a parallel approach that is, at present, undoubtedly preferable to the cascade one, has long been included in the diagnostic flowchart for TAA diagnosis. First of all, it allows for the identification of a co-existing condition with TAA, such as MFS or LDS, thus directing the most appropriate management in terms of periodic check-ups, time of intervention, risk-recurrence calculation for pregnancies, and screening for first-degree relatives. In addition, the constant implementation of molecular methodologies allowing for the interrogation of the entire genome or transcriptome in an “omic” approach could be, undoubtedly, beneficial for patients’ stratification. In fact, the combination of the data derived from the WES/WGS/RNA-seq approaches can help define profiles that could be highly specific for subgroups of TAA patients, not to mention the potential use of those data in deepening knowledge about the disease’s onset and progression as well as for identifying new targets for therapy. Even with the considerable limitations characterizing the omic approaches (production of a large amount of bioinformatic data that need to be correctly interpreted, safely stored, and validated through functional studies; the possibility of VUSs and incidental findings), the future benefits they may represent for the improvement of the TAA diagnostic work-up have to be considered and perhaps should be addressed more closely and in greater detail in the international guidelines

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